Reactions of Primary and Secondary Amines with Substituted Hydroquinones: Nuclear Amination, Side-Chain Amination, and Indolequinone Formation

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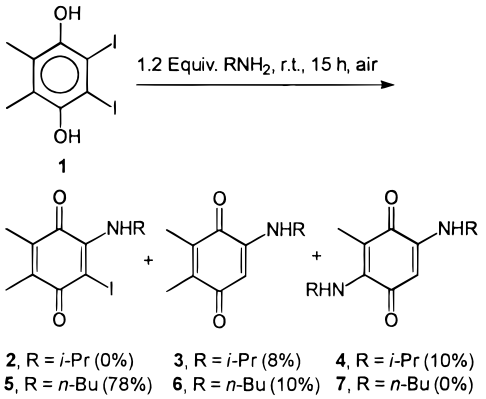
Introduction

Nitrogen addition and substitution chemistry[1] of quinonoid systems is very rich, versatile, and important from a synthetic point of view. Michael addition reactions and substitution chemistry[2,3] of quinones have been studied since the 19th century.[4,5] Nitrogen addition to quinonoid compounds can occur in two ways, (1) nuclear amination and (2) side-chain substitution. Nuclear amination[6] of a quinonoid ring occurs by the substitution of hydrogen, alkyl groups, or halides by an amine moiety. Side-chain substitution or amination[7,8] takes place by the replacement of hydrogen from an alkyl group on the quinonoid ring by an amine. Both primary and secondary amines are known to give nuclear and side-chain amination. However, nuclear amination (Scheme 1) is more usual in the case of primary amines while side-chain amination is more typical with secondary amines having bulky alkyl groups. Recently the nuclear amination reaction has been used to form quinonamine polymers for coatings on metal surfaces.[9−11]

The study of the syntheses of N-heterocycles is of interest because such systems are present in large numbers of biologically important natural[12,13] and unnatural compounds. A broad spectrum of antimicrobials contains heterocycles as structural units, and some of them have the quinonoid nucleus present. There has been significant interest in the study of antibacterial and antimicrobial properties of quinone−hydroquinone systems.[14] Indolequinone and isoindolequinones are present in naturally occurring compounds.[15] A novel high yield synthesis of isoindolequinones has been reported in our previous publication.[16]

Scheme 1



The Heck reaction, which involves the palladium-catalyzed coupling of vinyl or aryl halides with alkenes, is well-known.[17] It has been used to form polycyclic[18] and bicyclic nitrogen heterocycles from acyclic precursors.[19] Hegedus and co-workers have extensively studied palladium-mediated intramolecular amination of olefins with primary and secondary amines.[20] This reaction involves the formation of a new C−N bond by nucleophilic addition of an amine to an alkene that is η^2-bonded to a Pd(II) center. Cationic heterocycles have been formed using this synthetic strategy with polysubstituted alkenes and tertiary amines.[21] Palladium-catalyzed cyclization reactions of various allyl-containing diaminobenzoquinones to form substituted indolequinone systems have been reported.[22] Palladium catalyzed aryl halide amination with primary and secondary amines has been investigated by Hartwig[23] and Buchwald.[24]

