Synthesis of 5,8- and 5,6-Quinolinediones Using Oxidative Demethylation with Cerium(IV) Ammonium Nitrate

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4-Phenyl-5,8-quinolinediones (7, 8, 12, 13), 4-phenyl-5,6-quinolinediones (9, 14), and 2-dialkylamino-4-phenyl-5,8-quinolinediones (17, 18), were synthesized by oxidative demethylation of the corresponding 5,8-dimethoxy- or 5,6,8-trimethoxy-4-phenylquinolines with cerium(IV) ammonium nitrate. Sulfur-containing quinolinequinones (21, 24) were prepared by oxidation of the corresponding 5,8-dimethoxy- or 5,6,8-trimethoxy-2(1*H*)-quinolinethiones (20, 23).

Key words quinolinequinone; oxidative demethylation; cerium(IV) ammonium nitrate

Streptonigrin, a highly substituted 5,8-quinolinedione, is one of the most potent inhibitors of avian myeloblastosis virus reverse transcriptase (AMV-RT), and the 7-amino-6-methoxy-5,8-quinolinedione moiety of streptonigrin is the minimum structure for inhibition of AMV-RT.[1] Reverse transcriptase is considered to be an excellent target for the chemotherapy of retroviral diseases, such as human acquired immunodeficiency syndrome (AIDS). We observed that 6-methoxy-5,8-quinolinediones and 8-methoxy-5,6-quinolinediones were as potent (as inhibitors of AMV-RT) as streptonigrin, and much less toxic.[2] We also prepared various quinolinequinones, 2(1*H*)-quinolinonequinones, and isoquinolinequinones by oxidative demethylation of the corresponding 5,8-dimethoxy- or 5,6,8-trimethoxy(iso)quinolines with cerium(IV) ammonium nitrate (CAN) or silver(II) oxide, and examined their inhibitory activities.[2b,3] Here we report the synthesis of 4-phenylquinolinequinones and sulfur-containing quinolinequinones by oxidative demethylation of 4-phenylquinolines and 2(1*H*)-quinolinethiones.

4-Phenyl-5,8-quinolinediones (**7**, **8**, **12**, **13**, **17**, **18**) and 4-phenyl-5,6-quinolinediones (**9**, **14**) were prepared from 4-phenyl-2(1*H*)-quinolinones (**1**, **2**).[3c] 4-Phenyl-2-trifluoromethanesulfonyloxyquinolines (**3**, **4**), prepared from 2(1*H*)-quinolinones (**1**, **2**), were reduced with triethylammonium formate in the presence of palladium acetate and 1,1′-bis(diphenylphosphino)ferrocene (DPPF)[4] to afford the 2-unsubstituted quinolines (**5**, **6**) in 88—99% yields. 2-Chloro-4-phenylquinolines (**10**, **11**) prepared by chlorination of the 2(1*H*)-quinolinones (**1**, **2**) with phosphorus oxychloride, were treated with cyclic secondary amines (piperidine, pyrrolidine, morpholine, 1-methylpiperazine) to afford 2-dialkylaminoquinolines (**15**, **16**) in 94—99% yields.

Oxidative demethylation of 5,8-dimethoxy-4-phenylquinolines (**5**, **10**, **15**) with CAN in acetonitrile-water at 0—5 °C furnished the corresponding *p*-quinones (**7**, **12**, **17**) in 45—94% yields. Treatment of 5,6,8-trimethoxy-4-phenylquinolines (**6**, **11**) with CAN furnished *p*-quinones (**8**, **13**; 24—33% yields) and *o*-quinones (**9**, **14**; 24—75% yields). In contrast, 2-dialkylamino-5,6,8-trimethoxy-4-phenylquinolines (**16**) were oxidized with CAN to furnish exclusively *p*-quinones (**18**) in 43—87% yields.

Sulfur-containing quinolinequinones (**21**, **24**) were prepared from 2(1*H*)-quinolinones (**19**, **22**).[3c] Treatment of **19** (or **22**) with Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide) in 1,2-dimethoxyethane afforded the corresponding 2(1*H*)-quinolinethiones (**20**, **23**) in 91—99% yields. Oxidative demethylation of *N*-unsubstituted 2(1*H*)-quinolinethiones (**20**) with CAN in acetonitrile–water at 0—5 °C furnished "dimeric" quinones (**21**) in 56—76% yields. The *N*-methyl-2(1*H*)-quinolinethione (**23a**) was oxidatively demethylated with CAN to afford the expected quinone (**24a**) in 15% yield. However, attempted oxidation of **23b** with CAN failed, giving a complex mixture. The quinone (**24b**) was obtained by oxidative demethylation of **23b** with silver(II) oxide–nitric acid[5] in 49% yield.

Analytical and spectral data for the quinones (**7**—**9**, **12**—**14**, **17**, **18**, **21**, **24**) are given in Table I. These quinones showed no activity against human immunodeficiency virus.

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. ^{1}H-NMR spectra were measured at 270 MHz in $CDCl_3$ with tetramethylsilane as an internal standard. All reactions were run with magnetic stirring. Anhydrous sodium sulfate was used for drying organic solvent extracts, and the solvent was removed with a rotary evaporator and finally under high vacuum. Column chromatography (flash chromatography) was performed with Silica gel 60 (230—400 mesh).

