Highly Efficient and Practical Syntheses of Lavendamycin Methyl Ester and Related Novel Quinolindiones

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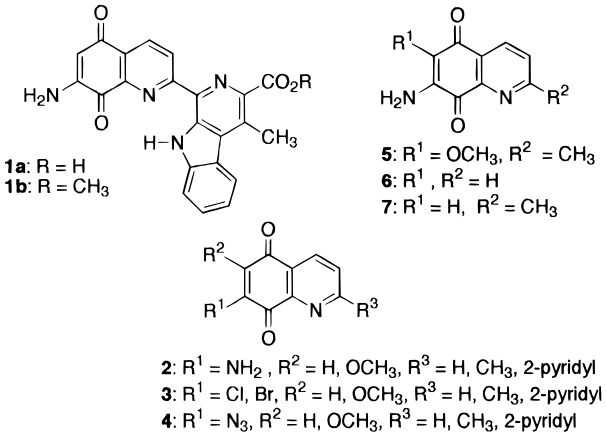
Received April 30, 1996[⊗]

The novel 7-(*N*-formyl-, 7-(*N*-acetyl-, and 7-(*N*-isobutyrylamino)-2-methylquinoline-5,8-diones were synthesized in excellent overall yields in three steps via the nitration of the commercially available 8-hydroxy-2-methylquinoline followed by a reduction−acylation step and then oxidation. Acid hydrolysis of 7-(*N*-acetylamino)-2-methylquinoline-5,8-dione (**14a**) afforded the novel 7-aminoquinoline-5,8-dione **7** in excellent yields. Due to our efficient preparation of dione **14a**, we now report a short and practical method for the total synthesis of the potent antitumor agent lavendamycin methyl ester (**1b**) with an excellent overall yield.

Introduction

Quinoline-5,8-diones are an important class of compounds because of their wide spectrum of biological activities as anitfungal,[1a,2,6] antibacterial,[1−3] antitumor,[1b,2,4,5] antiasthmatic,[1b] and antiparasitic[1−3,6] agents.

It has been proposed that the 7-aminoquinolinedione segment of the more complex anticancer agents streptonigrin,[7] streptonigrone,[8] and lavendamycin (**1a**)[9] is



most critical in determining the antitumor activity of these compounds.[10]

No short and efficient methods for the preparation of 7-aminoquinoline-5,8-diones (**2**) have been reported. This is mainly due to the fact that direct nucleophilic substitution−reoxidation reactions of quinolinediones cannot be used because they give mixtures of the C-6 and C-7 substituted products with the predominance of the undesired C-6 isomer.[11−13] Consequently, the current literature methods involve many steps such as halogenation, oxidation, azidation, and reduction. Serious drawbacks of these methods are that they are all lengthy and involve unstable intermediates such as halo- and azidoquinones (**3**, **4**).

For example, 7-amino-6-methoxy-2-methylquinolinedione (**5**; streptonigrin A−B ring system) was synthesized by Liao and co-workers[14b] from the commercially available 2-nitroanisidine in six steps with an overall yield of about 10%, and the preparation of 7-aminoquinoline-5,8-dione (**6**; A−B ring system of lavendamycin) from 8-hydroxy-2-nitroquinoline has been reported in six steps with an overall yield of 25%.[14a]

In our own laboratory, quinone **7** was synthesized in eight steps[16] with an overall yield of 10% from the commercially available 8-hydroxy-2-methylquinoline (**11**) using the existing literature methods for similar systems (Scheme 1).[14a,15]

7-Bromo-2-methylquinoline-5,8-dione (**8**) was prepared according to the method of Petrow and Sturgeon[15] and then converted to **7**, following Boger's method of preparation of 7-aminoquinoline-5,8-dione (**6**).[14a]

[⊗] Abstract published in *Advance ACS Abstracts,* August 15, 1996.

