Synthesis of 5,6-, 5,8- and 7,8-Isoquinolinediones from the Corresponding Isoquinolinols and Dimethoxyisoquinolines

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5,8-Isoquinolinediones (12, 18, 25), 7,8-isoquinolinediones (14, 19) and 5,6-isoquinolinediones (26) were synthesized by oxidative demethylation of the corresponding dimethoxyisoquinolines with cerium(IV) ammonium nitrate or silver(II) oxide. 8-Dialkylamino-5,6-isoquinolinediones (31) and 3,5-bis(dialkylamino)-7,8-isoquinolinediones (33) were prepared by copper(II)-catalyzed oxidation of the corresponding isoquinolinols with secondary amines. 5,8-Isoquinolinediones (29, 34, 40) were also prepared.

Keywords synthesis; 5,8-isoquinolinedione; 5,6-isoquinolinedione; 7,8-isoquinolinedione; oxidation; oxidative demethylation; cerium(IV) ammonium nitrate; silver(II) oxide; potassium nitrosodisulfonate

During the past fifteen years, various isoquinolinequinones have been isolated from Actinomycetes and marine sponges. Arai and co-workers have isolated satellite antibiotics, named mimosamycin (**1**)[1] and mimocin (**2**),[2] from *Streptomyces lavendulae*. Mimosamycin (**1**) showed activity against mycobacteria,[1] and was synthesized by using copper(II)-catalyzed autoxidation of 7-hydroxy-6-methylisoquinoline in the presence of morpholine or piperidine.[3] Mimocin (**2**) exhibited strong activity against *Bacillus* (*B.*) *subtilis* and *Candida* (*C.*) *albicans*.[2] In 1979 Faulkner and co-workers described the isolation and the structural determination of renierone (**3**), the major antibacterial metabolite of a marine sponge *Reniera* sp.[4] It showed strong antimicrobial activity against *Staphylococcus* (*S.*) *aureus*, *B. subtilis* and *C. albicans*. Further studies of *Reniera* sp. led to the isolation of **1**, **4**, and **5** from an ethanol extract possessing antimicrobial activity against *S. aureus*, *B. subtilis* and *C. albicans*.[5] In 1987 McKee and Ireland isolated renierol (**6**) from a hard blue sponge, *Xestospongia caycedoi*, which showed antimicrobial activity against *S. aureus* and mild cytotoxicity against L1210 cell line.[6] Furthermore, recently four new isoquinolinequinone metabolites **7**—**10** possessing activity against *B. subtilis* and *S. aureus* have been isolated from a marine sponge, *Xestospongia* sp. and its associated nudibranch *Jorunna funebris*.[7]

We have already described total synthesis of the above biologically active 5,8-isoquinolinediones (**2**—**10**) by using oxidative demethylation of the corresponding 5,8-dimethoxyisoquinolines with cerium(IV) ammonium nitrate (CAN) and silver(II) oxide (AgO), and oxidation of 8-aminoisoquinolines with potassium nitrosodisulfonate (Fremy's salt).[2,8,9] Furthermore, we have reported that 6-methoxy-5,8-quinolinedione and 6-methoxy-7-methyl-5,8-quinolinedione inhibited avian myeloblastosis virus reverse transcriptase to the same extent as streptonigrin, a highly substituted 5,8-quinolinedione, isolated from *Streptomyces flocculus*.[10] The potent biological activities of 5,8-isoquinolinediones (**1**—**10**) and 5,8-quinolinediones have prompted us to undertake the synthesis of various other isoquinolinequinones.

Oxidative demethylation of 5,8-dimethoxyisoquinoline (**11**)[11] with CAN or AgO in aqueous acetonitrile containing pyridine-2,6-dicarboxylic acid *N*-oxide[12] at 0—5 °C for 1—3 h afforded 5,8-isoquinolinedione (**12**) in 72—88% yield. 7,8-Dimethoxyisoquinoline (**13**)[11] was easily oxidized with CAN under the same conditions for 15 min to give unstable 7,8-isoquinolinedione (**14**) in 55% yield. Treatment of 5,7,8-trimethoxyisoquinoline (**17a**) and 5,8-diethoxy-7-methoxyisoquinoline (**17b**) prepared from **15**[13] with CAN at 0—5 °C for 15 min, gave the corresponding *p*-quinone (**18a**) (20—28% yield) and *o*-quinone (**19a**, **b**) (66—70% yield). 5,7,8-Trimethoxy-6-methylisoquinolines (**17c**—**e**)[8] were also oxidatively demethylated with CAN to give the corresponding *p*-quinones (**18c**—**e**) (8—35% yield) and *o*-quinones (**19c**—**e**) (29—44% yield). In contrast, oxidation of **17a**, **b** with AgO at 0—5 °C for 1 h gave the *p*-quinone **18a** as a main product (40—54% yield).

Next, we prepared 6-methoxy-5,8-isoquinolinediones (**25a**—**f**) and 8-methoxy-5,6-isoquinolinediones (**26a**—**f**).

