(dd, J = 6.0 and 6.0 Hz, 2 H), 4.70–5.50 (m, 2 H), 6.70 (br, 1 H), 7.00–8.15 (m, 5 H).

***N*-((1*R**,5*R**)-Carvyl)benzamide (56).** To a solution of carvylamine (**55**) (53 mg, 0.35 mmol) in CH_2Cl_2 (2.0 mL) was added triethylamine (0.35 mL). Benzoyl chloride (58 μL) was added to the solution. The reaction mixture was stirred at room temperature for 2 h. The reaction mixture was extracted with ether (10 mL) and washed with a 2 N HCl solution (5 mL) and saturated $NaHCO_3$ solution (5 mL). The extracts were dried over $MgSO_4$ and evaporated in vacuo. Benzamide **56** was purified by column chromatography (SiO_2, ether). An analytical sample was recrystallized from ether/pentane. Benzamide **56** (79 mg, 90%) was obtained as a colorless solid: mp 167–169 °C (lit.[33] mp 169 °C); ^1H NMR ($CDCl_3$, 60 MHz) δ 1.50–2.55 (m, 11 H), 4.70 (s, 2 H, CH_2=), 4.40–5.03 (m, 1 H, CHN), 5.42–5.82 (m, 1 H, CH=), 5.82–6.70 (br, 1 H, NHCO), 7.13–8.22 (m, 5 H, Ph).

***N*-Cinnamylacetamide (61).**[54] To a solution of cinnamyl azide (**15**) (0.159 g, 1.0 mmol) and acetic acid (0.360 g, 6.0 mmol) in benzene (5 mL) was added PPh_3 (0.262 g, 1.0 mmol). After the solution was heated at reflux for 30 h, saturated $NaHCO_3$ solution (10 mL) was added. The combined benzene extracts (10 mL × 3) were washed with a saturated $NaHCO_3$ solution (10 mL × 3), dried over $MgSO_4$, and evaporated. Preparative TLC (SiO_2, CH_2Cl_2, R_f = 0.14) gave *N*-cinnamylacetamide (**61**) (0.397 g, 57%), which contained triphenylphosphine oxide. The yield was determined by ^1H NMR analysis: ^1H NMR ($CDCl_3$, 60 MHz) δ 1.98 (s, 3 H), 3.90 (d, J = 6.0 Hz, 1 H), 4.00 (d, J = 6.0 Hz, 1 H), 6.07 (dt, J = 16 and 6.0 Hz, 1 H), 6.47 (d, J = 16 Hz, 1 H), 7.05–8.30 (m, 5 H).

Catalytic Hydrogenation of Azido Carboxylic Acids. A suspension of a mixture of azido carboxylic acids (**36a** or **36b**) (0.334 g, 2.00 mmol) and a catalyst in EtOH (5 mL) and water (2 mL) was stirred at room temperature for 2 days under a hydrogen atmosphere. Filtration through a pad of Celite using EtOH and water and evaporation gave an amino acid. Analytically pure samples were obtained by recrystallization ($EtOH/H_2O$).

***(Z)*-3-Aminocyclohexanecarboxylic Acid (62).** PtO_2 (23 mg) was used: quantitative yield (0.286 g, 100%); mp 277.5–278 °C (lit.[34] mp 284 °C); ^1H NMR (D_2O, 500 MHz) δ 1.21–1.49 (m, 4 H), 1.91 (d, J = 15 Hz, 2 H), 2.02 (d, J = 12 Hz, 1 H), 2.18 (d, J = 12 Hz, 1 H), 2.27 (t, J = 13 Hz, 1 H), 3.19–3.28 (m, 1 H). Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.24; H, 9.04; N, 9.57.

***(E)*-3-Aminocyclohexanecarboxylic Acid (63).** Five percent Pd/C (34 mg) was used: quantitative yield (0.284 g, 99%); mp 292.5–294 °C (lit.[34] mp 290–291 °C); ^1H NMR (D_2O, 500 MHz) δ 1.48–1.59 (m, 2 H), 1.59–1.67 (m, 2 H), 1.67–1.74 (m, 1 H), 1.75–1.83 (m, 1 H), 1.86–1.95 (m, 1 H), 2.09–2.17 (m, 1 H), 2.56–.264 (m, 1 H), 3.48–3.55 (m, 1 H). Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.36; H, 9.00; N, 9.66.

(54) Rosen, T.; Lico, I. M.; Chu, T. W. *J. Org. Chem.* **1988**, *53*, 1580.

Reductive Lactonization of Strategically Methylated Quinone Propionic Acid Esters and Amides

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It has been shown that the reduction of quinone propionic acid esters or amides bearing three methyl groups in the so-called "trialkyl lock" positions (*o*-, β-, β-positions) is accompanied by spontaneous lactonization with the release of alcohol or amine, respectively. A new convenient method is reported for introducing the β,β-dimethylpropionic acid side chain onto an appropriate hydroquinone nucleus via alkylative cyclization in methanesulfonic acid. Oxidation of the resulting lactone gives the quinone propionic acid, which can be converted by normal techniques to the corresponding ester or amide derivative. Initial model studies were carried out on pentamethylated systems **6** and **7**. In order to make available quinones of varying redox potential or enhanced solubility in physiological media, methoxy- and amino-substituted quinones **10a**, **10b**, and **17a,b** were synthesized. Upon reduction under mild conditions ($Na_2S_2O_4$), all model esters or amides underwent reductive cyclization with loss of alcohol or amine. In the case of **7a** the intermediate hydroquinone **19** could be isolated and its conversion to **4** with ejection of diethylamine followed by NMR techniques.

Numerous studies have established the importance of the quinone/hydroquinone equilibrium in biological systems. Among examples of the possible practical utilization of such effects in the rational development of new drugs is recent work on bioreductive alkylating agents.[1] A striking example grew out of mechanistic studies on the mode of action of mitomycin C and related synthetic analogues from which emerged an attractive theory that the key step in the biological activity of such materials involves a reductive step which triggers generation of a potent alkylating species.[2] Although definite proof is lacking, the theory is sufficiently attractive to justify further examination. Thus, if a known cytotoxic agent could be bound in a benign or relatively nontoxic form to a quinone such that upon reduction under physiological conditions the material is released in an activated toxic form, a method for the site-specific delivery of an antitumor agent to diseased tissue bathed in a reducing atmosphere might be available. The currently difficult-to-treat solid tumors may represent such a case.[3]

With such long term goals in mind, in this paper we demonstrate the feasibility of the basic delivery concept on model systems. Subsequent papers will deal with specific applications to antitumor and other biological systems as well as purely chemical applications such as the development of new amino protecting groups.

The initial system chosen for evaluation was based on the unique discoveries of Cohen and co-workers[4] who es-

(1) Reviews: (a) Moore, H. W. *Science* **1977**, *197*, 527. (b) Czerniak, R. *Med. Res. Rev.* **1981**, *1*, 249. (c) Adams, G. E.; Stratford, I. J. *Biochem. Pharm.* **1986**, *35*, 71.

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

(3) Denny, W. A.; Wilson, W. R. *J. Med. Chem.* **1986**, *29*, 879.

(4) (a) Milstien, S.; Cohen, L. A. *J. Am. Chem. Soc.* **1972**, *94*, 9158. (b) Borchardt, R. T.; Cohen, L. A. *J. Am. Chem. Soc.* **1972**, *94*, 9175.

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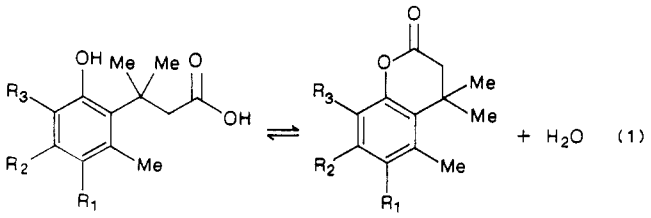
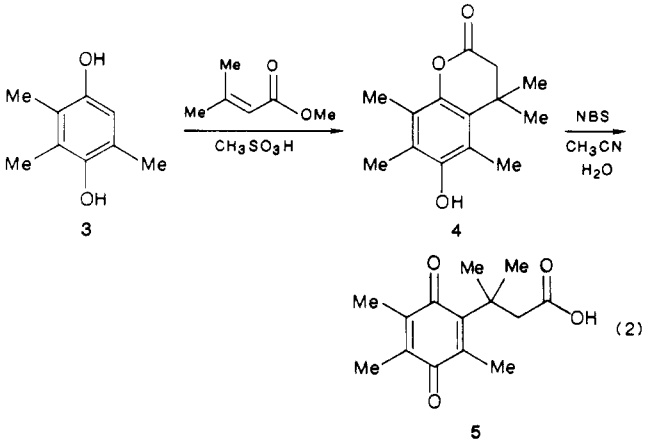
tablished the remarkable ease with which phenolic acids 1 undergo lactonization relative to analogues in which one or more of the methyl groups shown is lacking. Although



1 2 (1)

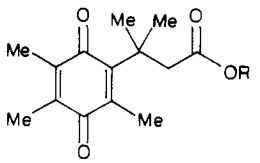
rate enhancements were numerically overstated[5] in the early work, this so-called "trialkyl lock" effect is clearly significant, and it is not unreasonable to suppose that esters or amides of 1 might also lactonize readily with consequent release of alcohol or amine.[6] If substituent R_1, which along with R_2 and R_3 does not influence the cyclization process, is made into a hydroxyl functon, system 1 becomes a hydroquinone and thus a partner in a redox equilibrium. As a vehicle for initial model studies we chose the known acid **5**, obtained essentially by the method of Cohen as outlined in eq 2.[4b] In our hands the



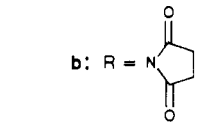
3 4 5 (2)

reported conditions for the first step which involved heating in benzene in the presence of sulfuric acid required a tedious workup procedure and resulted in poor yields (ca. 40%). Use of methanesulfonic acid as both solvent and catalyst simplified the isolation procedure and raised the yield to 88%. Oxidation of lactone **4** by means of NBS followed the earlier method (90%). Large quantities of **5** were thus available for further work. In order to establish general routes to esters and amides of **5** synthesis of the corresponding acid chloride was examined. Unfortunately, thionyl chloride led to intractable materials, and although oxalyl chloride gave a crude material which with methanol gave the desired ester **6a**, a pure acid chloride could not be isolated and reaction of the crude material with amines was generally unsatisfactory.

