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Preparation of 7-Alkylamino-2-methylquinoline-5,8-diones†

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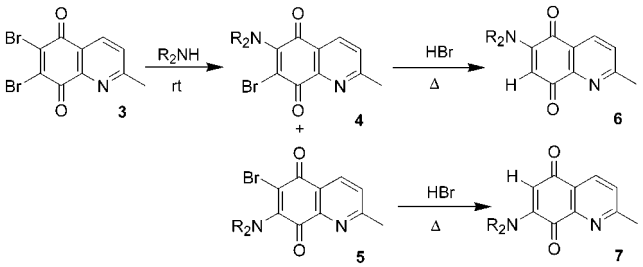
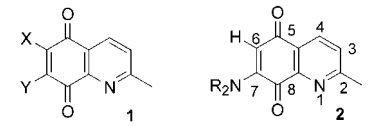
Abstract: Several novel 7-alkylamino-2-methylquinoline-5,8-diones (**2**) were synthesized from 2,5-dimethoxyaniline in five steps via the Skraup reaction followed by demethylations, oxidative bromination, amination, and debromination. We have achieved an unusual hydrobromic acid catalyzed debromination reactions of several 6-bromo-7-alkylamino-2-methylquinoline-5,8-diones, giving 7-alkylamino-2-methylquinoline-5,8-diones in good yields.

There has been much interest in the preparation of 6,7-functionalized quinoline-5,8-diones **1** because of their wide spectra of biological activities as antitumor, antibacterial, antifungal, antimalarial agents.[1] Over the past decades, the syntheses and the biological activities of 6,7-functionalized quinoline-5,8-diones **1** have been reported; the C6 and C7 substituents mainly include functionalities such as amino, hydroxyl, methoxy, thiol, and halogen.[1a−d,2] Among these various functionalized quinoline-5,8-diones, 7-amino-2-methylquinoline-5,8-dione has been the focus of synthetic efforts because it is the most critical segment in determining the antitumor activity of streptonigrin, steptonigrone, and lavendamycin.[3] Recently, Behforous reported a short and efficient synthetic method of 7-amino-2-methylquinoline-5,8-dione as well as lavendamycin from 7-(*N*-acetylamino)-2-methylquinoline-5,8-dione and *β*-methyltryptophan.[4] But to our knowledge, there has been no report on the syntheses of 7-(alkylamino)-2-methylquinoline-5,8-diones as a major products due to their synthetic problems such as preferential C6 substitution or addition of nucleophiles,[1a,2a,c,5] while 7-amino- or 7-acetylaminoquinoline-5,8-diones were prepared from the reduction of azide and nitro substituents.[4]

SCHEME 1



In this paper, we report the preparation of various 7-(alkylamino)-2-methylquinoline-5,8-diones (**2**) by a new efficient route. It is noteworthy that the conventional alkylation reactions do not proceed on the 7-amino group due to its lack of nucleophilicity. The C-2 methyl group could be used for coupling with the CD ring of lavendamycin by the reported method.[4]



The new synthetic route of 7-alkylaminoquinoline-5,8-diones has two simple steps—nucleophilic substitution of amines and debromination—from 6,7-dibromo-2-methylquinoline-5,8-dione (**3**) as shown in Scheme 1.

Recently, we reported an efficient three-steps-one-pot synthesis of **3** from inexpensive starting materials, 2,5-dimethoxyaniline and crotonaldehyde.[6] Compound **3** could easily be obtained in 20 g scale by this one-pot synthesis.

Amination. The regioselectivity of nucleophilic substitution reactions on C6 and/or C7 positions of 6,7-dihaloquinoline-5,8-dione derivatives are greatly affected by the electron density of pyridine ring, the kind of amine nucleophile, and the polarity of reaction media.[7] Although many reports have been published to produce an aminated isomer on C6 position,[1a,2a,c,5] the selective method for the preparation of C7 aminated isomers as major products has not been reported. Recently, we reported on the C7-regioselective nucleophilic amination of 6,7-dibromo- or 6,7-dichloroquinoline-5,8-dione which preferentially produced the C7-isomers as excellent yields (80−95%) in aprotic solvent such as THF.[7] In that report, we could assign the regiochemistry of the C6- or C7-isomer by X-ray crystallography and those isomers have R_f values as well as chemical shifts of ^{1}H NMR with

