Chemical Oxidation of 2,4-Diamino-pyrrolo[2,3-*d*]pyrimidines

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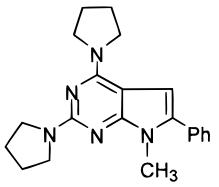
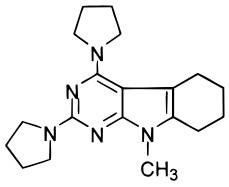
The synthesis of a series of novel, lipid-soluble antioxidants based on the pyrrolo[2,3-*d*]pyrimidine ring system has been reported recently.[1] Most members of this class, of which **1** and **2** are prototypical, were readily prepared in good yield under mild conditions by utilizing a modified Bischler-type protocol, starting with 2,4-di-1-pyrrolidinyl-6-methylamino-pyrimidine[2] and the appropriate α-bromoketone (phenacyl bromide for **1** and 2-bromocyclohexanone for **2**).



1 (PNU-87663)



2 (PNU-94430)

In addition to being electrochemically active, compounds **1** and **2** (and several congeners) were potent inhibitors of lipid peroxidation (measured by malondialdehyde formation in rat brain homogenates) and were also effective in protecting cultured mouse spinal neurons and human astrocytes from induced oxidative damage.[1] Hence, several of the pyrrolopyrimidines are currently undergoing a more in-depth pharmacological assessment to determine whether they might have value in the treatment of reactive-oxygen-mediated diseases,[3] initially chronic neurodegenerative diseases such as ALS and Alzheimer's and Parkinson's diseases.

Reported herein is a limited survey of the behavior of **1** (typical of the pyrrolopyrimidine class) under a variety of nonbiological oxidative conditions. This study was intended to provide an indication of the level of care required in the routine handling of these antioxidant compounds, a comparison with the heavily documented results of oxidation studies with simpler indoles, and finally authentic reference samples of several of the products that might be expected to be produced when **1** was subjected to in vivo experiments.

Despite the potent lipid peroxidation inhibiting activity of **1**, our initial concern that it might be difficult to handle proved unfounded. In fact, **1** could be recovered unchanged (>95%) following exposure to the following relatively mild oxidative conditions: (a) O_2-saturated ethyl acetate (solution), 18 h, 25 °C; (b) 5-fold excess of aqueous H_2O_2 in methanol, 18 h, 25 °C; (c) excess iodine, methylene chloride, 18 h, 25 °C; (d) *N*-methyl-morpholine *N*-oxide, CH_2Cl_2, 1 week, 25 °C; (e) urea−H_2O_2 complex, CH_2Cl_2, 48 h, 25 °C; (f) diphenylpicrylhydrazyl radical (used to detect good H• donors),[4] EtOH, 25 °C 2 h, reflux 2 h; and (g) trifluoroacetic acid (a one-electron oxidant[5]), 35 days, 25 °C. This lack of reactivity of **1** under these conditions may not be surprising in view of its 530-mV oxidation potential (cyclic voltammetry experiments) reported earlier.[1]

The first evidence for the solution instability of **1** came with the observation that NMR samples (in $CDCl_3$ which had been percolated through basic alumina immediately prior to use) turned from colorless to pink within several hours and to dark purple over several days. Although no new products could be noted by TLC at 18 h, chloroform solutions of **1** which were stirred in air for 1 week at 37 °C afforded small amounts of two new, less polar, crystalline products, the 2-pyrrolyl derivative **3** and 5-chloro derivative **4**, both of which presumably resulted from reaction with the small amounts of chlorine present in the chloroform (Scheme 1). The fact that oxidation of the pyrrolidine substituent to a pyrrole occurred at C-2 (and not C-4) was confirmed by the observation of NOE enhancement between the C-5 and the α-pyrrolidinyl proton signals. (The importance of the electron-donating properties of the pyrrolidinyl substituents to the overall antioxidant activity of **1** was readily demonstrated by the observation that the 2-pyrrolyl derivative **3** was approximately 300 mV less readily oxidized than **1** in cyclic voltammetry experiments.[6] Also, 2-pyrrolyl derivative **3** was 100 times less active than **1** as an inhibitor of Fe^{2+}-induced lipid peroxidation.) The 5-chloro derivative **4** could also be obtained by treating **1** with *N*-chlorosuccinimide or tris(4-bromophenyl)aminium hexachloroantimonate (a reagent commonly used for the generation of cation radicals via electron transfer[7]).

