Synthesis of 8-Amino-5,6-quinolinediones from 6-Quinolinols and 5,6-Dimethoxyquinolines

Yoshiyasu KITAHARA, Tatsuya NAKAI, Masaro SHIMIZU and Akinori KUBO*

Meiji College of Pharmacy, 1-35-23 Nozawa, Setagaya-ku, Tokyo 154, Japan. *Received February 21, 1990*

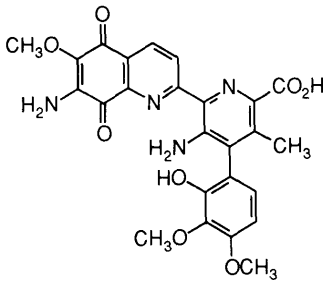
Twenty-five 8-amino-5,6-quinolinediones were prepared by copper(II)-catalyzed oxidation of 6-quinolinol in methanol with secondary amines, or by oxidative demethylation of the corresponding 5,6-dimethoxyquinolines in aqueous acetonitrile with cerium(IV) ammonium nitrate.

Keywords synthesis; 5,6-quinolinedione; 8-amino-5,6-quinolinedione; copper(II) acetate; oxidation; cerium(IV) ammonium nitrate; oxidative demethylation

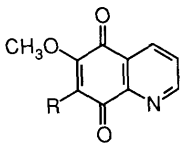
Streptonigrin (**1**), a highly substituted 5,8-quinolinedione, was originally reported as an antitumor antibiotic produced by *Streptomyces flocculus*.[1] Later, it was found to be a potent inhibitor of avian myeloblastosis virus (AMV) reverse transcriptase,[2] though the marked cytotoxicity of **1** made it difficult for its antiviral activity to be evaluated.[3] Recently, we observed that four synthetic quinoline quinones (**2**—**5**), especially 5,6-quinolinediones (**4**, **5**), were much less toxic than **1**, while the ID_{50} values against AMV reverse transcriptase were comparable to that of **1**[4] (Chart 1). Further efforts to discover specific inhibitors of reverse transcriptase have been continued employing various quinones. We wish to report here the synthesis of various 8-amino-5,6-quinolinediones.

In 1967, Tsizin and Rubtsov reported the synthesis of several 8-dialkylamino-5,6-quinolinediones by copper(II)-catalyzed oxidation of 6-quinolinols in methanol with secondary amines.[5] This procedure seems to be good for the preparation of a variety of 8-dialkylamino-5,6-quinolinediones from easily available 6-quinolinols (**6**—**8**),[6] but only a few kinds of secondary amines, such as morpholine, diethylamine, and methylalkylamines, were employed.[5,7] We re-examined this reaction. Treatment of 6-quinolinols (**6**—**8**) with dimethylamine (**9a**) or cyclic secondary amines (**9b**—**d**) in the presence of copper(II) acetate in methanol afforded the corresponding 8-dialkylamino-5,6-quinolinediones (**10**—**12**) in 23—88% yields. However, when secondary amines, *i.e.* dibutylamine (**9e**), dihexylamine and dioctylamine (**9f**), were employed, no 8-dialkylamino-5,6-quinolinedione was obtained. The 5,6-quinolinediones, **10e** and **10f**, were prepared by reaction of 8-methoxy-5,6-quinolinedione (**4**)[8] and dibutylamine (**9e**) or dioctylamine (**9f**) in methanol at room temperature. (Chart 2). The spectral data of **10**—**12** are given in Table I.

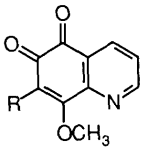
The structure of 8-dimethylamino-5,6-quinolinedione (**10a**) was confirmed by the following independent synthesis (Chart 3). 8-Amino-5,6-dimethoxyquinoline (**13**)[9] was treated with formalin and sodium cyanoborohydride[10] in acetonitrile to afford the *N*,*N*-dimethylaminoquinoline (**14**) in 93% yield. Oxidative demethylation of **14** with cerium (IV) ammonium nitrate (CAN) in aqueous acetonitrile[11] gave only 6-methoxy-5,8-quinolinedione (**2**) in 17% yield. Treatment of **14** with 48% hydrobromic acid followed by aqueous potassium hydroxide solution afforded the desired



1

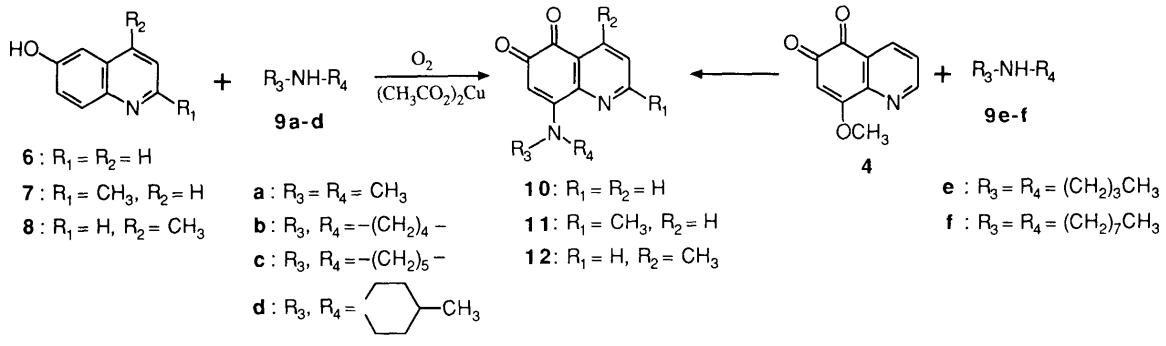


2 : R= H
3 : R= CH_3



4 : R= H
5 : R= CH_3

Chart 1



6 : $R_1 = R_2 = H$
7 : $R_1 = CH_3$, $R_2 = H$
8 : $R_1 = H$, $R_2 = CH_3$

9a-d

a : $R_3 = R_4 = CH_3$
b : R_3, $R_4 = -(CH_2)_4-$
c : R_3, $R_4 = -(CH_2)_5-$
d : R_3, R_4 =

