An Unusual Oxidation of a Benzylic Methylene Group by Thionyl Chloride: A Synthesis of 1,3-Dihydro-2-[2-(dimethylamino)ethyl]-1,3-dioxopyrrolo[3,4-*c*]acridine Derivatives

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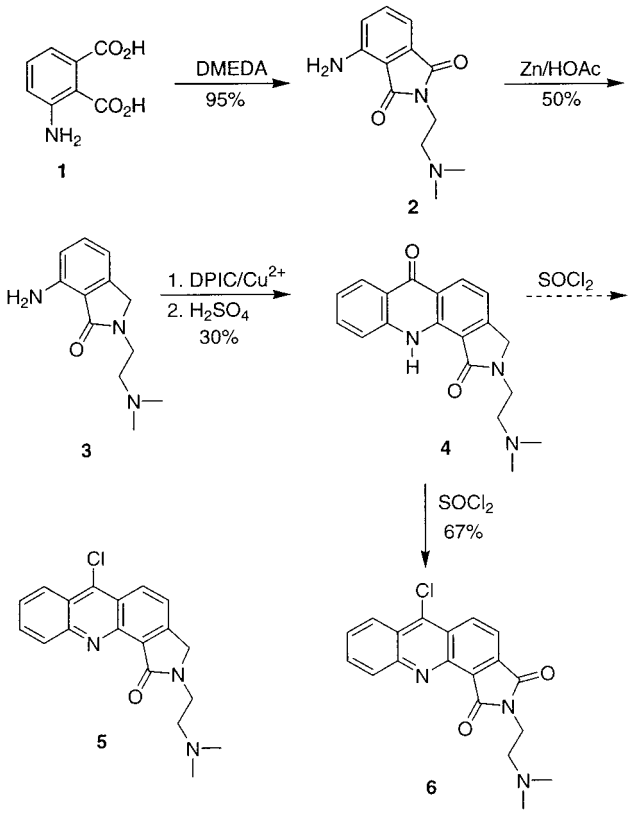
Introduction

Although thionyl chloride is routinely used as a chlorinating agent, "atypical" reactions have been reported. Some examples are the reactions of compounds with an active methylene group involving O-sulfinylation which produced gem dichlorides via addition reactions at a carbonyl group[1−3] or C-sulfinylation via the Hell−Volhard−Zelinsky reaction to give sulfinyl chlorides which may further undergo a Pummerer-type rearrangement and give various products, including α-chlorosulfenyl chlorides, sulfines, and thiones.[4−6] These compounds can be converted to ketones through acidic hydrolysis.[6−8] However, as far as we can determine, the direct oxidation of a methylene to a carbonyl group by thionyl chloride has not been reported. We report herein several cases of the unexpected direct oxidation of such a benzylic methylene in two fused-acridine systems by thionyl chloride.

Results and Discussion

During the course of studies on the synthesis of novel fused acridine derivatives as potential anticancer agents,[9] 6-chloroacridine, **5**, was needed as a desired intermediate. As shown in Scheme 1, the acridone **4** was expected to convert to **5** by treatment with a chlorinating agent such as thionyl chloride. The preparation of **4** started with 3-aminophthalic acid (**1**),[10] which was heated with *N*,*N*-dimethylethylenediamine (DMEDA) to give the phthalimide, **2**. Partial reduction of **2** with zinc in acetic acid[11,12] gave the isoindole **3**. The copper(II) catalyzed coupling reaction between **3** and diphenyliodonium-2-carboxylate[12,13] (DPIC) followed by intramolecular cyclization gave **4** in 30% yield.

Scheme 1



Several chlorinating agents including phosphorus oxychloride ($POCl_3$), oxalyl chloride (ClCOCOCl), and thionyl chloride ($SOCl_2$) were tried for the conversion of **4** to **5**. While the reactions between **4** and $POCl_3$ or ClCOCOCl gave neither any isolable product nor recovered starting material, the reaction of **4** and $SOCl_2$ gave a product in good yield. However, the spectral analysis revealed that it was not the desired product **5**. First, the ^{1}H NMR showed the absence of the benzylic methylene protons and the ^{13}C NMR showed the presence of two carbonyl groups with a very small difference in their chemical shifts. The two-dimensional HMBC (homonuclear multiple bond coherence) spectrum showed coupling between the NCH_2 protons and both carbonyl groups. The presence of one chlorine atom was indicated by GC−MS analysis which showed a single peak with *m*/*z* at 353 ($M^{+\bullet}$ for $C_{19}H_{16}ClN_3O_2$) and 355 ($M^{+\bullet}$ + 2, 39% relative to *m*/*z* 353). The formula was confirmed by HRMS. These data are consistent only with structure **6**. However, this compound is not very stable and undergoes hydrolysis after being exposed to air and moisture. Obviously, instead of the expected conversion of acridone to chloroacridine, the benzylic methylene group was unexpectedly oxidized (Scheme 1).