Although mechanistically a contentious area,[8] the facile reaction of diacyl peroxides with electron donors is well documented.[9] The reaction of **1** with benzoyl peroxide (CH_2Cl_2, 0 °C; the reaction is very exothermic at 25 °C) afforded initially 5-benzoyloxy derivative **5** and, upon longer exposure to excess reagent, the α-hydroxyketone **6**. The **5** → **6** conversion required excess benzoyl peroxide and was not observed upon prolonged vigorous stirring of **5** in an oxygen atmosphere. An analogous benzoyloxylation of *N*-methylindole has been reported.[10]

Because several indoles have been reported to function as antioxidants by electron-transfer mechanisms,[11,12] a

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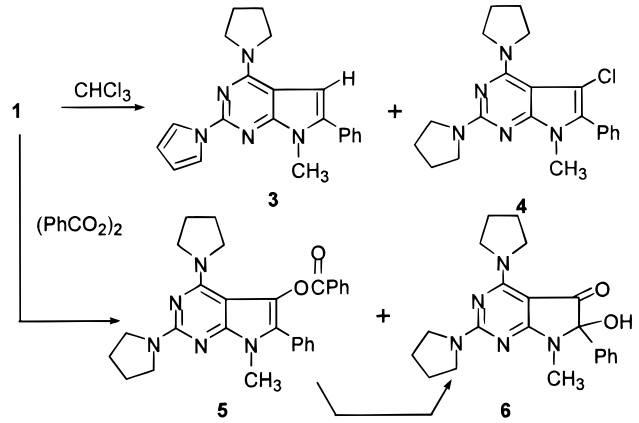
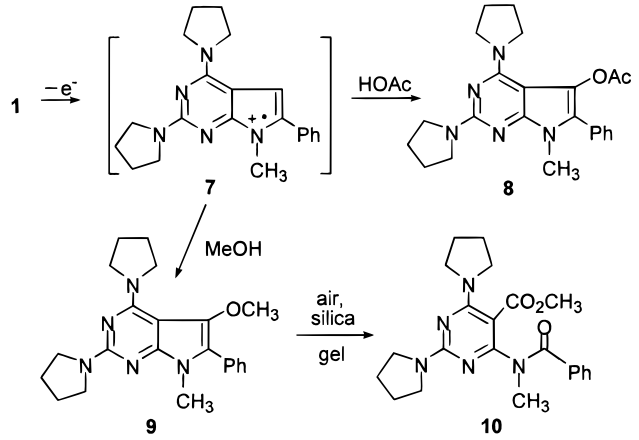
Scheme 1

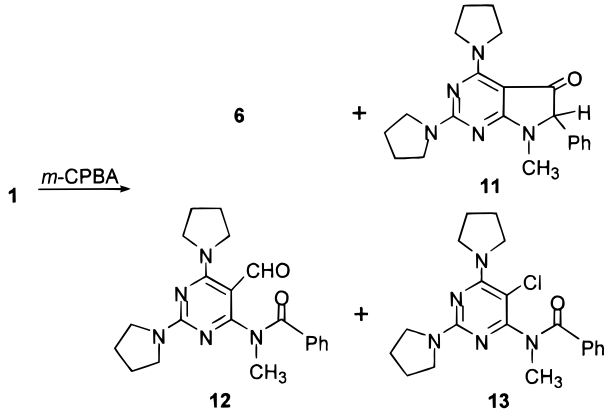


Scheme 2



brief investigation of the electrochemical behavior of **1** was undertaken.[13] When solutions of **1** in methanol (containing tetraethylammonium tetrafluoroborate as the supporting electrolyte) were oxidized at 600 mV (vs SCE, saturated calomel electrode), a three-component mixture was rapidly produced. Upon chromatographic purification on silica gel, the two more polar products were cleanly converted into the least polar, which was identified by NMR and mass spectrometry as the 5-methoxy derivative **9** (Scheme 2). Although detailed mechanistic work was not undertaken, a reasonable possibility for the structures of the unstable intermediates would be *E* and *Z* isomers of the corresponding 5,6-dimethoxy-dihydroindole (which would lose methanol on chromatography). The analogous electrooxidation of enamines in methanol to the corresponding *β*-methoxyenamines has been reported.[14] Although **9** was stable enough for isolation and spectral characterization, it was not sufficiently stable to allow any meaningful biological evaluation. On standing in air (more rapidly in the presence of silica gel), oxidative ring cleavage of **9** cleanly yielded amide/ester **10**. (The same 5-methoxy product **9** constituted the most abundant product when **1** was oxidized with potassium ferricyanide in aqueous methanol, presumably via a single-electron-transfer mechanism.[15])

Scheme 3



When the electrochemical oxidation of **1** was performed in acetic acid (at 800 mV vs SCE), the 5-acetoxy derivative **8** was formed in 33% yield. A single attempt to install a piperidine substituent at C-5 (for analogue studies) by performing the electrochemical oxidation in piperidine was unsuccessful, possibly due to the weak acidity of piperidine relative to MeOH and HOAc.

