troleum ether gave 130 mg (64%) of pure **8s** as a white solid: mp 68–69 °C, mmp 68–69 °C.

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Supplementary Material Available: Tables of atomic positional and thermal parameters and of bond distances and angles for **6s** (4 pages). Ordering information is given on any current masthead page.

Oxidative Cyclization of Unsaturated Aminoquinones. Synthesis of Quinolinoquinones. Palladium-Catalyzed Synthesis of Pyrroloindoloquinones

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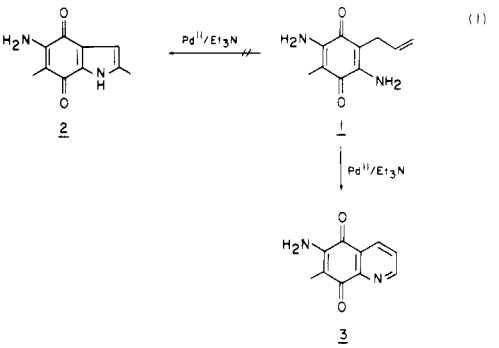
2-Allyl-3,6-diamino-5-methyl-1,4-benzoquinone (**1**) underwent a facile oxidative cyclization to produce quinolinoquinone **3** in the presence of a variety of oxidizing agents, including palladium(II) salts. Chloranil was the most efficient oxidizing agent and produced **3** in high yield. Under hydrolysis conditions, (hydroxyethyl)benzobis(oxazole) **4** underwent a retroaldol reaction, followed by an aldehyde amine condensation and an electrocyclic cyclization to form quinolinoquinones. In contrast, 2-allyl-3,6-bis(benzylamino)-5-methyl-1,4-benzoquinone (**13**) underwent smooth, palladium(II)-catalyzed cyclization to form the corresponding indoloquinone. The corresponding bis(allylamino)benzoquinone **17** underwent a similar cyclization, followed by an olefin insertion reaction to form pyrroloindoloquinones **20** and **21**.

The palladium-catalyzed intramolecular amination of olefins has recently been developed into an efficient process for the conversion of *o*-allylanilines to indoles.[1] The process involves coordination of the olefin to palladium(II) followed by nucleophilic attack at the *most substituted* olefin terminus. When the cyclization was carried out with *N*-acryloyl-*o*-allylaniline, a cyclization–insertion process ensued to give a tricyclic material, a pyrroloindole.[2] With the intent of using this chemistry to synthesize the pyrroloindoloquinone ring system common to the mitomycin antibiotics,[3] a general synthetic approach to 2,5-disubstituted 3,6-diamino-1,4-benzoquinones was recently developed in these laboratories.[4] Herein we report the results of the palladium-catalyzed cyclization reactions of various allyl-containing diaminobenzoquinones.

Results and Discussion

Initial studies centered on the palladium(II)-assisted cyclization of allylbenzoquinone **1** with the intent of producing indoloquinone **2** (eq 1). Treatment of **1** with a stoichiometric amount of $PdCl_2(CH_3CN)_2$ followed by sequential addition of 2 equiv of triethylamine (standard stoichiometric cyclization conditions[1]) resulted in exclusive formation of quinoline **3**, in modest yield (46%). No trace



(1)

of indole **2** was detected. Quinoline **3**, resulting from amination of the *less substituted* olefin terminus, was unexpected but not unprecedented in cyclizations using stoichiometric quantities of palladium(II) salts.[5] This reaction was then repeated under standard catalytic cyclization conditions (3 × 3% Pd(II) catalyst, 3 equiv of benzoquinone/equiv of substrate, THF, 110 °C). Again only quinoline **3** was obtained. Furthermore, in contrast to other palladium(II)-catalyzed cyclization reactions, this reaction was remarkably insensitive to the nature of the palladium catalyst, and all catalysts studied [Li_2PdCl_4, $Pd(OAc)_2$, $PdCl_2(CH_3CN)_2$, $PdCl_2(PhCN)_2$] gave the same product and the same conversion (~75% by NMR of the crude reaction mixture). Finally, the reaction was repeated in the absence of any palladium catalyst, using 4 equiv of benzoquinone per equiv of substrate. Again, quinoline **3**

(1) Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5800.
(2) (a) Hegedus, L. S.; Allen, G. F.; Olsen, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 3583. (b) Hegedus, L. S.; Winton, P. M.; Varaprath, S. *J. Org. Chem.* **1981**, *46*, 2215.
(3) Fransk, R. W. In "Progress in the Chemistry of Organic Natural Products"; Springer-Verlag: New York, 1979; Vol. 38, p 1.
(4) Hegedus, L. S.; Odle, R. R.; Winton, P. M.; Weider, P. R. *J. Org. Chem.* **1982**, *47*, 2607.
(5) *trans*-1-*N*-Tosyl-2-(2-propenyl)cyclopentylamine cyclized to the 6,5-fused ring system *trans*-*N*-tosyl-2-azabicyclo[4.3.0]non-3-ene when treated with a stoichiometric amount of palladium(II) chloride: Hegedus, L. S.; McKearin, J. M. *J. Am. Chem. Soc.* **1982**, *104*, 2444.

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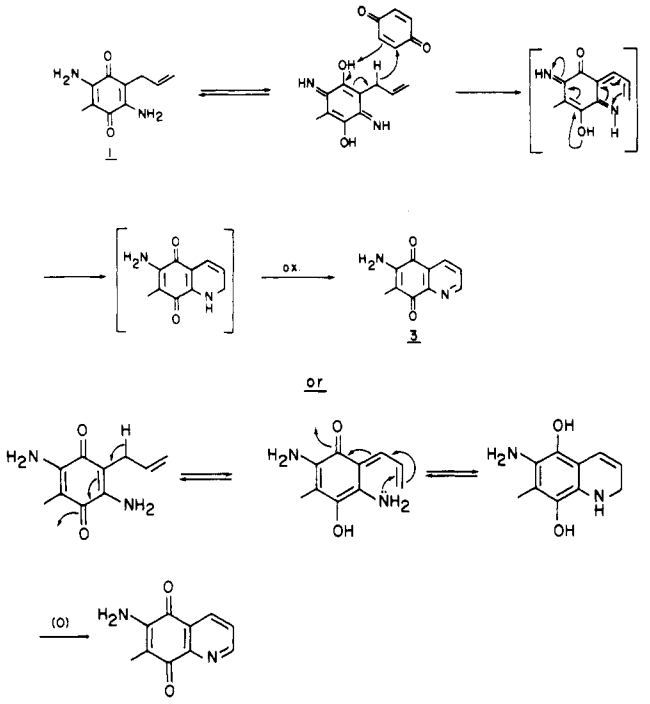
Scheme I. Oxidative Cyclizations of 1

