129 (48), 128 (100), 115 (38), 91 (23); HRMS, $C_{15}H_{18}O$ requires 214.1358, found 214.1358.

General Procedure for Equilibrations. Typically a sample of 10 mg (47–50 μmol) of ketone was dissolved at 25 °C in 2.0 mL of dry MeOH containing 5 μmol of NaOMe (10 mol % based on ketone) and stirred under N_2 at 25 °C. Samples of 50 μL were withdrawan periodically by syringe, quenched with HOAc, and analyzed by capillary GC. Equilibrations were generally carried out for at least twice as long as required to reach equilibrium, which was usually within 24 h. When equilibrium was reached, quantitative ^1H NMR data from larger-scale experiments could sometimes be used to supplement the GC data. Wherever possible equilibria were approached from both sides, with either pure epimers or mixtures enriched in one epimer relative to the equilibrium values.

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Synthesis and Electrochemistry of Pyrimidoquinazoline-5,10-diones. Design of Hydrolytically Stable High Potential Quinones and New Reductive Alkylation Systems

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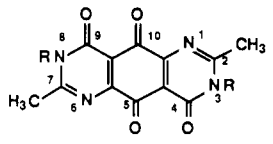
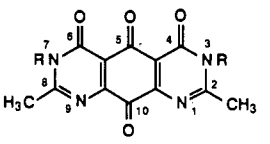
The synthesis of pyrimido[4,5-*g*]quinazoline-5,10-diones **1** and pyrimido[5,4-*g*]quinazoline-5,10-diones **2** was carried out in conjunction with the design of both hydrolytically stable high potential quinones and new purine-like reductive alkylators. These systems consist of a benzoquinone ring bearing two fused pyrimidin-4(3*H*)-one rings. The fused pyrimidinone rings serve to protect **1** and **2** from hydrolysis as well as to raise quinone redox potentials by stabilizing the hydroquinones with internal hydrogen bonds (65 mV increase per hydrogen bond). Synthesis of **1** and **2** involved pyrimidinone ring annelation to a 2,5-diamino-3-nitroterephthalic acid derivative and to a 2,4-diamino-1,5-dicarboxy-3-nitrobenzene derivative, respectively. The synthetic studies provided insights into the electronic effects of nitro and amino groups on the annelation process.

Pyrimidoquinazolines bearing 4,5-*g* and 5,4-*g* ring fusion were first prepared near the turn of the century[1] but have not received much attention since that time.[2] Our interest in quinone derivatives of these ring systems (**1** and **2**) stems from ongoing efforts to develop both new reductive alkylators and high potential quinones stable toward hydrolysis. Described here are the synthesis and electrochemistry of the pyrimido[4,5-*g*]quinazolines **1** and pyrimido[5,4-*g*]quinazolines **2** shown.



1



2

R = CH_3, a
R = H , b

Reductive alkylators based on the benzimidazole,[3] imidazo[4,5-*g*]quinazoline,[4,5] and quinazoline[6] ring systems have been designed by functionalizing the quinone derivatives of these ring systems with $-CH_2X$, where X is a leaving group. As is thought to be the case with many naturally occurring quinones,[7] these systems afford alkylating quinone methide species upon reduction to the corresponding hydroquinone species. Indeed, the imidazo[4,5-*g*]quinazoline derivatives act as active-site-directed reductive alkylators of xanthine oxidase by virtue of their purine-like structure.[5] Since many purine-utilizing enzymes tolerate drastic structural changes in their substrates,[8] the pyrimidoquinazolines may also interact with these enzymes. The synthetic studies described herein will be useful in preparing the bifunctional pyrimidoquinazoline reductive alkylators (i.e., derivatives with leaving groups substituted on the 2 and 7 methyls of **1** and on the 2 and 8 methyls of **2**).

Hydrolytic stability of the quinone derivatives **1** and **2** is crucial to both reductive alkylation and quinone-mediated oxidation studies. Reductive alkylation relies on stable quinone derivatives; only the hydroquinone derivatives should be active as an alkylator. Mechanistic studies of quinone–hydroquinone conversions mediated by various reducing substrates are ideally carried out without the accompanying reductive-addition and addition–elimination reactions typical of many quinones.[9] The studies described here indicate that the fused pyrimidine rings of **1** and **2** confer a great deal of hydrolytic stability on the benzoquinone system. Thus, the title quinones are stable in concentrated acids as well as in basic solutions. Nernst fits of E_m vs pH data provide, at a glance, the redox po-

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(2) Price, C. C.; Leonard, N. J.; Curtin, D. Y. *J. Org. Chem.* **1945**, *10*, 318.

(3) Skibo, E. B. *J. Org. Chem.* **1986**, *51*, 522.

(4) Lee, C.-H.; Gilchrist, J. H.; Skibo, E. B. *J. Org. Chem.* **1986**, *51*, 4784.

(5) Lee, C.-H.; Skibo, E. B. *Biochemistry* **1987**, *26*, 7355.

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(8) (a) Leonard, N. J. *Acc. Chem. Res.* **1982**, *15*, 128. (b) Leonard, N. J.; Hiremath, S. P. *Tetrahedron* **1986**, *42*, 1917.

(9) Finley, K. T. In *The Chemistry of the Quinonoid Compounds*, Part II; Patai, S., Ed.; Wiley Interscience: New York, 1974; pp 886–947.

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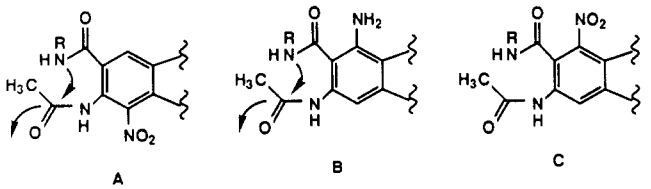
tentials of the protonated and anionic forms of quinones 1 and 2. These fits indicate that the high reduction potentials of **1b** and **2b** (E_0 = 800 mV, NHE) result from internal hydrogen bonding in the corresponding hydroquinone forms. This study shows that it is possible to design high reduction potential quinones exhibiting stability toward hydrolysis.

Results and Discussion

Synthesis. The preparations of various 5,10-unsubstituted pyrimidoquinazolines have been reported in the early chemical literature.[1] Convenient routes to the desired 5,10-diones 1 and 2 thus appeared to involve functionalization of these pyrimidoquinazoline derivatives. Neither nitration at the 5 or 10 positions nor nitrogen oxide oxidation[4] directly to the quinone were possible with these derivatives, however. In fact, the treatment of 5,10-unsubstituted pyrimidoquinazolines with concentrated H_2SO_4/fuming nitric acid merely provided highly purified starting material due to the oxidation of all impurities.

The approach that led to the title quinones involved pyrimidinone ring annelation to benzene derivatives already substituted with a nitro or amino group. The aminopyrimidoquinazolines that resulted were then oxidized to 1 and 2 with H_2SO_4/potassium dichromate. The good yields obtained in spite of these harsh oxidation conditions attest to the hydrolytic stability of the title quinones. Annelation of the pyrimidinone rings to nitro- or amino-substituted benzene derivatives is greatly affected by the presence of these substituents as discussed below.



A B C

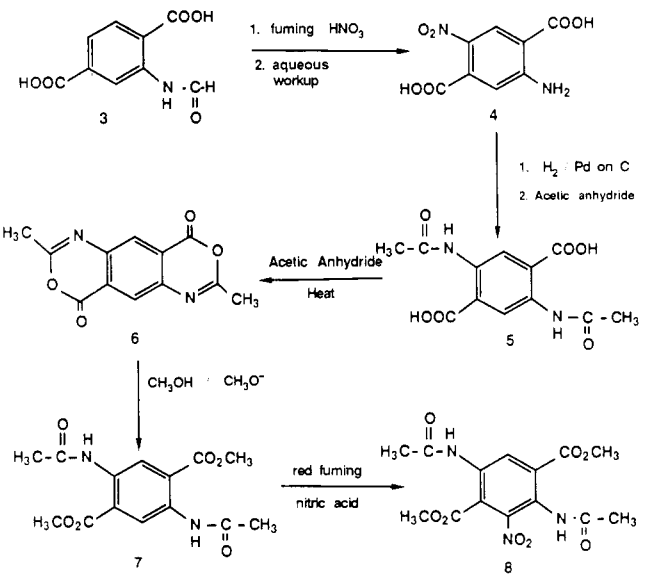
Cyclization of 1-carbamoyl-2-acetamidobenzene derivatives to fused pyrimidinones presumably involves nucleophilic attack by the carbamoyl nitrogen on the acetamido group as depicted with curved arrows in structures A and B. Either electron withdrawal from the acetamido group by an *o*-nitro group (structure A) or electron release to the carbamoyl group by an *o*-amino group (structure B) should facilitate the cyclization. On the other hand, electron withdrawal from the carbamyl group involved in nucleophilic attack (structure C) should slow cyclization. The above generalizations proved to be correct and it was possible to affect facile pyrimidinone ring annelations with appropriately placed nitro and amino groups.

The preparation of the nitrobenzene derivative 8, which was converted to quinones 1, is outlined in Scheme I. To provide the desired 4,5-*g* ring fusion of quinones 1, it was necessary to functionalize 2,5-diaminoterephthalic acid. A convenient, high-yield alternative to an earlier preparation[10] of this compound is shown in Scheme I. Nitration of formamidoterephthalic acid (3) provided the 5-nitro derivative exclusively and aqueous workup of the reaction resulted in deformylation of this product to give 4. Catalytic reduction of 4 afforded 2,5-diaminoterephthalic acid, which was converted to 8 by the steps shown in Scheme I.