The oxidation of pyrrolopyrimidine **1** with *m*-chloroperbenzoic acid (*m*-CPBA) (Scheme 3) in CH_2Cl_2 buffered with solid sodium bicarbonate afforded, in approximately equal amounts, the α-hydroxyketone **6**, 6-keto derivative **11**, indole ring cleavage product **12**, and chlorinated cleavage product **13**. While the first three of these can be readily rationalized on the basis of indole precedents,[16] the mechanistic origin of **13** is less certain. In a separate experiment, purified formyl derivative **12** could not be converted into **13** with excess *m*-CPBA. The 5-keto products **6** and **11** were also available via the potassium peroxymonosulfate-mediated oxidation of **1**. (The *m*-CPBA oxidation protocol was chronologically among the first attempted, in the hope that it might provide *N*-oxides of **1**, which would exhibit enhanced aqueous solubility.)

In experiments intended to determine the stability of **1** toward conditions which could be encountered during routine laboratory operations, ethanolic solutions of **1** were found to be completely stable for at least 4 h, even when purged continuously with oxygen under normal laboratory lighting conditions. Likewise, these solutions were completely stable to irradiation at 350 nm (Rayonet reactor) when the purge gas was nitrogen. However, irradiation at 350 nm in the presence of oxygen led rapidly and cleanly to the ring-cleaved formyl derivative **12** (Scheme 4). The same oxidative ring cleavage could also be effected, although less cleanly, with singlet oxygen generated either photochemically (rose bengal, methanol/methylene chloride, visible light) or chemically (sodium hypochlorite, hydrogen peroxide, 0 °C). In the direct, "unsensitized" photooxidation, it seems likely that **1**, with absorption maxima at 244 and 332 nm, is acting as its own photosensitizer and that the reaction is indeed singlet-oxygen-mediated. Analogous photooxidative ring cleavage reactions, postulated to proceed via intermedi-

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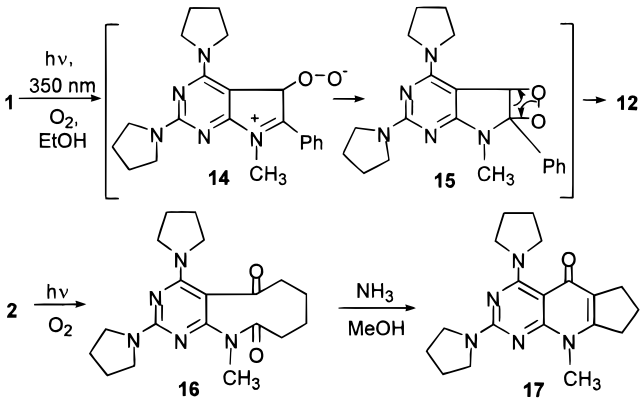
Scheme 4



ates of the **14** and **15** type, have been reported with several simpler indole-based substrates.[17] In these cases, the photooxidations were generally sensitized with rose bengal, and yields were often diminished by the intervention of dimeric byproducts not observed here.

When fused cyclohexyl-pyrrolopyrimidine **2** was subjected to the same "self-sensitized" photooxidation conditions, the resulting product **16** (formed in 67% yield), by virtue of the forced proximity of its two carbonyl groups, was transformed under very mild conditions (NH_3/MeOH or HCl/MeOH) into the tricyclic vinylogous amide **17**, whose structure was confirmed by X-ray crystallography. Internal cyclizations of the **16** → **17** variety have been noted in simpler substrates,[18] as have examples of the alternative mode of aldol-type ring closure (not seen in the present case), with the choice between the two regiochemical options apparently dependent upon substrate ring size.[18]

Several attempts were made to characterize the chemical reactivity of **1** toward oxidizing agents that more closely resembled those which **1** could encounter under physiological conditions. The oxidation of **1** with 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine iron(II) chloride (TPPFeCl), inspired by Iley's observation[19] that such oxidations were models for cytochrome P450 monooxygenase systems, provided a very complex (>10 components) mixture which included **12** and at least four dimeric products with "extra" oxygens. Further characterization of this difficultly resolved mixture was not undertaken. To assess the reactivity of **1** with alkylperoxyl radicals, solutions of **1** in ethanol containing oxygen and excess 2,2′-azobis(2,4-dimethylvaleronitrile) (AMVN) were heated at 37 °C. Unfortunately, this protocol also produced (slowly, over 3 days) a very complex mixture, several components of which were unstable to chromatographic purification on silica.