2-Trifluoromethanesulfonyloxy-4-phenylquinolines (3, 4) Trifluoromethanesulfonic anhydride (0.1 ml, 0.6 mmol) was added to a solution of 4-phenyl-2(1*H*)-quinolinone (**1**, **2**) (0.5 mmol) in dry CH_2Cl_2 (10 ml) containing triethylamine (0.2 ml, 1.4 mmol) at 0—5 °C. The mixture was stirred at 0—5 °C for 30 min, poured into ice-water (20 ml), and extracted with CH_2Cl_2 (3 × 20 ml). The extract was washed with water, dried, and evaporated. The residue was chromatographed (eluting with CH_2Cl_2 or ethyl acetate–hexane (1 : 19)) to afford **3** (or **4**).

3: Yield 99%. mp 119—121 °C (ether). MS *m/z* (%): 413 (M^+, 100), 280 (71), 264 (16). *Anal.* Calcd for $C_{18}H_{14}F_3NO_5S$: C, 52.30; H, 3.41; N, 3.39. Found: C, 52.34; H, 3.44; N, 3.34. ^{1}H-NMR δ: 3.46 (3H, s, C_5-OCH_3), 4.04 (3H, s, C_8-OCH_3), 6.84 (1H, d, J=8.6 Hz, C_6-H), 7.09 (1H, s, C_3-H), 7.12 (1H, d, J=8.6 Hz, C_7-H), 7.25—7.45 (5H, m, C_6H_5).

4: Yield 99%. mp 73—74 °C (ether–hexane). MS *m/z* (%): 457 (M^+, 100), 442 (43), 324 (53). *Anal.* Calcd for $C_{20}H_{18}F_3NO_6S$: C, 52.52; H, 3.97; N, 3.06. Found: C, 52.44; H, 3.95; N, 3.01. ^{1}H-NMR δ: 2.41 (3H, s, C_7-CH_3), 3.19 (3H, s, C_5-OCH_3), 3.87 (3H, s, C_6-OCH_3), 4.07 (3H, s, C_8-OCH_3), 6.97 (1H, s, C_3-H), 7.3—7.5 (5H, m, C_6H_5).

4-Phenylquinolines (5, 6) Formic acid (0.11 ml, 3 mmol) was added to a mixture of **3** (or **4**) (0.5 mmol), triethylamine (0.56 ml, 4 mmol), palladium acetate (30 mg, 0.13 mmol), and DPPF (140 mg, 0.25 mmol)

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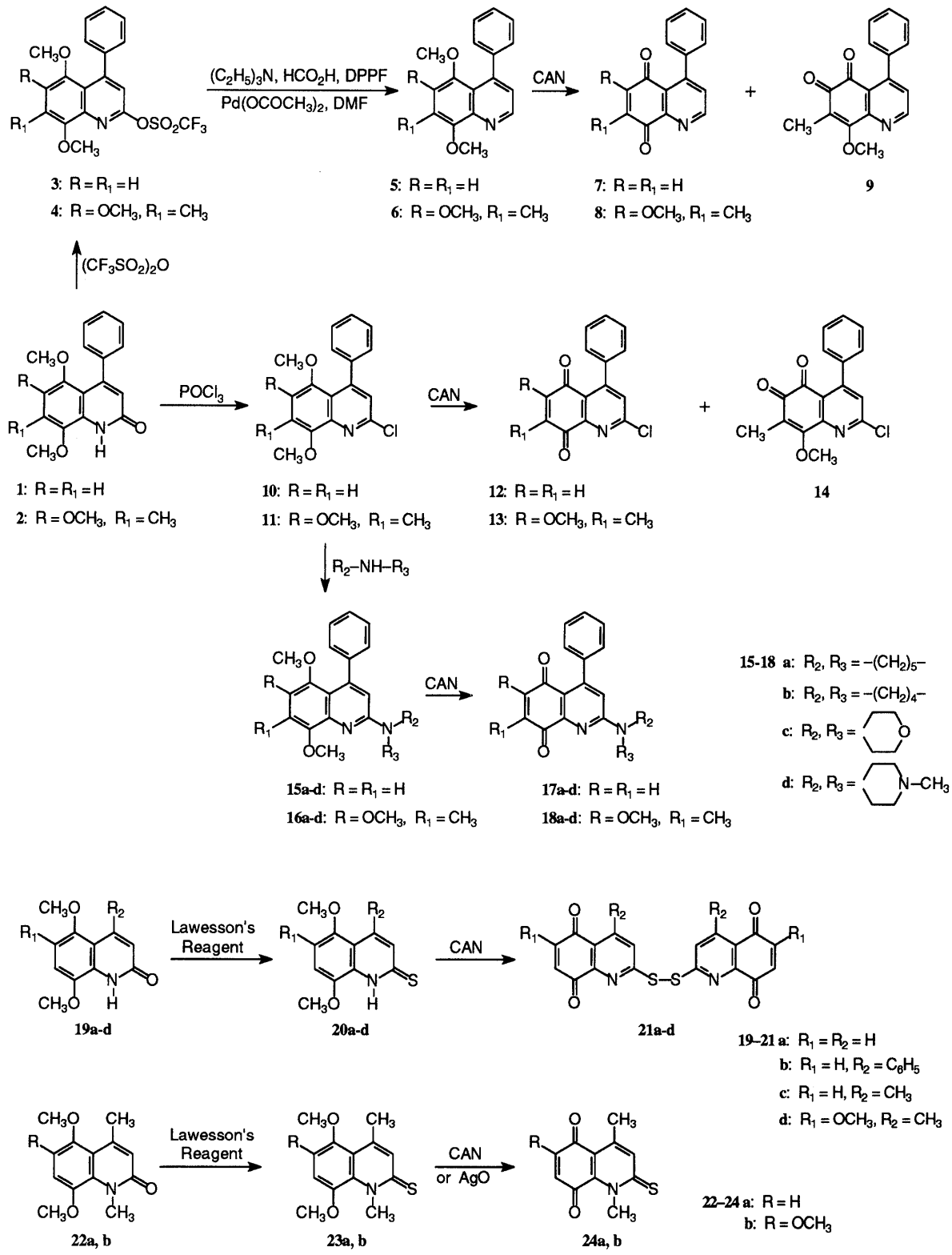