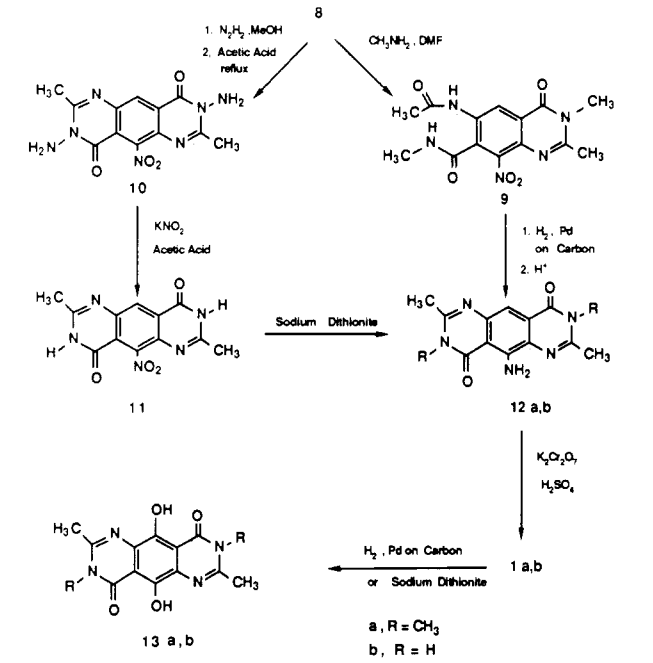
The conversion of 8 to the quinones **1a,b** and the respective hydroquinones is discussed below in conjunction with Scheme II. Treatment of 8 with methylamine in

(10) Bogert, M. T.; Kropff, A. H. *J. Am. Chem. Soc.* **1909**, *31*, 841.

Scheme I



Scheme II



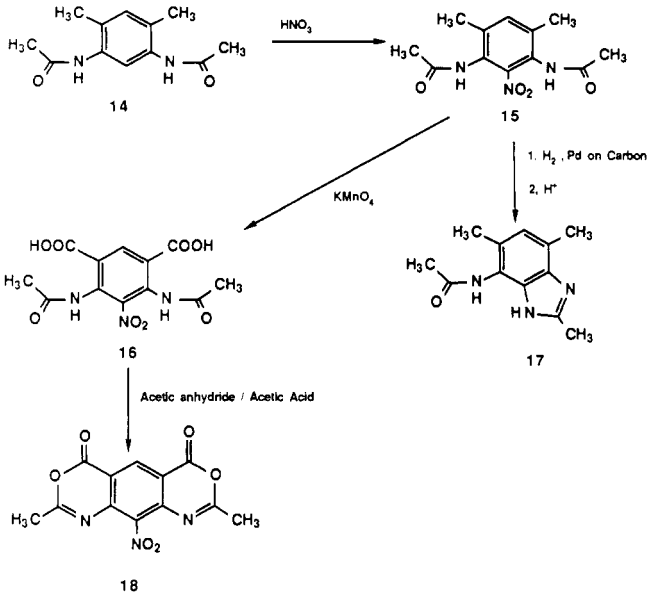
DMF at room temperature afforded the half-cyclized product **9**, which cannot be cyclized to the pyrimido[4,5-*g*]quinazoline system even under harsh conditions (refluxing concentrated HCl). The closure of the first pyrimidinone ring is favored due to electron withdrawal by the nitro group from the acetamido group undergoing nucleophilic attack. On the other hand, this nitro group precludes cyclization of the second pyrimidinone ring by electron withdrawal from the nucleophilic carbamyl group (structure C). **9** was reduced to the amine derivative to provide the electronically favorable arrangement shown in structure B. Cyclization of reduced **9** to the pyrimido[4,5-*g*]quinazoline **12a** was then possible under mild conditions. The formation of only **12a** in this reaction is taken as evidence of the 8-nitro group in **9**. The 5-nitro isomer of **9** could have afforded the fused imidazo derivative as well as **12a**.

The attempted ring closure of 8 with ammonia resulted in the recovery of starting material. Treatment of 8 with hydrazine in methanol, however, afforded the half-cyclized

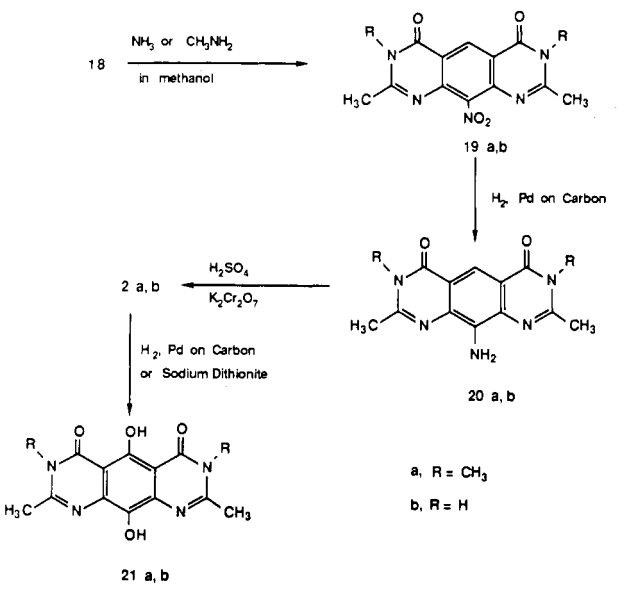
Table I. Quinone Acid Dissociations

entry	dissociation	pK_a	UV–vis, nm (ϵ)
1	**1aH**$^+$ ⇄ **1a** + H$^+$	−0.26 ± 0.05	**1aH**$^+$, 410 (1800); 326 (1 × 10^4) **1a**, [400] (1530); 350 (1.3 × 10^4); 246 (2.3 × 10^4)
2	**1bH**$^+$ ⇄ **1b** + H$^+$	−0.13 ± 0.05	**1bH**$^+$, [380] (1460); 320 (9000) **1b**, [400] (1250); 345 (1.1 × 10^4)
3	**1b** ⇄ **1b**$^-$ + H$^+$	6.53 ± 0.07	
4	**1b**$^-$ ⇄ **1b**$^{2-}$ + H$^+$	~6.5	**1b**$^{2-}$, 365 (1 × 10^4); 264 (1.85 × 10^4); 255 (1.87 × 10^4)
5	**2aH**$^+$ ⇄ **2a** + H$^+$	−0.46 ± 0.07	**2aH**$^+$, 400 (1500); 328 (4400); 245 (1.3 × 10^4) **2a**, 408 (2300); 344 (6200); 250 (1.6 × 10^4)
6	**2bH**$^+$ ⇄ **2b** + H$^+$	−0.51 ± 0.10	**2bH**$^+$, 400 (1300); 332 (4800); 246 (1.4 × 10^4) **2b**, 400 (1750); 338 (6400); 244 (1.5 × 10^4)
7	**2b** ⇄ **2b**$^-$ + H$^+$	6.77 ± 0.02	**2b**$^-$, 430 (2350); 352 (2700); 263 (1.6 × 10^4); 248 (1.5 × 10^4)
8	**2b**$^-$ ⇄ **2b**$^{2-}$ + H$^+$	~8.5	

Scheme III



Scheme IV



product analogous to **9**. Ring closure of this product to **10** was possible by treatment with refluxing acetic acid for a short time. Removal of the 3,8-diamino groups of **10** to give **11** was carried out by diazotization and then heating in acetic acid.

The preparation of the pyrimido[5,4-*g*]quinazoline quinones and hydroquinones **21a,b** was carried out starting with the benzobis(oxazine) derivative **18**. The preparation of **18** from the reported compound **14**[10] is shown in Scheme III. Evidence of nitration of the 3 position of **14** was obtained by reduction of the nitration product **15** and cyclization to the benzimidazole derivative **17**.

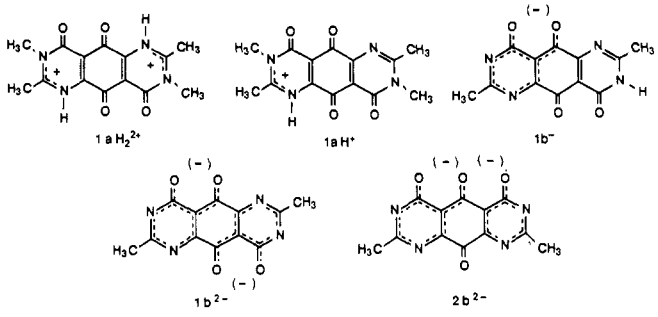
The nitro group of **18** is placed so as to facilitate annelation of the pyrimidinone rings under mild conditions; see structure A. The conversion of **18** to quinones **2a,b** is outlined in Scheme IV.

pK_a and UV–Vis Spectral Studies. The pK_a values of the quinone (**1** and **2**) and hydroquinone (**13** and **21**) derivatives were obtained spectrophotometrically in aqueous buffers (μ = 1.0, KCl) at 30 °C. In cases where the acid dissociation was not accompanied by large absorbance changes, approximate pK_a values were obtained from Nernst fits of E_m vs pH data. Found in Tables I and II are these pK_a values as well as the UV–vis spectra of the quinone and hydroquinone derivatives. These data were important in carrying out Nernst fits of the quinone/hydroquinone redox couples and in evaluating the presence of tautomerization in the quinone and hydroquinone derivatives. Tautomerization is, in fact, responsible for the high redox potentials of the couples **1b/13b** and **2b/21b**.

