Chemistry of Quinoline-5,8-diones

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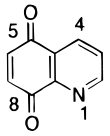
Room-temperature acid-catalyzed methanolysis of 7-formamido-, 7-acetamido-, or 7-isobutyramido-2-methylquinoline-5,8-diones (**3**, **4**, **5**) gives good to excellent yields of 7-amino-2-methylquinoline-5,8-dione (**6**). Simple methods for the synthesis of novel 7-amino-6-chloro-2-methylquinoline-5,8-dione (**7**), 7-alkoxy-2-methylquinoline-5,8-diones (**9**−**11**), and quinoline quinols (**12**, **13**) are described, and the corresponding mechanisms are discussed. The replacement of an amino group on a quinone ring by alkoxy groups to produce **9**−**11** is reported for the first time and offers easy routes for the syntheses of these alkoxy derivatives. Also, the 1,2-addition of an ethyl group (rather than the expected 1,4-addition of a cyano group) of the reagent diethylaluminum cyanide to a quinolinedione is another novel reaction for the efficient preparation of quinoline quinols **12** and **13**. An easy transformation of amino compound **6** to its acetamido derivative **4** is also described.

Introduction

Quinoline-5,8-diones (**1**) have been the focus of a large number of studies because of their wide spectrum of biological activity.[1]



1

This nucleus is also an important structural moiety in a number of more complex antibiotic agents such as streptonigrin,[2] streptonigrone,[3] and lavendamycin,[4] and it plays an important role in determining their biological activities.[5] Over several decades the synthesis and the biological activities of variously substituted quinolinediones have been reported.[6] The majority of these reports have dealt with the chemistry and/or bioassays of the C-6- and/or C-7-substituted quinolinediones.[1,6] The C-6 and C-7 substituents mainly include functionalities such as amino, hydroxyl, thiol, and their derivatives, as well as alkyl, halogen, and nitro groups.[1,6,7]

Scheme 1

2 **3:** R = H, **4:** R = CH_3, **5:** R = $CH(CH_3)_2$

Recently we reported short and practical syntheses for the novel 7-amino-2-methylquinoline-5,8-dione and three of its acyl derivatives (Scheme 1).[6b]

Results and Discussion

We now report the chemistry of these compounds and introduce efficient methods by which a number of novel C-5-, C-6-, and C-7-substituted derivatives of quinoline-5,8-diones can be prepared.

7-Acylamino-2-methylquinoline-5,8-diones **3**−**5** were prepared according to our previously reported methods.[6b] Room-temperature methanolysis of acyl compounds **3**−**5** in the presence of HCl or H_2SO_4 afforded the 7-amino dione **6** in yields of 40 to 98% (Scheme 2).

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Scheme 2

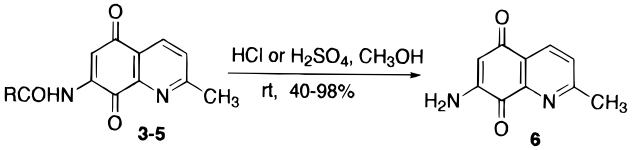
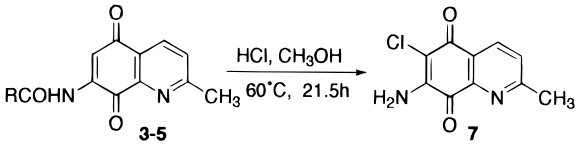


Table 1. Acid-Catalyzed Methanolysis of Acylamino Compounds at Room Temperature

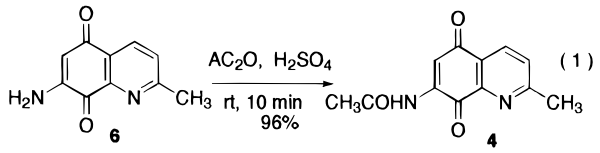
	dry HCl		conc H_2SO_4	
compd	time (h)	% yield of **6**	time (h)	% yield of **6**
3	0.08	98	0.33	86
4	20	88	1	82
5	20	40	24	67

Scheme 3



As shown in Table 1, the less hindered formamide **3** was more reactive and produced higher yields of **6**, followed by acetamide **4** and then isobutyramide **5**. The alcoholysis rate follows the expected reactivity order of formyl > acetyl > isobutyryl.