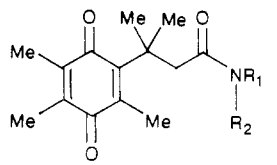
A stable acylating agent, the *N*-hydroxysuccinimide ester **6b**, was obtained via treatment of the acid and *N*-hydroxysuccinimide with dicyclohexylcarbodiimide (DCC)



6a, R = Me

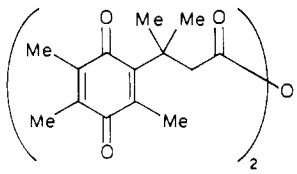


b: R = N



7a: $R_1 = R_2 = Et$
b: $R_1 = H$; $R_2 = n$-Bu
c: $R_1 = H$; $R_2 = Bn$
d: $R_1 = H$; $R_2 = p$-ClC_6H_4
e: $R_1 = R_2 = CH_2CH_2Cl$
f: $R_1 = R_2 = Me$

in THF.[7] This compound proved to be a convenient reagent for conversion to amides **7**. DCC[8] alone also allowed conversion of **5** to the more reactive symmetrical anhydride **8**, a generally useful acylating agent. By analogy



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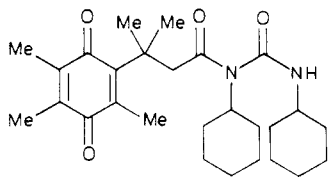

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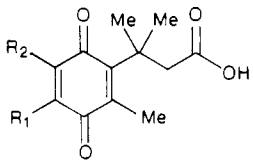
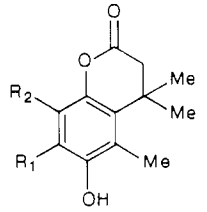
to peptide condensation reactions,[7,8] amide **7a** could be obtained directly from **5** and diethylamine in the presence of DCC although less reactive amines such as *p*-chloroaniline gave only urea **9** under these conditions.

Because of its accessibility most of the early work on model systems was carried out on the pentamethylated quinone acid **5**. On the other hand, related quinone acids substituted by electron-donating groups such as alkoxy or amino functions are likely to possess more appropriate redox potentials[9] and solubilities in physiological media. A number of such acids was synthesized. For the monomethoxylated acid **10a** and precursor lactone **11a**, quinone



10a: $R_1 = Me$; $R_2 = MeO$
b: $R_1 = R_2 = MeO$



11a: $R_1 = Me$; $R_2 = MeO$
b: $R_1 = R_2 = MeO$
c: $R_1 = Me$; $R_2 = MeNH$
d: $R_1 = Me$; $R_2 = MeNAc$

12a readily obtainable by the simple technique of Liotta,[10] appeared to be a convenient intermediate. Unfortunately, this quinone could not be methoxylated by standard methods.[11] Instead methoxyphenol **13**[12] was oxidized to **12b** by means of Fremy's salt[13] in 93% yield. The hydroquinone obtained upon reduction of **12b** was then converted to **11a** by the methanesulfonic acid modification

(5) (a) Danforth, C.; Nicholson, A. W.; James, J. C.; Loudon, G. M. *J. Am. Chem. Soc.* **1976**, *98*, 4275. (b) Winans, R. E.; Wilcox, C. F., Jr. *J. Am. Chem. Soc.* **1976**, *98*, 4281. (c) Caswell, M.; Schmir, G. L. *J. Am. Chem. Soc.* **1980**, *102*, 4815. (d) DeTar, D. F. *J. Am. Chem. Soc.* **1982**, *104*, 7205. (e) Hillery, P. S.; Cohen, L. A. *J. Org. Chem.* **1983**, *48*, 3465.

(6) For examples of the spontaneous lactonization of certain hydroxy esters and hydroxyamides, see: (a) Capon, B.; McDowell, S. T.; Raftery, W. V. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1118. (b) Bruice, T. C.; Marquardt, F. H. *J. Am. Chem. Soc.* **1962**, *84*, 365. (c) Zurn, L. *Justus Liebigs Ann. Chem.* **1960**, *631*, 56. Cain, B. F. *J. Org. Chem.* **1976**, *41*, 2029.

(7) Compare Bodanszky, M. *The Peptides: Analysis, Synthesis, Biology*; Gross, E., Meienhofer, J., Eds.; Academic Press: New York, 1979; Vol. 1, p 106.

(8) Rich, D. H.; Singh, J. *The Peptides: Analysis, Synthesis, Biology*; Gross, E., Meienhofer, J., Eds.; Academic Press: New York, 1979; Vol. 1, p 241.

(9) Lin, A. J.; Cosby, L. A.; Sartorelli, A. C. ACS Symposium Ser. No. 30, Cancer Chemotherapy, 1976, 71.

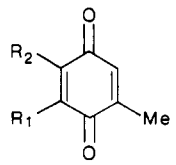
(10) Liotta, D.; Arbiser, J.; Short, J. W.; Saindane, M. *J. Org. Chem.* **1983**, *48*, 2932.

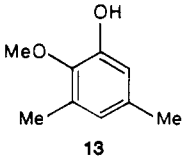
(11) Compare (a) Ashley, J. N. *J. Chem. Soc.* **1937**, 1471. (b) Singh, J. M.; Turner, A. B. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2294. (c) Singh, J. M.; Turner, A. B. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2556.

(12) Garofano, T.; Werber, G. *Ann. Chim. (Rome)* **1960**, *50*, 245.

(13) (a) Zimmer, H.; Lankin, D. C.; Horgan, S. W. *Chem. Rev.* **1971**, *71*, 229. (b) Moser, W.; Howie, R. A. *J. Chem. Soc. A* **1968**, 3039.

of Cohen's procedure. NBS oxidation provided **10a** (57%).

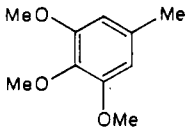




13

12a: R_1 = Me; R_2 = H
b: R_1 = Me; R_2 = MeO
c: R_1 = R_2 = MeO

For the dimethoxy acid **10b** the useful quinone intermediate **12c** is commercially available although costly. A simple route to **12c** was devised involving oxidation of triether **14**. Sodium borohydride reduction of **12c** was



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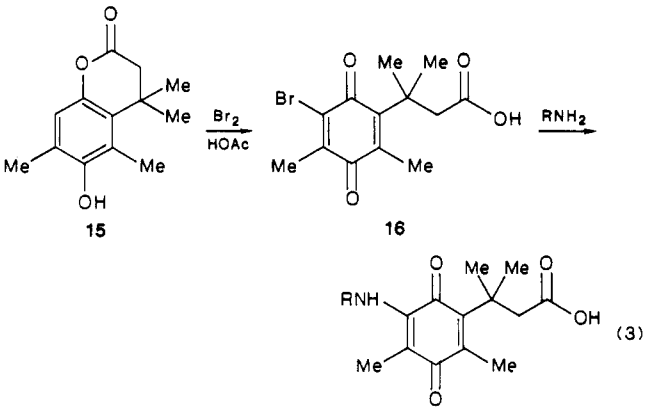
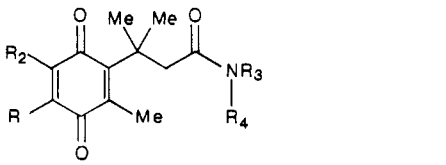
followed by standard lactonization and oxidation to give **10b** although in this case NBS was without effect and the stronger oxidant pyridinium dichromate[14] gave the best results (40%) among a large number of reagents examined.

Amino-substituted quinone acids **17** were obtained by bromide ion displacement on bromo acid **16**, which resulted from brominative oxidation of lactone **15**. Conversion of the various alkoxy- and amino-substituted quinone acids **10** and **17** to model amides **18** generally succeeded via the corresponding symmetric anhydrides, whether isolated or generated in situ by the DCC technique.