(1) Finley, K. T. *The Chemistry of the Quinonoid Compounds*; Patai, S., Ed.; John Wiley & Sons: London, New York, Sydney, Toronto, 1974; pp 900−1101.
(2) Yamaoka, T.; Nagakura, S. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 2971.
(3) Crosby, A. H.; Lutz, R. E. *J. Am. Chem. Soc.* **1956**, *78*, 1233.
(4) Plimpton, R. T. *J. Chem. Soc.* **1880**, *49*, 633.
(5) Meyer, G.; Suida, H. *Justus Liebigs Ann. Chem.* **1918**, *416*, 181.
(6) Cameron, D. W.; Giles, R. G. F.; Titman, R. B. *J. Chem. Soc. C* **1969**, 1245.
(7) Cameron, D. W.; Scott, P. M.; Todd, L. *J. Chem. Soc.* **1964**, 42.
(8) Cameron, D. W.; Cromartie, R. I. T.; Hamied, Y. K.; Scott, P. M.; Todd, L. *J. Chem. Soc.* **1964**, 62.
(9) Kaleem, K.; Chertok, F.; Erhan, S. *J. Polym. Sci., Part A: Polym. Chem.* **1989**, *27*, 865.
(10) (a) Nithianandam, V. S.; Erhan, S. *J. Appl. Polym. Sci.* **1991**, *42*, 2385. (b) Nithianandam, V. S.; Kaleem, K.; Chertok, F.; Erhan, S. *J. Appl. Polym. Sci.* **1991**, *42*, 2893. (c) Nithianandam, V. S.; Chertok, F.; Erhan, S. *J. Appl. Polym. Sci.* **1991**, *42*, 2899.
(11) Nithianandam, V. S.; Erhan, S. *Polymer* **1991**, *32*, 1146.
(12) Remers, W. A.; Spande, T. F. In *Indoles* Part Three; Houlihan, W. J., Ed.; The Chemistry of Heterocyclic Compounds Monograph; John Wiley & Sons: New York, 1979.
(13) Gilchrist, T. L. *Heterocyclic Chemistry*; John Wiley & Sons: New York, 1985.
(14) For example see: (a) Cooper, E. A.; Haines, R. B. *Biochem J.* **1928**, *22*, 317. (b) Cooper, E. A.; Haines, R. B. *Biochem. J.* **1929**, *23*, 4. (c) Johnson, M. G.; Kiyokawa, H.; Tani, S.; Koyama, J.; Morris-Natschke, S. L.; Mauger, A.; Bowers-Daines, M. M.; Lange, B. C.; Lee, K.-H. *Bioorg. Med. Chem.* **1997**, *5*, 1469.
(15) Thomson, R. H. *Naturally Occurring Quinones III: recent advances*; Chapman and Hall: New York, 1987; pp 657−658.
(16) Chakraborty, M.; McConville, D. B.; Koser, G. F.; Tessier, C. A.; Saito, T.; Rinaldi, P. L.; Youngs, W. J. *J. Org. Chem.* **1997**, *62*, 8193.
(17) (a) Heck, R. F. *Acc. Chem. Res.* **1979**, *12*, 146. (b) Heck, R. F. *Org. React.* **1982**, *27*, 345.
(18) Zhang, Y.; Wu, G.-Z.; Angel, G.; Negishi, E. *J. Am. Chem. Soc.* **1990**, *112*, 8590.
(19) Harris, G. D., Jr.; Herr, R. J.; Weinreb, S. M. *J. Org. Chem.* **1992**, *57*, 2528.
(20) Hegedus, L. S. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1113.
(21) van der Schaaf, P. A.; Sutter, J.-P.; Grellier, M.; van Mier, G. P. M.; Spek, A. L.; van Koten, G.; Pfeffer, M. *J. Am. Chem. Soc.* **1994**, *116*, 5134.
(22) Weider, P. R.; Hegedus, L. S.; Asada, H.; D'Andreq, S. V. *J. Org. Chem.* **1985**, *50*, 4276.
(23) (a) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609. (b) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969. (c) Hartwig, J. F.; Richards, S.; Barañano, D.; Paul F. *J. Am. Chem. Soc.* **1996**, *118*, 3626. (d) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 4206. (e) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217. (f) Louie, J.; Paul, F.; Hartwig, J. F. *Organometallics* **1996**, *15*, 2794.
(24) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215.

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Table 1. Yields (%) of Monoaminated (5, 6) and Diaminated (7) Compounds from Reactions of 1 and $BuNH_2$ under Different Reaction Conditions

1.2 equiv of amine, rt, air, CH_2Cl_2, 15 h		excess amine, air, rt, 15 h		excess amine, air, reflux, 20 min		excess amine, argon, reflux, 1 d		excess amine, Pd(II)[a], argon, reflux, 1 d	
mono(I) **5**	mono(II) **6**	mono **6**	di **7**	mono **6**	di **7**	mono **6**	di **7**	mono **6**	di **7**
78	10	none	27	none	44	37	48	43	50

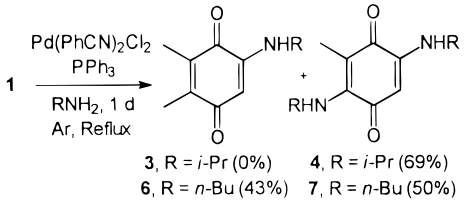
[a] $Pd(PhCN)_2Cl_2$ and PPh_3.

Here we present nuclear amination[25] and side-chain amination reactions[26,27] which were observed in the reaction of 2,3-diiodo-5,6-dimethylhydroquinone (**1**) or 2,3-dimethylhydroquinone (**8**) with primary and secondary amines and the first crystallographic characterization of the amination products. We have studied nuclear amination in regards to degree of amination, stages of amination, and diheteroamination using two different amines. Side-chain amination has been studied with secondary amines such as diethylamine and diisopropylamine. We also report a new palladium-catalyzed synthesis of an indolequinone derivative (**11**) from the reaction of **1** and *i*-Pr_2NH. The diaminated product (butyl derivative, **7**), indolequinone (**11**), and the side-chain aminated product (**12**) have been characterized crystallographically.

