SYNTHESIS OF 4-HYDROXY- AND 4-ALKOXYQUINOLINEQUINONES USING OXIDATIVE DEMETHYLATION WITH CERIUM(IV) AMMONIUM NITRATE

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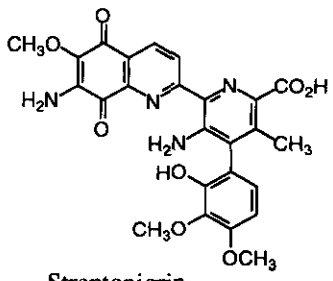
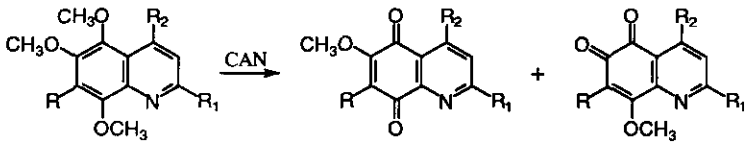
Abstract —— 4-Hydroxy-5,8-quinolinediones (**11**), 4-hydroxy-5,6-quinolinedione (**12**), 4-alkoxy-5,8-quinolinediones (**14, 15**), 4-alkoxy-5,6-quinolinediones (**16a, 17a**), and 4-alkoxy-7,8-quinolinediones (**16b, 17b**) were synthesized by oxidative demethylation of the corresponding 4(1*H*)-quinolinones (**6**) and 4-alkoxyquinolines (**9, 10**) with cerium (IV) ammonium nitrate.

Streptonigrin (STN), 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 in STN is the minimum entity to show the inhibition of AMV-RT.[1] We observed that 6-methoxy-5,8-quinolinediones (**2**) and 8-methoxy-5,6-quinolinediones (**3**), prepared by the oxidative demethylation of 5,6,8-trimethoxyquinolines (**1**) with cerium (IV) ammonium nitrate (CAN),[2] were as potent as inhibitors of AMV-RT as STN, and much less toxic.[3] We also prepared various 2(1*H*)-quinolinonequinones, quinolinequinones and isoquinolinequinones, and examined the inhibitory activities.[3b, 4] Now we report the synthesis of 4-hydroxy- and 4-alkoxyquinolinequinones by the oxidative demethylation of 4(1*H*)-quinolinones and 4-alkoxyquinolines with CAN.

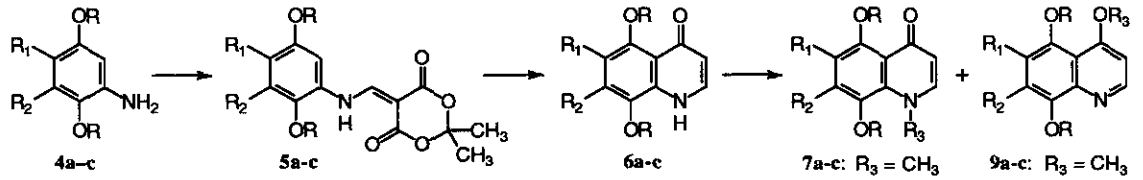


Streptonigrin



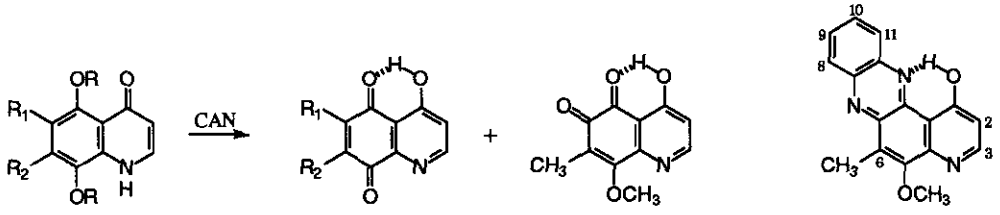
1 **2** **3**

5,6,8-Trimethoxy-7-methyl- (**6a**) and 5,7,8-trimethoxy-4(1*H*)-quinolinone (**6b**) were prepared from anilines (**4a, b**),[4a, 5] 2,2-dimethyl-1,3-dioxane-4,6-dione, and methyl orthoformate according to the Cassis' method.[6]

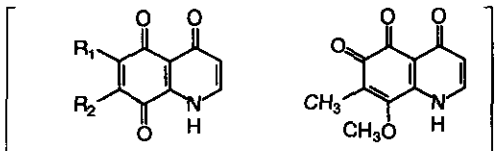


4a–c **5a-c** **6a-c** **7a-c**: $R_3 = CH_3$ **9a-c**: $R_3 = CH_3$
8a-c: $R_3 = C_2H_5$ **10a-c**: $R_3 = C_2H_5$

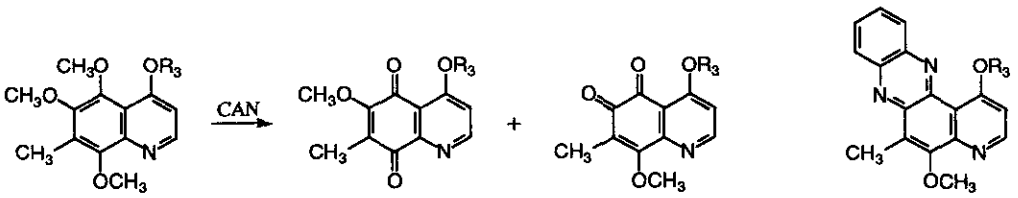
4-10 a: $R = CH_3$, $R_1 = OCH_3$, $R_2 = CH_3$
b: $R = CH_3$, $R_1 = H$, $R_2 = OCH_3$
c: $R = C_2H_5$, $R_1 = H$, $R_2 = OCH_3$