15 **16**

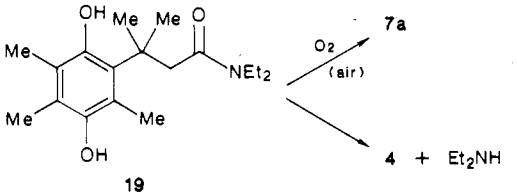
17a: R = Me
b: R = *n*-Pr



18a: R_1 = R_2 = MeO; R_3 = R_4 = Me
b: R_1 = Me; R_2 = MeO; R_3 = R_4 = CH_2CH_2Cl
c: R_1 = R_2 = MeO; R_3 = R_4 = CH_2CH_2Cl
d: R_1 = R_3 = R_4 = Me; R_2 = MeNH

Reductive Cyclization

Upon reduction under mild conditions ($Na_2S_2O_4$) all model esters or amides prepared from quinone acids **5**, **10**, and **17** underwent cyclization to the corresponding lactones. While in all cases the reduction step appeared to be instantaneous, cyclization of hydroquinone to lactone proceeded at varying rates. In the case of **7a** it was possible to isolate the colorless hydroquinone **19**, which in the presence of air was readily reoxidized to the precursor quinone amide **7a**. In solution, in the absence of air,



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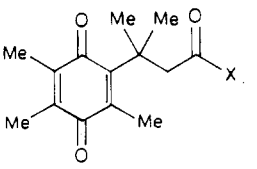
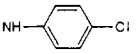
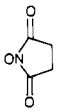
conversion to lactone **4** occurred by the expected neighboring group process. All lactones encountered in this work were stable toward isolation except those substituted with an amino function. Such amino lactones were so sensitive to air oxidation that attempted isolation gave only the corresponding quinone acids. In one case, that of **11c**, acetyl chloride selectively acylated the nitrogen atom and allowed isolation of the stable lactone amide **11d**.

In order to obtain a qualitative picture of the range of cyclization rates upon reductive ring closure, a series of esters and amides was examined by NMR techniques. In each case a solution of the quinone derivative in deuterated methanol was mixed with a solution of sodium dithionite in D_2O and the spectra recorded at regular intervals. Rates were easily determined by following the disappearance of hydroquinone signals and appearance of lactone peaks. The final spectrum was that of an equimolar mixture of lactone and amine or alcohol. Rough half-lives obtained in this way are collected in Table I for the pentamethyl derivatives. The *N,N*-dimethylamide **7f** was more reactive than the corresponding *N,N*-diethyl derivative with conversion to the lactone being complete after only 1 h in the former case. Reductive lactonization of the *N,N*-dimethyl amides derived from the dimethoxy and *N*-methylamino acids **10b** and **17a** was complete after 4.25 h and 15 min, respectively.

Table I. Half-Lives[a] for Reductive Cyclization of



X	$t_{1/2}$, min	X	$t_{1/2}$, min
OMe	<3		41
	<3	NEt_2	137
		$NHCH_2C_6H_5$	139
$NHCH_2CH_2CH_2CH_3$	36		

[a] Reactions were carried out in CD_3OD–D_2O in an NMR tube with $Na_2S_2O_4$ as reducing agent. See the Experimental Section for details.

Experimental Section

General. Melting points and boiling points were uncorrected. Infrared spectra were determined on Perkin-Elmer Model 237B, 1310, or 1420 spectrometers and ^1H NMR spectra on Perkin-Elmer R-12 (60 MHz) or R-32 (90 MHz) or Varian XL-200 (200 MHz) or XL-300 (300 MHz) instruments with Me_4Si as internal standard. All ^{13}C NMR spectra were recorded at 50 MHz on a Varian XL-200 and at 75 MHz on a Varian XL-300 spectrometer. Ultraviolet spectra were recorded on a Perkin-Elmer 202 in-

(14) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

strument with 1 cm path length cells and pure solvent as reference. Column flash chromatography was performed with use of silica gel 60 (Merck, mesh size 230–400). Alumina chromatography was performed with use of neutral alumina (Fisher, mesh size 80–200). Phosphate buffer (0.1 M, pH = 7.4) was prepared by addition of 200 mL of 0.2 M NaOH to 250 mL of 0.2 M NaH_2PO_4 and dilution of the resulting solution to 500 mL. Reaction vials of 3-mL capacity equipped with Teflon stirring vanes and Teflon-lined screw cap closures were obtained from Pierce Chemical Co.

6-Hydroxy-4,4,5,7,8-pentamethylhydrocoumarin (4). Methanesulfonic acid (10 mL) was heated to 70 °C in an oil bath, and 1.0 g (6.58 mmol) of hydroquinone **3** and 0.85 g (7.50 mmol) of methyl β,β-dimethylacrylate[15] were added together all at once with stirring. Stirring was continued at 70 °C for 90 min, and the reaction mixture was diluted to 125 mL with water and extracted with three 50-mL portions of ethyl acetate. The extracts were washed with water, saturated $NaHCO_3$, and NaCl solutions and dried ($MgSO_4$). Solvent removal with a rotary evaporator gave 1.36 g (88.3%) of the crude lactone as an off-white solid. Recrystallization from 30% $CHCl_3$ in hexane gave the pure lactone in 75% yield as a white powder, mp 183–6 °C (lit.[4b] mp 186–7 °C).

Methyl β,β,2,4,5-Pentamethyl-3,6-dioxo-1,4-cyclohexadiene-1-propanoate (6a). Quinone acid **5**[4b] (0.361 g) and 5 mL of oxalyl chloride were dissolved in 30 mL of benzene, and the solution was stirred at room temperature for 1 h and then evaporated with the aid of a vacuum pump (0.3 mm) without the application of heat. To the residue was added 15 mL of MeOH, the excess MeOH was evaporated, and the residue was chromatographed on silica gel with elution by 20% EtOAc in hexane to give 0.206 g (54%) of the methyl ester, bp 121 °C (0.4 mm) [lit.[4b] bp 125–7 °C (0.3 mm)]. The IR and NMR spectra were superimposable on corresponding spectral data obtained from a sample prepared according to the method of Cohen. In addition, because of possible structural ambiguities, confirmatory evidence for the simple quinone methyl ester structure was obtained from standard ADEPT and 2D heteronuclear correlation experiments[16] performed on a Varian XL-300 spectrometer.

***N*,*N*-Diethyl-β,β,2,4,5-pentamethyl-3,6-dioxo-1,4-cyclohexadiene-1-propanamide (7a). Method A.** Oxalyl chloride (4.8 mL) and quinone acid **5**[4b] (1.37 g) were dissolved in 50 mL of dry THF at 0 °C, and the solution was stirred at room temperature for 2 h. Excess oxalyl chloride was removed by evaporating the solution with the aid of a vacuum pump (0.3 mm) without the application of heat. The residue was taken up in 10 mL of dry THF, and the resulting solution was added, in one lot, to a solution of 5 mL of diethylamine in 25 mL of THF at 0 °C. The resulting solution was stirred at room temperature for 2 h, diluted with 150 mL of water, and extracted with ether (5 × 30 mL). The combined ether extracts were washed with 5% HCl and water, dried over $MgSO_4$, and evaporated to a yellow oil, which solidified on standing. Crystallization from hexane afforded 0.94 g (56%) of the amide: mp 68.5–70.5 °C; UV (EtOH) λ_{max} = 263 nm, ϵ = 14 600; IR (KBr) 1645 (C=O) and 1610 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.92–1.30 (m, 6 H, CH_2CH_3), 1.42 (s, 6 H, gem CH_3's), 1.91 (s, 6 H, 4- and 5-CH_3's), 2.11 (s, 3 H, 2-CH_3), 2.97 (s, 2 H, CH_2), 3.10–3.42 (m, 4 H, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.9, 12.4 and 14.2 (ring CH_3's), 13.0 and 14.2 (CH_2CH_3), 28.5 (gem CH_3's), 37.4 (Cβ), 40.1 and 42.1 (CH_2CH_3), 47.0 (Cα), 136.4, 138.7, 144.4 and 156.1 (C1, C2, C4, and C5), 171.3 (amide C=O), 188.4 and 192.1 (quinone C=O's). Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59. Found: C, 71.03; H, 9.01; N, 4.47.

Method B. A mixture of quinone ester **6b** (0.253 g, 0.73 mmol) and diethylamine (166 μL, 1.6 mmol), dissolved in 2 mL of benzene, was placed in a tightly capped Pierce vial and heated to 80 °C for 1 h. The solution was diluted with 20 mL of ether and washed with 10-mL portions of water, 5% HCl, and again with water. The resulting ether layer was dried over $MgSO_4$ and evaporated to a yellow solid, which was crystallized from hexane to afford 0.183 g (83%) of quinone amide, mp 70–71 °C. This sample was shown to be identical with that obtained via the oxalyl chloride method according to IR and ^1H NMR analyses.

Succinimidyl β,β,2,4,5-Pentamethyl-3,6-dioxo-1,4-cyclohexadiene-1-propanoate (6b). Dicyclohexylcarbodiimide (0.494 g, 2.23 mmol) was added to a solution of quinone acid **5**[4b] (0.494 g, 1.97 mmol) and *N*-hydroxysuccinimide (0.250 g, 2.17 mmol) in 15 mL of dry THF at 0 °C, and the mixture was stirred for 20 h. To remove dicyclohexylurea the solution was filtered, evaporated, treated with 5 mL of ethyl acetate, and filtered again. Evaporation of solvent and crystallization of the residue from ethyl acetate/hexane afforded 0.565 g (82%) of the active ester: mp 145 °C; UV (EtOH) λ_{max} = 260 nm, ϵ = 11 900; IR (KBr) 1800, 1780 (C=O), 1730 (C=O), 1640 (C=O), 1360, 1200, 1070, and 870 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55 (s, 6 H, gem CH_3's), 1.97 (s, 6 H, 4- and 5-CH_3's), 2.18 (s, 3 H, 2-CH_3), 2.28 (s, 4 H, succinimidyl CH_2's), 3.29 (s, 2 H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.8, 12.4 and 14.1 (ring CH_3's) 25.9 (succinimidyl CH_2's), 29.0 (gem CH_3's), 38.4 (Cβ), 43.9 (Cα), 138.6, 140.0, 142.6, and 149.6 (C1, C2, C4, and C5), 187.1 and 190.1 (C3 and C6). Anal. Calcd for $C_{18}H_{21}NO_6$: C, 62.24; H, 6.09; N, 4.03. Found: C, 62.39; H, 6.24; N, 4.03.