Chart 1

in *N*,*N*-dimethylformamide (5 ml). The mixture was stirred at 25 °C for 1 h, and then at 60 °C for 2 h. The reaction mixture was diluted with 1% $NaHCO_3$ solution (30 ml), and extracted with CH_2Cl_2 (3 × 20 ml). The extract was washed with water, dried and evaporated. The residue was chromatographed (eluting with CH_2Cl_2–ethyl acetate (19 : 1) or ethyl acetate–hexane (1 : 4)) to afford **5** (or **6**).

5: Yield 99%. mp 177—178 °C (CH_2Cl_2–ether). MS *m/z* (%): 265 (M^+, 69), 250 (100), 236 (16), 220 (20). *Anal.* Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 76.90; H, 5.73; N, 5.23. ^{1}H-NMR δ: 3.45 (3H, s, C_5-OCH_3), 4.08 (3H, s, C_8-OCH_3), 6.77 (1H, d, J = 8.6 Hz, C_6-H), 7.00 (1H, d, J = 8.6 Hz, C_7-H), 7.24 (1H, d, J = 4.3 Hz, C_3-H), 7.25—7.45 (5H, m, C_6H_5), 8.91 (1H, d, J = 4.3 Hz, C_2-H).

6: Yield 88%. mp 104—105 °C (hexane). MS *m/z* (%): 309 (M^+, 51), 294 (100). *Anal.* Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.53; H, 6.21; N, 4.48. ^{1}H-NMR δ: 2.43 (3H, s, C_7-CH_3), 3.19 (3H, s, C_5-OCH_3), 3.87 (3H, s, C_6-OCH_3), 4.07 (3H, s, C_8-OCH_3), 7.13 (1H, d, J = 4.3 Hz, C_3-H), 7.3—7.5 (5H, m, C_6H_5), 8.82 (1H, d, J = 4.3 Hz, C_2-H).

2-Chloro-4-phenylquinolines (10, 11) A mixture of 4-phenyl-2(1*H*)-quinolinone (**1**, **2**) (1 mmol) and phosphorus oxychloride (2 ml, 21.5 mmol) was heated at 60—70 °C for 30 min. The reaction mixture was cooled, poured into ice-water (50 ml), neutralized with $NaHCO_3$, and

Table 1. Analytical and Spectral Data for Quinolinequinones (**7—9**, **12—14**, **17**, **18**, **21**, **24**)

