

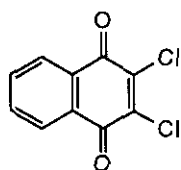
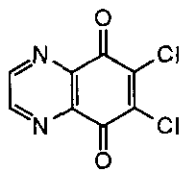
A NEW SYNTHETIC ROUTE TO 6,7-DICHLORO-5,8-QUINOXALINE-DIONE AND SYNTHESIS OF ITS DERIVATIVES

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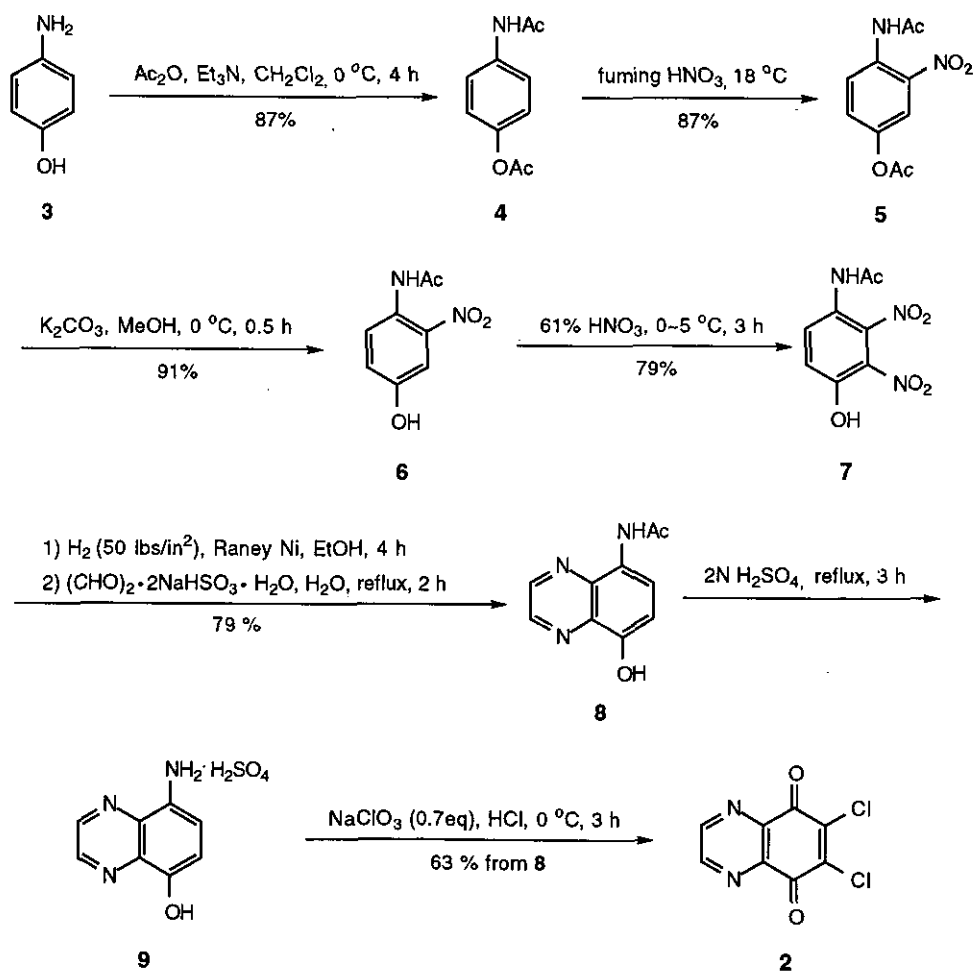
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Abstract - 6,7-Dichloro-5,8-quinoxalinedione (**2**), an analogue of Dichlone®, was prepared from 4-aminophenol (**3**) in 27% overall yield in 8 steps *via* chloroxidation of the sulfuric acid salt of 8-amino-5-quinoxalinol (**9**) as a key step. And two derivatives, 6-chloro-5-hydroxypyrazino[2,3-*a*]phenazine (**10**) and pyrido[1,2-*a*]imidazo[4,5-*g*]quinoxaline-6,11-dione (**11**), were prepared by reaction of **2** with 1,2-phenylenediamine and 2-aminopyridine in 79% and 46% yields, respectively.