Results and Discussion

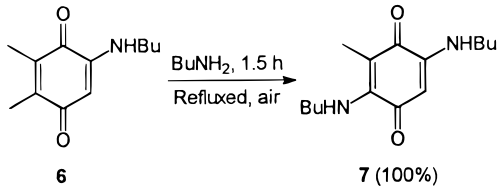
Nuclear amination of **1** appears to proceed in stages starting with the replacement of an iodide by an amine. This is followed by the replacement of the other iodide by hydrogen and the substitution of a methyl group by a second amine molecule. The second amine always bonds to the position para to the first amine even at the cost of methyl group replacement. Reaction of **1** with 1.2 equiv of *i*-$PrNH_2$ in CH_2Cl_2 for 15 h under air gives the monoaminated compound 2,3-dimethyl-6-(isopropylamino)-1,4-benzoquinone (**3**) and the diaminated compound 3,6-bis(isopropylamino)toluquinone (**4**, Scheme 1). None of the intermediate 2,3-dimethyl-5-iodo-6-(isopropylamino)-1,4-benzoquinone (**2**) remains after 15 h, but it is isolated when the reaction is run for 3.5 h. Butylamine gives two types of monoaminated compounds under the same conditions for 15 h: 2,3-dimethyl-5-iodo-6-(*n*-butylamino)-1,4-benzoquinone (**5**), containing a single iodine atom, and 2,3-dimethyl-6-(*n*-butylamino)-1,4-benzoquinone (**6**). Only the initial stages of monoamination products (**5**, **6**) are observed for $BuNH_2$, while *i*-$PrNH_2$ gives the final stage of amination forming the diaminated product **4** in 15 h. The low yields in case of *i*-$PrNH_2$ are due to the formation of uncharacterized black materials after the reaction, but no starting material is recovered.

The yields of the aminated compounds have been increased by running these reactions under argon using amines as reactants as well as solvents. Use of the catalyst {$Pd(PhCN)_2Cl_2/PPh_3$}, however, did not increase the yields significantly. Reaction of **1** with *i*-$PrNH_2$ under reflux and argon for 1 day (eq 1) gives only the diaminated product **4** in 69% yield. However, $BuNH_2$ gives both the monoaminated compound **6** in 37% yield and



(1)

the diaminated compound 3,6-bis(*n*-butylamino)toluquinone (**7**) in 48% yield. Reaction of $BuNH_2$ in the presence of palladium(II) gives **6** in 43% yield and **7** in 50% yield (eq 1). Table 1 shows the comparison of the yields of the aminated products under different reaction conditions. The monobutylaminated product **6** undergoes complete conversion to the dibutylaminated compound **7** in refluxing $BuNH_2$ in air (eq 2). The dibutylaminated product **7** has been characterized by NMR, IR, elemental analysis, mass spectrometry, and X-ray crystallography (see Supporting Information).



(2)

Compound **7** was previously synthesized[26a] in 32% yield from the reaction of toluquinone and $BuNH_2$. Formation of **4** is also described in a brief report[26b] from the reaction of toluquinone and *i*-$PrNH_2$ in EtOH.

Diamination using two different amines has been studied in the reactions of 2,3-dimethylhydroquinone (**8**) with octadecylamine and $BuNH_2$. Reaction of **8** with 5 equiv of octadecylamine in EtOH at room temperature under air gives the monoaminated product 2-octadecylamino-5,6-dimethylquinone (**9**) in 54% yield (Scheme 2). Due to the comparatively slow reaction rate for octadecylamine only the monoaminated product is obtained at room temperature. The yield of **9** decreases to 39% when only 1 equiv of octadecylamine is used. Reaction of **9** with excess $BuNH_2$ under reflux in air for 1.5 h gives the diheteroaminated product 2-octadecylamino-5-(*n*-butylamino)-6-methylquinone (**10**) in 80% yield (Scheme 2). Formation of the octadecylaminated product **9** shows that the primary amines with long chain alkyl groups can undergo nuclear amination. Successful formation of **10** offers the possibility of diheteroamination.

The suggested mechanism for nuclear amination in air has been reported[28a] to involve oxygen uptake and the formation of formaldehyde. Generally the quinonoid form is observed in the final products of nuclear amination. Alternatively, the reaction may be proceeding by a radical mechanism.

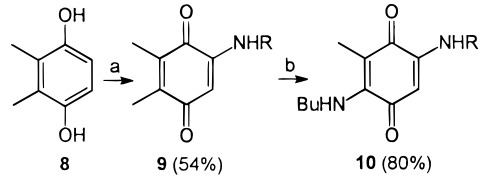
(25) (a) Kumanotani, J.; Kagawa, F.; Hikosaka, A. Sugita, K. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2118. (b) Yoshihira, K.; Sakaki, S.; Ogawa, H.; Natori, S. *Chem. Pharm. Bull.* **1968**, *16*, 2383.

(26) Hikosaka, A. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 3928.

(27) (a) Cameron, D. W.; Scott, P. M. *J. Chem. Soc.* **1964**, 5569. (b) Dean F. M.; Houghton, L. E.; Morton, R. B. *J. Chem. Soc. C* **1968**, 2065.

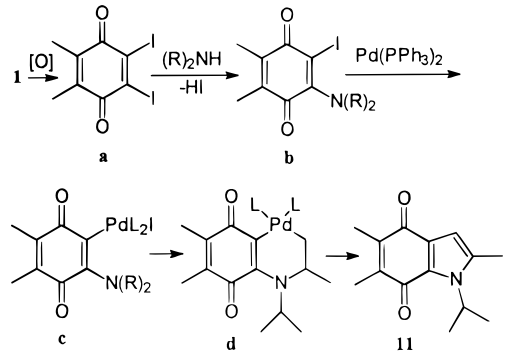
(28) Diao, L.; Yang, C.; Wan, P. *J. Am. Chem. Soc.* **1995**, *117*, 5369.