Reduction of Methyl β,β,2,4,5-Pentamethyl-3,6-dioxo-1,4-cyclohexadiene-1-propanoate (6a). Quinone methyl ester **6a** (0.56 g, 2.1 mmol) dissolved in 5 mL of ether was mixed with a solution of $Na_2S_2O_4$ (0.14 g, 8.0 mmol) dissolved in 1 mL of phosphate buffer (0.1 M, pH = 7.5). Upon addition of enough methanol (about 2 mL) to make the mixture homogeneous the yellow color of the quinone was completely discharged. The resulting solution was diluted with 25 mL of ether, the layers were separated, and the ether solution was washed with water. After the organic layer was dried over $MgSO_4$ and the solvent was evaporated, 0.10 g (20%) of the lactone **4** was obtained as a white solid, mp 186–187 °C. The identity of the lactone was confirmed by comparison of its IR and ^1H NMR spectral data with that of authentic material obtained by the method of Cohen.[4b]

***N*-(4-Chlorophenyl)-β,β,2,4,5-pentamethyl-3,6-dioxo-1,4-cyclohexadiene-1-propanamide (7d).** A solution of quinone ester **6b** (0.199 g, 0.573 mmol) and 4-chloroaniline (0.161 g, 1.26 mmol) in 2 mL of benzene was placed in a tightly capped Pierce vial and heated to 80 °C for 40 h. The vial was allowed to cool to room temperature, and the solution was diluted with 20 mL of ether. The ether solution was washed successively with 10-mL portions of 5% HCl and water and was dried over $MgSO_4$. Evaporation of the solvent followed by chromatography on silica gel (CH_2Cl_2 eluant) and crystallization from ethyl acetate/hexane afforded 0.131 g (64%) of quinone amide: mp 171–176 °C; UV (EtOH) λ_{max} = 245 nm; ϵ = 15 400; IR (KBr) 3280 (NH), 1650 (C=O), 1640 (C=O), and 1530 cm^{-1}; ^1H NMR δ 1.46 (s, 6 H, gem CH_3), 1.92 (s, 6 H, 4- and 5-CH_3), 2.13 (s, 3 H, 2-CH_3), 2.98 (s, 2 H, CH_2), 7.23–7.37 (m, 4 H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.3, 12.7 and 14.3 (vinyl CH_3's), 29.1 (gem CH_3's), 38.4 (Cβ), 50.4 (Cα), 121.4 (Ar), 129.5 (Ar), 136.5, 138.7, 143.4, and 152.8 (C1, C2, C4, and C5), 170.6 (amide C=O), 187.7, and 191.7 (quinone C=O). Anal. Calcd for $C_{20}H_{22}ClNO_3$: C, 66.76; H, 6.16; N, 3.89. Found: C, 66.56; H, 6.40; N, 3.88.

***N*-*n*-Butyl-β,β,2,4,5-pentamethyl-3,6-dioxo-1,4-cyclohexadiene-1-propanamide (7b).** Obtained as described for **7d** except that the reaction mixture was heated for only 1 h. The quinone amide was obtained in 73% yield: mp 117–119 °C; UV (EtOH) λ_{max} = 262 nm, ϵ = 15 100; IR (KBr) 3340 (NH) and 1630 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 0.80–1.00 (m, 3 H, CH_2CH_3), 1.10–1.60 (m, 4 H, CH_2CH_2), 1.40 (s, 6 H, gem CH_3), 1.97 (s, 6 H, 4- and 5-CH_3), 2.11 (s, 3 H, 2-CH_3), 2.27 (s, 2 H, CH_2), 3.00–3.25 (m, 2 H, NCH_2). Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59. Found: C, 70.76; H, 8.95; N, 4.75.

***N*-Benzyl-β,β,2,4,5-pentamethyl-3,6-dioxo-1,4-cyclohexadiene-1-propanamide (7c).** Obtained as described for **7b**. The quinone amide was obtained in 69% yield: mp 147–150 °C; UV (EtOH) λ_{max} = 262 nm, ϵ = 14 300; IR (KBr) 3320 (NH) and 1640 cm^{-1} (C=O); ^1H NMR ($CDCl_3$) δ 1.43 (s, 6 H, gem CH_3's), 1.92 (s, 6 H, 4- and 5-CH_3's), 2.13 (s, 3 H, 2-CH_3), 2.84 (s, 2 H, CH_2), 4.31 (d, J = 6 Hz, 2 H, benzyl CH_2), 7.26 (s, 5 H, Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.9, 12.5, and 13.9 (ring CH_3's), 28.6 (gem CH_3's), 37.8 (Cβ), 42.8 (benzyl CH_2), 48.4 (Cα), 130.1 and 131.4 (Ar), 140.2, 140.6, 145.5, and 154.9 (vinyl), 173.2 (amide C=O), 189.0 and 192.6 (quinone C=O's). Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.20; H, 7.47; N, 4.28.

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N,N-Diethyl-β,β,2,4,5-pentamethyl-3,6-dihydroxybenzene-1-propanamide (19). Quinone amide **7a** (31 mg, 0.10 mmol) and $Na_2S_2O_4$ (108 mg, 0.62 mmol) were dissolved in a mixture of 5 mL each of ether, THF, and phosphate buffer (0.1 M, pH = 7.4), and the resulting solution was stirred vigorously. The yellow color of the quinone was completely discharged within 3 min. The layers were separated, and the aqueous layer was washed quickly with ether (3 × 4 mL). The combined ether solutions were passed through a short column of $MgSO_4$ (1 × 8 cm) at 0 °C and collected in a two-necked round-bottomed flask under a constant stream of N_2. The flask containing the hydroquinone amide solution, under a N_2 atmosphere, was transferred to a N_2-purged glovebag in which all subsequent operations were performed. The ether solution was concentrated to about 3 mL under reduced pressure from a high-vacuum pump (no heat), and to the concentrate was added 10 mL of hexane with vigorous stirring. The resulting white precipitate was collected on a filter and transferred to a soft glass tube. The tube, with sample, was attached to the N_2 inlet hose, and the hose and tube assembly was removed from the glovebag. The sample was evacuated and maintained at low pressure for 1 h to remove any residual solvent and then was sealed under 1 atm of N_2. A sample for melting point determination was collected separately in a capillary tube by the same technique: mp 185–186 °C (sealed tube); ^1H NMR (90 MHz, $CDCl_3$) δ 1.08 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.16 (t, J = 7 Hz, 3 H, CH_2CH_3), 1.64 (s, 3 H, gem CH_3's), 2.15 (s, 3 H, ring CH_3), 2.22 (s, 3 H, ring CH_3), 2.33 (s, 3 H, ring CH_3), 2.92 (s, 2 H, CH_2), 2.32 (q, J = 7 Hz, 4 H, CH_2CH_3). Due to its sensitivity a completely pure sample was not obtained. Anal. Calcd for $C_{18}H_{29}NO_3$: C, 70.32; H, 9.51; N, 4.56. Found: C, 69.66; H, 9.33; N, 4.15.

N,N-Bis(2-chloroethyl)-β,β,2,4,5-pentamethyl-3,6-dioxo-1,4-cyclohexadiene-1-propanamide (7e). Quinone acid **5**[4b] (1.02 g, 4.1 mmol) was dissolved in 5 mL of CH_2Cl_2 at 0 °C, dicyclohexylcarbodiimide (0.428 g, 2.0 mmol) was added, and the solution was stored at −5 °C for 4 h. After allowing the solution to warm to room temperature, bis(2-chloroethyl)amine hydrochloride (0.364 g, 2.0 mmol) and triethyl amine (0.60 mL, 4.3 mmol), freshly distilled from CaH_2, were added. The mixture was stirred at room temperature for 12 h and then chromatographed on 50 g of adsorption alumina with 15% ethyl acetate/hexane as eluant. The first yellow component was collected. Crystallization from hexane afforded 0.235 g (31%) of the quinone amide: mp 122.5–123.5 °C; IR (KBr) 1650 (C=O) and 1620 cm^{-1}; UV (EtOH) λ_{max} = 263 nm, ε = 16 200; ^1H NMR ($CDCl_3$) δ 1.43 (s, 6 H, gem CH_3's), 1.90 (b s, 6 H, 4- and 5-CH_3), 2.13 (s, 3 H, 2-CH_3), 3.06 (s, 2 H, CH_2), 3.58 (b s, 4 H, NCH_2's), 3.70 (b s, 4 H, $ClCH_2$'s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.2, 12.6, and 14.4 (ring CH_3's), 28.9 (gem CH_3's), 38.3 (Cβ), 41.6, 41.9, 47.8, 49.6, 51.3, 138.1 (vinyl), 139.7 (vinyl), 144.1 (vinyl), 155.6 (vinyl), 174.5 (amide C=O), 189.5, and 193.2 (quinone C=O). Anal. Calcd for $C_{18}H_{25}Cl_2NO_3$: C, 57.76; H, 6.73; N, 3.74. Found: C, 58.07; H, 6.99; N, 4.15.