Finally, attempts to isolate and identify products from the reaction of **1** with hydroxyl radicals were unsuccessful. Reaction of **1** under "standard" Fenton conditions ($FeSO_4$, H_2O_2)[20] or an "organic" Fenton protocol ($FeSO_4$, H_2O_2, CH_3CN)[21] led to virtually complete destruction of the substrate. No UV-absorbing products could be extracted into organic solvents at any pH, and analysis of the aqueous layers, after concentration, likewise failed to detect any substrate-derived materials. Exposure of **1** to the modified Fenton conditions popularized by Cier[22] and Udenfriend[23] ($FeSO_4$, H_2O_2, ascorbic acid, EDTA, phosphate buffers, with or without emulsifying agents) yielded only unreacted starting material. Efforts to generate the hydroxyl radicals under milder, metal-independent conditions (*N*-hydroxy-2-pyridinethione[24]/CH_2Cl_2, 0 °C, visible light) afforded poorly characterized structures with the pyridinethione moiety (and extra oxygen) incorporated at C-5.

In summary, we have investigated the behavior of lipophilic antioxidant PNU-87663 (**1**) toward a variety of nonbiological oxidizing agents. Several of the oxidation products (**4**, **5**, **8**, and **9**) can be considered to have arisen from trapping of an extensively delocalized radical cation such as **7**; it is likely, in fact, that the efficacy of **1** as an inhibitor of lipid peroxidation may be related both to the ease with which that species (**7**) is formed and to its relative stability toward radical chain propagation reactions. As noted above, several of the oxidation products derived from **1** are analogous to those reported in the literature for the oxidation of simpler indoles. However, the clean, facile, apparently self-sensitized photooxidative cleavage of **1** (to **12**) without concomitant dimerization is noteworthy, as is the regiospecific cyclization of ketolactam **16**. As anticipated, none of the oxidation products reported herein retained significant levels of lipid peroxidation inhibiting activity.

Experimental Section

General. All reagents were obtained from Aldrich Chemical Co. and were used as received. Distilled, purified solvents were obtained from Burdick and Jackson, Inc., and were used without further purification. Except as noted, all reactions were carried out with magnetic stirring in flame-dried glassware in an atmosphere of nitrogen. Column chromatographic purifications were performed on E. Merck 230−400 mesh silica gel 60. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, on $CDCl_3$ solutions. Melting points are uncorrected.

7-Methyl-6-phenyl-2-(1-pyrrolyl)-4-(1-pyrrolidinyl)-7*H*-pyrrolo[2,3-d]pyrimidine (3). A solution of **1**[1] (2.8 g, 8.0 mmol) in 1.2 L of $CHCl_3$ was stirred at 37 °C for 1 week. Removal of the solvent afforded a green solid (3.0 g). Chromatographic purification (400 g of silica, 85/15 $CHCl_3$/hexane, gradient to 95/5 $CHCl_3$/acetone) afforded 51 mg of **3** as a white solid: mp 173−175 °C; ^{1}H NMR δ 7.88 (m, 2H), 7.45 (m, 5H), 6.55 (s, 1H), 6.28 (m, 2H), 3.88 (m, 4H), 3.78 (s, 3H), 2.05 (m, 4H), NOE enhancement was noted between the signals at 3.88 (α-pyrrolidine H) and 6.55 (C-5H); ^{13}C NMR δ 155.3, 153.2, 151.1, 136.1, 132.4, 128.6, 127.6, 118.9, 109.9, 100.9, 100.8, 47.7, 30.0, 25.2; HRMS calcd for $C_{21}H_{21}N_5$ 343.1797, found 343.1792.