Confirmation of the structure of **6** was achieved by direct synthesis from **7**, which was prepared by the coupling reaction between **2** and DPIC in the presence of a Cu(II) catalyst. When **7** was heated with $POCl_3$ at

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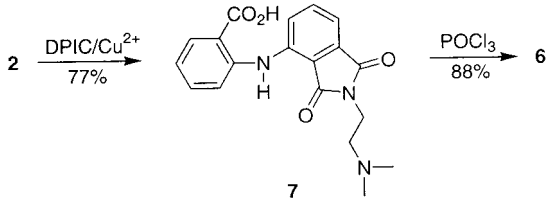
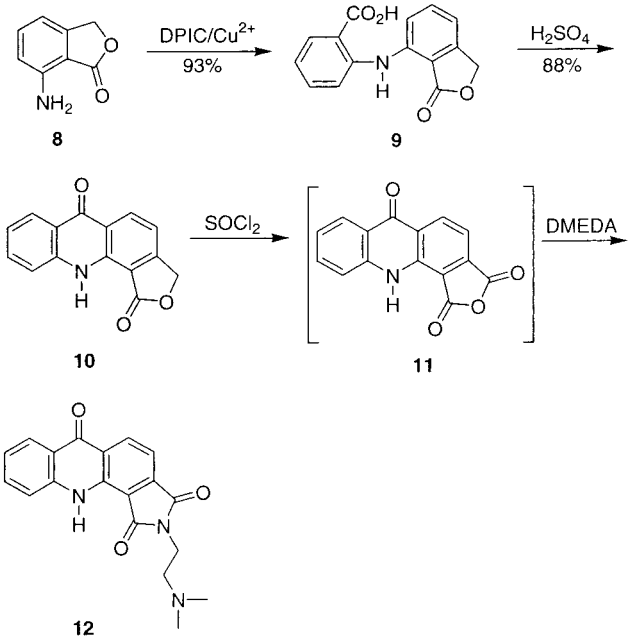
Scheme 2



Scheme 3

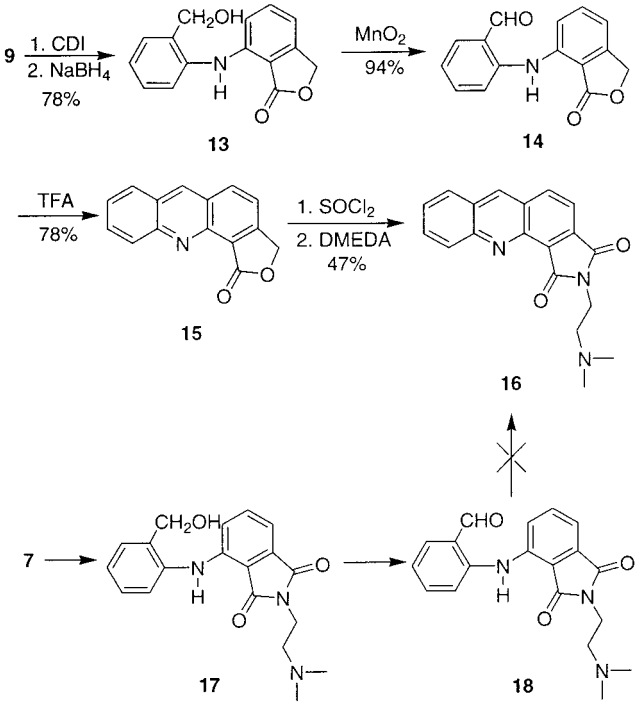


115 °C, it gave a product in high yield which was identical in all respects to **6** (Scheme 2).