Acylurea 9 via Reaction of Quinone Acid 5 with p-Chloroaniline in the Presence of Dicyclohexylcarbodiimide. Dicyclohexylcarbodiimide (0.13 g, 0.64 mmol) was added to a solution of quinone acid **5**[4b] (0.11 g, 0.44 mmol) and 4-chloroaniline (0.06 g, 0.50 mmol) in 30 mL of ether at 0 °C. After being stirred at 0 °C for 20 h the reaction mixture was filtered, and the filtrate was evaporated and chromatographed on silica gel (40% EtOAc/hexane). The crude product was crystallized from EtOAc/hexane to give 0.07 g (34%) of the *N*-acylurea **9**: mp 144–145 °C; IR (KBr) 3330 cm^{-1} (NH), 1680 (C=O), 1645 (C=O); ^1H NMR ($CDCl_3$) δ 1.10–2.10 (m, 22 H, cyclohexyl), 1.41 (s, 6 H, gem CH_3), 1.91 (s, 6 H, 4- and 5-CH_3), 2.11 (s, 3 H, 2-CH_3), 3.06 (s, 2 H, CH_2). Anal. Calcd for $C_{27}H_{40}N_2O_4$: C, 71.02; H, 8.83; N, 6.13. Found: C, 70.93; H, 9.05; N, 6.15.

2-Methoxy-3,5-dimethyl-2,5-cyclohexadiene-1,4-dione (12b) and 2-Methoxy-3,5-dimethyl-1,4-benzenediol. 2-Methoxy-3,5-dimethylphenol[12] (**13**) (4.86 g, 0.032 mol) was dissolved in 97 mL of methanol, and the solution was placed in a 2000-mL Erlenmeyer flask. An oxidizing solution was prepared from 25.7 g (0.096 mol) of potassium nitrosodisulfinate (Fremy's salt),[13] 320 mL of 0.5 M KH_2PO_4 and 1285 mL of water. The oxidizing solution was poured into the phenol solution, and the resulting dark purple solution was stirred at room temperature for 2 h. The mixture was extracted with four 250-mL portions of ether, and the combined ether extracts were washed with two 300-mL portions of water and dried over $MgSO_4$. Rotary evaporation gave 4.9 g (92.4%) of the crude quinone, **12b**, as a yellow-orange solid. Recrystallization from Skelly F gave the pure quinone as long yellow needles [mp 58–60 °C (lit.[17] mp 59 °C); ^1H NMR ($CDCl_3$) δ 1.93 (s, 3 H, CH_3), 2.05 (d, J = 1.7 Hz, 3 H, CH_3), 4.01 (s, 3 H, OCH_3), 6.45 (q, J = 1.7 Hz, 1 H, CH)], which was reduced according to the method of Karrer and Durr[17] to the corresponding hydroquinone: mp 101–102 °C (lit.[17] mp 101 °C); ^1H NMR ($CDCl_3$) δ 2.15 (s, 3 H, CH_3), 2.18 (s, 3 H, CH_3), 3.75 (s, 3 H, OCH_3), 4.42 (s, 1 H, OH), 5.35 (s, 1 H, OH), 6.62 (s, 1 H, aryl).

6-Hydroxy-8-methoxy-4,4,5,7-tetramethylhydrocoumarin (11a). Methanesulfonic acid (65 mL) was heated to 70 °C in an oil bath and 2-methoxy-3,5-dimethyl-1,4-benzenediol (7.10 g, 0.0423 mol) and methyl β,β-dimethylacrylate (5.70 g, 0.050 mol) were added all at once with stirring. Stirring was continued at 70 °C for 2.5 h, and the mixture was diluted to 400 mL with water and extracted with ether (4 × 100 mL). The combined ether extracts were washed with 100 mL of water, three 100-mL portions of saturated $NaHCO_3$, and 100 mL of saturated NaCl and dried ($MgSO_4$). Removal of solvent with a rotary evaporator afforded a red-brown oil, which was dissolved in 5 mL of 5% ethyl acetate in methylene chloride and flushed through a pad of silica gel (4 in. × 2 in.) using more solvent. A dark impurity was removed by the treatment with silica, and solvent removal from the collected eluent (275 mL) provided a tan solid, which was recrystallized from 30% chloroform in Skelly B to afford 6.51 g (61.5%) of the pure lactone as a white solid: mp 128–129 °C; IR (KBr) 3390 (OH), 1730 (C=O), and 1065 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (s, 6 H, gem CH_3), 2.13 (s, 3 H, 7-CH_3), 2.29 (s, 3 H, 5-CH_3), 2.52 (s, 2 H, CH_2), 3.75 (s, 3 H, OCH_3), 4.61 (s, 1 H, OH). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.17; H, 7.26. Found: C, 67.19; H, 7.08.

5-Methoxy-β,β,2,4-tetramethyl-3,6-dioxo-1,4-cyclohexadiene-1-propanoic Acid (10a). Lactone **11a** (2.27 g, 9.08 mmol) was suspended in 110 mL of 15% aqueous acetonitrile, and a solution of *N*-bromosuccinimide (2.19 g, 12.3 mmol) in 35 mL of 40% aqueous acetonitrile was added dropwise with stirring over a period of 1 h. After the addition was complete, the reaction mixture was stirred for an additional 30 min, diluted to 400 mL with water, and extracted with ether (3 × 75 mL). The combined ether extracts were washed with water (2 × 100 mL) and dried over $MgSO_4$. Removal of solvent with a rotary evaporator afforded an orange oil, which was chromatographed on a silica gel column (6 in. × 2 in.) using as eluant methylene chloride/ethyl acetate/acetic acid (20:1:1). The major yellow fraction was collected, washed with water (3 × 100 mL) to remove HOAc, and dried over $MgSO_4$. Solvent removal with a rotary evaporator provided a granular yellow solid, which was recrystallized from 10% chloroform in Skelly B to afford 1.38 g (57.0%) of the pure quinone acid as small yellow needles: mp 111–112 °C; IR (KBr) 3100 (OH), 1710 (acid C=O), and 1640 cm^{-1} (quinone C=O); ^1H NMR ($CDCl_3$) δ 1.43 (s, 6 H, gem CH_3), 1.83 (s, 3 H, 4-CH_3), 2.12 (s, 3 H, 2-CH_3), 3.01 (s, 2 H, CH_2), 3.83 (s, 3 H, OCH_3), 10.95 (b s, 1 H, OH). Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.13; H, 6.83. Found: C, 63.38; H, 6.83.

2,3-Dimethoxy-5-methyl-2,5-cyclohexadiene-1,4-dione (12c). Method A. According to the method of Morimoto et al.,[19] trimethoxytoluene (**14**)[18] (4.30 g, 0.025 mol), 30% H_2O_2 (8.6 mL, 0.084 mol), acetic acid (21.5 mL), and 10% H_2SO_4 (2.8 mL) were stirred at room temperature with exclusion of light for 43.5 h. The red reaction mixture was diluted with 100 mL of water and extracted with chloroform (4 × 50 mL). The combined chloroform extracts were washed with 100 mL of water, 100 mL of 5% $NaHCO_3$, and 100 mL of saturated NaCl and dried over $MgSO_4$. Solvent removal with a rotary evaporator afforded a dark red oil, which was chromatographed on a silica gel column (15 in. × 1 in., 30% ethyl acetate in hexane) to provide 1.49 g (32.7%) of the quinone as a red solid. Recrystallization from Skelly B afforded the pure quinone as an orange-red solid: mp 55–57 °C (lit.[19] mp 59 °C); IR (KBr) 1650 (quinone C=O) and 1275 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.60 (d, J = 1.5 Hz, 3 H, CH_3), 3.95 (s, 3 H, OCH_3), 3.98 (s, 3

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H, OCH_3), 6.40 (q, J = 1.5 Hz, 1 H, CH).

Method B. Also according to the method of Morimoto et al.,[19] trimethoxytoluene (14)[18] (43.46 g, 0.239 mol), 30% H_2O_2 (48.4 mL, 0.472 mol), and 240 mL of HOAc were stirred at room temperature with exclusion of light for 8 days. The reaction mixture was diluted to 1500 mL with water and extracted with ether (4 × 300 mL). The combined ether extracts were washed with saturated $NaHCO_3$ (5 × 250 mL) and dried over $MgSO_4$. Solvent removal with a rotary evaporator afforded an oily red solid, which was chromatographed as in method A to provide the pure quinone as a red solid (20.59 g, 47.0%), which was used directly for reduction to the hydroquinone.

2,3-Dimethoxy-5-methyl-1,4-benzenediol. Sodium borohydride (10.4 g, 0.275 mol) was dissolved in 300 mL of water, and a solution of quinone **12c** (10.0 g, 0.0549 mol) in a mixture of 150 mL of ether and 75 mL of methanol was added at room temperature with stirring. After stirring for 15 min, the mixture was placed in a separatory funnel, and the layers were allowed to separate. The ether phase was removed, and the aqueous phase was extracted twice with 100-mL portions of ether. The combined ether extracts were washed with 250 mL of saturated NaCl and dried over $MgSO_4$. Solvent removal with a rotary evaporator afforded 9.30 g (92.1%) of the hydroquinone as a white solid. The crude solid was used directly in the preparation of **11b**: ^{1}H NMR ($CDCl_3$) δ 2.13 (s, 3 H, $ArCH_3$), 3.83 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 5.20 (s, 1 H, OH), 5.32 (s, 1 H, OH), 6.45 (s, 1 H, ArH).