5-Chloro-7-methyl-6-phenyl-2,4-di-1-pyrrolidinyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (4). Method a. Continued elution of the preceding chromatogram yielded 64 mg of **4** as a yellow solid: mp 147−152 °C; ^{1}H NMR: δ 7.49−7.36 (m, 5H), 3.86−3.81 (m, 4H), 3.63−3.58 (m, 4H), 3.51 (s, 3H), 1.97−1.91 (m, 8H); HRMS calcd for $C_{21}H_{24}ClN_5$ 381.1720, found 381.1713. **Method b.** A stirred 0 °C solution of **1** (2.0 g, 5.76 mmol) in 20 mL of methylene chloride was treated with a suspension of 770 mg (5.76 mmol) of *N*-chlorosuccinimide in 20 mL of methylene

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chloride, added over about 10 min (homogeneous purple solution). The reaction mixture was stirred at 0 °C for 1 h and 25 °C for 17 h, poured into aqueous sodium bicarbonate, and extracted with methylene chloride. The combined organic layers were dried over sodium sulfate and evaporated. Chromatographic purification of the crude product (280 g silica, 5% EtOAc/hexane) gave **4** as an off-white solid (1.58 g, 72%) identical to the material from part (a) above by NMR, TLC, and MS. **Method c.** A stirred solution of **1** (200 mg, 0.576 mmol) in 20 mL of methylene chloride was cooled to 0 °C and treated with 460 mg (0.576 mmol) of tris(4-bromophenyl)aminium hexachloroantimonate added in portions as a solid over 2−3 min. The resulting dark purple solution was stirred under nitrogen at 0 °C for 1 h and then 25 °C for 20 h. The mixture was then recooled to 0 °C, poured into ice/aqueous sodium bicarbonate, and extracted with methylene chloride. The organic layers were dried with sodium sulfate, filtered through a pad of silica gel on a 60M sintered glass funnel and concentrated in vacuo. Chromatographic purification of the crude product (20 g silica, 2% acetone/CH_2Cl_2) yielded 95 mg (43%) of pure **4**, identical in all respects to the material from parts (a) and (b).

5-Benzoyloxy-7-methyl-6-phenyl-2,4-di-1-pyrrolidinyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (5). A solution of **1** (347 mg, 1.0 mmol) in 2.5 mL of oxygen-saturated CH_2Cl_2 was treated with benzoyl peroxide (242 mg, 1.0 mmol) added as a solid at 0 °C in small portions over 15 min. The dark blue reaction mixture was stirred at 25 °C for 18 h in an atmosphere of oxygen and then evaporated to dryness. Chromatographic purification (70 g silica, 20% EtOAc/$CHCl_3$) afforded **5** (262 mg, 56%) as a white solid: mp 200−202 °C; ^{1}H NMR: δ 8.07−8.05 (m, 2H), 7.60−7.55 (m, 1H), 7.46−7.20 (m, 7H), 3.62−3.57 (s at 3.60 superimposed on m, 11H), 1.96−1.92 (m, 4H), 1.77−1.73 (m, 4H); MS (EI) 467 (M^+), 362, 118.

6,7-Dihydro-6-hydroxy-7-methyl-6-phenyl-2,4-di-1-pyrrolidinyl-5*H*-pyrrolo[2,3-*d*]pyrimidin-5-one (6). Continued elution of the preceding chromatogram yielded **6** (54 mg, 14%) as a white solid: mp 237−239 °C; ^{1}H NMR: δ 7.44−7.26 (m, 5H), 5.38 (s, 1H, exchangeable with D_2O), 4.13−4.04 (m, 1H), 3.74−3.55 (m, 7H), 2.92 (s, 3H), 2.05−1.70 (m, 8H); IR (mineral oil mull) 3279, 1655, 1603, 1598; MS (EI) 379 (M^+), 364, 350, 322, 295, 274, 246, 218.

In a separate experiment, 5 mg of benzoate **5** in 1 mL of methylene chloride was treated with 5 mg (excess) of benzoyl peroxide. After 16 h at room temperature, TLC indicated conversion to hydroxyketone **6** in approximately 80% yield. A sample of **5** in methylene chloride (5 mg/mL), stirred vigorously for the same length of time in an oxygen atmosphere, was recovered completely unchanged. (Both **5** and **6** were stable to prolonged exposure to silica gel.) Hydroxyketone **6** was also formed in the *m*-CPBA oxidation of **1** described in a later experiment.