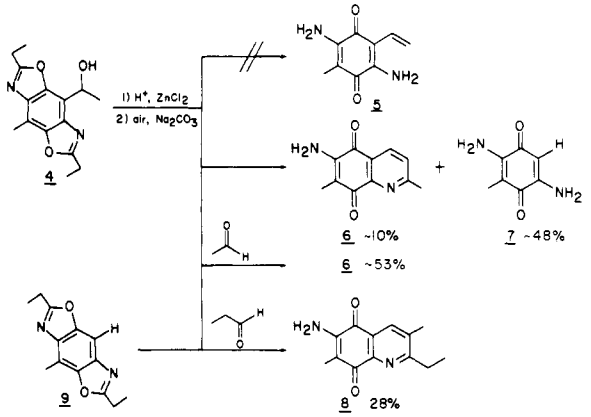


was produced, with ~50% conversion. Thus, although palladium(II) facilitated this cyclization reaction, it was not required for it to occur. Rather this cyclization was an oxidative process, effected by the benzoquinone, since only benzoquinone was required for cyclization. To demonstrate this, quinone 1 was treated with 3 equiv of chloranil in THF at 110 °C for 19 h. This reaction proceeded with 100% conversion and produced the quinoline 3 in 80% isolated, purified yield. A reasonable route for this oxidative cyclization is shown in Scheme I and involves allylic oxidation followed by an electrocyclic reaction. The dihydroquinoline is then further oxidized to the quinoline. Alternatively, a simple enolization–Michael addition–oxidation process would produce the same product.[6] Chloranil, being the strongest of the three oxidants studied, is most efficient in this process, although palladium(II) *alone* can effect this oxidative cyclization. In all cases studied, the oxidative cyclization to form quinoline proceeded to the exclusion of the palladium(II)-catalyzed olefin amination to form indole.

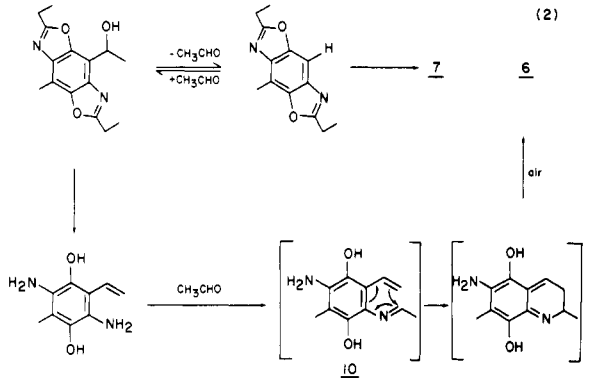
An alternative approach to the indoloquinone system starting from the 2-ethenylaminoquinone 5, which cannot undergo the oxidative cyclization shown in Scheme I, was also attempted. However, the planned synthesis of the requisite starting material from the (hydroxyethyl)benzobis(oxazole) 4[4] by acid-catalyzed hydrolysis and elimination failed to give 5. Rather, under the standard conditions used to hydrolyze benzobis(oxazoles), compound 4 gave a new methylquinoline 6, having two more carbon atoms than expected, as well as the diaminoquinone 7, lacking the hydroxyethyl (or ethenyl) group altogether (Scheme II). Repetition of this reaction in the presence of added acetaldehyde led to an increase in the amount of 6 formed, while running the deprotection reaction in the presence of added propionaldehyde produced the 2-ethyl-3-methylquinoline 8, a molecule incorporating 2 equiv of propionaldehyde. Clearly, (hydroxyethyl)benzobis(oxazole) 4 underwent a retroaldol reaction during deprotection, and the acetaldehyde liberated condensed with

(6) We thank Professor M. F. Semmelhack for this suggestion.

Scheme II. Attempted Hydrolysis of (Hydroxyethyl)bis(benzoxazole) 4



5 to produce the imine 10, which can undergo an electrocyclic reaction to form quinoline 8 (eq 2). Supportive of



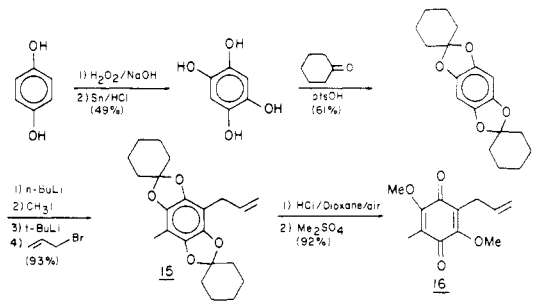
this is the observation that the benzobis(oxazole) 9, which lacks the hydroxyethyl side chain, also converted to quinoline 8 when subjected to the deprotection conditions in the presence of added propionaldehyde.

Since ethenylquinone 5 was not accessible by this route, efforts were again turned to allylquinone 1. Infrared spectroscopy revealed that N-unsubstituted aminoquinones existed in equilibrium with the imino tautomer (C=NH) and that this tautomer predominated over the amino tautomer (=C—NH_2). In contrast, N-alkylated aminoquinones existed predominantly as the amino tautomer.[7] Indeed, diaminoquinone 1 showed *no* absorption in the 1600–1650 cm^{-1} region, indicating that it exists exclusively as the imino tautomer. It was thought that the imino tautomer would be both sterically and electronically less susceptible to palladium-catalyzed intramolecular amination processes, and thus N-alkylated analogues of 1 were desired.

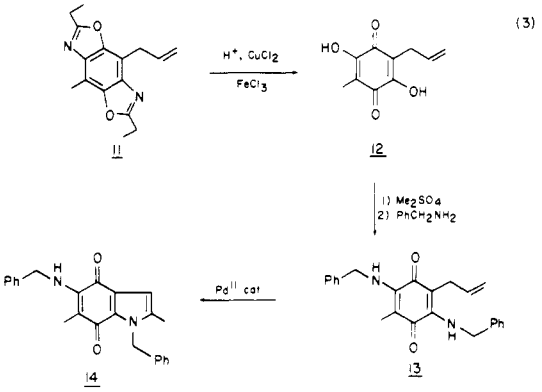
Aminoquinones are vinylogous amides, and as such, do not undergo N-alkylation cleanly. Thus the desired substrates were not directly available from 1. However, deprotection of methylallylbenzobis(oxazole) 11 under acidic oxidizing ($CuCl_2/FeCl_3$) conditions produced the corresponding dihydroxyquinone 12.[4] Methylation with dimethyl sulfate followed by treatment with benzylamine produced bis(benzylamino)quinone 13 in good yield. The infrared spectrum of this compound had a strong band at 1650 cm^{-1}, indicating predominance of the amino tautomer. Palladium(II)-catalyzed cyclization of this substrate pro-

(7) Zee-Cheng, K.-Y.; Cheng, C. C. *J. Med. Chem.* **1968**, *13*, 1107.

