# Articles

## Incorporation of the Quinoline-5,8-quinone Moiety into Polyaza Cavities

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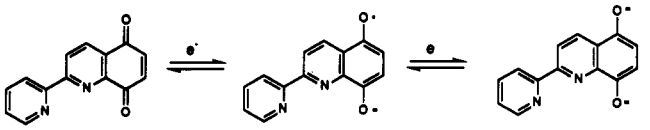
Silica gel supported nitric acid treatment of 2,5-dimethoxybenzaldehyde followed by reduction with iron powder provides 3,6-dimethoxy-2-aminobenzaldehyde. Friedländer condensation of this species with a variety of ketones and diketones leads to 5,8-dimethoxyquinoline derivatives which may be oxidized by ceric ammonium nitrate (CAN) and pyridine-2,6-dicarboxylic acid *N*-oxide (PDANO) to the corresponding quinones. The quinone functionality can be incorporated into larger cavities by a selective stepwise Friedländer approach and the CAN/PDANO oxidation appears to work preferentially for 5,8-dimethoxyquinoline.

### Introduction

The quinoline-5,8-quinone functionality has received considerable attention particularly with regard to the biological activity of the antitumor antibiotics streptonigrin and lavendamycin.[1] Both molecules exhibit potent cytotoxic properties but have seen only limited use as drugs due to their unfortunate toxicity. The principle mode of activity appears to involve oxidative cleavage of DNA. Dioxygen and metal ions such as Fe(II) and Cu(II) have been implicated in this process.[2]

Both streptonigrin and lavendamycin are substituted derivatives of 2-(2'-pyridyl)quinoline-5,8-dione (1c).[3] This molecule may be considered as a 2,2'-bipyridine annelated to a 1,4-benzoquinone. We were intrigued by the prospect of juxtaposing a potent redox center such as a 1,4-quinone with an excellent chelator such as bipyridine.



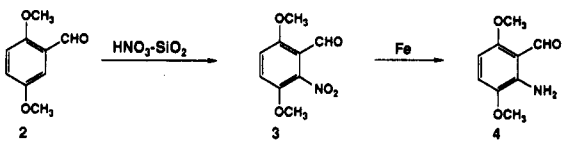
1c

The parent system 1c exhibits redox potentials of −0.53 and −1.07 V. Metal ions bound at the bipyridine site of 1c having oxidation potentials greater than −0.53 V should spontaneously transfer an electron to the quinone. The resulting semiquinone radical anion could either be reoxidized by molecular oxygen or could enter the coordination sphere of the metal. In light of the evidence for the involvement of oxygen and metal ions in the activity of streptonigrin, it would be of considerable interest to study various analogs of 1c to better understand the activity of the drug.

This paper will discuss a general synthetic approach which can be used to incorporate the quinoline-5,8-quinone moiety into a variety of cavity-shaped ligand systems.

### Results and Discussion

Readily available 2,5-dimethoxybenzaldehyde may be nitrated with a 10:1 molar excess of silica gel supported nitric acid under ultrasonic agitation[4] to provide a 78% yield of 3,6-dimethoxy-2-nitrobenzaldehyde (3) accompanied by 18% of 2,5-dimethoxy-4-nitrobenzaldehyde.[5] When only a 5:1 molar excess of the reagent is employed, the latter product predominates (63%) and only 23% of 3 is obtained. These isomers may be readily separated by chromatography on silica gel eluting with 1:1 hexane/ethyl acetate. Reduction of 3 with iron powder[6] affords the corresponding amino aldehyde 4 (mp 67–68 °C) in 76% yield. A previous report of the preparation of 4 by catalytic hydrogenation describes this material as an air-unstable oil.[7]




2 3 4

When this amino aldehyde is condensed with the aryl ketones **5a–d** in absolute ethanol under basic conditions, the expected Friedländer products **6a–d** were obtained in generally good yields.[8] We find that dimethoxy substitution improves the Friedländer reaction either by increasing the nucleophilicity of the aniline moiety or by

(1) (a) Hibino, S. *Heterocycles* **1977**, *6*, 1485. (b) Shaikh, I. A.; Johnson, F.; Grollman, A. P. *J. Med. Chem.* **1986**, *29*, 1329. (c) Fiallo, M. M. L.; Garnier-Suillerot, A. *Inorg. Chem.* **1990**, *29*, 893.

(2) (a) Cone, R.; Hasan, S. K.; Lown, J. W.; Morgan, A. R. *Can. J. Biochem.* **1976**, *54*, 219. (b) Lown, J. W.; Sim, S. K. *Can. J. Biochem.* **1976**, *54*, 2563. (c) White, J. R. *Biochem. Biophys. Res. Commun.* **1977**, *77*, 387.

(3) (a) Boger, D. L.; Yasuda, M.; Mitscher, L. A.; Drake, S. D.; Kitos, P. A.; Thompson, S. C. *J. Med. Chem.* **1987**, *30*, 1918. (b) Yasuda, M.; Boger, D. L. *J. Heterocycl. Chem.* **1987**, *24*, 1253. (c) Boger, D. L.; Duff, S. R.; Panek, J. S.; Yasuda, M. *J. Org. Chem.* **1985**, *50*, 5790. (d) Boger, D. L.; Duff, S. R.; Panek, J. S.; Yasuda, M. J. *Org. Chem.* **1985**, *50*, 5782. (e) Kende, A. S.; Ebetino, F. H.; Battista, R.; Boatman, R. J.; Lorah, D. P.; Lodge, E. *Heterocycles* **1984**, *21*, 91. (f) Hibino, S.; Weinreb, S. M. *J. Org. Chem.* **1977**, *42*, 232. (g) Rao, K. V. *J. Heterocycl. Chem.* **1977**, *14*, 653. (h) Rao, K. V. *J. Heterocycl. Chem.* **1975**, *12*, 725.

(4) Tapia, R.; Torres, G.; Valderrama, J. A. *Synth. Commun.* **1986**, *16*, 681.

(5) Rubenstein, L. *J. Chem. Soc.* **1925**, 1998.

(6) Guay, V.; Brassard, P. *J. Heterocycl. Chem.* **1987**, *24*, 1649.

(7) Fernández, M.; López, F.; Tapia, R.; Valderrama, J. A. *Synth. Commun.* **1989**, *19*, 3087.

(8) (a) Caluwe, P. *Tetrahedron* **1980**, *36*, 2359. (b) Cheng, C.-C.; Yan, S.-J. *Org. React.* **1982**, *28*, 37.

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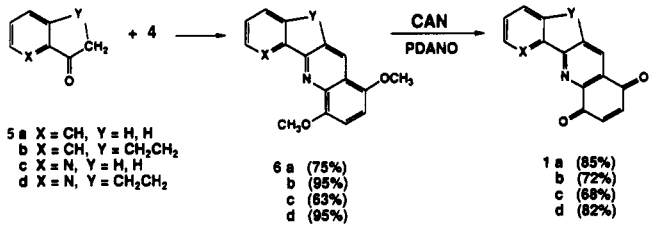
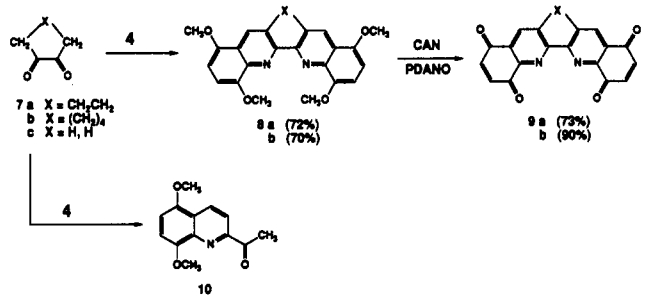
hindering self-condensation of the amino aldehyde. The