Scheme 2

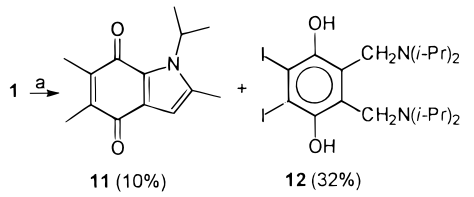


a: 5 eq. RNH_2, EtOH, 1 d, r. t., air; R= $(CH_2)_{17}CH_3$
b: excess $BuNH_2$, reflux, 1.5 h, air

Scheme 3



During the investigation of the amination of **1** with *i*-Pr_2NH in the presence of a palladium catalyst we encountered an unexpected reaction forming an indolequinone derivative and a side-chain aminated product. The cascade reaction of **1** with *i*-Pr_2NH in the presence of a stoichiometric amount of bis(benzonitrile)palladium-(II) dichloride [$Pd(PhCN)_2Cl_2$] and PPh_3 under argon gave 1-isopropyl-2,5,6-trimethylindole-4,7-quinone (**11**) in 10% yield and the side-chain aminated product 2,3-diiodo-5,6-bis((diisopropylamino)methyl)hydroquinone (**12**) in 32% yield (eq 3).



(3)

a: $Pd(PhCN)_2Cl_2$, PPh_3, $(i\text{-}Pr)_2NH$, refluxed, 1 d

Formation of **11** was not observed when this reaction was run at room temperature. This new Pd-catalyzed formation of an indolequinone derivative **11** from the diiodohydroquinone (**1**) and *i*-Pr_2NH seems promising, as it is a multistep, one-pot synthesis from readily available precursors. The proposed mechanism for this multistep reaction is shown in Scheme 3. The low overall yield (10%) from the cascade reaction can be rationalized with respect to the involvement of at least six steps (of average 68% yield) in the formation of **11**: (1) oxidation of the hydroquinone to quinone **a**; (2) an addition elimination reaction of an amine with a quinone to form **b**; (3) coordination and insertion of palladium into the carbon−halogen bond to form **c**; (4) activation of a C−H bond of a methyl of isopropylamine to form the six-membered cyclic intermediate **d** containing Pd in the ring; (5) reductive elimination of Pd; (6) dehydrogenation to form the five-membered pyrrole ring. It is conceivable that the aforementioned steps may not occur in the sequence shown and that other steps may also be involved.

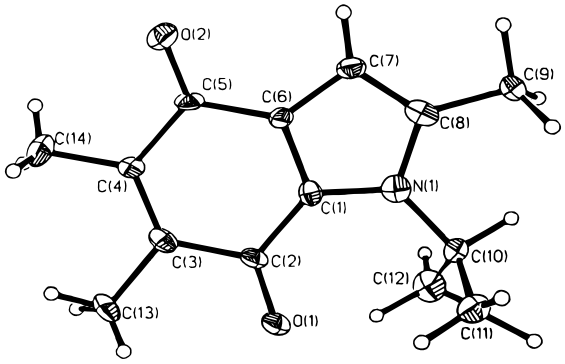


Figure 1. Thermal ellipsoid plot of indolequinone **11**.

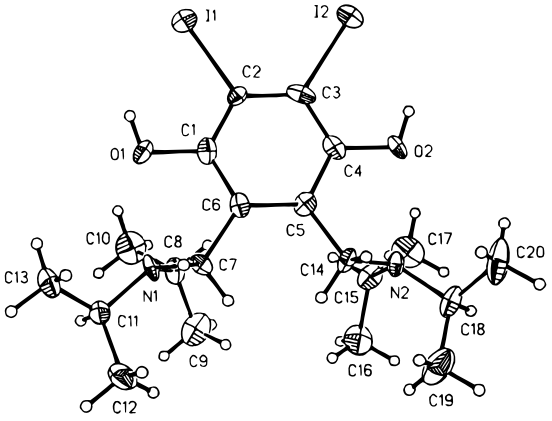


Figure 2. Thermal ellipsoid plot of side-chain aminated product **12**.

Compound **11** has been characterized by X-ray crystallography (Figure 1) and spectroscopy.

The side-chain aminated product **12** was first observed as one of the products from the Pd-assisted synthesis of indolequinone. Later, it was synthesized in 37% yield without Pd catalyst from the reaction of **1** with *i*-Pr_2NH in air at 50 °C. The structure of **12** has also been confirmed by X-ray crystallography (Figure 2). Reaction of **1** with diethylamine gives a side-chain aminated product that has been characterized spectroscopically. The mechanism of side-chain amination is not defined.[6] However a tandem reaction involving formation of quinone methides,[28,29] Michael addition of *i*-Pr_2NH to the CH_2 groups, and proton transfers is proposed as the mechanism for the formation of **12** from **1**.