10: $R_1 = R_2 = H$
11: $R_1 = CH_3$, $R_2 = H$
12: $R_1 = H$, $R_2 = CH_3$

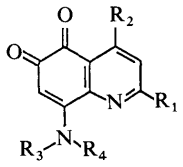
4

9e-f

e : $R_3 = R_4 = (CH_2)_3CH_3$
f : $R_3 = R_4 = (CH_2)_7CH_3$

Chart 2

TABLE I. 8-Dialkylamino-5,6-quinolinediones (**10**—**12**)



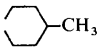
	R_1	R_2	R_3	R_4	Yield [%]	mp [°C] [lit. mp]	Formula	Analysis or HRMS Calcd (Found) C	H	N	MS *m/z* (%)	IR (KBr) [cm^{-1}]	^{1}H-NMR (400 MHz) δ ($CDCl_3$, J=Hz)
10a	H	H	CH_3	CH_3	69	161—163	$C_{11}H_{10}N_2O_2$	65.34 (65.14)	4.98 4.79	13.85 13.37)	202 (M^+, 34) 174 (M^+-CO, 100)	1692 1602	3.49 (6H, s, $N(CH_3)_2$), 6.06 (1H, s, C_7-H), 7.49 (1H, dd, J=5, 8, C_3-H), 8.39 (1H, dd, J=2, 8, C_4-H), 8.81 (1H, dd, J=2, 5, C_2-H)
10b	H	H	$-(CH_2)_4-$		50	160—162 (dec.)	$C_{13}H_{12}N_2O_2 \cdot 1/10H_2O$	67.87 (68.06	5.35 5.19	12.18 12.32)	228 (M^+, 75) 200 (M^+-CO, 88) 144 (100)	1686 1611	2.0—2.1 (4H, m), 3.63 (2H, br s) and 4.44 (2H, br s) for $-(CH_2)_4-$, 6.00 (1H, s, C_7-H), 7.48 (1H, dd, J=5, 8, C_3-H), 8.40 (1H, dd, J=2, 8, C_4-H), 8.79 (1H, dd, J=2, 5, C_2-H)
10c	H	H	$-(CH_2)_5-$		83	134—136 [135—137][7]	$C_{14}H_{14}N_2O_2 \cdot 1/10H_2O$	68.89 (68.92	5.86 5.75	11.48 11.52)	242 (M^+, 79) 214 (M^+-CO, 100)	1692 1618	1.7—1.9 (6H, m) and 3.8—3.9 (4H, m) for $-(CH_2)_5-$, 6.17 (1H, s, C_7-H), 7.47 (1H, dd, J=5, 8, C_3-H), 8.38 (1H, dd, J=2, 8, C_4-H), 8.80 (1H, dd, J=2, 5, C_2-H)
10d	H	H			41	166—167	$C_{15}H_{16}N_2O_2$	70.29 (70.19	6.29 6.25	10.93 10.86)	256 (M^+, 85) 228 (M^+-CO, 100)	1690 1613	1.03 (3H, d, J=6, CH_3-CH), 1.4—1.9 (5H, m), 3.22 (2H, dt, J=2, 13) and 4.49 (2H, d, J=13) for $-(CH_2)_2CH(CH_2)_2-$, 6.17 (1H, s, C_7-H), 7.47 (1H, dd, J=5, 8, C_3-H), 8.38 (1H, dd, J=2, 8, C_4-H), 8.80 (1H, dd, J=2, 5, C_2-H)
10e	H	H	C_4H_9	C_4H_9	88	Oil	$C_{17}H_{22}N_2O_2$	286.1681 (286.1710)			286 (M^+, 42) 229 ($M^+-C_4H_9$, 100)	1698 1612	0.99 (6H, t, J=7, 2×CH_3), 1.40 (4H, sextet, J=7, 2×CH_3CH_2), 1.7—1.9 (4H, m, 2×$CH_3CH_2CH_2$), 3.8 (4H, br s, 2×CH_2N), 6.06 (1H, s, C_7-H), 7.48 (1H, dd, J=5, 8, C_3-H), 8.39 (1H, dd, J=2, 8, C_4-H), 8.77 (1H, dd, J=2, 5, C_2-H)
10f	H	H	C_8H_{17}	C_8H_{17}	57	Oil	$C_{25}H_{38}N_2O_2$	398.2933 (398.2914)			398 (M^+, 32) 285 ($M^+-C_8H_{17}$, 100)	1700 1614	0.89 (6H, t, J=7, 2×CH_3), 1.1—1.9 (24H, m, 2×CH_3-$(CH_2)_6CH_2$), 3.77 (4H, br s, 2×CH_2N), 6.06 (1H, s, C_7-H), 7.48 (1H, dd, J=5, 8, C_3-H), 8.39 (1H, dd, J=2, 8, C_4-H), 8.77 (1H, dd, J=2, 5, C_2-H)