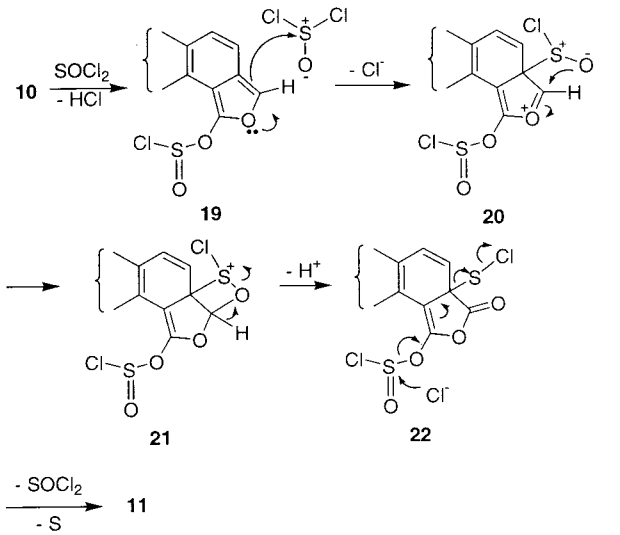
This unusual oxidation reaction was again observed when the furoacridone **10** was treated with thionyl chloride (Scheme 3). 7-Aminophthalide (**8**)[14] was treated with DPIC and Cu(II) to give the carboxylic acid **9**, which was cyclized in concentrated sulfuric acid to afford **10**. After **10** was heated with $SOCl_2$ under nitrogen, excess reagent was removed to give a very labile product. Mass spectrum showed *m*/*z* 265 ($C_{15}H_7NO_4$), which is consistent with structure **11**. Although no pure product could be obtained, the formation of this anhydride was confirmed by its conversion to **12**, which was also obtained by either the hydrolysis of **6** or the cyclization of **7** with concentrated H_2SO_4. It was noted that, during the workup, a very small amount of insoluble material was obtained whose total sulfur content was 87% by elemental analysis. This was assumed to be elemental sulfur.

This unusual oxidation was found to be useful in the synthesis of 1,3-dihydro-2-[2-(dimethylamino)amino]-1,3-dioxopyrrolo[3,4-*c*]acridine (**16**), a potent DNA topoisomerase II inhibitor.[9] Reduction of **9** using conditions developed by Sharma[15] gave the alcohol **13**, which was oxidized with MnO_2 in acetone to afford the aldehyde **14**. Cyclization of **14** in TFA under nitrogen afforded the furo[3,4-*c*]acridine **15**. Treatment of **15** with $SOCl_2$ followed by DMEDA gave the desired product **16**, presumably through an anhydride intermediate. In contrast, the

Scheme 4



Scheme 5



aldehyde **18**, prepared from the carboxylic acid **7** in a two-step sequence similar to the transformation of **9** to **14**, failed to cyclize to **16** (Scheme 4).

The experimental facts about this oxidation are the following: (1) the oxidation occurred even under a nitrogen atmosphere and in the dark; (2) the carbonyl group formed without acidic hydrolysis; (3) heating at the refluxing temperature was required; (4) elemental sulfur was probably a byproduct. On the basis of the above observations, we propose a possible mechanism for the thionyl chloride oxidation of the benzylic methylene groups of **4**, **10**, and **15**. The reaction between **10** and thionyl chloride is illustrated in Scheme 5.

The initial step was perhaps the tautomerization of **10** to form the enol ester **19**. Thionyl chloride then adds to the enol double bond to give **20**, in a way much like the Hell−Volhard−Zelinsky reaction.[6] Subsequent attack of the oxygen anion to the C=O$^+$ double bond yields a four-

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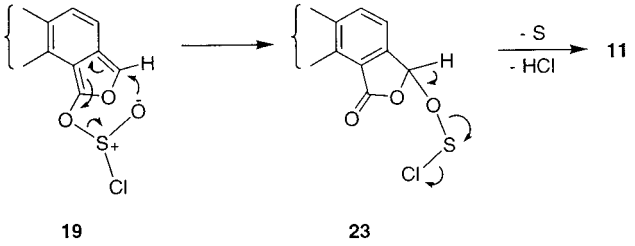
Scheme 6



membered ring intermediate.[16] Loss of a proton and the cleavage of the S−O bond gave **22**, which proceeds to form **11** with the loss of a molecule of $SOCl_2$ and elemental sulfur. The strain of the four-membered ring and the strong polarization of the S−O bond due to the positive charge on sulfur atom were, perhaps, the driving forces for the cleavage of the S−O bond.

Alternatively,[17] **19** could form **11** directly by an internal oxidation which involves a simple, smooth transformation through a six-membered ring transition state (Scheme 6).