	Yield (%)	Appearance (Recrystn. solv.)	mp (°C)	Formula	Analysis or HRMS[a] Calcd (Found) C	H	N	MS *m/z* (%)	IR (KBr) $\nu_{C=O}$ (cm^{-1})	^{1}H-NMR (270 MHz) δ ($CDCl_3$, J=Hz)
7	74	Orange prisms (CH_2Cl_2–ether)	135—138	$C_{15}H_9NO_2$	76.59 (76.55)	3.86 (3.94)	5.95 (5.79)	235 (M^+, 85) 234 (100) 206 (21)	1666	6.93, 7.13 (each 1H, d, J=10.2, C_6-H, C_7-H), 7.25—7.55 (6H, m, C_3-H, C_6H_5), 9.01 (1H, d, J=5.0, C_2-H)
8	33	Yellow plates (ethyl acetate–ether)	172—176	$C_{17}H_{13}NO_3$	73.11 (72.88)	4.69 (4.75)	5.02 (4.93)	279 (M^+, 100) 264 (28) 249 (30)	1672 1652	2.15 (3H, s, C_7-CH_3), 4.01 (3H, s, OCH_3), 7.25—7.55 (5H, m, C_6H_5), 7.42 (1H, d, J=5.0, C_3-H), 8.94 (1H, d, J=5.0, C_2-H)
9	24	Orange needles (ether–hexane)	154—155	$C_{17}H_{13}NO_3$	73.11 (72.97)	4.69 (4.75)	5.02 (4.89)	279 (M^+, 12) 251 (74) 250 (55) 222 (100)	1700 1656	2.10 (3H, s, C_7-CH_3), 4.20 (3H, s, OCH_3), 7.2—7.5 (6H, m, C_3-H, C_6H_5), 8.93 (1H, d, J=5.3, C_2-H)
12	94	Yellow plates (CH_2Cl_2–hexane)	176—177	$C_{15}H_8ClNO_2$	66.81 (66.46)	2.99 (2.76)	5.19 (5.17)	271 (M^++2, 34) 269 (M^+, 71) 268 (100)	1666	6.93, 7.13 (each 1H, d, J=10.2, C_6-H, C_7-H), 7.54 (1H, s, C_3-H), 7.25—7.55 (5H, m, C_6H_5)
13	24	Yellow needles (CH_2Cl_2–hexane)	166—169	$C_{17}H_{12}ClNO_3$	65.08 (64.93)	3.86 (3.88)	4.46 (4.40)	315 (M^++2, 35) 313 (M^+, 100) 300 (11), 298 (32) 286 (17), 284 (44)	1668	2.13 (3H, s, C_7-CH_3), 4.01 (3H, s, OCH_3), 7.20—7.55 (6H, m, C_3-H, C_6H_5)
14	75	Orange needles (ether)	162—163	$C_{17}H_{12}ClNO_3$	65.08 (64.91)	3.86 (4.06)	4.46 (4.32)	315 (M^++2, 3) 313 (M^+, 7) 287 (26), 285 (76) 258 (37), 256 (100)	1696 1666	2.09 (3H, s, C_7-CH_3), 4.21 (3H, s, OCH_3), 7.2—7.5 (6H, m, C_3-H, C_6H_5)
17a	45	Dark red prisms (CH_2Cl_2–hexane)	179—181 (dec.)	$C_{20}H_{18}N_2O_2 \cdot 1/3H_2O$	74.05 (73.93)	5.80 (5.50)	8.64 (8.60)	318 (M^+, 100) 317 (79) 289 (29)	1678 1644	1.6—1.8 (6H, m, $CH_2(C\underline{H}_2)_3CH_2$), 3.7—3.9 (4H, m, CH_2NCH_2), 6.60 (1H, s, C_3-H), 6.71, 6.88 (each 1H, d, J=10.2, C_6-H, C_7-H), 7.2—7.5 (5H, m, C_6H_5)
17b	48	Red prisms (CH_2Cl_2–hexane)	181—182	$C_{19}H_{16}N_2O_2$	74.98 (74.85)	5.30 (5.14)	9.20 (9.23)	304 (M^+, 100) 303 (67) 275 (64)	1676 1646	2.0—2.1 (4H, m, $CH_2(C\underline{H}_2)_2CH_2$), 3.66 (4H, br s, CH_2NCH_2), 6.38 (1H, s, C_3-H), 6.71, 6.88 (each 1H, d, J=10.3, C_6-H, C_7-H), 7.2—7.5 (5H, m, C_6H_5)
17c	47	Red prisms (CH_2Cl_2–hexane)	177—178	$C_{19}H_{16}N_2O_3$	71.23 (70.84)	5.03 (4.85)	8.74 (8.70)	320 (M^+, 100) 319 (85) 263 (14)	1676 1650	3.82 (8H, br s, $(CH_2)_2O(CH_2)_2$), 6.62 (1H, s, C_3-H), 6.74, 6.91 (each 1H, d, J=10.3, C_6-H, C_7-H), 7.2—7.5 (5H, m, C_6H_5)
17d	71	Dark red prisms (CH_2Cl_2–hexane)	187—189	$C_{20}H_{19}N_3O_2 \cdot 1/3H_2O$	70.78 (70.69)	5.84 (5.61)	12.38 (12.29)	333 (M^+, 100) 332 (42) 265 (37) 263 (37)	1674 1648	2.36 (3H, s, NCH_3), 2.54 (4H, t, J=5.0, $C\underline{H}_2$–$N(CH_3)$–$C\underline{H}_2$), 3.85 (4H, t, J=5.0, CH_2NCH_2), 6.62 (1H, s, C_3-H), 6.73, 6.90 (each 1H, d, J=10.3, C_6-H, C_7-H), 7.2—7.5 (5H, m, C_6H_5)
18a	43	Dark red prisms (CH_2Cl_2–ether)	187—188	$C_{22}H_{22}N_2O_3 \cdot 1/10H_2O$	72.55 (72.43)	6.14 (6.10)	7.69 (7.55)	362 (M^+, 100) 347 (78) 319 (19)	1660	1.6—1.8 (6H, m, $CH_2(C\underline{H}_2)_3CH_2$), 2.05 (3H, s, C_7-CH_3), 3.75—3.85 (4H, m, CH_2NCH_2), 3.96 (3H, s, OCH_3), 6.52 (1H, s, C_3-H), 7.2—7.5 (5H, m, C_6H_5)
18b	55	Red needles (CH_2Cl_2–ether)	187—189	$C_{21}H_{20}N_2O_3$	72.40 (72.05)	5.79 (5.84)	8.04 (7.94)	348 (M^+, 100) 333 (70) 319 (22) 305 (29)	1648	1.95—2.10 (4H, m, $CH_2(C\underline{H}_2)_2CH_2$), 2.05 (3H, s, C_7-CH_3), 3.64 (4H, br s, CH_2NCH_2), 3.95 (3H, s, OCH_3), 6.29 (1H, s, C_3-H), 7.2—7.5 (5H, m, C_6H_5)
18c	68	Red needles (CH_2Cl_2–hexane)	196—200	$C_{21}H_{20}N_2O_4$	69.22 (69.00)	5.53 (5.60)	7.69 (7.49)	364 (M^+, 100) 349 (50) 307 (48)	1664	2.06 (3H, s, C_7-CH_3), 3.81 (8H, s, $(CH_2)_2O(CH_2)_2$), 3.97 (3H, s, OCH_3), 6.54 (1H, s, C_3-H), 7.2—7.5 (5H, m, C_6H_5)
18d	87	Dark red prisms (ethyl acetate–ether)	192—193	$C_{22}H_{23}N_3O_3$	70.01 (69.65)	6.14 (6.14)	11.13 (10.99)	377 (M^+, 100) 362 (29) 307 (59)	1658	2.06 (3H, s, C_7-CH_3), 2.35 (3H, s, NCH_3), 2.51 (4H, t, J=5.0, $C\underline{H}_2$–$N(CH_3)$–$C\underline{H}_2$), 3.84 (4H, t, J=5.0, CH_2NCH_2), 3.96 (3H, s, OCH_3), 6.55 (1H, s, C_3-H), 7.2—7.5 (5H, m, C_6H_5)
21a	76	Yellow needles ($CHCl_3$–hexane)	210	$C_{18}H_8N_2O_4S_2$	379.9925 (379.9930)			380 (M^+, 34) 191 (100)	1664	7.05, 7.14 (each 2H, d, J=10.2, $2C_6$-H, $2C_7$-H), 8.04 (2H, d, J=8.6, $2C_3$-H), 8.32 (2H, d, J=8.6, $2C_4$-H)
21b	56	Yellow needles ($CHCl_3$–hexane)	245 (dec.)	$C_{30}H_{16}N_2O_4S_2$	67.66 (67.28)	3.03 (3.24)	5.26 (5.14)	532 (M^+, 8) 267 (100)	1662	6.89, 7.07 (each 2H, d, J=10.2, $2C_6$-H, $2C_7$-H), 7.15—7.50 (10H, m, $2C_6H_5$), 7.82 (2H, s, $2C_3$-H)
21c	60	Pale yellow needles (ethyl acetate)	201 (dec.)	$C_{20}H_{12}N_2O_4S_2$	408.0238 (408.0248)			408 (M^+, 38) 205 (100)	1664	2.74 (6H, s, $2C_4$-CH_3), 6.97, 7.07 (each 2H, d, J=10.6, $2C_6$-H, $2C_7$-H), 7.83 (2H, s, $2C_3$-H)
21d	72	Yellow needles (ethyl acetate)	210	$C_{22}H_{16}N_2O_6S_2 \cdot H_2O$	54.31 (54.36)	3.73 (3.37)	5.76 (5.73)	468 (M^+, 2) 235 (100)	1680 1663	2.74 (6H, s, $2C_4$-CH_3), 3.93 (6H, s, $2OCH_3$), 6.29 (2H, s, $2C_7$-H), 7.79 (2H, s, $2C_3$-H)
24a	15	Dark red powder (ether–hexane)	137—142 (dec.)	$C_{11}H_9NO_2S$	219.0354 (219.0352)			219 (M^+, 100)	1660	2.52 (3H, s, C_4-CH_3), 4.23 (3H, s, NCH_3), 6.81, 6.89 (each 1H, d, J=10.2, C_6-H, C_7-H), 7.78 (1H, s, C_3-H)
24b	49	Dark red needles (ethyl acetate–hexane)	185—190 (dec.)	$C_{12}H_{11}NO_3S \cdot 1/10H_2O$	57.40 (57.37)	4.50 (4.46)	5.58 (5.40)	249 (M^+, 100) 234 (76)	1674	2.53 (3H, d, J=1.0, C_4-CH_3), 3.91 (3H, s, OCH_3), 4.25 (3H, s, NCH_3), 6.04 (1H, s, C_7-H), 7.74 (1H, q, J=1.0, C_3-H)