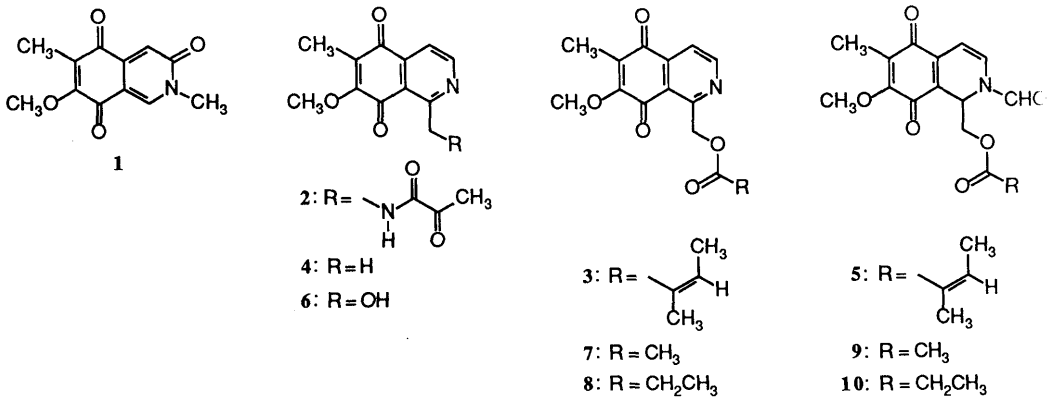

Chart 1

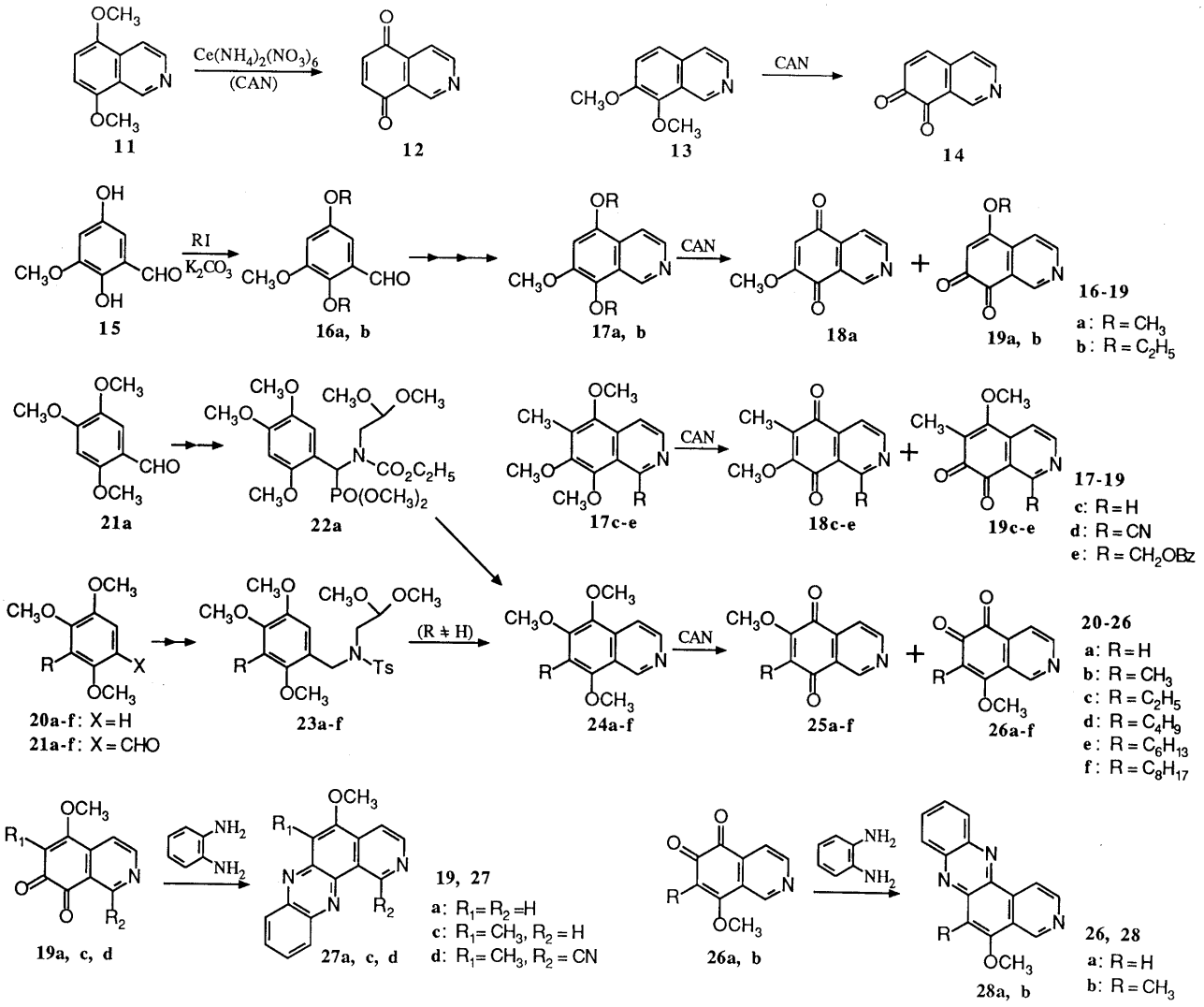

Chart 2

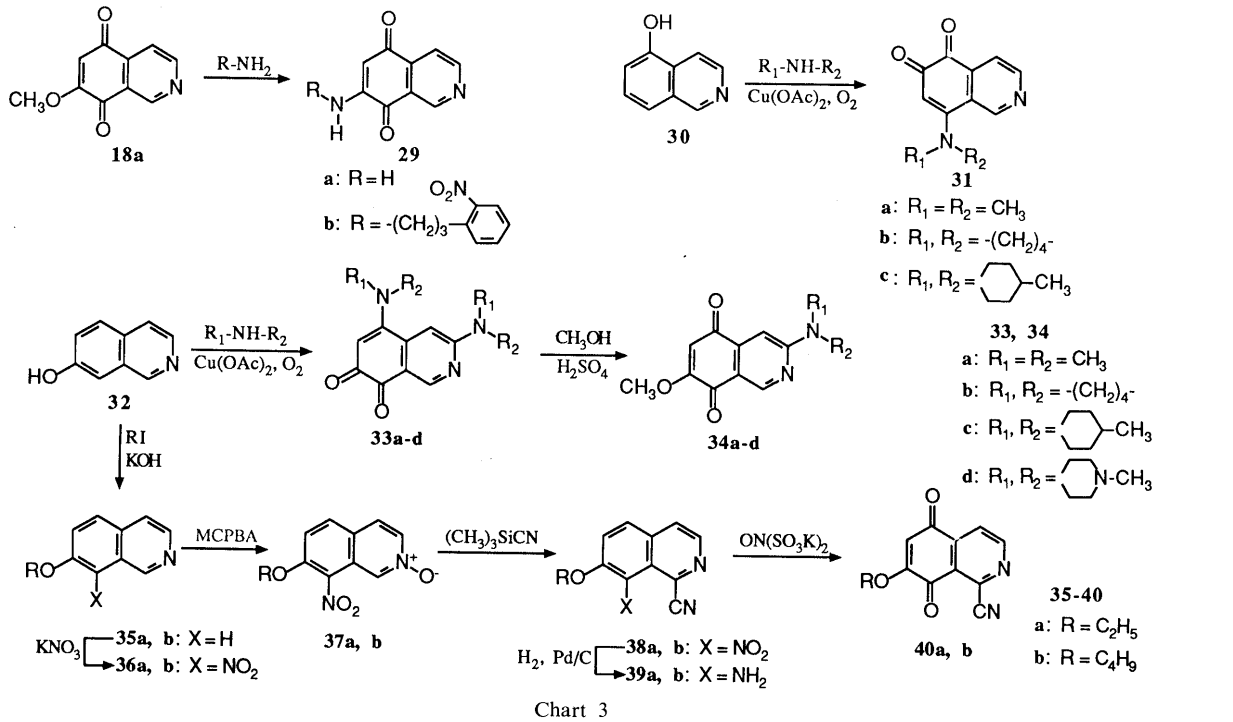

Chart 3

TABLE I. Isoquinolinequinones

	Yield[a] (%)	Appearance (Recrystn. solv.)	mp (°C)	Formula	Analysis or HRMS[b] Calcd (Found) C	H	N	MS m/z	IR (KBr) (cm^{-1})	^{1}H-NMR (400 MHz)[c] δ ($CDCl_3$, J=Hz)
5,8-Isoquinolinediones										
12	88 [72]	Yellow needles (CH_2Cl_2–ether)	136—137 (dec.)[d]	$C_9H_5NO_2$	67.93 (68.09	3.17 2.87	8.80 8.59)	159 (M^+, 100) 105 (26)	1665	7.14 and 7.16 (each 1H, d, J=9, C_6-H, C_7-H), 7.91 (1H, d, J=5, C_4-H), 9.12 (1H, d, J=5, C_3-H), 9.32 (1H, s, C_1-H)
18a	20[e] [40]	Yellow needles (CH_2Cl_2–ether)	219—220[f]	$C_{10}H_7NO_3$	63.49 (63.33	3.73 3.59	7.41 7.30)	189 (M^+, 100) 174 (30) 159 (35)	1680 1649	3.95 (3H, s, OCH_3), 6.28 (1H, s, C_6-H), 7.89 (1H, d, J=5, C_4-H), 9.06 (1H, d, J=5, C_3-H), 9.37 (1H, s, C_1-H)
18c	8	Yellow needles (CH_2Cl_2–ether)	130—131	$C_{11}H_9NO_3$	65.02 (65.08	4.46 4.65	6.89 6.72)	203 (M^+, 100)	1670 1658	2.07 (3H, s, C_6-CH_3), 4.18 (3H, s, OCH_3), 7.82 (1H, d, J=5, C_4-H), 8.96 (1H, d, J=5, C_3-H), 9.24 (1H, s, C_1-H)
18d	35	Yellow needles (CH_2Cl_2–ether)	175—177	$C_{12}H_8N_2O_3$	63.16 (62.87	3.53 3.38	12.28 12.12)	228 (M^+, 100) 198 (40)	2240 1680 1648	2.09 (3H, s, C_6-CH_3), 4.26 (3H, s, OCH_3), 8.11 (1H, d, J=5, C_4-H), 9.05 (1H, d, J=5, C_3-H)
18e	18	Yellow needles (CH_2Cl_2–ether)	138—139	$C_{19}H_{15}NO_5$	67.65 (67.58	4.48 4.46	4.15 4.13)	337 (M^+, 4) 105 (100) 77 (32)	1718 1672	2.03 (3H, s, C_6-CH_3), 4.09 (3H, s, OCH_3), 5.91 (2H, s, CH_2), 7.3—7.7 (3H, m) and 8.10 (2H, dd, J=2, 8) for C_6H_5, 7.83 (1H, d, J=5, C_4-H), 8.87 (1H, d, J=5, C_3-H)
25a	29	Yellow needles (CH_2Cl_2–hexane)	181—182	$C_{10}H_7NO_3$	63.49 (63.36	3.73 3.54	7.40 7.31)	189 (M^+, 100) 159 (48)	1690 1648	3.94 (3H, s, OCH_3), 6.23 (1H, s, C_7-H), 7.92 (1H, dd, J=5, 0.7, C_4-H), 9.07 (1H, d, J=5, C_3-H), 9.37 (1H, d, J=0.7, C_1-H)
25b	27 [52]	Yellow needles (Ether–hexane)	110—111	$C_{11}H_9NO_3$	65.02 (65.12	4.46 4.39	6.89 6.74)	203 (M^+, 100)	1673 1653	2.12 (3H, s, C_7-CH_3), 4.16 (3H, s, OCH_3), 7.84 (1H, d, J=5, C_4-H), 9.03 (1H, d, J=5, C_3-H), 9.33 (1H, s, C_1-H)
25c	32 [48]	Yellow needles (Hexane)	57—58	$C_{12}H_{11}NO_3$	66.35 (66.38	5.10 5.02	6.45 6.30)	217 (M^+, 100) 202 (68)	1676 1654	1.13 (3H, t, J=7, $CH_2C\underline{H}_3$), 2.64 (2H, q, J=7, $C\underline{H}_2CH_3$), 4.16 (3H, s, OCH_3), 7.84 (1H, dd, J=5, 0.6, C_4-H), 9.02 (1H, d, J=5, C_3-H), 9.33 (1H, d, J=0.6, C_1-H)
25d	20 [58]	Yellow needles (Hexane)	37—38	$C_{14}H_{15}NO_3$	68.56 (68.52	6.16 6.18	5.71 5.54)	245 (M^+, 95) 230 (26) 203 (100) 188 (44)	1674 1650	0.94 (3H, t, J=7, $CH_2C\underline{H}_3$), 1.35—1.55 (4H, m, $(C\underline{H}_2)_2CH_3$), 2.61 (2H, t, J=8, $C\underline{H}_2$-$(CH_2)_2CH_3$), 4.15 (3H, s, OCH_3), 7.84 (1H, dd, J=5, 0.6, C_4-H), 9.02 (1H, d, J=5, C_3-H), 9.32 (1H, d, J=0.6, C_1-H)
25e	8 [42]	Yellow needles (Hexane)	52—55	$C_{16}H_{19}NO_3$	70.31 (70.25	7.01 7.09	5.12 4.99)	273 (M^+, 100) 204 (48) 203 (89)	1674 1650	0.89 (3H, t, J=7, $CH_2C\underline{H}_3$), 1.2—1.55 (8H, m, $(C\underline{H}_2)_4CH_3$), 2.60 (2H, t, J=8, $C\underline{H}_2$-$(CH_2)_4CH_3$), 4.15 (3H, s, OCH_3), 7.85 (1H, dd, J=5, 0.6, C_4-H), 9.02 (1H, d, J=5, C_3-H), 9.33 (1H, d, J=0.6, C_1-H)