Interestingly, treatment of **10** with $SOCl_2$ only facilitates the benzylic oxidation to form **11** but does not convert **11** to the corresponding chloroacridine. This is in contrast to the reaction of **4** with $SOCl_2$ to give **6** in which both oxidation and chlorination are involved. As to the chlorination, it is not necessary to postulate a tautomeric enol intermediate because 10-methyl-9-acridone gives 9-chloro-10-methyl-acridinium dichlorophosphate in refluxing $POCl_3$ as reported by Gleu et al.[18] As compared to $POCl_3$, $SOCl_2$ is a relatively weaker chlorinating agent and it is known that many acridones are reluctant to undergo chlorination under the same conditions. In many cases, a catalytic amount of DMF is added to facilitate the chlorination with $SOCl_2$. In the case of **4** going to **6** with $SOCl_2$, it appears that the oxidation occurs before the chlorination because **4** does not convert to **5** with $POCl_3$.

This oxidation has thus far only worked effectively for acridine derivatives, including the 10-methyl-substituted analogue of **15** (unpublished result). Phthalide did not react with $SOCl_2$ at all, and only the starting material was recovered. Although the reaction of 2(*5H*)-furanone with $SOCl_2$ for 1 h at refluxing temperature did produce maleic anhydride, the conversion rate was only about 1% by GC−MS analysis, the major component was the unchanged starting material.

Conclusion

A novel oxidation reaction of a benzylic methylene to a carbonyl group, in pyrroloacridone or furoacridone ring systems, has been observed. This oxidation reaction is useful in the synthesis of 1,3-dihydro-2-[2-(dimethylamino)amino]-1,3-dioxopyrrolo[3,4-*c*]acridine derivatives which are potential anticancer agents.

Experimental Section

General. ^{1}H NMR and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively. Mass spectra were obtained by GC−MS using electron-impact (EI) ionization mode (70 eV). HRMS spectra were recorded using the electrospray ionization (ESI) method. Elemental analyses were performed by either Galbraith Laboratories, Inc., Knoxville, Tennessee, or Atlantic Microlabs, Inc., Norcross, Georgia.

3-Amino-*N*-[2-(dimethylamino)ethyl]phthalimide (2). 3-Aminophthalic acid (4.0 g, 0.017 mole) and 3.5 mL of *N*,*N*-dimethylethylenediamine were heated in a 165 °C oil bath for 2.5 h. After the mixture was cooled to room temperature, methylene chloride was added until the solid mass had dissolved. The solution was passed through an alumina column (50 g) and eluted with methylene chloride. The fraction containing the product (**2**) was collected, and the solvent was evaporated to give 4.9 g (95% yield) of a yellow solid: mp 103−103.5 °C; GC−MS *m*/*z* 233 (M^+); IR (KBr) 3466, 3436, 3360, 3288, 1748, 1694 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.38 (t, 1H, J = 7.2 Hz), 7.11 (d, 1H, J = 7.2 Hz), 6.80 (d, 1H, J = 7.2 Hz), 5.22 (br s, 2H), 3.74 (t, 2H, J = 6.6 Hz), 2.57 (t, 2H, J = 6.5 Hz), 2.29 (s, 6H). Anal. Calcd for $C_{12}H_{15}N_3O_2$: C, 61.80; H, 6.44; N, 18.02. Found: C, 62.06; H, 6.41; N, 18.06.

Compound **2** (5.2 g, 0.022 mole) was dissolved in 50 mL of acetone. Concentrated HCl (3.8 mL) was added, and the solid formed was filtered and washed with acetone−ethyl acetate (2:1). The monohydrochloride was obtained as a yellow solid (5.9 g, 98% yield): mp 239−241 °C. Anal. Calcd for $C_{12}H_{15}N_3O_2$·HCl: C, 53.43; H, 5.94; Cl, 13.17; N, 15.58. Found: C, 53.35; H, 5.99; Cl, 13.37; N, 15.54.