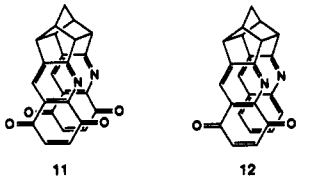



dimethoxybenzo ring of **6** can be oxidized to the corresponding quinones **1a–d** using ceric ammonium nitrate (CAN) and respectable yields are obtained by employing pyridine-2,6-dicarboxylic acid *N*-oxide (PDANO) as a catalyst.[9,10]

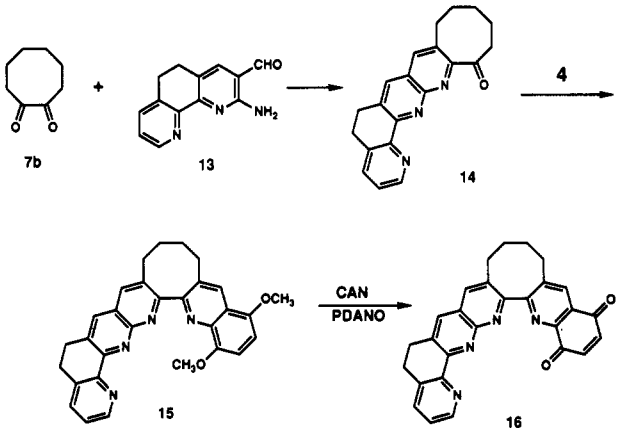
When enolizable diketones are treated with 2 equiv of **4**, a double Friedländer reaction occurs. Thus 1,2-cyclohexanedione and 1,2-cyclooctanedione provide **8a** and **8b**, respectively. The condensation of **4** with 2,3-butanedione gives only 30% of the monocondensation product 2-acetyl-5,8-dimethoxyquinoline (**10**). The poor reactivity of **7c** has been noted in other instances.[11] Oxidation of **8a,b** with CAN/PDANO gives the corresponding quinones **9a,b**.



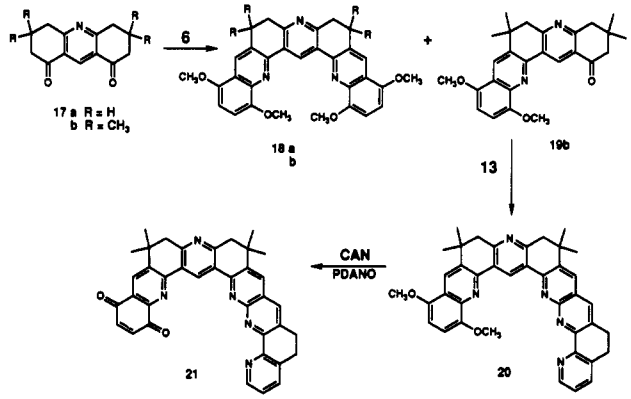

In terms of preparing larger cavity-shaped molecules incorporating a quinolinequinone, we attempted the monocondensation of **4** with diketones such as **7**. In earlier work we found that treatment of the cage diketone tetracyclo[6.3.0.0$^{4,11}$.0$^{5,9}$]undecane-2,7-dione with amino aldehyde **4** resulted in a 72% overall yield of the layered bi(dimethoxyquinoline).[12] Oxidative cleavage of this species with CAN/PDANO leads to the biquinone **11** in 90% yield. A analogous stepwise process utilizing 1 equiv of **4** and 1 equiv of 2-aminobenzaldehyde provided the unsymmetrical cage molecule **12**.




With 1,2-cyclohexanedione, however, we were unable to arrest the reaction at the monocondensation stage. Treatment of **7a** with 1 equiv of **4** led to the isolation of **8a** and unreacted diketone. The reaction of **7a** with the dihydrophenanthroline amino aldehyde **13**[13] gave similar results. With **7b**, however, monocondensation was possible and treatment with 1 equiv of **13** provided the monoketone **14** in 74% yield. This material could then be condensed with **4** to provide the dimethoxy derivative **15** which was subsequently oxidized in 64% yield to the quinone **16**. Two 1,4-bidentate sites are potentially available in **16**; however studies with analogous large cavities indicate that the distal site with a dimethylene bridge will undergo preferential coordination due to its more planar geometry.[15]




One objective of increasing the cavity size of these species is to move the quinolinequinone functionality further from the bidentate chelation site. This movement should tend to increase "insulation" between these two functionalities and allow one to better assess their ability to communicate electronically. To this end we utilized the diketone **17** as a large cavity quinone precursor.[16] For the parent octahydroacridinedione **17a**, only dicondensation to provide **18a** could be realized but with its tetramethyl analog **17b** we obtained 72% of **19b** along with 11% of the tetramethoxy derivative **18b**. These materials could be separated by chromatography on alumina and subsequent treatment of **19b** with **13** provided **20** which upon CAN/PDANO oxidation gave the quinone **21**.




We speculated that the carbonyl component involved in our Friedländer approach might also serve as a quinone

(9) (a) Syper, L.; Kloc, K.; Mlochowski, J.; Szulc, Z. *Synthesis* **1979**, 521. (b) Croisy-Delcey, M.; Rautureau, M.; Huel, C.; Bisagni, E. *J. Org. Chem.* **1988**, *53*, 5301.

(10) A similar sequence has recently been carried out using 2,4-pentanedione in place of **5**.[7]

(11) Thummel, R. P.; Lefoulon, F.; Cantu, D.; Mahadevan, R. *J. Org. Chem.* **1984**, *49*, 2208.

(12) Lim, J.-L.; Chirayil, S.; Thummel, R. P. *J. Org. Chem.* **1991**, *56*, 1492.

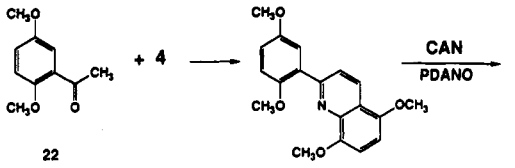
(13) Thummel, R. P.; Lefoulon, F.; Williamson, D.; Chavan, M. *Inorg. Chem.* **1986**, *25*, 1675. For related Friedländer condensations, see ref 14.

(14) (a) Majewicz, T. G.; Caluwe, P. *J. Org. Chem.* **1979**, *44*, 531. (b) Evens, G.; Caluwe, P. *Macromolecules* **1979**, *12*, 803. (c) Caluwe, P.; Majewicz, T. G. *J. Org. Chem.* **1975**, *40*, 2566.

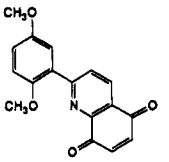
(15) Thummel, R. P.; Williamson, D.; Hery, C. *Inorg. Chem.* In press.

(16) Wolfbeis, O. S.; Junek, H. *Z. Naturforsch.* **1975**, *30b*, 249.

precursor. To this end we examined the reaction of 2,5-dimethoxyacetophenone (22) which underwent smooth Friedländer condensation with 4 to afford the tetramethoxy-2-phenylquinoline derivative 23. Treatment with CAN/PDANO effected efficient oxidation of only the dimethoxyquinoline moiety to provide the quinone 24.

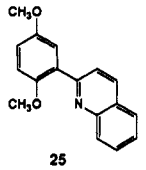



22 23 (75%)




24 (85%)

To test the reluctance of the dimethoxybenzene portion of this molecule toward oxidation, we prepared the quinoline derivative 25 by the reaction of 22 with 2-aminobenzaldehyde. This species was essentially inert toward oxidation under the previously described conditions.




25

We have demonstrated that the quinoline-5,8-quinone moiety can be successfully introduced into organized assemblies via a two-step Friedländer approach which utilizes readily available 3,6-dimethoxy-2-aminobenzaldehyde as the quinoline precursor. CAN oxidation appears to be quite specific for the 5,8-dimethoxyquinoline ring. It is noteworthy that the quinolinequinones prepared in this study were somewhat labile in solution and turned brown upon prolonged exposure to light. Further studies will explore the coordination chemistry of **1c,d**, **9**, **16**, and **21**.