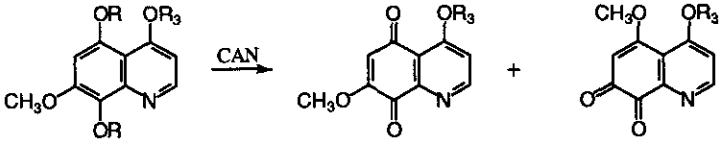
6a-c **11a**: $R_1 = OCH_3$, $R_2 = CH_3$ **12** **13**
11b: $R_1 = H$, $R_2 = OCH_3$



11a': $R_1 = OCH_3$, $R_2 = CH_3$ **12'**
11b': $R_1 = H$, $R_2 = OCH_3$



9a: $R_3 = CH_3$ **14a**: $R_3 = CH_3$ **16a**: $R_3 = CH_3$ **18**: $R_3 = CH_3$
10a: $R_3 = C_2H_5$ **15a**: $R_3 = C_2H_5$ **17a**: $R_3 = C_2H_5$ **19**: $R_3 = C_2H_5$



9b, c: $R_3 = CH_3$ **14b**: $R_3 = CH_3$ **16b**: $R_3 = CH_3$
10b, c: $R_3 = C_2H_5$ **15b**: $R_3 = C_2H_5$ **17b**: $R_3 = C_2H_5$

TABLE I. Analytical and Spectral Data for Quinolinequinones (**11, 12, 14–17**)

	Yield[a] (%)	Appearance (Recrystn. solv.)	mp (°C)	Formula	Analysis or Hrms[b] 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)
11a	39	Yellow powder ($CHCl_3$-hexane)	164-166	$C_{11}H_9NO_4$	219.0531 (219.0524)			219 (M^+, 87) 204 (100) 176 (28)	1672 1630	2.16 (3H, s, C_7-CH_3) 4.14 (3H, s, OCH_3) 7.08 (1H, d, *J* = 5.9, C_3-H) 8.65 (1H, d, *J* = 5.9, C_2-H)
11b	46 [21]	Yellow powder ($CHCl_3$)	196-198	$C_{10}H_7NO_4$	58.54 (58.79	3.44 3.69	6.83 6.70)	205 (M^+, 100) 176 (14) 119 (30)	1698 1632	3.97 (3H, s, OCH_3) 6.17 (1H, s, C_6-H) 7.14 (1H, d, *J* = 5.6, C_3-H) 8.71 (1H, d, *J* = 5.6, C_2-H) 12.24 (1H, s, OH)
12	17	Yellow needles ($CHCl_3$-hexane)	185	$C_{11}H_9NO_4$	60.28 (59.95	4.14 4.19	6.39 6.44)	219 (M^+, 34) 190 (70) 176 (48) 162 (100) 134 (50)	1668 1628	2.08 (3H, s, C_7-CH_3) 4.20 (3H, s, OCH_3) 6.94 (1H, d, *J* = 5.9, C_3-H) 8.58 (1H, d, *J* = 5.9, C_2-H) 11.74 (1H, s, OH)
14a	39	Yellow needles (ether-CH_2Cl_2)	192-196 (dec.)	$C_{12}H_{11}NO_4 \cdot 1/10\ H_2O$	61.33 (61.30	4.80 4.80	5.96 5.80)	233 (M^+, 100) 218 (67) 190 (33)	1666 1632	2.11 (3H, s, C_7-CH_3) 4.07 (3H, s, C_4-OCH_3) 4.12 (3H, s, C_6-OCH_3) 7.11 (1H, d, *J* = 5.6, C_3-H) 8.80 (1H, d, *J* = 5.6, C_2-H)
14b	36 [28]	Yellow needles (CH_2Cl_2-ether)	250-255 (dec.)	$C_{11}H_9NO_4$	60.28 (59.94	4.14 4.18	6.39 6.23)	219 (M^+, 100) 190 (16)	1698 1652	3.91 (3H, s, C_7-OCH_3) 4.07 (3H, s, C_4-OCH_3) 6.14 (1H, s, C_6-H) 7.17 (1H, d, *J* = 5.6, C_3-H) 8.82 (1H, d, *J* = 5.6, C_2-H)
15a	33	Yellow needles (CH_2Cl_2)	157-159	$C_{13}H_{13}NO_4$	63.15 (62.85	5.30 5.33	5.67 5.68)	247 (M^+, 77) 229 (30) 218 (100) 204 (57) 188 (39)	1668 1630	1.58 (3H, t, *J* = 6.9, CH_2CH_3) 2.10 (3H, s, C_7-CH_3) 4.12 (3H, s, OCH_3) 4.29 (2H, q, *J* = 6.9, CH_2CH_3) 7.08 (1H, d, *J* = 5.9, C_3-H) 8.75 (1H, d, *J* = 5.9, C_2-H)
15b	58 [46]	Yellow needles (CH_2Cl_2-ether)	260-265 (dec.)	$C_{12}H_{11}NO_4$	61.80 (61.43	4.75 4.75	6.01 5.94)	233 (M^+, 100) 218 (90) 190 (27) 188 (34) 160 (29) 159 (38)	1694 1656 1642	1.59 (3H, t, *J* = 6.9, CH_2CH_3) 3.90 (3H, s, OCH_3) 4.29 (2H, q, *J* = 6.9, CH_2CH_3) 6.10 (1H, s, C_6-H) 7.13 (1H, d, *J* = 5.9, C_3-H) 8.78 (1H, d, *J* = 5.9, C_2-H)
16a	43	Orange needles ($CHCl_3$)	116-118	$C_{12}H_{11}NO_4$	61.80 (61.44	4.75 4 83	6.01 5.94)	233 (M^+, 3) 205 (70) 204 (70) 190 (36) 188 (23) 176 (100)	1690 1660 1650	2.07 (3H, s, C_7-CH_3) 4.04 (3H, s, C_4-OCH_3) 4.12 (3H, s, C_8-OCH_3) 6.96 (1H, d, *J* = 5.9, C_3-H) 8.68 (1H, d, *J* = 5.9, C_2-H)
16b	2	Orange needles (CH_2Cl_2-ether)	225-230 (dec.)	$C_{11}H_9NO_4$	219.0531 (219.0537)			221 (M^++2, 9) 219 (M^+, 4) 191 (100) 190 (31) 133 (44)	1716 1656	3.99 (3H, s, OCH_3) 4.00 (3H, s, OCH_3) 5.99 (1H, s, C_6-H) 7.11 (1H, d, *J* = 5.9, C_3-H) 8.70 (1H, d, *J* = 5.9, C_2-H)
17a	46	Yellow powder (CH_2Cl_2)	185-187	$C_{13}H_{13}NO_4$	63.15 (62.92	5.30 5.30	5.67 5.62)	247 (M^+, 6) 219 (73) 204 (54) 191 (100) 190 (98) 175 (67) 162 (66)	1692 1650	1.54 (3H, t, *J* = 6.9, CH_2CH_3) 2.06 (3H, s, C_7-CH_3) 4.12 (3H, s, OCH_3) 4.27 (2H, q, *J* = 6.9, CH_2CH_3) 6.93 (1H, d, *J* = 5.9, C_3-H) 8.64 (1H, d, *J* = 5.9, C_2-H)
17b	2	Orange needles (CH_2Cl_2-ether)	217-220 (dec.)	$C_{12}H_{11}NO_4$	233.0688 (233.0684)			235 (M^++2, 20) 233 (M^+, 2) 205 (100) 192 (19) 132 (24) 119 (30)	1716 1646	1.53 (3H, t, *J* = 6.9, CH_2CH_3) 3.99 (3H, s, OCH_3) 4.21 (2H, q, *J* = 6.9, CH_2CH_3) 5.98 (1H, s, C_6-H) 7.07 (1H, d, *J* = 5.9, C_3-H) 8.66 (1H, d, *J* = 5.9, C_2-H)