1,6-Dioxo-2-[2-(dimethylamino)ethyl]-1,3,6,11-tetrahydropyrrolo[3,4-*c*]acridine (4). A suspension of **3** (2.92 g, 13.3 mmol), diphenyliodonium-2-carboxylate (5.17 g, 16.0 mmol), and cupric acetate (0.121 g, 0.665 mmol) in 21 mL of 2-propanol was heated under reflux for 72 h. The solvent was removed in vacuo until dryness. The brown oily residue was triturated with hexane (50 mL) to precipitate a yellow solid. It was filtered, and the filter cake was immediately dried in a vacuum desiccator to give 5.75 g of an amorphous powder (the solid material was extremely hygroscopic). It was added to 30 mL of concentrated sulfuric acid, and the resulting mixture was heated at 100 °C for 2 h. The mixture was cooled to room temperature and poured slowly into ice (300 g) with stirring. Concentrated NH_4OH was added until a pH of 9 resulted while the temperature was kept below 10 °C. The mixture was extracted with $CHCl_3$ (6 × 80 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed to give an oily residue which was chromatographed ($CHCl_3$−MeOH, 9:1) to give a total of 1.27 g (30% yield) of **4**: mp 178−180 °C; GC−MS *m*/*z* 321 (M^+); IR (KBr) 3328, 1672, 1654, 1606 cm^{-1}; ^{1}H NMR ($CDCl_3$) 8.53 (d, 1H, J = 8.2 Hz), 8.46 (d, 1H, J = 8.0 Hz), 8.12 (br s, 1H), 7.69 (m, 1H), 7.40 (d, 1H, J = 8.3 Hz), 7.28 (m, 1H), 7.22 (d, 1H, J = 8.2 Hz), 4.58 (s, 2H), 3.71 (t, 2H, J = 6.3 Hz), 2.61 (t, 2H, J = 6.3 Hz), 2.31 (s, 6H); ^{13}C NMR ($CDCl_3$) 177.5, 168.9, 147.8, 139.7, 137.9, 133.8, 131.1, 127.2, 122.2 (C-6a, C-8), 120.6, 117.4, 117.1, 115.2, 57.8, 51.3, 45.4, 39.8. HRMS calcd for $C_{19}H_{20}N_3O_2$ (MH^+), 322.1551; found, 322.1525.

3-(*o*-Carboxyphenyl)amino-*N*-[2-(dimethylamino)ethyl]-phthalimide (7). A mixture of 1.4 g (4.3 mmol) of diphenyliodonium carboxylate (DPIC), 1.0 g (4.3 mmol) of **2**, and 40 mg (0.22 mmol) of cupric acetate in 10 mL of 2-propanol was heated under reflux for 12 h. Another portion of DPIC (0.70 g, 2.2 mmol) was added, and the mixture continued to be heated under reflux temperature for another 12 h. The mixture was filtered while it was still hot, and the yellow solid was washed successively with hot 2-propanol (15 mL) and warm water (30 mL). The solid was dried to give 1.2 g (77% yield) of **7**: mp 263−265 °C dec.

Compound **7** was converted to its HCl salt as follows: 2-Propanol (5 mL) was added to a solution of **7** (100 mg, 0.283 mmol) in 2 mL of 0.3 N HCl. The precipitate was filtered and washed with 2-propanol and ethyl acetate and was then dried in vacuo to give 86 mg (74% yield) of a yellow solid: mp 175−177 °C; ^{1}H NMR (D_2O) 7.63 (d, 1H, J = 7.8 Hz), 7.55 (d, 1H, J = 8.6 Hz), 7.34 (t, 1H, J = 7.8 Hz), 7.28 (m, 2H), 7.01 (d, 1H, J = 7.1 Hz), 6.84 (m, 1H), 3.86 (t, 2H, J = 6.2 Hz), 3.41 (t, 2H, J = 6.2 Hz), 3.00 (s, 6H); ^{13}C NMR (D_2O) 173.3, 172.3, 171.7, 144.4, 142.6, 138.7, 136,3, 134.9, 134.6, 123.9, 123.8, 119.8, 119.5, 118.0, 115.9, 58.1, 46.0, 35.5. Anal. Calcd for $C_{19}H_{19}N_3O_4$·HCl·H_2O: C, 55.95; H, 5.44; Cl, 8.69; N, 10.38. Found: C, 56.04; H, 5.42; Cl, 8.74; N, 10.30.

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6-Chloro-1,3-dihydro-2-[2-(dimethylamino)ethyl]-1,3-dioxopyrrolo[3,4-*c*]acridine (6). 1. Method A. A suspension of **4** (19 mg, 0.059 mmol) in 0.5 mL of thionyl chloride was heated under nitrogen for 1.5 h. It was cooled to room temperature and slowly added to a vigorously stirring mixture of $CHCl_3$ (2 mL) and concentrated NH_4OH (1 mL) with ice cooling. The mixture was filtered, and the $CHCl_3$ layer was separated and washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by column chromatography ($CHCl_3$−MeOH, 97:3) to give 14 mg (67% yield) of yellow solid: mp 206−208 °C dec; GC−MS *m*/*z* 353 (M^+), 355 ($M^+ + 2$, 39% relative to *m*/*z* 353); IR (KBr) 1773, 1709, 1625 cm^{-1}; ^1H NMR ($CDCl_3$) 8.72 (d, 1H, $J = 8.7$ Hz), 8.34 (d, 2H, $J = 9.8$ Hz), 7.88 (d, 1H, $J = 8.8$ Hz), 7.83 (m, 1H), 7.64 (m, 1H), 3.85 (t, 2H, $J = 6.5$ Hz), 2.62 (t, 2H, $J = 6.6$ Hz), 2.25 (s, 6H); ^{13}C NMR ($CDCl_3$) 168.2, 167.4, 151.1, 142.7, 142.6, 136.5, 132.7, 132.1, 131.1, 128.7, 127.5, 126.9, 124.7 (C-6a, C-7), 118.8, 57.2, 45.5, 36.1. HRMS calcd for $C_{19}H_{17}ClN_3O_2$ (MH^+), 354.1006; found, 354.0979.