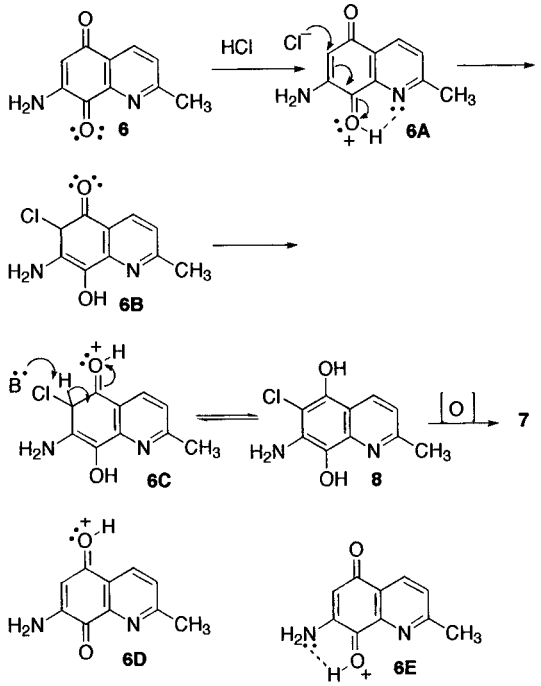
Although amide **3** gives a higher yield of **6** upon methanolysis, considering the ease of amide preparation as well as its methanolysis, we found that the preparation of **4** followed by its methanolysis in the presence of sulfuric acid is the method of choice for the preparation of **6**. Amino dione **6** was easily reconverted to the acetamido derivatives **4** in 96% yield upon treatment with acetic anhydride in the presence of H_2SO_4 at 0 °C for 10 min (eq 1).



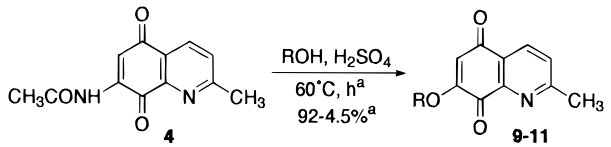
When solutions of **3**, **4**, or **5** in dry methanol were treated with HCl gas at 60 °C, 7-amino-6-chloro-2-methylquinoline-5,8-dione (**7**) was obtained in 97, 88, and 85% yields, respectively (Scheme 3).

On the basis of TLC of the reaction mixture and the direct conversion of **6** to **7**, the first step of this transformation is the generation of **6** (Scheme 2), followed by the addition of HCl to produce chlorohydroquinone **8** and its oxidation to **7**. It should be noted that the major part of hydroquinone **8** is oxidized to **7** by air during the reaction workup. Any remaining hydroquinone is converted to **7** upon treatment with a small volume of ferric chloride solution, as described in the Experimental Section. A possible mechanism for the production of **8** from **6** is given in Scheme 4. As shown, these reactions give in high yield the 6-chlorinated product only. These results are in agreement with those of the literature where the C-6 rather than the C-7 chloro isomers are obtained even when the unsubstituted quinolinediones are treated with HCl gas.[1j,l,7c,8] This would be expected on the basis of the fact that the course of the reaction would be determined by the generation of the more stable **6A** (H-bonded) rather than **6D**.