Scheme III. Synthesis of Dialkylated Dimethoxyquinone 16

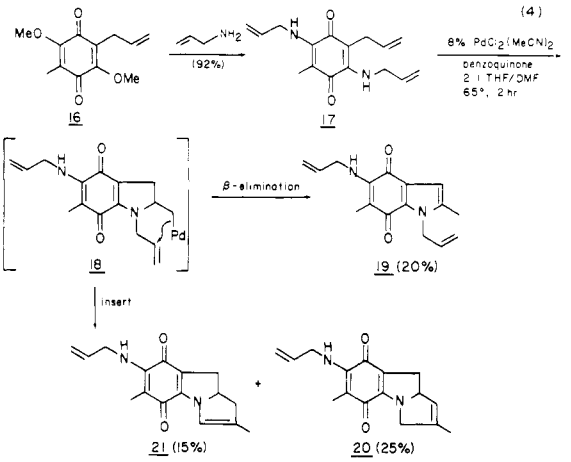


duced the indoloquinone **14** in excellent yield (93%) (eq 3).



To facilitate more extensive cyclization studies a more efficient route to dihydroxyquinone **12**, avoiding the introduction, loss, and reintroduction of the amine in eq 3, was developed (Scheme III). Hydroquinone was oxidized to 2,5-dihydroxyquinone, which was then reduced to 1,2,4,5-tetrahydroxybenzene by metallic tin and hydrochloric acid.[8] Ketalization followed by direct lithiation–alkylation afforded methylallylbisketal **15** in excellent yield.[9] Hydrolysis followed by air oxidation and methylation by dimethyl sulfate produced the dimethoxyquinone **16** in 25% overall yield from hydroquinone itself. This process was easily carried out on a 20–40-g scale and made large amounts of **16** available for further conversion to the desired aminoquinones.

Treatment of **16** with allylamine produced quinone **17** (a substrate having all the carbons necessary to form the desired pyrroloindoloquinone ring system) in excellent yield. The palladium-catalyzed cyclization–insertion process to form this tricyclic ring system[10] was studied in detail (eq 4). Two major problems had to be overcome—competitive β-hydride elimination from the initial cyclization adduct **18**, producing the undesired indole **19**, and decomposition of the desired, relatively unstable tricyclic materials **20** and **21** under the reaction conditions. Several general trends were noted. Polar solvents such as DMF accelerated the cyclization reaction but favored indole formation over formation of tricyclic compounds. Less polar solvents, such as THF, favored formation of tricyclic material, but the reactions were slow and ceased after 30–40% consumption of starting material. Elevated temperatures favored indole formation, and long



reaction times resulted in selective decomposition of the desired tricyclic compounds. Balancing these factors led to the use of a mixed THF/DMF solvent system, which permitted the reaction to proceed to completion at a reasonable rate under mild conditions. A 10-mmol (2.8-g) scale reaction was complete in 2 h and gave a 40% isolated, purified yield of tricyclic compounds **20** and **21** along with a 20% yield of indole **19**. This culminated a nine-step synthesis of the desired ring system in an overall yield of 8% from hydroquinone.

Experimental Section

General. All melting points were determined with a Mel-Temp capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra (270 MHz) were recorded on an IBM WP270SY; ^{1}H NMR spectra (360 MHz) were recorded on a Nicolet NTCFT 1180, all using tetramethylsilane as an internal standard and all reported in parts per million. Infrared spectra were recorded on a Beckman 2440 spectrophotometer and are reported in reciprocal centimeters. UV–vis spectra were obtained on a Varian 636 instrument, and data are given in nanometers. A Vacuum Generators MM16 spectrometer with a digital PDP8A computer at 70 eV was used for routine mass spectra. Solvents and reagents were dried and purified prior to use when deemed necessary. Tetrahydrofuran was heated at reflux over sodium wire and benzophenone and distilled at atmospheric pressure under N_2 just prior to use. Triethylamine was purified by distillation from CaH_2 at atmospheric pressure under argon. Dimethyl sulfate was purified by allowing commercial material to stand over $CaSO_4$ 3 days followed by filtration and fractional distillation at reduced pressure. Copper(I) iodide was purified by recrystallization.[11] *n*-Butyllithium/hexanes and *tert*-butyllithium were titrated prior to use by reaction with 1,3-diphenyl-2-propanone tosylhydrazone.[12] $PdCl_2(RCN)_2$ complexes were prepared by rapidly stirring $PdCl_2$ with the appropriate nitrile as solvent, for 3 days, followed by filtration to yield the complex as a powdery solid. All reactions were carried out under an inert atmosphere (argon) in a vacuum–flame-dried flask. Chromatographic separations were achieved by column chromatography over Baker silica gel (60–200 mesh) or by centrifugally accelerated, radial, thin-layer chromatography on a Harrison Research Model 7924 chromatotron utilizing silica gel PF-254 (Merck 7749) in standard 1-, 2–, or 4–mm plate thickness.

6-Allyl-2,4-dihydroxy-3-methyl-1,4-benzoquinone (12). To a solution of 1.66 g (6.16 mmol) of allylmethylbenzobis(ethyloxazole) **11**[4] and 3.23 g (18.9 mmol) of $CuCl_2 \cdot 2H_2O$ in 60 mL of absolute ethanol was added 16.2 mL of 4 N HCl. The resulting homogeneous mixture was heated at reflux in the air for 7 h, at which time no starting material could be detected by thin-layer chromatography (silica gel; 66:34 hexane–ethyl acetate). To the

(8) Jones, R. G.; Shonle, H. A. *J. Am. Chem. Soc.* **1945**, *67*, 1034.
(9) Boeckman, J.; Schill, G. *Chem. Ber.* **1977**, *110*, 763.
(10) Related pyrroloindoloquinones have recently been made from metal-catalyzed azide decomposition processes: Naruta, Y.; Arita, Y.; Nagai, N.; Uno, H.; Maruyama, K. *Chem. Lett.* **1982**, 1859. Naruta, Y.; Nagai, N.; Maruyama, K. *Chem. Lett.* **1983**, 1383.
(11) Kauffman, G. B.; Teter, L. A. *Inorg. Synth.* **1963**, *7*, 9.
(12) Lipton, M. F.; Sorensen, L. M.; Sadler, A. C.; Shapiro, R. H. *J. Organomet. Chem.* **1980**, *186*, 155.

