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Synthesis of 4,7-Indolequinones. The Oxidative Demethylation of 4,7-Dimethoxyindoles with Ceric Ammonium Nitrate

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The oxidative demethylation of 4,7-dimethoxyindoles to the corresponding 4,7-dihydroindole-4,7-diones with ceric ammonium nitrate is described.

Keywords——ceric ammonium nitrate; CAN; oxidative demethylation; heterocyclic quinone; indole quinone

There is much interest at present in the chemistry and biological activity of heterocyclic quinones.[1] In connection with our studies on the synthesis of isoquinoline quinone antibiotics, *i.e.*, mimocin (**1**),[2] renierone (**2**),[3] 7-methoxy-1,6-dimethyl-5,8-dihydroisoquinoline-5,8-dione (**3**)[4] and *N*-formyl-1,2-dihydrorenierone (**4**),[4] we have already synthesized a variety of isoquinoline and quinoline quinones using oxidative demethylation of hydroquinone dimethyl ethers with ceric ammonium nitrate (CAN)[5] or oxidation of amines with potassium nitrosodisulfonate (Fremy's salt).[6,7] We wish to report here the results of oxidative demethylation of 4,7-dimethoxyindoles with CAN.

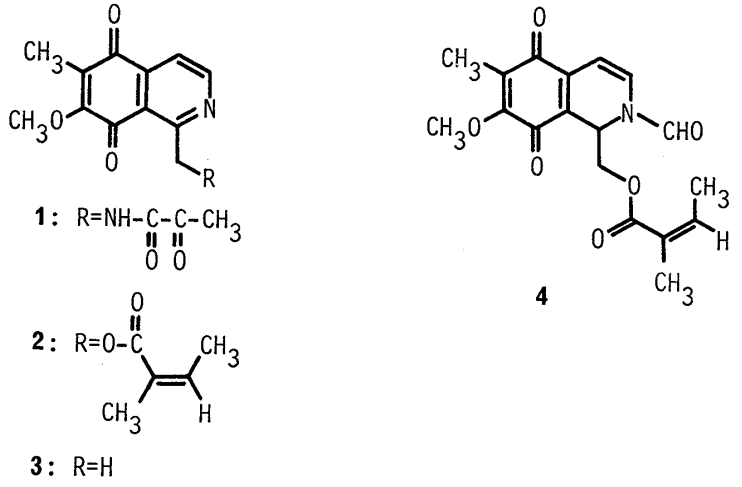

Fig. 1

The oxidative demethylation of 1-ethoxycarbonyl-4,7-dimethoxy-2,3-dimethylindole (**6**, prepared by treatment of **5**[8] with sodium hydride and ethyl chloroformate) with CAN in aqueous acetonitrile containing pyridine-2,6-dicarboxylic acid *N*-oxide[9] afforded the corresponding *p*-quinone **7** (49%) and 4,7-dihydro-2,3-dimethylindole-4,7-dione (**8**, 21%). The ethoxycarbonyl group of the quinone **7** was removed with aqueous acetic acid to yield **8** (34%). However, attempted oxidation of the indole **5** under the same conditions as used for **6**

failed, giving an inseparable mixture.