The biological activity of naphthoquinones has received considerable attention since the fungicidal properties of Dichlone® (2,3-dichloro-1,4-naphthoquinone, **1**) were first described in 1949.¹ Many series of substituted 1,4-naphthoquinones derived from **1** have been reported because of their chemical and biological activities.²⁻⁴ However, synthetic studies for analogues to **1** and their derivatives have not been fully examined. In the case of 6,7-dichloro-5,8-quinoxalinedione (**2**), it was first prepared in 1986 in only 1.1% yield.⁵

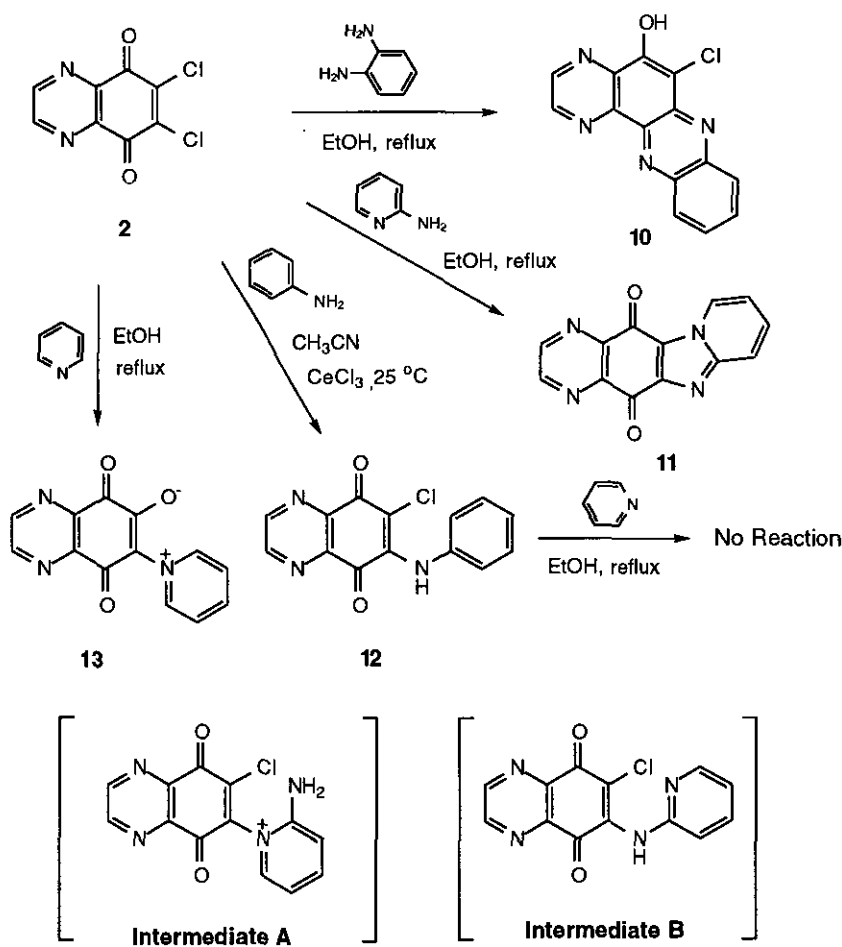
**1****2**

Because of its extremely low yield, we have developed an improved synthetic and versatile method by chloroxidation of the sulfuric acid salt of 8-amino-5-quinoxalinol (**9**). As we have known that the sulfuric acid salt of 5-amino-8-quinololinol is a suitable substrate for synthesis of 6,7-dichloro-5,8-quinolinedione, an analogue of **2**, we have adapted this methodology to the synthesis of **2**.⁶ Intermediate (**9**) was easily obtained by deacetylation of 8-acetamido-5-quinoxalinol (**8**),⁷ which was prepared from commercially available 4-aminophenol (**3**) in 6 steps. In the previous publication, however, compound (**8**) was prepared from **3** in only 2.7% overall yield in 6 steps.⁸ Now we report here a new synthetic route to 6,7-dichloro-5,8-quinoxalinolone (**2**) and preparation of two derivatives by reaction of **2** with 2-aminopyridine and 1,2-phenylenediamine (Scheme 1).