Table II. Hydroquinone Acid Dissociations

entry	dissociation	pK_a	UV–vis, nm (ϵ)
1	**13aH**$^+$ ⇄ **13a** + H$^+$	2.41 ± 0.09	**13aH**$^+$, [425] (5700); 364 (1.3 × 10^4); 270 (3 × 10^4); 260 (3 × 10^4) **13a**, [430] (6700); 412 (9000); 348 (1.3 × 10^4); 270 (2.3 × 10^4); 260 (3 × 10^4)
2	**13a** ⇄ **13a**$^-$ + H$^+$	10.34 ± 0.16	**13a**$^-$, 450 (9600); 392 (1 × 10^4); 258 (2.4 × 10^4)
3	**13bH**$^+$ ⇄ **13b** + H$^+$	~3	**13b**, [430] (6600); 410 (8000); [390] (6400); 340 (1.2 × 10^4); 271 (2.6 × 10^4); 259 (2.7 × 10^4)
4	**13b** ⇄ **13b**$^-$ + H$^+$	8.26 ± 0.15	**13b**$^-$, [435] (5000); 410 (7000); 358 (1.4 × 10^4); 267 (3.3 × 10^4); [260] (3 × 10^4)
5	**21aH**$^+$ ⇄ **21a** + H$^+$	~2	**21a**, 370 (1.2 × 10^4); 280 (2.4 × 10^4); 268 (2.8 × 10^4)
6	**21a** ⇄ **21a**$^-$ + H$^+$	9.84 ± 0.07	**21a**$^-$, 426 (1.2 × 10^4); [280] (2 × 10^4); 268 (2.5 × 10^4)
7	**21bH**$^+$ ⇄ **21b** + H$^+$	~3	**21b**, 368 (1 × 10^4); 278 (3.2 × 10^4); 268 (3.5 × 10^4)
8	**21b** ⇄ **21b**$^-$ + H$^+$	8.52 ± 0.15	**21b**$^-$, 376 (1 × 10^4); 280 (3 × 10^4)

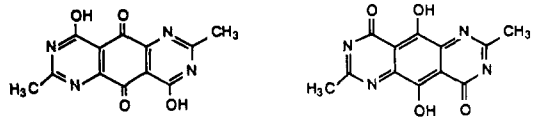
Acid dissociations from the quinone species are discussed below in conjunction with Table I. All the quinone species



studied can be protonated at the N(1) position (e.g., **1aH**$^+$) to afford cations somewhat stabilized by amidine resonance but destabilized by the electron-deficient benzoquinone ring. Thus, acid dissociation from the monoprotonated quinones is in the range of pK_a = −0.13 to −0.51 (see entries 1, 2, 5, and 6 of Table I). The magnitude of these pK_a values is consistent with nitrogen protonation; carbonyl oxygen protonation considered in an earlier study[4] would occur at much lower pK_a values. The quinone species studied can also be diprotonated in strong acid to afford dications, an example of which is **1aH$_2$**$^{2+}$. These dications could not be detected photometrically; their presence was inferred from Nernst fits of E_m vs pH data (vide infra).

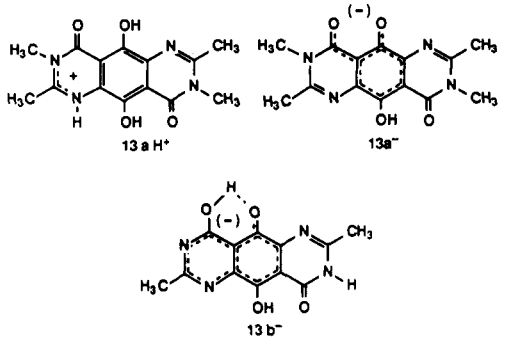
Quinones without *N*-methyls (**1b** and **2b**, entries 3, 4, 7, and 8 in Table I) dissociate near neutrality to afford resonance-stabilized anions and dianions (e.g. **1b**$^-$, **1b**$^{2-}$, and **2b**$^{2-}$). Double acid dissociation from **1b** to afford **1b**$^{2-}$ is proposed to occur at pK_a = 6.5. Spectrophotometric studies indicate the presence of a pK_a at 6.53 (entry 3 of Table I), but the Nernst fit for the couple **1b**/**13b** indicates that two protons dissociate from **1b** at pH values ≥6.5 (vide infra). Dissociation of the second proton from **1b**$^-$ is expected to be favorable since the two anions of **1b**$^{2-}$ are resonance delocalized over different atoms. It is noteworthy that acid dissociations from the two pyrimidine rings of a pyrimido[5,4-*g*]quinoxoline also occur at the same pK_a value.[11,12] The two acid dissociations from **2b** to afford **2b**$^{2-}$ appear to occur at different pK_a values, however. The pK_a value for acid dissociation from **2b** to afford **2b**$^-$ was measured spectrophotometrically at pK_a = 6.77 (entry 7 of Table I). The Nernst fit for **2b**/**21b** indicates single proton loss associated with this pK_a value (vide infra). This fit also indicates that the second acid dissociation to afford **2b**$^{2-}$ must be occurring at pK_a ~ 8.5. A possible explanation for the higher second pK_a value is the proximity of the anion-bearing oxygens in **2b**$^{2-}$.

The structures of the N-unsubstituted quinones **1b** and **2b** suggest that they can undergo tautomerization; two possible tautomeric forms of **1b** are shown below. If these



and other possible tautomeric forms of **1b** predominate over the oxo tautomer shown earlier, the UV–vis spectrum of **1b** should differ from that of **1a**, which can only exist as the oxo tautomer. Inspection of Table I reveals that **1b** and **1a**, as well as **2b** and **2a**, possess nearly identical UV–vis spectra. Thus it is concluded that **1b** and **2b** exist primarily as the oxo tautomers shown in eq 1. The results of previous studies[13] indicate that the predominant form of quinazolin-4(3*H*)-ones is indeed the oxo tautomer. The UV–vis spectral studies of the hydroquinone derivatives **13a,b** and **21a,b** suggest that this generalization is not always true, however.

Acid dissociations from the hydroquinone species are discussed below in conjunction with Table II. As with the



quinone derivatives, all the hydroquinone derivatives can be protonated at the N(1) position (e.g. **13aH**$^+$). The resulting cations are stabilized by amidine resonance as well as by the electron-releasing effect of the hydroxyl groups. pK_a values for N(1) acid dissociation range from 2 to 3 (entries 1, 3, 5, and 7 in Table II). With the exception of entry 1, the pK_a values had to be estimated from Nernst fits (vide infra) due to the small absorbance changes accompanying acid dissociation. Nernst fits also provided evidence that the hydroquinones are diprotonated in strong acid.

The presence of N-methylation in the title hydroquinones has a dramatic effect on the pK_a values for hydroxyl group acid dissociation. The N-methylated derivatives (**13a** and **21a**) possess pK_a values of 10.34 and 9.84, respectively, for this acid dissociation (entries 2 and 6 in Table II). In contrast, the N-unsubstituted derivatives (**13b** and **21b**) possess much lower pK_a values, 8.26 and 8.52, respectively (entries 4 and 8 in Table II). The best explanation for the lower pK_a values is amide tautomerization and internal hydrogen bonding. In the N-unsubstituted derivatives, the tautomerized amide would stabilize the hydroxyl anion by internal hydrogen bonding (e.g. **13b**$^-$) and thereby lower the pK_a. The N-methylated hydroxy anions, on the other hand, can only be stabilized by resonance delocalization of the anion (e.g. **13a**$^-$). Consistent with the structural differences proposed for **13a**$^-$ and **13b**$^-$, the UV–vis spectra of these anions are quite different (entries 2 and 4 in Table II). The same is true for the anions **21a**$^-$ and **21b**$^-$ as well as the neutral hydroquinone derivatives.

The results of spectral and pK_a studies discussed above explain the base stability and high redox potentials observed for the N-unsubstituted couples **1b**/**13b** and **2b**/**21b**. Quinones **1b** and **2b** are converted to anions in moderate to strong base and are thereby protected from hydroxide attack. In contrast, **1a** and **2a** cannot be converted to anions and hydrolyze in strong base (vide infra, Hydrolysis Studies). Tautomerization and internal hydrogen bonding stabilize the hydroquinones **13b** and **21b** and thereby raise the redox potentials of the corresponding quinones **1b** and **2b**. Hydroquinones **13a** and **21a**, on the

(11) Skibo, E. B.; Bruice, T. C. *J. Am. Chem. Soc.* **1982**, *104*, 4982.
(12) Skibo, E. B.; Bruice, T. C. *J. Am. Chem. Soc.* **1983**, *105*, 3304.
(13) (a) Hearn, J. M.; Morton, R. A.; Simpson, J. C. E. *J. Chem. Soc.* **1951**, 3318. (b) Armarego, W. L. F. In *Fused Pyrimidines*, Part 1, Quinazolines; Brown, D. J., Ed.; Interscience: New York, 1967; pp 102–104.

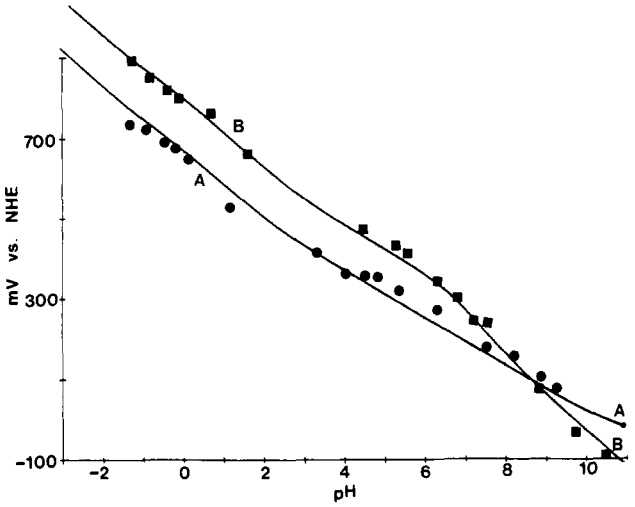


Figure 1. E_m vs pH data for the two-electron couples **1a**/**13a** (A) and **1b**/**13b** (B) measured at 25–26 °C in anaerobic, μ = 1.0 ($NaClO_4$), buffer. The solid curves were generated by employing the Nernst equation.