6-Hydroxy-7,8-dimethoxy-4,4,5-trimethylhydrocoumarin (11b). Method A. 2,3-Dimethoxy-5-methyl-1,4-benzenediol (9.17 g, 0.0498 mol), methyl β,β-dimethylacrylate (5.93 g, 0.052 mol), and methanesulfonic acid (110 mL) were heated at 70 °C in an oil bath with stirring for 90 min. The mixture was diluted to 800 mL with water and extracted with ether (3 × 150 mL). The combined ether extracts were washed with 500 mL of water, saturated $NaHCO_3$ (3 × 150 mL), and 400 mL of saturated NaCl and dried over $MgSO_4$. Removal of solvent with a rotary evaporator afforded a tan solid, which was recrystallized from methanol to provide the pure lactone as a white solid (9.44 g, 71.2%): mp 160.5–162 °C; IR (KBr) 3320 (OH), 1740 (C=O), and 1070 cm^{-1} (C—O); ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 6 H, gem CH_3), 2.33 (s, 3 H, CH_3), 2.57 (s, 2 H, CH_2), 3.91 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3), 5.97 (s, 1 H, OH). Anal. Calcd for $C_{14}H_{18}O_5$: C, 63.15; H, 6.82. Found: C, 62.96; H, 6.78.

Method B. Quinone amide **18a** (150 mg, 0.485 mmol) was dissolved in a mixture of 3 mL of ether and 3 mL of methanol, and a solution of sodium dithionite (340 mg, 1.94 mmol) in 8 mL of water was added at room temperature with stirring. The course of the reaction was followed by TLC, and after 4.25 h the starting material had been completely consumed. The mixture was diluted to 40 mL with water and extracted with ether (3 × 20 mL). The combined ether extracts were washed with 25 mL of saturated NaCl and dried over $MgSO_4$, and solvent removal afforded a white solid. Recrystallization from methanol afforded the pure lactone as white granules (107 mg, 77.0%): mp 160.5–161.5 °C. Spectral data were identical with those obtained in method A.

4,5-Dimethoxy-β,β,2-trimethyl-3,6-dioxo-1,4-cyclohexadiene-1-propanoic Acid (10b). Lactone **11b** (500 mg, 1.88 mmol) in 2 mL of DMF was added to a stirred solution of pyridinium dichromate[14] (3.17 g, 8.46 mmol) in 7 mL of DMF at room temperature, and stirring was continued for 4 h. The mixture was diluted to 400 mL with water and extracted with ether (4 × 25 mL). The combined ether extracts were washed with 30 mL of water followed by saturated $NaHCO_3$ (4 × 25 mL). The combined bicarbonate washes were made just acidic by the slow addition of 30% HCl, and the resulting aqueous solution was extracted with ether (3 × 25 mL). The combined organic extracts were washed with 30 mL of saturated NaCl and dried over $MgSO_4$. Solvent removal with the aid of a rotary evaporator provided an orange oil that was chromatographed on a silica gel column (6 in. × $^1/_2$ in.) using as eluant hexane/ethyl acetate/acetic acid (16:4:1). Concentration of the major yellow-orange fraction afforded an oil, which was taken up in 20 mL of methylene chloride and washed with water (2 × 25 mL) to remove HOAc. After drying with $MgSO_4$, solvent removal with the aid of a rotary evaporator provided the quinone acid as an orange oil (210 mg, 40.4%). Although TLC showed only one spot a solid could not be obtained, and the oil was used directly for ester and amide formation: ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 6 H, gem CH_3), 2.18 (s, 3 H, CH_3), 2.98 (s, 2 H, CH_2), 3.88 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 8.05 (b s, 1 H, OH). The acid was characterized as the **4-nitrobenzyl ester**: mp 92–93 °C; IR (KBr) 1730 (ester C=O) and 1665 cm^{-1} (quinone C=O); UV (EtOH) λ_{max} = 273 nm, ϵ = 36460; ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 6 H, gem CH_3), 2.17 (s, 3 H, CH_3), 3.13 (s, 2 H, CH_2), 3.86 (s, 3 H, OCH_3), 3.98 (s, 3 H, OCH_3), 5.17 (s, 2 H, OCH_2), 7.48 (d, J = 8 Hz, 2 H, ArH), 8.25 (d, J = 8 Hz, 2 H, ArH). Anal. Calcd for $C_{21}H_{23}NO_8$: C, 60.42; H, 5.55; N, 3.36. Found: C, 60.60; H, 5.53; N, 3.42.

2,6-Dimethyl-2,5-cyclohexadiene-1,4-dione (12a). According to the method of Liotta,[10] 2,6-dimethylphenol (60.0 g, 0.490 mol) was dissolved in 700 mL of ether, and this solution was placed in a 3-L three-neck round-bottom flask equipped with a mechanical stirrer and addition funnel. The Jones reagent[20] was prepared from $Na_2Cr_2O_7$·$2H_2O$ (330 g, 1.108 mol), H_2O (470 mL), and concentrated H_2SO_4 (210 mL), and the solution was poured into the addition funnel. The flask was immersed in an ice bath, and the oxidant was added dropwise with stirring over a period of 4.5 h. When the addition was complete, the ice bath was removed and stirring was continued at room temperature for 46 h. The dark reaction mixture was diluted to 2700 mL with water and divided into three equal portions. Each portion was placed in a separatory funnel, and the ether layers were separated. The aqueous phases were each extracted twice more with 200-mL portions of ether. The combined ether extracts were concentrated to 700 mL with a rotary evaporator, washed with water (3 × 200 mL), and dried over $MgSO_4$. Solvent removal with a rotary evaporator afforded 50.72 g (76.4%) of a yellow solid, which was heated with 400 mL of Skelly F. The yellow solution was decanted from the residue, and this process was repeated with three additional 400-mL portions of solvent. The combined Skelly F decantates were concentrated to 700 mL, decolorizing charcoal was added, and the mixture was filtered and cooled. Suction filtration provided 36.98 g (55.5%) of the bright yellow quinone: mp 70–72 °C (lit.[21] mp 72–73 °C); ^{1}H NMR ($CDCl_3$) δ 2.10 (s, 6 H, 2 CH_3), 6.60 (b s, 2 H, 2 CH).

2,6-Dimethyl-1,4-benzenediol. Sodium dithionite (78.7 g, 0.452 mol) was dissolved in 550 mL of water, and a solution of dimethylquinone **12a**, (15.40 g, 0.113 mol) in a mixture of 250 mL of ether and 150 mL of methanol was added at room temperature with stirring. After stirring for 15 min, the mixture was placed in a separatory funnel, and the layers were allowed to separate. The ether phase was removed, and the aqueous phase was extracted twice with 200-mL portions of ether. The combined ether extracts were washed with 200 mL of water and 200 mL of saturated NaCl and dried over $MgSO_4$. Solvent removal with a rotary evaporator provided 14.24 g (91.3%) of the hydroquinone as a tan solid. The crude material was recrystallized from hexane/chloroform (3:2) to afford the pure hydroquinone as a white solid: mp 145–148 °C [lit.[22] mp 148–149 °C]; ^{1}H NMR ($CDCl_3$/DMSO-d_6) δ 2.10 (s, 6 H, 2 CH_3), 6.37 (s, 2 H, ArH), 6.92 (s, 1 H, OH), 8.13 (s, 1 H, OH).

6-Hydroxy-4,4,5,7-tetramethylhydrocoumarin (15). A solution of 1 g (7.0 mmol) of 2,6-dimethyl-1,4-benzenediol and 0.84 g (7.5 mmol) of methyl β,β-dimethylacrylate in 10 mL of methanesulfonic acid was heated at 70 °C in an oil bath with stirring for 2 h. The mixture was diluted to 100 mL with water and extracted with three 25-mL portions of ethyl acetate. The extracts were washed with 50 mL of water, two 50-mL portions of saturated $NaHCO_3$ solution, and 50 mL of saturated NaCl solution and dried over $MgSO_4$. Removal of solvent with a rotary evaporator gave a tan solid, which was recrystallized from 40% $CHCl_3$ in hexane to give 1.23 g (76.9%) of the lactone as a white solid: mp 143–144 °C (lit.[23] mp 141–142 °C); ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 6 H, gem CH_3), 2.20 (s, 3 H, 7-CH_3), 2.35 (s, 3 H, 5-CH_3), 2.55 (s, 2 H, CH_2), 4.53 (s, 1 H, OH), 6.70 (s, 1 H, aryl).

5-Bromo-β,β,2,4-tetramethyl-3,6-dioxo-1,4-cyclohexadiene-1-propanoic Acid (16). Lactone **15** (4.0 g, 0.0182

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mol) was dissolved in 150 mL of HOAc, and with stirring at room temperature a solution of bromine (6.4 g, 0.040 mol) in 24 mL of HOAc was added slowly. After the addition was complete, the reaction mixture was stirred for 6.5 h. The resulting mixture was diluted to 850 mL with water and extracted with methylene chloride (3 × 100 mL). The combined organic extracts were washed with 200 mL of water followed by saturated $NaHCO_3$ (5 × 150 mL). The combined bicarbonate washes were made just acidic by slow addition of 30% HCl, and the resulting aqueous solution was extracted with methylene chloride (3 × 100 mL). The combined organic extracts were washed with 200 mL of water and dried over $MgSO_4$. Solvent removal with the aid of a rotary evaporator provided a yellow oil (3.60 g, 62.8%). Despite numerous purification attempts by crystallization, column chromatography, and preparative thin-layer chromatography, a clean solid sample could not be obtained. Therefore, the crude oil was used directly in amination reactions: ^1H NMR ($CDCl_3$) δ 1.45 (s, 6 H, gem CH_3), 2.15 (s, 3 H, CH_3), 2.18 (s, 3 H, CH_3), 3.03 (s, 2 H, CH_2), 10.68 (b s, 1 H, OH).