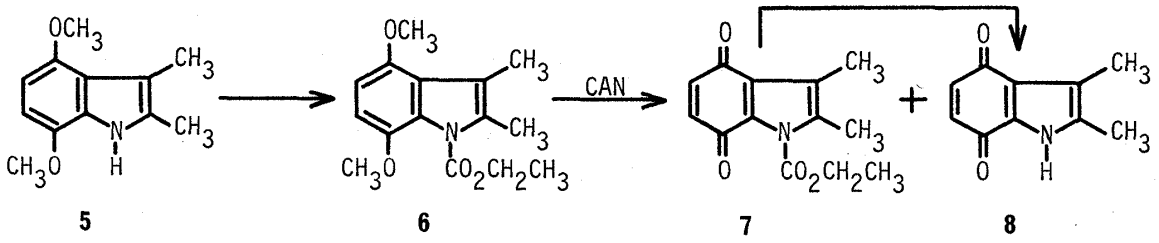

Chart 1

Furthermore, the oxidative demethylation of 1-ethoxycarbonyl-4,5,7-trimethoxy-6-methylindole (**15a**) with CAN was examined (the formation of the *p*-quinone and/or *o*-quinone is possible). The indole **15a** was prepared in six steps starting from 2,4-dimethoxy-3-methylphenol[10] (**9a**). Treatment of the phenol **9a** with hexamethylenetetramine in acetic acid yielded 2-hydroxy-3,5-dimethoxy-4-methylbenzaldehyde (**10a**), which was methylated to **11a**. The aldehyde **11a** was condensed with nitromethane, and the resulting *β*-nitrostyrene **12a** was nitrated with nitric acid to furnish the *o*,*β*-dinitrostyrene **13a**. The reductive cyclization of **13a** with iron powder in acetic acid yielded 4,5,7-trimethoxy-6-methylindole (**14a**), which was converted to the carbamate **15a**. The oxidative demethylation of the indole **15a** with CAN under the same conditions as used for the 4,7-dimethoxyindole **6** afforded the corresponding *p*-quinone **16** (75%) and 4,7-dihydro-5-methoxy-6-methylindole-4,7-dione (**17**, 15%); but no *o*-quinone, *i.e.*, 1-ethoxycarbonyl-4,5-dihydro-7-methoxy-6-methylindole-4,5-dione or 4,5-dihydro-7-methoxy-6-methylindole-4,5-dione. Treatment of **16** with aqueous ammonia yielded **17** quantitatively.

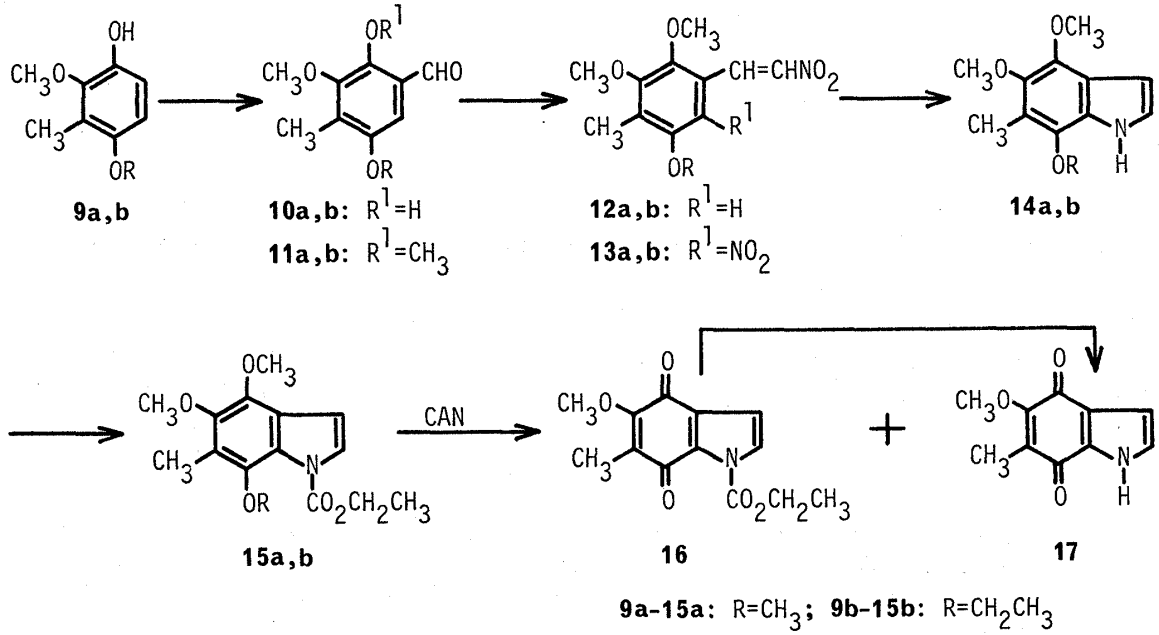

Chart 2

The structure of the methoxy *p*-quinones **16** and **17** was further confirmed by the following synthesis. The oxidation of 7-ethoxy-1-ethoxycarbonyl-4,5-dimethoxy-6-methylindole (**15b**, prepared from **9b** by the same procedure as used for **15a**) with CAN afforded 1-ethoxycarbonyl-4,7-dihydro-5-methoxy-6-methylindole-4,7-dione (34% yield), which was identical with the quinone **16** obtained by the oxidative demethylation of the

trimethoxyindole **15a** in terms of infrared (IR), nuclear magnetic resonance (NMR) and mass spectra, and mixed melting point. Furthermore, the debenzylation of 4,7-dibenzyloxy-5-methoxy-6-methylindole (**24**) with 10% palladium on carbon in methanol under hydrogen yielded 4,7-dihydro-5-methoxy-6-methylindole-4,7-dione, which was identical with the quinone **17** obtained by the oxidative demethylation of the trimethoxyindole **15a**. The required indole **24** was prepared in seven steps starting from **10a** *via* 2-methoxy-3,6-dimethyl-1,4-benzoquinone[11] (**19**). The quinone **19**, obtained by reduction of **10a** with hydrazine hydrate, followed by oxidation with CAN, was reduced with sodium dithionite and the resulting hydroquinone **20** was condensed with benzyl bromide to furnish the dibenzyl ether **21**. The nitration of **21** yielded **22**, which was treated with *N*,*N*-dimethylformamide dimethyl acetal (DMF–DMA)[12] to afford (2,5-dibenzyloxy-3-methoxy-4-methyl-6-nitrophenyl)acetaldehyde (**23**). The reductive cyclization of **23** with ammonium acetate and titanium trichloride[13] yielded the 4,7-dibenzyloxyindole **24**.