Scheme 1

Diacetate (**4**) was obtained by treatment of **3** with acetic anhydride and triethylamine at 0 °C in 87% yield. Nitration of **4** with fuming nitric acid gave mononitro compound (**5**) in 87% yield. Poor yield for deacetylation of **5** with hot sodium hydroxide solution in the previous publication (26%)⁸ was overcome by using methanolic potassium carbonate at 0 °C (91%). Careful temperature control below 5 °C for nitration of **6** with 61% nitric acid gave single isomer, 2,3-dinitro compound (**7**) in 79% yield. Compound (**7**) was hydrogenated in the presence of Raney Ni (W-4) catalyst to afford 2,3-diamino-4-acetaminophenol, which was not isolated but allowed to be reacted with glyoxal sodium bisulfite to form compound (**8**) in 79% yield. Under these conditions, the overall yield of **8** in 6 steps from **3** was improved (32%). Compound (**8**) was readily converted to intermediate (**9**) with refluxing 2N sulfuric acid and unisolated intermediate (**9**) reacted with sodium chlorate in hydrochloric acid solution at 0 °C



Scheme 2

to form the title compound (**2**) in 63% yield. The yield of **2** from isolated compound (**9**) was slightly lower (59%) than that through one-pot reaction from **8**.

Treatment of 1,2-phenylenediamine with **2** in hot ethanol solution⁹ gave the tetracyclic compound (**10**) in 79% yield. The chloride atom in **2** was replaced by one amino group in 1,2-phenylenediamine and another amino group in 1,2-phenylenediamine attacked to the carbonyl group in **2** to give a cyclization product. Treatment of **2** with 2-aminopyridine gave the ring closure product (**11**) under the same condition in 46% yield. Interesting tetracyclic compound (**11**) might be formed from intermediate A rather than the intermediate B, since 6-benzamino-7-chloro-5,8-quinoxalinedione (**12**) did not react with pyridine under the same condition and the positive charge in intermediate A could be relieved by attacking of the exo-amino group.¹⁰ In the case of the addition of pyridine to **2** under these conditions, we could obtain only zwitterionic compound (**13**)¹¹ (Scheme 2).

EXPERIMENTAL

Melting points were determined on Thomas-Hoover capillary apparatus and were uncorrected. Ir spectra were obtained on Perkin-Elmer 1710 spectrophotometer. Nmr measurements were taken by Varian Gemini 300. MS spectra were performed by Hewlett Packard 5790 (70eV). Elemental analysis was performed with Carlo Erba 1106 elemental analyzer.

4-Acetyloxyacetanilide (4). To a solution of 4-aminophenol (100 g, 0.92 mol) in CH_2Cl_2 (920 ml) were added Et_3N (265 ml, 2 mol) and Ac_2O (191 ml, 2 mol) in many portions over 2 h at 0 °C. After being stirred for 2 h, the reaction was quenched by MeOH (100 ml). The reaction mixture was concentrated under reduced pressure. The residue was poured into ice-cold water (2 l). The resulting precipitate was collected by filtration and washed with ice-cold water. The crude product was recrystallized from EtOAc/hexane to yield 154 g (87%) of **4** as a white solid: mp 151~154 °C (lit.,⁸ 151~154 °C).

4-Acetyloxy-2-nitroacetanilide (5). To a solution of fuming nitric acid (87%, sp. gr. 1.56, 42 ml, 0.83 mol) that was cooled to 18 °C in ice bath was added compound (**4**) (40 g, 0.21 mol) in many portions over 1 h. After being stirred for 0.5 h at 18 °C, the mixture was poured into ice-cold water (500 ml).

The resulting precipitate was collected by suction filtration and washed with ice-cold water. After dried *in vacuo*, crude product was recrystallized from 50% aq. EtOH to yield 43.5 g (87%) of **5** as a yellow solid: mp 143–146 °C (lit.,⁸ 145–146 °C).

4-Acetamino-2-nitrophenol (6). To a solution of compound (**5**) (17.5 g, 73.5 mmol) in MeOH (370 ml) was added K₂CO₃ (10.4 g, 73.5 mmol) in a portion at 0 °C. After being stirred for 0.5 h at 0 °C, the reaction was quenched by 1N HCl (74 ml). The mixture was concentrated under reduced pressure and the residue was diluted with ice-cold water (200 ml). The resulting precipitate was collected by filtration to yield 13.1 g (91%) of **6** as a bright red solid: mp 218–222 °C (lit.,⁸ 218–220 °C).

4-Acetamino-2,3-dinitrophenol (7). To a solution of HNO₃ (61%, sp. gr. 1.38, 13 ml, 0.28 mol) was added the compound (**6**) (8.4 g, 43 mmol) in many portions over 3 h at 0 °C. The reaction temperature was held below 5 °C during the reaction. After being stirred for 0.5 h, the reaction mixture was poured into ice-cold water (150 ml). The resulting precipitate was collected by filtration, washed with ice cold water and dried *in vacuo*. The crude product was recrystallized from 50% aq. EtOH solution to yield 8.23 g (79%) of **7** as a yellow solid: mp 195–198 °C (lit.,⁸ 195–198 °C).