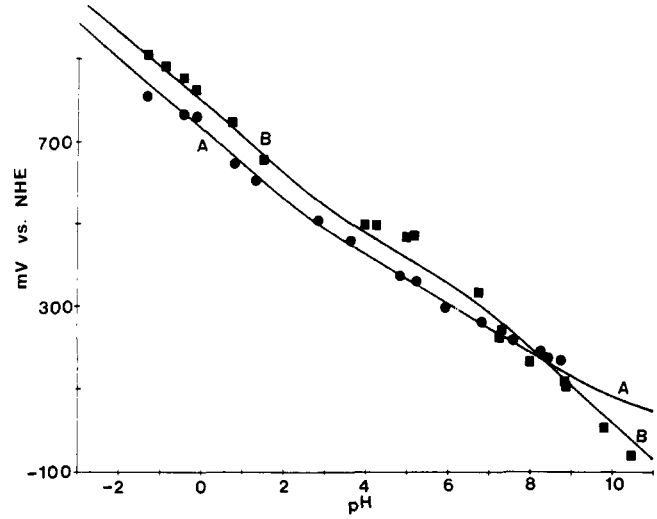


Figure 2. E_m vs pH data for the two-electron couples **2a**/**21a** (A) and **2b**/**21b** (B) measured at 25–26 °C in anaerobic, μ = 1.0 ($NaClO_4$), buffer. The solid curves were generated by employing the Nernst equation.

other hand, cannot be stabilized in this fashion and the corresponding quinones **1a** and **2a** possess lower redox potentials. Another notable observation is the intense visible spectra exhibited by the hydroquinones compared to the corresponding quinones. Hydroquinones **13a,b** are bright yellow and fluorescent whereas the corresponding quinones **1a,b** are light tan and nonfluorescent. The intense visible spectra of the hydroquinones are probably due to the conjugated anthracene-like structure; azaanthracenes possess similar spectra.[14]

Hydrolysis Studies. The hydrolysis of the quinones **1** and **2** was studied in aqueous buffer (μ = 1.0, KCl) over the pH range of 6 to 13. The N-unsubstituted quinones **1b** and **2b** were resistant to hydrolysis over this pH range. As noted above, the formation of anionic and dianionic forms of these quinones afford protection from nucleophilic attack. The methylated quinones **1a** and **2a**, on the other hand, hydrolyze by a process second order in hydroxide. The disappearance of **1a**, for example, obeys the rate law $v = kK_w^2[\mathbf{1a}]/a_H^2$, where $k = 1.7 \times 10^5$ M^{-2} s^{-1}, K_w = the autoprotolysis constant of water at 30 °C (pK_w = 13.86), and a_H is the proton activity determined with a pH electrode. Since the reaction is second order in hydroxide, the hydrolysis of **1a** and **2a** is extremely slow in buffers held at pH values ≤9. Thus, the E_m vs pH studies of **1a** and **2a** were not extended to pH values much above 9. Product studies of **1a** and **2a** hydrolysis utilizing TLC revealed that a multitude of products are formed. The structures of these products were not elucidated and a mechanism is not presented.

The stability of the title quinones was also studied in strong acid. In all cases hydrolytic decomposition was not observed. Concentrated hydrohalides (HCl and HBr) reduce **1a** to the corresponding hydroquinone **13a**, however. Other hydrohalide-mediated quinone reductions have been observed in this laboratory[4] and elsewhere.[15]

Electrochemical Studies. Comparative electrochemical studies of the couples **1a**/**13a**, **1b**/**13b**, **2a**/**21a**, and **2b**/**21b** provided insights into the influence of fused pyrimidinone rings on quinone redox potentials. The fused pyrimidin-4(3*H*)-one ring releases electrons and can also hydrogen bond to hydroquinone hydroxyl groups. The latter interaction has a large effect on quinone redox potential: 65 mV increase in potential per hydrogen bond. The electron-releasing effect, on the other hand, lowers redox potentials significantly.

Quinone redox potentials were determined as a function of pH, employing conventional cyclic voltammetry with a graphite or glassy carbon electrode (vs NHE) (see the Experimental Section). Quinones **1b** and **2b** were studied over the pH range −2 to 10.3 while the base-labile quinones **1a** and **2a** were studied over the pH range −2 to 9. The voltammograms for quinones **1** and **2** show reversible or quasi-reversible behavior. Found in Figures 1 and 2 are the E_m vs pH plots for the title quinones as well as curves computer generated with the Nernst equation.

The computer-generated curves were obtained by fitting E_m vs pH data to the Nernst equation substituted with pK_a values of the quinone/hydroquinone redox couples (see the Experimental Section). In cases where the pK_a values could not be measured spectrally, approximate values were obtained by using the Nernst equation, other accurately determined pK_a values, and E_m vs pH data. The changes in slope observed in the computer-generated curves can be understood intuitatively by considering that electron-deficient (protonated) couples have higher potentials than electron-rich (anionic) couples.[16]

Discussions follow of the conclusions derived from the redox potential data in Figures 1 and 2. The potentials of the title quinones are compared to benzoquinone (E_0 = 690 mV[17] and E_7 = 287 mV[18]).

Discussed first are the Nernst plots for the N-methylated quinones shown in plots A of Figures 1 and 2. The calculated E_0 values for **1a** and **2a** are 674 mV and 735 mV, respectively, and the E_7 values are 203 mV and 248 mV, respectively. Unfavorable electrostatic interactions between the three carbonyl groups aligned on one side of **2a** may raise the potentials of this quinone relative to **1a**. The E_7 values for **1a**, **2a**, and benzoquinone could be compared

(14) Badger, G. M. In *Six-Membered Heterocyclic Nitrogen Compounds With Three Condensed Rings*; Allen, C. F. H., Ed.; Interscience: New York, 1958; Chapter 9.
(15) Moore, H. W.; Maurer, D. L.; Pearce, D. S.; Lee, M. S. *J. Org. Chem.* **1972**, *37*, 1984.
(16) Becker, H.-D. In *The Chemistry of the Quinonoid Compounds*, Part I; Patai, S., Ed.; Wiley: New York, 1974; Chapter 7.
(17) Determined in pH 0.0 perchlorate buffer using a graphite working electrode. The literature value is 699 mV (NHE): Conant, J. B.; Fieser, L. F. *J. Am. Chem. Soc.* **1923**, *45*, 2194.
(18) Carlson, B. W.; Miller, L. L. *J. Am. Chem. Soc.* **1985**, *107*, 479.

since all three represent two-proton, two-electron transfer (i.e. $Q \rightarrow QH_2$). The lower E_7 values for **1a** and **2a** than benzoquinone indicate that the fused pyrimidinone rings exert an electron-releasing effect.

Comparisons are now made between the N-methylated (plots A) and N-unsubstituted (plots B) derivatives in each of the figures. The N-unsubstituted derivative **1b** (E_0 = 799 mV) possesses substantially higher redox potentials than the methylated derivative **1a**, Figure 1. The 125-mV average difference is attributed to stabilization of the hydroquinone form of **1b** (**13b**) by two internal hydrogen bonds (~62.5 mV increase per hydrogen bond). Spectral studies and pK_a measurements have provided evidence of internal hydrogen bond formation in **13b** as well as in the hydroquinone form of **2b** (**21b**) (loc cit). Hydroquinone **21b** can form only one internal hydrogen bond and **2b** should thus be 62.5 mV higher in potential than its methylated analogue **2a**. In fact, the potential of **2b** (E_0 = 800 mV) is 65 mV higher than that of **2a**, Figure 2.

A comparative electrochemical study of 1,2-dimethylbenzimidazole-4,7-dione and its imidazo[4,5-*g*]quinazoline-4,9-dione analogue carried out in this laboratory indicated that the fused pyrimidinone ring has little effect on quinone redox potentials.[4] A push-pull electronic effect by the fused pyrimidinone ring was postulated to explain this finding. The pyrimidinone ring may still exert a push-pull effect, but the present study indicates that electron release prevails. The findings of the previous study are better explained by the opposing effects of internal hydrogen bond formation and electron release.

Conclusions

Conclusions regarding the design of new reductive alkylators and hydrolytically stable high potential quinones are presented below.

Functionalization of the title quinones as reductive alkylators may or may not be fruitful. At physiological pH, the title quinones possess potentials (200–300 mV) that are much higher than effective antitumor reductive alkylators.[19] Apparently, a low redox potential reductive alkylator is necessary for selective activation in hypoxic tumor cells.[20] On the other hand, the high potentials of the title quinones suggest that reductive alkylator analogues would be selective nucleophile traps.[21] Another encouraging finding is the slow oxidation of the title hydroquinones to the corresponding quinones in aerobic buffers near neutrality ($k_{obsd} \sim 2 \times 10^{-4}$ s^{-1}). Low redox potential reductive alkylators cycle between the reduced (semiquinone or hydroquinone) and oxidized forms and thereby produce toxic oxygen species, which are responsible for the side effects of these agents.[22] A relatively oxygen-stable hydroquinone may thus be useful in minimizing the toxicity of reductive alkylators.

The hydrolytically stable high potential quinones resulting from this study are the N-unsubstituted analogues **1b** and **2b**. The E_0 value of both systems is 800 mV, a potential as high as some benzoquinone derivatives bearing electron-withdrawing substituents[16] but still less than that of DDQ (E_0 = 941 mV[23]). These systems also possess high potentials near neutrality (~300 mV), but the redox potentials decrease with increasing pH due to quinone anion and dianion formation. Unlike benzoquinone derivatives bearing electron-withdrawing substituents, however, **1b** and **2b** do not undergo addition–elimination and reductive-addition reactions. The fused pyrimidinone rings of **1b** and **2b** serve to protect against such reactions as well as to raise redox potentials by internal hydrogen bonding in the hydroquinone forms (65 mV increase in potential per hydrogen bond). The N-methylated quinones **1a** and **2a** possess somewhat lower potential than that of benzoquinone. In these systems hydroquinone stabilization by hydrogen bonding is not possible and the electron-releasing influence of the pyrimidinone ring prevails. The fused pyrimidinone rings of **1a** and **2a** still protect the systems from hydrolysis up to pH 9.

Ongoing efforts include oxidation studies utilizing the title quinones, mechanistic studies of oxygen-mediated hydroquinone to quinone conversion, and testing the title quinones as reductive alkylators. The results of these studies will be reported in due course.

Experimental Section

Elemental analyses were performed by Desert Analytics, Tucson, AZ. All analytically pure compounds were dried under high vacuum in a drying pistol heated with refluxing methanol. Some of these compounds still contained water of crystallization that was determined from the elemental analyses found. Experimental nitrogen percentages for **5**, **6**, **1a**, **17**, **19b**, and **2b** deviated from theoretical values by >0.4%. Repeat nitrogen analyses for these compounds showed wide variations in the percentage of nitrogen determined (up to 1%). Experimental carbon and hydrogen percentages as well as spectral data (MS, ^{1}H NMR) support the assigned structures, however. No elemental analyses were obtained for the hydroquinones **13a,b** since spectral data support the assigned structures and these compounds can be air-oxidized to the corresponding quinones **1a,b**. Nearly all of the compounds prepared melt with decomposition above 300 °C, as determined with a Mel-Temp apparatus. All TLC was run with Merck silica gel 60 (F_{254}) plates, employing a variety of solvents. IR spectra were taken as KBr pellets or thin films, employing a Nicolet MX-1 FT IR spectrophotometer; the strongest IR absorbances are reported. ^{1}H NMR spectra were obtained with a Bruker WH-90 spectrometer. All chemical shifts (δ) are reported relative to tetramethylsilane. UV/vis spectra were obtained with Perkin-Elmer 559 and Lambda-3 spectrometers. Mass measurements were carried out in the electron-impact (EI) mode with a Varian MAT 200 spectrometer. Measurements of pH were made with a Radiomater PHM84 pH meter equipped with a Radiometer GK2401C combination electrode.

pK_a constants were determined by spectrometric titration in μ = 1.0 (KCl) aqueous solvent at 30 ± 0.2 °C. Measurements were usually carried out under aerobic conditions; acid dissociations from hydroquinones in strong base were measured under an argon atmosphere, however. Details of the methodology employed are found in a previous publication.[12] In cases where acid dissociation resulted in small UV/vis spectral changes, Nernst fits were employed to provide approximate pK_a values.