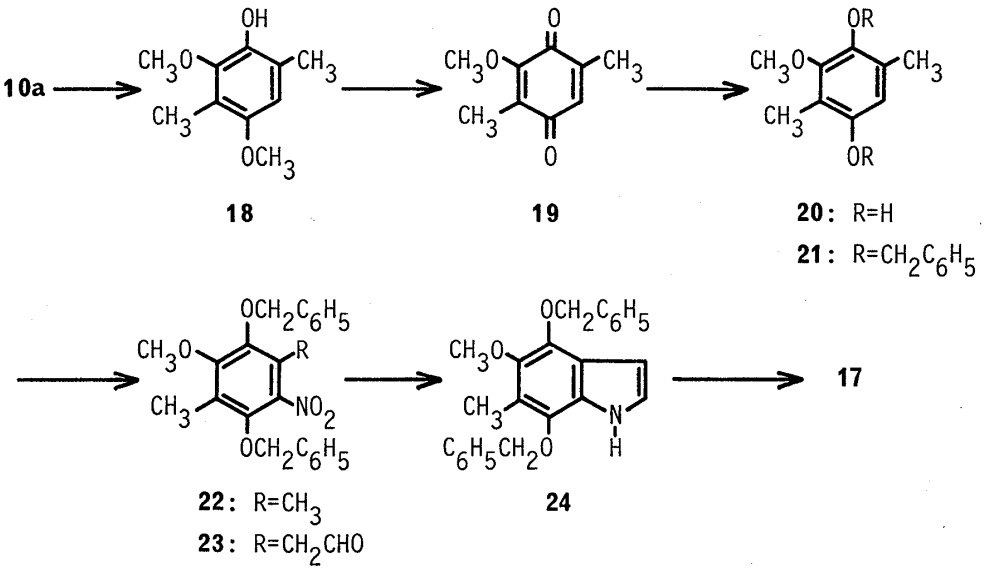

Chart 3

In summary, the oxidative demethylation of the 1-ethoxycarbonyl-4,7-dimethoxyindoles with CAN afforded the corresponding *p*-quinones in good yield. In particular, it is noteworthy that the oxidative demethylation of the 1-ethoxycarbonyl-4,5,7-trimethoxyindole **15a** yielded only *p*-quinones, but no *o*-quinones. The present method should be generally applicable for the synthesis of other 4,7-indolequinones possessing a labile functional group.

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Mass spectra were taken on a JEOL JMS-D300 instrument and IR spectra were recorded with a JASCO DS-701G spectrometer. ^{1}H-NMR spectra were measured with Hitachi R-24, JEOL PS-100 and GX 400 spectrometers, with tetramethylsilane as an internal standard.

1-Ethoxycarbonyl-4,7-dimethoxy-2,3-dimethylindole (6)——A solution of 4,7-dimethoxy-2,3-dimethylindole[8] (**5**, 410 mg) in *N*,*N*-dimethylformamide (DMF, 2 ml) was added to sodium hydride (240 mg), and the mixture was stirred for 1 h under nitrogen. Then a solution of ethyl chloroformate (0.96 ml) in DMF (2 ml) was added, and the whole was stirred at 60 °C for 18 h. Methanol (0.2 ml) was added and the solvent was evaporated off *in vacuo*. The residue was dissolved in CH_2Cl_2, then the solution was washed with 5% $NaHCO_3$ and water, and dried over Na_2SO_4. The solvent was removed, and the residue was recrystallized from CH_2Cl_2–ether to afford 422 mg (76%) of **6**, mp 88—90 °C. *Anal.* Calcd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 64.66; H, 6.97; N, 5.05. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, t, J=7 Hz), 2.32 (6H, s), 3.82 (6H, s), 4.38 (2H, q, J=7 Hz), 6.48 (1H, d, J=8 Hz), 6.54 (1H, d, J=8 Hz).

The Oxidative Demethylation of 6——A cooled solution of CAN (890 mg, 1.62 mmol) in a mixtute of acetonitrile (2.5 ml) and water (2.5 ml) was added to **6** (175 mg, 0.63 mmol) dissolved in a mixture of acetonitrile (3.5 ml) and water (1.5 ml) containing suspended pyridine-2,6-dicarboxylic acid *N*-oxide (297 mg, 1.62 mmol) with stirring. During this addition, the reaction vessel was cooled in an ice-water bath. Then the mixture was stirred for an additional 10 min, poured into water and extracted with CH_2Cl_2. The extract was washed with 5% $NaHCO_3$ and water, then dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was chromatographed on a silica gel column. Elution with ethyl acetate–hexane (1 : 9, v/v) afforded a less polar quinone **7** (76 mg, 49%) and further elution with ethyl acetate–hexane (2 : 8, v/v) afforded a more polar quinone **8** (23 mg, 21%).