a) High-resolution MS.

extracted with CH_2Cl_2 (3 × 20 ml). The extract was washed with water, dried, and evaporated. The residue was chromatographed (eluting with ethyl acetate–hexane (1 : 9)) to afford 2-chloro-4-phenylquinoline (**10**, **11**).

10: Yield 99%. mp 186—187 °C (CH_2Cl_2–hexane). MS *m/z* (%): 301 (M^++2, 19), 299 (M^+, 57), 286 (34), 284 (100). *Anal.* Calcd for $C_{17}H_{14}ClNO_2$: C, 68.12; H, 4.71; N, 4.67. Found: C, 68.16; H, 4.51; N, 4.68. ^{1}H-NMR δ: 3.44 (3H, s, C_5-OCH_3), 4.05 (3H, s, C_8-OCH_3), 6.77 (1H, d, J=8.6 Hz, C_6-H), 7.03 (1H, d, J=8.6 Hz, C_7-H), 7.2—7.5 (6H, m, C_3-H, C_6H_5).

11: Yield 98%. mp 131—133 °C (ether–hexane). MS *m/z* (%): 345 (M^++2, 21), 343 (M^+, 57), 330 (36), 328 (100). *Anal.* Calcd for $C_{19}H_{18}ClNO_3$: C, 66.38; H, 5.28; N, 4.07. Found: C, 66.25; H, 5.24; N, 4.03. ^{1}H-NMR δ: 2.41 (3H, s, C_7-CH_3), 3.18 (3H, s, C_5-OCH_3), 3.85 (3H, s, C_6-OCH_3), 4.07 (3H, s, C_8-OCH_3), 7.12 (1H, s, C_3-H), 7.30—7.45 (5H, m, C_6H_5).

2-Dialkylaminoquinolines (15, 16) A mixture of a 2-chloroquinoline (**10**, **11**) (1 mmol) and 1-methylpiperazine (or piperidine, pyrrolidine, or morpholine; 2 ml) was refluxed for 2—3 h, and then evaporated. The residue was chromatographed using ethyl acetate–methanol (19 : 1—7 : 3) (or ethyl acetate–hexane (1 : 19—2 : 3)) as the eluent to afford 2-(4-methyl-1-piperazinyl)quinoline (or 2-(1-piperidinyl)quinoline, 2-(1-pyrrolidinyl)quinoline, or 2-morpholinoquinoline; **15**, **16**).