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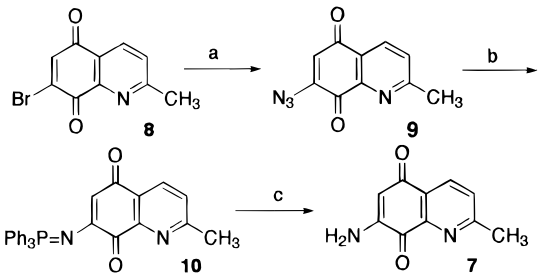
(16) Azidoquinone **9** was purified by column chromotography (silica gel, ethyl acetate-hexane 30−70) as a red-orange solid (91%, mp 105−106°). ^{1}H NMR ($CDCl_3$) δ 8.29 (d, J = 8 Hz, 1H), 7.56 (d, J = 8Hz, 1H), 6.49 (s, 1H), 2.78 (s, 3H); HRMS calcd for $C_{10}H_6N_4O_2$ 214.0491, found 214.0484. Triphenylphosphine amino compound **10** was purified by column chromotography (silica gel, ethyl acetate−hexane, 3:5, then 7:5) to give purple crystals (62%, mp 215−216°). ^{1}H NMR ($CDCl_3$) δ 8.23 (d, J = 8 Hz, 1H), 7.75−7.9 (m, 5H), 7.4−7.6 (m, 10H), 7.38 (d, J = 8 Hz, 1H), 6.52 (s, 1H), 2.64 (s, 3H); HRMS calcd for $C_{22}H_{21}N_2O_2P$ 448.1341, found 448.1332. Aminoquinone **7** was purified by column chromotography (silica gel, ethyl acetate−hexane 1:2, then 1:1) as a red solid (87%).

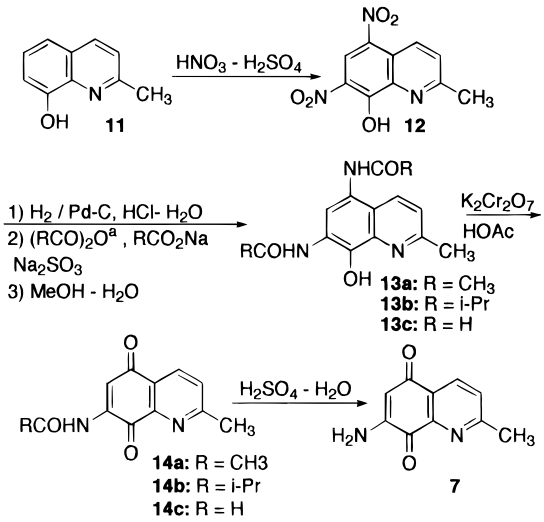
S0022-3263(96)00794-3 CCC: $12.00

Scheme 1



(a) NaN_3 (5% excess), THF-H_2O, rt, 2h, 91%
(b) Ph_3P (1.1 eq.), CH_2Cl_2, rt, 1h, 62%
(c) THF-AcOH-H_2O (2:5:3), rt, 10 min, 87%

Scheme 2



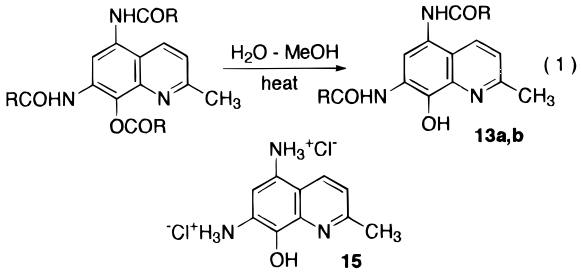
[a] For R = H, formic trimethylacetic anhydride was used

Results and Discussion

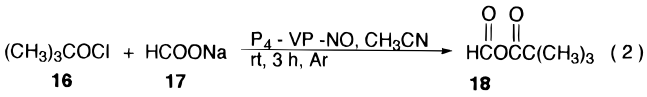
We now report short and practical syntheses of the novel 7-amino-2-methylquinoline-5,8-dione (**7**) and three of its *N*-acyl derivatives (**14a**−**c**). Except for our previous report,[17a] which describes the preparation of dione **14a** via an azadiene Diels−Alder reaction (Scheme 3), to our knowledge no 7-(*N*-acylamino)-2-methylquinoline-5,8-dione has ever been reported. Even for similar systems there are only two reports in which the isolation of a small amount of 7-acetamidoquinoline-5,8-dione as a minor product[18] or its 6-chloro derivative as an intermediate[19] have been described.

Our preliminary biological activity studies have shown that these novel diones are potent antitumor agents.[20] Diones **7** and **14a**−**c** were synthesized from the commercially available 8-hydroxy-2-methylquinoline (**11**) according to Scheme 2.