25f	11 [46]	Yellow needles (Hexane)	68—70	$C_{18}H_{23}NO_3$	71.73 (71.67	7.69 7.84	4.65 4.53)	301 (M^+, 100) 204 (42) 203 (61)	1674 1650	0.88 (3H, t, J=7, $CH_2C\underline{H}_3$), 1.2—1.55 (12H, m, $(C\underline{H}_2)_6CH_3$), 2.60 (2H, t, J=8, $C\underline{H}_2$-$(CH_2)_6CH_3$), 4.14 (3H, s, OCH_3), 7.84 (1H, d, J=5, C_4-H), 9.02 (1H, d, J=5, C_3-H), 9.33 (1H, s, C_1-H)
29a	61	Dark red needles (Methanol)	287—289 (dec.)	$C_9H_6N_2O_2$	62.07 (62.02	3.47 3.22	16.09 16.03)	174 (M^+, 100)	3416 1692	6.02 (1H, s, C_6-H), 7.96 (1H, d, J=5, C_4-H), 8.96 (1H, d, J=5, C_3-H), 9.14 (1H, s, C_1-H)
29b	90	Red plates ($CHCl_3$)	191—192	$C_{18}H_{15}N_3O_4$	64.09 (63.89	4.48 4.40	12.46 12.38)	337 (M^+, 15) 187 (100)	3300 1690 1520 1340	2.11 (2H, quintet, J=7, $CH_2C\underline{H}_2CH_2$), 3.02 (2H, t, J=7, $ArCH_2$), 3.33 (2H, q, J=7, $C\underline{H}_2NH$), 5.83 (1H, s, C_6-H), 6.14 (1H, br, NH), 7.35 and 7.97 (each 1H, dd, J=1.2, 8), 7.40 and 7.56 (each 1H, dt, J=1.2, 8) for C_6H_4, 7.91 (1H, d, J=5, C_4-H), 9.02 (1H, d, J=5, C_3-H), 9.27 (1H, s, C_1-H)
34a	55	Red needles (CH_2Cl_2–hexane)	189—190	$C_{12}H_{12}N_2O_3$ ·1/10H_2O	61.58 (61.60	5.25 5.04	11.97 11.77)	232 (M^+, 100) 217 (59) 203 (59)	1666 1650	3.29 (6H, s, $N(CH_3)_2$), 3.90 (3H, s, OCH_3), 6.12 (1H, s, C_6-H), 7.04 (1H, s, C_4-H), 8.93 (1H, s, C_1-H)
34b	55	Red needles (CH_2Cl_2–hexane)	202—203	$C_{14}H_{14}N_2O_3$	65.11 (65.00	5.46 5.37	10.85 10.79)	258 (M^+, 100) 230 (38) 229 (97)	1664	2.1 (4H, br s, $CH_2(C\underline{H}_2)_2CH_2$), 3.55 and 3.75 (each 2H, br s, $C\underline{H}_2(CH_2)_2C\underline{H}_2$), 3.90 (3H, s, OCH_3), 6.12 (1H, s, C_6-H), 6.89 (1H, s, C_4-H), 8.93 (1H, s, C_1-H)
34c	48	Orange needles (CH_2Cl_2–hexane)	185—186	$C_{16}H_{18}N_2O_3$	67.12 (66.86	6.34 6.41	9.78 9.81)	286 (M^+, 100) 271 (41) 243 (39) 217 (30)	1666 1646	0.99 (3H, d, J=6, $CHC\underline{H}_3$), 1.1—1.9 (5H, m, CH_2CHCH_2), 2.9—3.1 (2H, m) and 4.61 (2H, br d, J=13) for $(CH_2)_2N$, 3.89 (3H, s, OCH_3), 6.12 (1H, s, C_6-H), 7.13 (1H, s, C_4-H), 8.90 (1H, s, C_1-H)
34d	66	Orange needles (CH_2Cl_2–hexane)	223—224 (dec.)	$C_{15}H_{17}N_3O_3$ ·1/5H_2O	61.93 (61.68	6.03 5.93	14.44 14.46)	287 (M^+, 32) 217 (36) 70 (100)	1670 1648	2.39 (3H, s, NCH_3), 2.57 and 3.90 (each 4H, t, J=5, $(CH_2)_2N(CH_2)_2$), 3.90 (3H, s, OCH_3), 6.13 (1H, s, C_6-H), 7.13 (1H, s, C_4-H), 8.91 (1H, s, C_1-H)
40a	54	Yellow needles (CH_2Cl_2–ether)	177—179	$C_{12}H_8N_2O_3$	63.16 (63.07	3.53 3.29	12.28 12.25)	228 (M^+, 100) 184 (51) 172 (85)	2225 1688 1655	1.57 (3H, t, J=7, $CH_2C\underline{H}_3$), 4.16 (2H, q, J=7, $C\underline{H}_2CH_3$), 6.32 (1H, s, C_6-H), 8.16 (1H, d, J=5, C_4-H), 9.13 (1H, d, J=5, C_3-H)
40b	55	Pale yellow needles (CH_2Cl_2–ether)	148—149	$C_{14}H_{12}N_2O_3$	65.62 (65.47	4.72 4.62	10.93 11.02)	256 (M^+, 41) 200 (33) 172 (100)	2230 1692 1648	1.00 (3H, t, J=7, $CH_2C\underline{H}_3$), 1.54 (2H, sextet, J=7, $C\underline{H}_2CH_3$), 1.90 (2H, quintet, J=7, $C\underline{H}_2CH_2CH_3$), 4.08 (2H, t, J=7, $C\underline{H}_2$-$(CH_2)_2CH_3$), 6.33 (1H, s, C_6-H), 8.16 (1H, d, J=5, C_4-H), 9.13 (1H, d, J=5, C_3-H)