15a: Yield 99%. mp 114—115 °C (CH_2Cl_2–hexane). MS *m/z* (%): 348 (M^+, 100), 333 (26), 319 (48), 265 (44). *Anal.* Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 76.05; H, 7.02; N, 7.99. ^{1}H-NMR δ: 1.67 (6H, br s, $CH_2(C\underline{H}_2)_3CH_2$), 3.37 (3H, s, C_5-OCH_3), 3.74 (4H, br s, CH_2NCH_2), 4.01 (3H, s, C_8-OCH_3), 6.44 (1H, d, J=8.6 Hz, C_6-H), 6.73 (1H, s, C_3-H), 6.88 (1H, d, J=8.6 Hz, C_7-H), 7.2—7.5 (5H, m, C_6H_5).

15b: Yield 99%. mp 182—183 °C (CH_2Cl_2–hexane). MS *m/z* (%): 334 (M^+, 100), 319 (54), 305 (37). *Anal.* Calcd for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.21; H, 6.60; N, 8.37. ^{1}H-NMR δ: 2.02 (4H, br s, $CH_2(C\underline{H}_2)_2CH_2$), 3.37 (3H, s, C_5-OCH_3), 3.65 (4H, br s, CH_2NCH_2), 4.02 (3H, s, C_8-OCH_3), 6.41 (1H, d, J=8.3 Hz, C_6-H), 6.49 (1H, s, C_3-H), 6.89 (1H, d, J=8.6 Hz, C_7-H), 7.25—7.45 (5H, m, C_6H_5).

15c: Yield 98%. mp 139—140 °C (CH_2Cl_2–hexane). MS *m/z* (%): 350 (M^+, 100), 319 (53), 293 (42). *Anal.* Calcd for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 7.99. Found: C, 71.87; H, 6.29; N, 7.98. ^{1}H-NMR δ: 3.39 (3H, s, C_5-OCH_3), 3.74 (4H, t, J=5.0 Hz, CH_2NCH_2), 3.85 (4H, t, J=5.0 Hz, CH_2OCH_2), 4.01 (3H, s, C_8-OCH_3), 6.49 (1H, d, J=8.6 Hz, C_6-H), 6.71 (1H, s, C_3-H), 6.92 (1H, d, J=8.6 Hz, C_7-H), 7.2—7.5 (5H, m, C_6H_5).

15d: Yield 99%. mp 172—174 °C (CH_2Cl_2–hexane). MS *m/z* (%): 363 (M^+, 7), 293 (100), 280 (23), 263 (22). *Anal.* Calcd for $C_{22}H_{25}N_3O_2$: C, 72.70; H, 6.93; N, 11.56. Found: C, 72.49; H, 6.96; N, 11.55. ^{1}H-NMR δ: 2.36 (3H, s, NCH_3), 2.56 (4H, t, J=5.0 Hz, $C\underline{H}_2$–N(CH_3)–$C\underline{H}_2$), 3.38 (3H, s, C_5-OCH_3), 3.80 (4H, t, J=5.0 Hz, CH_2NCH_2), 4.01 (3H, s, C_8-OCH_3), 6.47 (1H, d, J=8.6 Hz, C_6-H), 6.73 (1H, s, C_3-H), 6.90 (1H, d, J=8.6 Hz, C_7-H), 7.2—7.5 (5H, m, C_6H_5).

16a: Yield 94%. mp 106—107 °C (hexane). MS *m/z* (%): 392 (M^+, 100), 377 (67), 363 (18). *Anal.* Calcd for $C_{24}H_{28}N_2O_3$: C, 73.44; H, 7.19; N, 7.14. Found: C, 73.22; H, 7.25; N, 7.07. ^{1}H-NMR δ: 1.67 (6H, br s, $CH_2(C\underline{H}_2)_3CH_2$), 2.35 (3H, s, C_7-CH_3), 3.17 (3H, s, C_5-OCH_3), 3.72 (4H, br s, CH_2NCH_2), 3.78 (3H, s, C_6-OCH_3), 4.08 (3H, s, C_8-OCH_3), 6.70 (1H, s, C_3-H), 7.3—7.5 (5H, m, C_6H_5).

16b: Yield 96%. mp 119—120 °C (hexane). MS *m/z* (%): 378 (M^+, 100), 363 (90), 335 (25). *Anal.* Calcd for $C_{23}H_{26}N_2O_3$: C, 72.99; H, 6.92; N, 7.40. Found: C, 72.89; H, 7.05; N, 7.25. ^{1}H-NMR δ: 1.95—2.10 (4H, m, $CH_2(C\underline{H}_2)_2CH_2$), 2.35 (3H, s, C_7-CH_3), 3.16 (3H, s, C_5-OCH_3), 3.55—3.70 (4H, m, CH_2NCH_2), 3.77 (3H, s, C_6-OCH_3), 4.11 (3H, s, C_8-OCH_3), 6.44 (1H, s, C_3-H), 7.30—7.45 (5H, m, C_6H_5).

16c: Yield 99%. mp 154—156 °C (ether). MS *m/z* (%): 394 (M^+, 100), 379 (63). *Anal.* Calcd for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10. Found: C, 70.03; H, 6.76; N, 6.91. ^{1}H-NMR δ: 2.36 (3H, s, C_7-CH_3), 3.17 (3H, s, C_5-OCH_3), 3.70 (4H, t, J=5.0 Hz, CH_2NCH_2), 3.79 (3H, s, C_6-OCH_3), 3.85 (4H, t, J=5.0 Hz, CH_2OCH_2), 4.06 (3H, s, C_8-OCH_3), 6.67 (1H, s, C_3-H), 7.3—7.5 (5H, m, C_6H_5).