## Experimental Section

NMR spectra were obtained on a General Electric QE-300 spectrometer at 300 MHz for $^1H$ and 75 MHz for $^{13}C$, and chemical shifts are reported in ppm from $Me_4Si$. IR spectra were obtained on a Perkin-Elmer 1330 spectrometer. In general, samples which could be recrystallized were analyzed by combustion rather than HRMS. In cases where neither method was appropriate complete NMR data are supplied with the supplementary material. Elemental analyses were performed by Canadian Microanalytical Service, Ltd., Delta, B.C., and HRMS were obtained by Dr. Terry Marriott at Rice University. All solvents are reagent grade and melting points are uncorrected.

**Preparation of Silica Gel Supported Nitric Acid.**[4] A mixture of $SiO_2$ (60 g, 60–200 mesh) in 8 N $HNO_3$ (140 mL) was magnetically agitated for 2 h at 25 °C. After filtration, the impregnated $SiO_2$ was left to dry in the air and stored in an airtight bottle. The $HNO_3$ content was estimated to be 15–20% (by weight) by titration of a $H_2O$ suspension of the reagent with 0.1 N NaOH.

**3,6-Dimethoxy-2-nitrobenzaldehyde (3).** A solution of 2,5-dimethoxybenzaldehyde (2.5 g, 0.015 mol) in $CH_2Cl_2$ (100 mL) containing $HNO_3$–$SiO_2$ (50 g, 10 equiv) was submitted to agitation for 10 min using an ultrasonic bath. The solution was then filtered and washed with $CH_2Cl_2$ (2 × 25 mL). Evaporation of the solvent afforded a yellow material which was chromatographed on $SiO_2$ (70 g). Eluting with hexane/EtOAc (1:1) first gave 2,5-dimethoxy-4-nitrobenzaldehyde (0.6 g, 18%),[17] mp 157–161 °C: $^1H$ NMR ($CDCl_3$) $\delta$ 10.47 (s, 1 H, CHO), 7.55 (s, 1 H), 7.45 (s, 1 H), 3.96 (s, 6 H, OMe); IR (KBr) 2970, 2870, 1690, 1510, 1485, 1386, 1284, 1212, 1125, 1025, 885, 875, 735 $cm^{-1}$; GC/MS, *m/e* (relative intensity) 211 (100, $M^+$), 165 (22), 135 (26), 77 (42), 53 (42), 51 (35), 44 (47). Further elution with EtOAc provided 3,6-dimethoxy-2-nitrobenzaldehyde (2.5 g, 78%), mp 163–165 °C (lit.[5] mp 159 °C): $^1H$ NMR ($CDCl_3$) $\delta$ 10.36 (s, 1 H, CHO), 7.28 (d, 1 H, $J_{4,5}$ = 9.4 Hz, $H_4$ or $H_5$), 7.11 (d, 1 H, $H_4$ or $H_5$), 3.95 (s, 3 H, $OCH_3$), 3.87 (s, 3 H, $OCH_3$); IR (KBr) 3102, 2892, 1684, 1528, 1483, 1450, 1430, 1376, 1368, 1280, 1270, 1182, 1089, 1050, 946, 816, 803, 714 $cm^{-1}$; GC/MS, *m/e* (rel intensity) 211 (31, $M^+$), 151 (84), 136 (62), 79 (80), 77 (84), 53 (100).

**3,6-Dimethoxy-2-aminobenzaldehyde (4).** A mixture of **3** (2.5 g, 11.6 mmol), iron powder (4.8 g, 0.087 g-atom), and concd HCl (0.05 mL) in 100 mL of a mixture of EtOH, $CH_3CO_2H$, and $H_2O$ (2:2:1) was refluxed for 15 min with mechanical stirring. The solution was filtered, diluted with $H_2O$ (300 mL), and extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (200 mL) and $H_2O$ (2 × 200 mL) and dried over $MgSO_4$. Evaporation of the solvent afforded a yellow solid (1.6 g, 76%), mp 67–68 °C: $^1H$ NMR ($CDCl_3$)[7] $\delta$ 10.32 (s, 1 H, CHO), 6.69 (d, 1 H, $J_{4,5}$ = 8.7 Hz, $H_4$), 6.8–6.5 (br s, $NH_2$), 5.90 (d, 1 H, $H_5$), 3.74 (s, 6 H, $OCH_3$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 191.3, 156.3, 142.1, 140.4, 114.4, 108.0, 94.2, 55.6, 55.1; IR ($CHCl_3$) 3515, 3345, 3000, 2932, 1648, 1552, 1480, 1402, 1265, 1173, 1093, 918 $cm^{-1}$; GC/MS, *m/e* (rel intensity) 181 (63, $M^+$), 166 (100), 152 (15), 138 (13), 123 (16), 67 (13).

**2-Phenyl-5,8-dimethoxyquinoline (6a).** A mixture of acetophenone (0.24 g, 2 mmol), **4** (0.40 g, 2.2 mmol), and 10% ethanolic KOH (0.5 mL) in absolute EtOH (25 mL) was refluxed under Ar for 18 h. The oily residue obtained upon evaporation of the solvent was chromatographed on $Al_2O_3$ (30 g) eluting with EtOH/hexane (1:2) to afford **6a** (0.4 g, 75%) as a pale yellow solid, mp 105 °C: $^1H$ NMR ($CDCl_3$) $\delta$ 8.43 (d, 1 H, $J_{3,4}$ = 8.8 Hz, $H_3$), 8.08 (overlapping d, 2 H, $H_{2'}$ and $H_{6'}$), 7.73 (d, 1 H, $H_4$), 7.29–7.39 (overlapping m, 3 H, $H_{3'}$, $H_{4'}$, and $H_{5'}$), 6.76 (d, 1 H, $J_{6,7}$ = 8.5 Hz, $H_6$ or $H_7$), 6.53 (d, 1 H, $H_6$ or $H_7$), 3.90 (s, 3 H, $OCH_3$), 3.25 (s, 3 H, $OCH_3$), 1.90 (0.2 H, $H_2O$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 156.7, 149.9, 149.0, 140.8, 139.9, 131.9, 129.4, 128.9, 127.9, 120.7, 118.6, 108.1, 103.7, 56.6, 55.9; IR (KBr) 2920, 2820, 1608, 1588, 1460, 1390, 1322, 1245, 1090, 682 $cm^{-1}$. Anal. Calcd for $C_{17}H_{15}NO_2$·0.1$H_2O$: C, 76.46; H, 5.70; N, 5.25. Found: C, 76.43; H, 5.76; N, 5.23.

**[5,6]Benzo-1,4-dimethoxy-7,8-dihydroacridine (6b).** The procedure described for **6a** was followed using 1-tetralone (0.2 g, 1.4 mmol) and **4** (0.3 g, 1.65 mmol) to give **6b** (0.39 g, 95%) after chromatography on $Al_2O_3$ (30 g) eluting with EtOAc, mp 160–162 °C: $^1H$ NMR ($CDCl_3$) $\delta$ 8.62 (d, 1 H, $J_{5',6'}$ = 7.5 Hz, $H_{6'}$), 8.30 (s, 1 H, $H_9$), 7.40 (dd, 1 H, $J$ = 7.4, 7.2 Hz, $H_{4'}$ or $H_{5'}$), 7.33 (dd, 1 H, $H_{4'}$ or $H_{5'}$), 7.13 (d, 1 H, $J_{3',4'}$ = 7.2 Hz, $H_{3'}$), 6.86 (d, 1 H, $J_{2,3}$ = 8.4 Hz, $H_2$ or $H_3$), 6.67 (d, 1 H, $H_2$ or $H_3$), 4.05 (s, 3 H, $OCH_3$), 3.93 (s, 3 H, $OCH_3$), 3.12 (dd, 2 H, $J$ = 7.3, 6 Hz, $CH_2$), 2.98 (dd, 2 H, $CH_2$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 152.4, 149.6, 148.4, 139.7, 139.1, 134.6, 130.1, 129.5, 128.8, 127.7, 127.1, 126.4, 120.9, 106.7, 103.3, 56.4 ($OCH_3$), 55.6 ($OCH_3$), 28.8 ($CH_2$), 28.3 ($CH_2$); IR (KBr) 2982, 2934, 2920, 1602, 1483, 1456, 1385, 1254, 1183, 1169, 1110, 1097, 1088, 791, 775, 722 $cm^{-1}$. Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.35; H, 5.84; N, 4.81. Found: C, 78.13; H, 5.89; N, 4.83.