a) Yields from 5,8-diethoxyquinolines (**6c, 9c, 10c**) are given in blackets. *b*) High-resolution ms.

Treatment of the quinolinones (**6a, b**) with sodium hydride followed by methyl (or ethyl) iodide in *N,N*-dimethylformamide gave the corresponding *N*-alkyl-4(1*H*)-quinolinones (**7a, b, 8a, b**) and 4-alkoxyquinolines (**9a, b, 10a, b**). Oxidative demethylation of **6a** with CAN in acetonitrile–water containing pyridine-2,6-dicarboxylic acid *N*-oxide[7] at 0–5°C afforded *p*-quinone (**11a**, 39%) and *o*-quinone (**12**, 17%). In contrast, **6b** was oxidized with CAN to furnish exclusively *p*-quinone (**11b**) in 46% yield. We confirmed that these quinones are 4-hydroxyquinolinequinones (**11a, b, 12**), but not 4(1*H*)-quinolinonequinones (**11a', b', 12'**), by ^{1}H-nmr ($J_{2,3\text{-H}}$ = 5–6 Hz) and ^{13}C-nmr ($\delta_{C\text{-}4}$ = 166–167 ppm). 4-Alkoxyquinolines (**9a, b, 10a, b**) were smoothly oxidized with CAN to furnish the corresponding *p*-quinones (**14a, b, 15a, b**, 33–58% yields) and *o*-quinones (**16a, b, 17a, b**, 2–46% yields), whereas attempted oxidative demethylation of *N*-alkyl-4(1*H*)-quinolinones (**7a, b, 8a, b**) failed, giving complex mixtures. The *o*-quinone structures for **12, 16a,** and **17a** were confirmed by way of the *o*-phenylenediamine condensation products, *i.e.* pyridophenazines (**13, 18, 19**). Analytical and spectral data for the quinones (**11, 12, 14–17**) are given in Tables I and II.