16d: Yield 96%. oil. MS *m/z* (%): 407 (M^+, 9), 337 (100), 324 (25), 307 (18). High-resolution MS Calcd for $C_{24}H_{29}N_3O_3$: 407.2209. Found: 407.2209. ^{1}H-NMR δ: 2.35 (6H, s, C_7-CH_3, NCH_3), 2.55 (4H, t, J=5.0 Hz, $C\underline{H}_2$–N(CH_3)–$C\underline{H}_2$), 3.17 (3H, s, C_5-OCH_3), 3.76 (4H, t, J=5.0 Hz, CH_2NCH_2), 3.78 (3H, s, C_6-OCH_3), 4.07 (3H, s, C_8-OCH_3), 6.69 (1H, s, C_3-H), 7.30—7.45 (5H, m, C_6H_5).

(4-Phenyl-)2(1*H*)-quinolinethiones (20a, b) Lawesson's reagent (809 mg, 2 mmol) was added to a solution of 2(1*H*)-quinolinone (**19a**, **b**) (2 mmol) in 1,2-dimethoxyethane (40 ml). The resulting solution was refluxed for 1 h, and then evaporated. The residue was chromatographed (eluting with CH_2Cl_2) to afford **20a**, **b**.

20a: Yield 96%. mp 212—214 °C (ethyl acetate). MS *m/z* (%): 221 (M^+, 100), 206 (88), 191 (43). *Anal.* Calcd for $C_{11}H_{11}NO_2S$: C, 59.71; H, 5.01; N, 6.33. Found: C, 59.45; H, 5.11; N, 6.04. ^{1}H-NMR δ: 3.91, 3.95 (each 3H, s, $2OCH_3$), 6.59 (1H, d, J=8.6 Hz, C_6-H), 6.91 (1H, d, J=8.6 Hz, C_7-H), 7.43 (1H, dd, J=9.2, 1.3 Hz, C_3-H), 7.96 (1H, d, J=9.2 Hz, C_4-H), 10.85 (1H, br, NH).

20b: Yield 94%. mp 217—221 °C (decomp.) (CH_2Cl_2–hexane). MS *m/z* (%): 297 (M^+, 100), 282 (83), 267 (16). *Anal.* Calcd for $C_{17}H_{15}NO_2S$: C, 68.66; H, 5.08; N, 4.71. Found: C, 68.53; H, 4.94; N, 4.72. ^{1}H-NMR δ: 3.41 (3H, s, C_5-OCH_3), 3.99 (3H, s, C_8-OCH_3), 6.58 (1H, d, J=8.6 Hz, C_6-H), 6.97 (1H, d, J=8.6 Hz, C_7-H), 7.20—7.45 (6H, m, C_3-H, C_6H_5), 11.04 (1H, br, NH).

4-Methyl-2(1*H*)-quinolinethiones (20c, d) Lawesson's reagent (2.0 g, 5 mmol) was added to a solution of 2(1*H*)-quinolinone (**19c**, **d**) (4 mmol) in 1,2-dimethoxyethane (50 ml). The resulting solution was stirred at 25 °C for 3 h, and evaporated. The residue was chromatographed (eluting with CH_2Cl_2–ethyl acetate (3 : 2) or CH_2Cl_2) to afford **20c**, **d**.

20c: Yield 99%. mp 201 °C (ethyl acetate). MS *m/z* (%): 235 (M^+, 94), 220 (100), 205 (37). *Anal.* Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95. Found: C, 61.29; H, 5.57; N, 5.91. ^{1}H-NMR δ: 2.64 (3H, s, C_4-CH_3), 3.86, 3.95 (each 3H, s, $2OCH_3$), 6.61 (1H, d, J=8.9 Hz, C_6-H), 6.92 (1H, d, J=8.9 Hz, C_7-H), 7.27 (1H, s, C_3-H), 10.82 (1H, br, NH).

20d: Yield 96%. mp 213—216 °C (CH_2Cl_2–ether). MS *m/z* (%): 265 (M^+, 90), 250 (100). *Anal.* Calcd for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28. Found: C, 58.66; H, 5.62; N, 5.28. ^{1}H-NMR δ: 2.66 (3H, s, C_4-CH_3), 3.84, 3.96, 4.00 (each 3H, s, $3OCH_3$), 6.79 (1H, s, C_7-H), 7.28 (1H, s, C_3-H), 10.72 (1H, br, NH).

1,4-Dimethyl-2(1*H*)-quinolinethiones (23) Lawesson's reagent (1.0 g, 2.5 mmol) was added to a solution of 2(1*H*)-quinolinone (**22**) (2 mmol) in 1,2-dimethoxyethane (50 ml). The resulting solution was refluxed for 3 h, and then evaporated. The residue was chromatographed (eluting with CH_2Cl_2 or ethyl acetate–hexane (1 : 2)) to afford **23**.

23a: Yield 91%. mp 136—139 °C (ethyl acetate). MS *m/z* (%): 249 (M^+, 100), 234 (94), 219 (39). *Anal.* Calcd for $C_{13}H_{15}NO_2S$: C, 62.62; H, 6.06; N, 5.62. Found: C, 62.69; H, 6.05; N, 5.61. ^{1}H-NMR δ: 2.58 (3H, s, C_4-CH_3), 3.85, 3.87 (each 3H, s, $2OCH_3$), 4.25 (3H, s, NCH_3), 6.73 (1H, d, J=8.9 Hz, C_6-H), 7.06 (1H, d, J=8.9 Hz, C_7-H), 7.47 (1H, s, C_3-H).