(i) 1-Ethoxycarbonyl-4,7-dihydro-2,3-dimethylindole-4,7-dione (**7**): mp 118—120 °C (yellow needles from CH_2Cl_2–ether). *Anal.* Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.67. Found: C, 63.16; H, 5.32; N, 5.66. IR (KBr): 1650, 1750 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, t, J=7 Hz), 2.22 (3H, s), 2.28 (3H, s), 4.48 (2H, q, J=7 Hz), 6.53 (2H, s).

(ii) 4,7-Dihydro-2,3-dimethylindole-4,7-dione (**8**): mp 202—204 °C (red prisms from benzene). *Anal.* Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.68; H, 5.08; N, 8.03. IR (KBr): 1635 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 2.11 (3H, s), 2.14 (3H, s), 6.47 (1H, d, J=9 Hz), 6.49 (1H, d, J=9 Hz).

The Conversion of 7 to 8——A 1 : 1 mixture of acetic acid and water (0.5 ml) was added to a solution of **7** (25 mg) in methanol (2 ml). The mixture was refluxed for 18 h, cooled, diluted with water and extracted with CH_2Cl_2. The extract was washed with 5% $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated to dryness. The residue was chromatographed on a silica gel column with ethyl acetate–hexane (1 : 4, v/v) to yield **8** (6 mg, 34%) [less polar quinone **7** (16 mg) was recovered].

2-Hydroxy-3,5-dimethoxy-4-methylbenzaldehyde (10a)——Hexamethylenetetramine (60 g) was added to a boiling solution of 2,4-dimethoxy-3-methylphenol[10] (**9a**, 12.0 g) in acetic acid (400 ml). The mixture was refluxed for 2 h, then diluted with water (1000 ml) and extracted with CH_2Cl_2. The extract was washed with 5% $NaHCO_3$ and water, dried over Na_2SO_4 and evaporated to dryness. The residue was chromatographed on a silica gel column with CH_2Cl_2–hexane (3 : 7, v/v) to afford **10a** (9.27 g, 66%), mp 108.5—109 °C (pale yellow needles from hexane). *Anal.* Calcd for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.11; H, 6.16. ^{1}H-NMR ($CDCl_3$) δ: 2.17 (3H, s), 3.81 (3H, s), 3.86 (3H, s), 6.68 (1H, s), 9.86 (1H, s), 10.92 (1H, s, exchangeable with D_2O).

2,3,5-Trimethoxy-4-methylbenzaldehyde (11a)——Methyl iodide (90 ml) was added to a solution of **10a** (9.00 g) in 15% KOH (90 ml). The mixture was refluxed for 96 h with vigorous stirring, then cooled and extracted with CH_2Cl_2. The extract was washed with 5% KOH and water, dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column with CH_2Cl_2–hexane (1 : 1, v/v) to afford 9.13 g (95%) of **11a**, mp 48—49 °C (pale yellow needles from hexane). High-resolution MS, Calcd for $C_{11}H_{14}O_4$: 210.0890. Found: 210.0875. ^{1}H-NMR ($CDCl_3$) δ: 2.15 (3H, s), 3.83 (6H, s), 3.92 (3H, s), 6.99 (1H, s), 10.38 (1H, s).

2,3,5-Trimethoxy-4-methyl-β-nitrostyrene (12a)——A mixture of **11a** (2.70 g), ammonium acetate (2.10 g) and nitromethane (25 ml) was refluxed for 3 h with stirring. The mixture was cooled and poured into water. The precipitated crystals were collected by filtration, dried *in vacuo* and chromatographed on a silica gel column with ethyl acetate–hexane (1 : 9, v/v). Recrystallization from ethyl acetate–hexane gave 2.73 g (84%) of **12a** as yellow needles melting at 110—112 °C. *Anal.* Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.88; H, 5.96; N, 5.48. ^{1}H-NMR ($CDCl_3$) δ: 2.18 (3H, s), 3.86 (6H, s), 3.90 (3H, s), 6.62 (1H, s), 7.70 (1H, d, J=13 Hz), 8.11 (1H, d, J=13 Hz).

2,3,5-Trimethoxy-4-methyl-6,β-dinitrostyrene (13a)——Conc. HNO_3 (5.5 ml) was added dropwise to a stirred solution of **12a** (2.73 g) in acetic acid (55 ml) at below 18 °C. The mixture was stirred for an additional 1 h at room temperature, then poured into water (1000 ml) and extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column with ethyl acetate–hexane (1 : 9, v/v). Recrystallization from ethyl acetate–hexane gave 2.00 g (62%) of **13a** as orange prisms melting at 137—138 °C. *Anal.* Calcd for $C_{12}H_{14}N_2O_7$: C, 48.32; H, 4.73; N, 9.39. Found: C, 48.33; H, 4.76; N, 9.27. ^{1}H-NMR ($CDCl_3$) δ: 2.30 (3H, s), 3.85 (3H, s), 3.91 (6H, s), 7.72 (1H, d, J=13 Hz), 7.84 (1H, d, J=13 Hz).