11a	CH_3	H	CH_3	CH_3	60	171—173 [168—170][5c]	$C_{12}H_{12}N_2O_2$	66.65 (66.43	5.59 5.44	12.96 12.87)	216 (M^+, 31) 188 (M^+-CO, 92) 159 (100)	1686 1610	2.66 (3H, s, C_2-CH_3), 3.51 (6H, s, $N(CH_3)_2$), 6.11 (1H, s, C_7-H), 7.33 (1H, d, J=8, C_3-H), 8.28 (1H, d, J=8, C_4-H)
11b	CH_3	H	$-(CH_2)_4-$		88	181—183 (dec.)	$C_{14}H_{14}N_2O_2 \cdot 1/5H_2O$	68.39 (68.32	5.90 5.79	11.39 11.48)	242 (M^+, 56) 214 (M^+-CO, 100)	1682 1602	2.06 (4H, br s), 3.62 (2H, br s) and 4.47 (2H, br s) for $-(CH_2)_4-$, 2.65 (3H, s, C_2-CH_3), 5.99 (1H, s, C_7-H), 7.31 (1H, d, J=8, C_3-H), 8.29 (1H, d, J=8, C_4-H)
11c	CH_3	H	$-(CH_2)_5-$		65	166—168 [170—171][5c]	$C_{15}H_{16}N_2O_2$	70.29 (70.15	6.29 6.25	10.93 10.79)	256 (M^+, 41) 228 (M^+-CO, 100)	1690 1617	1.7—1.9 (6H, m) and 3.85 (4H, br s) for $-(CH_2)_5-$, 2.65 (3H, s, C_2-CH_3), 6.12 (1H, s, C_7-H), 7.31 (1H, d, J=8, C_3-H), 8.27 (1H, d, J=8, C_4-H)
11d	CH_3	H			58	122—124	$C_{16}H_{18}N_2O_2$	71.09 (71.27	6.71 6.66	10.36 10.29)	270 (M^+, 45) 242 (M^+-CO, 100)	1694 1617	1.03 (3H, d, J=6, CH_3-CH), 1.4—1.9 (5H, m), 3.20 (2H, dt, J=2, 13) and 4.40 (2H, br s) for $-(CH_2)_2CH(CH_2)_2-$, 2.65 (3H, s, C_2-CH_3), 6.12 (1H, s, C_7-H), 7.31 (1H, d, J=8, C_3-H), 8.27 (1H, d, J=8, C_4-H)
12a	H	CH_3	CH_3	CH_3	53	180—182	$C_{12}H_{12}N_2O_2 \cdot 1/10H_2O$	66.10 (66.26	5.64 5.47	12.85 12.80)	216 (M^+, 29) 188 (M^+-CO, 82) 159 (100)	1686 1605	2.73 (3H, s, C_4-CH_3), 3.40 (6H, s, $N(CH_3)_2$), 5.99 (1H, s, C_7-H), 7.24 (1H, d, J=5, C_3-H), 8.59 (1H, d, J=5, C_2-H)
12b	H	CH_3	$-(CH_2)_4-$		60	185—188 (dec.)	$C_{14}H_{14}N_2O_2 \cdot 1/10H_2O$	68.89 (68.64	5.86 5.74	11.48 11.19)	242 (M^+, 62) 214 (M^+-CO, 100)	1682 1607	2.02 (4H, br s), 3.60 (2H, br s) and 4.35 (2H, br s) for $-(CH_2)_4-$, 2.74 (3H, s, C_4-CH_3), 5.94 (1H, s, C_7-H), 7.24 (1H, d, J=5, C_3-H), 8.57 (1H, d, J=5, C_2-H)
12c	H	CH_3	$-(CH_2)_5-$		26	107—109	$C_{15}H_{16}N_2O_2$	70.29 (70.07	6.29 6.25	10.93 10.79)	256 (M^+, 69) 228 (M^+-CO, 100)	1692 1620	1.80 (6H, br s) and 3.75 (4H, br s) for $-(CH_2)_5-$, 2.73 (3H, s, C_4-CH_3), 6.10 (1H, s, C_7-H), 7.23 (1H, d, J=5, C_3-H), 8.60 (1H, d, J=5, C_2-H)