The *p*-quinone structure for **11b**, **14b**, and **15b** was confirmed by the following independent synthesis. 5,8-Diethoxy-7-methoxy-4(1*H*)-quinolinone (**6c**), 5,8-diethoxy-4,7-dimethoxyquinoline (**9c**), and 4,5,8-triethoxy-7-methoxyquinoline (**10c**) were prepared from **4c**[4a] by the same method used for the corresponding 5,8-dimethoxyquinolines (**6b, 9b, 10b**). The 4(1*H*)-quinolinone (**6c**) and quinolines (**9c, 10c**) were oxidized with CAN to furnish exclusively the corresponding 5,8-quinolinediones, which were identical to the quinones (**11b, 14b, 15b**) from **6b**, **9b**, and **10b**, respectively.

TABLE II. ^{13}C-Nmr Chemical Shift Data for Quinolinequinones (**11, 14–17**) in $CDCl_3$.

	C_2	C_3	C_4	C_{4a}	C_5	C_6	C_7	C_8	C_{8a}	C_7-CH_3	OCH_3	C_4-OCH_3	OCH_2	CH_2CH_3
11a[a]	154.68	116 93	167.01	113.87	186.56	156.60	133.82	183.22	148.68	9.62	61.40			
11b[a]	155.07	117.55	166.56	114.09	190.71	108.64	161.22	177.70	147.73		57.02			
14a[b]	154 93	111.07	165.68	117.43	179.96	158.22	129.72	184.11	149.81	9.15	61.22	56.85		
14b	154.82	111.57[c]	165.55	117.95	183.66	111.30[c]	158.74	178.49	149.16		56.46[d]	56.84[d]		
15a[a]	154.80	111.34	164.83	117.45	179.71	158.07	129.67	184.26	150.10	9.18	61.15		65.61	14.30
15b[b]	154.09	112.38	164.82	117.59	183.50	111.03	158.44	178.29	148.64		56.21		65.61	13.80
16a	154.97	108.82	166 61	115.65	177.55	180.97	127.24	164.58	153.67	9.15	61.80	56.68		
17a[a]	154.65	109.36	165.91	115.69	177.52	181.13	127.10	164.56	153.62	9.11	61.76		65.52	14.23

a) Assignments were aided by direct and long-range C-H correlations. *b*) In $CDCl_3$-CD_3OD. *c, d*) Assignments may be interchanged.

EXPERIMENTAL

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. ^{1}H- and ^{13}C-nmr spectra were measured at 270 and 67.5 MHz, respectively, in $CDCl_3$ (unless otherwise noted) 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).

5-[Phenylaminomethylidene]-2,2-dimethyl-1,3-dioxane-4,6-diones (5a–c) A solution of 2,2-dimethyl-1,3-dioxane-4,6-dione (2.88 g, 20 mmol) in methyl orthoformate (20 ml) was refluxed for 2 h, and aniline (**4a–c**) (20 mmol) was added. The mixture was refluxed for another 4 h, and evaporated. The residue was chromatographed (eluting with ethyl acetate-hexane 3:7–2:1) to afford **5a–c**.

5a: Yield 89%. mp 119–121°C (ethyl acetate). Ms *m/z* (%): 351 (M^+, 18), 293 (9), 219 (16), 218 (100). *Anal.* Calcd for $C_{17}H_{21}NO_7$: C, 58.11; H, 6.02; N, 3.99. Found: C, 57.96; H, 5.99; N, 3.96. Ir (KBr): 1720, 1670, 1632, 1598, 1456, 1420, 1284, 1272, 1236, 1218, 1090 cm^{-1}. ^{1}H-Nmr δ: 1.76 (6H, s, $C(CH_3)_2$), 2.25 (3H, s, Ar-CH_3), 3.80, 3.81, 3.89 (each 3H, s, $3OCH_3$), 6.70 (1H, s, Ar-H), 8.61 (1H, d, J = 14.8 Hz, CH=C), 11.70 (1H, d, J = 14.8 Hz, NH).

5b: Yield 66%. mp 166–168°C (ethyl acetate). Ms *m/z* (%): 337 (M^+, 25), 279 (9), 205 (15), 204 (100). *Anal.* Calcd for $C_{16}H_{19}NO_7$: C, 56.97; H, 5.68; N, 4.15. Found: C, 57.09; H, 5.64; N, 4.13. Ir (KBr): 1718, 1678, 1628, 1596, 1504, 1462, 1440, 1422, 1274, 1218, 1208 cm^{-1}. ^{1}H-Nmr δ: 1.76 (6H, s, $C(CH_3)_2$), 3.82, 3.87, 3.90 (each 3H, s, $3OCH_3$), 6.36, 6.42 (each 1H, d, J = 2.6 Hz, 2Ar-H), 8.63 (1H, d, J = 14.5 Hz, CH=C), 11.69 (1H, d, J = 14.5 Hz, NH).