4,5,7-Trimethoxy-6-methylindole (14a)——Iron powder (45 g) was added in portions to a boiling solution of **13a** (1.0 g) in acetic acid (180 ml) with vigorous stirring. The mixture was refluxed for an additional 20 min with stirring, then cooled and poured into a solution of $Na_2SO_3 \cdot 7H_2O$ (225 g) in water (225 ml). The solid was filtered off and washed with CH_2Cl_2. The filtrate was extracted with CH_2Cl_2, and the combined extract and washings were washed with water, dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column with ethyl acetate–hexane (1 : 9, v/v). The crude indole **14a** was recrystallized from ethyl acetate–hexane to afford 0.61 g (82%) of colorless prisms, mp 139—141 °C. *Anal.* Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.22; H, 6.97; N, 6.25. ^{1}H-NMR ($CDCl_3$) δ: 2.33 (3H, s), 3.90 (6H, s), 4.07 (3H, s), 6.62 (1H, t, J=3 Hz), 7.08 (1H, t, J=3 Hz), 8.2 (1H, br).

1-Ethoxycarbonyl-4,5,7-trimethoxy-6-methylindole (15a)——The indole **14a** was treated with sodium hydride and ethyl chloroformate in DMF by the same procedure as used for **5** to afford **15a** (85% yield) as an oil. *Anal.* Calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.24; H, 6.59; N, 4.59. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, t, J=7 Hz), 2.29 (3H, s), 3.70 (3H, s), 3.83 (3H, s), 3.93 (3H, s), 4.42 (2H, q, J=7 Hz), 6.60 (1H, d, J=4 Hz), 7.45 (1H, d, J=4 Hz).

The Oxidative Demethylation of 15a——The oxidative demethylation of **15a** was carried out by the same procedure as used for **6** to afford a less polar quinone **16** (75%) and a more polar quinone **17** (15%).

(i) 1-Ethoxycarbonyl-4,7-dihydro-5-methoxy-6-methylindole-4,7-dione (**16**): mp 63—65 °C (yellow needles from ether–hexane). *Anal.* Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.45; H, 4.99; N, 5.20. IR (KBr): 1655, 1665, 1745 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (3H, t, J=7 Hz), 2.02 (3H, s), 4.01 (3H, s), 4.51 (2H, q, J=7 Hz), 6.62 (1H, d, J=4 Hz), 7.43 (1H, d, J=4 Hz).

(ii) 4,7-Dihydro-5-methoxy-6-methylindole-4,7-dione (**17**): mp 165—167 °C (red needles from ether). *Anal.* Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.65; H, 4.66; N, 7.32. IR (KBr): 1650 cm^{-1}: ^{1}H-NMR ($CDCl_3$) δ: 1.99 (3H, s), 4.04 (3H, s), 6.62 (1H, t, J=3 Hz), 6.98 (1H, t, J=3 Hz), 9.4 (1H, br).

The Conversion of 16 to 17——A solution of the quinone **16** (16 mg) in methanol (1 ml) containing conc. NH_4OH (0.1 ml) was stirred for 5 min at room temperature, then diluted with water and extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4 and evaporated to dryness. The residue was chromatographed on a silica gel column with benzene–ethyl acetate (50 : 2, v/v) to afford 11 mg (95%) of **17**.

4-Ethoxy-2-methoxy-2-methylphenol (9b)——This phenol was prepared in 4 steps from 4-ethoxy-2-methoxybenzaldehyde[14] (**25**).

(i) 4-Ethoxy-2-methoxyphenol (**26**): *m*-Chloroperbenzoic acid (4.60 g) was added to a stirred solution of **25** (4.00 g) in CH_2Cl_2 (50 ml). The mixture was refluxed for 4 h with stirring and then cooled. The precipitated crystals were filtered off. The filtrate was washed with saturated aq. $NaHCO_3$ solution until effervescence ceased, and then with water, and dried over Na_2SO_4. Removal of the solvent left 4-ethoxy-2-methoxyphenyl formate, which was dissolved in methanol (50 ml) and hydrolyzed with 5% NaOH (30 ml) for 30 min at room temperature. The mixture was diluted with water (150 ml), acidified with conc. HCl and extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column with CH_2Cl_2 to afford 2.80 g (75%) of **26**, mp 34—36 °C (colorless needles from ether–hexane). *Anal.* Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.33; H, 7.19. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, t, J=7 Hz), 3.83 (3H, s), 3.97 (2H, q, J=7 Hz), 5.27 (1H, s), 6.37 (1H, dd, J=8, 2 Hz), 6.51 (1H, d, J=2 Hz), 6.81 (1H, d, J=8 Hz).