TABLE I. (continued)

	R_1	R_2	R_3	R_4	Yield [%]	mp [°C] [lit. mp]	Formula	Analysis or HRMS Calcd (Found) C	H	N	MS m/z (%)	IR (KBr) [cm^{-1}]	^{1}H-NMR (400 MHz) δ ($CDCl_3$, J=Hz)
12d	H	CH_3		CH_3	23	127—129	$C_{16}H_{18}N_2O_2$	71.09 (70.98	6.71 6.67	10.36 10.16)	270 (M^+, 78) 242 (M^+−CO, 100)	1685 1619	1.02 (3H, t, J=6, CH_3-CH), 1.4—1.9 (5H, m), 3.17 (2H, t, J=12) and 4.32 (2H, d, J=12) for −$(CH_2)_2CH(CH_2)_2$−, 2.73 (3H, s, C_4-CH_3), 6.11 (1H, s, C_7-H), 7.23 (1H, d, J=5, C_3-H), 8.60 (1H, d, J=5, C_2-H)

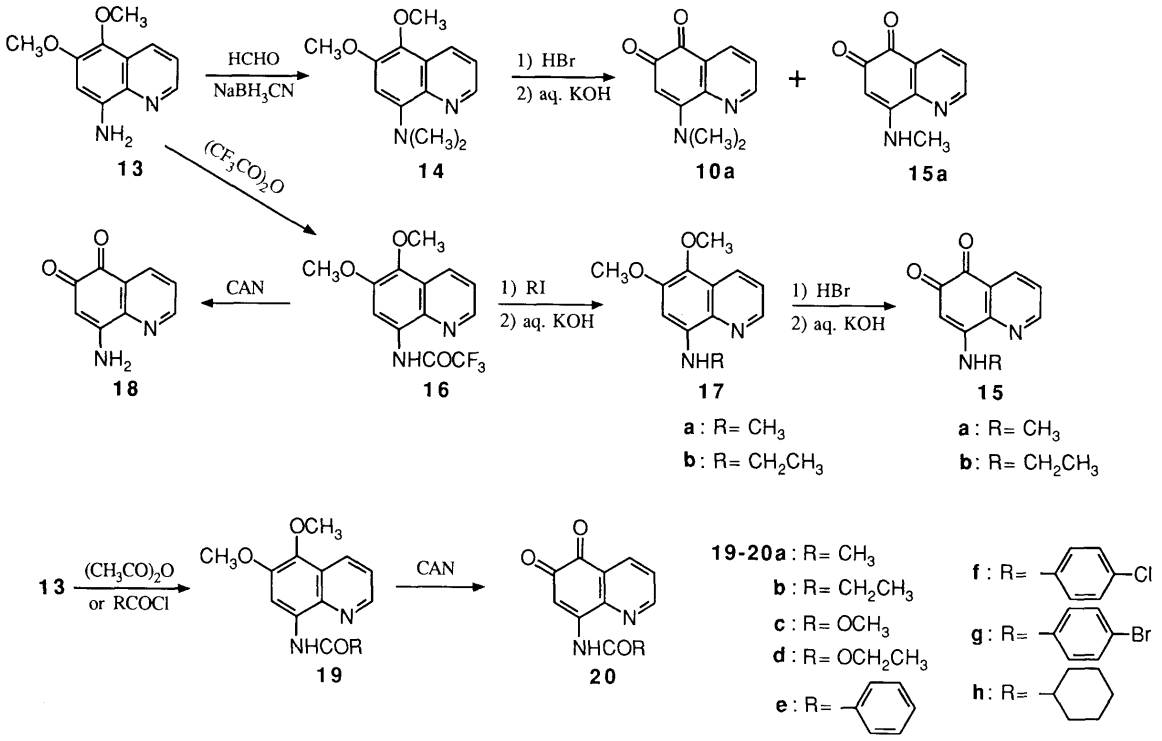


Chart 3

8-dimethylamino-5,6-quinolinedione (**10a**) (16% yield) in addition to 8-methylamino-5,6-quinolinedione (**15a**) (9% yield). The dimethylaminoquinoline (**10a**) thus obtained was identical with the quinone **10a** obtained from **6** in terms of mixed melting point, and infrared (IR), proton nuclear magnetic resonance (^{1}H-NMR) and mass (MS) spectra.

Next, we prepared 8-alkylamino-5,6-quinolinediones (**15**). 5,6-Dimethoxy-8-trifluoroacetylaminoquinoline (**16**), obtained from **13**, was treated with methyl (or ethyl) iodide followed by aqueous potassium hydroxide[12] to give the corresponding 8-alkylaminoquinolines (**17**). Treatment of **17** with 48% hydrobromic acid followed by aqueous potassium hydroxide gave the desired 8-alkylamino-5,6-quinolinediones (**15**). Alternatively, oxidative demethylation of **17a** with CAN gave the *o*-quinone **15a** (32% yield) in addition to a small amount of the methoxy *p*-quinone (**2**). Treatment of **16** with CAN afforded 8-amino-5,6-quinolinedione (**18**)[13] in 38% yield. However, attempted oxidative demethylation of **13** failed, giving a complex mixture.

Finally, we prepared 8-acylamino-5,6-quinolinediones (Chart 3). Acylation of **13** in a usual manner gave the intermediates **19**, which were oxidatively demethylated with CAN to give the corresponding 8-acylamino-5,6-quinolinediones (**20**) in 52—86% yields. The spectral data of **15**, **18** and **20** are given in Table II.

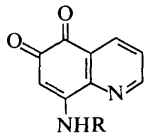
Biological activities of these 8-amino-5,6-quinolinediones (**10**—**12**, **15**, **18** and **20**) will be reported elsewhere.

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. ^{1}H-NMR spectra were measured in $CDCl_3$ (unless otherwise noted) at 60 or 400 MHz, 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 was performed with E. Merck Silica gel 60 (230—400 mesh) unless otherwise noted.

8-Dialkylamino-5,6-quinolinediones (10—12) from the Corresponding 6-Quinolinols (6—8) Copper(II) acetate (100 mg) and dimethylamine **9a** (0.8 ml of 50% aqueous solution) (or 0.4 ml of a cyclic secondary amine **9b—d**) were added to a solution of the 6-quinolinol **6** (or **7**, **8**) (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 (**10**—**12**) thus obtained was dissolved in a small amount of CH_2Cl_2, and triturated with hexane

TABLE II. 8-Alkylamino- and 8-Acylamino-5,6-quinolinediones (**15a**, **b**, **18** and **20a—h**)