cooled solution was added 3.00 g (11.1 mmol) of $FeCl_3 \cdot 6H_2O$. This solution was heated at reflux for an additional 13 h. The resulting black solution was cooled to room temperature and added to 50 mL of a saturated aqueous EDTA solution and 100 mL of water. This aqueous solution was extracted with $CHCl_3$ until the organic layer was colorless (7 × 50 mL). The combined organics were dried ($MgSO_4$), filtered through Celite, and concentrated in vacuo to afford 1.22 g of an orange solid. This material was recrystallized from hexane to afford 1.10 g (94%) of **12** as an orange solid: mp 172–173 °C; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.94 (s, 3, CH_3), 3.20 (d, J = 6 Hz, 2, CH_2), 5.09 (m, 2, CH=CH_2), 5.84 (m, 1, CH=CH_2), 7.3 (s, 2, OH); IR (KBr) 3300 (br s), 1610 (s), 1300 (s), 1190 (s), 760 (m) cm^{-1}; UV ($CHCl_3$) 293 (log ϵ 4.33), 400 (2.52) nm; mass spectrum, m/e (relative intensity) 194 (100), 193 (32), 179 (17), 83 (27), 55 (29). Anal. Calcd for $C_{10}H_{10}O_4$: C, 61.86; H, 5.15. Found: C, 61.62; H, 5.25.

6-Allyl-2,4-dimethoxy-3-methyl-1,4-benzoquinone (16). To 9.06 g (46.7 mmol) of dihydroxyquinone **12** in 450 mL of dry distilled acetone was added 25.60 g (185.6 mmol) of finely powdered potassium carbonate. To the rapidly stirred purple mixture was added 17.56 mL of dimethyl sulfate (23.40 g; 185.6 mmol). The reaction mixture was heated at reflux under an argon atmosphere for 5 h. The resulting brown mixture was filtered hot and concentrated in vacuo to approximately 100 mL of residual oil. The oil was partitioned between 500 mL of water and 300 mL of hexane. The organic phase was washed with 100 mL of H_2O, and the separate aqueous layers were back-extracted with 100 mL of hexane. The combined organics were dried ($MgSO_4$), decolorized (carbon), and filtered through Celite. The filtrate was concentrated in vacuo to afford 9.55 g (92.0%) of dimethoxyquinone **16** as a yellow oil: ^1H NMR ($CDCl_3$, 270 MHz) δ 1.90 (s, 3, CH_3), 3.18 (d, J = 8 Hz, CH_2 CH=CH_2), 3.99 (s, 6, OCH_3), 5.1 (m, 2, CH=CH_2), 5.8 (m, 1, CH=CH_2); IR (neat) 3270 (w), 2940 (s), 2840 (s), 1770 (s), 1730 (s), 1650 (vs, C=O), 1600 (s), 1450 (s), 1375 (s), 1280 (s), 760 (m) cm^{-1}. This was used without further purification.

General Procedure for the Catalytic Cyclization of 6-Allyl-2,4-diamino-3-methyl-1,4-benzoquinone (1). In a 5-mL acylation tube were placed $PdCl_2(CH_3CN)_2$ (3 mol %), benzoquinone (1–3 equiv), Na_2CO_3 (1–3 equiv), and LiCl (5–10 equiv). Diaminoquinone 1 (50 mg, 0.26 mmol) was then added in tetrahydrofuran (15 mL/mmol). The solution produced was degassed and put under argon, and the acylation tube was sealed. The sealed tube was placed in a preheated oil bath (110 °C) for 24 h. The tube was then removed from heat and cooled, and another 3 mmol % of $PdCl_2(CH_3CN)_2$ was added. The solution was degassed, sealed, and heated an additional 24 h. Fresh catalyst was added by the same method and the reaction heated a final 24 h. The resultant solution was cooled and concentrated in vacuo. The residual solid was dissolved in 10 mL of water and 30 mL of chloroform. The two-phase mixture was transferred, with the aid of small portions of water and chloroform, to a small continuous extractor and extracted with chloroform (30 mL). The chloroform layer was dried (Na_2SO_4), filtered through a glass frit, and concentrated in vacuo. The residual solid was examined by FT NMR (360 MHz) to obtain product ratios, and care was taken that dissolution of solid was nonselective (i.e., dilute solutions). The same procedure was followed using $Pd(OAc)_2$ and Li_2PdCl_4 as catalysts, with the same results. The material was purified by chromatography (silica gel; 9:1 ethyl acetate–methanol) to give two fractions, the first of which was starting material. The second fraction contained **3** as an orange-red solid: mp 220 °C dec; ^1H NMR ($CDCl_3$, 360 MHz) δ 2.09 (s, 3, CH_3), 5.05 (br s, 2, NH_2), 7.55 (d of d, J = 7.77, 4.78 Hz, 1, C2-H), 8.33 (d of d, J = 7.77, 1.46 Hz, 1, C4-H), 8.96 (d of d, J = 4.78, 1.46 Hz, 1, C3-H); IR (KBr) 3280 (br), 1660 (m, C=O), 1620 (m), 1595 (s), 1570 (s), 1555 (s), 1400 (m), 1350 (s) cm^{-1}; mass spectrum, m/e (relative intensity) 188 (100), 160 (14), 159 (14), 131 (32), 105 (30), 79 (28), 77 (21), 71 (22), 43 (53); UV ($CHCl_3$) 267 (log ϵ 3.88), 435 (3.08) nm. Anal. Calcd for $C_{10}H_8N_2O_2$: C, 63.83; H, 4.29; N, 14.89. Found: C, 63.65; H, 4.39; N, 14.74.

Preparation of 3 by Reaction with Stoichiometric Amounts of $PdCl_2(CH_3CN)_2$. Diaminoquinone 1 (51 mg, 0.26 mmol) in 2 mL of THF was added to $PdCl_2(CH_3CN)_2$ (68 mg, 0.26 mmol) in 4 mL of THF. After the resulting, deep red, solution was stirred for 2 h, portions of Et_3N (38 μL, 1 mmol) were added dropwise every 2 h until 5 equiv had been added. Methanol (2 mL) was added, and the mixture was stirred under an atmosphere (balloon) of carbon monoxide overnight to reduce palladium. Filtration, concentration in vacuo, dissolution in $CHCl_3$, washing with water (2 × 25 mL), drying over Na_2SO_4, and removal of solvent under vacuum gave 45 mg of a maroon solid. Separation of this material by column chromatography (silica gel; 8:1 ethyl acetate–methanol) gave quinoline **3**, (22 mg, 48%) identical in all respects with the material obtained above.