(ii) (4-Ethoxy-2-methoxyphenoxy)methyl Ethyl Ether[15] (**27**): A solution of the phenol **26** (2.75 g) in dry DMF (7 ml) was slowly added to a stirred solution of sodium hydride (0.47 g) in dry DMF (7 ml) at 0 °C; chloromethyl ethyl ether (1.85 g) was added over 30 min. The reaction mixture was stirred at 0 °C for 10 min, then diluted with ether (15 ml) and water (100 ml), and extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The residue was chromatographed on a silica gel column with ethyl acetate–hexane (1 : 9, v/v) to afford 3.39 g (92%) of **27** as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7 Hz), 1.38 (3H, t, J=7 Hz), 3.76 (2H, q, J=7 Hz), 3.81 (3H, s), 3.95 (2H, q, J=7 Hz), 5.15 (2H, s), 6.36 (1H, dd, J=8, 2 Hz), 6.49 (1H, d, J=2 Hz), 7.03 (1H, d, J=8 Hz).

(iii) (4-Ethoxy-2-methoxy-3-methylphenoxy)methyl Ethyl Ether[15] (**28**): *n*-Butyllithium (10.3 ml of 1.61 M hexane solution) was added to a stirred solution of the ether **27** (3.0 g) in dry tetrahydrofuran (THF, 15 ml) at 0 °C. The reaction mixture was stirred for 1 h at room temperature. Dimethyl sulfate (2.09 g) was added at 0 °C with stirring. The mixture was stirred for 2 h at room temperature, quenched with water (300 ml) and extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column with ethyl acetate–hexane (1 : 9, v/v) to afford 2.40 g (75%) of **28** as an oil. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7 Hz), 1.38 (3H, t, J=7 Hz), 2.16 (3H, s), 3.75 (2H, q, J=7 Hz), 3.80 (3H, s), 3.97 (2H, q, J=7 Hz), 5.18 (2H, s), 6.50 (1H, d, J=9 Hz), 6.95 (1H, d, J=9 Hz).

(iv) 4-Ethoxy-2-methoxy-3-methylphenol[15] (**9b**): Conc. HCl (0.03 ml) was added to a stirred solution of the ether **28** (3.00 g) in ethanol (20 ml). The resulting solution was stirred at reflux for 2 h. The solvent was evaporated off, and saturated aq. $NaHCO_3$ solution was added. The mixture was extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4 and evaporated. The residue was chromatographed on a silica gel column with ethyl acetate–hexane (1 : 9, v/v) to afford 1.83 g (81%) of the phenol **9b**, mp 56—57 °C (colorless needles from ether–hexane). *Anal.* Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.77; H, 7.79. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, t, J=7 Hz), 2.17 (3H, s), 3.75 (3H, s), 3.94 (2H, q, J=7 Hz), 5.39 (1H, s), 6.50 (1H, d, J=9 Hz), 6.71 (1H, d, J=9 Hz).

5-Ethoxy-2-hydroxy-3-methoxy-4-methylbenzaldehyde (10b)——The formylation of **9b** was carried out by the same procedure as used for **9a** to afford the aldehyde **10b** in 60% yield, mp 90—90.5 °C (pale yellow needles from ether–hexane). *Anal.* Calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 62.95; H, 6.79. ^{1}H-NMR ($CDCl_3$) δ: 1.44 (3H, t, J=7 Hz), 2.23 (3H, s), 3.88 (3H, s), 4.01 (2H, q, J=7 Hz), 6.69 (1H, s), 9.80 (1H, s), 10.83 (1H, s, exchangeable with D_2O).

5-Ethoxy-2,3-dimethoxy-4-methylbenzaldehyde (11b)——The phenol **10b** (0.50 g) in dry DMF (5 ml) and methyl iodide (3.38 g) were added to a stirred solution of sodium hydride (0.29 g) in dry DMF (2 ml) at 0 °C under nitrogen. The resulting mixture was stirred for an additional 1 h, then quenched with water (300 ml) and extracted with CH_2Cl_2. The extract was washed with 5% NaOH and water, dried over Na_2SO_4 and evaporated to dryness. The residue was chromatographed on a silica gel column with ethyl acetate–hexane (1 : 9, v/v) to afford 0.53 g of **11b** in quantitative yield, mp 72.5—73.5 °C (colorless plates from ether–hexane). *Anal.* Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.16; H, 7.35. ^{1}H-NMR ($CDCl_3$) δ: 1.42 (3H, t, J=7 Hz), 2.20 (3H, s), 3.86 (3H, s), 3.95 (3H, s), 4.04 (2H, q, J=

7 Hz), 7.01 (1H, s), 10.33 (1H, s).

5-Ethoxy-2,3-dimethoxy-4-methyl-β-nitrostyrene (12b)——The aldehyde **11b** and nitromethane were condensed by the same procedure as used for **11a** to afford the nitrostyrene **12b** in 81% yield, mp 117—118 °C (yellow needles from ethyl acetate–hexane). *Anal.* Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.56; H, 6.40; N, 4.99. ^{1}H-NMR ($CDCl_3$) δ: 1.44 (3H, t, J=7 Hz), 2.18 (3H, s), 3.83 (3H, s), 3.88 (3H, s), 4.01 (2H, q, J=7 Hz), 6.62 (1H, s), 7.75 (1H, d, J=14 Hz), 8.15 (1H, d, J=14 Hz).