5-Acetoxy-7-methyl-6-phenyl-2,4-di-1-pyrrolidinyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (8). (a) Via Electrochemical Oxidation. A solution of 200 mg of **1** in 140 mL of 0.1 M potassium acetate/acetic acid was oxidized at 800 mV (vs SCE) using a Princeton Applied Research Model 173 potentiostat. After 3 h at 25 °C, the reaction had slowed considerably, and the mixture had changed from the initial dark purple to light brown. Following removal of the acetic acid in vacuo, the residue was partitioned (carefully) between cold aqueous sodium bicarbonate and cold ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, and concentrated. Chromatographic purification (20 g silica, 10/30/60 EtOAc/$CHCl_3$/hexane) afforded acetoxy derivative **8** (75 mg, 32%) as a white solid: mp 153−155 °C; ^{1}H NMR: δ 7.44−7.25 (m, 5H), 3.68−3.58 (m, 8H), 3.55 (s, 3H), 2.08 (s, 3H), 1.95−1.90 (m, 8H); HRMS (FAB) calcd for $C_{23}H_{28}N_5O_2$ (M + H) 406.2243, found 406.2253. **(b) Via Mn(OAc)$_3$ Oxidation.** Following the general procedure of Cresmonesi,[25] a solution of **1** (347 mg, 1.0 mmol) and manganese(III) acetate dihydrate (536 mg, 2.0 mmol) in 10 mL of acetic acid was stirred at 25 °C for 3 h. Removal of the acetic acid in vacuo, followed by chromatography (75 g silica, 5% EtOAc/$CHCl_3$) afforded **8** (180 mg, 44%) as a white solid: mp 153−155 °C, identical by TLC and ^{1}H NMR to the product from part (a).

5-Methoxy-7-methyl-6-phenyl-2,4-di-1-pyrrolidinyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (9). (a) Via Electrochemical Oxidation. A solution of **1** (200 mg, 0.57 mmol) in 140 mL of 0.1 M tetraethylammonium tetrafluoroborate/methanol was oxidized at 600 mV (vs SCE). (The reaction mixture turned dark purple the instant the current was turned on.) After about 5 min, the reaction mixture had warmed to about 35 °C. A cold water bath was added to keep the reaction temperature in the 10−15 °C range. After about 15 min, the color of the mixture had changed to light tan, and the current flow became negligibly small. The solvent was removed in vacuo, and the residue was partitioned between aqueous sodium bicarbonate and chloroform. The combined organic layer was dried over sodium sulfate and concentrated. Rapid chromatographic purification of the crude product (20 g silica, 2% acetone/CH_2Cl_2) afforded **9** (52 mg, 24%) as a colorless oil: ^{1}H NMR: δ 7.51−7.27 (m, 5H), 3.81−3.77 (m, 4H), 3.63−3.59 (m, 4H), 3.56 (s, 3H), 3.46 (s, 3H), 1.96−1.92 (m, 8H); MS (EI) 377 (M^+), 362, 351, 334, 188, 167, 118, 70. **(b) Via Chemical Oxidation.** Following the general procedure of Audeh and Smith,[26] a suspension of **1** (500 mg, 1.44 mmol) in 200 mL of methanol was treated with 20 mL of 1 M aqueous potassium hydroxide, followed by 2.0 g of solid potassium ferricyanide (both added in one portion), and the resulting heterogeneous mixture was stirred at 25 °C for 18 h. TLC analysis of an aliquot (partitioned between water and chloroform) showed the presence of starting material (50%) and three more polar products (25/25/50 EtOAc/$CHCl_3$/hexane). An additional 5 mL of 1 M aqueous KOH was added, and stirring was continued for 9 h, by which time no starting material remained. The reaction mixture was cooled to 0 °C, poured into 600 mL of ice/water, and extracted with three 100-mL portions of chloroform. After three extractions, 200 mL of saturated aqueous sodium sulfate was added to the aqueous layer, which was then extracted three additional times with chloroform. The extracts were dried over sodium sulfate and concentrated in vacuo. Chromatographic purification (170 g silica, 25/25/50 EtOAc/$CHCl_3$/hexane) yielded 120 mg of **9**, identical by TLC, ^{1}H NMR, and MS to the material from part (a) above. (The other major product was **12**, characterized in a subsequent experiment.)