2. Method B. A mixture of the carboxylic acid **7** (50 mg, 0.14 mmol) and 0.5 mL of phosphorus oxychloride (0.82 g, 5.4 mmol) was heated at 115 °C for 24 h. After the mixture was cooled to room temperature, it was added dropwise with vigorous stirring to a mixture of 6 mL of 30% ammonium hydroxide and 10 g of crushed ice. The temperature was kept below 5 °C during the addition. After the addition, the resulting mixture was extracted with chloroform (3 × 10 mL). The organic layers were combined, washed with brine, and dried over $MgSO_4$. The solvent was evaporated to give a solid residue which was recrystallized from $CHCl_3$−EtOH to give 44 mg (88% yield) of **6** as a yellow solid: mp 206 °C dec; this material was identical in all respects to the sample obtained from method A.

7-(*o*-Carboxyphenyl)aminophthalide (9). A mixture of 5.0 g (0.034 mole) of **8**, 13 g (0.040 mole) of diphenyliodonium-2-carboxylate (DPIC), and 0.30 g (1.65 mmol) of cupric acetate in 70 mL of 2-propanol was heated under reflux for 24 h. The precipitate was filtered and washed with 2-propanol and water. The crude **9** (8.4 g, 93% yield) was obtained as a green powder. A portion of this crude product was converted to its sodium salt as follows: 1 g of it was added to a stirred solution of 19 mL of 0.2 N NaOH and heated to 45 °C. It was filtered, and the filtrate was concentrated to a small volume. The product precipitated upon addition of 2-propanol. The solid was filtered and washed with H_2O−2-propanol (1:2) to give 0.92 g (85% yield) of a sodium salt of **9** as a white solid: mp >300 °C; ^1H NMR (d_6-DMSO) 12.13 (s, 1H), 7.95 (d, $J = 7.6$ Hz, 1H), 7.39−7.52 (m, 3H), 7.26 (m, 1H), 6.89 (m, 2H), 5.29 (s, 2H). Anal. Calcd for $C_{15}H_{10}NO_4Na\cdot{}^1/_2H_2O$: C, 60.00; H, 3.67; N, 4.67. Found: C, 59.83; H, 3.57; N, 4.74.

Pure **9** was obtained by acidifing the aqueous solution of its sodium salt. It melted at 258−259 °C.

Conversion of 10 to 2-[2-(Dimethylamino)ethyl]-1,3,6-trioxo-11*H*-1,3,6,11-tetra-hydropyrrolo[3,4-*c*]acridine (12) by Sequential Treatment with Thionyl Chloride and *N*,*N*-Dimethylethylenediamine. A suspension of **10** (100 mg, 0.398 mmol) in thionyl chloride (1.5 mL) was heated to the reflux temperature under nitrogen for 1.5 h. The excess thionyl chloride was removed under reduced pressure to give an orange solid residue (*m*/*z* 256) which was suspended in dry chloroform (30 mL). *N*,*N*-Dimethylethylenediamine (67 mg, 0.76 mmol) and 3 mL of dry chloroform were added. The resulting mixture was stirred at room temperature for 1 h. Water (10 mL) was added, and the mixture was stirred for an additional 5 min. The mixture was filtered, and the chloroform layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated, and the residue was chromatographed ($CHCl_3$−MeOH, 97:3). A yellow band ($R_f = 0.4$, $CHCl_3$−MeOH 4:1) was collected to give 40 mg (30% yield) of a solid: mp 204−205 °C; *m*/*z* 335 (M^+); IR (KBr) 3370, 1764, 1701, 1636, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) 9.60 (s, 1H), 8.69 (d, 1H, $J = 7.9$ Hz), 8.39 (d, 1H, $J = 10.0$ Hz), 7.70 (t, 1H, $J = 8.3$ Hz), 7.55 (d, 1H, $J = 7.9$ Hz), 7.31 (m, 2H), 3.82 (t, 2H, $J = 6.4$ Hz), 2.62 (t, 2H, $J = 6.4$ Hz), 2.30 (s, 6H); ^{13}C NMR ($CDCl_3$) 176.8, 169.5, 167.5, 139.9, 136.5, 136.0, 134.8, 134.6, 127.4, 125.3, 123.0, 122.1, 117.0, 115.8, 114.9, 57.1, 45.5, 36.1. HRMS calcd for $C_{19}H_{18}N_3O_3$ (MH^+), 336.1344; found, 336.1319.