23b: Yield 91%. mp 164—166 °C (ethyl acetate). MS *m/z* (%): 279 (M^+, 100), 264 (65), 249 (19), 234 (22). *Anal.* Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01. Found: C, 60.01; H, 6.11; N, 4.97. ^{1}H-NMR δ: 2.60 (3H, d, J=0.7 Hz, C_4-CH_3), 3.83, 3.91, 3.96 (each 3H, s, $3OCH_3$), 4.24 (3H, s, NCH_3), 6.85 (1H, s, C_7-H), 7.45 (1H, q, J=0.7 Hz, C_3-H).

Oxidative Demethylation of 5,8-Dimethoxy- and 5,6,8-Trimethoxy-4-phenylquinolines (5, 6, 10, 11, 15, 16) Method A: A solution of CAN (1370 mg, 2.5 mmol) in acetonitrile–water (1 : 1, 5 ml) was added dropwise to 4-phenylquinoline (**5**, **11**) (0.5 mmol) dissolved in acetonitrile–water (4 : 1, 20 ml) containing pyridine-2,6-dicarboxylic acid *N*-oxide[6] (458 mg, 2.5 mmol) at 0—5 °C. The mixture was stirred at 0—5 °C for 30 min, diluted with water (60 ml), and extracted with CH_2Cl_2 (4 × 40 ml). The extract was washed with brine, dried and evaporated. The residue was chromatographed (eluting with ethyl acetate–hexane (1 : 9—3 : 7)) to afford *p*-quinone (**7**, **13**) and/or *o*-quinone (**14**).

Method B: A solution of CAN (4.11 g, 7.5 mmol) in acetonitrile–water (1 : 1, 20 ml) was added dropwise to 4-phenylquinoline (**6**) (157 mg, 0.5 mmol) dissolved in acetonitrile–water (4 : 1, 40 ml) containing pyridine-2,6-dicarboxylic acid *N*-oxide (1373 mg, 7.5 mmol) at 0—5 °C. The mixture was stirred at 0—5 °C for 30 min, diluted with water (100 ml), and extracted with CH_2Cl_2 (4 × 40 ml). The extract was washed with brine, dried and evaporated. The residue was chromatographed. Elution with ethyl acetate–hexane (3 : 7) afforded the less polar *o*-quinone (**9**, 34 mg, 24%), and further elution with ethyl acetate–hexane (1 : 1) afforded the more polar *p*-quinone (**8**, 46 mg, 33%).

Method C: A solution of CAN (685 mg, 1.25 mmol) in acetonitrile–water (1 : 1, 5 ml) was added dropwise to 2-chloro-, 2-(1-piperidinyl)-, 2-(1-pyrrolidinyl)-, or 2-morpholinoquinoline (**10**, **15a—c**, **16a—c**) (0.5 mmol) dissolved in acetonitrile–water (4 : 1, 10 ml) containing pyridine-2,6-dicarboxylic acid *N*-oxide (229 mg, 1.25 mmol) at 0—5 °C. The mixture was stirred at 0—5 °C for 15—30 min, diluted with water

(60 ml), and extracted with CH_2Cl_2 (4 × 40 ml). The extract was washed with brine, dried and evaporated. The residue was chromatographed (eluting with ethyl acetate–hexane (1 : 4—1 : 1)) to afford the corresponding *p*-quinone (**12**, **17a—c**, **18a—c**).

Method D: A solution of CAN (685 mg, 1.25 mmol) in acetonitrile–water (1 : 1, 5 ml) was added dropwise to 2-(4-methyl-1-piperazinyl)-quinoline (**15d**, **16d**) (0.5 mmol) dissolved in acetonitrile–water (4 : 1, 10 ml) containing pyridine-2,6-dicarboxylic acid *N*-oxide (229 mg, 1.25 mmol) at 0—5 °C. The mixture was stirred at 0—5 °C for 15—30 min, diluted with water (60 ml), neutralized with $NaHCO_3$ and extracted with CH_2Cl_2 (4 × 40 ml). The extract was washed with brine, dried and evaporated. The residue was chromatographed (eluting with ethyl acetate–methanol (9 : 1—7 : 3)) to afford the corresponding *p*-quinone (**17d**, **18d**).

Oxidative Demethylation of 2(1*H*)-Quinolinethiones (20, 23) Method A: A solution of CAN (822 mg, 1.5 mmol) in water (6 ml) was added dropwise to a 2(1*H*)-quinolinethione (**20**, **23a**) (0.5 mmol) dissolved in acetonitrile (30 ml) at 0—5 °C. The mixture was stirred at 0—5 °C for 30 min, diluted with water (100 ml), and extracted with CH_2Cl_2 (3 × 100 ml). The extract was washed with brine, dried and evaporated. The residue was chromatographed (eluting with CH_2Cl_2–methanol (99 : 1, **21a**), ethyl acetate–hexane (3 : 7—1 : 1, **21b**), $CHCl_3$–acetone (49 : 1, **21c**), CH_2Cl_2–ethyl acetate (17 : 3, **21d**), and $CHCl_3$–acetone (99 : 1, **24a**)) to afford the corresponding *p*-quinone (**21**, **24a**).

Method B: Nitric acid (6 N, 7.5 ml) and AgO (248 mg, 2 mmol) were added to a solution of **23b** (56 mg, 0.2 mmol) in 1,4-dioxane (15 ml). The mixture was stirred at 25 °C for 1 h, diluted with water (100 ml), and extracted with CH_2Cl_2 (3 × 100 ml). The extract was washed with brine, dried and evaporated. The residue was chromatographed (eluting with $CHCl_3$–acetone (99 : 1)) to afford **24b** (24 mg, 49%).

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