TABLE I. (continued)

	Yield[a] (%)	Appearance (Recrystn. solv.)	mp (°C)	Formula	Analysis or HRMS[b] Calcd (Found) C	H	N	MS *m/z*	IR (KBr) (cm^{-1})	^{1}H-NMR (400 MHz)[c] δ ($CDCl_3$, J=Hz)
7,8-Isoquinolinediones										
14	55	Dark red needles (CH_2Cl_2–ether)	170—175 (dec.)	$C_9H_5NO_2 \cdot 1/10H_2O$	67.16 (66.88	3.26 3.03	8.70 8.80)	159 (M^+, 26) 131 (M^+-CO, 100) 103 (45)	1698 1680	6.70 and 7.66 (each 1H, d, J=10, C_5-H, C_6-H), 7.52 (1H, d, J=5, C_4-H), 8.93 (1H, d, J=5, C_3-H), 9.18 (1H, s, C_1-H)
19a	66 [17]	Orange needles (CH_2Cl_2–ether)	184—186 (dec.)	$C_{10}H_7NO_3$	63.49 (63.75	3.73 3.61	7.41 7.31)	189 (M^+, 23) 161 (M^+-CO, 100) 103 (59)	1700 1650	4.04 (3H, s, OCH_3), 6.12 (1H, s, C_6-H), 7.72 (1H, d, J=5, C_4-H), 8.93 (1H, d, J=5, C_3-H), 9.24 (1H, s, C_1-H)
19b	70 [25]	Orange prisms ($CHCl_3$–ether)	194—195	$C_{11}H_9NO_3$	65.02 (65.08	4.46 4.30	6.89 6.76)	203 (M^+, 1) 175 (M^+-CO, 98) 147 (88) 106 (100)	1703 1653	1.59 (3H, t, J=7, $CH_2C\underline{H}_3$), 4.26 (2H, q, J=7, $C\underline{H}_2CH_3$), 6.12 (1H, s, C_6-H), 7.78 (1H, d, J=5, C_4-H), 8.97 (1H, d, J=5, C_3-H), 9.27 (1H, s, C_1-H)
19c	44	Orange needles (CH_2Cl_2–ether)	142—144	$C_{11}H_9NO_3$	65.02 (65.10	4.46 4.35	6.89 6.88)	203 (M^+, 1) 175 (M^+-CO, 100) 160 (87)	1700 1665	2.09 (3H, s, C_6-CH_3), 4.02 (3H, s, OCH_3), 7.55 (1H, d, J=6, C_4-H), 7.92 (1H, d, J=6, C_3-H), 9.19 (1H, s, C_1-H)
19d	41	Orange needles (CH_2Cl_2–ether)	183—186 (dec.)	$C_{12}H_8N_2O_3$	63.16 (63.06	3.53 3.34	12.28 12.25)	228 (M^+, 22) 200 (M^+-CO, 80) 185 (100)	1700 1665	2.14 (3H, s, C_6-CH_3), 4.09 (3H, s, OCH_3), 7.80 (1H, d, J=5, C_4-H), 8.93 (1H, d, J=5, C_3-H)
19e	29	Orange needles (CH_2Cl_2–ether)	148—149	$C_{19}H_{15}NO_5$	67.65 (67.70	4.48 4.40	4.15 4.13)	337 (M^+, 1) 309 (M^+-CO, 5) 105 (100) 77 (56)	1727 1688 1650	2.15 (3H, s, C_6-CH_3), 4.08 (3H, s, OCH_3), 5.90 (2H, s, CH_2), 7.3—7.7 (4H, m) and 8.10 (2H, dd, J=2, 8) for C_6H_5 and C_4-H, 8.86 (1H, d, J=4, C_3-H)
33a	51	Red needles (CH_2Cl_2–hexane)	199—201 (dec.)	$C_{13}H_{15}N_3O_2$	63.66 (63.51	6.16 6.12	17.13 16.78)	245 (M^+, 30) 217 (M^+-CO, 100) 202 (58) 188 (78)	1670	3.11 (6H, s, $N(CH_3)_2$), 3.28 (6H, s, $N(CH_3)_2$), 5.99 (1H, s, C_6-H), 6.66 (1H, s, C_4-H), 8.87 (1H, s, C_1-H)
33b	80	Red needles (CH_2Cl_2–hexane)	190—193 (dec.)	$C_{17}H_{19}N_3O_2$	68.67 (68.78	6.44 6.46	14.13 13.98)	299 (M^++2, 81) 297 (M^+, 33) 269 (M^+-CO, 89) 240 (100)	1660	2.0—2.2 (8H, m, 2 × $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 3.5—3.8 (8H, m, 2 × $C\underline{H}_2CH_2CH_2C\underline{H}_2$), 5.89 (1H, s, C_6-H), 6.68 (1H, s, C_4-H), 8.87 (1H, s, C_1-H)
33c	34	Red needles (CH_2Cl_2–hexane)	221—224	$C_{21}H_{27}N_3O_2 \cdot 1/5H_2O$	70.64 (70.66	7.73 7.62	11.77 11.58)	355 (M^++2, 52) 353 (M^+, 13) 325 (M^+-CO, 100) 98 (58)	1665 1635	1.00 and 1.06 (each 3H, d, J=7, 2 × $CHC\underline{H}_3$), 1.1—1.9 (10H, m, 2 × CH_2CHCH_2), 2.8—3.1 (4H, m), 3.65 (2H, d, J=13) and 4.53 (2H, br d, J=11) for 4 × CH_2N, 6.06 (1H, s, C_6-H), 6.69 (1H, s, C_4-H), 8.86 (1H, s, C_1-H)
33d	39	Dark red prisms (CH_2Cl_2–ether)	215—218 (dec.)	$C_{19}H_{25}N_5O_2 \cdot 1/5H_2O$	63.56 (63.59	7.13 7.11	19.51 19.43)	357 (M^++2, 21) 355 (M^+, 23) 327 (M^+-CO, 24) 257 (100)	1664 1636	2.39 (3H, s, NCH_3), 2.41 (3H, s, NCH_3), 2.57 and 2.64 (each 4H, t, J=5, 2 × $C\underline{H}_2N(CH_3)$-$C\underline{H}_2$), 3.33 and 3.84 (each 4H, t, J=5, 2 × CH_2NCH_2), 6.06 (1H, s, C_6-H), 6.69 (1H, s, C_4-H), 8.86 (1H, s, C_1-H)
5,6-Isoquinolinediones										
26a	44	Orange needles (CH_2Cl_2–hexane)	182—183 (dec.)	$C_{10}H_7NO_3$	63.49 (63.21	3.73 3.55	7.40 7.29)	189 (M^+, 5) 161 (M^+-CO, 100) 103 (65)	1712 1642	4.08 (3H, s, OCH_3), 6.07 (1H, s, C_7-H), 7.88 (1H, dd, J=5, 0.7, C_4-H), 8.97 (1H, d, J=5, C_3-H), 9.19 (1H, d, J=0.7, C_1-H)
26b	28 [9]	Orange needles (Ether–hexane)	115—117	$C_{11}H_9NO_3$	65.02 (64.81	4.46 4.42	6.89 6.72)	203 (M^+, 1) 175 (M^+-CO, 100) 160 (54)	1707 1662	2.13 (3H, s, C_7-CH_3), 4.11 (3H, s, OCH_3), 7.81 (1H, d, J=5, C_4-H), 8.88 (1H, d, J=5, C_3-H), 9.04 (1H, s, C_1-H)
26c	14 [12]	Orange needles (Hexane)	95—97	$C_{12}H_{11}NO_3$	66.35 (66.28	5.10 5.01	6.45 6.26)	217 (M^+, 2) 189 (M^+-CO, 59) 174 (100)	1714 1664	1.17 (3H, t, J=8, $CH_2C\underline{H}_3$), 2.61 (2H, q, J=8, $C\underline{H}_2CH_3$), 4.10 (3H, s, OCH_3), 7.82 (1H, dd, J=5, 1, C_4-H), 8.88 (1H, d, J=5, C_3-H), 9.02 (1H, d, J=1, C_1-H)
26d	10 [13]	Red oil		$C_{14}H_{15}NO_3$	245.1052 (245.1067)			245 (M^+, 11) 217 (M^+-CO, 43) 175 (69) 174 (100)	1712 1662	0.95 (3H, t, J=7, $CH_2C\underline{H}_3$), 1.41 (2H, sextet, J=7, $C\underline{H}_2CH_3$), 1.45—1.55 (2H, m, $C\underline{H}_2$-CH_2CH_3), 2.58 (2H, t, J=8, $C\underline{H}_2(CH_2)_2CH_3$), 4.08 (3H, s, OCH_3), 7.81 (1H, dd, J=5, 0.6, C_4-H), 8.87 (1H, d, J=5, C_3-H), 9.00 (1H, d, J=0.6, C_1-H)
26e	7 [17]	Red oil		$C_{16}H_{19}NO_3$	273.1365 (273.1385)			273 (M^+, 10) 245 (M^+-CO, 37) 175 (82) 174 (100)	1712 1664	0.89 (3H, t, J=7, $CH_2C\underline{H}_3$), 1.2—1.6 (8H, m, $(C\underline{H}_2)_4CH_3$), 2.55 (2H, t, J=8, $C\underline{H}_2(CH_2)_4$-CH_3), 4.07 (3H, s, OCH_3), 7.81 (1H, dd, J=5, 0.7, C_4-H), 8.87 (1H, d, J=5, C_3-H), 9.00 (1H, d, J=0.7, C_1-H)
26f	12 [15]	Red oil		$C_{18}H_{23}NO_3$	301.1678 (301.1686)			301 (M^+, 26) 273 (M^+-CO, 54) 175 (95) 174 (100)	1708 1656	0.88 (3H, t, J=7, $CH_2C\underline{H}_3$), 1.2—1.7 (12H, m, $(C\underline{H}_2)_6CH_3$), 2.55 (2H, t, J=8, $C\underline{H}_2$-$(CH_2)_6CH_3$), 4.07 (3H, s, OCH_3), 7.82 (1H, dd, J=5, 0.7, C_4-H), 8.87 (1H, d, J=5, C_3-H), 9.00 (1H, d, J=0.7, C_1-H)
31a	11	Red needles ($CHCl_3$–hexane)	177—178 (dec.)	$C_{11}H_{10}N_2O_2$	65.34 (65.10	4.98 4.83	13.85 13.65)	204 (M^++2, 14) 202 (M^+, 7) 174 (M^+-CO, 100)	1690	3.12 (6H, s, $N(CH_3)_2$), 6.00 (1H, s, C_7-H), 7.44 (1H, d, J=6, C_4-H), 8.84 (1H, d, J=6, C_3-H), 9.17 (1H, s, C_1-H)
31b	37	Dark red needles (CH_2Cl_2–hexane)	*ca.* 265 (dec.)	$C_{13}H_{12}N_2O_2$	68.41 (68.29	5.30 5.21	12.27 12.21)	230 (M^++2, 24) 228 (M^+, 30) 200 (M^+-CO, 100) 171 (54)	1701	2.1—2.2 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 3.8—3.9 (4H, m, $C\underline{H}_2CH_2CH_2C\underline{H}_2$), 5.93 (1H, s, C_7-H), 7.91 (1H, d, J=5, C_4-H), 8.87 (1H, d, J=5, C_3-H), 9.18 (1H, s, C_1-H)

TABLE I. (continued)

	Yield[a] (%)	Appearance (Recrystn. solv.)	mp (°C)	Formula	Analysis or HRMS[b] Calcd (Found) C	H	N	MS m/z	IR (KBr) (cm^{-1})	^{1}H-NMR (400 MHz)[c] δ ($CDCl_3$, J=Hz)
31c	60	Red needles (CH_2Cl_2–hexane)	260—262	$C_{15}H_{16}H_2O_2$	70.29 (70.31	6.29 6.27	10.93 10.81)	258 (M^++2, 24) 256 (M^+, 16) 228 (M^+−CO, 100) 199 (31)	1696 1620	1.07 (3H, d, J=6, $CHC\underline{H}_3$), 1.4—2.0 (5H, m, CH_2CHCH_2), 3.09 (2H, dt, J=2, 13) and 3.83 (2H, br d, J=13) for CH_2NCH_2, 6.09 (1H, s, C_7-H), 7.88 (1H, d, J=5, C_4-H), 8.86 (1H, d, J=5, C_3-H), 9.00 (1H, s, C_1-H)

a) Yields by oxidation with AgO in brackets. *b*) HRMS: High-resolution MS. *c*) Measured at 100 MHz (**12**, **14**, **18**, **19**), at 270 MHz (**25a**, **26**, **31**, **33a**, **34**), and in CD_3OD (**29a**). *d*) Lit.[19] mp 135—138 °C (dec.). *e*) Yields from **17a**. Yields from **17b**: 28% (CAN), 54% (AgO). *f*) Lit.[20] mp 215—216 °C.

The required 7-alkyl-5,6,8-trimethoxyisoquinolines (**24b—f**) were obtained by employing the modified Pomeranz–Fritsch reaction.[11] Tosylamides (**23b—f**) prepared from the corresponding aldehydes (**21b—f**) in 87—93% yields, were treated with 6 N hydrochloric acid in dioxane followed by potassium *tert*-butoxide in *tert*-butyl alcohol to give the corresponding isoquinolines (**24b—f**) in 11—31% yields. When concentrated hydrochloric acid, or concentrated hydrochloric acid-zinc chloride was used instead of 6 N hydrochloric acid, the yields of **24c—f** from **23c—f** were remarkably improved (67—89%). However, attempted cyclization of a tosylamide (**23a**) failed. 5,6,8-Trimethoxyisoquinoline (**24a**) was prepared from 2,4,5-trimethoxybenzaldehyde (**21a**) *via* the carbamate **22a** by Hendrickson and Rodriguez's method[14] in 36% yield. Oxidative demethylation of **24a—f** with CAN containing pyridine-2,6-dicarboxylic acid *N*-oxide at 0—5 °C for 30 min gave the corresponding *p*-quinones (**25a—f**) (8—32% yield) and *o*-quinones (**26a—f**) (7—44% yield). The yields of the quinones (**25a—f** and **26a—f**) decrease as the alkyl group at the C-7 position on the isoquinolines (**24a—f**) is lengthened. In contrast, the isoquinolines (**24b—f**) were smoothly oxidized to the corresponding *p*-quinones (**25b—f**) (42—58% yield) and *o*-quinones (**26b—f**) (9—17% yield) with AgO–nitric acid in dioxane[15] at 20 °C for 30 min.

The *o*-quinone structures for **19a**, **c**, **d** and **26a**, **b** were further characterized by way of the *o*-phenylenediamine condensation product, *i.e.* pyridophenazines (**27a**, **c**, **d** and **28a**, **b**, respectively).

Treatment of 7-methoxy-5,8-isoquinolinedione (**18a**) with ammonia or 3-(2-nitrophenyl)propylamine[16] afforded 7-amino-5,8-isoquinolinediones (**29a**, **b**).

Oxidation of 5-isoquinolinol (**30**) with oxygen in the presence of copper acetate and dimethylamine (or pyrrolidine, or 4-methylpiperidine) in methanol gave 8-dialkylamino-5,6-isoquinolinediones (**31a—c**). In contrast 7-isoquinolinol (**32**) was oxidized under the same conditions to 3,5-bis(dialkylamino)-7,8-isoquinolinediones (**33a—d**) in 34—80% yield. The *o*-quinones (**33a—d**) were refluxed with sulfuric acid in methanol to afford the corresponding 3-dialkylamino-7-methoxy-5,8-isoquinolinediones (**34a—d**) in 48—66% yield.