Nitration of 8-hydroxy-2-methylquinoline (**11**) with a 70−30 (v/v) mixture of HNO_3−H_2SO_4 at ice-bath temperature afforded the known dinitro **12** in 73% yield.[21] Compound **12** was reduced with hydrogen in the presence of 5%Pd/C in 10% HCl solution at room temperature for 15 h. The catalyst was filtered off and the red solution was treated with excess amounts of acetic or isobutyric anhydrides in the presence of large amounts of sodium acetate and sodium sulfite.[22] The yellowish white solids (76−85%) were filtered off. The resulting products were either 5,7-bis(acylamino)-8-(acyloxy)-2-methylquinolines and/or their 8-hydroxy derivatives. Treatment of the products with MeOH−H_2O under reflux caused the acyloxy groups to hydrolyze and produce pure samples of **13a** and**13b** (eq 1).



To prepare **13c**, the hydrochloride salt **15** had to be isolated (98%) in the hydrogenation step and then treated with the mixed anhydride **18** in the presence of sodium sulfite and sodium formate. Formic trimethylacetic anhydride (**18**) was prepared according to Fife's method[23] with a slight modification (eq 2).



Acyl chloride **16** was treated with 4 equiv (literature method[23] requires 1 equiv) of sodium formate (**17**) in the presence of catalyst poly(4-vinylpyridine 1-oxide) to give the pure **18** in 78% yield (lit. 48%).[23]

Compounds **13a**−**c** were oxidized with potassium dichromate in a solution of H_2O−acetic acid at room temperature to give the (acylamino)quinones **14a**−**c** in 71−94% yields. Hydrolysis of **14a** in the presence of concentrated H_2SO_4 gave the aminoquinolinedione **7** in 88% yield. As expected the formamido group was sensitive to acid hydrolysis and caused low yields of **14c**. To avoid this, **13c** was oxidized on small scale, using less acetic acid and shorter reaction times.

The advantages of the method of Scheme 2 are that (a) it introduces the C-7 nitrogen atom in the early stage of the synthesis, and consequently, the use of unstable intermediates such as **3** and **4** is avoided; (b) it produces the diones in three to four steps with high overall yields;[24] (c) none of the steps require chromotography or even recrystallization for product purification; (d) as our data indicate, stable diones **14**, specifically **14a** and **14b**, can

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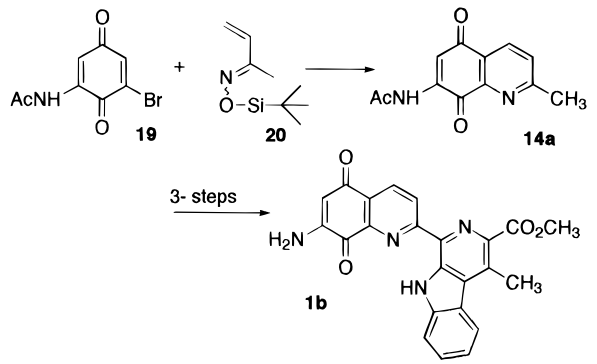
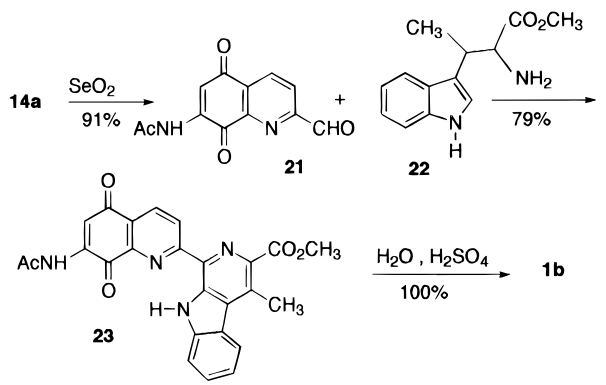
(24) Dione **7** was obtained in four steps with an overall yield of 35% from the commercially available **11**.

Scheme 3



Scheme 4



easily be functionalized to give other derivatives substituted at C-2, C-4, C-6, and C-7 positions.[25]

The synthesis of quinolinediones is part of our ongoing research in the total synthesis of a series of lavendamycin esters and analogs. Recently we reported a five-step synthesis of lavendamycin methyl ester (**1b**) via the Diels−Alder condensation of azadiene **20** with bromoquinone **19** and transformation of the resulting dione to the final ester as shown in Scheme 3.[17a]

Although the method of Scheme 3[17a] is much more efficient than the previously reported syntheses,[17b−h] it still involves a three-step preparation of bromoquinone **19** from the commercially available 2,4-dibromo-6-nitrophenol.[22] Using our present method of synthesis of 7-acetamido-2-methylquinoline-5,8-dione (**14a**; Scheme 2) in place of our reported Diels−Alder method and following our previously described transformations,[17a] we can now prepare gram quantities of lavendamycin methyl ester (**1b**) according to Scheme 4 in only five-steps from the known dinitro compound **12** and β-methyltryptophan methyl ester (**22**) in excellent overall yields of 37−43% (Scheme 4).