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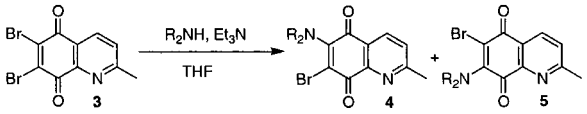
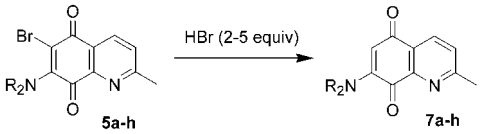
TABLE 1. Amination of 6,7-Dibromo-2-methylquinoline-5,8-dione



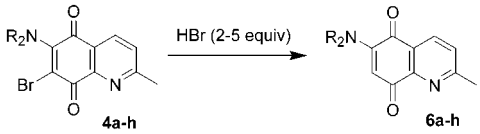
entry	R_2NH	time/*T* (min/°C)	R_2N- (**4**)	yield (%)	R_2N- (**5**)	yield (%)	total yield (%)
1	piperidine	rt/5	piperidine (**4a**)	39	piperidine (**5a**)	47	86
2	amino	rt/120	amino (**4b**)	36	amino (**5b**)	40	76
3	*n*-butylamine	rt/5	*n*-butylamine (**4c**)	43	*n*-butylamine (**5c**)	40	83
4	benzylamine	rt/5	benzylamine (**4d**)	48	benzylamine (**5d**)	44	92
5	2-methylaziridine	rt/20	2-methylaziridine (**4e**)	36	2-methylaziridine (**5e**)	47	83
6	*c*-hexylamine	rt/10	*c*-hexylamine (**4f**)	34	*c*-hexylamine (**5f**)	54	88
7	*c*-pentylamine	rt/10	*c*-pentylamine (**4g**)	37	*c*-pentylamine (**5g**)	57	94
8	*tert*-butylamine	refux/60	*tert*-butylamine (**4h**)	24	*tert*-butylamine (**5h**)	35	59

TABLE 2. Debromination of 7-Alkylamino-6-bromoquinoline-5,8-diones (5)



R_2N-	solvent	*T*/time (°C/min)	product (yield, %)
piperidinyl (**5a**)	dioxane	60/5	**7a** (85)
	AcOH	80/5	**7a** (60)
amino (**5b**)	dioxane	reflux/60	no reaction
	AcOH	reflux/60	**7b** (62)
n-butylamino (**5c**)	dioxane	80/10	**7c** (74), **5b** (20)
benzylamino (**5d**)	dioxane	reflux/10	**7b** (65), **5b** (25)
2-methylaziridinyl (**5e**)	dioxane	rt/1	ring-opened
c-hexylamino (**5f**)	dioxane	60/10	**7f** (88)
c-pentylamino (**5g**)	dioxane	60/10	**7g** (73)
tert-butylamino (**5h**)	dioxane	50/5	**7h** (29), **5b** (62)

TABLE 3. Debromination of 6-Alkylamino-7-bromoquinoline-5,8-diones



R_2N-	solvent	*T*/time (°C/min)	product (yield, %)
piperidinyl (**4a**)	dioxane	80/10	**6a** (85)
amino (**4b**)	dioxane	reflux/60	no reaction
	AcOH	reflux/100	**6b** (70)
n-butylamino (**4c**)	dioxane	80/10	**6c** (44), **4b** (33), **6b** (21)
benzylamino (**4d**)	dioxane	reflux/10	**4b** (52)
2-methylaziridinyl (**4e**)	dioxane	rt/1	ring-opened
c-hexylamino (**4f**)	dioxane	60/10	**6f** (61)
c-pentylamino (**4g**)	dioxane	60/10	**6g** (79)
tert-butylamino (**4h**)	dioxane	50/5	**6h** (33), **4b** (59)

consistent tendency. Due to the large R_f difference between the two regioisomers **4** and **5** as shown in Table 1, two regioisomers could easily be isolated by column chromatography. In this report, 6-bromo-7-alkylamino-2-methylquinoline-5,8-diones (**5**) were only produced in moderate yields (45−70%). The methyl group of C2 position might greatly influence the regioselectivity between C6 and C7. Eight amines—piperidine, ammonia, *n*-butylamine, benzylamine, 2-methylaziridine, cyclohexylamine, cyclopentylamine, and *tert*-butylamine—were used for the substitution reaction of **3** (Table 1). As a catalytic amount of Lewis acid increases regioselectivity for the formation of C6 isomers, excessive triethylamine (3−10 equiv) was used as a scavenger of generated HBr to reduce acidity in the reaction medium. Nucleophilic substitution reactions with all amines except *tert*-butylamine and ammonia were completed within 20 min at room temperature. Ammonia required longer reaction time than other primary and secondary amines, due to its poor nucleophilicity. Furthermore, *tert*-butylamine required much more vigorous reaction conditions to reflux because of its large steric hindrance.