Finally we prepared 1-cyano-5,8-isoquinolinediones (**40a**, **b**). 8-Nitroisoquinolines (**36a**, **b**) prepared by nitration of **35a**,[17] **b** were treated with *m*-chloroperoxybenzoic acid followed by trimethylsilyl cyanide to afford 1-cyano-8-nitroisoquinolines (**38a**, **b**). Fremy's salt oxidation of 8-amino-1-cyanoisoquinolines (**39a**, **b**) obtained by catalytic reduction of **38a**, **b**, gave 1-cyano-5,8-isoquinolinediones (**40a**, **b**) in 54—55% yield.

The spectral data of 5,8-isoquinolinediones (**12**, **18**, **25**, **29**, **34**, **40**), 7,8-isoquinolinediones (**14**, **19**, **33**) and 5,6-isoquinolinediones (**26**, **31**) are collected in Table I.

We have examined the effects on the growth of lymphoblastoma L5178Y cells, and inhibition of avian myeloblastosis virus reverse transcriptase, human immunodeficiency virus reverse transcriptase and cellular deoxyribonucleic acid (DNA) polymerases α and β of various 5,8-isoquinolinediones (**12**, **18a**, **c**, **d**, **29a**, **b**, and **40a**, **b**), 7,8-isoquinolinediones (**19a**, **c**, **d** and **33a**, **b**) and 5,6-isoquinolinedione (**31a**).[18] Extensive biological studies are in progress.

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were measured at 100, 270 or 400 MHz, 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 evaporater and finally under high vacuum. Column chromatography was performed with Silica gel 60 (230—400 mesh).

5,8-Isoquinolinedione (12) (a) A solution of CAN (8.76 g, 16 mmol) in acetonitrile–water (1 : 1, 15 ml) was added dropwise to 5,8-dimethoxyisoquinoline (**11**) (189 mg, 1 mmol) dissolved in acetonitrile–water (1 : 1, 18 ml) containing suspended pyridine-2,6-dicarboxylic acid *N*-oxide (2.93 g, 16 mmol) at 0—5 °C. The mixture was stirred at 0—5 °C for 3 h, adjusted to pH 8 with saturated aqueous $NaHCO_3$ solution, and extracted with CH_2Cl_2 (3 × 30 ml). The extract was washed with water, dried, concentrated to 3 ml, and triturated with ether. The precipitated crystals were collected by filtration. Yield 139 mg (88%).

(b) AgO (620 mg, 5 mmol) was added in portions to **11** (189 mg, 1 mmol) dissolved in acetonitrile–water (1 : 1, 10 ml) containing suspended pyridine-2,6-dicarboxylic acid *N*-oxide (916 mg, 5 mmol) at 0—5 °C. The mixture was stirred at 0—5 °C 1 h, and insoluble compounds were filtered off. The filtrate was diluted with saturated aqueous $NaHCO_3$ solution (20 ml) and extracted with CH_2Cl_2 (3 × 20 ml). The extract was washed with water, dried, and evaporated. The residue was chromatographed using ethyl acetate as the eluent to give 114 mg (72%) of **12**.

7,8-Isoquinolinedione (14) A solution of CAN (2.74 g, 5 mmol) in acetonitrile–water (1 : 1, 10 ml) was added dropwise to 7,8-dimethoxyisoquinoline (**13**) (189 mg, 1 mmol) dissolved in acetonitrile–water (1 : 1, 10 ml) containing suspended pyridine-2,6-dicarboxylic acid *N*-oxide (916 mg, 5 mmol) at 0—5 °C. The mixture was stirred at 0—5 °C for 15 min, adjusted to pH 8 with saturated aqueous $NaHCO_3$ solution, and extracted with CH_2Cl_2 (3 × 30 ml). The extract was washed with water, dried, concentrated to 3 ml, and triturated with ether. The precipitated crystals were collected by filtration. Yield 87 mg (55%).

2,5-Diethoxy-3-methoxybenzaldehyde (16b) Ethyl iodide (5 ml) and K_2CO_3 (2.76 g, 20 mmol) were added to a solution of 2,5-dihydroxy-3-methoxybenzaldehyde (**15**)[13] (670 mg, 4 mmol) in dry acetone (50 ml). The whole was refluxed for 4 h, and the solid was filtered off. The filtrate was evaporated and the residue was chromatographed (eluting with ethyl

acetate–hexane 3:17) to afford 290 mg (33%) of **16b**, mp 42—43.5 °C (recrystallized from hexane). *Anal.* Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.20; H, 7.32. ^{1}H-NMR (400 MHz) δ: 1.39 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.41 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.86 (3H, s, OCH_3), 4.04 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.13 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 6.73 (1H, d, J=3 Hz, C_4-H), 6.84 (1H, d, J=3 Hz, C_6-H), 10.40 (1H, s, CHO).

5,7,8-Trimethoxyisoquinoline (17a) **17a** was prepared from **16a**[21] as described.[11] Yield 46%. mp 85—86°C (recrystallized from ether). *Anal.* Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.67; H, 5.96; N, 6.35. ^{1}H-NMR (270 MHz) δ: 3.98 (3H, s, OCH_3), 4.01 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 6.82 (1H, s, C_6-H), 7.90 (1H, dd, J=6, 1 Hz, C_4-H), 8.42 (1H, d, J=6 Hz, C_3-H), 9.46 (1H, d, J=1 Hz, C_1-H).

5,8-Diethoxy-7-methoxyisoquinoline (17b) **17b** was prepared from **16b** as described.[11] Yield 33%, mp 88—89 °C (recrystallized from ether–hexane). *Anal.* Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.05; H, 6.97; N, 5.64. ^{1}H-NMR (100 MHz) δ: 1.47 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.52 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 3.95 (3H, s, OCH_3, 4.15 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 4.18 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$, 6.80 (1H, s, C_6-H), 7.92 (1H, d, J=6 Hz, C_4-H), 8.43 (1H, d, J=6 Hz, C_3-H), 9.50 (1H, s, C_1-H).

3-Alkyl-1,2,4-trimethoxybenzene (20c—f) *n*-Butyllithium (16 ml of 1.5 M hexane solution) was added dropwise to a solution of 1,2,4-trimethoxybenzene (**20a**) (3.36 g, 20 mmol) in dry tetrahydrofuran (30 ml) at 0—5 °C. The whole was kept at 0—5 °C for 1 h, then ethyl (or butyl, hexyl, octyl) iodide (22 mmol) in dry tetrahydrofuran (10 ml) was added dropwise at 0—5 °C. The mixture was allowed to warm to room temperature for 30 min, kept for 1.5 h, quenched with water (150 ml), and extracted with ether (3 × 80 ml). The extract was washed with brine, dried, and evaporated. The residue was chromatographed (eluting with ethyl acetate–hexane 1:9) to afford **20c—f** as an oil.

20c: Yield 96%. ^{1}H-NMR (400 MHz) δ: 1.12 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.67 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 3.78 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 6.55 (1H, d, J=9 Hz, C_5-H), 6.70 (1H, d, J=9 Hz, C_6-H). High-resolution MS (HRMS) Calcd for $C_{11}H_{16}O_3$: 196.1099. Found: 196.1092

20d: Yield 80%. ^{1}H-NMR (400 MHz) δ: 0.92 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.37 (2H, sextet, J=7 Hz, $C\underline{H}_2CH_3$), 1.43—1.53 (2H, m, $C\underline{H}_2CH_2CH_3$), 2.63 (2H, t, J=8 Hz, $C\underline{H}_2CH_2CH_2CH_3$), 3.77 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 6.54 (1H, d, J=9 Hz, C_5-H), 6.69 (1H, d, J=9 Hz, C_6-H). HRMS Calcd for $C_{13}H_{20}O_3$: 224.1412. Found: 224.1436.

20e: Yield 80%. ^{1}H-NMR (400 MHz) δ: 0.88 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.2—1.6 (8H, m, $(C\underline{H}_2)_4CH_3$), 2.62 (2H, t, J=8 Hz, $C\underline{H}_2(CH_2)_4CH_3$), 3.77 (3H, s, OCH_3), 3.81 (6H, s, 2 × OCH_3), 6.54 (1H, d, J=9 Hz, C_5-H), 6.69 (1H, d, J=9 Hz, C_6-H). HRMS Calcd for $C_{15}H_{24}O_3$: 252.1725. Found: 252.1725.

20f: Yield 83%. ^{1}H-NMR (400 MHz) δ: 0.88 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.2—1.6 (12H, m, $(C\underline{H}_2)_6CH_3$), 2.62 (2H, t, J=8 Hz, $C\underline{H}_2(CH_2)_4CH_3$), 3.78 (3H, s, OCH_3), 3.81 (6H, s, 2 × OCH_3), 6.54 (1H, d, J=9 Hz, C_5-H), 6.69 (1H, d, J=9 Hz, C_6-H). HRMS Calcd for $C_{17}H_{28}O_3$: 280.2038. Found: 280.2025.

3-Alkyl-2,4,5-trimethoxybenzaldehyde (21c—f) Phosphoryl chloride (1.5 ml) was added dropwise to dry *N*,*N*-dimethylformamide (2.5 ml) during 15 min with cooling in ice. The whole was allowed to warm to room temperature, and a solution of **20c—f** (8 mmol) in dry *N*,*N*-dimethylformamide (2.5 ml) was added. The mixture was heated at 100—110 °C (bath) for 2 h, poured into ice-water, and 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—2:8) to afford the aldehyde **21c—f** as an oil.

21c: Yield 75%. ^{1}H-NMR (400 MHz) δ: 1.20 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.69 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 3.88 (6H, s, 2 × OCH_3), 3.93 (3H, s, OCH_3), 7.24 (1H, s, C_6-H), 10.28 (1H, s, CHO). HRMS Calcd for $C_{12}H_{16}O_4$: 224.1048. Found: 224.1044.