Conclusions

Though nuclear amination and side-chain amination reactions have been studied before, we have increased the yields of the aminated compounds. We have also confirmed the structures of these products by X-ray crystallography. This is the first crystallographic proof of the methyl group replacement in nuclear amination, presumably by a series of steps culminating in a retro-Mannich reaction and hydrogen replacement in side-chain amination reactions. The effects of nucleophilicity, basicity, and steric requirements determine whether nuclear versus side-chain amination takes place in these systems. Electronic factors have been shown to be important in determining whether nuclear or side chain

(29) Skibo, E. B. *J. Org. Chem.* **1992**, *57*, 5874.

amination occurs in related systems.[30] The presence of bulky alkyl groups on amines generally promotes side-chain amination. Therefore, side-chain amination is observed in the case of *i*-Pr_2NH due to its higher basicity and larger steric requirement but not for reactions of primary amines (i.e. *i*-$PrNH_2$, $BuNH_2$, octadecylamine) with **1**. The rate of nuclear amination is slower for primary amines with larger R groups as evidenced by the comparatively slower reaction rates of butylamine and octadecylamine compared to that of isopropylamine. When amination occurs with excess amine, the first monoaminated product with iodine ortho to the amine is not isolable. Usually monoaminated products are reactive and convert to diaminated products. Degree of amination depends on the reaction time, amount of amine, and reaction temperature. The new multistep one-pot synthesis of the indolequinone seems promising for the synthesis of related derivatives with other secondary amines. Synthesis of indolequinones and amination reactions are under further investigation. These nuclear aminated and side-chain aminated compounds can be used as novel redox active ligands.

Experimental Section

Materials. All chemicals were reagent grade materials. The compounds 2,3-diiodo-5,6-dimethylhydroquinone (**1**)[31] and bis-(benzonitrile)palladium dichloride[32] were prepared by literature procedures. The compounds 2,3-dimethylhydroquinone (**8**), butylamine, octadecylamine (Aldrich), isopropylamine, diisopropylamine (Lancaster), triphenylphosphine (Janssen Chimica), carbon tetrachloride, acetonitrile (Fisher), and deuterated chloroform (Cambridge Isotope Laboratory) were used as received. Diisopropylamine was distilled from KOH.

General Techniques. Field desorption mass spectra (FDMS) were obtained on a Finnigan MAT95Q mass spectrometer by Dr. Robert Lattimer at B F Goodrich. Some of the reactions were carried out in air and some under argon using standard Schlenk techniques[33] as mentioned. Reaction temperatures were monitored externally. Melting points were recorded under air. All reactions were monitored by thin-layer chromatography carried out on E. Merck silica gel plates (60F-254) using UV light. Flash column chromatography[34] was carried out using silica gel (Baker 40 μm). Elemental analyses were done by Midwest Microlab in Indianapolis, IN, and Schwarzkopf Microanalytical Laboratory in Woodside, NY.

2,3-Dimethyl-6-(isopropylamino)-1,4-benzoquinone (3). To **1** (400 mg, 1.02 mmol) in CH_2Cl_2 (8 mL) was added *i*-$PrNH_2$ (0.1 mL, 1.2 mmol) at room temperature, and the yellow solution was stirred in air. The solution gradually turned violet after 0.5 h and was stirred for 15 h. The volatiles were removed under vacuum. Flash column chromatography of the crude solid with 7% ethyl acetate in petroleum ether gave orange-violet solid **3** in 8% yield (15 mg): mp 89−90 °C; ^{1}H NMR ($CDCl_3$) δ 1.24 (d, 6 H, J = 6.5 Hz, 2 CH_3 on isopropyl), 1.98 (vw q, 3 H, J = 1.1 Hz, CH_3 on quinone), 2.04 (vw q, 3 H, J = 1.1 Hz, CH_3 on quinone), 3.50 (dh, 1H, J = 6.3, 7.1 Hz, H on isopropyl), 5.43 (s, H, vinyl H), 5.43 (br s, 1 H, N−H); ^{13}C NMR ($CDCl_3$) δ 12.0, 13.0, 21.9, 44.0, 98.0, 136.5, 144.7, 145.5, 184.5, 185.9; IR (CCl_4) ν 3383 (m, N−H) 1642 (s, C═C), 1602 (vs, C═O), 1507 (s, amido type), 2927 (m, CH_3) cm^{-1}; UV−vis (CH_3CN) λ_{max} (log ϵ) 212 (4.51), 288 (4.26), 480 (3.52) nm; HRMS (EI) calcd for $C_{11}H_{15}NO_2$ *m/e* 193.1103, found *m/e* 193.1101 (error −1.1 ppm).