β,β,2,4-Tetramethyl-5-(*N*-methylamino)-3,6-dioxo-1,4-cyclohexadiene-1-propanoic Acid (17a). Bromo acid **16** (1.88 g, 5.97 mmol) was dissolved in 50 mL of methanol, and 40% aqueous methylamine (1.65 g, 20.90 mmol) was added with stirring at room temperature. The flask was tightly stoppered, and stirring was continued for 46 h. The mixture was diluted to 700 mL with water, 50 mL of 5% HCl was added, and the resulting solution was extracted with ethyl acetate (3 × 150 mL). The combined organic extracts were washed with 300 mL of saturated NaCl and dried over $MgSO_4$. Solvent removal with the aid of a rotary evaporator afforded a deep red-purple oil, which was chromatographed on a silica gel column (10 in. × 1 in.) using as eluant Skelly B/ethyl acetate/acetic acid (14:6:1). Concentration of the major red-purple fraction afforded an oil, which was taken up in 100 mL of methylene chloride and washed with water (2 × 300 mL) to remove HOAc. After drying with $MgSO_4$, solvent removal with the aid of a rotary evaporator provided the aminoquinone acid as a purple oil (0.89 g, 56.3%). The crude oil was used directly in the preparation of amide derivatives: ^1H NMR ($CDCl_3$) δ 1.43 (s, 6 H, gem CH_3), 2.02 (s, 3 H, 4-CH_3), 2.15 (s, 3 H, 2-CH_3), 2.93 (s, 2 H, CH_2), 3.05 (s, 3 H, NCH_3), 7.40 (b s, 1 H, NH).

β,β,2,4-Tetramethyl-3,6-dioxo-5-(*N*-*n*-propylamino)-1,4-cyclohexadiene-1-propanoic Acid (17b). Bromo acid **16** (2.60 g, 8.26 mmol) was treated with propylamine (2.44 g, 41.30 mmol) as described above for the corresponding reaction with methylamine. The aminoquinone acid was obtained as small purple needles: mp 111.5–113.5 °C; IR (KBr) 3310 (NH), 2950 (OH), 1700 (acid C=O), and 1630 cm^{-1} (quinone C=O); ^1H NMR ($CDCl_3$) δ 0.93 (t, 3 H, propyl CH_3), 1.45 (s, 6 H, gem CH_3), 1.57 (m, 2 H, $CH_2CH_2CH_3$), 2.02 (s, 3 H, 4-CH_3), 2.20 (s, 3 H, 2-CH_3), 2.96 (s, 2 H, CH_2), 3.37 (t, 2 H, NCH_2). Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.78. Found: C, 65.53; H, 7.78; N, 4.98.

***N*,*N*-Bis(2-chloroethyl)-5-methoxy-β,β,2,4-tetramethyl-3,6-dioxo-1,4-cyclohexadiene-1-propanamide (18b).** Methoxyquinone acid **10a** (2.20 g, 8.27 mmol) was dissolved in 20 mL of methylene chloride, and the solution was cooled to 0 °C in an ice bath. *N*,*N*′-dicyclohexylcarbodiimide (854 mg, 4.14 mmol) was added, and stirring was continued for 2–3 min before the flask was stoppered and placed in a freezer at −20 °C for 4 h. The mixture was allowed to warm to room temperature, and *N*,*N*-bis(2-chloroethyl)amine hydrochloride (739 mg, 4.14 mol) and triethylamine (1.15 mL, 8.27 mmol) were added all at once. Stirring was continued for 7 h at room temperature, and the solution was concentrated to 2–3 mL with a rotary evaporator. The resulting slurry was chromatographed on an alumina column (9 in. × 1 $^1/_2$ in., 20% ethyl acetate in hexane) to provide the quinone amide as an oily yellow solid (1.37 g, 85.1%). Recrystallization from hexane afforded the pure amide as a powdery yellow solid: mp 89–90 °C; IR (KBr) 1640 cm^{-1} (C=O); UV (EtOH) λ_{max} = 280 nm, ϵ = 11 157; ^1H NMR ($CDCl_3$) δ 1.46 (s, 6 H, gem CH_3), 1.88 (s, 3 H, 4-CH_3), 2.16 (s, 3 H, 2-CH_3), 3.14 (s, 2 H, CH_2), 3.62–3.81 (m, 8 H, 4 CH_2), 3.83 (s, 3 H, OCH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 8.6 and 14.3 (ring CH_3), 28.6 (gem CH_3), 37.7 (Cβ), 41.4, 41.6, 46.9, 48.8 and 50.7 (5 CH_2), 59.3 (OCH_3), 124.6, 136.8, 151.4, and 157.8 (vinyl), 172.8 (amide C=O), 186.1, and 188.1 (quinone C=O). Anal. Calcd for $C_{18}H_{25}Cl_2NO_4$: C, 55.39; H, 6.46; N, 3.59. Found: C, 55.33; H, 6.50; N, 3.52.

***N*,*N*-Bis(2-chloroethyl)-4,5-dimethoxy-β,β,2-trimethyl-3,6-dioxo-1,4-cyclohexadiene-1-propanamide (18c).** Dimethoxy acid **10b** (1.056 g, 3.75 mmol), *N*,*N*′-dicyclohexylcarbodiimide (0.388 g, 1.88 mmol), *N*,*N*-bis(2-chloroethyl)amine hydrochloride (0.336 g, 1.88 mmol), and triethylamine (0.52 mL, 3.76 mmol) were treated as described above for the corresponding monomethoxy derivative. The quinone amide was obtained as a yellow solid (0.41 g, 53.9%). Recrystallization from hexane afforded the pure amide as a powdery yellow solid: mp 85–87 °C; IR (KBr) 1665 and 1630 cm^{-1} (C=O); UV (EtOH) λ_{max} = 283 nm, ϵ = 20 690; ^1H NMR ($CDCl_3$) δ 1.45 (s, 6 H, gem CH_3), 2.16 (s, 3 H, CH_3), 3.12 (s, 2 H, CH_2), 3.63–3.78 (m, 8 H, 4-CH_2), 3.88 (s, 3 H, OCH_3), 4.01 (s, 3 H, OCH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.1 (ring CH_3), 29.1 (gem CH_3), 38.3 (Cβ), 41.9, 42.2, 48.1, 49.6, and 51.8 (5-CH_2), 62.0 and 62.1 (OCH_3), 136.2, 143.0, 146.5, and 152.9 (vinyl), 173.8 (amide C=O), 187.7, and 191.3 (quinone C=O). Anal. Calcd for $C_{18}H_{25}Cl_2NO_5$: C, 53.21; H, 6.20; N, 3.45. Found: C, 53.41; H, 6.04; N, 3.48.

β,β,2,4,5-Pentamethyl-3,6-dioxo-1,4-cyclohexadiene-1-propanoic Anhydride (8). Quinone acid **5**[4b] (5.87 g, 0.0235 mol) was dissolved in 100 mL of methylene chloride, and the solution was cooled to 0 °C in an ice bath. *N*,*N*′-Dicyclohexylcarbodiimide (2.43 g, 0.0118 mol) was added, and stirring was continued for 2–3 min before the flask was stoppered and placed in a freezer at −20 °C for 17 h. The mixture was allowed to warm to room temperature and was filtered by suction to remove 1,3-dicyclohexylurea. Removal of solvent from the filtrate afforded the crude anhydride, which was recrystallized from hexane to provide the pure quinone anhydride as yellow needles (4.19 g, 73.6%): mp 116.5–117.5 °C; IR (KBr) 1755, 1655 (C=O), and 1125 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (s, 6 H, gem CH_3), 1.95 (s, 6 H, 4- and 5-CH_3), 2.16 (s, 3 H, 2-CH_3), 3.06 (s, 2 H, CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.3, 12.8 and 14.6 (ring CH_3), 25.0 (gem CH_3), 38.2 (Cβ), 49.0 (CH_2), 138.7, 139.6, 142.1, and 150.8 (vinyl), 167.9 (anhydride C=O), 187.3, and 190.7 (quinone C=O). Anal. Calcd for $C_{28}H_{34}O_7$: C, 69.69; H, 7.10. Found: C, 69.49; H, 7.04.

***N*,*N*-Dimethyl-4,5-dimethoxy-β,β,2-trimethyl-3,6-dioxo-1,4-cyclohexadiene-1-propanamide (18a).** Dimethoxyquinone acid **10b** (920 mg, 3.26 mmol) was dissolved in 20 mL of methylene chloride, and the solution was cooled to 0 °C in an ice bath. *N*,*N*′-Dicyclohexylcarbodiimide (340 mg, 1.63 mmol) was added, and stirring was continued for 2–3 min before the flask was stoppered and placed in a freezer at −20 °C for 17 h. The mixture was allowed to warm to room temperature, and dimethylamine was bubbled through with stirring for 1 h. Removal of solvent with a rotary evaporator afforded an orange slurry, which was chromatographed on a silica gel column (8 in. × 1 in.) using as eluate hexane/ethyl acetate/acetic acid (14:6:1). Quinone acid **10b** eluted first followed by a second orange fraction, which was concentrated to afforded an oil. The oil was dissolved in 30 mL of hot 20% ethyl acetate in hexane, and the solution was placed in a freezer at −20 °C for 2 days. Subsequent filtration provided the quinone amide as an orange solid, which was recrystallized from 25% ethyl acetate in hexane to afford the pure amide as fine orange needles (295 mg, 61.3%): mp 95.5–96 °C; IR (KBr) 1660–1620 cm^{-1} (C=O); UV (EtOH) λ_{max} = 284 nm, ϵ = 12 629; ^1H NMR ($CDCl_3$) δ 1.42 (s, 6 H, gem CH_3), 2.10 (s, 3 H, CH_3), 2.82 (s, 2 H, CH_2), 2.98 (s, 6 H, 2 NCH_3), 3.84 (s, 3 H, OCH_3), 3.95 (s, 3 H, OCH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.3 (ring CH_3), 29.1 (gem CH_3), 35.7 and 37.6 (NCH_3), 38.2 (Cβ), 47.8 (CH_2), 60.5 and 61.1 (OCH_3), 134.5, 142.2, 145.8, and 153.0 (vinyl), 172.2 (amide C=O), 184.3 and 186.4 (quinone C=O). Anal. Calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 62.20; H, 7.66; N, 4.52.