Scheme 4



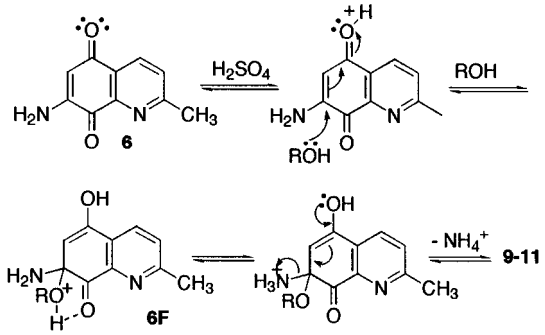
Scheme 5



[a] for **9**: 24h, 92%; for **10**: 36h, 47% for **11**: 40h, 4.5%

9: R = CH_3, **10**: R = C_2H_5, **11**: R = $CH(CH_3)_2$

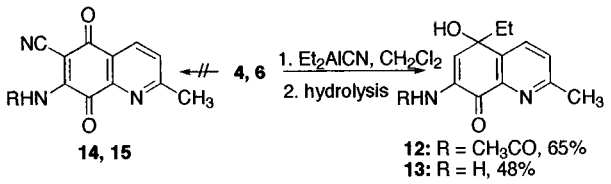
Scheme 6



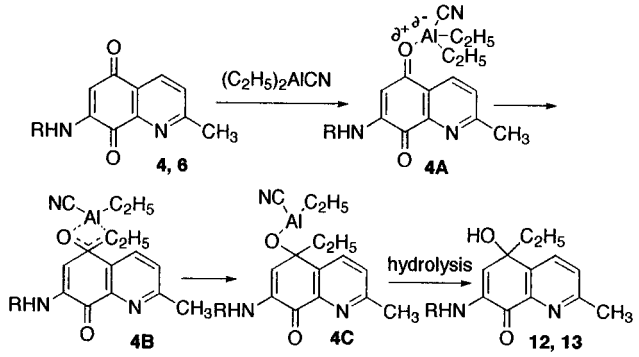
In another series of reactions when alcoholic (methanol, ethanol, and 2-propanol) solutions of acetyl derivative **4** were refluxed in the presence of concentrated sulfuric acid, 7-alkoxydiones **9**, **10**, and **11** were obtained in yields of 92, 47, and 4.5%, respectively (Scheme 5)

As expected, the alcohol reactivity is determined by the stability of the intermediate **6F** (Scheme 6) which in turn is governed by the alcohol steric hindrance: methanol > ethanol > 2-propanol. To our knowledge, no reaction of this type on a quinone ring has ever been reported. This chemistry offers a simple method for the synthesis of the C-7 alkoxyquinolinediones from their corresponding amino derivatives. The first step in this transformation is the generation of the vinylogous amide **6** through the alcoholysis of **4**, followed by the conversion of the former to **9**−**11**, probably according to the mechanism described in Scheme 6.

Scheme 7



Scheme 8



One of the well-known methods for the preparation of β-cyano carbonyl compounds is via the Michael addition of diethylaluminum cyanide to α,β-unsaturated carbonyl compounds.[9] When quinolinediones **4** and **6** were treated with diethylaluminum cyanide under similar conditions, products **12** and **13** rather than the expected 6-cyano derivatives **14** and **15** were obtained (Scheme 7).

To our knowledge, this is the first example of diethylaluminum cyanide adding an alkyl group (more basic) in a 1,2-fashion rather than adding a cyano group (more nucleophilic) in a 1,4-fashion to an α,β-unsaturated carbonyl system. The resulting products are quinoline quinols, which may be of some pharmaceutical interest.[10] This method, compared to the previously reported three-step synthesis of quinoline quinols,[10] is simpler and offers higher product yields.[11] This transformation may occur by the mechanism described in Scheme 8.

The postulated four-center transition state **4B** may be similar to those proposed for the cyanation of ketosulfonides by diethylaluminum cyanide[12] or that proposed for hydroboration of alkenes.[13]

Experimental Section

General Procedures. See ref 6d.

7-Amino-2-methylquinoline-5,8-dione (6).[6b] **(1) From Methanolysis of Compounds 3−5 in the Presence of H_2SO_4.** Methanolic solutions of 7-acylamino derivatives **3**, **4**, or **5**[6b] were treated with concentrated H_2SO_4 at room temperature according to our previously reported procedure[6b] to give **6** in 86, 82, and 67% yields, respectively. Table 1 shows the reaction times for each acylamino dione.

(2) From Methanolysis of Compounds 3−5 in the Presence of HCl Gas. A moderate stream of dry HCl gas was passed through a solution of 7-formamido-2-methylquinoline-5,8-dione (**3**; 65 mg, 0.3 mmol) in 10 mL of dry methanol for 1 min at room temperature. The reaction mixture was stirred for 5 min more and the red mixture containing some red solid was neutralized with 10 mL of a 2% sodium bicarbonate solution. The aqueous solution was extracted with 5×30 mL of CH_2Cl_2, and the combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo* to give 55 mg (98%) of the bright reddish orange crystals of amino dione **6**.[6b] Methanolysis of **4** gave 88% of **6** and that of **5** gave 40% of **6**. Table 1 shows the times required for the alcoholysis of **3**−**5**.