8-Acetamino-5-quinoxalinol (8). To a solution of compound (**7**) (12.5 g, 51.9 mmol) in EtOH (100 ml) was hydrogenated with H₂ (50 lbs/in²) in the presence of Raney Ni (W-4) (305 mg, 5.2 mmol) catalyst for 4 h. The mixture was diluted with water (150 ml) and filtrated through a pad of celite. The dark filtrate was concentrated under reduced pressure. The residue was diluted with warm water (100 ml) and added to a warm solution of glyoxal sodium bisulfite (16.2 g, 57.1 mmol) in water (150 ml). The mixture was heated to reflux for 2 h under N₂ atmosphere. The mixture was concentrated under reduced pressure. The residue was diluted with sat. NaHCO₃ solution (100 ml) and continuously extracted with Et₂O to yield 8.3 g (79%) of **8** as a yellow solid: mp 240–245 °C (lit.,⁸ 246–247 °C).

6,7-Dichloroquinoxalinedione (2). A solution of compound (**8**) (5 g, 24.6 mmol) in 2N H₂SO₄ solution (62 ml) was heated to reflux for 3 h. The mixture was concentrated under reduced pressure and the residue was diluted with conc. HCl (123 ml). To the dark solution was added NaClO₃ (1.8 g, 17.2 ml) in many portions over 3 h at 0 °C. The reaction was quenched by distilled water (250 ml).

The blood red solution was extracted with ether (100 ml) *via* continuous extraction apparatus. The combined organic layer was washed with water (2x50 ml), dried over MgSO_4 and concentrated under reduced pressure. The residue was recrystallized from ether to yield 3.6 g (63%) of **2** as a pale yellow solid: mp 251~254 °C. ^1H Nmr (300 MHz, CDCl_3) δ 9.10 (s, 2H_{arom}); ^{13}C nmr (75 MHz, $\text{DMSO}-d_6$) δ 142.5, 143.6, 148.6, 174.3; ir (KBr) 1700 cm^{-1} ; ms m/z (relative intensity) 228, 230, 232 (14, 72, 100, M^+), 200, 202, 204 (10, 55, 78); Anal. Calcd for $\text{C}_8\text{H}_2\text{N}_2\text{O}_2\text{Cl}_2$: C, 42.0; H, 0.87; N, 12.2. Found: C, 41.8; H, 0.77; N, 11.9.

6-Chloro-5-hydroxypyrazino[2,3-*a*]phenazine (10). A suspension of **2** (100 mg, 0.44 mmol) in EtOH (20 ml) was heated until the starting material was dissolved. To the solution was added 1,2-phenylenediamine (70 mg, 0.65 mmol). After being stirred for 0.5 h at 60 °C, the solution was cooled. The dark yellow solid was collected by filtration to yield 95 mg (79%) of **10**: mp >300 °C. ^1H Nmr (300 MHz, $\text{DMSO}-d_6$) δ 7.98 (m, 2H_{arom} , $H-9,10$), 8.29 (d, 1H_{arom} , $J=8.25$ Hz, $H-11$), 8.38 (d, 1H_{arom} , $J=7.14$ Hz, $H-8$), 8.95 (s, 1H , OH), 9.23 (dd, 2H_{arom} , $J=1.8, 17.2$ Hz, $H-2,3$); ^{13}C nmr (75 MHz, $\text{DMSO}-d_6$) δ 128.4, 128.5, 129.6, 129.9, 132.0, 138.1, 139.2, 140.0, 142.2, 145.5, 145.7, 15.25, 152.6; ir (KBr) 3420 cm^{-1} ; ms m/z (relative intensity) 282, 284 (100, 38, M^+); Anal. Calcd for $\text{C}_{14}\text{H}_7\text{N}_4\text{OCl}$: C, 59.5; H, 2.5; N, 19.8. Found: C, 58.4; H, 2.5; N, 19.1.