5-Ethoxy-2,3-dimethoxy-4-methyl-6,β-dinitrostyrene (13b)——The nitration of **12b** with HNO_3 was carried out by the same procedure as used for **12a** to afford the dinitrostyrene **13b** in 91% yield, mp 93—94 °C (orange needles from ether–hexane). *Anal.* Calcd for $C_{13}H_{16}N_2O_7$: C, 50.00; H, 5.16; N, 8.97. Found: C, 50.18; H, 5.18; N, 8.67. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, t, J=7 Hz), 2.28 (3H, s), 3.89 (3H, s), 3.91 (3H, s), 3.99 (2H, q, J=7 Hz), 7.73 (1H, d, J=14 Hz), 7.87 (1H, d, J=14 Hz).

7-Ethoxy-4,5-dimethoxy-6-methylindole (14b)——The reductive cyclization of **13b** with iron powder in acetic acid was carried out by the same procedure as used for **13a** to afford the indole **14b** in 58% yield, mp 122—122.5 °C (colorless prisms from ethyl acetate–hexane). *Anal.* Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.39; H, 7.35; N, 5.89. ^{1}H-NMR ($CDCl_3$) δ: 1.43 (3H, t, J=7 Hz), 2.30 (3H, s), 3.85 (3H, s), 4.04 (3H, s), 4.04 (2H, q, J=7 Hz), 6.60 (1H, dd, J=3, 2 Hz), 7.08 (1H, t, J=3 Hz), 8.2 (1H, br).

7-Ethoxy-1-ethoxycarbonyl-4,5-dimethoxy-6-methylindole (15b)——The indole **14b** and ethyl chloroformate were condensed by the same procedure as used for **5** to afford the carbamate **15b** (82% yield) as an oil. High-resolution MS, Calcd for $C_{16}H_{21}NO_5$: 307.1420. Found: 307.1450. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, t, J=7 Hz), 1.43 (3H, t, J=7 Hz), 2.31 (3H, s), 3.85 (2H, q, J=7 Hz), 3.86 (3H, s), 3.96 (3H, s), 4.44 (2H, q, J=7 Hz), 6.63 (1H, d, J=4 Hz), 7.47 (1H, d, J=4 Hz).

1-Ethoxycarbonyl-4,7-dihydro-5-methoxy-6-methylindole-4,7-dione (16)——The oxidation of the carbamate **15b** was carried out by the same procedure as used for **6** to afford the quinone **16** in 34% yield.

2,4-Dimethoxy-3,6-dimethylphenol (18)——Hydrazine hydrate (1.70 g) was slowly added to the aldehyde **10a** (1.96 g). The mixture was refluxed for 15 min, then cooled, and 5.25 g of KOH (pellet) was added. The resulting mixture was heated at 120 °C for 30 min, and then at 140 °C for 30 min. The mixture was cooled, diluted with water, acidified with conc. HCl and extracted with ether. The extract was washed with brine, and dried over Na_2SO_4. Removal of the solvent afforded 1.56 g (86%) of **18**, mp 68—69 °C (pale yellow prisms from hexane) [lit.[10] mp 68.5—69 °C].

2-Methoxy-3,6-dimethyl-1,4-benzoquinone (19)——A solution of CAN (14.1 g) in water (40 ml) was added dropwise to an ice-cooled solution of the phenol **18** (1.56 g) in acetonitrile (40 ml) with stirring. The mixture was stirred for 45 min at room temperature, then diluted with water, and extracted with CH_2Cl_2. The extract was washed with 5% $NaHCO_3$ and brine, and dried over Na_2SO_4. Removal of the solvent afforded the crude quinone **19**, which was purified by sublimation and then by recrystallization from $CHCl_3$. Yield 1.09 g (77%), mp 58—59 °C [lit.[11] mp 64 °C].

2-Methoxy-3,6-dimethylhydroquinone (20)——A solution of sodium dithionite (5.7 g) in water (40 ml) was added to the benzoquinone **19** (1.09 g) in ether (40 ml). The mixture was vigorously stirred for 2 h, and then partitioned between ether and water. The organic phase was washed with brine, dried over Na_2SO_4 and evaporated to dryness. The crude hydroquinone **20** thus obtained (quantitative yield) was used without further purification.