5c: Yield 87%. mp 128–130°C (CH_2Cl_2–hexane). Ms *m/z* (%): 365 (M^+, 21), 218 (100). *Anal.* Calcd for $C_{18}H_{23}NO_7$: C, 59.17; H, 6.35; N, 3.83. Found: C, 59.13; H, 6.29; N, 3.81. Ir (KBr): 1728, 1684, 1632, 1598, 1504, 1452, 1432, 1396, 1272, 1202, 1160 cm^{-1}. ^{1}H-Nmr δ: 1.43, 1.45 (each 3H, t, J = 6.9 Hz, $2CH_2CH_3$), 1.75 (6H, s, $C(CH_3)_2$), 3.85 (3H, s, OCH_3), 4.02, 4.09 (each 2H, t, J = 6.9 Hz, $2CH_2CH_3$), 6.36, 6.42 (each 1H, d, J = 2.3 Hz, 2Ar-H), 8.61 (1H, d, J = 14.5 Hz, CH=C), 11.73 (1H, d, J = 14.8 Hz, NH).

5,6,8-Trimethoxy-7-methyl-4(1*H*)-quinolinone (6a) A mixture of **5a** (351 mg, 1 mmol) and diphenyl ether (5 ml) was refluxed for 30 min. The reaction mixture was cooled, and chromatographed. Elution with ethyl acetate was discarded, and further elution with ethyl acetate–methanol (10:1) afforded **6a** (180 mg, 72%).

mp 157–158°C (CH_2Cl_2–ether). Ms *m/z* (%): 249 (M^+, 31), 234 (100). *Anal.* Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.44; H, 6.08; N, 5.48. Ir (KBr): 3164, 3116, 1614, 1582, 1570, 1518, 1372, 1130, 1096, 1074, 808 cm^{-1}. ^{1}H-Nmr δ: 2.35 (3H, s, C_7-CH_3), 3.89, 3.92, 3.96 (each 3H, s, $3OCH_3$), 6.30 (1H, d, J = 7.0 Hz, C_3-H), 7.75 (1H, d, J = 7.0 Hz, C_2-H).

5,7,8-Trimethoxy- and 5,8-Diethoxy-7-methoxy-4(1*H*)-quinolinones (6b, c) A mixture of **5b, c** (1 mmol) and diphenyl ether (20 ml) was refluxed for 20 min. The reaction mixture was cooled, and diluted with hexane (40 ml). The precipitated crystals were collected by filtration and chromatographed (eluting with CH_2Cl_2–methanol (100:1–20:1) or ethyl acetate–methanol (10:1)) to afford **6b, c**.

6b: Yield 56%. mp 220–223°C (CH_2Cl_2). Ms *m/z* (%): 235 (M^+, 42), 220 (100), 206 (14). *Anal.* Calcd for $C_{12}H_{13}NO_4 \cdot 1/10\ H_2O$: C, 60.80; H, 5.61; N, 5.91. Found: C, 60.71; H, 5.50; N, 5.89. Ir (KBr): 3252, 1616, 1576, 1528, 1452, 1430, 1360, 1242, 1212, 1122, 1110, 1078, 790 cm^{-1}. ^{1}H-Nmr δ: 3.89, 3.93, 3.99

(each 3H, s, $3OCH_3$), 6.17 (1H, d, J = 7.3 Hz, C_3-H), 6.36 (1H, s, C_6-H), 7.57 (1H, d, J = 7.3 Hz, C_2-H). ^{13}C-Nmr δ: 56.12 (OCH_3), 56.41 (OCH_3), 61.13 (OCH_3), 91.45 (C_6), 111.50, 111.77 (C_3), 129.04, 136.46 (C_2), 136.93, 153.19, 157.00, 178.42 (C_4).

6c: Yield 65%. mp 212–214°C (CH_2Cl_2–hexane). Ms *m/z* (%): 263 (M^+, 33), 248 (100), 234 (42), 220 (29), 206 (60). *Anal.* Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.61; H, 6.47; N, 5.25. Ir (KBr): 3132, 3092, 1620, 1564, 1530, 1458, 1372, 1356, 1238, 1216, 1120, 1074, 1024, 832 cm^{-1}. ^{1}H-Nmr δ: 1.40, 1.54 (each 3H, t, J = 6.9 Hz, $2CH_2CH_3$), 3.95 (3H, s, OCH_3), 4.15, 4.16 (each 2H, q, J = 6.9 Hz, $2CH_2CH_3$), 6.12 (1H, d, J = 7.3 Hz, C_3-H), 6.40 (1H, s, C_6-H), 7.55 (1H, d, J = 7.3 Hz, C_2-H).

Alkylation of 4(1*H*)-Quinolinones (6a–c) Sodium hydride (288 mg, 12 mmol) was added to a solution of **6a–c** (4 mmol) in *N,N*-dimethylformamide (60 ml) with stirring. The whole was left for 60 min, and methyl iodide (or ethyl iodide) (12 mmol) was added dropwise. The mixture was left for 60 min, quenched with water (100 ml), and extracted with CH_2Cl_2 (3 x 100 ml). The extract was washed with water, dried, and evaporated. The residue was chromatographed. Elution with ethyl acetate-methanol (100:1) (or CH_2Cl_2–methanol 97:3) afforded the less polar 4-alkoxyquinoline (**9a–c**, **10a–c**), and further elution with ethyl acetate-methanol (100:3) (or CH_2Cl_2–methanol 47:3) afforded the more polar *N*-alkylquinolinone (**7a–c**, **8a–c**).