**2-(2'-Pyridyl)-5,8-dimethoxyquinoline (6c).** The procedure described for **6a** was followed using 2-acetylpyridine (0.36 g, 3 mmol) and **4** (0.6 g, 3.3 mmol) to give **6c** (0.5 g, 63%) after chromatography on $Al_2O_3$ (30 g) eluting with EtOAc, mp 132–134 °C: $^1H$ NMR ($CDCl_3$) $\delta$ 8.8–8.6 (overlapping m, 4 H, $H_3$, $H_4$, $H_{3'}$, $H_{6'}$), 7.93 (t, 1 H, $J$ = 7.8 Hz, $H_{4'}$), 7.40 (t, 1 H, $J$ = 6.2 Hz, $H_{5'}$), 6.98 (d, 1 H, $J_{6,7}$ = 8.5 Hz, $H_6$ or $H_7$), 6.79 (d, 1 H, $H_6$ or $H_7$), 4.09 (s, 3 H, $OCH_3$), 3.99 (s, 3 H, $OCH_3$); $^{13}C$ NMR ($CDCl_3$) $\delta$

(17) The alternative structure, 2,5-dimethoxy-3-nitrobenzaldehyde (lit.[5] mp 113 °C), appears less likely on the basis of mp and the (accidental) equivalence of the OMe NMR signals.

156.0, 155.0, 149.5, 148.8, 148.7, 140.0, 137.0, 131.8, 124.0, 122.2, 121.5, 118.5, 107.5, 104.0, 56.5 ($OCH_3$), 55.8 ($OCH_3$); IR (KBr) 2945, 1614, 1597, 1583, 1475, 1395, 1255, 1096, 807, 775 $cm^{-1}$; HRMS calcd for $C_{16}H_{14}N_2O_2$ 266.10551 (M+), found 266.10568.

**[5,6-*b*]Pyrido-1,4-dimethoxy-7,8-dihydroacridine (6d).** The procedure described for **6a** was followed using 5,6,7,8-tetrahydro-8-quinolone[11] (0.2 g, 1.4 mmol) and **4** (0.3 g, 1.65 mmol) to give **6d** (0.39 g, 95%) as a yellow solid after chromatography on $Al_2O_3$ (30 g) eluting with MeOH/EtOAc (5:95), mp 156–158 °C: $^1H$ NMR ($CDCl_3$) $\delta$ 8.60 (d, 1 H, $J_{5',6'}$ = 4.1 Hz, $H_{6'}$), 8.26 (s, 1 H, $H_9$), 7.49 (d, 1 H, $J_{4',5'}$ = 7.6 Hz, $H_{4'}$), 7.14 (dd, 1 H, $J_{4',5'}$ = 7.6 Hz, $J_{5',6'}$ = 4.7 Hz, $H_{5'}$), 6.77 (d, 1 H, $J_{2,3}$ = 8.4 Hz, $H_2$ or $H_3$), 6.65 (d, 1 H, $H_2$ or $H_3$), 3.90 (s, 3 H, $OCH_3$), 3.86 (s, 3 H, $OCH_3$), 3.07 (dd, 2 H, $CH_2$, $J$ = 7.4, 6.1 Hz), 2.93 (dd, 2 H, $CH_2$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 151.5, 150.9, 149.9, 148.8, 147.9, 139.8, 135.9, 134.8, 131.1, 128.9, 123.7, 121.3, 105.7, 104.1, 55.6 ($OCH_3$), 55.5 ($OCH_3$), 27.9 ($CH_2$), 27.6 ($CH_2$); IR (KBr) 2910, 2830, 1618, 1601, 1480, 1440, 1385, 1260, 1160, 1110, 965, 810, 788, 725 $cm^{-1}$; HRMS calcd for $C_{18}H_{18}N_2O_2$ 294.13681 ($M^+$), found 294.1367.

**3,3'-Dimethylene-2,2'-bi[5,8-dimethoxyquinoline] (8a).** The procedure described for **6a** was followed using 1,2-cyclohexanedione[18] (0.38 g, 3.6 mmol) and **4** (1.32 g, 7.2 mmol) to give **8a** (0.99 g, 72%) after chromatography on $Al_2O_3$ (30 g) eluting with MeOH/EtOAc (5:95), mp 138–139 °C: $^1H$ NMR ($CDCl_3$) $\delta$ 8.42 (s, 2 H, $H_4$), 6.87 (d, 2 H, $J_{6,7}$ = 8.4 Hz, $H_6$ or $H_7$), 6.75 (d, 2 H, $H_6$ or $H_7$), 4.02 (s, 6 H, $OCH_3$), 3.96 (s, 6 H, $OCH_3$), 3.75 (br s, 2 H, $H_2O$), 3.23 (s, 4 H, $CH_2$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 150.8, 149.7, 148.1, 139.8, 132.4, 130.2, 121.7, 106.5, 104.7, 55.9 ($OCH_3$), 55.4 ($OCH_3$), 28.4 ($CH_2$); IR (KBr) 2930, 2840, 1602, 1600, 1470, 1370, 1260, 1205, 1165, 1121, 1110, 1089, 797, 725 $cm^{-1}$; HRMS calcd for $C_{24}H_{22}N_2O_4$ 402.15793 ($M^+$), found 402.15812.

**3,3'-Tetramethylene-2,2'-bi[5,8-dimethoxyquinoline] (8b).** The procedure described for **6a** was followed using 1,2-cyclooctanedione[19] (0.26 g, 1.9 mmol) and **4** (0.72 g, 4.0 mmol) to give **8b** (0.52 g, 70%) after chromatography on $Al_2O_3$ (30 g) eluting with EtOAc, mp 278–279 °C: $^1H$ NMR (DMSO-$d_6$) $\delta$ 8.44 (s, 2 H, $H_4$), 7.08 (d, 2 H, $J_{6,7}$ = 8.2 Hz, $H_6$ or $H_7$), 6.98 (d, 2 H, $H_6$ or $H_7$), 3.98 (s, 6 H, $OCH_3$), 3.88 (s, 6 H, $OCH_3$), 3.35 (s, $H_2O$), 3.02 (m, 2 H), 2.14 (m, 4 H), 1.56 (m, 2 H); $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 156.7, 149.3, 147.5, 138.1, 135.6, 130.0, 121.0, 107.1, 104.5, 55.8 ($OCH_3$), 55.4 ($OCH_3$), 30.8 ($CH_2$), 30.7 ($CH_2$); IR (KBr) 2895, 2790, 1612, 1608, 1570, 1440, 1380, 1298, 1117, 1098, 968, 790, 700 $cm^{-1}$; HRMS calcd for $C_{26}H_{26}N_2O_4$ 430.18923 ($M^+$), found 430.18991.