	R	Yield [%]	Appearance (Recrystn. solv.)	mp [°C] [lit. mp]	Formula	Analysis Calcd (Found) C	H	N	MS *m/z* (%)	IR (KBr) [cm^{-1}]	^{1}H-NMR (400 MHz) δ (DMSO-d_6, J=Hz)[a]
15a	CH_3	37	Dark red prisms (MeOH)	>220 (dec.)	$C_{10}H_8N_2O_2 \cdot 1/10H_2O$	63.22 (63.08	4.35 4.08	14.75 14.54)	188 (M^+, 55) 160 (M^+-CO, 100)	1696 1604	3.04 (3H, d, J=7, CH_3), 5.75 (1H, s, C_7-H), 7.73 (1H, dd, J=5, 8, C_3-H), 8.31 (1H, dd, J=2, 8, C_4-H), 8.80 (1H, br, NH), 8.88 (1H, dd, J=2, 5, C_2-H)
15b	CH_2CH_3	59	Red plates (EtOH)	160—161	$C_{11}H_{10}N_2O_2$	65.34 (65.39	4.98 4.88	13.85 13.73)	202 (M^+, 49) 174 (M^+-CO, 93) 159 (100)	1700 1630	1.24 (3H, t, J=7, $CH_2C\underline{H}_3$), 3.46 (2H, quint, J=7, $C\underline{H}_2CH_3$), 5.82 (1H, s, C_7-H), 7.75 (1H, dd, J=5, 8, C_3-H), 8.31 (1H, dd, J=2, 8, C_4-H), 8.71 (1H, br, NH), 8.89 (1H, dd, J=2, 5, C_2-H)
18	H	38	Red needles (EtOH)	>300	$C_9H_6N_2O_2$	62.07 (62.01	3.47 3.27	16.08 16.23)	174 (M^+, 24) 146 (M^+-CO, 100)	1698 1664	5.91 (1H, s, C_7-H), 7.74 (1H, dd, J=5, 8, C_3-H), 8.08, 8.57 (each 1H, br, NH_2), 8.29 (1H, dd, J=2, 8, C_4-H), 8.89 (1H, dd, J=2, 5, C_2-H)
20a	$COCH_3$	81	Orange needles (EtOH)	207—209 [210.5—211][13]	$C_{11}H_8N_2O_3$	61.11 (60.98	3.73 3.46	12.96 12.79)	216 (M^+, 6) 188 (M^+-CO, 55) 146 (100)	1724 1698 1650	2.37 (3H, s, CH_3), 7.60 (1H, dd, J=4, 7, C_3-H), 7.80 (1H, s, C_7-H), 8.40 (1H, dd, J=2, 7, C_4-H), 8.80 (1H, dd, J=2, 4, C_2-H), 9.70 (1H, br, NH)
20b	$COCH_2CH_3$	62	Red prisms (EtOH)	209—210	$C_{12}H_{10}N_2O_3$	62.61 (62.68	4.38 4.26	12.17 11.99)	230 (M^+, 7) 202 (M^+-CO, 51) 146 (100)	1710 1648 1620	1.10 (3H, t, J=8, $CH_2C\underline{H}_3$), 2.68 (2H, q, J=8, $C\underline{H}_2CH_3$), 7.57 (1H, s, C_7-H), 7.76 (1H, dd, J=5, 8, C_3-H), 8.35 (1H, dd, J=2, 8, C_4-H), 8.91 (1H, dd, J=2, 5, C_2-H), 10.08 (1H, s, NH)
20c	CO_2CH_3	86	Orange needles (EtOH)	189—189.5	$C_{11}H_8N_2O_4$	56.90 (56.99	3.47 3.34	12.06 11.88)	232 (M^+, 2) 204 (M^+-CO, 100)	1750 1734 1702 1650	3.81 (3H, s, CH_3), 7.19 (1H, s, C_7-H), 7.77 (1H, dd, J=5, 8, C_3-H), 8.36 (1H, dd, J=2, 8, C_4-H), 8.89 (1H, dd, J=2, 5, C_2-H), 9.40 (1H, s, NH)
20d	$CO_2CH_2CH_3$	67	Orange needles (Benzene)	178—179	$C_{12}H_{10}N_2O_4$	58.54 (58.49	4.09 3.85	11.38 11.13)	246 (M^+, 2) 218 (M^+-CO, 100)	1740 1702 1652	1.57 (3H, t, J=7, $CH_2C\underline{H}_3$), 4.46 (2H, q, J=7, $C\underline{H}_2CH_3$), 7.51 (1H, s, C_7-H), 7.66 (1H, dd, J=4, 7, C_3-H), 8.46 (1H, dd, J=2, 7, C_4-H), 8.87 (1H, dd, J=2, 4, C_2-H), 9.26 (1H, br, NH)
20e	—CO—C$_6$H$_5$	54	Orange needles (EtOH)	242—244	$C_{16}H_{10}N_2O_3$	69.06 (69.16	3.62 3.33	10.07 10.08)	278 (M^+, 2) 250 (M^+-CO, 13) 105 (100)	1704 1680 1644	7.6—7.75 and 7.9—8.1 (5H, m, C_6H_5), 7.70 (1H, s, C_7-H), 7.82 (1H, dd, J=5, 8, C_3-H), 8.42 (1H, dd, J=2, 8, C_4-H), 8.97 (1H, dd, J=2, 5, C_2-H), 10.69 (1H, br, NH)
20f	—CO—C$_6$H$_4$—Cl	52	Red prisms (EtOAc)	250—251 (dec.)	$C_{16}H_9ClN_2O_3$	61.45 (61.46	2.90 2.62	8.96 9.00)	314 (M^++2, 1) 312 (M^+, 4) 286 (M^++2−CO, 8) 284 (M^+-CO, 23) 141 (34), 139 (100)	1698 1640 1612	7.64 (1H, s, C_7-H), 7.72, 8.02 (each 2H, d, J=7, C_6H_4Cl), 7.80 (1H, dd, J=5, 8, C_3-H), 8.41 (1H, dd, J=2, 8, C_4-H), 8.96 (1H, dd, J=2, 5, C_2-H), 10.65 (1H, s, NH)
20g	—CO—C$_6$H$_4$—Br	79	Red prisms (EtOH)	262—263 (dec.)	$C_{16}H_9BrN_2O_3$	53.81 (53.75	2.54 2.38	7.84 7.83)	358 (M^++2, 5) 356 (M^+, 6) 330 (M^++2−CO, 29) 328 (M^+-CO, 29) 185 (96), 183 (100)	1694 1638 1612	7.64 (1H, s, C_7-H), 7.80 (1H, dd, J=5, 8, C_3-H), 7.86, 7.94 (each 2H, d, J=7, C_6H_4Br), 8.41 (1H, dd, J=2, 8, C_4-H), 8.96 (1H, dd, J=2, 5, C_2-H), 10.65 (1H, s, NH)
20h	—CO—C$_6$H$_{11}$	82	Orange needles (EtOH)	210—211	$C_{16}H_{16}N_2O_3$	67.59 (67.62	5.67 5.57	9.85 9.75)	284 (M^+, 7) 256 (M^+-CO, 66) 83 (100)	1706 1650	1.2—2.8 (11H, m, C_6H_{11}), 7.56 (1H, s, C_7-H), 7.76 (1H, dd, J=5, 8, C_3-H), 8.35 (1H, dd, J=2, 8, C_4-H), 8.92 (1H, dd, J=2, 5, C_2-H), 10.08 (1H, s, NH)

a) Quinones **20a** and **20d** were measured at 60 MHz in $CDCl_3$.

to afford the desired product as dark red needles (or powder).

8-Dibutyl- (or 8-Dioctyl-)amino-5,6-quinolinedione (10e, f) A solution of 8-methoxy-5,6-quinolinedione (**4**, 95 mg, 0.5 mmol) and 5 mmol of dibutylamine (**9e**) (or dioctylamine, **9f**) in methanol (10 ml) was kept at 20 °C for 30 min. The solvent was removed and the residue was subjected to column chromatography (elution with ethyl acetate–hexane 2:3) to afford **10e** (or **10f**) as a dark red oil.