2-Methoxy-3,6-dimethylhydroquinone Dibenzyl Ether (21)——Benzyl bromide (5.46 ml) was added dropwise to a stirred mixture of the hydroquinone **20** (2.58 g) in dry DMF (100 ml) containing anhydrous K_2CO_3 (6.35 g) at 0 °C under nitrogen. The resulting mixture was stirred for 18 h at room temperature. The solvent was evaporated off *in vacuo* and saturated aq. $NaHCO_3$ solution was added. The mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4 and evaporated to dryness. The residue was chromatographed on a silica gel column with benzene to afford 3.04 g (57%) of the dibenzyl ether **21** as an oil. ^{1}H-NMR ($CDCl_3$) δ: 2.20 (6H, s), 3.85 (3H, s), 4.92 (2H, s), 5.01 (2H, s), 6.50 (1H, s), 7.35 (10H, m).

2-Methoxy-3,6-dimethyl-5-nitrohydroquinone Dibenzyl Ether (22)[16]——Cupric nitrate trihydrate (1.93 g) was added to a stirred solution of the dibenzyl ether **21** (1.39 g) in acetic anhydride (20 ml) at 0 °C. The mixture was stirred for an additional 30 min, then poured into ice-cooled water, and extracted with benzene. The extract was washed with 5% $NaHCO_3$ and brine, dried over Na_2SO_4 and evaporated to dryness. The residue was chromatographed on a silica gel column with benzene. The nitro compound **22** thus obtained was recrystallized from hexane to afford 0.68 g (44%) of pale yellow plates, mp 85—86 °C. *Anal.* Calcd for $C_{23}H_{23}NO_5$: C, 70.21; H, 5.89; N, 3.56. Found: C, 70.39; H, 5.86; N, 3.45. ^{1}H-NMR ($CDCl_3$) δ: 2.14 (3H, s), 2.24 (3H, s), 3.88 (3H, s), 4.93 (2H, s), 4.96 (2H, s), 7.41 (10H, m).

(2,5-Dibenzyloxy-3-methoxy-4-methyl-6-nitrophenyl)acetaldehyde (23)——DMF–DMA (1.19 g) and pyrrolidine (0.36 g) were added to the nitro compound **22** (0.39 g) in DMF (5 ml). The mixture was stirred at 130 °C for 3 h under nitrogen. The solvent was removed *in vacuo*, and the residue was chromatographed on a silica gel column with benzene. The aldehyde **23** thus obtained was recrystallized from hexane to afford 0.24 g (57%) of pale yellow prisms, mp 92—93 °C. *Anal.* Calcd for $C_{24}H_{23}NO_6$: C, 68.40; H, 5.50; N, 3.33. Found: C, 68.39; H, 5.30; N, 3.32. ^{1}H-NMR ($CDCl_3$) δ: 2.29 (3H, s), 3.62 (2H, d, J=1.5 Hz), 3.89 (3H, s), 4.97 (2H, s), 5.00 (2H, s), 7.37 (10H, m), 9.55 (1H, t, J=1.5 Hz).

4,7-Dibenzyloxy-5-methoxy-6-methylindole (24)——Ammonium acetate (1.5 g) in water (3.75 ml) and 17% $TiCl_3$ in water (4.41 ml) were added to a solution of the aldehyde **23** (0.32 g) in methanol (35 ml). The mixture was stirred for 7 min, then poured into water and extracted with $CHCl_3$. The extract was washed with saturated aq. $NaHCO_3$ solution and water, and dried over Na_2SO_4. The solvent was removed and the residue was chromatographed on a silica gel column with benzene. The indole **24** thus obtained was recrystallized from $CHCl_3$–hexane to afford 0.20 g (71%) of colorless needles, mp 95—96 °C. *Anal.* Calcd for $C_{24}H_{23}NO_3$: C, 77.19; H, 6.21; N, 3.75. Found: C, 77.22; H, 6.10; N, 3.55. ^{1}H-NMR ($CDCl_3$) δ: 2.34 (3H, s), 3.87 (3H, s), 4.99 (2H, s), 5.20 (2H, s), 6.52 (1H, t, J=3 Hz), 6.93 (1H, t, J=3 Hz), 7.4 (10H, m), 7.8 (1H, br).

4,7-Dihydro-5-methoxy-6-methylindole-4,7-dione (17)——The indole **24** (91 mg) in methanol (6 ml) containing 10% palladium on carbon (50 mg) was treated with hydrogen at 1 atm for 2.5 h. The catalyst was filtered off and the solvent was removed. The residue was dissolved in $CHCl_3$. The solution was washed with water, dried over Na_2SO_4 and evaporated to dryness. The residue was recrystallized from ether to furnish 36 mg (77%) of the quinone **17**.

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