3,6-Bis(isopropylamino)toluquinone (4). To a degassed mixture of **1** (400 mg, 1.02 mmol), $Pd(PhCN)_2Cl_2$ (19.6 mg, 0.04 mmol), and PPh_3 (32.2 mg, 0.12 mmol), degassed *i*-$PrNH_2$ (15 mL) was added and the violet solution was refluxed for 1 d under argon. Excess amine was removed under vacuum. Flash column chromatography of the crude solid with 7% ethyl acetate in petroleum ether gave violet solid **4** in 69% yield (166 mg): mp 126.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.24 (d, 6 H, 2 CH_3), 1.26 (d, 6 H, 2 CH_3), 2.05 (s, 3 H, CH_3), 3.59 (h, 1 H on isopropyl), 4.24 (h, 1 H on isopropyl), 5.25 (s, 1 vinyl H), 6.52 (br d, N−H), 6.65 (br d, N−H); ^{13}C NMR ($CDCl_3$) δ 10.4, 21.9, 24.3, 44.2, 45.5, 92.2, 101.8, 147.1, 149.9, 179.4, 179.6; IR (CCl_4) ν 3277 (w, N−H), 3338 (w, N−H), 1641 (w, C═C), 1611 (s, C═O), 1578 (s, C═O), 1497 (vs, amido type), 2932 (w, CH_3) cm^{-1}; UV−vis (CH_3CN) λ_{max} (log ϵ) 220 (4.48), 334 (4.53) nm; FDMS found for $C_{13}H_{20}O_2N_2$ *m/e* 236 (M^+). Anal. Calcd for $C_{13}H_{20}O_2N_2$: C, 66.10; H, 8.47; N, 11.86. Found: C, 66.01; H, 8.62; N, 11.65.

2,3-Dimethyl-5-iodo-6-(*n*-butylamino)-1,4-benzoquinone (5). To **1** (400 mg, 1.02 mmol) in CH_2Cl_2 (8 mL), was added *n*-$BuNH_2$ (0.1 mL, 1.2 mmol) at room temperature, and the yellow solution was stirred in air. The solution gradually turned violet after 0.5 h and was stirred for 15 h. The volatiles were removed under vacuum. Flash column chromatography of the crude solid with 7% ethyl acetate in petroleum ether gave orange-violet solid **5** in 78% yield (264 mg): mp 77−78 °C; ^{1}H NMR ($CDCl_3$) δ 0.96 (t, 3 H, J = 7.1 Hz, CH_3), 1.48 (m, 2 H, CH_2), 1.68 (m, 2 H, CH_2), 2.00 (q, 3 H, J = 1.3 Hz, CH_3), 2.12 (q, 3 H, J = 1.1 Hz, CH_3), 3.80 (td, 2 H, J = 6.86, 7.1 Hz, CH_2), 5.85 (br s, 1 H, N−H); ^{13}C NMR ($CDCl_3$) δ 12.3, 13.9, 14.6, 19.9, 32.8, 45.2, 136.1, 143.5, 149.2, 179.9, 182.0; IR (CCl_4) ν 3342 (m, N−H) 1661 (s, C═C), 1583 (vs, C═O), 1514 (m, amido type), 2942 (m, CH_3) cm^{-1}; UV−vis (CH_3CN) λ_{max} (log ϵ) 212 (4.25), 285 (4.03), 502 (3.34) nm; FDMS found for $C_{12}H_{16}NO_2I$, *m/e* 333 (M^+). Anal. Calcd for $C_{12}H_{16}NO_2I$: C, 43.24; H, 4.80; N, 4.20. Found: C, 43.85; H, 4.93; N 4.09.

2,3-Dimethyl-6-(*n*-butylamino)-1,4-benzoquinone (6). To a degassed mixture of **1** (400 mg, 1.02 mmol), $Pd(PhCN)_2Cl_2$ (19.6 mg, 0.04 mmol), and PPh_3 (32.2 mg, 0.12 mmol) was added degassed *n*-$BuNH_2$ (15 mL), and the violet solution was refluxed for 1 d under argon. Excess amine was removed under vacuum. Flash column chromatography of the crude solid with 7% ethyl acetate in petroleum ether gave orange-violet solid **6** in 43% yield (90 mg): mp 80 °C; ^{1}H NMR ($CDCl_3$) δ 0.94 (t, 3 H, J = 7.1 Hz, CH_3 on butyl group), 1.40 (m, 2 H, CH_2 on butyl), 1.61 (m, 2 H, CH_2 on butyl), 1.98 (vwq, 3 H, J = 1.1 Hz, CH_3 on quinone ring), 2.04 (vwq, 3 H, J = 1.1 Hz, CH_3 on quinone ring), 3.07 (td, 2 H, J = 7.1, 5.7 Hz, N−CH_2 on butyl), 5.42 (s, 1 H, vinyl H), 5.64 (br s, N−H); ^{13}C NMR ($CDCl_3$) δ 12.0, 13.0, 13.8, 20.3, 30.4, 42.3, 97.8, 136.4, 144.8, 146.7, 184.3, 185.9; IR (CCl_4) ν 3396 (m, N−H) 1642 (s, C═C), 1604 (vs, C═O), 1508 (s, amido type), 2932 (m, CH_3) cm^{-1}; UV−vis (CH_3CN) λ_{max} (log ϵ) 212 (4.01), 288 (3.73), 478 (3.01) nm; FDMS found for $C_{12}H_{17}NO_2$, *m/e* 207 (M^+). Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.56; H, 8.21; N, 6.76. Found: C, 69.26; H, 8.37; N 6.60.