8-Dimethylamino-5,6-dimethoxyquinoline (14) Formalin (1.7 ml, 20

mmol), sodium cyanoborohydride (377 mg, 6 mmol) and acetic acid (0.15 ml) were added to a solution of 8-amino-5,6-dimethoxyquinoline (**13**, 408 mg, 2 mmol) in acetonitrile (10 ml). The resulting mixture was kept at 20 °C for 30 min, and then acetic acid (0.15 ml) was added. The whole was kept at 20 °C for 30 min, and extracted with ether (20 ml). The extract was washed with 5% NaOH (3 × 10 ml) and brine, dried and evaporated. The residue was subjected to column chromatography on alumina (elution with ethyl acetate–hexane 1 : 10) to afford **14** (433 mg, 93%). mp 89—90 °C (hexane). *Anal.* Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.05; H, 6.89; N, 12.01. MS *m/z*: 232 (M^+, 91), 217 (100). ^{1}H-NMR (60 MHz) δ: 3.08 (6H, s, $N(CH_3)_2$), 3.92 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 6.93 (1H, s, C_7-H), 7.34 (1H, dd, J=4, 7 Hz, C_3-H), 8.46 (1H, dd, J=2, 7 Hz, C_4-H), 8.74 (1H, dd, J=2, 4 Hz, C_2-H).

Demethylation of 14 Method A: A solution of CAN (1013 mg, 1.85 mmol) in acetonitrile–water (1 : 1, 5 ml) was added to an ice-cooled solution of **14** (143 mg, 0.62 mmol) in acetonitrile–water (1 : 1, 5 ml). The whole was kept at 0—5 °C for 10 min, neutralized with saturated aqueous $NaHCO_3$ solution, and extracted with $CHCl_3$ (3 × 10 ml). The extract was washed with brine, dried and evaporated. The residue was recrystallized from ethyl acetate to give 6-methoxy-5,8-quinolinedione (**2**) (20 mg, 17%) as yellow needles (mp 245—248 °C (dec.)); this product was identical with an authentic sample[8] in terms of mixed melting point, and IR and ^{1}H-NMR spectra.

Method B: A mixture of **14** (116 mg, 0.5 mmol) and 48% HBr (1 ml) was heated at 100 °C for 5 h under argon, and then cooled. The precipitated crystals were collected by filtration and dissolved in 1 N KOH (5 ml). The resulting solution was left for 5 min, and extracted with $CHCl_3$ (5 × 10 ml). The extract was washed with brine, dried, and evaporated. The residue was subjected to preparative thin-layer chromatography (TLC) (silica gel, ethyl acetate–methanol 20 : 1) to afford a less polar quinone **15a** (8 mg, 9%) and a more polar quinone **10a** (16 mg, 16%).

5,6-Dimethoxy-8-trifluoroacetylaminoquinoline (16) Trifluoroacetic anhydride (5 ml) was added to **13** (1.02 g, 5 mmol) at 0 °C. The mixture was kept at 0 °C for 15 min, then poured into ice-water, and extracted with $CHCl_3$ (3 × 10 ml). The extract was washed with 10% $NaHCO_3$ and water, dried and evaporated. The residue was subjected to column chromatography (elution with $CHCl_3$) to afford **16** (1.244 g, 83%). mp 109—110 °C (hexane). *Anal.* Calcd for $C_{13}H_{11}F_3N_2O_3$: C, 52.01; H, 3.69; N, 9.33. Found: C, 52.10; H, 3.57; N, 9.31. MS *m/z*: 300 (M^+, 100), 285 (51), 231 (95), 216 (55). IR (KBr): 1712 (C=O), 3312 (NH) cm^{-1}. ^{1}H-NMR (60 MHz) δ: 3.91 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 7.42 (1H, dd, J=4, 7 Hz, C_3-H), 8.46 (1H, dd, J=2, 7 Hz, C_4-H), 8.62 (1H, s, C_7-H), 8.68 (1H, dd, J=2, 4 Hz, C_2-H), 10.5 (1H, br, NH).

8-Methyl- (or 8-Ethyl-)amino-5,6-dimethoxyquinoline (17a, b) A solution of **16** (450 mg, 1.5 mmol) and methyl (or ethyl) iodide (6 mmol) in acetone (10 ml) was warmed nearly to reflux, and powdered KOH (336 mg, 6 mmol) was added. The whole was refluxed for 3 h, then excess methyl (or ethyl) iodide and acetone were evaporated off. The residue was diluted with water (10 ml), heated at 100 °C for 1 h, then cooled and extracted with $CHCl_3$ (3 × 10 ml). The extract was washed with brine, dried and evaporated. The residue was subjected to column chromatography (elution with ethyl acetate–hexane 1 : 4) to afford **17**.

17a: Yield 82%. mp 59—60 °C (pentane). *Anal.* Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.90; H, 6.47; N, 12.80. MS *m/z*: 218 (M^+, 21), 203 (100). ^{1}H-NMR (60 MHz) δ: 2.98 (3H, s, NCH_3), 3.84 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 6.0 (1H, br, NH), 6.42 (1H, s, C_7-H), 7.36 (1H, dd, J=4, 7 Hz, C_3-H), 8.36 (1H, dd, J=2, 7 Hz, C_4-H), 8.69 (1H, dd, J=2, 4 Hz, C_2-H).

17b: Yield 77%. mp 39—40 °C (pentane). *Anal.* Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 66.98; H, 7.01; N, 11.99. MS *m/z*: 232 (M^+, 52), 217 (100). ^{1}H-NMR (60 MHz) δ: 1.38 (3H, t, J=7 Hz, $CH_2\underline{CH}_3$), 3.28 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 3.88 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 5.90 (1H, br, NH), 6.40 (1H, s, C_7-H), 7.29 (1H, dd, J=4, 7 Hz, C_3-H), 8.31 (1H, dd, J=2, 7 Hz, C_4-H), 8.55 (1H, dd, J=2, 4 Hz, C_2-H).