**2-Acetyl-5,8-dimethoxyquinoline (10).** A mixture of 2,3-butanedione (0.08 g, 1 mmol), **4** (0.41 g, 0.23 mmol), and three drops of concd HCl in $CH_3CO_2H$ (20 mL) was refluxed for 5 h. The reaction mixture was poured into ice–water and extracted with $CH_2Cl_2$. The combined organic layers were washed with 5% aqueous KOH and dried over $MgSO_4$. The solvent was evaporated and the crude product was chromatographed on $SiO_2$ (Chromatotron) eluting with EtOAc/hexane (3:7) to give 2-acetyl-5,8-dimethoxyquinoline (0.07 g, 30%), mp 149–150 °C: $^1H$ NMR ($CDCl_3$) $\delta$ 8.65 (d, 1 H, $J_{3,4}$ = 8.5 Hz, $H_4$), 8.13 (d, 1 H, $H_3$), 7.00 (d, 1 H, $J_{6,7}$ = 8.5 Hz, $H_6$ or $H_7$), 6.85 (d, 1 H, $H_6$ or $H_7$), 4.07 (s, 3 H, $OCH_3$), 3.97 (s, 3 H, $OCH_3$), 2.90 (s, 3 H, $COCH_3$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 200.6 (C=O), 152.4, 149.9, 148.7, 139.5, 132.0, 123.0, 117.8, 108.3, 105.9, 56.7 ($OCH_3$), 55.9 ($OCH_3$), 25.6 ($COCH_3$); IR (KBr) 2952, 2890, 1695 (CO), 1496, 1465, 1353, 1279, 1252, 1110, 1089, 982, 842, 747 $cm^{-1}$; GC/MS, *m/e* (relative intensity) 231 (52, $M^+$), 230 (27), 216 (100), 202 (20), 159 (11), 145 (10), 130 (13); HRMS calcd for $C_{13}H_{13}NO_3$ 231.08953 ($M^+$), found 231.08954.

**2-(2',5'-Dimethoxyphenyl)-5,8-dimethoxyquinoline (23).** The procedure described for **6a** was followed using 2,5-dimethoxyacetophenone (0.18 g, 1 mmol) and **4** (0.181 g, 1 mmol) to afford **23** (0.31 g, 95%) as a solid, mp 84–85 °C: $^1H$ NMR ($CDCl_3$) $\delta$ 8.52 (d, 1 H, $J_{3,4}$ = 8.8 Hz, $H_4$), 7.95 (d, 1 H, $H_3$), 7.52 (s, 1 H, $H_{6'}$), 6.92 (d, 2 H, $H_{3'}$, $H_{4'}$), 6.87 (d, 1 H, $J_{6,7}$ = 8.5 Hz, $H_7$), 6.71 (d, 1 H, $H_6$), 4.01 (s, 3 H, $OCH_3$), 3.93 (s, 3 H, $OCH_3$), 3.84 (s, 3 H, $OCH_3$), 3.76 (s, 3 H, $OCH_3$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 155.8, 154.1, 151.7, 149.6, 148.6, 140.4, 130.7, 129.9, 122.9, 120.3, 116.6, 115.8, 113.4, 107.2, 103.5, 56.6, 56.1, 55.8, 55.7; IR (KBr) 3000, 2950, 2830, 1620, 1600, 1494, 1460, 1418, 1400, 1322, 1256, 1106, 1092, 1040, 840, 710 $cm^{-1}$.

**2-(2',5'-Dimethoxyphenyl)quinoline (25).** A mixture of 2,5-dimethoxyacetophenone (0.18 g, 1 mmol), 2-aminobenzaldehyde[20] (0.121 g, 1 mmol), and one pellet of KOH in 20 mL of absolute ethanol was refluxed under an Ar atmosphere for 14 h. The solvent was evaporated and the crude product chromatographed on $Al_2O_3$ (20 g) eluting with $CH_2Cl_2$/hexane (1:1) to afford **25** (0.219 g, 73%) as a pale yellow oil: $^1H$ NMR ($CDCl_3$) $\delta$ 8.17 (d, 1 H, $J_{3,4}$ = 8.3 Hz, $H_4$), 8.12 (d, 1 H, $J_{7,8}$ = 8.7 Hz, $H_8$), 7.9 (d, 1 H, $H_3$), 7.8 (d, 1 H, $J_{5,6}$ = 8.1 Hz, $H_5$), 7.69 (t, 1 H, $J_{7,8}$ = 8.3, $J_{6,7}$ = 6.8 Hz, $H_7$), 7.51 (t, 1 H, $H_6$), 7.46 (s, 1 H, $H_{6'}$), 6.95 (d, 2 H, $J_{3',4'}$ = 1.5 Hz, $H_{3'}$, $H_{4'}$), 3.84 (s, 3 H, $OCH_3$), 3.78 (s, 3 H, $OCH_3$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 156.8, 154.1, 151.6, 148.2, 135.1, 130.4, 129.6, 129.7, 127.3, 127.0, 126.1, 123.3, 116.2, 116.0, 113.3, 56.5, 55.8; IR (KBr) 3000, 2950, 2830, 1594, 1490, 1462, 1428, 1310, 1260, 1176, 1040, 830, 716 $cm^{-1}$. Anal. Calcd for $C_{17}H_{15}NO_2 \cdot 0.4H_2O$: C, 74.94; H, 5.80; N, 5.14. Found: C, 75.01; H, 5.67; N, 5.05.

**Pyridine-2,6-dicarboxylic Acid *N*-Oxide (PDANO).**[21] A mixture of pyridine-2,6-dicarboxylic acid (16.7 g, 0.1 mol) and $Na_2WO_4 \cdot 2H_2O$ (1.0 g, 3.3 mmol) in 30% hydrogen peroxide (50 mL) was heated at 100 °C with vigorous stirring for 1 h. Additional 30% hydrogen peroxide (120 mL) was added portionwise over a period of 2 h until all insoluble material had disappeared. The reaction mixture was heated for additional 3 h and allowed to stand for several hours. A white crystalline solid was formed, filtered, washed with cold water (3 × 70 mL), and dried in the air to provide PDANO (9.2 g, 50%), mp 162 °C (lit.[9] mp 158–160 °C): $^1H$ NMR (DMSO-$d_6$) $\delta$ 8.27 (d, 2 H, $H_3$, $H_5$), 7.98 (t, 1 H, $J$ = 7.8 Hz, $H_4$); $^{13}C$ NMR (DMSO-$d_6$) $\delta$ 161.0, 139.4, 132.5, 129.0; IR (KBr) 3105, 3094, 2500 (br), 1740, 1690, 1470, 1410, 1308, 1160, 875, 833, 760, 660, 630 $cm^{-1}$.

**2-Phenylquinoline-5,8-quinone (1a).** A solution of ceric ammonium nitrate (CAN, 2.2 g, 4 mmol) in $CH_3CN/H_2O$ (1:1, 20 mL) was added dropwise to a stirred, ice-cold suspension of **6a** (0.265 g, 1 mmol) and PDANO (0.732 g, 4 mmol) in 25 mL of $CH_3CN/H_2O$ (2:1) at 0 °C. After the addition was complete, the reaction mixture was stirred for 30 min at 0 °C and for an additional 30 min at 20 °C. If the reaction was not yet complete as determined by TLC analysis, additional CAN and PDANO were added at once to the mixture and it was stirred for an additional 30 min at 20 °C. The mixture was then diluted with $H_2O$ (100 mL), made basic (pH 9–10) by the addition of saturated $NaHCO_3$, and extracted with $CH_2Cl_2$ (5 × 25 mL). The combined extracts were washed with $H_2O$, dried over anhydrous $MgSO_4$, and concentrated at 25 °C to give **1a** (0.20 g, 85%) as a yellow crystalline solid, mp 121–123 °C: $^1H$ NMR ($CDCl_3$) $\delta$ 8.48 (d, 1 H, $J_{3,4}$ = 8.2 Hz, $H_4$), 8.17–8.20 (overlapping d, 1 H, $H_{2'}$ or $H_{8'}$), 8.13 (d, 1 H, $H_3$), 7.53–7.55 (overlapping m, 3 H, $H_{3'}$, $H_{4'}$, $H_{5'}$), 7.18 (d, 1 H, $J_{6,7}$ = 10.6 Hz, $H_6$ or $H_7$), 7.08 (d, 1 H, $H_6$ or $H_7$); IR (KBr) 1658, 1568, 1430, 1304, 1246, 1072, 996, 828 $cm^{-1}$; HRMS calcd for $C_{15}H_9NO_2$ 235.06332, found 235.06365.