7-(*o*-Hydroxymethyl)phenylaminophthalide (13). 1,1′-Carbonyldiimidazole (51 mg, 0.32 mmol) was added to a suspension of **9** (57 mg, 0.21 mole) in 1.5 mL of dry THF. The mixture was stirred at room temperature for 24 h. It was added dropwise to $NaBH_4$ (55 mg, 1.5 mmol) in 4 mL of THF−H_2O (1:1). The resulting mixture was stirred for 20 min. The excess reagent was decomposed by the addition of 6 N HCl until a pH of 5 resulted. It was basified again with saturated $NaHCO_3$ solution until it attained a pH of 8. The product was precipitated by removing the THF in vacuo. Filtration followed by recrystallization from acetone−H_2O gave a white solid (42 mg, 78% yield): mp 145−147 °C; ^1H NMR ($CDCl_3$) δ 8.67 (s, 1H), 7.03−7.51 (m, 6H), 6.75 (d, 1H, $J = 7.3$ Hz), 5.26 (s, 2H), 4.74 (s, 2H), 2.24 (br s, 1H). Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.59; H, 5.10; N, 5.49. Found: C, 70.21; H, 5.10; N, 5.78.

7-(*o*-Formyl)phenylaminophthalide (14). MnO_2 (2.6 g) was added to a solution of **13** (0.85 g, 3.3 mmol) in 50 mL of acetone, and the mixture was stirred at room temperature for 4 days. The MnO_2 was filtered, and the filter cake was washed with hot chloroform. The filtrate was evaporated in vacuo to give 0.84 g of a yellow solid which was recrystallized from acetone to give 0.79 g (94% yield) of **14** as a yellow solid: mp 204−205 °C; GC−MS *m*/*z* 253 (M^+); ^1H NMR ($CDCl_3$) 10.88 (s, 1H), 10.00 (s, 1H), 7.47−7.71 (m, 5H), 7.09 (dd, 1H, $J = 7.8$, 7.8 Hz), 6.96 (br d, 1H, $J = 6.4$ Hz), 5.28 (s, 2H); ^{13}C NMR ($CDCl_3$) 193.3, 170.9, 148.3, 143.0, 141.5, 136.3, 135.2, 134.9, 123.2, 120.7, 116.3, 114.8, 113.5, 112.7, 69.1. Anal. Calcd for $C_{15}H_{11}NO_3$: C, 71.15; H, 4.35; N, 5.53. Found: C, 71.00; H, 4.43; N, 5.67.

1,3-Dihydro-2-[2-(dimethylamino)ethyl]-1,3-dioxopyrrolo-[3,4-*c*]acridine (16). A mixture of **15** (50 mg, 0.21 mmol) and thionyl chloride (2 mL) was heated at 80 °C under nitrogen for 1.5 h. The excess reagent was removed in vacuo to give a residue which was dissolved in dry chloroform (2 mL). *N*,*N*-Dimethylethylenediamine (75 mg, 0.85 mmol) in dry chloroform (1 mL) was added. The resulting mixture was stirred at room temperature for 30 min. Chloroform (20 mL) was added, and the solution was washed with 10 mL of 1.5% NH_4OH and brine and dried over $MgSO_4$. The solvent was evaporated to give a residue which was chromatographed ($CHCl_3$−MeOH, 95:5) to give 32 mg (47% yield) of pure **16**: mp 206−208 °C; GC−MS *m*/*z* 319 (M^+); IR (KBr) 1764, 1716, 1627 cm^{-1}; ^1H NMR ($CDCl_3$) 8.87 (s, 1H), 8.43 (d, 1H, $J = 8.9$ Hz), 8.35 (d, 1H, $J = 8.4$ Hz), 8.02 (d, 1H, $J = 8.5$ Hz), 7.88 (m, 2H), 7.63 (t, 1H, $J = 7.5$ Hz), 3.92 (t, 2H, $J = 6.5$ Hz), 2.69 (t, 2H, $J = 6.5$ Hz), 2.32 (s, 6H); ^{13}C NMR ($CDCl_3$) 169.2, 168.3, 151.8, 143.3, 137.8, 136.8, 136.7, 132.3, 131.2, 129.8, 128.9, 127.9, 127.7, 127.4, 118.3, 57.7, 45.9, 36.4. Anal. Calcd for $C_{19}H_{17}N_3O_2\cdot{}^1/_2H_2O$: C, 69.51; H, 5.49; N, 12.80. Found: C, 69.78; H, 5.31; N, 12.74.