Debromination. We found the debromination reactions of 6-bromo-7-alkylaminoquinoline-5,8-diones (**5**) by treatment with 48% HBr (Table 2). Based on this debromination reaction, we reported the investigation of its reaction mechanism as well as the application as a general useful method of selective debromination on aromatic bromine by hydrobromic acid.[8] It was also detected that some alkylamines were unstable in the acidic condition and proceeded dealkylation in the debromination condition. The C6 isomers showed nearly the same results as the C7 isomers (Table 3). The debromination reactions for **4a**−**h** and **5a**−**h** have been checked as shown in Tables 2 and 3.

Dioxane and acetic acid were used as debromination reaction solvents, but all protic and aprotic solvents miscible with aqueous HBr can be used. Methanol, ethanol, and 2-propanol as a debromination reaction solvent provided nearly the same results. In the case of aminobromoquinoline-5,8-diones **4(a**−**h)** and **5(a**−**h)**, there was no need of scavenger for the debromination reaction, unlike the general aromatic bromo compounds. When we used the aniline as a scavenger and the acetic acid as a solvent to accelerate the reaction rate, but the debrominated products were obtained in lower yields. Sodium sulfite could not be used either as a scavenger because the quinone moiety was reduced to hydroquinone.

Debromination proceeded along with dealkylation. In some cases, dealkylation competitively proceeded in the condition of debromination. Piperidinyl, *c*-hexylamino, and *c*-pentylamino compounds are relatively stable under the debromination reaction conditions; thus, the desired debrominated products were obtained in reasonably high yields (70−90%). In these cases, debrominations are much faster than dealkylations. On the other hand, we could not obtain the desired debrominated products of 2-methylaziridinyl and benzylamino compounds at all,

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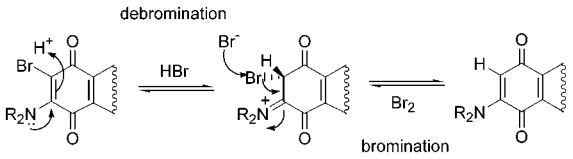
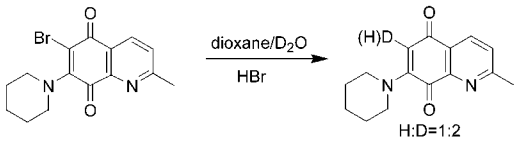
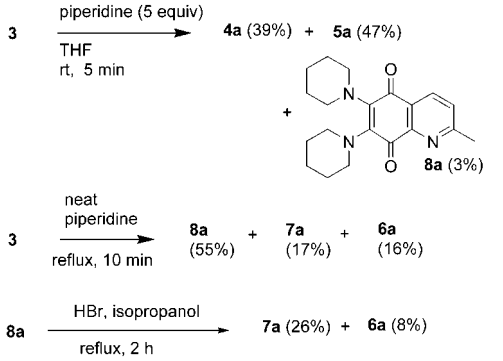
SCHEME 2