**[5,6]Benzo-7,8-dihydroacridine-1,4-dione (1b).** The same procedure described for **1a** was followed using **6b** (0.1 g, 0.35 mmol), CAN (0.82 g, 1.5 mmol), and PDANO (0.29 g, 1.5 mmol) to give **1b** (65 mg, 72%) as a yellow solid which turned brown upon prolonged exposure to light:[22] $^1H$ NMR ($CDCl_3$) $\delta$ 8.56 (dd, 1 H, $H_{3'}$), 8.18 (s, 1 H, $H_9$), 7.42 (dd, 2 H, $H_{4'}$ and $H_{5'}$), 7.27 (d, 1 H, $H_{6'}$), 7.12 (d, 1 H, $J_{2,3}$ = 10.4 Hz, $H_2$ or $H_3$), 7.02 (d, 1 H, $H_2$ or $H_3$), 3.14 (dd, 2 H, $J$ = 7.8, 6.2 Hz, $CH_2$), 3.01 (dd, 2 H, $CH_2$); IR (KBr) 1675, 1660 (conjugated CO), 1595, 1322, 1070, 840, 738 $cm^{-1}$; HRMS calcd for $C_{17}H_{11}NO_2$ 261.07896, found 261.07848.

**2-(2'-Pyridyl)quinoline-5,8-quinone (1c).** The same procedure described for **1a** was followed using **6c** (0.2 g, 0.75 mmol), CAN (2.0 g, 3.7 mmol), and PDANO (0.6 g, 3.7 mmol). After flash chromatography in the dark on silica gel (15 g) eluting with EtOAc, **1c** (0.12 g, 68%) was obtained which turned dark upon standing:[22] $^1H$ NMR ($CDCl_3$) $\delta$ 8.84 (d, 1 H, $J_{3,4}$ = 8.2 Hz, $H_4$),

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(22) Decomposed on heating over a 50–60° range before melting. Some samples were unstable in solution and $^{13}C$ NMR spectra could not be obtained.

8.66 (2 overlapping d, 2 H, $H_{8'}$ and $H_{3'}$), 8.48 (d, 1 H, $H_3$), 7.87 (dd, 1 H, $H_{4'}$), 7.39 (dd, 1 H, $H_{5'}$), 7.12 (d, 1 H, $J_{6,7}$ = 10.4 Hz, $H_6$ or $H_7$), 7.02 (d, 1 H, $H_6$ or $H_7$); $^{13}$C NMR ($CDCl_3$) δ 184.4 (CO), 183.1 (CO), 148.8, 147.1, 139.2, 138.1, 137.9, 137.7, 135.7, 128.9, 125.4, 125.3, 123.2, 104.9; IR (KBr) 2957, 1677, 1665, 1580, 1328, 1297, 1260, 1092, 1088, 1031, 1028, 840, 797, 780 cm$^{-1}$; HRMS calcd for $C_{14}H_8N_2O_2$ 236.05856, found 236.05804.

**[5,6-*b*]Pyrido-7,9-dihydroacridine-1,4-dione (1d).** The procedure described for **1a** was followed using **6d** (0.1 g, 0.34 mmol), CAN (0.94 g, 1.7 mmol), and PDANO (0.32 g, 1.7 mmol) to give **1d** (0.075 g, 82%) as a yellow solid which rapidly turned brown:[22] $^1$H NMR ($CDCl_3$) δ 8.79 (d, 1 H, $H_{8'}$), 8.22 (s, 1 H, $H_9$), 7.62 (d, 1 H, $J_{4',5'}$ = 7.2 Hz, $H_{4'}$), 7.33 (dd, 1 H, $H_{5'}$), 7.11 (d, 1 H, $J_{2,3}$ = 10.4 Hz, $H_2$ or $H_3$), 6.99 (d, 1 H, $H_2$ or $H_3$), 3.13 (dd, 2 H, $J$ = 6.4, 7.2 Hz, $CH_2$), 3.04 (dd, 2 H, $J$ = 5.8 Hz, $CH_2$); IR (KBr) 2952, 1661, 1582, 1410, 1318, 1257, 1084, 1008, 793 cm$^{-1}$; HRMS calcd for $C_{16}H_{10}N_2O_2$ 262.07421, found 262.0742.

**3,3'-Dimethylene-2,2'-bi[quinoline-5,8-quinone] (9a).** The procedure described for **1a** was followed using **8a** (0.1 g, 0.25 mmol), CAN (0.82 g, 1.5 mmol), and PDANO (0.28 g, 1.5 mmol) to give **9a** (0.065 g, 72%) as a yellow solid which slowly turned brown:[22] $^1$H NMR ($CDCl_3$) δ 8.37 (s, 2 H, $H_4$), 7.22 (d, 2 H, $J_{6,7}$ = 10.5 Hz, $H_6$ or $H_7$), 7.10 (d, 2 H, $H_6$ or $H_7$), 3.29 (s, 4 H, $CH_2$); IR (KBr) 2965, 1682 (sh), 1665, 1588, 1307, 1260, 1090, 1065, 1020, 800 cm$^{-1}$.

**3,3'-Tetramethylene-2,2'-bi[quinoline-5,8-quinone] (9b).** The procedure described for **1a** was followed using **8b** (55 mg, 0.14 mmol), CAN (0.75 g, 1.37 mmol), and PDANO (0.29 g, 1.6 mmol) to give **9b** (0.045 g, 90%) as a yellow solid:[22] $^1$H NMR ($CDCl_3$) δ 8.29 (s, 2 H, $H_4$), 7.13 (d, 2 H, $J_{6,7}$ = 10.4, $H_6$ or $H_7$), 7.03 (d, 2 H, $H_6$ or $H_7$), 2.25 (m, 2 H), 2.30–2.18 (2 overlapping m, 4 H), 1.57 (m, 2 H); IR (KBr) 2990, 2940, 1680, 1667, 1580, 1310, 1252, 1091, 1065, 835, 820, 800 cm$^{-1}$.

**2-(2',5'-Dimethoxyphenyl)quinoline-5,8-quinone (24).** The procedure described for **1a** was followed using **23** (0.23 g, 0.71 mmol), CAN (3.2 g, 5.7 mmol), and PDANO (1.04 g, 5.7 mmol) to afford **24** (0.13 g, 63%) as a red solid:[22] $^1$H NMR ($CDCl_3$) δ 8.4 (d, 1 H, $J_{3,4}$ = 7.9 Hz, $H_4$), 8.3 (d, 1 H, $H_3$), 7.57 (d, 1 H, $J_{3',4'}$ = 2.8 Hz, $H_{4'}$), 7.15 (d, 1 H, $J_{6,7}$ = 10.0 Hz, $H_7$), 7.06 (d, 1 H, $H_6$), 6.99 (d, 1 H, $H_{3'}$), 6.97 (s, 1 H, $H_{6'}$), 3.86 (s, 3 H, $OCH_3$), 3.84 (s, 3 H, $OCH_3$); $^{13}$C NMR ($CDCl_3$) δ 184.7 (CO), 183.2 (CO), 161.1, 154.2, 151.9, 147.2, 139.1, 137.9, 133.9, 129.2, 128.0, 127.3, 117.6, 116.5, 113.2, 56.4 ($OCH_3$), 56.0 ($OCH_3$); IR (KBr) 1670, 1580, 1498, 1458, 1318, 1082, 840, 715 cm$^{-1}$; HRMS calcd for $C_{17}H_{13}NO_4$ 295.08444, found 295.08465.