7-Acetamido-2-methylquinoline-5,8-dione (4). To a stirred solution of 7-amino-2-methylquinoline-5,8-dione (**6**; 27 mg, 0.14 mmol) in 2 mL of acetic anhydride was added one drop of concentrated H_2SO_4 at 0−5 °C. The red color of the solution immediately turned into bright yellow. The reaction mixture was stirred for 15 min at 0−5 °C and then diluted with 5 mL of H_2O. The solution was extracted with 4×10 mL of CH_2Cl_2, and the combined organic extracts were washed with 20 mL of saturated sodium bicarbonate solution and then 10 mL of H_2O. The organic solvent was evaporated *in vacuo* to give 31 mg (96%) of pure **4** as a bright yellow solid.[6b]

7-Amino-6-chloro-2-methylquinoline-5,8-dione (7). A slow stream of HCl was passed through a stirred solution of **4** (345.3 mg, 1.5 mmol) in 23 mL of dry methanol for 21.5 h at 60 °C. Excess HCl gas was flushed out by a stream of argon for 0.5 h, followed by evaporation of the solvent under reduced pressure. The resulting red solid was extracted with 2×200 mL of CH_2Cl_2. To the residue was added 200 mL of CH_2Cl_2 followed by 10 mL of 3% $NaHCO_3$ solution in 40 mL of brine to bring the pH to about 7−8. The organic layer was separated and the aqueous solution was extracted with 2×200 mL of CH_2Cl_2. To the aqueous solution was added 500 mg of $FeCl_3$ and the mixture was allowed to stand for 5 min with occasional swirling and then extracted with 2×100 mL of CH_2Cl_2. The combined organic extracts were washed with 200 mL of brine containing 20 mL of 3% $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated. The resulting red material was dried on a vacuum pump to give 294 mg (88%) of the red solid **7**: mp 270 °C (dec, CH_3OH); IR (KBr) 3471, 3329, 1649, 1605, 1587, 1370, 1326, 1164 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.35 (d, $J = 8.0$ Hz, 1H), 7.51 (d, $J = 8.0$ Hz, 1H), 5.70 (br s, 2H), 2.74 (s, 3H); MS, *m*/*z* (rel inten) 224 ($M^+ + 2$, 27), 222 (M^+, 97), 195 (7), 187 (100), 166 (5), 131 (10), 104 (12), 77 (15). Anal. Calcd for $C_{10}H_7ClN_2O_2$: C, 53.95; H, 3.17; N, 12.58. Found: C, 53.92; H, 3.13; N, 12.34. Formamido **3** and butyramido **5** gave **7** in 97 and 85% yields, respectively, when treated with HCl gas according to the procedure used for the acetamido **4**.

7-Methoxy-2-methylquinoline-5,8-dione (9). To a stirred solution of 7-acetamido-2-methylquinoline-5,8-dione (**4**, 115 mg, 0.5 mmol) in 15 mL of dry methanol was added 1 mL of concentrated sulfuric acid, and the resulting brownish red solution was stirred at 60 °C under argon for 24 h. The reaction mixture was evaporated, then 50 mL of CH_2Cl_2 was added and the mixture was neutralized to pH ~7 by the addition of about 20 mL of saturated $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with 4×25 mL of CH_2Cl_2. The combined organic extracts were washed with 15 mL of brine solution, dried ($MgSO_4$), and evaporated to give 93.3 mg (92%) of nearly pure product. A pure sample was obtained either by recrystallization of the material from methanol or flash chromatography using a 9:1 EtOAc−CH_2Cl_2 mixture as the eluting solvent: mp 247−8 °C (CH_3OH); IR (KBr) 3057, 2944, 1703, 1650, 1612, 1585, 1291, 1248, 1068, 840 cm^{-1}, ^1H NMR ($CDCl_3$) δ 8.29 (d, $J = 8.0$ Hz, 1H), 7.52 (d, $J = 8.0$ Hz, 1H), 6.18 (s, 1H), 3.91 (s, 3H), 2.76 (s, 3H); MS, *m*/*z* (rel inten) 203 (M^+, 11), 202 (61), 189 (100), 187 (88), 174 (21), 162 (29), 149 (26). Anal. Calcd for $C_{11}H_9NO_3$: C, 65.02; H, 4.46; N, 6.89. Found: C, 64.94; H, 4.57; N, 6.89.

7-Ethoxy-2-methylquinoline-5,8-dione (10). Compound **10** was obtained according to the procedure used for the preparation of **9**, except that the dried (Na_2SO_4) CH_2Cl_2

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(10) Kubo, A.; Kitahara, Y.; Inaba, K. *Heterocycles* **1985**, *23*, 387 and references therein.

(11) We plan to expand this reaction to other quinolinediones and quinones.