Pyrido[1,2-*a*]imidazo[4,5-*g*]quinoxaline-6,11-dione (11). A suspension of **2** (100 mg, 0.44 mmol) in EtOH (20 ml) was heated until the starting material was dissolved. To the solution was added 2-aminopyridine (80 mg, 0.85 mmol). After being stirred for 1 h at 60 °C, the solution was cooled. The dark red solid was collected by filtration to yield 50 mg (46%) of **11**: mp >300 °C. ^1H Nmr (300 MHz, $\text{DMSO}-d_6$) δ 7.45 (t, 1H_{arom} , $J=6.6$ Hz, $H-2$), 7.83 (t, 1H_{arom} , $J=8.9$ Hz, $H-3$), 8.02 (d, 1H_{arom} , $J=8.9$ Hz, $H-4$), 8.85 (d, 2H_{arom} , $J=20.9$ Hz, $H-8,9$), 9.28 (d, 1H_{arom} , $J=6.6$ Hz, $H-1$); ^{13}C nmr (75 MHz, $\text{DMSO}-d_6$) δ 112.0, 112.7, 117.8, 118.6, 128.3, 132.5, 137.1, 145.0, 146.2, 147.5, 166.7, 178.9; ir (KBr) 1638 cm^{-1} ; Anal. Calcd for $\text{C}_{13}\text{H}_6\text{N}_4\text{O}_2$: C, 62.4; H, 2.4; N, 22.4. Found: C, 61.8; H, 2.6; N, 21.7.

6-Chloro-7-phenylamino-5,8-quinoxalinedione (12). To a solution of **2** (81 mg, 0.35 mmol) in CH_3CN (10 ml) was added cerium chloride heptahydrate (130 mg, 0.35 mmol), and the reaction mixture was stirred for 10 min at 25 °C. Aniline (0.1 ml, 1.05 mmol) was added to reaction mixture at 25 °C.

After being stirred for 24 h at 25 °C, the solvent was evaporated in diminished pressure. To the residue were added water (10 ml) and hexane (10 ml). The mixture was stirred for 30 min vigorously and filtered. The filter cake was purified by recrystallization with 95 % EtOH to give 81 mg (81 %) of **12** as a deep blue solid: mp 262~264 °C. ¹H Nmr (300 MHz, DMSO-*d*₆) δ 7.16 (d, 3H_{arom}, *J*=7.4 Hz), 7.33 (dd, 2H_{arom}, *J*=7.4, 8.2 Hz), 9.02 (d, 2H_{arom}, *J*=6.8 Hz, *H*-2,3), 9.53 (s, 1H, *NH*); ¹³C nmr (75 MHz, DMSO-*d*₆) δ 123.9, 124.6, 127.9, 129.1, 138.8, 143.3, 143.9, 144.2, 147.6, 148.5, 174.9, 178.2; ir (KBr) 3234, 1697, 1647 cm⁻¹; Anal. Calcd for C₁₄H₈N₃O₂Cl: C, 58.8; H, 2.8; N, 14.7. Found: C, 58.7; H, 3.0; N, 13.9.

6-Pyridinium-5,8-quinoxalinedione-7-oxide (13). A suspension of **2** (200 mg, 0.88 mmol) in absolute EtOH (40 ml) was heated until the starting material was dissolved. To the solution was added pyridine (0.1 ml, 1.32 mmol). After being stirred for 3 h at 60 °C, the solution was cooled. The orange-colored solid was collected by filtration to yield 185 mg (85 %) of **13**: mp >300 °C. ¹H Nmr (300 MHz, DMSO-*d*₆) δ 8.21 (dd, 2H_{arom}, *J*=6.3, 7.3 Hz, *H'*-3,5), 8.63 (t, 1H_{arom}, *J*=7.3 Hz, *H'*-4), 8.88 (d, 2H_{arom}, *J*=6.3 Hz, *H'*-2,6), 8.99 (d, 2H_{arom}, *J*=16.5 Hz, *H*-2,3); ir (KBr) 3437, 1707 cm⁻¹; Anal. Calcd for C₁₃H₇N₃O₃: C, 61.7; H, 2.8; N, 16.6. Found: C, 61.5; H, 2.7; N, 16.2.

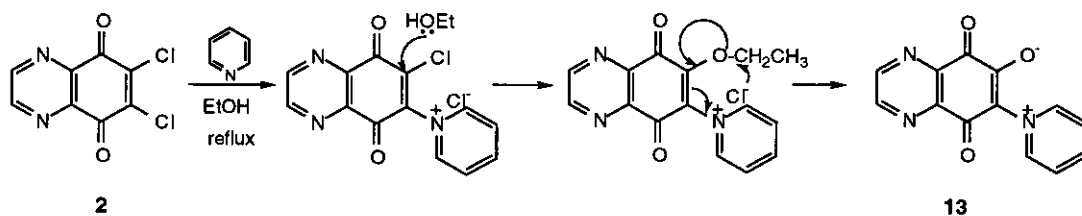
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