Preparation of Quinoline 3 by Chloranil Oxidation of 1. Quinone 1 (82 mg, 0.43 mmol) and 315 mg (1.28 mmol) of chloranil were carefully weighed into a 5-mL sealed tube apparatus. To this was added 5 mL of THF, the mixture was stirred to dissolve the solids, and the tube was sealed. The reaction vessel was immersed in a 110 °C oil bath for 28 h, removed, cooled, and opened. The reaction mixture was poured into 25 mL of 0.5 N NaOH and extracted with $CHCl_3$ (10 × 20 mL). The $CHCl_3$ extracts were dried (Na_2SO_4), filtered through Celite, and concentrated in vacuo to afford 66 mg (83%) of quinoline **3** after chromatographic purification as an orange-red solid. This material was homogeneous by TLC, NMR, and UV and was identical with that obtained above.

(1-Hydroxyethyl)methylbenzobis(ethyloxazole) 4. To 2.42 mmol of the lithio compound formed via a standard procedure[4] in 75 mL of dry, distilled THF from 0.746 g (2.42 mmol) of 6-bromo-3-methyl-*anti*-1,2,4,5-benzobis(ethyloxazole) at −78 °C was added 370 μL (6.58 mmol) of freshly distilled acetaldehyde. Immediately upon addition of the acetaldehyde a color change, from orange to yellow, occurred. The resultant solution was warmed to room temperature, poured into 100 mL of saturated aqueous ammonium chloride, and extracted with dichloromethane (2 × 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and evaporated in vacuo to afford a light brown oil, which was purified by medium-pressure liquid chromatography (silica gel; 1:1 hexane–ethyl acetate) to give carbinol **4** as a light yellow solid (434 mg; 65.5%): mp 100–101 °C; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.47 (t, J = 8 Hz, 6, CH_2CH_3), 1.77 (d, J = 6 Hz, 3, CH(OH)CH_3), 2.70 (s, 3, CH_3), 2.97 (m, 4, CH_2CH$_3$), 4.30 (d, J = 7.3 Hz, 1, OH), 5.58 (m, 1, CH(OH)CH_3); IR (KBr) 3350 (br s), 2970 (s), 2920 (s), 1585 (s), 1330 (s), 1170 (s), 1080 (s), 920 (s), 880 (s) cm^{-1}. Anal. Calcd for $C_{15}H_{18}O_3N_2$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.41; H, 6.42; N, 10.23.

Hydrolysis of Methyl-1-(1-hydroxyethyl)benzobis(ethyloxazole) 4. To 103 mg (0.38 mmol) of carbinol **4** in 9.3 mL of ethanol was added 259 mg (1.90 mmol) of anhydrous zinc chloride under an argon atmosphere. To this solution was added 2.4 mL of argon saturated 4 N HCl and the resulting homogeneous solution was heated at reflux 17 h, at which time thin-layer chromatography (silica gel, 2:1 ethyl acetate–hexane) showed no mobile spots. The solution was cooled to room temperature followed by addition of 1.12 g of Na_2CO_3, 12 mL of saturated aqueous EDTA, and 12 mL of water. The reaction mixture was transferred to an open beaker and stirred in the air 24 h. The resulting solution was continuously extracted with 30 mL of $CHCl_3$. The extract was dried (Na_2SO_4), filtered, and concentrated in vacuo to afford 60.2 mg of a purple solid residue. Purification of this material by preparative thin-layer chromatography (silica gel, ethyl acetate) afforded two bands.

7: R_f 0.64; 28 mg (48%); purple solid; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.83 (s, 3, CH_3), 5.50 (s, 1, C6-H), 5.0–6.0 (br, 4, NH_2's); mass spectrum, m/e (relative intensity) 152 (66), 137 (100), 54 (81).

Quinolinoquinone **6**: R_f 0.32; 8 mg (10%); orange solid; mp 222–224 °C; ^1H NMR ($CDCl_3$, 360 MHz) δ 2.03 (s, 3, 7-Me), 2.71 (s, 3, 2-Me), 5.02 (br s, 2, NH_2), 7.40 (d, J = 7.9 Hz, 1, C3-H), 8.21 (d, J = 7.9 Hz, 1, C4-H); IR (KBr) 3300 (s, br), 1680 (m), 1610 (s), 1580 (vs), 1410 (m), 1350 (s) cm^{-1}; UV ($CHCl_3$) 267, 278, 300, 315, 328, 440 nm; mass spectrum, m/e (relative intensity) 202 (27), 154 (40), 84 (15), 58 (32), 43 (100); exact mass calcd for $C_{11}H_{10}N_2O_2$ 202.0745, found 202.0745.

Repeating this reaction in the presence of added acetaldehyde (10 equiv) increased the yield of **6** to 53% and completely supressed formation of **7**.

Hydrolysis of (1-Hydroxyethyl)methylbenzobis(ethyloxazole) 4 in the Presence of Added Propionaldehyde. To 97 mg (0.35 mmol) of carbinol **4** in 9.3 mL of ethanol was added

241 mg (1.77 mmol) of anhydrous zinc chloride. To this solution was added 2.4 mL of argon saturated 4 N HCl and 100 μL (82 mg, 1.42 mmol) of propionaldehyde. The resulting homogeneous solution was heated at reflux 24 h. The reaction mixture was poured into an open beaker, and 1 g of Na_2CO_3, 12 mL of saturated aqueous EDTA, and 12 mL of water were added. This was stirred in the open air 24 h (oxidation was very slow), during which time the solution turned dark purple. The oxidized reaction mixture was extracted with dichloromethane (3 × 25 mL). The organic extracts were combined, dried (Na_2SO_4), filtered, and concentrated in vacuo to afford 70 mg of a dark red solid. The residual solid was purified by radial chromatography (silica gel, 2 mm, ethyl acetate). The main fraction afforded 22 mg of quinolinoquinone 8 as an orange solid (28%): mp 200–215 °C dec; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.32 (t, J = 7.6 Hz, 3, CH_2CH_3), 2.05 (s, 3, C7-Me), 2.45 (s, 3, C3-Me), 2.99 (q, J = 7.6 Hz, 2, CH_2CH_3), 4.99 (br s, 2, NH_2), 8.01 (s, 1, C4-H); IR (KBr) 1677 (C=O) cm^{-1}; mass spectrum, m/e (relative intensity) 230 (100), 229 (66), 215 (9), 187 (9), 165 (11), 84 (20); UV (EtOH) 238, 267, 275, 300 nm. Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.12; N, 12.17. Found: C, 68.04; H, 6.08; N, 11.93.