SCHEME 3



SCHEME 4

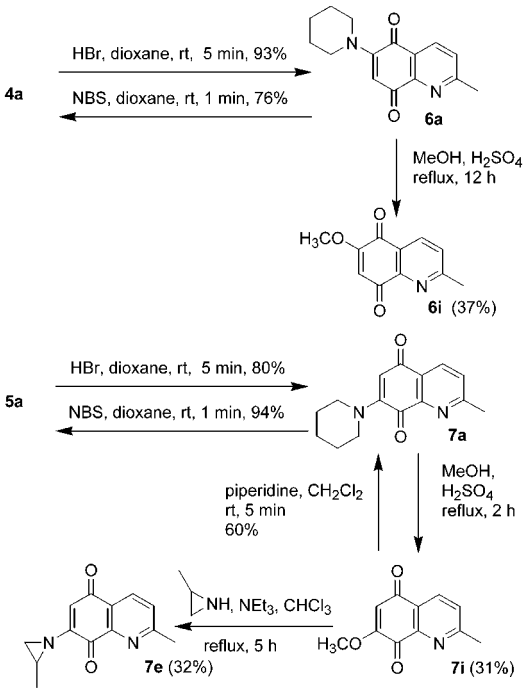


due to their instability under hydrobromic acid conditions. 2-Methylaziridinyl compound is so unstable in the presence of hydrobromic acid that aziridine ring was immediately opened with the ratio of 2:1 (7-(2-bromo-1-methylethyl)amino/7-(2-bromo-*n*-propyl)amino) within 1 min. Benzylamino compound was partly debrominated as well as completely debenzylated under the reflux conditions, providing **5b** (25%, debenzylated) and **7b** (65%, debenzylated and debrominated). In the case of amino compounds **4b** and **5b**, surprisingly debromination did not proceed at all under reflux conditions in dioxane but proceeded in good yields (**6b**, 70%; **7b**, 62%) in acetic acid. *tert*-Butylamino compound produced the debrominated compound **7h** as a minor product (29%) and dealkylated compound **5b** as a major product (62%).

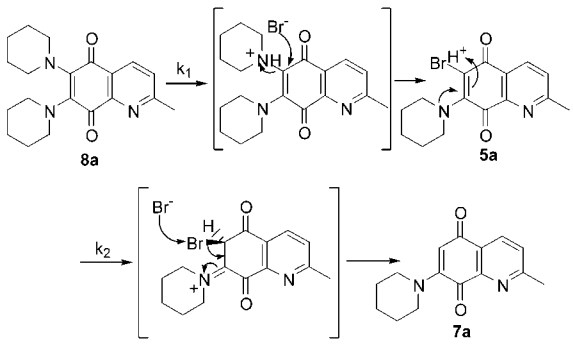
Debromination Mechanism Study. The mechanism of the debromination reactions of **4** and **5** are shown in Scheme 2 according to our previous report.[8] When the debromination reaction of bromopiperidinylcompound **5a** was performed in dioxane in the presence of D_2O and concentrated HBr, deuterated compound was identified by NMR integration of the C7 proton and the M^+ peak on the mass spectrum (Scheme 3).

Scheme 4 shows the preparation of 6,7-dipiperidinylquinolinedione **8a** and its depiperidination reaction, and Scheme 5 shows the preparation of 6- or 7-methoxyquinolinedione **6i** or **7i** and its amination reaction. When 5 equiv of piperidine was added to the solution of **3** in THF at room temperature, 6- and 7-piperidinyl compounds **4a** and **5a** were formed within 5 min. The isolation yields of **4a** and **5a** by flash column chromatography were 39 and 47%, respectively. In addition, 3% of dipiperidinylquinolinedione **8a** was isolated under those conditions. When **3** was refluxed for 10 min in neat

SCHEME 5



SCHEME 6



piperidine to synthesize **8a**, unexpectedly **7a** and **6a** were isolated in 17% and 16% yields as well as the desired **8a** in 55% yield. The treatment of **8a** with concentrated HBr in 2-propanol at reflux for 2 h gave **7a** and **6a** in 26% and 8% yields, respectively. Although depiperidinylhydrogenation reaction underwent slower than debromohydrogenation, we considered that both depiperidinylhydrogenation (from **8a** to **7a** or **6a**) and debromohydrogenation reactions (from **4a** to **6a** and from **5a** to **7a**) occurred via the same debromination mechanism. We propose the reaction mechanism as shown in Scheme 6 that is composed of two steps: depiperidinylation of protonated **8a** by bromide and successive debromination. But we could not detect **5a** at all. This fact means that debromination is much faster than depiperidinylation under these reaction conditions. Compound **5a** is rapidly debrominated to **7a** as soon as it formed; k_2 is much larger than k_1. Since the C6 position is more positive under acidic conditions, C6 piperidine is more rapidly substituted by bromide, as a result of that we obtained the 7-piperidinylquinoline-5,8-dione as the major product.

Monopiperidinyl compounds **6a** and **7a** were easily reconverted to the corresponding bromopiperidinyl com-

pounds **4a** and **5a** in 76% and 94% yield by treatment with NBS in dioxane at room temperature within 1 min.