Demethylation of 17a, b Method A: A solution of CAN (822 mg, 1.5 mmol) in acetonitrile–water (1 : 1, 5 ml) was added to an ice-cooled solution of **17a** (109 mg, 0.5 mmol) in acetonitrile–water (1 : 1, 5 ml). The whole was kept at 0—5 °C for 10 min, neutralized with saturated aqueous $NaHCO_3$ solution, and extracted with $CHCl_3$ (3 × 10 ml). The extract was washed with brine, dried and evaporated. The residue was subjected to column chromatography (elution with ethyl acetate) to afford a less polar methoxy *p*-quinone **2** (4 mg, 4% yield) and a more polar *o*-quinone **15a** (30 mg, 32% yield), which were recrystallized from methanol.

Method B: A mixture of **17a** (or **17b**) (0.5 mmol) and 48% HBr (1 ml) was heated at 100 °C for 5 h under argon, and then cooled. The precipitated crystals were collected by filtration and dissolved in 1 N KOH (5 ml). The resulting solution was left for 5 min, and extracted with $CHCl_3$ (5 × 10 ml). The extract was washed with brine, dried, and evaporated. The residue was recrystallized from methanol to afford **15a** in 37% yield (or **15b**, 59% yield).

8-Acetylamino-5,6-dimethoxyquinoline (19a) A solution of **13** (408 mg, 2 mmol) in acetic anhydride (2 ml) was kept for 30 min, then poured into ice-water, and extracted with $CHCl_3$ (3 × 10 ml). The extract was washed with 10% $NaHCO_3$ and water, dried and evaporated. The residue was subjected to column chromatography (elution with ethyl acetate–hexane 1 : 1) to afford **19a**, which was recrystallized from hexane. Yield 398 mg (81%), mp 82—83 °C. *Anal.* Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.14; H, 5.68; N, 11.26. MS *m/z*: 246 (M^+, 60), 189 (100). IR (KBr): 1682 (C=O), 3332, 3356 (NH) cm^{-1}. ^{1}H-NMR (60 MHz) δ: 2.32 (3H, s, $COCH_3$), 3.94 (3H, s, OCH_3), 4.02 (3H, s, OCH_3), 7.35 (1H, dd, J=4, 8 Hz, C_3-H), 8.40 (1H, dd, J=2, 8 Hz, C_4-H), 8.59 (1H, dd, J=2, 4 Hz, C_2-H), 8.74 (1H, s, C_7-H), 9.70 (1H, br, NH).

8-Acylamino-5,6-dimethoxyquinolines (19b—h) Acyl chloride (or methyl chloroformate, ethyl chloroformate) (1.2 mmol) was added to a solution of **13** (204 mg, 1 mmol) in pyridine (2 ml) at 0—5 °C. The whole was kept at 0—5 °C for 30 min, then poured into ice-water, and extracted with $CHCl_3$ (3 × 10 ml). The extract was washed successively with water, 10% HCl, water, 10% $NaHCO_3$, and water, dried and evaporated. The residue was subjected to column chromatography (elution with ethyl acetate–hexane 1 : 4—1 : 1) to afford the corresponding product (**19b—h**), which was recrystallized.

19b: Yield 91%. mp 112—113 °C (70% ethanol). *Anal.* Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.59; H, 6.19; N, 10.73. MS *m/z*: 260 (M^+, 59), 189 (100). IR (KBr): 1682 (C=O), 3364 (NH) cm^{-1}. ^{1}H-NMR (60 MHz) δ: 1.32 (3H, t, J=7 Hz, $CH_2\underline{CH}_3$), 2.61 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 3.96 (3H, s, OCH_3), 4.04 (3H, s, OCH_3), 7.38 (1H, dd, J=4, 7 Hz, C_3-H), 8.42 (1H, dd, J=2, 7 Hz, C_4-H), 8.62 (1H, dd, J=2, 4 Hz, C_2-H), 8.79 (1H, s, C_7-H), 9.70 (1H, br, NH).

19c: Yield 81%. mp 94—95 °C (70% ethanol). *Anal.* Calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68. Found: C, 59.33; H, 5.33; N, 10.62. MS *m/z*: 262 (M^+, 63), 215 (100). IR (KBr): 1738 (C=O), 3356 (NH) cm^{-1}. ^{1}H-NMR (60 MHz) δ: 3.82 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 4.01 (3H, s, OCH_3), 7.34 (1H, dd, J=4, 7 Hz, C_3-H), 8.34 (1H, s, C_7-H), 8.35 (1H, dd, J=2, 7 Hz, C_4-H), 8.57 (1H, dd, J=2, 4 Hz, C_2-H), 9.08 (1H, br, NH).

19d: Yield 68%. mp 60—60.5 °C (pentane). *Anal.* Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.67; H, 5.82; N, 10.07. MS *m/z*: 276 (M^+, 85), 215 (100). IR (KBr): 1722, 1740 (C=O), 3368 (NH) cm^{-1}. ^{1}H-NMR (60 MHz) δ: 1.36 (3H, t, J=7 Hz, $CH_2\underline{CH}_3$), 3.93 (3H, s, OCH_3), 4.02 (3H, s, OCH_3), 4.29 (2H, q, J=7 Hz, $C\underline{H}_2CH_3$), 7.35 (1H, dd, J=4, 7 Hz, C_3-H), 8.36 (1H, dd, J=2, 7 Hz, C_4-H), 8.39 (1H, s, C_7-H), 8.61 (1H, dd, J=2, 4 Hz, C_2-H), 9.08 (1H, br, NH).

19e: Yield 88%. mp 118—119 °C (ethanol). *Anal.* Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.20; H, 5.08; N, 9.08. MS *m/z*: 308 (M^+, 70), 105 (100). IR (KBr): 1680 (C=O), 3364 (NH) cm^{-1}. ^{1}H-NMR (60 MHz) δ: 3.95 (3H, s, OCH_3), 4.05 (3H, s, OCH_3), 7.4—7.7 (5H, m, C_6H_5), 8.10 (1H, dd, J=4, 7 Hz, C_3-H), 8.44 (1H, dd, J=2, 7 Hz, C_4-H), 8.67 (1H, dd, J=2, 4 Hz, C_2-H), 8.95 (1H, s, C_7-H), 10.65 (1H, br, NH).