Hydrolysis of Methylprotiobenzobis(ethyloxazole) 9 in the Presence of Propionaldehyde. A solution of 4 N HCl (8 mL) was added to 0.41 g (1.78 mmol) of 9 and 1.00 g (7.34 mmol) of anhydrous zinc chloride in 30 mL of distilled ethanol under an argon atmosphere. This mixture was heated at reflux for 24 h and cooled, and the product was isolated and purified as above to give 66 mg (16%) of 8 as an orange solid, identical in all respects with material obtained above.

Preparation of 6-Allyl-2,5-bis(benzylamino)-3-methyl-1,4-benzoquinone (13). Benzylamine (0.23 mL, 2.1 mmol) in 5 mL of absolute ethanol was added to dimethoxyquinone 16 (222 mg, 1.00 mmol) in 15 mL of absolute ethanol, and the resulting mixture was heated at reflux for 3 h. The solvent was removed in vacuo, and the deep purple residue was purified by column chromatography (silica gel, $CHCl_3$ eluent). The resulting deep purple solid was recrystallized from 2:1 hexane–ether to give 13 as deep purple needles (362 mg, 97%): mp 123–124 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.06 (s, 3, CH_3), 3.23 (d, 2, J = 2.0 Hz, $CH_2CH{=}CH_2$), 4.68 (d, 2, J = 6.3 Hz, $NHCH_2$), 4.75 (d, 2, J = 6.3 Hz, $NHCH_2$), 5.04 (m, 2, $CH{=}CH_2$), 5.98 (m, 1, $CH_2CH{=}CH_2$), 6.94 (m, 1, NH), 7.05 (m, 1, NH), 7.30 (m, 10, Ph); IR (KBr) 3260 (NH), 1650 (C=O) cm^{-1}; UV (EtOH), 216 (log ε 4.48), 349 (4.43). Anal. Calcd for $C_{24}H_{24}N_2O_2$: C, 77.39; H, 6.49; N, 7.52. Found: C, 77.20; H, 6.61; N, 7.52.

Cyclization of 13 to Indole 14. Quinone 13 (48.4 mg, 0.13 mmol), $PdCl_2(CH_3CN)_2$ (3.40 mg, 0.013 mmol), anhydrous Na_2CO_3 (14.4 mg, 0.14 mmol), LiCl (58.1 mg, 1.37 mmol), benzoquinone (16.3 mg, 0.15 mmol), and 2 mL of dry THF were placed in a heavy wall hydrolysis tube, sealed under an argon atmosphere, and heated at 110 °C (external) for 20 h. After cooling, the tube was opened, and the contents were poured into 20 mL of 1 N NaOH and 10 mL of saturated NaCl. This mixture was extracted with chloroform (3 × 25 mL). The chloroform extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. Recrystallization from hexane gave indole 14 as a brown-purple crystalline solid (45 mg, 93%): mp 134–135 °C; ^{1}H NMR ($CDCl_3$, 270 MHz) δ 2.03 (s, 3, C6-Me), 2.14 (s, 3, C2-Me), 4.66 (s, 2, $NHCH_2Ph$), 5.65 (s, 2, NCH_2Ph), 5.95 (br s, 1, CH_2NH), 6.32 (s, 1, C3-H), 7.0 (m, 2, Ar H), 7.36 (m, 8, Ar H); IR (KBr) 3340 (NH), 1656 (C=O), 1616 cm^{-1}; UV (EtOH) 210 (log ε 4.38), 315 (4.14). Anal. Calcd for $C_{24}H_{22}N_2O_2$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.63; H, 6.05; N, 7.68.

Preparation of 1,2,4,5-Tetrahydroxybenzene. To a mixture of 32.2 g (230 mmol) of 2,5-dihydroxy benzene[8] in 700 mL of 36% hydrochloric acid was slowly added 32.8 g (276 mmol) of granular tin metal. This mixture was slowly heated to reflux for 1 h, during which time the reaction mixture changed from an orange slurry to a black slurry then to a homogeneous, colorless solution (vigorous gas evolution took place during this time). The solution was filtered hot through a coarse glass frit and allowed to cool slowly to room temperature and then cooled to 0 °C. The large colorless crystals of tetrahydroxybenzene were collected by filtration drying in vacuo affords 24.42 g (75%) of a white solid. This could be recrystallized from tetrahydrofuran to afford 20.27 g (62%) of 1,2,4,5-tetrahydroxybenzene[13] as a white crystalline solid: IR (KBr) 3400–3200 (vs, OH), 1550 (m), 1480 (s), 1365 (m), 1180 (s), 860 (m), 840 (m) cm^{-1}.

Preparation of 1,2:4,5-Bis(cyclohexylidenedioxy)benzene. To 17.19 g (121 mmol) of 1,2,4,5-tetrahydroxybenzene in 250 mL of toluene were added 2.30 g of p-toluenesulfonic acid monohydrate (12.1 mmol), 37.5 mL of cyclohexanone (363 mmol), and 10 mL of N,N-dimethylformamide. This mixture was heated at reflux with continuous water removal (Dean–Stark trap) for 46 h. The resulting light green solution was cooled in an ice bath 20 min followed by the careful addition of 200 mL of saturated aqueous sodium bicarbonate. The neutralized reaction mixture was poured into a separatory funnel with 400 mL of chloroform. The mixture was shaken for 5 min and allowed to separate and the organic layer removed. The aqueous layer was extracted with 150 mL of chloroform. The combined organics were dried ($MgSO_4$), decolorized (carbon), filtered through Celite, and concentrated in vacuo to 41.65 g of a wet pink solid. This was diluted with 300 mL of hexane, cooled, and filtered. The filtrate was concentrated in vacuo and diluted with 100 mL of acetone. The acetone mixture was heated to reflux, cooled to 0 °C, and filtered. The solids collected were recrystallized from toluene to afford 22.46 g (61%) of the bisketal as a white crystalline solid: mp 190–191 °C; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.45 (m, 4), 1.70 (m, 8), 1.87 (m, 8), 6.33 (s, 2, Ar H's); IR (KBr) 2940 (s), 2860 (m), 1640 (w), 1490 (s), 1480 (s), 1150 (s), 1055 (s), 970 (s), 865 (s), 830 (m) cm^{-1}.