21d: Yield 74%. ^{1}H-NMR (400 MHz) δ: 0.95 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.41 (2H, sextet, J=7 Hz, $C\underline{H}_2CH_3$), 1.47—1.57 (2H, m, $C\underline{H}_2CH_2CH_3$), 2.64 (2H, t, J=8 Hz, $C\underline{H}_2CH_2CH_2CH_3$), 3.87 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 7.24 (1H, s, C_6-H), 10.28 (1H, s, CHO). HRMS Calcd for $C_{14}H_{20}O_4$: 252.1361. Found: 252.1356.

21e: Yield 70%. ^{1}H-NMR (400 MHz) δ: 0.89 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.2—1.7 (8H, m, $CH_2(C\underline{H}_2)_4CH_3$), 2.63 (2H, t, J=8 Hz, $C\underline{H}_2(CH_2)_4CH_3$), 3.86 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 7.24 (1H, s, C_6-H), 10.27 (1H, s, CHO). HRMS Calcd for $C_{16}H_{24}O_4$: 280.1674. Found: 280.1660.

21f: Yield 53%. ^{1}H-NMR (400 MHz) δ: 0.88 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.2—1.7 (12H, m, $CH_2(C\underline{H}_2)_6CH_3$), 2.63 (2H, t, J=8 Hz, $C\underline{H}_2(CH_2)_4CH_3$), 3.86 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 7.24 (1H, s, C_6-H), 10.27 (1H, s, CHO). HRMS Calcd for $C_{18}H_{28}O_4$: 308.1987. Found: 308.2018.

***N*-(3-Alkyl-2,4,5-trimethoxybenzyl)-2,2-dimethoxy-*N*-tosylethylamine (23a—f)** **23a—f** was obtained as an oil from 2,4,5-trimethoxybenzaldehyde (**21a**, **b**,[22] **c—f**) according to the reported method.[11]

23a: Yield 92%. ^{1}H-NMR (100 MHz) δ: 2.40 (3H, s, $C_6H_4C\underline{H}_3$), 3.29 (6H, s, $CH(OC\underline{H}_3)_2$), 3.29 (2H, d, J=6 Hz, $C\underline{H}_2CH$), 3.70 (3H, s, $ArOCH_3$), 3.77 (3H, s, $ArOCH_3$), 3.87 (3H, s, $ArOCH_3$), 4.44 (1H, t, J=6 Hz, $CH_2C\underline{H}$), 4.44 (2H, s, $ArCH_2N$), 6.40 (1H, s, ArH), 6.82 (1H, s, ArH), 7.22 and 7.61 (each 2H, d, J=8 Hz, $C_6\underline{H}_4CH_3$).

23b: Yield 92%. ^{1}H-NMR (100 MHz) δ: 2.17 (3H, s, CH_3), 2.43 (3H, s, $C_6H_4C\underline{H}_3$), 3.25 (6H, s, $CH(OC\underline{H}_3)_2$), 3.28 (2H, d, J=6 Hz, $C\underline{H}_2CH$), 3.62 (3H, s, $ArOCH_3$), 3.72 (3H, s, $ArOCH_3$), 3.77 (3H, s, $ArOCH_3$), 4.40 (1H, t, J=6 Hz, $CH_2C\underline{H}$), 4.50 (2H, s, $ArCH_2N$), 6.68 (1H, s, ArH), 7.30 and 7.75 (each 2H, d, J=8 Hz, $C_6\underline{H}_4CH_3$). HRMS Calcd for $C_{22}H_{31}NO_7S$: 453.1821. Found: 453.1839.

23c: Yield 92%. ^{1}H-NMR (400 MHz) δ: 1.15 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.42 (3H, s, $C_6H_4C\underline{H}_3$), 2.62 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 3.23 (6H, s, $CH(OC\underline{H}_3)_2$), 3.27 (2H, d, J=6 Hz, $C\underline{H}_2CH$), 3.64 (3H, s, $ArOCH_3$), 3.71 (3H, s, $ArOCH_3$), 3.81 (3H, s, $ArOCH_3$), 4.37 (1H, t, J=6 Hz, $CH_2C\underline{H}$), 4.49 (2H, s, $ArCH_2N$), 6.68 (1H, s, ArH), 7.29 and 7.72 (each 2H, d, J=8 Hz, $C_6\underline{H}_4CH_3$). HRMS Calcd for $C_{23}H_{33}NO_7S$: 467.1977. Found: 467.1956.

23d: Yield 92%. ^{1}H-NMR (400 MHz) δ: 0.92 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.38 (2H, sextet, J=7 Hz, $C\underline{H}_2CH_3$), 1.43—1.55 (2H, m, $C\underline{H}_2CH_2CH_3$), 2.42 (3H, s, $C_6H_4C\underline{H}_3$), 2.57 (2H, t, J=8 Hz, $C\underline{H}_2CH_2CH_2CH_3$), 3.23 (6H, s, $CH(OC\underline{H}_3)_2$), 3.26 (2H, d, J=6 Hz, $C\underline{H}_2CH$), 3.63 (3H, s, $ArOCH_3$), 3.71 (3H, s, $ArOCH_3$), 3.80 (3H, s, $ArOCH_3$), 4.37 (1H, t, J=6 Hz, $CH_2C\underline{H}$), 4.49 (2H, s, $ArCH_2N$), 6.68 (1H, s, ArH), 7.29 and 7.72 (each 2H, d, J=8 Hz, $C_6\underline{H}_4CH_3$). HRMS Calcd for $C_{25}H_{37}NO_7S$: 495.2290. Found: 495.2292.

23e: Yield 93%. ^{1}H-NMR (400 MHz) δ: 0.88 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.25—1.55 (8H, m, $CH_2(C\underline{H}_2)_4CH_3$), 2.42 (3H, s, $C_6H_4C\underline{H}_3$), 2.56 (2H, t, J=8 Hz, $(CH_2)_4CH_3$), 3.23 (6H, s, $CH(OC\underline{H}_3)_2$), 3.26 (2H, d, J=6 Hz, $C\underline{H}_2CH$), 3.63 (3H, s, $ArOCH_3$), 3.71 (3H, s, $ArOCH_3$), 3.79 (3H, s, $ArOCH_3$), 4.37 (1H, t, J=6 Hz, $CH_2C\underline{H}$), 4.49 (2H, s, $ArCH_2N$), 6.67 (1H, s, ArH), 7.29 and 7.72 (each 2H, d, J=8 Hz, $C_6\underline{H}_4CH_3$). HRMS Calcd for $C_{27}H_{41}NO_7S$: 523.2603. Found: 523.2577.

23f: Yield 87%. ^{1}H-NMR (400 MHz) δ: 0.88 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.2—1.55 (12H, m, $CH_2(C\underline{H}_2)_6CH_3$), 2.42 (3H, s, $C_6H_4C\underline{H}_3$), 2.56 (2H, t, J=8 Hz, $C\underline{H}_2(CH_2)_4CH_3$), 3.23 (6H, s, $CH(OC\underline{H}_3)_2$), 3.26 (2H, d, J=6 Hz, $C\underline{H}_2CH$), 3.63 (3H, s, $ArOCH_3$), 3.71 (3H, s, $ArOCH_3$), 3.79 (3H, s, $ArOCH_3$), 4.37 (1H, t, J=6 Hz, $CH_2C\underline{H}$), 4.49 (2H, s, $ArCH_2N$), 6.67 (1H, s, ArH), 7.29 and 7.72 (each 2H, d, J=8 Hz, $C_6\underline{H}_4CH_3$). HRMS Calcd for $C_{29}H_{45}NO_7S$: 551.2916. Found: 551.2927.

5,6,8-Trimethoxyisoquinoline (24a) **24a** was prepared from **21a** as described.[14] Yield 36% (from **21a**). mp 99—100 °C (recrystallized from CH_2Cl_2–hexane). *Anal.* Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found; C, 65.79; H, 6.02; N, 6.32. ^{1}H-NMR (270 MHz) δ: 3.91 (3H, s, OCH_3), 4.04 (3H, s, OCH_3), 4.05 (3H, s, OCH_3), 6.68 (1H, s, C_7-H), 7.81 (1H, d, J=6 Hz, C_4-H), 8.46 (1H, d, J=6 Hz, C_3-H), 9.48 (1H, s, C_1-H).

7-Alkyl-5,6,8-trimethoxyisoquinoline (24b—f) A solution of **23b—f** (1 mmol) and 6 N (or concentrated) HCl (2.4 ml) (and $ZnCl_2$ 240 mg) in dioxane (12 ml) was refluxed for 2 h, then cooled, poured into water (50 ml) and extracted with ether (3 × 40 ml). The extract was washed with brine, dried and evaporated. The residue was dissolved in *tert*-butyl alcohol (8 ml), and potassium *tert*-butoxide (673 mg, 6 mmol) was added. The whole was refluxed for 30 min, diluted with water (50 ml), and extracted with CH_2Cl_2 (3 × 30 ml). The extract was washed with water, dried and evaporated. The residue was chromatographed (eluting with ethyl acetate–hexane 2:8—1:1) to afford **24b—f**. The picrates of **24c—f** were prepared by the usual method, and recrystallized from ethanol.

24b: Yield 31% (6 N HCl). mp 52—53 °C (recrystallized from hexane). ^{1}H-NMR (270 MHz) δ: 2.37 (3H, s, C_7-CH_3), 3.94 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 4.02 (3H, s, OCH_3), 7.85 (1H, dd, J=6, 1 Hz, C_4-H), 8.47 (1H, d, J=6 Hz, C_3-H), 9.38 (1H, d, J=1 Hz, C_1-H). *Anal.* Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.76; H, 6.53; N, 5.86.