Piperidine of monopiperidinyl compounds **6a** and **7a** was substituted by methanol in the presence of H_2SO_4 in low yields. The resulting methoxy compound **7i** could be changed to methylaziridinyl compound by S_NAr of methylaziridine. We anticipate that the alkylamino compounds that cannot be prepared by the debromination reaction can be prepared from methoxy compound. From **7i**, **7a** and **7e** were obtained 60% and 32%, respectively.

A comparison of chemical shifts in ^{1}H NMR and R_f values of 7-alkylamino compounds (**5a**−**h**) with 6-alkylamino compounds (**4a**−**h**) shows general tendencies.[7] The peaks of H-4 of **5a**−**h** appeared in more downfield than those of H-4 of **4a**−**h**.[9] The peaks of H-6 of **7a**−**h** appeared in more upfield than those of H-7 of **6a**−**h**.[9] In addition, the 6-hydro- or 6-bromo-7-alkylamino compounds (**5a**−**h**) or (**7a**−**h**), respectively, have larger R_f values than the 7-hydro- or bromo-6-alkylamino compounds (**4a**−**h**) or (**6a**−**h**) in the eluent condition of ethyl acetate/hexane.

In conclusion, 7-alkylamino-2-methylquinoline-5,8-diones were synthesized by the new synthetic route—nucleophilic substitution of amines and debromination—from 6,7-dibromo-2-methylquinoline-5,8-dione. Some alkylamino compounds cannot be prepared by this synthetic route due to their instability during debromination. But, these compounds could be prepared by another pathway via methoxyquinoline-5,8-diones in low yields. However, this new synthetic route presented in this paper would be useful and efficient to synthesize quinolinediones and to study their biological activities.

Experimental Section

General Procedure for 4a−h and 5a−h. Piperidine (0.7 mL, 7.08 mmol, 5 equiv) or piperidine (1.2 equiv) and triethylamine (5 equiv) were added to the mixture of **3** (460 mg, 1.39 mmol) and THF (15 mL) with stirring at 20 °C. The mixture was stirred for 5 min and was concentrated in vacuo at 20 °C in a water bath. The residue was purified by flash column chromatography (40% EtOAc/hexane) to give **5a** (226 mg, 0.675 mmol, 47%) as a red solid and **4a** (183 mg, 0.546 mmol, 39%) as a red solid.

6-Bromo-2-methyl-7-piperidinylquinoline-5,8-dione (5a): mp 122−124 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.31 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 3.59 (bs, 4H), 2.74 (s, 3H), 1.77 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 179.6, 176.5, 163.4, 153.0, 146.1, 134.3, 127.2, 125.5, 113.4, 53.0, 26.3, 24.5, 23.6; MS (EI) 336 (M^+, 100), 334 (M^+), 255, 253, 227, 225, 197, 195, 174, 117, 89, 84, 41. Anal. Calcd for $C_{15}H_{15}BrN_2O_2$: C, 53.75; H, 4.51; N, 8.36. Found: C, 53.53; H, 4.57; N, 8.02.

7-Bromo-2-methyl-6-piperidinylquinoline-5,8-dione (4a): mp 134−135 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.20 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 3.56 (bs, 4H), 2.75 (s, 3H), 1.76 (bs, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 181.2, 176.7, 164.9, 152.5, 146.5, 135.0, 126.7, 125.9, 116.4, 53.4, 26.7, 25.2, 23.9; MS (EI) 336 (M^+, 100), 334 (M^+), 281, 257, 227, 173, 116, 89, 41. Anal. Calcd for $C_{15}H_{15}BrN_2O_2$: C, 53.75; H, 4.51; N, 8.36. Found: C, 53.79; H, 4.66; N, 8.11.

General Procedure for 6a−h and 7a−h. Method A. In Dioxane without Scavenger. Concentrated HBr (48%, 0.1 mL, 1.3 equiv) was added to the mixture of **5a** (226 mg, 0.68 mmol) and dioxane (10 mL) in a two-neck flask (100 mL) with stirring at 20 °C. The mixture was stirred for 5 min at 60 °C in a water bath, concentrated in vacuo, basified with aqueous $NaHCO_3$ (10 mL), and extracted with EtOAc. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (70% EtOAc/hexane) to give **7a** (147 mg, 0.58 mmol, 85%) as a yellow solid.