Methylation of the Bisketal. To 22.76 g (75.38 mmol) of diprotio bisketal in a 500-mL three-necked round-bottomed flask fitted with a serum stopper, a low-temperature thermometer, and a gas inlet was added 320 mL of freshly distilled tetrahydrofuran. This was warmed to 48 °C to dissolve the solid and then cooled to 0 °C. As *soon* as the internal temperature reached 0 °C, 33.5 mL of 2.37 M n-butyllithium/hexanes (79.40 mmol; 1.05 equiv) was added via cannula. The rate of addition was controlled such that the internal temperature did not rise above 5 °C. The resulting light yellow solution was stirred 30 min at 0 °C. This was allowed to warm to room temperature and stir 2 h, followed by warming to 35 °C. The colorless, homogeneous solution was cooled to 0 °C followed by the addition of 4.9 mL (11.2 g; 78.7 mmol; 1.04 equiv) of methyl iodide dropwise such that the temperature did not rise above 10 °C. The reaction mixture was allowed to warm to room temperature and stir overnight (17 h). The resulting solution was poured into 300 mL of water and 300 mL of diethyl ether. This was shaken and the aqueous layer removed. The organic layer was washed with 300 mL of water and 300 mL of saturated aqueous sodium chloride. The separate aqueous layers were back-extracted with 200 mL of diethyl ether. The combined organics were dried ($MgSO_4$), decolorized (carbon), filtered through Celite, and concentrated in vacuo to afford 23.92 g of an off-white solid (100%). This was recrystallized from acetone to afford 23.34 g (98%) of the methylated derivative as large white crystals: mp 136–139 °C; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.47 (m, 4), 1.67 (m, 8), 1.85 (m, 8), 2.08 (s, 3, CH_3), 6.19 (s, 1). IR (KBr) 2940 (s), 2860 (m), 1465 (s), 1370 (s), 1330 (s), 1180 (s), 1120 (s), 1080 (s), 870 (s) cm^{-1}.

Preparation of 1-Allyl-4-methyl-2,3:5,6-bis(cyclohexylidenedioxy)benzene 15. To 15.00 g (47.47 mmol) of methylprotio bisketal in a 500-mL Airlessware flask was added 425 mL of tetrahydrofuran. This was warmed to 35 °C to dissolve the starting material. The reaction vessel was immersed in a dry ice/acetone bath 15 min followed by the addition of 28 mL of 2.04 M *tert*-butyllithium/pentane (57.12 mmol; 1.2 equiv) via cannula. The resultant yellow solution was allowed to warm to room temperature. The reaction mixture was stirred at room temperature for 3.5 h. The clear, colorless solution produced was cooled to −78 °C followed by the addition of 0.301 g (2.37 mmol, 5%) of copper iodide and then 4.9 mL (6.89 g, 56.96 mmol) of allyl bromide. This reaction mixture was allowed to warm to room temperature and stir overnight. The resulting black solution was partitioned between 400 mL of diethyl ether and 300 mL of saturated aqueous NH_4Cl. The organic layer was separated and washed with 300 mL of saturated aqueous ammonium chloride and 300 mL of brine. The separate aqueous layers were back-

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extracted with 300 mL of diethyl ether. The combined organics were dried ($MgSO_4$), decolorized (carbon), filtered through Celite, and concentrated in vacuo to afford 17.37 g of a yellow oil, which eventually solidified. This material was recrystallized from 100 mL of acetone (reflux to −78 °C) to afford 15.97 g (95%) of **15** as a white solid: mp 64–66 °C; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.45 (m, 4), 1.65 (m, 8), 1.85 (m, 8), 2.06 (s, 3, CH_3), 3.24 (d, J = 7.5 Hz, 2, $CH_2CH{=}CH_2$), 4.90–5.15 (m, 2, $CH{=}CH_2$), 5.85–6.10 (m, 1, $CH{=}CH_2$); IR (KBr) 2940 (s), 2860 (m), 1640 (w), 1450 (s), 1370 (s), 1320 (s), 1150 (s), 1075 (s), 980 (s) cm^{-1}.

Acid Hydrolysis of Methylallyl Bisketal 15. The bisketal **15** (16.755 g, 45.90 mmol) was dissolved in 330 mL of 1,4-dioxane followed by the addition of 66 mL of 4 N HCl. The homogeneous solution was heated at reflux in the air 5 h, cooled to room temperature, and poured into an open 600-mL beaker. This solution was made basic by addition of 2 N NaOH, and the purple solution was allowed to stir in the open air overnight. The dark solution was acidified with concentrated hydrochloric acid and extracted with three portions of chloroform. The organic layer was dried ($MgSO_4$), filtered through Celite, and concentrated in vacuo to afford a wet golden solid. This was slurried in boiling hexane, cooled, and filtered, and the golden crystals were dried in vacuo to afford 8.89 g (100%) of the dihydroxyquinone. This material was identical in all respects with that previously reported.[4]

Preparation of 6-Allyl-3,6-bis(allylamino)-3-methyl-1,4-benzoquinone 17. To a solution of 295 mg (1.33 mmol) of 6-allyl-2,5-dimethoxy-3-methyl-1,4-benzoquinone (**16**) in 20 mL of distilled ethanol was added 225 μL of allylamine dropwise over a 2-min period. The reaction mixture was heated at reflux under an argon atmosphere for 2 h, cooled to room temperature, and concentrated in vacuo. The purple residual solid was purified via radial chromatography (2 mm, silica gel, 4:1 hexane–ethyl acetate eluent) to afford 296 mg of 6-allyl-2,5-bis(*N*-allylamino)-3-methyl-1,4-benzoquinone (**17**) as a purple solid (82%). This material was recrystallized from diethyl ether for characterization: mp 109–110 °C; ^1H NMR ($CDCl_3$, 360 MHz) δ 2.06 (s, 3, CH_3), 3.25 (m, 2, $CH_2CH{=}CH_2$), 4.08 (m, 2, $NCH_2CH{=}CH_2$), 4.17 (m, 2, $NCH_2CH{=}CH_2$), 4.97 (dd, J = 17.2, 1.8 Hz, 1, $CH{=}CH_2$), 5.20 (dd, J = 10.2, 1.8 Hz, 1, $CH{=}CH_2$), 5.23 (m, 4, $NCH_2CH{=}CH_2$), 5.90 (m, 3, $CH_2CH{=}CH_2$), 6.75 (br s, 1, NH), 6.87 (br s, 1, NH); IR ($CHCl_3$) 3260 (br, NH), 1645 (C=O, m), 1580 (s), 1470 (s), 1350 (s), 900 (m) cm^{-1}. Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.38; H, 7.53; N, 10.52.