**Monoketone 14.** Following the same procedure as described for **25**, 1,2-cyclooctanedione[19] (0.50 g, 0.036 mol) and 2-amino-5,6-dihydro-1,10-phenanthroline-3-carboxaldehyde[13] (0.73 g, 0.032 mol) were refluxed for 16 h. The crude material obtained upon solvent evaporation was chromatographed on $Al_2O_3$ eluting with 1:8 hexane–$CHCl_3$ followed by $CHCl_3$ to afford a yellow solid which was washed with ethanol to afford 0.786 g (74%) of **14**, mp 127–131 °C: $^1$H NMR ($CDCl_3$)[23] δ 8.80 (dd, 1 H, $J_{2,3}$ = 4.7, $J_{2,4}$ = 1.1 Hz, $H_2$), 7.98 (s, 1 H, $H_7$ or $H_8$), 7.91 (s, 1 H, $H_7$ or $H_8$), 7.62 (dd, 1 H, $J_{3,4}$ = 7.4 Hz, $H_4$), 7.31 (dd, 1 H, $H_3$), 3.21 (t, 2 H), 3.08 (t, 2 H), 2.90 (m, 4 H), 1.85–1.70 (m, 4 H), 1.65 (m, 2 H); $^{13}$C NMR ($CDCl_3$) δ 208.5 (CO), 162.5, 155.0, 153.8, 150.9, 149.3, 135.8, 135.4, 135.0, 134.4, 133.0, 132.3, 124.3, 122.7, 45.0, 31.1, 30.6, 27.7, 27.4, 26.9, 23.6; IR ($CHCl_3$) 3030, 2960, 2880, 1720, 1620, 1580, 1545, 1460, 1430, 1115, 930 cm$^{-1}$.

**Dimethoxyquinoline Derivative 15.** Following the same procedure as described for **6a**, a mixture of **14** (0.123 g, 0.37 mmol) and **4** (0.074 g, 0.45 mmol) was refluxed for 28 h. The crude solid obtained upon solvent evaporation was chromatographed on $Al_2O_3$ eluting with $CHCl_3$ followed by $CHCl_3$/$CH_3OH$ (98:2) to afford **15** (0.067 g, 38%), mp 236–239 °C: $^1$H NMR ($CDCl_3$)[23] δ 8.77 (d, 1 H, $J_{2,3}$ = 3.9 hz, $H_2$), 8.45 (s, 1 H, $H_{13}$), 8.02 (s, 1 H, $H_7$ or $H_8$), 8.01 (s, 1 H, $H_7$ or $H_8$), 7.61 (d, 1 H, $J_{3,4}$ = 7.2 Hz, $H_4$), 7.27 (m, 1 H, $H_3$), 6.90 (d, 1 H, $J$ = 8.4 Hz, $H_{15}$ or $H_{16}$), 6.77 (d, 1 H, $H_{15}$ or $H_{16}$), 4.00 (br s, 6 H, $OCH_3$), 3.22 (m, 2 H), 3.09 (m, 2 H), 2.95 (m, 2 H), 2.39 (m, 2 H), 2.25 (m, 2 H), 1.74 (m, 2 H); $^{13}$C NMR ($CDCl_3$) δ 160.9, 156.2, 154.7, 154.2, 151.0, 149.9, 149.0, 148.0, 139.0, 137.8, 135.8, 135.6, 135.3, 135.0, 134.0, 132.6, 130.7, 124.1, 122.9, 121.8, 106.4, 103.8, 56.0, 55.7, 31.4, 31.3, 30.8, 30.6, 27.7, 27.4; IR (KBr) 3480, 2900, 2820, 1580, 1460, 1420, 1400, 1240, 1110, 1080, 890 cm$^{-1}$.

**Heptacyclic Quinolinequinone 16.** The procedure described for **1a** was followed using **15** (0.20 g, 0.422 mmol), CAN (0.88 g, 1.6 mmol), and PDANO (0.303 g, 1.6 mmol) to give **16** (0.12 g, 64%): $^1$H NMR ($CDCl_3$)[23] δ 8.89 (d, 1 H, $H_2$), 8.33 (s, 1 H, $H_{13}$), 8.10 (s, 1 H, $H_7$ or $H_8$), 8.68 (s, 1 H, $H_7$ or $H_8$), 7.70 (d, 1 H, $H_4$), 7.37 (dd, 1 H, $H_3$), 7.14 (dd, 2 H, $H_{15}$ or $H_{16}$), 3.5–2.9 (overlapping m, 6 H), 2.3 (m, 4 H), 1.7 (m, 2 H); IR (KBr) 2910, 1670, 1660, 1590, 1570, 1295, 1243, 1090, 1058 cm$^{-1}$.

**2,3':6,3''-Bisdimethylene-3,5-bis[5',8'-dimethoxyquinolyl]-pyridine (18a).** A mixture of octahydroacridine-1,8-dione[16] (0.215 g, 1 mmol), **4** (0.398 g, 2.2 mmol), and 10% ethanolic KOH (10 drops) was refluxed in absolute EtOH (25 mL) for 18 h. The reaction mixture was cooled and the precipitated product was collected. A second crop was obtained by concentration of the solvent. The crude product was recrystallized from EtOAc/$CH_2Cl_2$ (9:1) to provide **18a** (0.30 g, 59%), mp 292–295 °C: $^1$H NMR ($CDCl_3$) δ 9.97 (s, 1 H, $H_3$), 8.37 (s, 1 H, $H_{4'}$), 6.95 (d, 1 H, $J_{8',7'}$ = 8.4 Hz, $H_{8'}$ or $H_{7'}$), 6.74 (d, 1 H, $H_{8'}$ or $H_{7'}$), 4.15 (s, 3 H, $OCH_3$), 3.98 (s, 3 H, $OCH_3$), 3.27 (s, 4 H, $CH_2CH_2$), 1.95 (s, $H_2O$); $^{13}$C NMR ($CDCl_3$) δ 159.6, 151.3, 150.2, 149.0, 140.5, 131.7, 129.9, 129.2, 128.9, 121.4, 108.6, 103.9, 57.3, 55.9, 31.3, 28.2; IR (KBr) 2910, 2800, 1588, 1574, 1462, 1420, 1365, 1332, 1296, 1245, 1160, 1138, 1080, 1070, 890, 780, 704 cm$^{-1}$. Anal. Calcd for $C_{31}H_{27}N_3O_4 \cdot {}^1/_4H_2O$: C, 73.01; H, 5.40; N, 8.24. Found: C, 73.05; H, 5.42; N, 8.25.

**Monoketone 19b.** A mixture of diketone **17b**,[16] (0.271 g, 1 mmol), **4** (0.38 g, 2.1 mmol), and one pellet of KOH in 20 mL of absolute EtOH was refluxed under Ar for 24 h. The reaction mixture was cooled and the precipitated monoketone was collected and recrystallized from $CH_3OH$ to afford monoketone **19b** (0.3 g, 72%) as a yellow microcrystalline solid, mp 280–281 °C: $^1$H NMR ($CDCl_3$)[23] δ 9.39 (s, 1 H, $H_{14}$), 8.51 (s, 1 H, $H_6$), 6.9 (d, 1 H, $H_3$ or $H_4$), 6.75 (d, 1 H, $H_3$ or $H_4$), 4.07 (s, 3 H, $OCH_3$), 3.98 (s, 3 H, $OCH_3$), 3.14 (s, 2 H, $CH_2$), 3.07 (s, 2 H, $CH_2$), 2.59 (s, 2 H, $CH_2$), 1.44 (s, 6 H), 1.14 (s, 6 H); $^{13}$C NMR ($CDCl_3$) δ 196.8, 162.1, 162.0, 149.3, 148.9, 148.2, 139.1, 137.3, 131.7, 128.6, 126.3, 125.5, 121.1, 106.9, 103.6, 55.9, 55.2, 51.7, 46.2, 45.8, 34.7, 32.4, 28.1, 27.8; IR ($CHCl_3$) 2960, 2940, 2840, 1700, 1690, 1620, 1600, 1580, 1485, 1465, 1390, 1380, 1340, 1275, 1240, 1200, 1125, 1000, 982 cm$^{-1}$. Anal. Calcd for $C_{28}H_{26}N_2O_3$: C, 75.36; H, 6.28; N, 6.76. Found: C, 74.91; H, 6.71; N, 7.16.