Electrochemistry. Determination of E_m values was carried out with a BAS 27 voltamograph. The working electrode material was either a carbon paste[24] or glassy carbon. The reference electrode was Ag/AgCl, which was calibrated with a calomel electrode. Measurements were carried out in μ = 1.0 ($NaClO_4$)

(19) Remer, W. A. *The Chemistry of Antitumor Antibiotics*, Vol. 1; Wiley-Interscience: New York, 1979; p 221.

(20) Kennedy, K. A.; Teicher, B. A.; Rockewell, S.; Sartorelli, A. C. *Biochem. Pharm.* **1980**, *29*, 1.

(21) The quinone methide intermediates involved in reductive alkylation can either ketonize to quinones or undergo nucleophilic attack (ref 5 and 3). If a high potential quinone results from ketonization, nucleophilic attack (alkylation) appears to be preferred (ref 5).

(22) Doroshow, J. H. *Cancer Res.* **1983**, *43*, 460.

(23) Determined in pH 0.0 perchlorate buffer using a graphite working electrode. The potential measurement was carried out immediately upon dissolution of DDQ in the buffer. After a few minutes the solution became red due to DDQ hydrolysis (Becker, H. D.; Skelton, B. W.; White, A. H. *Aust. J. Chem.* **1987**, *40*, 625) and voltammograms showed the presence of low redox potential quinone species.

(24) (a) McCreery, R. L.; Dreiling, R.; Adams, R. N. *Brain Res.* **1974**, *73*, 23. (b) Kissinger, P. T.; Hart, J. B.; Adams, R. N. *Brain Res.* **1973**, *55*, 209.

aqueous buffer at 25–26 °C under an atmosphere of argon employing scan speeds of 100 mV s^{-1}. The midpoint potential E_m was determined from the average of the anodic ($E_{p,a}$) and cathodic ($E_{p,c}$) potentials. The anodic and cathodic waves are highly symmetric ($\alpha \sim 0.5$) and display reversible or quasi-reversible behavior.[25]

Nernst Fits. For each redox couple, 15 to 19 E_m values were determined over the pH range studied. For each E_m value, an E_0 value was calculated from the Nernst equation,[26] containing previously determined acid dissociation constants and the proton activity determined with a pH meter. The average of all E_0 determinations was substituted into the Nernst equation, with which the solid curve was generated.

Synthesis and physical properties of new compounds are provided below. **Formamidoterephthalic Acid (3).** A solution of 50 g (0.23 mol) of nitroterephthalic acid[27] was prepared in 400 mL of water containing KOH and 1 g of 5% Pd on charcoal and then shaken under 50 psi H_2. After H_2 uptake ceased (~12 h), the catalyst was removed by filtration through Celite and the filtrate acidified with concentrated HCl to give aminoterephthalic acid. Yield upon filtration, washing with water, and vacuum drying over P_2O_5 was 42.4 (~100%).

A suspension of 20.8 g (0.114 mol) of aminoterephthalic acid in 100 mL of formamide was rapidly heated to 150 °C, resulting in the formation of a clear solution. Formamidoterephthalic acid crystallized from this solution upon cooling to room temperature. Recrystallization was carried out by dissolving the product in dilute aqueous sodium bicarbonate, filtering, and acidifying the filtrate with acetic acid: 12.8 g, 53%; mp >260 °C dec; ^1H NMR (Me_2SO-d_6) δ 9.10 (1 H, br s, formamide C–H), 8.55 (1 H, br s, aromatic C(3)-H), 8.07 and 7.70 (2 H, ABX pattern, J_{ortho} = 8.2 Hz, J_{meta} = 1.3 Hz, $J_{para} \simeq 0$, C(5) and C(6)); MS (EI), m/z 209 (P^+), 181 ($P^+ - H_2O$).

2-Amino-5-nitroterephthalic Acid (4). A paste consisting of 5.1 g (0.024 mol) of **3** and 20 mL of fuming nitric acid was chilled in an ice–salt bath. Concentrated sulfuric acid (10 mL) was then added to the paste at a rate which maintained a 5–10 °C reaction temperature (about 30 min addition time). The resulting clear yellow solution was poured over 100 g of ice and chilled overnight in a refrigerator. Formyl group deblocking occurred during the workup, resulting in crystallization of **4** as a yellow solid, 2.8 g (51%). Recrystallization from hot water afforded light brown needles: mp >250 °C dec; TLC (1-butanol, acetic acid, H_2O [5:2:3]), R_f 0.65; IR (KBr) 3476, 3368, 3339, 2900, 1712, 1680, 1623, 1485, 1327, 1284, 1248 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.48 and 6.88 (2 H, 2 s, aromatic protons); MS (EI), m/z 226 (P^+), 196 ($P^+ - NO$), 178 ($P^+ - NO_2$).

Anal. Calcd for $C_8H_6N_2O_6$: C, 42.49; H, 2.67; N, 12.38. Found: C, 42.56; H, 2.60; N, 12.45.

2,5-Diacetamidoterephthalic Acid (5). A solution of 5.3 g (23 mmol) of **4** was prepared in 250 mL of water containing 2.5 g of KOH and 0.5 g of 5% Pd on charcoal. This solution was then hydrogenated under 50 psi H_2 for 2 h. The complete reaction mixture was filtered through Celite into a flask containing 50 mL of acetic anhydride. The product began to crystallize immediately; crystallization was completed by chilling for 3 h. The crude product (4.8 g, 74% yield) was sufficiently pure to use in the next step. Recrystallization from hot dimethyl sulfoxide provided light tan needles: mp >300 °C dec; TLC (butanol, acetic acid, water [5:2:3]), fluorescent blue spot at R_f 0.56; IR (KBr) 2900, 2580, 1701, 1641, 1549, 1589, 1410, 1302, 1209, 961, 797, 747 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.9 (2 H, aromatic protons), 2.11 (6 H, s, acetamido methyl).

Anal. Calcd for $C_{12}H_{12}N_2O_6$: C, 51.43; H, 4.31; N, 9.99. Found: C, 51.17; H, 4.51; N, 9.51.

2,5-Diacetamidoterephthalic Acid Dimethyl Ester (7). A suspension of 4.8 g (0.017 mol) of **5** in a mixture consisting of 100 mL of acetic acid and 100 mL of acetic anhydride was heated at reflux for 2 h. The reaction mixture slowly became homogeneous during reflux with crystallization of **6** occurring toward the end of the 2-h period. Crystallization was completed by storing the completed reaction at room temperature for several hours. Yield of **6** was 3.9 g (87%).

Sodium methoxide (100 mg) was added to a suspension of 1.0 g (4.09 mmol) of **6** in 50 mL of methanol. The reaction was then stirred vigorously and heated at reflux for 1 h. The yellow-green solid was filtered off and washed with methanol, 1.21 g crude yield (96%). Recrystallization from acetic acid provided yellow-green needles: mp 280–285 °C dec; TLC (acetone), a fluorescent blue spot at R_f 0.63; IR (KBr) 3308, 1707, 1565, 1402, 1257, 1228 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.35 (2 H, s, aromatic), 3.95 (6 H, s, ester methyls), 2.23 (6 H, s, acetamido methyls); MS (EI), m/z 308 (P^+), 266 ($P^+ - H_2C{=}C{=}O$), 224 ($P^+ - 2\ H_2C{=}C{=}O$).

Anal. Calcd for $C_{14}H_{16}N_2O_6$: C, 54.54; H, 5.23; N, 9.08. Found: C, 54.57; H, 5.24; N, 9.62.

2,5-Diacetamido-3-nitroterephthalic Acid Dimethyl Ester (8). Red fuming nitric acid was prepared by adding 2 mL of formaldehyde to ~200 mL of fuming nitric acid and allowing the mixture to stand at room temperature for several hours in a loosely stoppered flask. To 1 mL of red fuming nitric acid was added 500 mg (1.62 mmol) of **7** and the mixture stirred at room temperature for 10 min. The reaction mixture was then combined with 20 g of crushed ice and the resulting solution extracted three times with 20-mL portions of chloroform. Drying of the chloroform extracts ($MgSO_4$) was followed by concentration in vacuo to a solid residue, which was dissolved in 100 mL of boiling acetone. After filtration to remove insoluble material, the volume of the acetone solution was doubled with hexane and chilled overnight, resulting in crystallization of crude **8** 322 mg (56%). Recrystallization was carried out by dissolution of **8** in a minimum volume of boiling chloroform and adding an equal volume of hexane: mp 240–241 °C; TLC (acetone), R_f 0.6; IR (thin film) 3293, 1727, 1677, 1549, 1531, 1267, 1247, 1141 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 10.30 and 10.02 (2 H, 2 s, amide N–H groups), 8.04 (1 H, s, aromatic), 3.82 and 3.75 (6 H, 2 s, ester methyls), 2.05 and 1.98 (6 H, 2 s, acetamido methyls); MS (EI), m/z 353 (P^+), 307 ($P^+ - NO_2$), 269 ($P^+ - 2\ CH_2{=}C{=}O$).

Anal. Calcd for $C_{14}H_{15}N_3O_8$: C, 47.59; H, 4.28; N, 11.89. Found: C, 47.32; H, 4.17; N, 11.64.