19f: Yield 89%. mp 131.5—132.5 °C (ethanol). *Anal.* Calcd for $C_{18}H_{15}ClN_2O_3$: C, 63.07; H, 4.41; N, 8.17. Found: C, 63.08; H, 4.22; N, 8.19. MS *m/z*: 344 (M^+ + 2, 21), 342 (M^+, 59), 141 (33), 139 (100). IR (KBr): 1682 (C=O), 3388 (NH) cm^{-1}. ^{1}H-NMR (60 MHz) δ: 3.94 (3H, s, OCH_3), 4.03 (3H, s, OCH_3), 7.35 (1H, dd, J=4, 7 Hz, C_3-H), 7.43, 7.94 (each 2H, d, J=8 Hz, C_6H_4Cl), 8.39 (1H, dd, J=2, 7 Hz, C_4-H), 8.63 (1H, dd, J=2, 4 Hz, C_2-H), 8.84 (1H, s, C_7-H), 10.54 (1H, br, NH).

19g: Yield 86%. mp 136—136.5 °C (ethanol). *Anal.* Calcd for $C_{18}H_{15}BrN_2O_3$: C, 55.83; H, 3.90; N, 7.23. Found: C, 55.99; H, 3.70; N, 7.30. MS *m/z*: 388 (M^+ + 2, 73), 386 (M^+, 75), 185 (98), 183 (100). IR (KBr): 1678 (C=O), 3384 (NH) cm^{-1}. ^{1}H-NMR (60 MHz) δ: 3.93 (3H, s, OCH_3), 4.02 (3H, s, OCH_3), 7.34 (1H, dd, J=4, 7 Hz, C_3-H), 7.57, 7.86 (each 2H, d, J=8 Hz, C_6H_4Br), 8.38 (1H, dd, J=2, 7 Hz, C_4-H), 8.61 (1H, dd, J=2, 4 Hz, C_2-H), 8.83 (1H, s, C_7-H), 10.56 (1H, br, NH).

19h: Yield 94%. mp 82—83 °C (pentane). *Anal.* Calcd for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.59; H, 7.12; N, 8.81. MS *m/z*: 314 (M^+, 92), 189 (100). IR (KBr): 1664 (C=O), 3360 (NH) cm^{-1}. ^{1}H-NMR (60 MHz) δ: 1.1—2.8 (11H, m, C_6H_{11}), 3.92 (3H, s, OCH_3), 4.01 (3H, s, OCH_3), 7.35 (1H, dd, J=4, 7 Hz, C_3-H), 8.38 (1H, dd, J=2, 7 Hz, C_4-H), 8.62 (1H, dd, J=2, 4 Hz, C_2-H), 8.79 (1H, s, C_7-H), 10.79 (1H, br, NH).

8-Amino-5,6-quinolinedione (18) and 8-Acylamino-5,6-quinolinediones (20a—h) A solution of CAN (1644 mg, 3 mmol) in acetonitrile–water (1 : 1, 10 ml) was added to an ice-cooled solution of **16** (or **19a—h**) (1 mmol) in acetonitrile–water (1 : 1, 10 ml). The whole was kept at 0—5 °C for 5 min (15—30 min for **19a—h**), neutralized with saturated $NaHCO_3$, and extracted with $CHCl_3$ (3 × 10 ml). The extract was washed with brine, dried and evaporated. The residue was recrystallized to afford **18** (or **20a—h**).

References

1) K. V. Rao and W. P. Cullen, "Antibiotics Annual, 1959—1960," ed. by H. Welch and F. Marti-Ibañez, Medical Encyclopedia Inc., New York, 1960, pp. 950—953.
2) M. A. Chirigos, J. W. Pearson, T. S. Papas, W. A. Woods, H. B. Wood, Jr. and G. Spahn, *Cancer Chemother. Rep.*, **57**, 305 (1973).
3) Y. Inouye, Y. Take, S. Nakamura, H. Nakashima, N. Yamamoto and H. Kawaguchi, *J. Antibiot.*, **40**, 100 (1987).
4) Y. Take, K. Oogose, T. Kubo, Y. Inouye, S. Nakamura, Y. Kitahara and A. Kubo, *J. Antibiot.*, **40**, 679 (1987).
5) *a*) Yu. S. Tsizin and M. V. Rubtsov, U.S.S.R. Patent 188495 [*Chem. Abstr.*, **67**, 90696*s* (1967)]; *b*) *Idem*, *Khim. Geterotsikl. Soedin., Sb. 1: Azotsoderzhashchie Geterotsikly*, **1967**, 291 [*Chem. Abstr.*, **70**, 87516*q* (1969)]; *c*) *Idem*, *ibid.*, **1967**, 285 [*Chem. Abstr.*, **70**, 87520*m* (1969)].
6) *a*) K. N. Campbell and I. J. Schaffner, *J. Am. Chem. Soc.*, **67**, 86 (1945); *b*) M. A. Clapp and R. S. Tipson, *ibid.*, **68**, 1332 (1946).
7) F. J. Bullock and J. F. Tweedie, *J. Med. Chem.*, **13**, 261 (1970).
8) A. Kubo, Y. Kitahara, S. Nakahara and R. Numata, *Chem. Pharm. Bull.*, **31**, 341 (1983).
9) R. C. Elderfield, W. J. Gensler, T. A. Williamson, J. M. Griffing, S. M. Kupchan, J. T. Maynard, F. J. Kreysa and J. B. Wright, *J. Am. Chem. Soc.*, **68**, 1584 (1946).
10) R. F. Borch and A. I. Hassid, *J. Org. Chem.*, **37**, 1673 (1972).
11) P. Jacob, III, P. S. Callery, A. T. Shulgin and N. Castagnoli, Jr., *J. Org. Chem.*, **41**, 3627 (1976).
12) R. A. W. Johnstone, D. W. Payling and C. Thomas, *J. Chem. Soc. (C)*, **1969**, 2223.
13) N. L. Drake and Y. T. Pratt, *J. Am. Chem. Soc.*, **73**, 544 (1951).