2-Methyl-7-piperidinylquinoline-5,8-dione (7a): mp 157−158 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.24 (d, J = 7.8 Hz, 1H), 7.47 (d, J = 8.2 Hz, 1H), 6.01 (s, 1H), 3.56 (bs, 4H), 2.73 (s, 3H), 1.73 (bs, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 182.1, 182.0, 162.9, 154.0, 148.0, 133.8, 127.5, 126.9, 108.3, 50.4, 25.7, 24.9, 24.2; MS (EI) 256 (M^+, 100), 227, 213, 201, 189, 174, 161, 145, 117, 101, 84, 41. Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.07; H, 6.61; N, 11.11.

Method B. In Acetic Acid with Scavenger. Concentrated HBr (48%, 2.0 mL) was excessively added to the mixture of **5b** (228 mg, 0.85 mmol), aniline (0.5 mL), and acetic acid (10 mL) in a two-neck flask (100 mL) with stirring at 20 °C. The mixture was refluxed for 1 h, basified with aqueous $NaHCO_3$, and extracted with EtOAc. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (70% EtOAc/hexane) to give **7b** (98 mg, 0.52 mmol, 62%) as a yellow solid.

7-Amino-2-methylquinoline-5,8-dione (7b): mp 224−225 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.29 (d, J = 8.2 Hz, 1H), 7.50 (d, J = 8.6 Hz, 1H), 6.03 (s, 1H), 5.35 (bs, 2H), 2.74 (s, 3H);^{13}C NMR (50 MHz, DMSO-d_6 + $CDCl_3$) δ179.7, 178.6, 160.1, 147.9, 143.9, 131.8, 126.2, 125.8, 100.4, 22.6; MS (EI) 188 (M^+, 100), 132, 119, 104, 93, 64, 52, 32. Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.28; N, 14.89. Found: C, 63.44; H, 4.63; N, 15.28.

7-Methoxy-2-methylquinoline-5,8-dione (7i). Compound **7a** (344 mg, 1.34 mmol) was dissolved in methanol (20 mL) at 20 °C, and H_2SO_4 (1 mL) was added. The mixture was refluxed for 2 h, concentrated in vacuo, neutralized by $NaHCO_3$, and extracted with EtOAc. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (50% EtOAc/hexane) to give **7i** (85 mg, 0.42 mmol, 31%) as a yellow solid: mp 170−172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 6.21 (s, 3H), 3.95 (s, 3H), 2.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.7, 178.4, 164.5, 160.7, 146.3, 134.4, 127.9, 126.9, 109.1, 56.6, 25.1; MS (EI) 203 (M^+, 100), 174, 145, 132, 117, 104, 77, 64, 53, 39. Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.02; H, 4.49; N, 7.17.

6-Methoxy-2-methylquinoline-5,8-dione (6i). Compound **6i** was prepared by the same method as for **7i** in 37% yield: mp 204−206 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 6.34 (s, 3H), 3.97 (s, 3H), 2.78 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 182.9, 179.1, 165.0, 159.6, 146.7, 134.4, 126.9, 125.4, 109.9, 56.3, 24.9; MS (EI) 203 (M^+, 100), 188, 175, 145, 117, 104, 77, 69, 53, 39. Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 65.32; H, 4.55; N, 7.10.

2-Methyl-7-methylaziridinylquinoline-5,8-dione (7e). Compound **7i** (85 mg, 0.42 mmol) was dissolved in chloroform (10 mL) at 20 °C, and triethylamine (1 mL) was added. The mixture was refluxed for 5 h and was concentrated in vacuo. The residue was purified by flash column chromatography (50% EtOAc/hexane) to give **7e** (31 mg, 0.14 mmol, 32%) as a yellow solid: mp 106−107 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.03 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 6.14 (s, 1H), 2.64 (s, 3H), 2.25−2.40 (m, 1H), 2.10−2.20 (m, 2H), 1.37 (d, J = 5.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 183.4, 180.0, 163.7, 157.8, 146.6, 134.0, 127.4, 126.9, 117.4, 36.3, 34.4, 24.8, 17.3; MS (CI) 229 (M^+ + 1), 215, 201, 189, 57, 43; HRMS m/z (EI) 228.0917, calcd for $C_{13}H_{12}N_2O_2$ 228.0899.

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Supporting Information Available: Characterization of the rest of the compounds synthesized and ^{1}H and ^{13}C NMR spectra of **4a**−**h**, **5a**−**h**, **6a**−**c**,**f**−**i**, **7a**−**c**,**e**−**i**, and **8a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Detail data are in the Supporting Information.