3,6-Bis(*n*-butylamino)toluquinone (7). To a degassed mixture of **1** (400 mg, 1.02 mmol), $Pd(PhCN)_2Cl_2$ (19.6 mg, 0.04 mmol), and PPh_3 (32.2 mg, 0.12 mmol), was added degassed *n*-$BuNH_2$ (15 mL), and the violet solution was refluxed for 1 d under argon. Excess amine was removed under vacuum. Flash column chromatography of the crude solid with 7% ethyl acetate in petroleum ether gave violet solid **7** in 50% yield (134 mg): mp 108 °C; ^{1}H NMR ($CDCl_3$) δ 0.92 (t, 3 H, CH_3), 0.96 (t, 3 H, CH_3), 1.41 (m, 4 H, 2 CH_2), 1.62 (m, 4 H, 2 CH_2), 2.08 (s, 3 H, CH_3), 3.14 (dt, 2 H, N−CH_2), 3.58 (dt, 2 H, N−CH_2), 5.24 (s, 1 H, vinyl H), 6.62 (s, 1 H, N−H), 6.72 (s, 1 H, N−H); ^{13}C NMR ($CDCl_3$) δ 10.5, 13.9, 13.9, 20.1, 20.4, 30.5, 33.0, 42.4, 44.9, 91.9, 102.0, 148.2, 151.0, 179.2, 179.3; IR (CCl_4) ν 3295 (m, N−H), 3351 (m, N−H), 1643 (m, C═C), 1609 (s, C═O), 1497 (s, amido type), 2930 (s, CH_3) cm^{-1}; UV−vis (CH_3CN) λ_{max} (log ϵ) 216 (3.35), 240 (1.30, sh), 342 (3.45) nm; FDMS found for $C_{15}H_{24}O_2N_2$, *m/e* 264 (M^+). Anal. Calcd for $C_{15}H_{24}O_2N_2$: C, 68.18; H, 9.09; N, 10.60. Found: C, 68.55; H, 9.34; N, 10.61.

Procedure for the Conversion of 6 to 7. Orange compound **6** was refluxed in butylamine for 1.5 h in air, and the volatiles were removed under vacuum. TLC and NMR showed complete conversion to **7**. The solid residue did not require column chromatography.

5,6-Dimethyl-2-(octadecylamino)-1,4-benzoquinone (9). To **1** (138 mg, 1 mmol) in EtOH (100 mL) was added octadecy-

(30) Skibo, E. B.; Islam, I.; Schulz, W. G.; Zhou, R.; Bess, L.; Boruah, R. *Synlett* **1996**, 297.
(31) Nicolaou, K. C.; Liu, A.; Zeng, Z.; McComb, S. *J. Am. Chem. Soc.* **1992**, *114*, 9279.
(32) Hartley F. R. *Organomet. Chem. Rev. A* **1970**, *6*, 119.
(33) Shriver, D. F.; Drezdzon, M. A. *The Manipulation of Air-Sensitive Compounds*, 2nd ed.; John Wiley and Sons: New York, 1986.
(34) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

lamine (1.347 g, 5 mmol) under air. The solution gradually turned red and was stirred for 17 h at room temperature. The volatiles were removed under vacuum. Flash column chromatography of the crude solid with 5% ethyl acetate in petroleum ether gave red solid **9** in 54% yield (218 mg): mp 77−77.5 °C; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 6.5 Hz, CH_3), 1.25 (m, 30 H, 15 CH_2), 1.62 (t, 2 H, J = 7.1 Hz, CH_2), 1.99 (vwq, 3 H, J = 1.1 Hz, CH_3), 2.05 (vwq, 3 H, J = 1.1 Hz, CH_3), 3.08 (q, 2 H, J = 6.7 Hz, N−CH_2), 5.42 (s, 1 H, vinyl H), 5.61 (s, 1 H, N−H); ^{13}C NMR ($CDCl_3$) δ 11.8, 12.8, 14.2, 22.8, 27.1, 28.2, 29.3, 29.5, 29.6, 29.7, 32.0, 42.4, 97.6, 136.1, 144.4, 146.3, 183.9, 185.4; IR (CCl_4) ν 3397 (m, N−H), 2927 (vs, CH_3), 2855 (s, CH_3), 1642 (s, C═C), 1604 (vs, C═O), 1506 (m, amido type) cm^{-1}; UV−vis (CH_2Cl_2) λ_{max} (log ϵ) 226 (4.33), 289 (4.36), 479 (3.53) nm; HRMS (FAB) calcd for (MH^+) m/e $C_{26}H_{46}NO_2$ 404.3529, found m/e 404.3514 (error −3.6 ppm).