After removal of the monoketone, the filtrate was evaporated and the residue chromatographed on $Al_2O_3$ (20 g) eluting with EtOAc/hexane (1:1) to afford **18b** (0.060 g, 11%) which crystallized from MeOH as pale yellow needles, mp 250–251 °C: $^1$H NMR ($CDCl_3$)[23] δ 9.99 (s, 1 H, $H_{18}$), 8.52 (s, 2 H, $H_6$ and $H_{12}$), 6.93 (d, 2 H, $H_3$ or $H_4$ and $H_{14}$ or $H_{15}$), 6.72 (d, 2 H, $H_3$ or $H_4$ and $H_{14}$ or $H_{15}$), 4.14 (s, 6 H, $OCH_3$), 3.99 (s, 6 H, $OCH_3$), 3.17 (s, 4 H, $CH_2$), 1.47 (s, 12 H); $^{13}$C NMR ($CDCl_3$) δ 158.5, 150.4, 149.8, 148.9, 139.7, 138.0, 131.5, 129.4, 125.6, 121.4, 108.1, 103.6, 56.9, 55.7, 45.9, 35.3, 28.5; IR ($CHCl_3$) 3700, 2960, 2940, 2840, 1620, 1600, 1485, 1465, 1390, 1340, 1270, 1240, 1200, 1130, 1100 cm$^{-1}$. Anal. Calcd for $C_{35}H_{35}N_3O_4 \cdot {}^3/_4H_2O$: C, 73.11; H, 6.35; N, 7.31. Found: C, 73.22; H, 6.09; N, 7.16.

**Dimethoxyquinoline Derivative 20.** A mixture of monoketone **19b** (0.208 g, 0.5 mmol), amino aldehyde **4** (0.200 g, 0.9 mmol), and one pellet of KOH in 25 mL of absolute EtOH was refluxed under Ar for 24 h. The solvent was evaporated under vacuum and the residue chromatographed on $Al_2O_3$ (20 g) eluting with EtOAc/hexane (1:1) to afford unreacted monoketone **19b** (0.060 g). Further elution with EtOAc/MeOH (95:5) afforded **20** (0.20 g, 66%) which was crystallized from a mixture of $CH_2Cl_2$/hexane as yellow needles, mp 223–225 °C: $^1$H NMR ($CDCl_3$)[23] δ 10.04 (s, 1 H, $H_{20}$), 8.85 (d, 1 H, $J_{2,3}$ = 4.0 Hz, $H_2$), 8.52 (s, 1 H, $H_{14}$), 8.06 (s, 1 H), 7.99 (s, 1 H), 7.60 (d, 1 H, $J_{3,4}$ = 7.3 Hz, $H_4$), 7.29 (dd, 1 H, $H_3$), 6.90 (d, 1 H, $J_{16,17}$ = 8.4 Hz, $H_{16}$ or $H_{17}$), 6.74 (d, 1 H, $H_{16}$ or $H_{17}$), 4.13 (s, 3 H, $OCH_3$), 3.97 (s, 3 H, $OCH_3$), 3.75 (s, $H_2O$), 3.18 (s, 2 H, $CH_2$), 3.17 (m under singlets, 2 H, $CH_2$), 3.16 (s, 2 H, $CH_2$), 3.06 (s, 2 H, $CH_2$), 1.49 (s, 6 H, $CH_3$), 1.47 (s, 6 H, $CH_3$); $^{13}$C NMR ($CDCl_3$) δ 159.2, 158.4, 155.0, 154.8, 154.5,

(23) For NMR purposes, compounds **14–16** and **18b–21** are numbered such that the nitrogen of the terminal pyridyl or quinolyl (in **18b** and **19b**) ring is assigned the number one. Proceeding away from the center, around the periphery of the molecule each nonbridgehead atom is then numbered successively.

151.4, 150.2, 149.3, 140.0, 139.5, 137.9, 135.8, 135.1, 134.7, 132.3, 132.2, 130.7, 129.9, 129.2, 125.5, 124.1, 122.5, 121.3, 106.4, 103.8, 55.9, 55.7, 46.0, 45.6, 35.2, 28.4, 27.9, 27.6; IR ($CHCl_3$) 3700, 2950, 2930, 2840, 1620, 1590, 1460, 1445, 1390, 1380, 1340, 1275, 1240, 1200, 1130, 1110, 980, 925, 740 $cm^{-1}$. Anal. Calcd for $C_{39}H_{35}N_5O_7 \cdot 2H_2O$: C, 73.01; H, 6.08; N, 10.92. Found: C, 73.19; H, 5.99; N, 11.00.

**Nonacyclic Quinolinequinone 21.** A mixture of **20** (0.1 g, 0.16 mmol) and PDANO (0.13 g, 0.66 mmol) in 15 mL of $CH_3CN/H_2O$ (2:1) was stirred at 0 °C. A solution CAN of (0.36 g, 0.66 mmol) was added dropwise over a period of 10 min. The mixture was stirred at 0 °C for 1 h and then poured into $H_2O$ (100 mL). The aqueous solution was extracted with $CH_2Cl_2$ (4 × 25 mL), and the extracts were washed with $H_2O$ and dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded **21** (0.06 g, 62%): $^1H$ NMR ($CDCl_3$)[23] $\delta$ 10.02 (s, 1 H, $H_{20}$), 8.92 (d, 1 H, $J_{2,3}$ = 4.3 Hz, $H_2$), 8.41 (s, 1 H, $H_{14}$), 8.11 (s, 1 H, $H_7$ or $H_8$), 8.05 (s, 1 H, $H_7$ or $H_8$), 7.67 (d, 1 H, $J_{3,4}$ = 7.4 Hz, $H_4$), 7.38 (dd, 1 H, $H_3$), 7.20 (d, 1 H, $J_{16,17}$ = 10.4 Hz, $H_{16}$ or $H_{17}$), 7.07 (d, 1 H, $H_{16}$ or $H_{17}$), 3.23–3.12 (overlapping m, 8 H, $CH_2$), 1.48 (br s, 12 H, $CH_3$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 185.0 (CO), 182.5 (CO), 159.8, 158.6, 155.3, 155.0, 154.9, 153.7, 151.1, 149.5, 144.9, 140.0, 139.6, 137.7, 136.6, 135.5, 135.1, 133.6, 132.9, 131.2, 130.6, 130.0, 128.7, 128.6, 124.7, 123.0, 96.3, 45.4, 44.8, 35.4, 28.7, 28.1 (2 peaks), 27,8; IR ($CHCl_3$), 2940, 2250, 1630, 1550, 1434, 1415, 1296, 920 $cm^{-1}$.

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**Supplementary Material Available:** $^1H$ NMR spectra for compounds **1a–d, 4, 6c,d, 8a,b, 9a,b, 10, 14–16, 21, 23,** and **24** and $^{13}C$ NMR spectra for compounds **4, 6c,d, 8a,b, 9b, 10, 14, 15, 21, 23,** and **24** (19 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.