***N*-(5-Carbomethoxy-2,6-di-1-pyrrolidinyl-4-pyrimidinyl)-*N*-methylbenzamide (10)**. During the purification of 5-methoxy derivative **9** above, it became apparent that, upon prolonged contact with silica gel, **9** was converted cleanly to a much more polar product. Therefore, 20 g of 40−60 μm silica gel was suspended in 100 mL of chloroform containing 40 mg of 5-methoxy derivative **9**. The solvent was then removed in vacuo, and the free-flowing silica (containing **9**) was allowed to stand in air for 17 h at 25 °C. The silica was transferred to a sintered glass funnel and eluted with 250 mL of 25% acetone/methylene chloride. Removal of the solvent from the eluate afforded 32 mg of the more polar product, approximately 85−90% pure. Chromatographic purification (20 g silica, 8% acetone/CH_2Cl_2, yielded **10** (29 mg) as a colorless oil: ^{1}H NMR: δ 7.46−7.16 (m, 5H), 3.72 (s, 3H), 3.50−2.94 (s at 3.43 superimposed on m, 11H total), 1.94−1.74 (m, 8H); MS (FAB) 410 (M + 1), 378, 362, 350, 304, 272, 118, 105.

***m*-CPBA Oxidation of 1.** A solution of **1** (3.0 g, 8.63 mmol) in 600 mL of CH_2Cl_2 was treated with sodium bicarbonate (3.55 g, 42 mmol) and *m*-CPBA (3.0 g, 14 mmol). After 18 h at 25 °C, an additional 1.5 g of $NaHCO_3$ and 2 g of *m*-CPBA were added. After 7 h, the mixture was washed with aqueous sodium thiosulfate and brine, dried (Na_2SO_4), and concentrated. Chromatographic purification (300 g silica, 3% acetone/$CHCl_3$) yielded the following four products, in order of increasing polarity. **11** (166 mg, yellow solid): mp 162−164 °C; ^{1}H NMR: δ 7.39−7.26 (m, 5H), 4.49 (s, 1H), 4.1 (br, 1H), 3.80−3.60 (m, 7H), 3.03 (s, 3H), 1.96 (m, 4H), 1.85 (m, 4H); ^{13}C NMR: δ 189.2, 174.5, 161.6, 175.8, 136.1, 128.8, 127.9, 127.1, 86.9, 72.0, 50.0, 48.1, 46.9, 46.4, 28.9, 26.2, 25.5, 25.3, 24.1; HRMS calcd for $C_{21}H_{25}N_5O$ 363.2059, found 363.2070. **13** (122 mg, orange solid): mp 142−145 °C; ^{1}H NMR δ 7.55−7.53 (m, 2H), 7.34−7.21 (m, 3H), 3.5−3.2 (s at

(25) Cresmonesi, P.; Hietbrink, B.; Rogan, E. G.; Cavaleri, E. L. *J. Org. Chem.* **1992**, *57*, 3309.

(26) Audeh, C. A.; Smith, J. R. L. *J. Chem. Soc. B* **1970**, 1280.

3.39 superimposed on m, 11H total), 1.88 (m, 4H), 1.81 (m, 4H); ^{13}C NMR δ 171.3, 160.9, 159.4, 157.4, 136.5, 129.8, 128.1, 127.5, 96.6, 48.5, 46.5, 35.0, 25.5; HRMS calcd for $C_{20}H_{24}ClN_5O$ 385.1669, found 385.1664. **12** (98 mg, tan solid): characterized in the next experiment. **6** (94 mg, yellow solid): identical by NMR and MS to material from an earlier experiment.