7a: Yield 62%. mp 119–121°C (ethyl acetate). Ms *m/z* (%): 263 (M^+, 33), 248 (100). *Anal.* Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.72; H, 6.49; N, 5.28. Ir (KBr): 1620, 1572, 1492, 1448, 1398, 1360, 1166, 1106, 1080, 1010, 832 cm^{-1}. ^{1}H-Nmr δ: 2.34 (3H, s, C_7-CH_3), 3.66, 3.89, 3.92, 3.93 (each 3H, s, $4CH_3$), 6.08 (1H, d, J = 7.6 Hz, C_3-H), 7.25 (1H, d, J = 7.6 Hz, C_2-H). ^{13}C-Nmr δ: 10.24 (C_7-CH_3), 45.17 (NCH_3), 60.95 (OCH_3), 61.51 (OCH_3), 61.67 (OCH_3), 110.92 (C_3), 121.87, 131.16, 133.69, 144.20, 144.80 (C_2), 148.14, 148.66, 177.72 (C_4).

7b: Yield 51%. mp 66–68°C (CH_2Cl_2–ether). Ms *m/z* (%): 249 (M^+, 75), 234 (100), 204 (24), 190 (23). *Anal.* Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.36; H, 6.07; N, 5.54. Ir (KBr): 1636, 1596, 1580, 1450, 1422, 1390, 1364, 1320, 1208, 1198, 1176, 1162, 1078, 1020, 1012, 824 cm^{-1}. ^{1}H-Nmr δ: 3.75, 3.94, 3.96, 3.99 (each 3H, s, NCH_3, $3OCH_3$), 6.07 (1H, d, J = 7.9 Hz, C_3-H), 6.47 (1H, s, C_6-H), 7.17 (1H, d, J = 7.9 Hz, C_2-H). ^{13}C-Nmr δ: 45.68 (NCH_3), 56.14 (OCH_3), 56.66 (OCH_3), 61.83 (OCH_3), 92.49 (C_6), 111.62 (C_3), 113.37, 131.43, 138.18, 144.81 (C_2), 155.70, 157.81, 178.27 (C_4).

7c: Yield 73%. mp 147–150°C (ethyl acetate). Ms *m/z* (%): 277 (M^+, 69), 248 (100), 220 (96), 205 (53), 204 (52). High-resolution ms Calcd for $C_{15}H_{19}NO_4$: 277.1314. Found: 277.1308. Ir (KBr): 1630, 1588, 1426, 1386, 1350, 1322, 1176, 1112, 1078, 1030 cm^{-1}. ^{1}H-Nmr ($CDCl_3$–CD_3OD) δ: 1.39, 1.52 (each 3H, t, J = 6.9 Hz, $2CH_2CH_3$), 3.97, 4.00 (each 3H, s, NCH_3, OCH_3), 3.92, 4.14 (each 2H, q, J = 6.9 Hz, $2CH_2CH_3$), 6.08 (1H, d, J = 7.6 Hz, C_3-H), 6.52 (1H, s, C_6-H), 7.29 (1H, d, J = 7.6 Hz, C_2-H).

8a: Yield 18%. mp 69–73°C (ethyl acetate). Ms *m/z* (%): 277 (M^+, 34), 262 (100). *Anal.* Calcd for $C_{15}H_{19}NO_4 \cdot H_2O$: C, 61.00; H, 7.17; N, 4.74. Found: C, 60.80; H, 7.10; N, 4.69. Ir (KBr): 1620, 1570, 1478, 1448, 1398, 1380, 1262, 1160, 1108, 1082, 1018, 836 cm^{-1}. ^{1}H-Nmr δ: 1.23 (3H, t, J = 6.9 Hz, CH_2CH_3), 2.34 (3H, s, C_7-CH_3), 3.65, 3.90, 3.93 (each 3H, s, $3OCH_3$), 4.34 (2H, q, J = 6.9 Hz, CH_2CH_3), 6.12 (1H, d, J = 7.9 Hz, C_3-H), 7.29 (1H, d, J = 7.9 Hz, C_2-H).

8b: Yield 51%. mp 44–46°C (ethyl acetate–ether). Ms *m/z* (%): 263 (M^+, 74), 248 (100). *Anal.* Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.68; H, 6.47; N, 5.26. Ir (KBr): 1634, 1588, 1442, 1396, 1370, 1326, 1284, 1246, 1210, 1158, 1086, 1012, 824 cm^{-1}. ^{1}H-Nmr δ: 1.32 (3H, t, J = 6.9 Hz,

CH_2CH_3), 3.77, 3.96, 4.00 (each 3H, s, $3OCH_3$), 4.32 (2H, q, J = 6.9 Hz, CH_2CH_3), 6.10 (1H, d, J = 7.9 Hz, C_3-H), 6.48 (1H, s, C_6-H), 7.23 (1H, d, J = 7.9 Hz, C_2-H).