6-Acetamido-7-(methylcarbamoyl)-2,3-dimethyl-8-nitroquinazolin-4(3*H*)-one (9). To a solution of 137 mg (0.38 mmol) of **8** in 1.4 mL of DMF was added 0.5 mL of 10% methylamine in methanol. The reaction mixture was placed in a stoppered flask and allowed to stir at room temperature for 15 h. During this time fiberous crystals of product had formed. Yield of crude product after filtration and washing with acetone was 66 mg (51%). Recrystallization of the product was carried out from dimethyl sulfoxide: mp 283–286 °C dec; TLC (10% methanol in chloroform) R_f 0.52; IR (KBr) 3269, 3095, 1684, 1668, 1653, 1642, 1593, 1579, 1537, 1456, 1375, 1330 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.76 (1 H, br s, NH of 6-acetamido group), ~8.7 (1 H, br q, NH of 7-methylcarbamoyl group), 8.62 (1 H, s, aromatic), 3.53 (3 H, s, N(3)-methyl), 2.72 (3 H, d, J = 5 Hz, CH_3NH of 7-methylcarbamoyl group), 2.54 (3 H, s, 2-methyl), 2.08 (3 H, s, 6-acetamido methyl); MS (EI), m/z 333 (P^+), 315 ($P^+ - H_2O$), 291 ($P^+ - CH_2{=}C{=}O$).

Anal. Calcd for $C_{14}H_{15}N_5O_5$: C, 50.45; H, 4.53; N, 21.00. Found: C, 50.44; H, 4.49; N, 20.83.

3,8-Diamino-5-nitro-2,7-dimethylpyrimido[4,5-*g*]quinazoline-4,9(3*H*,8*H*)-dione (10). Dissolution of 500 mg (1.41 mmol) of **8** in 100 mL of boiling methanol was followed immediately by addition of 1 mL of hydrazine monohydrate. The reaction was then stirred for 24 h without further heating. The half-cyclized product crystallized from the methanol solution as a light tan solid, 327 mg (69%) yield. The high-field chemical shift of one of the methyl groups indicates the presence of an uncyclized acetamido group: ^1H NMR (Me_2SO-d_6) δ 8.80 (1 H, s, aromatic proton) 5.85 (5 H, br s, hydrazine protons), 2.55 (3 H, s, 2-methyl), 2.11 (3 H, s, acetamido methyl).

To obtain the fully cyclized product, 327 mg (0.47 mmol) of the half-cyclized material was dissolved in 50 mL of boiling acetic acid. Yellow needles of **10** crystallized from the solution while it stood at room temperature for 12 h: 234 mg (76%) yield; mp >325 °C dec; TLC (acetone), R_f 0.56; IR (KBr) 3434, 3312, 1681, 1603, 1552, 1462, 1372 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.37 (1 H, s, aromatic), 5.84 (4 H, br s, amino protons), 2.62 and 2.58 (6 H,

(25) Bard, A. J.; Faulkner, L. R. *Electrochemical Methods*; Wiley: New York, 1980; pp 227–231.
(26) For pH- and H_0-dependent Nernst equations, see: Eberlein, G. A.; Bruice, T. C. *J. Am. Chem. Soc.* **1983**, *105*, 6685.
(27) Burkhardt, G. A. *Ber. Dtsch. Chem. Ges.* **1877**, *10*, 145.

2 s, 2,7-dimethyl); MS (EI), m/z 317 (P^+).

Anal. Calcd for $C_{12}H_{11}N_7O_4$: C, 45.43; H, 3.49; N, 30.89. Found: C, 45.54; H, 3.45; N, 30.81.

5-Nitro-2,7-dimethylpyrimido[4,5-*g*]quinazoline-4,9-(3*H*,8*H*)-dione (11). To a suspension of 100 mg (0.315 mmol) of **10** in 5 mL of acetic acid was added 214 mg (2.5 mmol) of KNO_2. The mixture was then stirred and heated at reflux for 2 min. After the reaction had cooled to room temperature, a second 214 mg portion of KNO_2 was added and the reaction refluxed for 2 min again. The completed reaction was diluted with 20 mL of water resulting in crystallization of the off-white **11**; yield 88 mg (97%). An analytical sample was obtained by recrystallization from dimethyl sulfoxide: mp >300 °C dec; TLC (1-butanol, acetic acid, water [5:2:3]), R_f 0.65; IR (KBr) 3055, 2961, 2931, 2884, 1689, 1627, 1527, 1460, 1374, 873 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.29 (1 H, s, aromatic), 2.38 and 2.35 (6 H, 2 s, 2,7-dimethyl); MS (EI), m/z 287 (P^+), 257 (P^+ – NO).

Anal. Calcd for $C_{12}H_9N_5O_4 \cdot 0.25H_2O$: C, 49.40; H, 3.29; N, 23.99. Found: C, 49.28; H, 3.08; N, 23.97.

5-Amino-2,3,7,8-tetramethylpyrimido[4,5-*g*]quinazoline-4,9(3*H*,8*H*)-dione (12a·HCl). A solution of 497 mg (1.49 mmol) of **9** in 50 mL of DMF, containing 50 mg of 5% Pd on carbon, was shaken under 50 psi H_2 for 1 h. The reaction mixture was filtered through Celite and the filtrate acidified with ~0.5 mL of concentrated HCl. The colorless filtrate was then heated at reflux for 1 min, resulting in a change to a bright yellow solution. Chilling this solution in a refrigerator for several hours resulted in crystallization of the yellow **12a** hydrochloride salt. The product was filtered and washed with methanol; yield was 275 mg (57%). An additional 60 mg (12%) was obtained by concentrating the mother liquor. The hydrochloride salt was of suitable purity for quinone elaboration. Recrystallization of **12a**·HCl for characterization and analysis was carried out from dimethylformamide: mp >300 °C dec; TLC (10% methanol in chloroform) fluorescent blue spot at R_f 0.61; IR of **12a** (KBr) 3479, 3350, 1674, 1651, 1601, 1580, 1521, 1460, 1382, 1347, 1325, 789 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.25 (1 H, s, C(10) aromatic proton), 3.55 and 3.48 (6 H, 2 s, N(3) and N(8) methyls), 2.71 and 2.63 (6 H, 2 s, C(2) and C(7) methyls); MS (EI), m/z 285 (P^+).

Anal. Calcd for $C_{14}H_{15}N_5O_2 \cdot HCl$: C, 52.26; H, 5.01; N, 21.75. Found: C, 52.41; H, 5.03; N, 21.67.

5-Amino-2,7-dimethylpyrimido[4,5-*g*]quinazoline-4,9-(3*H*,8*H*)-dione (12b). To a suspension of 128 mg (4.46 mmol) of **11** in 3 mL of DMF was added a solution of 85% sodium dithionite (400 mg) in 1 mL of water. The mixture was refluxed for 5 min and then cooled to room temperature. Dilution of the completed reaction with 25 mL of water afforded **12b** as a bright yellow solid; 101 mg (88%) yield. The **12b** thus obtained was suitable for conversion to **1b**. An analytical sample of the hydrochloride salt was prepared by dissolving **12b** in hot DMF and adding concentrated HCl; crystals of **12b**·HCl formed immediately: mp >350 °C dec; TLC (1-butanol, acetic acid, water [5:2:3]), R_f 0.65; IR (KBr) 2802, 2631, 1693, 1679, 1655, 1621, 1585 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.23 (1 H, s, aromatic), 2.52 and 2.41 (6 H, 2 s, 2,7-dimethyl); MS (EI), m/z 257 (P^+).

Anal. Calcd for $C_{12}H_{11}N_5O_2 \cdot HCl \cdot 0.25H_2O$: C, 48.33; H, 4.22; N, 23.47. Found: C, 48.27; H, 3.94; N, 23.35.

2,3,7,8-Tetramethylpyrimido[4,5-*g*]quinazoline-4,5,9,10-(3*H*,8*H*)-tetrone (1a). A mixture consisting of 50 mg (0.155 mmol) of **12a** and 90 mg (0.310 mmol) of potassium dichromate in 7.5 mL of 0.1 M sulfuric acid was heated at 90 °C for 5 min. During this time the reaction mixture changed from a yellow suspension to an amber homogeneous solution. The solution was filtered while still hot and chilled in a refrigerator for 2 h, resulting in crystallization of the analytically pure product as yellow flakes. The product was filtered and washed with water and then acetone: yield 25 mg (54%); mp >300 °C dec; IR (KBr) 1706, 1652, 1562, 1521, 1428, 1372, 1358, 1070, 977, 791 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.51 (6 H, s, N(3) and N(8) methyls), 2.67 (6 H, s, C(2) and C(7) methyls); MS (EI with solids probe), m/z 300 (P^+).

Anal. Calcd for $C_{14}H_{12}N_4O_4 \cdot 0.45H_2O$: C, 54.53; H, 4.21; N, 18.16. Found: C, 54.20; H, 3.80; N, 17.22.

5,10-Dihydroxy-2,3,7,8-tetramethylpyrimido[4,5-*g*]quinazoline-4,9(3*H*,8*H*)-dione (13a). A suspension consisting of **1a** (13.5 mg, 0.045 mmol) and 5 mg of 5% Pd on charcoal in 20 mL of methanol was treated with 50 psi H_2 for 1 h. The reaction mixture was filtered through Celite and the crystallized **13a** washed from the filter cake with chloroform. The filtrate containing the methanol reaction solvent and the chloroform washings was evaporated to dryness. Recrystallization of the residue from methanol afforded **11a** as a bright yellow needles: 9 mg yield (66%); mp >350 °C dec; TLC (10% methanol in chloroform), R_f 0.5; IR (KBr) 2955, 1636, 1607, 1420, 1384, 1372, 1332, 1243, 1159, 999, 794 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.63 (6 H, s, N(3) and N(8) methyls) 2.69 (6 H, s, C(2) and C(7) methyls); MS (EI), m/z 302 (P^+).

2,7-Dimethylpyrimido[4,5-*g*]quinazoline-4,5,9,10-(3*H*,8*H*)-tetrone (1b). Dissolution of 39.5 mg (0.145 mmol) of **12b** in 300 μL of ice-cold concentrated sulfuric acid was followed by dropwise addition of a solution of 64 mg (0.217 mmol) of potassium dichromate in 600 μL of water. Cooling was continued during the addition and for 5 min after addition was completed. The reaction mixture was diluted with 500 μL of water and stored in a refrigerator for an hour. The crystallized product was filtered off and washed with water, 27.7 mg (47%) yield. Recrystallization from dimethyl sulfoxide afforded light tan needles: mp >300 °C dec; TLC (-butanol, acetic acid, water [5:2:3]), R_f 0.25; IR (KBr) 2918, 1711, 1642, 1572, 1547, 1475, 1464, 1141 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.46 (6 H, s, 2,7-dimethyl); MS, (EI), m/z 272 (P^+).