Cyclization of 6-Allyl-3-methyl-2,5-bis(allylamino)-1,4-benzoquinone 17. Bis(allylamino)quinone **17** (2.747 g, 10.09 mmol), $PdCl_2(CH_3CN)_2$ (0.392 g, 1.51 mmol), and benzoquinone (1.307 g, 12.10 mmol) were weighed into a round-bottomed flask and dissolved in 120 mL of tetrahydrofuran. This was diluted with 60 mL of *N,N*-dimethylformamide. The resulting solution was alternately evacuated and put under argon (four cycles). The reaction vessel was then immersed in a preheated (75 °C) oil bath and heated at reflux 32 min. The reaction vessel was removed from the oil bath and immersed in an ice/salt bath for 15 min. The cooled solution was poured into 500 mL of diethyl ether and 500 mL of saturated aqueous sodium chloride, shaken, and allowed to separate. The lower gelatinous layer was removed and filtered. The filtrate was extracted 4 times with 125 mL of diethyl ether. The combined organics were washed with water (3 × 200 mL) and brine (400 mL). The separate aqueous washes were back-extracted with two 100-mL portions of diethyl ether. The organics were combined, dried ($MgSO_4$), filtered through Celite, and concentrated in vacuo to afford 3.090 g of a green residue. The residue was separated by column chromatography over 200 g of silica gel using hexane–ethyl acetate (75:25) as eluent, to yield sequentially 0.534 g (20%) of allylindole **19**, 0.589 g (25%) of Δ^1 tricyclic compound **20**, and 0.42 g (15%) of Δ^2 tricyclic compound **21**. These materials were recrystallized from hexane for analytical purposes. The physical properties of these compounds are given below.

5-(Allylamino)-1-allyl-2,6-dimethyl-4,7-dioxoindole (19): Purple solid; mp 62–64 °C; ^1H NMR ($CDCl_3$, 360 MHz) δ 2.04 (s, 3, C6-Me), 2.21 (s, 3, C2-Me), 4.07 (d, J = 1.9 Hz, 2, $NHCH_2CH{=}CH_2$), 4.15 (br s, 1, NH), 4.8–5.3 (m, 6, $CH_2{=}$CH's and $CH_2CH{=}CH_2$), 5.90 (m, 2, $CH{=}CH_2$), 6.28 (s, 1, C3-H); IR (KBr) 3420 (m), 3255 (s), 1655 (s), 1590 (s), 1550 (m), 1505 (s), 1300 (m), 740 (m) cm^{-1}. Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.96; H, 6.92; N, 10.33.

7-(Allylamino)-2,6-dimethyl-3*H*-pyrrolo[1,2-*a*]indole-5,8-dione 20: blue green solid; mp 104–105 °C; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.77 (s, 3, C2-Me), 2.02 (s, 3, C6-Me), 2.76 (A of ABX, J_{AB} = 15.7 Hz, J_{AX} = 7.2 Hz, 1, C9-H), 2.95 (B of ABX, J_{AB} = 15.7 Hz, J_{BX} = 11.7 Hz, 1, C9-H), 4.00 (d, J = 16.0 Hz, 1, C3-H), 4.15 (s, 2, $CH_2CH{=}CH_2$), 4.33 (d, J = 16.0 Hz, 1, C3-H), 5.00 (m, 1, C9a-H), 5.25 (m, 2, $CH_2{=}$CH), 5.45 (s, 1, C1-H), 5.92 (m, 1, $CH_2{=}CH$), 6.51 (br s, 1, NH); IR (KBr) 3280 (m), 1630 (s), 1580 (s), 1500 (s), 1420 (s), 1320 (s), 1300 (s), 1270 (s), 1260 (s), 700 (s), 550 (s) cm^{-1}; mass spectrum, m/e (relative intensity) 270 (86), 255 (43), 253 (base), 241 (85). Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.84; H, 6.78; N, 10.27.

7-(Allylamino)-2,6-dimethyl-1*H*-pyrrolo[1,2-*a*]indole-5,8-dione 21: green solid; mp 63–65 °C; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.85 (s, 3, C2-Me), 2.01 (s, 3, C6-Me), 2.38 (m, 1, C1-H), 2.60 (m, 2, C1-H and C9-H), 3.13 (dd, J = 15, 10 Hz, C9-H), 4.10 (m, 2, $CH_2CH{=}CH_2$), 4.50 (m, 1, C9a-H), 5.20 (m, 2, $CH_2CH{=}CH_2$), 5.90 (m, 1, $CH_2CH{=}CH_2$), 6.80 (br s, 1, NH), 7.00 (s, 1, C3-H); IR (KBr) 3400 (NH), 1620 (m), 1590 (m), 1540 (s), 1480 (s), 740 (m) cm^{-1}; mass spectrum, m/e (relative intensity) 270 (74), 255 (base), 253 (47), 241 (19); exact mass calcd for $C_{16}H_{18}N_2O_2$ 270.1363, found 270.1367.

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Registry No. **1**, 81534-93-2; **3**, 98332-05-9; **4**, 98332-06-0; **6**, 64636-85-7; **7**, 31679-94-4; **8**, 98332-07-1; **9**, 98332-08-2; **11**, 81534-90-9; **12**, 81534-92-1; **13**, 98332-09-3; **14**, 98332-10-6; **15**, 98332-12-8; **16**, 81534-96-5; **17**, 98332-13-9; **19**, 98332-14-0; **20**, 98332-15-1; **21**, 98332-16-2; $PdCl_2(CH_3CN)_2$, 14592-56-4; $Pd(OAc)_2$, 3375-31-3; Li_2PdCl_4, 15525-45-8; lithiomethylbenzobis(ethyloxazole), 81534-94-3; acetaldehyde, 75-07-0; propionaldehyde, 123-38-6; benzylamine, 100-46-9; 2,5-dihydroxybenzene, 615-94-1; 1,2,4,5-tetrahydroxybenzene, 636-32-8; 1,2:4,5-bis(cyclohexylidenedioxy)benzene, 182-86-5; 1,2:4,5-bis(cyclohexylidenedioxy)-3-methylbenzene, 98332-11-7; allylamine, 107-11-9; chloranil, 118-75-2.