3-(*o*-Hydroxymethyl)phenylamino-*N*-[2-(dimethylamino)-ethyl]phthalimide (17). A suspension of the carboxylic acid **7** (100 mg, 0.283 mmol) in 1 mL of thionyl chloride was heated under reflux for 30 min. The excess of reagent was removed in vacuo. The residue was suspended in 4 mL of dry THF and 76 mg (0.752 mmol) of triethylamine. Imidazole (40 mg, 0.59 mmol) was added, and the resultant mixture was refluxed for 24 h. It was cooled to 5 °C. Cold water (5 °C) (1.5 mL) was added, and the mixture became clear. $NaBH_4$ (a total of 24 mg, 0.63 mmol) was added in three equal portions every 5 min. The mixture was stirred vigorously during the addition and for a further 10 min after the addtion was completed. The excess of reagent was decomposed by addition of 6 N HCl until a pH of 5 was attained. The pH was then adjusted to 9 by concentrated NH_4OH. The THF was evaporated in vacuo, and the residue was extracted with $CHCl_3$ (3 × 10 mL). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was chromatographed ($CHCl_3$−acetone, 9:1) to give 45 mg (47% yield) of **17** as a yellow solid product: mp 133−134 °C; GC−MS *m*/*z* 339 (M^+); ^1H NMR ($CDCl_3$) 8.76 (br s, 1H), 7.11−7.48 (m, 7H), 4.74 (s, 2H), 4.06 (t, 2H, $J = 7.5$ Hz), 3.04 (t, 2H, $J = 7.6$ Hz), 2.70 (s, 6H), 2.27 (br s, 1H); ^{13}C NMR ($CDCl_3$) 169.5, 167.9, 143.1, 138.5, 135.5, 132.9, 132.7, 129.7, 128.8, 124.4, 121.7, 118.8, 113.5, 112.2, 63.3, 61.1, 51.9, 32.7. Anal. Calcd for $C_{19}H_{21}N_3O_3\cdot{}^5/_4H_2O$: C, 63.07; H, 6.50; N, 11.62. Found: C, 62.92; H, 6.67; N, 11.49.

3-(*o*-Formyl)phenylamino-*N*-[2-(dimethylamino)ethyl]-phthalimide (18). A mixture of **17** (400 mg, 1.18 mmol) and activated MnO_2 (435 mg) in 40 mL of acetone was stirred at room temperature for 48 h. After two additional portions of MnO_2 (435 mg each) were added at 24 h intervals, a TLC indicated that

the starting material has disappeared. The mixture was filtered, and the filter cake was washed with hot acetone. The combined filtrate was evaporated to give 356 mg (89% crude yield) of a yellow solid: mp 132−134 °C dec. An analytical sample was obtained by recrystalliztion from MeOH−H_2O: mp 132−133 °C dec; GC−MS *m*/*z* 337 (M^+); ^{1}H NMR ($CDCl_3$) 11.02 (br s, 1H), 9.99 (s, 1H), 7.82 (d, 1H, J = 8.4 Hz), 7.72 (dd, J = 7.6, 1.3 Hz), 7.51−7.61 (m, 3H), 7.38 (d, 1H, J = 7.1 Hz), 7.13 (t, 1H, J = 6.9 Hz), 4.10 (t, 2H, J = 7.5 Hz), 3.07 (t, 2H, J = 7.6 Hz), 2.72 (s, 6H); ^{13}C NMR ($CDCl_3$) 193.7, 168.3, 167.4, 142.5, 139.7, 136.6, 135.2, 135.0, 133.1, 122.8, 121.6, 121.0, 116.0, 115.9 (C-5, C-6), 61.0, 51.9, 32.9. Anal. Calcd for $C_{19}H_{19}N_3O_3 \cdot {}^3/_4H_2O$: C, 65.04; H, 5.89; N, 11.98. Found: C, 64.88; H, 6.28; N, 11.85.

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Supporting Information Available: ^{1}H NMR spectra of compounds **4**, **6**, **7**, **9**, **12**, **16**, **17**, and **18**, and ^{13}C NMR spectra of compounds of **4**, **6**, **7**, **12**, **16**, **17**, and **18**. This information is available free of charge via the Internet at http://pubs.acs.org.

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