8c: Yield 37%. mp 108–110°C (ethyl acetate). Ms *m/z* (%): 291 (M^+, 64), 262 (100), 234 (31), 219 (50), 206 (50). *Anal.* Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.81; H, 7.29; N, 4.81. Ir (KBr): 1642, 1590, 1432, 1394, 1374, 1322, 1282, 1248, 1176, 1164, 1110, 1086, 1028, 814 cm^{-1}. ^{1}H-Nmr δ: 1.27, 1.38, 1.54 (each 3H, t, J = 6.9 Hz, $3CH_2CH_3$), 3.95 (3H, s, OCH_3), 3.93, 4.13, 4.36 (each 2H, q, J = 6.9 Hz, $3CH_2CH_3$), 6.06 (1H, d, J = 7.9 Hz, C_3-H), 6.50 (1H, s, C_6-H), 7.20 (1H, d, J = 7.9 Hz, C_2-H).

9a: Yield 32%. oil. Ms *m/z* (%): 263 (M^+, 51), 248 (100). High-resolution ms Calcd for $C_{14}H_{17}NO_4$: 263.1157. Found: 263.1157. Ir (KBr): 1592, 1568, 1502, 1462, 1394, 1380, 1368, 1284, 1106, 1074, 1008, 986 cm^{-1}. ^{1}H-Nmr δ: 2.40 (3H, s, C_7-CH_3), 3.88, 3.96, 4.01, 4.05 (each 3H, s, $4OCH_3$), 6.72 (1H, d, J = 5.3 Hz, C_3-H), 8.66 (1H, d, J = 5.3 Hz, C_2-H). ^{13}C-Nmr δ: 9.92 (C_7-CH_3), 55.87 (OCH_3), 60.68 (OCH_3), 61.44 (OCH_3), 61.60 (OCH_3), 100.65 (C_3), 115.60, 127.42, 141.94, 143.59, 149.31 (C_2), 149.74, 150.46, 162.91.

9b: Yield 8%. mp 130–132°C (ether–hexane). Ms *m/z* (%): 249 (M^+, 52), 234 (100). *Anal.* Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.58; H, 6.04; N, 5.58. Ir (KBr): 1594, 1458, 1398, 1320, 1286, 1240, 1208, 1138, 1118, 1080, 1042, 1000, 814 cm^{-1}. ^{1}H-Nmr δ: 3.96 (3H, s, OCH_3), 4.01 (6H, s, $2OCH_3$), 4.03 (3H, s, OCH_3), 6.64 (1H, d, J = 5.3 Hz, C_3-H), 6.67 (1H, s, C_6-H), 8.72 (1H, d, J = 5.3 Hz, C_2-H). ^{13}C-Nmr δ: 55.87 (OCH_3), 56.73 ($2OCH_3$), 61.49 (OCH_3), 96.10 (C_6), 99.39 (C_3), 108.82, 136.93, 146.09, 151.55 (C_2), 151.64, 153.37, 164.22.

9c: Yield 11%. mp 78–80°C (ethyl acetate). Ms *m/z* (%): 277 (M^+, 25), 262 (100), 248 (29), 220 (46). *Anal.* Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.06; H, 7.02; N, 5.04. Ir (KBr): 1592, 1580, 1468, 1410, 1380, 1314, 1280, 1242, 1134, 1072, 1048, 918, 816 cm^{-1}. ^{1}H-Nmr δ: 1.44, 1.52 (each 3H, t, J = 6.9 Hz, $2CH_2CH_3$), 3.98, 3.99 (each 3H, s, $2OCH_3$), 4.12, 4.24 (each 2H, q, J = 6.9 Hz, $2CH_2CH_3$), 6.61 (1H, d, J = 5.3 Hz, C_3-H), 6.70 (1H, s, C_6-H), 8.68 (1H, d, J = 5.3 Hz, C_2-H).

10a: Yield 73%. mp 53–55°C (ethyl acetate). Ms *m/z* (%): 277 (M^+, 95), 262 (98), 234 (100). *Anal.* Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.01; H, 6.96; N, 4.96. Ir (KBr): 1590, 1502, 1448, 1394, 1380, 1366, 1290, 1106, 1068, 1000, 966 cm^{-1}. ^{1}H-Nmr δ: 1.61 (3H, t, J = 6.9 Hz, CH_2CH_3), 2.40 (3H, s, C_7-CH_3), 3.88, 3.95, 4.00 (each 3H, s, $3OCH_3$), 4.24 (2H, q, J = 6.9 Hz, CH_2CH_3), 6.68 (1H, d, J = 5.3 Hz, C_3-H), 8.63 (1H, d, J = 5.3 Hz, C_2-H).

10b: Yield 47%. mp 52–53°C (ether–hexane). Ms *m/z* (%): 263 (M^+, 100), 248 (86), 234 (45), 220 (74). *Anal.* Calcd for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 64.01; H, 6.49; N, 5.28. Ir (KBr): 1608, 1584, 1484, 1388, 1346, 1316, 1284, 1254, 1240, 1210, 1138, 1078, 1050, 1014, 918, 812 cm^{-1}. ^{1}H-Nmr δ: 1.56 (3H, t, J = 6.9 Hz, CH_2CH_3), 3.94, 4.01, 4.03 (each 3H, s, $3OCH_3$), 4.21 (2H, q, J = 6.9 Hz, CH_2CH_3), 6.61 (1H, d, J = 5.3 Hz, C_3-H), 6.67 (1H, s, C_6-H), 8.68 (1H, d, J = 5.3 Hz, C_2-H).