6-Methyl-5-(*n*-butylamino)-2-(octadecylamino)-1,4-benzoquinone (10). To **9** (45 mg, 0.1 mmol) was added *n*-$BuNH_2$ (0.5 mL, 5 mmol) under air. The solution was refluxed for 1.5 h, and it gradually turned violet. The volatiles were removed under vacuum. Flash column chromatography of the crude solid with 5% ethyl acetate in petroleum ether gave violet solid **10** in 80% yield (36 mg): mp 90−90.5 °C; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 6.5 Hz, CH_3), 0.95 (t, 3 H, J = 7.2 Hz, CH_3), 1.26 (m, 32 H, 16 CH_2), 1.63 (m, 4 H, 2 CH_2), 2.08 (s, 3 H, CH_3), 3.13 (q, 2 H, J = 6.6 Hz, N−CH_2), 3.58 (q, 2 H, J = 6.6 Hz, N−CH_2), 5.24 (s, 1 H, vinyl H), 6.63 (s, 1 H, N−H), 6.71 (s, 1 H, N−H); ^{13}C NMR ($CDCl_3$) δ 10.5, 13.9, 14.3, 20.1, 22.9, 27.2, 19.9, 32.8, 45.2, 136.1, 143.5, 149.2, 179.8, 182.0; IR (CCl_4) ν 3295 (m, N−H), 3353 (m, N−H), 1643 (m, C═C), 1612 (s, C═O), 1580 (s, C═O), 1500 (vs, amido type), 2928 (s, CH_3), 2855(s, CH_3) cm^{-1}; UV−vis (CH_3CN) λ_{max} (log ϵ) 226 (4.22), 344 (4.62) nm; MS (FAB) found for $C_{29}H_{52}O_2N_2$, m/e 460. Anal. Calcd for $C_{29}H_{52}O_2N_2$: C, 75.65; H, 11.30; N, 6.08. Found: C, 75.88; H, 11.27; N, 6.06.

1-Isopropyl-2,5,6-trimethylindole-4,7-quinone (11). A mixture of **1** (400 mg, 1.02 mmol), $Pd(PhCN)_2Cl_2$ (19.6 mg, 0.04 mmol), and PPh_3 (32.2 mg, 0.12 mmol) was placed in a Schlenk flask, and it was degassed thoroughly by three pump−fill cycles. Degassed *i*-Pr_2NH (20 mL) was added, and the solution was refluxed for 1 d under argon. Excess amine was removed under vacuum. Flash column chromatography of the crude solid with 4% ethyl acetate in petroleum ether gave orange solid **11** in 10% yield (23.8 mg) along with yellow solid **12** in 32% yield (192 mg). Characterization data for **11** are as follows: mp 102−103 °C; ^{1}H NMR ($CDCl_3$) δ 1.54 (d, 6 H, 2 CH_3 of isopropyl group), 2.01 (q, 3 H, CH_3 on quinone ring), 2.03 (q, 3 H, CH_3 on quinone ring), 2.35 (s, 3 H, CH_3 on N), 6.31 (s, 1 H, vinyl H); ^{13}C NMR ($CDCl_3$) δ 12.2, 12.7, 14.4, 20.9, 49.0, 108.2, 129.1, 138.2, 139.3, 141.6, 177.2, 184.1; IR (CCl_4) ν 2928 (m, CH_3), 2972 (m, CH_3), 1637 (vs, C═O) cm^{-1}; UV−vis (CH_3CN) λ_{max} (log ϵ) 196 (4.40), 228 (4.33), 272 (4.27), 280 (4.25), 336 (3.61, br), 434 (3.28, sh) nm; FDMS found for $C_{14}H_{17}O_2N$, m/e 231 (M^+). Anal. Calcd for $C_{14}H_{17}O_2N$: C, 72.72; H, 7.35; N, 6.06. Found: C, 73.01; H, 7.71; N 5.93.

5,6-Bis((diisopropylamino)methyl)-2,3-diiodohydroquinone (12). A suspension of **1** (100 mg, 0.25 mmol) in *i*-Pr_2NH (15 mL) was heated under air. Within 0.5 h the mixture turned into a solution and was heated at 50 °C for 1 d. It was filtered to remove insoluble materials. The solid was washed with ethyl acetate, and the combined filtrate was concentrated under vacuum. Flash column chromatography of the solid residue with 20% ethyl acetate in petroleum ether gave a pale yellow solid **12** in 37% yield (55.7 mg): mp, starts getting black at 180 °C and does not melt until 263 °C; ^{1}H NMR ($CDCl_3$) δ 1.15 (d, 24 H, 8 CH_3), 3.13 (h, 4 H, 4 C−H), 3.74 (s, 4 H, 2 CH_2); ^{13}C NMR ($CDCl_3$) δ 19.9, 44.7, 48.7, 98.6, 120.2, 152.1; IR (CCl_4) ν 2930 (m, CH_3), 2971 (s, CH_3), 2702 (w, br due to strongly H-bonded OH) cm^{-1}; UV−vis (CH_3CN) λ_{max} (log ϵ) 214 (4.51), 318 (3.88) nm; FDMS found for $C_{20}H_{34}O_2N_2I_2$, m/e 588 (M^+). Anal. Calcd for $C_{20}H_{34}O_2N_2I_2$: C, 40.81; H, 5.78; N, 4.76. Found: C, 41.03; H, 6.00; N, 4.78.

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Supporting Information Available: Tables of X-ray data for compound **7** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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