Experimental Section

General Procedures. See ref 17a.

Formic Trimethylacetic Anhydride (18). For the preparation of anhydride **18**, the method of Fife and Zhang[23] was modified as follows.

To a 500 mL round-bottomed flask equipped with a stirring bar and containing dry sodium formate[26] (13.60 g, 200 mmol) and poly(4-vinylpyridine 1-oxide; 2.00 g) under Ar was added dry acetonitrile (200 mL) with a syringe. To the vigorously stirred mixture was added trimethylacetyl chloride (6.00 g, 50 mmol), and the reaction mixture was allowed to stir at 25 °C under Ar for 3 h. The resulting mixture was filtered, and the filtrate was evaporated in vacuo to give 5.11 g (78%) of a light yellow liquid: ^{1}H NMR ($CDCl_3$) δ 9.49 (s, 1H), 1.27 (s, 9H).

8-Hydroxy-2-methyl-5,7-dinitroquinoline (12).[21] To an ice-bath cooled and stirred solution of 70% (v−v) HNO_3−H_2SO_4 (300 mL) was added 8-hydroxy-2-methylquinoline (**11**, 40.60 g, 0.25 mol) portionwise. The mixture was allowed to stir in the ice bath for 2 h and then poured into a 2 L beaker containing 1 L of ice−water (1:1) with vigorous stirring. The bright yellow precipitate was filtered, washed with ice−water (500 mL), washed with diethyl ether (300 mL), and air-dried to give 45.5 g (72%) of **12**: mp 296−300 °C; ^{1}H NMR (DMSO-d_6) δ 9.67 (d, J = 8.9 Hz, 1H), 9.21 (s, 1H), 8.15 (d, J = 8.9 Hz), 2.95 (s, 3H).

5,7-Bis(acylamino)-8-hydroxy-2-methylquinolines (13a−c). To a suspension of finely powdered 8-hydroxy-2-methyl-5,7-dinitroquinoline (**12**, 5.98 g, 24 mmol) and 100 mL of 10% hydrochloric acid solution (10 mL conc. HCl + 90 mL H_2O) in a 500 mL hydrogenation bottle was added 2.0 g of 5% Pd−C. This mixture was hydrogenated (30 psi initial pressure) for 15 h using a Parr hydrogenator. The reaction mixture was filtered, the filter cake was washed with 10 mL H_2O, and the filtrate containing the ammonium salt **15** was used for the preparation of **13a−c** as follows.

5,7-Diacetamido-8-hydroxy-2-methylquinoline (13a). The ammonium salt solution of **15** was treated with 20.0 g of sodium acetate and 10.0 g of sodium sulfite. To this gently stirred red solution was added 67 mL of acetic anhydride (excess) dropwise over 1 h. The warm mixture was allowed to stir for 1 h and then for an additional 30 min in an ice bath. The lemon yellow product was filtered and washed with 2 × 10 mL of cold water. The filtrate was concentrated to about one-quarter of its original volume, and then with stirring 13 mL of acetic anhydride was dropwise added over 15 min. The mixture was allowed to stir for an additional 15 min at room temperature and then for 15 min in an ice bath. The solid was filtered off and carefully washed with 3 × 10 mL of cold water to remove any inorganic salt. The two product samples were added together and dried (6.42 g, 85%). This compound was shown (by NMR) to be 5,7-diacetamido-8-acetoxy-2-methylquinoline and decomposed at 260.5 °C. Treatment of this product with 400 mL MeOH−H_2O (10:1) under reflux for 30 min and then evaporation of the solution produced 5.57 g (100%) of 5,7-diacetamido-8-hydroxy-2-methylquinoline (**13a**) as a white solid. An analytical sample of **13a** was obtained by the recrystallization of the product with MeOH−H_2O. Melting point and spectral and elemental analyses are reported in Table 1.