***N*-(5-Formyl-2,6-di-1-pyrrolidinyl-4-pyrimidinyl)-*N*-methylbenzamide (12). (a) Via Unsensitized Photooxidation.** A solution of **1** (1.0 g, 2.88 mmol) in 1000 mL of absolute EtOH was irradiated (350 nm) in a preparative scale Rayonet RS reactor. Oxygen was introduced via a gas dispersion tube into the bottom of the reaction vessel, both as a reactant and to effect stirring. During irradiation, the reaction temperature was maintained at 30−35 °C by cooling with a coldfinger condenser and a small fan in the bottom of the reactor. After 5 h, the solvent was removed in vacuo, and the product was purified by chromatography (70 g silica, 25/25/50 EtOAc/$CHCl_3$/hexane) to afford **12** (950 mg, 87%) as a light yellow solid. Trituration with pentane (8 mL, 0 °C, 1 h), followed by filtration and drying (3 h, 0.05 mm, 40 °C) gave pure **12** (794 mg, 73%) as a white solid: mp 150−152 °C; ^{1}H NMR: δ 9.33 (s, 1H), 7.40−7.17 (m, 5H), 3.61 (s, 3H), 3.52−2.80 (m, 8H), 1.95−1.91 (m, 4H), 1.72 (broad s, 4H); ^{13}C NMR: δ 181.3, 172.3, 167.3, 161.1, 158.5, 136.9, 129.7, 127.8, 102.3, 49.6, 46.5, 36.0, 25.3, 25.0; HRMS (FAB) calcd for $C_{21}H_{26}N_5O_2$ (M + 1) 380.2086, found 380.2083. **(b) Via Photochemically Generated Singlet Oxygen.** A solution of **1** (100 mg, 0.288 mmol) in 25 mL of CH_2Cl_2 was cooled to 0 °C and treated with a solution of 2.5 mg of rose bengal in 0.5 mL of MeOH. Oxygen was continuously introduced beneath the surface of the reaction mixture via a syringe needle, and the stirred 0 °C solution was irradiated for 1 h with visible light (a 625 W Sun Gun, Sylvania). Following filtration of the reaction mixture through a pad of silica to remove the dye, chromatographic purification (20 g silica, 25/25/50 EtOAc/$CHCl_3$/hexane) yielded **12** (12 mg), in addition to several unresolved, less polar impurities. **(c) Via Chemically Generated Singlet Oxygen.** A stirred, 25 °C solution of 50 mg of **1** in 100 mL of methanol was treated with 1 mL of 30% hydrogen peroxide, followed by 3 mL of aqueous sodium hypochlorite (5% minimum available chlorine), the latter added dropwise over 5 min. After 15 min at 25 °C, another equal portion of both reagents was added, and stirring was continued for 1 h at 25 °C. The reaction mixture was poured into 1:1 brine/water (containing sodium bicarbonate) and extracted with chloroform. TLC analysis of the extract (25/25/50 EtOAc/$CHCl_3$/hexane) showed a 1:1 mixture of starting material **1** and oxidative cleavage product **12**.

11-Methyl-2,4-di-1-pyrrolidinyl-6,7,8,9-tetrahydro-5*H*-pyrimido [4,5-*b*]azonine-5,10(11*H*)-dione (16). A solution of **2**[1] (1.60 g, 4.92 mmol) in 1.4 L of absolute EtOH was irradiated (350 nm) as described above for the **1** → **12** conversion. After 16 h, the solvent was removed in vacuo, the product was combined with that from an equal-sized parallel run, and the combined product was chromatographed (300 g silica, 75% EtOAc/$CHCl_3$), thereby affording ketolactam **16**. Trituration with 10 mL of 10% EtOAc/hexane gave **16** (2.38 g, 67%) as a white solid: mp 163−164 °C; ^{1}H NMR δ 3.60−3.25 (m, 8H), 3.10 (s, 3H), 2.80−2.25 (m, 4H), 2.05−1.80 (m, 12H); IR (Nujol mull) 1674, 1658, 1573, 1548, 1500; HRMS calcd for $C_{19}H_{27}N_5O_2$ 357.2165, found 357.2161. Anal. Calcd for $C_{19}H_{27}N_5O_2$: C, 63.84; H, 7.61; N, 19.59. Found: C, 63.89; H, 7.60; N, 19.47.

9-Methyl-2,4-di-1-pyrrolidinyl-6,7,8,9-tetrahydro-5*H*-cyclopenta[5,6]pyrido[2,3-*d*]pyrimidin-5-one (17). A solution of ketolactam **16** (1.26 g, 3.52 mmol) in 50 mL of 4 M NH_3/MeOH was allowed to stand under nitrogen in a stoppered flask at 25 °C for 86 h (far longer than necessary, reaction was >90% complete in 8 h). Removal of the solvent in vacuo and recrystallization of the residue yielded **17** (1.19 g, 100%) as a white solid: mp 225−227 °C; IR (Nujol mull) 1632, 1593, 1538; ^{1}H NMR: δ 3.65−3.55 (s at 3.60, superimposed on m, 11H), 2.99−2.94 (m, 2H), 2.87−2.83 (m, 2H), 2.12−2.01 (m, 2H), 1.98−1.92 (m, 8H); HRMS calcd for $C_{19}H_{25}N_5O$ 339.2059, found, 339.2052. Anal. Calcd for $C_{19}H_{25}N_5O$: C, 67.23; H, 7.42; N, 20.63. Found: C, 66.72; H, 7.34; N, 20.44. See ORTEP representation of X-ray structure in Supporting Information Section.

Supporting Information Available: ^{1}H NMR spectra for compounds **1**−**6**, **8**−**13**, **16**, and **17** and an ORTEP representation of the X-ray structure of compound **17** (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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