Anal. Calcd for $C_{12}H_8N_4O_4 \cdot 0.25H_2O$: C, 52.08; H, 3.09; N, 20.23. Found: C, 52.29; H, 2.90; N, 19.97.

5,10-Dihydroxy-2,7-dimethylpyrimido[4,5-*g*]quinazoline-4,9(3*H*,8*H*)-dione (13b). A suspension of 20 mg (0.073 mmol) of **1b** in 2 mL of DMF was combined with a solution consisting of 50 mg of 85% sodium dithionite in 0.5 mL of water, and then the resulting solution was heated at reflux for 2 min. The reaction mixture was diluted with 5 mL of water and the orange-yellow **13b** collected by filtration, 15.1 mg (75%) yield. Purification for characterization was carried out by recrystallization from Me_2SO: mp >350 °C dec; TLC (1-butanol, acetic acid, water [5:2:3]), fluorescent yellow spot at R_f 0.07; IR (KBr) 3474, 3056, 3017, 2960, 1663, 1620, 1382, 1278, 1238, 1223 cm^{-1}; ^1H NMR (Me_SO-d_6) δ 2.37 (6 H, s, 2,7-dimethyl); MS (EI), m/z 274 (P^+).

2,4-Diacetamido-3-nitro-1,5-dimethylbenzene (15). Addition of 10 g (45.4 mmol) of 2,4-diacetamido-1,5-dimethylbenzene (**14**) to 120 mL of fuming nitric acid was carried out with stirring at 5–10 °C. Following the addition, the reaction mixture was stirred for 20 min at 5–10 °C and then poured over 800 mL of ice water. Pale yellow crystals of **15** were then collected by filtration and washed with water, 10 g (83%) yield. Analytically pure **15** was obtained as needles by recrystallization from 100% ethanol: mp 353–354 °C dec; ^1H NMR (Me_2SO-d_6) δ 9.62 (2 H, br s, exchangeable with D_2O, acetamido N–H), 7.40 (1 H, s, aromatic), 2.16 and 1.97 (12 H, 2 s, ring methyls and acetamido methyls, no assignments made); IR (KBr) 3256, 1690, 1664, 1620, 1580, 1547, 1523, 1457, 1373, 1263 cm^{-1}; MS (EI), m/z 265 (P^+).

Anal. Calcd for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.33; H, 5.83; N, 15.58.

2,4-Diacetamido-1,5-dicarboxy-3-nitrobenzene (16). A suspension of **15** (5.0 g, 18.9 mmol) in 500 mL of water containing 0.7 g of glacial acetic acid was heated to 95–100 °C and potassium permanganate added in 2.0-g (12.7 mmol) portions at 2-h intervals. A total of 18 g of potassium permanganate was required to convert **15** to **16**. Acetic acid was added along with the potassium permanganate portions to maintain the pH of the reaction at 6 to 7. TLC [2-propanol, ammonia, water (7:1:2)] showed the formation of an intermediate (probably the monoacid), which was eventually converted to **16**. The product was isolated by adjusting the pH of the reaction to 8 with K_2CO_3, filtering off the MnO_2, evaporating the reaction to 200 mL in vacuo, and adjusting the pH of the resulting liquor to 1 with concentrated HCl. Chilling of the acidified liquor afforded 3.3 g (54%) of **16** as a pale yellow solid. Analytically pure **16** was obtained by recrystallization from methanol: mp >250 °C dec; TLC [2-propanol, ammonia, water (7:1:2)], R_f 0.4; ^1H NMR (Me_2SO-d_6) δ 8.37 (1 H, s, aromatic), 2.00 (6 H, s, acetamido methyls); IR (KBr) 3314, 1726, 1683, 1572, 1550, 1501, 1366, 1295, 1253, 1154 cm^{-1}; MS (EI), m/z 289 ($P^+ - 2H_2O$), 265 ($P^+ - H_2C{=}C{=}O$, H_2O), 259 ($P^+ - 2H_2O$, NO), 247 ($P^+ - 2H_2O$, NO_2).

Anal. Calcd for $C_{12}H_{11}N_3O_8 \cdot 1.0H_2O$: C, 41.99; H, 3.82; N, 12.24. Found: C, 42.00; H, 3.78; N, 12.08.

4-Acetamido-2,5,7-trimethyl-3*H*-benzimidazole (17). A mixture consisting of 246 mg (0.92 mmol) of **15** and 50 mg of 5% Pd on charcoal in 100 mL of methanol was reduced under 50 psi H_2 for 1 h. The completed reaction was filtered through Celite to remove the catalyst and the filtrate acidified with concentrated HCl. Concentration of the filtrate in vacuo was followed by dissolution of the residue in water and adjustment of the pH to 7 with sodium bicarbonate. The product was removed by multiple extractions with chloroform. Drying ($MgSO_4$) and then concentration of the chloroform extracts to a small volume, followed by addition of hexane, afforded crystallized **17** (25 mg, 12%, yield). The yield is unoptimized; much of **17** remains in the aqueous phase due to its low solubility in chloroform. Physical properties were consistent with the structure of **17**: mp >150 °C dec; TLC (-butanol, acetic acid, water [5:2:3]), R_f 0.51; IR (KBr) 3230, 2924, 1662, 1540, 1440, 1372 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 6.74 (1 H, s, aromatic), 2.44, 2.40, 2.17, and 2.07 (12 H, 4 s, four nonequivalent methyls of **17**); MS (EI), m/z 217 (P^+), 275 ($P^+ - H_2C{=}C{=}O$), 274 (P^+ - acetyl).

Anal. Calcd for $C_{12}H_{15}N_3O{\cdot}0.75H_2O$: C, 62.45; H, 7.20; N, 18.20. Found: C, 62.81; H, 6.96; N, 16.73.

2,8-Dimethyl-10-nitro-4,6-benzo[1,2-*d*:5,4-*d'*]bis[1,3]oxazine-4,6-dione (18). A mixture consisting of 2 g (6.1 mmol) of **16**, 100 mL of acetic anhydride, and 15 mL of glacial acetic acid was heated for 8 h at reflux. The solvent was then removed in vacuo and the residue dissolved in 50 mL of boiling benzene. Filtration of the boiling solution to remove a dark brown gum was followed by addition of enough hexane to cloud the solution. Chilling resulted in crystallization of **18**, which was collected by filtration and washed with hexane, 1.6 g (90%) yield. Recrystallization was carried out from benzene: mp 223–224 °C; ^1H NMR (Me_2SO-d_6) δ 8.69 (1 H, s, aromatic), 2.46 (6 H, s, 2,8-dimethyl); IR (KBr) 1783, 1762, 1645, 1617, 1606, 1555, 1373, 1325, 1222, 981 cm^{-1}; MS (EI), m/z 289 (P^+), 259 (P^+ - NO), 247 (P^+ - NO_2).

Anal. Calcd for $C_{12}H_7N_3O_6{\cdot}0.75H_2O$: C, 47.61; H, 2.83; N, 13.87. Found: C, 47.36; H, 2.73; N, 13.83.

2,3,7,8-Tetramethyl-10-nitropyrimido[5,4-*g*]quinazoline-4,6(3*H*,7*H*)-dione (19a). A mixture of 100 mL of 29% ethanolic methylamine and 2.26 g (7.81 mmol) of **18** was heated at 50–60 °C for 6 h. The volume of the reaction was maintained at ca. 100 mL during this time by periodic additions of 29% ethanolic methylamine. The reaction mixture was then concentrated in vacuo to a residue, to which 50 mL of water was added along with acetic acid to adjust the pH to 6. Collection of **19a** by filtration provided a 2.4-g (97%) yield. Analytically pure **19a** was obtained by dissolving the crude material in boiling acetic acid, adding enough ethanol to cloud the solution, and then chilling the mixture: mp >360 °C dec; TLC (1-butanol, acetic acid, water [5:2:3]), R_f 0.73; IR (KBr) 1696, 1587, 1562, 1555, 1538, 1458, 1415, 1379, 1288, 808 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 8.85 (1 H, s, aromatic), 3.54 (6 H, s, *N*-methyls), 2.60 (6 H, s, 2,6-dimethyl); MS (EI), m/z 315 (P^+), 285 (P^+ - NO).

Anal. Calcd for $C_{14}H_{13}N_5O_4$: C, 53.32; H, 4.15; N, 22.20. Found: C, 53.23; H, 4.18; N, 22.09.

2,8-Dimethyl-10-nitropyrimido[5,4-*g*]quinazoline-4,6-(3*H*,7*H*)-dione (19b). A mixture of 50 mL of ammonia-saturated methanol, prepared at 0 °C, and 2.74 g (9.48 mmol) of **18** was heated at reflux. Every 15 min an additional 50 mL of ammonia-saturated methanol was added to the refluxing reaction mixture. After a total reaction time of 1 h, the mixture was evaporated to dryness, and the residue was dissolved in 1 N KOH. Acidification of this solution with acetic acid resulted in crystallization of **19b**, 1.77 g (65%) yield. Analytically pure **19b** was obtained by recrystallization from acetic acid: mp >320 °C dec; TLC (1-butanol, acetic acid, water [5:2:3]), R_f 0.66; IR (KBr) 3060, 2913, 1708, 1586, 1548, 1422, 1375, 758 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 12.6 (2 H, br s, amide protons), 8.82 (1 H, s, aromatic), 2.38 (6 H, s, 2,8-dimethyl); MS (EI), m/z 287 (P^+).

Anal. Calcd for $C_{12}H_9N_5O_4$: C, 50.18; H, 3.16; N, 24.38. Found: C, 50.34; H, 3.08; N, 23.97.