24c: Yield 31% (6 N HCl), 84% (concentrated HCl), 89% (concentrated HCl–$ZnCl_2$). Oil. ^{1}H-NMR (400 MHz) δ: 1.25 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 2.84 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 3.94 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 4.06 (3H, s, OCH_3), 7.83 (1H, d, J=6 Hz, C_4-H), 8.47 (1H, d, J=6 Hz, C_3-H), 9.37 (1H, s, C_1-H). HRMS Calcd for $C_{14}H_{17}NO_3$: 247.1208. Found: 247.1197. Picrate: mp 186—188 °C. *Anal.* Calcd for $C_{14}H_{17}NO_3 \cdot C_6H_3N_3O_7$: C, 50.42; H, 4.23; N, 11.76. Found: C, 50.39;

H, 4.14; N, 11.77.

24d: Yield 11% (6 N HCl), 86% (concentrated HCl), 86% (concentrated HCl–$ZnCl_2$). Oil. ^{1}H-NMR (400 MHz) δ: 0.98 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.46 (2H, sextet, J=7 Hz, $C\underline{H}_2CH_3$), 1.55—1.65 (2H, m, $C\underline{H}_2CH_2CH_3$), 2.79 (2H, t, J=8 Hz, $C\underline{H}_2CH_2CH_2CH_3$), 3.94 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 4.05 (3H, s, OCH_3), 7.84 (1H, dd, J=6, 1 Hz, C_4-H), 8.47 (1H, d, J=6 Hz, C_3-H), 9.37 (1H, d, J=1 Hz, C_1-H). HRMS Calcd for $C_{16}H_{21}NO_3$: 275.1521. Found: 275.1498. Picrate: mp 158—159 °C. *Anal.* Calcd for $C_{16}H_{21}NO_3 \cdot C_6H_3N_3O_7$: C, 52.38; H, 4.80; N, 11.11. Found: C, 52.27; H, 4.73; N, 11.11.

24e: Yield 16% (6 N HCl), 67% (concentrated HCl), 85% (concentrated HCl–$ZnCl_2$). Oil. ^{1}H-NMR (400 MHz) δ: 0.91 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.2—1.7 (8H, m, $CH_2(C\underline{H}_2)_4CH_3$), 2.78 (2H, t, J=8 Hz, $C\underline{H}_2(CH_2)_4CH_3$), 3.94 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 4.05 (3H, s, OCH_3), 7.84 (1H, d, J=6 Hz, C_4-H), 8.47 (1H, d, J=6 Hz, C_3-H), 9.37 (1H, s, C_1-H). HRMS Calcd for $C_{18}H_{25}NO_3$: 303.1834. Found: 303.1828. Picrate: mp 138—139 °C. *Anal.* Calcd for $C_{18}H_{25}NO_3 \cdot C_6H_3N_3O_7$: C, 54.13; H, 5.30; N, 10.52. Found: C, 53.85; H, 5.27; N, 10.54.

24f: Yield 14% (6 N HCl), 71% (concentrated HCl), 81% (concentrated HCl–$ZnCl_2$). Oil. ^{1}H-NMR (400 MHz) δ: 0.89 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.2—1.7 (12H, m, $CH_2(C\underline{H}_2)_6CH_3$), 2.78 (2H, t, J=8 Hz, $C\underline{H}_2(CH_2)_4CH_3$), 3.94 (3H, s, OCH_3), 3.97 (3H, s, OCH_3), 4.05 (3H, s, OCH_3), 7.83 (1H, dd, J=6, 1 Hz, C_4-H), 8.47 (1H, d, J=6 Hz, C_3-H), 9.37 (1H, d, J=1 Hz, C_1-H). HRMS Calcd for $C_{20}H_{29}NO_3$: 331.2147. Found; 331.2161. Picrate: mp 120—121 °C. *Anal.* Calcd for $C_{20}H_{29}NO_3 \cdot C_6H_3N_3O_7$: C, 55.71; H, 5.75; N, 10.00. Found: C, 55.60; H, 5.81; N, 9.97.

7-Methoxy-5,8-isoquinolinediones (18, 25) and 5-Methoxy- (or 5-Ethoxy)-7,8-isoquinolinediones (19, 26) (a) A solution of CAN (2.74 g, 5 mmol) in acetonitrile–water (1 : 1, 10 ml) was added dropwise to an isoquinoline (**17**, **24**) (1 mmol) dissolved in acetonitrile–water (1 : 1, 10 ml) containing suspended pyridine-2,6-dicarboxylic acid *N*-oxide (0.92 g, 5 mmol) at 0—5 °C. The mixture was stirred at 0—5 °C for 15 min (or 30 min for **24**), adjusted to pH 8 with saturated aqueous $NaHCO_3$ solution, and extracted with CH_2Cl_2 (3 × 30 ml). The extract was washed with water, dried, and evaporated. The residue was chromatographed (eluting with ethyl acetate–CH_2Cl_2 or ethyl acetate–hexane) to afford a less polar *p*-quinone (**18**, **25**) and a more polar *o*-quinone (**19**, **26**).

(b) AgO (620 mg, 5 mmol) was added in portions to **17a**, **b** (1 mmol) dissolved in acetonitrile–water (1 : 1, 10 ml) containing suspended pyridine-2,6-dicarboxylic acid *N*-oxide (916 mg, 5 mmol) at 0—5 °C. The mixture was stirred at 0—5 °C for 1 h, and insoluble compounds were filtered off. The filtrate was diluted with saturated aqueous $NaHCO_3$ solution (20 ml) and extracted with CH_2Cl_2 (3 × 20 ml). The extract was washed with water, dried, and evaporated. The residue was chromatographed. Elution with ethyl acetate–hexane (1 : 1) gave a less polar *p*-quinone (**18a**), and further elution with ethyl acetate–hexane (7 : 3) gave a more polar *o*-quinone (**19a**, **b**).

(c) AgO (495 mg, 4 mmol) and 6 N HNO_3 (1 ml) was added to a solution of **24b—f** (1 mmol) in dioxane (15 ml). The whole was stirred for 30 min, diluted with water (50 ml), and extracted with CH_2Cl_2 (3 × 40 ml). The extract was washed with water, dried, and evaporated. The residue was chromatographed. Elution with ethyl acetate–hexane (1 : 4—3 : 7) gave a less polar *p*-quinone (**25b—f**), and further elution with ethyl acetate–hexane (2 : 3—1 : 1) gave a more polar *o*-quinone (**26b—f**).

Condensation of the *o*-Quinones (19a, c, d and 26a, b) with *o*-Phenylenediamine A mixture of an *o*-quinone (**19a**, **c**, **d** and **26a**, **b**) (0.2 mmol) and *o*-phenylenediamine (22 mg, 0.2 mmol) in ethanol (8 ml) containing acetic acid (0.1 ml) was refluxed for 30 min, and then evaporated. The residue was chromatographed (eluting with ethyl acetate–benzene or ethyl acetate–hexane) to afford the corresponding pyridophenazine (**27a**, **c**, **d** and **28a**, **b**).

27a: Yield 87%. mp 213—214 °C (recrystallized from ethyl acetate–ether). *Anal.* Calcd for $C_{16}H_{11}N_3O$: C, 73.55; H, 4.24; N, 16.08. Found: C, 73.46; H, 3.97; N, 15.80.

27c: Yield 88%. mp 195—196 °C (recrystallized from ethyl acetate–ether). *Anal.* Calcd for $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N, 15.26. Found: C, 74.40; H, 4.62; N, 15.32.

27d: Yield 92%. mp 278—279 °C (recrystallized from CH_2Cl_2–ether). *Anal.* Calcd for $C_{18}H_{12}N_4O$: C, 71.99; H, 4.03; N, 18.66. Found: C, 72.23; H, 3.73; N, 18.66.

28a: Yield 97%. mp 246—248 °C (recrystallized from CH_2Cl_2–hexane). *Anal.* Calcd for $C_{16}H_{11}N_3O$: C, 73.55; H, 4.24; N, 16.08. Found: C, 73.24; H, 4.01; N, 16.01.

28b: Yield 94%. mp 204—205 °C (recrystallized from $CHCl_3$–ether). *Anal.* Calcd for $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N, 15.26. Found: C, 73.83; H, 4.55; N, 15.09.

7-Amino-5,8-isoquinolinedione (29a) A solution of **18a** (945 mg, 5 mmol) in 10% NH_3–methanol (100 ml) was kept at 40 °C for 1 h, and cooled. The precipitated crystals were collected and recrystallized from methanol to afford 495 mg (57%) of **29a**.

7-(3-(2-Nitrophenyl)propylamino)-5,8-isoquinolinedione (29b) A solution of **18a** (378 mg, 2 mmol) and 3-(2-nitrophenyl)propylamine (432 mg, 2.4 mmol) in methanol (50 ml) was kept at room temperature for 6 h. The precipitated crystals were collected and recrystallized from $CHCl_3$ to afford 608 mg (90%) of **29b**.

8-Dialkylamino-5,6-isoquinolinedione (31) and 3,5-Bis(dialkylamino)-7,8-isoquinolinedione (33) Copper(II) acetate (100 mg) and dimethylamine (0.8 ml of 50% aqueous solution) (or 0.4 ml of pyrrolidine, 4-methylpiperidine, *N*-methylpiperazine) were added to a solution of 5-isoquinolinol **30** (or 7-isoquinolinol (**32**)) (1 mmol) in methanol (10 ml). A steady stream of air was bubbled through this red reaction mixture for 2 h with external ice-cooling. The solvent was removed and the oily residue was dissolved in CH_2Cl_2 (50 ml). The solution was washed with water, dried and evaporated to leave a dark red oil, which was subjected to column chromatography (elution with ethyl acetate–hexane or ethyl acetate-methanol). The crude quinone (**31**, **33**) thus obtained was dissolved in a small amount of CH_2Cl_2, and triturated with hexane to afford the desired product.

3-Dialkylamino-7-methoxy-5,8-isoquinolinedione (34) A solution of **33** (0.2 mmol) in a mixture of methanol (5 ml) and concentrated H_2SO_4 (0.5 ml) was refluxed for 3 h. The reaction mixture was cooled, diluted with ice-water (30 ml), neutralized with pyridine and extracted with CH_2Cl_2 (5 × 20 ml). The extract was washed with water, dried and evaporated. The residue was chromatographed (elution with ethyl acetate–hexane or ethyl acetate–methanol) to afford **34**.