10c: Yield 61%. mp 144–146°C (ethyl acetate). Ms *m/z* (%): 291 (M^+, 28), 276 (100), 262 (21), 206 (37). *Anal.* Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.88; H, 7.27; N, 4.80. Ir (KBr): 1606, 1580, 1474, 1384, 1318, 1290, 1240, 1206, 1142, 1122, 1110, 1076, 1052, 934, 812 cm^{-1}. ^{1}H-Nmr δ: 1.43, 1.53, 1.56 (each 3H, t, J = 6.9 Hz, $3CH_2CH_3$), 3.99 (3H, s, OCH_3), 4.11, 4.19, 4.23 (each 2H, q, J = 6.9 Hz, $3CH_2CH_3$), 6.58 (1H, d, J = 5.3 Hz, C_3-H), 6.65 (1H, s, C_6-H), 8.65 (1H, d, J = 5.3 Hz, C_2-H).

Oxidative Dealkylation of 4(1*H*)-Quinolinones (6a–c) and 4-Alkoxyquinolines (9a–c, 10a–c) A solution of CAN (1370 mg, 2.5 mmol) in acetonitrile–water (1:1, 10 ml) was added dropwise to 4(1*H*)-

quinolinone (**6a–c**) (0.5 mmol) dissolved in acetonitrile–water (7:3, 10 ml) [or 4-alkoxyquinoline (**9a–c**, **10a–c**) (0.5 mmol) in acetonitrile (10 ml)] containing pyridine-2,6-dicarboxylic acid *N*-oxide (458 mg, 2.5 mmol) at 0–5°C. The mixture was kept at 0–5°C for 30 min, diluted with water (40 ml), and extracted with CH_2Cl_2 (4 x 30 ml). The extract was washed with brine, dried and evaporated. The residue was chromatographed (eluting with CH_2Cl_2 or CH_2Cl_2–methanol (100:1–10:1)) to afford the corresponding *p*-quinone (**11a**, **b**, **14a**, **b**, **15a**, **b**) and *o*-quinone (**12**, **16a**, **b**, **17a**, **b**).

***Condensation of o-Quinones* (12, 16a, 17a) *with o*-Phenylenediamine** A mixture of *o*-quinone (**12**, **16a**, **17a**) (0.2 mmol) and *o*-phenylenediamine (22 mg, 0.2 mmol) in ethanol (6 ml) containing acetic acid (0.2 ml) was refluxed for 10 min. The reaction mixture was cooled, diluted with water (30 ml), basified with saturated aqueous $NaHCO_3$ solution, and extracted with CH_2Cl_2 (3 x 20 ml). The extract was washed with water, dried, evaporated, and chromatographed (eluting with CH_2Cl_2 or CH_2Cl_2–methanol (24:1)) to afford the corresponding pyridophenazine (**13**, **18**, **19**).

13: Yield 98%. mp 251–253°C ($CHCl_3$-hexane). Ms *m/z* (%): 291 (M^+, 100), 276 (75), 262 (58). High-resolution ms Calcd for $C_{17}H_{13}N_3O_2$: 291.1008. Found: 291.1007. ^{1}H-Nmr δ: 2.89 (3H, s, C_6-CH_3), 4.21 (3H, s, OCH_3), 7.19 (1H, d, J = 5.6 Hz, C_2-H), 7.9–8.0 (2H, m, C_9-H, C_{10}-H), 8.2–8.4 (2H, m, C_8-H, C_{11}-H), 8.87 (1H, d, J = 5.6 Hz, C_3-H), 14.99 (1H, s, OH).

18: Yield 70%. mp 188–189°C (CH_2Cl_2-hexane). Ms *m/z* (%): 305 (M^+, 100), 290 (59), 276 (39). High-resolution ms Calcd for $C_{18}H_{15}N_3O_2$: 305.1164. Found: 305.1172. ^{1}H-Nmr δ: 2.90 (3H, s, C_6-CH_3), 4.17 (3H, s, C_5-OCH_3), 4.28 (3H, s, C_1-OCH_3), 7.19 (1H, d, J = 5.6 Hz, C_2-H), 7.8–7.9 (2H, m, C_9-H, C_{10}-H), 8.2–8.4 (2H, m, C_8-H, C_{11}-H), 8.95 (1H, d, J = 5.6 Hz, C_3-H).

19: Yield 73%. mp 196–197°C (CH_2Cl_2-hexane). Ms *m/z* (%): 319 (M^+, 100), 304 (32), 290 (44), 276 (47), 262 (27). High-resolution ms Calcd for $C_{19}H_{17}N_3O_2$: 319.1321. Found: 319.1317. ^{1}H-Nmr δ: 1.82 (3H, t, J = 6.9 Hz, CH_2CH_3), 2.89 (3H, s, C_6-CH_3), 4.17 (3H, s, OCH_3), 4.48 (2H, q, J = 6.9 Hz, CH_2CH_3), 7.16 (1H, d, J = 5.6 Hz, C_2-H), 7.8–7.9 (2H, m, C_9-H, C_{10}-H), 8.25–8.35 (2H, m, C_8-H, C_{11}-H), 8.92 (1H, d, J = 5.6 Hz, C_3-H).

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