10-Amino-2,3,7,8-tetramethylpyrimido[5,4-*g*]quinazoline-4,6(3*H*,7*H*)-dione (20a). A suspension of 0.51 g (16 mmol) of **19a** and 50 mg of 5% Pd on charcoal in 70 mL of glacial acetic acid was shaken under 60 psi H_2 for 6 h. The catalyst was removed by filtration and the filtrate heated to a boil and acidified with concentrated HCl. Dissolution of the hydrochloride salt in water and adjusting the pH to 9 with K_2CO_3 afforded **20a** (0.36 g, 78%) as a yellow solid. An analytical sample was obtained by recrystallization from 70% ethanol in water: mp >320 °C dec; TLC (1-butanol, acetic acid, water [5:2:3]), R_f 0.64; IR (KBr) 3309, 1670, 1590, 1554, 1468, 1416, 1385, 1368, 1330, 1157 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.98 (1 H, s, aromatic), 6.4 (2 H, br s, amine) 3.54 (6 H, s, *N*-methyl), 2.70 (6 H, s, 2,8-dimethyl); MS (EI), m/z 285 (P^+).

Anal. Calcd for $C_{14}H_{15}N_5O_2$: C, 58.94; H, 5.29; N, 24.54. Found: C, 58.90; H, 5.29; N, 24.40.

10-Amino-2,8-dimethylpyrimido[5,4-*g*]quinazoline-4,6-(3*H*,7*H*)-dione (20b). A solution of 1.5 g (5.2 mmol) of **19b** in 100 mL of pH 11 buffer (KOH) was reduced under 50 psi H_2 in the presence of 70 mg of 5% Pd on carbon for 2 h. The reaction mixture was filtered through Celite to remove the catalyst and the pH of the filtrate adjusted to pH 7 with K_2CO_3. Bright yellow **20b** was collected by filtration and then washed with water and acetone, 900 mg (67%) yield. Recrystallization from dimethyl sulfoxide afforded yellow needles: mp >300 °C dec; TLC (1-butanol, acetic acid, water [5:2:3]), R_f 0.67; IR (KBr) 3038, 2909, 1694, 1665, 1630, 1599, 1379 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.95 (1 H, s, aromatic), 2.54 (6 H, s, 2,8-dimethyl); MS (EI), m/z 257 (P^+).

Anal. Calcd for $C_{12}H_{11}N_5O_2{\cdot}0.75H_2O$: C, 53.23; H, 4.65; N, 25.85. Found: C, 53.41; H, 4.60; N, 24.15.

2,3,7,8-Tetramethylpyrimido[5,4-*g*]quinazoline-4,5,6,10-(3*H*,7*H*)-tetrone (2a). A suspension of **20a** (286 mg, 1 mmol) in 30 mL of 0.1 M aqueous H_2SO_4 was added dropwise to 4.8 mL of 0.14 M aqueous potassium dichromate at room temperature. After the addition, the reaction mixture was stirred for 15 min at room temperature. Chilling the reaction mixture afforded crude **2a** as an orange solid. Recrystallization was carried out from a minimum volume of boiling water: 116 mg (39%) yield; mp >300 °C dec; IR (KBr) 1722, 1709, 1562, 1526, 1435, 1389, 1359, 1297, 1018, 1008 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.50 (6 H, s, *N*-methyls), 2.65 (6 H, s, 2,6-dimethyl); MS (EI), m/z 300 (P^+), 272 (P^+ - CO).

Anal. Calcd for $C_{14}H_{12}N_4O_4$: C, 56.00; H, 4.03; N, 18.65. Found: C, 55.53; H, 4.00; N, 18.51.

2,8-Dimethylpyrimido[5,4-*g*]quinazoline-4,5,6,10-(3*H*,7*H*)-tetrone (2b). To a solution of **20b** (169 mg, 0.7 mmol) in 3.5 mL of ice-cold concentrated sulfuric acid was added a solution of 270 mg of potassium dichromate in 3.5 mL of water. The addition was carried out dropwise over a period of 20 min with stirring and cooling at 5–10 °C. After the addition was completed, 3.5 mL of ice water was added to the reaction mixture and cooling was continued for an hour. The light tan sulfate salt of **2b** was collected by filtration and then dispersed in a small amount of water. The crystallized **2b** was collected by filtration and dried, yield 116 mg (61%). Recrystallization was carried out from Me_2SO: mp >300 °C dec; TLC (1-butanol, acetic acid, water [5:2:3]), R_f 0.22; IR (KBr) 2927, 2841, 1726, 1701, 1676, 1623, 1575, 1473, 1110, 535 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.41 (6 H, s, 2,8-dimethyl); MS (EI), m/z 272 (P^+).

Anal. Calcd for $C_{12}H_8N_4O_4{\cdot}1.75H_2O$: C, 47.45; H, 3.81; N, 18.43. Found: C, 47.50; H, 3.46; N, 16.91.

5,10-Dihydroxy-2,3,7,8-tetramethylpyrimido[5,4-*g*]-quinazoline-4,6(3*H*,7*H*)-dione (21a). A suspension of 22 mg (0.073 mmol) of **2a** and 4 mg of 5% Pd on charcoal in 20 mL of methanol was shaken for 1 h under 50 psi H_2. Crystallization of **21a** occurred during the reduction and 20 mL of chloroform was added to redissolve the product. Removal of the catalyst by filtration was followed by evaporation of the filtrate in vacuo. The resulting solids were recrystallized from a minimum volume of methanol: 13 mg (59%) yield; mp >300 °C dec; IR (KBr) 1692, 1639, 1591, 1455, 1420, 1388, 1301, 1235, 1158, 994 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.48 (6 H, s, *N*-methyls), 2.59 (6 H, s, 2,6-dimethyl); MS (EI), m/z 302 (P^+).

Anal. Calcd for $C_{14}H_{14}N_4O_4{\cdot}0.25H_2O$: C, 54.80; H, 4.76; N, 18.25. Found: C, 54.89; H, 4.64; N, 18.04.

5,10-Dihydroxy-2,8-dimethylpyrimido[5,4-*g*]quinazoline-4,6(3*H*,7*H*)-dione (21b). A solution of 64 mg (0.23 mmol) of **2b** in 5 mL of DMF, containing 5 mg of 5% Pd on charcoal, was shaken under 50 psi H_2 for 1 h. The reaction mixture was then filtered through Celite to remove the catalyst and the filtrate diluted with water. Crystallization of **21b** occurred from the

aqueous filtrate: 28.6 mg (45%) yield; mp >300 °C dec; IR (KBr) 3429, 3042, 2920, 2852, 1691, 1613, 1444, 1424, 1210, 818 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.37 (6 H, s, 2,8-dimethyl); MS (EI), m/z 274 (P^+).

Anal. Calcd for $C_{12}H_{10}N_4O_4 \cdot 0.25H_2O$: C, 51.71; H, 3.79; N, 20.09. Found: C, 51.53; H, 3.58; N, 19.92.

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A Convenient Synthesis of Substituted Quinolines by Thermal Electrocyclic Rearrangement of *o*-Vinyl Anils under Nonacidic Conditions

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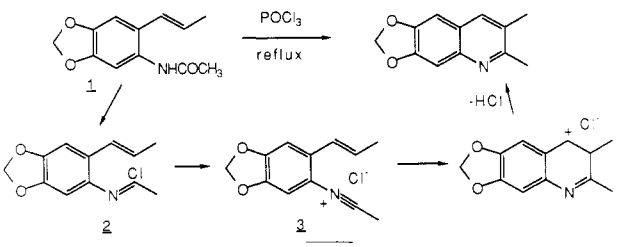
Anils **8a–g** (Table II) underwent smooth rearrangement and oxidation to the quinolines **9a–g** at 155–200 °C via formation of the 2–3 carbon–carbon bond. These cyclizations proceeded in high yields under nonacidic conditions. It was often possible to prepare the quinolines directly in one step from the appropriately substituted aniline and aldehyde. These cyclization conditions eliminate the formation of unwanted byproducts common to some acidic Bischler–Napieralski type quinoline syntheses. The scope and mechanism of the reaction are discussed.

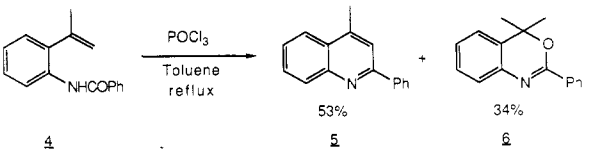
The Bischler–Napieralski synthesis is one of the most useful methods for the synthesis of isoquinolines and has been extensively reviewed.[2] A popular modification of this reaction, introduced by Foulds and Robinson[3] for the synthesis of quinolines, involves treatment of 2-vinylic anilide derivatives **1** with phosphorus oxychloride at reflux. As shown in Scheme I, the reaction involves an electrophilic cyclization of the carbonyl carbon of an amide to an adjoining site of unsaturation. Under these conditions, the cyclization in believed to proceed via the nitrilium ion[4] **3**, which is thought to result from dissociation of the precursor imidoyl chloride **2** upon heating. Other modifications have included phosphorus oxychloride treatment of amidines[5] or ureas,[6] which produce good yields of phenanthrenes and quinolines, respectively.

We have observed cases where the use of acidic reagents such as phosphorus oxychloride results in the formation of substantial amounts of undesired byproducts. For example, cyclization of **4** under the standard conditions resulted in a 53% yield of quinoline **5** and a 34% yield of 4,4-dimethyl-2-phenyl-4*H*-3,1-benzoxazine (**6**), as shown in Scheme II. In an effort to improve the selectivity and yield of this reaction, we sought to develop a convenient nonacidic method for the synthesis of quinolines from 2-aminostyrenes.

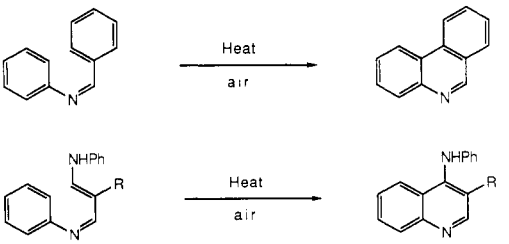
Scheme I



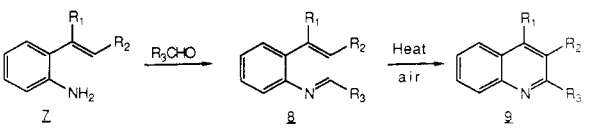
Scheme II



Scheme III



Scheme IV



In contrast to the electrophilic cyclizations described above, there have been relatively few reports of the thermal electrocyclic synthesis of quinolines under nonacidic con-

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