7-Butoxyisoquinoline (35b) A solution of 7-isoquinolinol (**32**) (1.45 g, 10 mmol), KOH (1.35 g, 24 mmol) and butyl iodide (4.41 g, 24 mmol) in butyl alcohol (50 ml) was refluxed for 30 min. The mixture was then cooled, and water (100 ml) was added. The resulting organic layer was separated, dried and evaporated. The residue was chromatographed (eluting with ethyl acetate–hexane 2 : 1) to afford 0.75 g (37%) of **35b** as an oil. ^{1}H-NMR (270 MHz) δ: 1.01 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.55 (2H, sextet, J=7 Hz, $C\underline{H}_2CH_3$), 1.86 (2H, quintet, J=7 Hz, $C\underline{H}_2CH_2CH_3$), 4.11 (2H, t, J=7 Hz, $C\underline{H}_2CH_2CH_2CH_3$), 7.21 (1H, d, J=3 Hz, C_8-H), 7.36 (1H, dd, J=3, 9 Hz, C_6-H), 7.58 (1H, d, J=6 Hz, C_4-H), 7.72 (1H, d, J=9 Hz, C_5-H), 8.40 (1H, d, J=6 Hz, C_3-H), 9.14 (1H, s, C_1-H). HRMS Calcd for $C_{13}H_{15}NO$: 201.1153. Found: 201.1174.

7-Alkoxy-8-nitroisoquinoline (36) A solution of KNO_3 (4.65 g, 0.046 mol) in H_2SO_4 (35 ml) was added dropwise to **35** (0.04 mol) in H_2SO_4 (95 ml) at 0—5 °C. The whole was kept at 0—5 °C for 1.5 h, poured onto ice (400 g), adjusted to pH 8—9 by addition of 20% aqueous NaOH solution and extracted with CH_2Cl_2. The extract was washed with water, dried and evaporated. The residue was chromatographed (eluting with CH_2Cl_2) to afford **36**.

36a: Yield 53%. mp 127—128 °C (recrystallized from CH_2Cl_2–ether). ^{1}H-NMR (100 MHz) δ: 1.48 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 4.32 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 7.52 (1H, d, J=9 Hz, C_6-H), 7.62 (1H, d, J=6 Hz, C_4-H), 7.94 (1H, d, J=9 Hz, C_5-H), 8.54 (1H, d, J=6 Hz, C_3-H), 9.18 (1H, s, C_1-H). *Anal.* Calcd for $C_{11}H_{10}N_2O_3$: C, 60.55; H, 4.62; N, 12.84. Found: C, 60.44; H, 4.45; N, 12.85.

36b: Yield 58%. mp 74—75 °C (recrystallized from CH_2Cl_2–hexane). ^{1}H-NMR (400 MHz) δ: 0.98 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.51 (2H, sextet, J=7 Hz, $C\underline{H}_2CH_3$), 1.82 (2H, quintet, J=7 Hz, $C\underline{H}_2CH_2CH_3$), 4.25 (2H, t, J=7 Hz, $C\underline{H}_2CH_2CH_2CH_3$), 7.55 (1H, d, J=9 Hz, C_6-H), 7.64 (1H, d, J=6 Hz, C_4-H), 7.95 (1H, d, J=9 Hz, C_5-H), 8.55 (1H, d, J=6 Hz, C_3-H), 9.18 (1H, s, C_1-H). *Anal.* Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.34; H, 5.66; N, 11.41.

7-Alkoxy-8-nitroisoquinoline *N*-Oxide (37) *m*-Chloroperoxybenzoic acid (80% purity, 4.75 g, 22 mmol) was added to a solution of **36** (20 mmol) in CH_2Cl_2 (100 ml). The whole was stirred at 20 °C for 4 h, and chromatographed. The fraction eluting with ethyl acetate was discarded, and the *N*-oxide **37** was obtained from the fraction eluting with ethyl acetate–ethanol (7 : 3). An analytical specimen was prepared by recrystallization from CH_2Cl_2–ether.

37a: Yield 94%. mp 208—211 °C. ^{1}H-NMR (100 MHz) δ: 1.49 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 4.36 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 7.40 (1H, d, J=9 Hz, C_6-H), 7.66 (1H, d, J=7 Hz, C_4-H), 7.94 (1H, d, J=9 Hz, C_5-H), 8.09 (1H, dd, J=7, 2 Hz, C_3-H), 8.70 (1H, d, J=2 Hz, C_1-H). *Anal.* Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.96. Found: C, 56.30; H, 4.22; N,

11.72.

37b: Yield 98%. mp 151—152 °C. ^{1}H-NMR (400 MHz) δ: 0.98 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.50 (2H, sextet, J=7 Hz, $C\underline{H}_2CH_3$), 1.82 (2H, quintet, J=7 Hz, $C\underline{H}_2CH_2CH_3$), 4.25 (2H, t, J=7 Hz, $C\underline{H}_2CH_2CH_2CH_3$), 7.40 (1H, d, J=9 Hz, C_6-H), 7.66 (1H, d, J=7 Hz, C_4-H), 7.90 (1H, d, J=9 Hz, C_5-H), 8.05 (1H, dd, J=7, 1.5 Hz, C_3-H), 8.66 (1H, d, J=1.5 Hz, C_1-H). *Anal.* Calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.35; H, 5.22; N, 10.65.

7-Alkoxy-1-cyano-8-nitroisoquinoline (38) Trimethylsilyl cyanide (6 ml, 45 mmol) was added to a suspension of **37** (15 mmol) in 1-methyl-2-pyrrolidinone (30 ml). The whole was kept at 50—60 °C for 20 min, and then 20 °C for 20 h, and diluted with water (150 ml). The precipitated crystals were collected by filtration, washed with water, dried and recrystallized.

38a: Yield 65%. mp 203—204 °C (recrystallized from CH_2Cl_2–ether). ^{1}H-NMR (400 MHz) δ: 1.49 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 4.39 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 7.71 (1H, d, J=9 Hz, C_6-H), 7.96 (1H, d, J=6 Hz, C_4-H), 8.11 (1H, d, J=9 Hz, C_5-H), 8.67 (1H, d, J=6 Hz, C_3-H). IR (KBr): 2220 cm^{-1} (CN). *Anal.* Calcd for $C_{12}H_9N_3O_3$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.21; H, 3.53; N, 17.24.

38b: Yield 64%. mp 94—95 °C (recrystallized from ether–hexane). ^{1}H-NMR (400 MHz) δ: 0.98 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.50 (2H, sextet, J=7 Hz, $C\underline{H}_2CH_3$), 1.84 (2H, quintet, J=7 Hz, $C\underline{H}_2CH_2CH_3$), 4.30 (2H, t, J=7 Hz, $C\underline{H}_2CH_2CH_2CH_3$), 7.70 (1H, d, J=9 Hz, C_6-H), 7.94 (1H, d, J=6 Hz, C_4-H), 8.09 (1H, d, J=9 Hz, C_5-H), 8.66 (1H, d, J=6 Hz, C_3-H). IR (KBr): 2220 cm^{-1} (CN). *Anal.* Calcd for $C_{14}H_{13}N_3O_3$: C, 61.99; H, 4.83; N, 15.49. Found: C, 61.85; H, 4.78; N, 15.45.

7-Alkoxy-8-amino-1-cyanoisoquinoline (39) The 8-nitroisoquinoline (**38**) (2.5 g) in *N*,*N*-dimethylformamide (100 ml) was hydrogenated for 9 h using 10% palladium on carbon (2.5 g) as a catalyst. The catalyst was filtered off and the solvent was removed *in vacuo*. The residue was chromatographed with ethyl acetate–hexane (2 : 3) as the eluent to afford **39**, which was recrystallized from CH_2Cl_2–ether.

39a: Yield 41%. mp 95—96 °C. ^{1}H-NMR (400 MHz) δ: 1.51 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 4.24 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 5.38 (2H, br, NH_2), 7.27 (1H, d, J=9 Hz, C_6-H), 7.44 (1H, d, J=9 Hz, C_5-H), 7.70 (1H, d, J=6 Hz, C_4-H), 8.37 (1H, d, J=6 Hz, C_3-H). IR (KBr): 2210 cm^{-1} (CN); 3370, 3460 cm^{-1} (NH_2). *Anal.* Calcd for $C_{12}H_{11}N_3O$: C, 67.59; H, 5.20; N, 19.71. Found: C, 67.86; H, 5.08; N, 19.57.

39b: Yield 56%. mp 84—85 °C. ^{1}H-NMR (400 MHz) δ: 1.02 (3H, t, J=7 Hz, $CH_2C\underline{H}_3$), 1.56 (2H, sextet, J=7 Hz, $C\underline{H}_2CH_3$), 1.87 (2H, quintet, J=7 Hz, $C\underline{H}_2CH_2CH_3$), 4.17 (2H, t, J=7 Hz, $C\underline{H}_2CH_2CH_2CH_3$), 5.38 (2H, br, NH_2), 7.27 (1H, d, J=9 Hz, C_6-H), 7.45 (1H, d, J=9 Hz, C_5-H), 7.70 (1H, d, J=6 Hz, C_4-H), 8.36 (1H, d, J=6 Hz, C_3-H). IR (KBr): 2215 cm^{-1} (CN); 3370, 3460 cm^{-1} (NH_2). *Anal.* Calcd for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.41. Found: C, 69.43; H, 6.32; N, 17.34.

7-Alkoxy-1-cyano-5,8-isoquinolinedione (40) A solution of **39** (4 mmol) in acetone (20 ml) was added to a solution of Fremy's salt (5.37 g, 20 mmol) in 1/15 M KH_2PO_4 (225 ml). The mixture was kept at 60 °C for 5 min and then at 20 °C for 1 h, and extracted with CH_2Cl_2 (3 × 120 ml). The extract was washed with 10% HCl (150 ml) and water (150 ml), dried and evaporated. The residue was chromatographed (eluting with CH_2Cl_2) to afford the quinone **40**, which was recrystallized from CH_2Cl_2–ether.

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