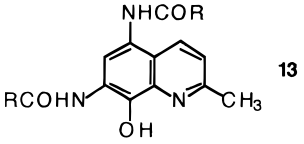
5,7-Diisobutyramido-8-hydroxy-2-methylquinoline (13b). To the stirred ammonium salt solution of **15** were added sodium acetate (17.0 g) and sodium sulfite (12.5 g), and then 67.5 mL (64.4 g, 0.407 mol) of isobutyric anhydride was added dropwise over a period of 1 h while the reaction mixture was cooled in an ice bath. The mixture was vigorously stirred for an additional hour. The white solid was filtered, washed with 200 mL of H_2O and 100 mL diethyl ether, and then air-dried (7.5 g). NMR showed the product to be a mixture of **13b** and 5,7-diisobutyramido-8-isobutyroxy-2-methylquinoline. Treatment of this mixture with 400 mL of MeOH−H_2O (1:1) for 30 min under reflux, followed by the concentration of the resulting solution to 200 mL and then cooling afforded 5.76 g (75%) of white crystalline **13b**. Melting point and spectral and elemental analyses are given in Table 1.

5,7-Diformamido-8-hydroxy-2-methylquinoline (13c). Evaporation of the solution of ammonium salt **15** in vacuo gave 6.2 g (98%) of **15** as bright orange crystals, mp 200 °C (dec). A stirred solution of **15** (2.1 g, 8 mmol) in 80 mL of H_2O sodium sulfite (4.0 g) and sodium formate (4.08 g) was treated with formic trimethylacetic anhydride (**18**, 5.2g, 40 mmol) at 25 °C under Ar for 3 h. The white precipitate was filtered and washed with ether to give 1.65 g (82%) of pure **13c**. Recrystallization from MeOH−H_2O gave a white solid, mp 271−273 °C. The spectroscopic and elemental analyses are given in Table 1.

(25) References 5 and 17a and unpublished results.

(26) Anhydrous sodium formate (Sigma Chemical Co.) was dried overnight in a 130 °C oven and then on a vacuum pump for 12 h before use.

Table 1. 5,7-Bis(acylamino)-8-hydroxy-2-methylquinolines

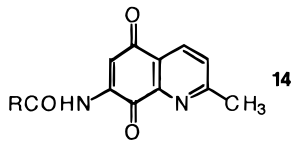


13

compd	R	% yield	mp,[a] °C	^{1}H NMR, δ[b]	mass spectrum,[c] *m/z* (relative intensity)	elemental analysis
13a	CH_3	85	229 (dec) ($MeOH-H_2O$)	2.12 (s, 3), 2.14 (s, 3), 2.7 (s, 3), 7.37 (d, 1, J = 8.6 Hz), 8.03 (s, 1), 8.14 (d, 1, J = 8.6 Hz), 9.57 (s,1), 9.79 (s, 1)	273 (M^+, 82), 189 (73), 188 (100)	Calcd for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.43; H, 5.49; N, 15.33
13b	$(CH_3)_2CH$	76	242−243 (dec) ($MeOH-H_2O$)	1.13 (d, 6, J =7.0 Hz), 1.16 (d, 6, J = 7.0 Hz), 2.71 (s, 3), 2.86 (m, 2), 7.39 (d, 1, J = 8.7 Hz), 7.99 (s, 1), 8.08 (d, 1, J = 8.7 Hz), 9.45 (s, 1), 9.69 (s, 1)	329 (M^+, 100), 286 (82), 259 (95), 188 (92)	Calcd for $C_{18}H_{23}N_3O_3$: C, 65.63; H, 7.04; N, 12.76. Found: C, 65.67; H, 7.06; N, 12.6
13c	H	82	271−273 ($MeOH-H_2O$)	2.70 (s, 3), 7.40 (d,1, J = 8.5 Hz), 8.21 (d, 1, J = 8.5 Hz), 8.34 (s, 1), 8.38 (s, 1), 8.60 (s, 1), 9.97 (s, 1), 10.11 (s, 1)	246 (M^+ + 1, 85), 245 (M^+, 15), 155 (100)	Calcd for $C_{12}H_{11}N_3O_3$: C, 58.77; H, 4.52; N, 17.14. Found: C, 58.56; H, 4.64; N, 17.09

[a] Uncorrected. [b] 200 MHz, DMSO-d_6. [c] All EIMS except FAB for **13c**.