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extracts were concentrated to about 1 mL to produce a precipitate. This precipitate (impurity) was filtered off and the filtrate was evaporated to give 51.2 mg (47%) of **10**. Recrystallization from ethanol or flash chromatography (9:1 EtOAc−CH_2Cl_2) gave **10** as beige crystals: mp 151−2°; IR (KBr) 3060, 2980, 1700, 1655, 1608, 1584, 1328, 1247, 1106, 1085 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.27 (d, J = 8.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 6.15 (s, 1H), 4.10 (q, J = 7.0 Hz, 2H), 2.75 (s, 3H), 1.52 (t, J = 7.0 Hz, 3H); MS, *m/z* (rel inten) 217 (M^+, 74), 202 (22), 173 (30), 133 (41), 117 (100), 104 (55), 77 (17), 69 (21). Anal. Calcd for $C_{12}H_{11}NO_3$; C, 66.35; H, 5.10; N, 6.45. Found: C, 65.93; H, 5.05; N, 6.16.

7-Isopropoxy-2-methylquinoline-5,8-dione (11). Dione **11** was prepared according to the method used for the synthesis of **9**. Flash chromatography of the crude product (9:1 EtOAc−CH_2Cl_2) gave **11** as a bright beige crystalline material in a low yield of 4.5%: mp 122° (ether−petroleum ether); IR (KBr), 3053, 2925, 1697, 1656, 1610, 1584, 1323, 1248, 1107, 1066 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.26 (d, J = 8.0 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 6.14 (s, 1H), 4.57 (septet, J = 6.0 Hz, 1H), 2.75 (s, 3H), 1.44 (d, J = 6.0 Hz, 6H); MS, *m/z* (rel inten) 231 (M^+, 19), 191 (100), 167 (18), 161 (21), 149 (21), 97 (17), 85 (15); HRMS calcd for $C_{13}H_{13}NO_3$ 231.0896, found 231.0895.

7-Acetamido-5-ethyl-5-hydroxy-2-methylquinoline-8-one (12). A solution of diethylaluminum cyanide (1 mL of 1 M in toluene, 1 mmol) was added to a stirred solution of acetamido **4** (46 mg, 0.2 mmol) in 2 mL of dry CH_2Cl_2 under an Ar atmosphere. The reaction mixture was allowed to stir at 25 °C for 1 h and then added into 8 mL of an ice-cooled saturated solution of potassium sodium tartarate. The mixture was stirred for 15 min and then 20 mL of CH_2Cl_2 and 8 mL of a saturated potassium sodium tartarate solution were added. The resulting mixture was allowed to stir for an additional 15 min. The organic layer was separated and the aqueous layer was extracted with 3 × 20 mL of CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and then concentrated to 1 mL *in vacuo*. Flash chromatography of the material (9:1 EtOAc−CH_2Cl_2) gave 8 mg of the starting material **4** and 28 mg of **12** (65% based on reacted **4**). Recrystallization of the solid (CH_2Cl_2−petroleum ether) gave bright yellow crystals of **12**: mp 220 °C; IR (KBr) 3287, 3211, 2978, 1713, 1631, 1527, 1467, 1234, 1127, 1029 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.21 (d, J = 8.0 Hz, 1H), 7.86 (br s, 1H), 7.44 (s, 1H), 7.28 (d, J = 8.0 Hz, 1H), 4.45 (s, 1H) 2.62 (s, 3H), 2.24 (s, 3H), 1.96 (q, J = 7.5 Hz, 2H), 0.57 (t, J = 7.5 Hz, 3H); MS, *m/z* (rel inten) 260 (M^+, 0.2), 242 (4.8), 231 (100), 203 (78), 202 (45), 189 (48), 188 (70). Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.60; H, 6.27; N, 10.80

7-Amino-5-ethyl-5-hydroxy-2-methylquinoline-8-one (13). Compound **13** was prepared from amino dione **6** according to the procedure used for the synthesis of **12**. On the basis of the reacted **6** (~30% unreacted), the overall yield of the yellowish white crystalline **13** was 48%: mp 184 °C (CH_2Cl_2−petroleum ether); IR (KBr) 3448, 3289, 3110, 2969, 1641, 1620, 1596, 1376, 1256, 1119, 822, 527 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.17 (d, J = 8.0 Hz, 1H), 7.17 (d, J = 28.0 Hz, 1H), 5.51 (s, 1H), 5.10 (s, 2H), 4.27 (br s, 1H), 2.54 (s, 3H), 1.97 (q, J = 7.5 Hz, 2H), 0.56 (t, J = 7.5 Hz, 3H); MS, *m/z* (rel inten) 218 (M^+, 3.4), 202 (3), 190 (4), 189 (100), 162 (7). Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.46; N, 12.84. Found: C, 65.98; H, 6.40; N, 12.93.

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