***N*,*N*-Dimethyl-β,β,2,4-tetramethyl-5-(*N*-methylamino)-3,6-dioxo-1,4-cyclohexadiene-1-propanamide (18d).** (Methylamino)quinone acid **17a** (1.22 g, 4.60 mmol) and *N*,*N*′-dicyclohexylcarbodiimide (480 mg, 2.30 mmol) were treated with dimethylamine as described for the corresponding dimethoxy derivative **18a**. The pure amide was obtained as shiny red plates (408 mg, 63.8%): mp 136–137.5 °C; IR (KBr) 3390 (NH), 1650 and 1625 (C=O), and 1575 cm^{-1} (C=C); UV (EtOH) λ_{max} = 229 nm, ϵ = 19 316; ^1H NMR ($CDCl_3$) δ 1.40 (s, 6 H, gem CH_3), 1.97 (s, 3 H, 4-CH_3), 2.15 (s, 3 H, 2-CH_3), 2.85 (s, 3 H, NCH_3), 2.95 (s, 2 H, CH_2), 3.00 (s, 3 H, amide NCH_3), 3.05 (s, 3 H, amide NCH_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 10.9 and 15.0 (ring CH_3),

29.3 (gem CH_3), 32.8 and 35.9 (2 NCH_3), 38.2 (Cβ), 38.8 (NCH_3), 47.5 (CH_2), 108.3, 138.7, 148.2, and 148.6 (vinyl), 172.1 (amide C=O), 186.6 and 188.2 (quinone C=O). Anal. Calcd for $C_{16}H_{24}N_2O_3$: C, 65.72; H, 8.27; N, 9.58. Found: C, 65.86; H, 7.89; N, 9.60.

***N,N*-Dimethyl-β,β,2,4,5-pentamethyl-3,6-dioxo-1,4-cyclohexadiene-1-propanamide (7f).** Quinone acid **5**[4b] (1.30 g, 5.20 mmol) in 25 mL of methylene chloride was treated with DCC and dimethyl amine according to the method described for **18a**. The crude quinone amide was recrystallized from hexane to afford the pure amide (74%) as a yellow powder: mp 91.5–92.5 °C; IR (KBr) 1640 and 1620 cm^{-1} (C=O); UV (EtOH) λ_{max} = 264 nm, ϵ = 15 722; ^1H NMR ($CDCl_3$) δ 1.43 (s, 6 H, gem CH_3), 1.90 (s, 6 H, 4- and 5-CH_3), 2.13 (s, 3 H, 2-CH_3), 2.84 (s, 2 H, CH_2), 3.03 (b s, 6 H, 2 NCH_3); ^{13}C NMR ($CDCl_3$) δ 12.3, 12.7, and 14.2 (3 ring CH_3), 29.4 (gem CH_3), 35.1 and 37.2 (NCH_3), 37.6 (Cβ), 47.6 (CH_2), 136.0, 137.8, 144.2, and 155.3 (vinyl), 172.3 (amide C=O), 188.1, and 191.8 (quinone C=O). Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.28; H, 8.36; N, 5.05. Found: C, 69.21; H, 8.38; N, 5.03.

6-Hydroxy-4,4,5,7-tetramethyl-8-(*N*-methylamino)hydrocoumarin (11c). Method A. Aminoquinone acid **17a** (450 mg, 1.70 mmol) was dissolved in 20 mL of methanol, and a solution of sodium dithionite (870 mg, 5.00 mmol) in 20 mL of water was added at room temperature with stirring. The deep red color was immediately discharged. After being stirred for 16 h, the mixture was diluted to 90 mL with water and extracted with ethyl acetate (3 × 25 mL). The combined ethyl acetate extracts were washed with 50 mL of saturated NaCl and dried over $MgSO_4$. Removal of solvent with a rotary evaporator provided a tan oil (391 mg, 92.9%). Further purification attempts including recrystallization and chromatography resulted in reoxidation to aminoquinone acid **17a**. However, the ^1H NMR spectrum of the oil matched that of the lactone obtained by reduction of the corresponding aminoquinone *N,N*-dimethylamide **18d** (method B) and corresponded to the expected spectrum for the lactone: IR (neat) 3410 (OH), 1740 (C=O), and 1250 cm^{-1} (C—O); ^1H NMR ($CDCl_3$) δ 1.46 (s, 6 H, gem CH_3), 2.23 (s, 3 H, CH_3), 2.34 (s, 3 H, CH_3), 2.58 (s, 2 H, CH_2), 2.76 (s, 3 H, NCH_3), 4.05 (b s, 1 H, OH).

Method B. Aminoquinone amide **18d** (100 mg, 0.342 mmol) was dissolved in a mixture of 3 mL of ether and 3 mL of methanol, and a solution of sodium dithionite (240 mg, 1.37 mmol) in 8 mL of water was added at room temperature with stirring. The course of the reaction was followed by TLC. After 15 min the initially formed hydroquinone had been completely consumed, and TLC showed only one colorless component with the same R_f value as that of the product of the reduction of (methylamino)quinone acid **17a** (method A). The reaction mixture was diluted to 30 mL with water and extracted with ether (3 × 10 mL). The combined ether extracts were washed with 30 mL of saturated NaCl and dried over $MgSO_4$. Removal of solvent with a rotary evaporator afforded a colorless oil that slowly solidified on standing (81 mg, 93.7%). All attempts to crystallize or otherwise purify the material failed, but the ^1H NMR spectrum of the oil was identical with that obtained in method A. For characterization see below.

8-(*N*-Acetyl-*N*-methylamino)-6-hydroxy-4,4,5,7-tetramethylhydrocoumarin (11d). The oily amino lactone **11c** (310 mg, 1.25 mmol) obtained as described in method A above was dissolved in 10 mL of dry pyridine, and acetyl chloride (220 mg, 2.75 mmol) was added with stirring under nitrogen at room temperature. After 1 h, the mixture was diluted to 90 mL with 5% HCl and extracted with ethyl acetate (3 × 20 mL). The combined ethyl acetate extracts were washed with 50 mL of 5% HCl and 50 mL of saturated NaCl and dried over $MgSO_4$. Solvent removal with a rotary evaporator afforded a white solid, which was recrystallized from 30% ethyl acetate in hexane to provide the pure acetamido lactone as a white powder (206 mg, 56.4%): mp 242–243 °C dec; IR (KBr) 3180 (OH), 1765 (lactone C=O), and 1635 cm^{-1} (amide C=O); ^1H NMR ($CDCl_3$) δ 1.48 (s, 6 H, gem CH_3), 1.75 (s, 3 H, acetyl CH_3), 2.14 (s, 3 H, CH_3), 2.42 (s, 3 H, CH_3), 2.57 (s, 2 H, CH_2), 3.12 (s, 3 H, NCH_3), 5.55 (b s, 1 H, OH). Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.83; H, 7.26; N, 4.94.

Cyclization Half-Lives. The rate of lactonization was followed by ^1H NMR on either an XL-200 (200 MHz) or an XL-300 (300 MHz) spectrometer. All spectra were referenced to the *gem*-dimethyl absorption of the lactone **4**, which was present in final spectra for each case and was set equal to δ 1.40 relative to tetramethylsilane. In this rough study the reactions were run in unbuffered aqueous methanol solution at ambient temperature (22 °C).

In a typical case 4.0 mg of the quinone ester or amide was dissolved in 0.6 mL of deuterated methanol and placed in an NMR sample tube. A solution of 4 equiv of sodium dithionite (e.g., 9 mg in the case of **7b**) in 0.4 mL of deuterium oxide was introduced into the sample tube rapidly through a syringe to effect thorough mixing. The yellow color of the quinone was quenched instantly. The sample tube was quickly placed in the probe, and the acquisition commenced.

Each spectrum of a set was accumulated using eight transients of pulse width 2.5 μs, pulse delay 1.0 s, and acquisition 1.0 s. Spectra were collected at regular intervals, and half-lives were calculated by the appropriate peak integral verses time data fit to an exponential curve. All of the experimental curves gave correlation coefficients of 0.96 or better.

The integral taken was, in each case, of the hydroquinone peak most separated from other peaks. In general, it was not possible to find a peak that was completely free from the interference of neighboring absorption. An attempt was made to correct for base-line noise by integrating several blank portions of each spectrum and subtracting the average value from the peak integral. No attempt was made to correct for variations in peak shape which may have occured during the course of the reaction. Likewise, no accounting was made of any slight variability in the baseline. Results are shown in Table I.

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