Table 2. 7-(Acylamino)-2-methylquinoline-5,8-diones



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compd	R	% yield	mp,[a] °C	^{1}H NMR,[b] d	MS,[c] *m/z* (rel. intensity)	elemental analysis
14a	CH_3	71	for mp, NMR, MS, and elemental analysis see ref. 17a			
14b	$(CH_3)_2CH$	73	189−190 (dec) (EtOAc)	1.26 (d, 6, J = 6.6 Hz), 2.70 (m, 1), 2.75 (s, 3), 7.54 (d, 1, J = 8.0 Hz), 7.90 (s, 1), 8.29 (d, 1, J = 8.0 Hz), 8.42 (br s, 1)	258 (M^+, 100), 215 (26), 189 (41)	Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 64.99; H, 5.43; N, 10.85
14c	H	94	199−200 (CH_2Cl_2−pet .ether)	2.72 (s, 3), 7.54 (d, 1, J = 8.0 Hz), 7.86 (s, 1), 8.28 (d, 1, J = 8.0 Hz), 8.50 (s, 1), 8.65 (s, 1)	216 (M^+, 0.2), 188 (M^+ − 28, 100), 161 (30)	Calcd for $C_{11}H_8N_2O_3$: C, 61.11; H, 3.73; N, 12.96. Found: C, 60.99; H, 3.69; N, 12.97

[a] Uncorrected. [b] 200 MHz, $CDCl_3$. [c] All CIMS except FAB for **14c**.

7-Isobutyramido-2-methylquinoline-5,8-dione (14b). To a stirred suspension of 5,7-diisobutyramido-8-hydroxy-2-methylquinoline (**13b**, 3.29 g, 10 mmol) in 122 mL of glacial acetic acid was added a solution of potassium dichromate (8.8 g, 30 mmol) in 115 mL of water. The resulting dark mixture was allowed to stir for 1.5 h and then extracted with CH_2Cl_2 (12 × 50 mL). The combined organic extracts were washed with 3% sodium bicarbonate solution (2 × 100 mL). The aqueous layer was extracted with 2 × 50 mL of CH_2Cl_2 , added to the original extracts, and dried ($MgSO_4$). Evaporation under vacuum gave an orange yellow solid (**14b**, 1.89 g, 73%), which was recrystallized from ethyl acetate. The melting point, and spectral and elemental analyses are given in Table 2.

7-Acetamido-2-methylquinoline-5,8-dione (14a). This was prepared according to the procedure used for **14b** in 60 or 71% yield using 5,7-diacetamido-8-acetoxy-2-methylquinoline or its hydroxy derivative **13a**, respectively. The reaction time for the former was 15 h.

7-Formamido-2-methylquinoline-5,8-dione (14c) was prepared according to the method used for **14b**, except that the reaction was carried out on smaller amounts of **13c** using less acetic acid and shorter reaction times. Thus, a solution of 0.446g (1.5 mmol) of potassium dichromate in 6 mL of H_2O−AcOH (1:5) was added to 0.123 g (0.5 mmol) of **13c** and stirred for 10 min at 25 °C. The reaction mixture was extracted with 5 × 10 mL of CH_2Cl_2 and then washed with 5% $NaHCO_3$ solution to pH ∼8. The aqueous layer was extracted with 2 × 10 mL of CH_2Cl_2 and the combined extracts were washed with 10 mL of brine, dried (Na_2SO_4), and evaporated to give light yellow crystals of **14c** (0.102 g, 94%). Melting point and spectral and elemental analyses are reported in Table 2.

7-Amino-2-methylquinoline-5,8-dione (7). A solution of 7-acetamido-2-methylquinoline-5,8-dione (**14a**, 0.23 g, 1 mmol) in 15 mL of dry methanol was treated with 1 mL of concentrated H_2SO_4 at 25 °C under Ar for 1 h. The resulting red solution was neutralized with 10 mL of 5% sodium bicarbonate solution and extracted with 5 × 40 mL of CH_2Cl_2 . The combined extracts were dried (Na_2SO_4) and evaporated in vacuo to give 0.155 g (82%) of **7** as a red solid. Recrystallization of this material from MeOH gave red needle-shaped crystals: mp 240 °C; ^{1}H NMR ($CDCl_3$) δ 8.22 (d, J = 7.9 Hz, 1H), 7.43 (d, J = 7.9 Hz, 1H), 5.96 (s, 1H), 5.23 (br s, 2H), 2.67 (s, 3H); EIMS, *m/e* (rel intensity) 189 (M + 1, 62), 188 (M^+, 100), 179 (44), 174 (20), 161 (65), 149 (22), 120 (28), 107 (36); Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.28; N, 14.89. Found: C, 63.75; H, 4.37; N, 14.70.

Acknowledgment. We thank the National Institute of Health (Grant Nos. GM37491, CA 54517), The American Cancer Society (Grant No. DHP-110), the donors of the Petroleum Research Fund, administered by the American Chemical Society, Eli Lilly and Company, and Ball State University for financial support of this work.

JO960794T