Extension of the Nenitzescu Reaction to Simple Ketones Provides an Efficient Route to 1′-Alkyl-5′-hydroxynaltrindole Analogues, Potent and Selective δ-Opioid Receptor Antagonists

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The well-established Nenitzescu reaction of imines of β-dicarbonyl systems, as their enamine tautomers, with benzoquinone has been applied to a wide range of such imines to give 5-hydroxyindoles, some of which are of significant biological importance. This reaction has now been extended to the benzylimines of simple ketones, including those of the potent μ-opioid receptor antagonists naltrexone and naloxone. The products of the latter reactions, 1′-benzyl-5′-hydroxyindolomorphinans (**7**), are potent δ-opioid receptor (DOR) antagonists, confirming the enhancement of DOR antagonist potency and selectivity resulting from the introduction of the 1′-benzyl group.

Introduction

The remarkable range of biological activity shown by molecules containing indole nuclei encourages the development of new or improved methods for the construction of this ring system. Since its discovery 75 years ago, the Nenitzescu synthesis of 5-hydroxyindoles has been applied to the synthesis of complicated indolic molecules, including several of physiological significance.[1−3] The mechanism of the Nenitzescu reaction involves the Michael addition of the secondary enamine of a β-dicarbonyl system to a *p*-benzoquinone followed by several steps, including an internal oxidation−reduction.[4,5] To our knowledge there are no reports in the literature of the Nenitzescu reaction involving the imines of simple ketones, which would be required to react in their enamine tautomeric form.

Our interest in indole chemistry has been particularly directed to the indolomorphinan structure since the discovery of naltrindole (NTI, **1a**; Chart 1), the first nonpeptidic δ-opioid receptor (DOR) antagonist.[6] We have been attracted to the reactions of ketone benzylimines (as their enamine tautomers) with Michael acceptors and have adapted these reactions to give pyrrolomorphinan structures (**2a**, **3**, **4**) and the analogous pyridomorphinan structures (**5**) from oxymorphone benzylimines (**6**).[7−9] We now report that we have successfully used these imines in the Nenitzescu reaction to give 1′-benzyl-5′-hydroxyindolomorphinans (**7a**, **7b**), which are high potency, selective DOR antagonists. The Nenitzescu reaction has also been applied successfully to the benzylimines of several other ketones, proving that a stabilized enamine tautomeric form of the imine of a β-dicarbonyl system is not a structural prerequisite for the Nenitzescu reaction.

Results and Discussion

Investigation of the reaction of the in situ generated benzylimines of naltrexone (**6a**) and naloxone (**6b**) with benzoquinone used conditions very similar to those that had been used in our earlier studies of the reaction of these imines with other Michael acceptors.[8,9] This involved one-pot reaction conditions somewhat similar to those employed by Meyer[10] but allowing the imine to form before introduction of the Michael acceptor in ethanol solution. From naltrexone, 1′-benzyl-5′-hydroxynaltrindole (**7a**) was obtained in 55% yield, but the yield of the equivalent 17-allyl analogue (**7b**) from naloxone was only 20% (Scheme 1). To allow selective derivatization of the indole phenolic group in **7a**, the Nenitzescu reaction with the benzylimine of the 3-O-benzyl ether of naltrexone (**6c**) was investigated. When the benzoquinone was introduced into the reaction mixture in ethanol solution, the reaction gave a dirty mixture from which only 10% of the desired product could be isolated. Since nitromethane is the usually preferred solvent for the Nenitzescu reaction,[4] the reaction was repeated in this solvent and a 55% isolated yield of **7c** obtained.

For the investigation of the reaction of the benzylimines of some simpler ketones with benzoquinone, nitromethane was used as solvent. Color changes similar to those reported for standard Nenitzescu reactions, which have been attributed to the formation of an electron-transfer complex, were observed.[4] The benzylimines of cyclohexanone and 2-methylcyclohexanone were converted in 60% and 40% yield, respectively, into tetrahydrocarbazole derivatives **8a** and **8b**. Deoxybenzoin benzylimine gave a 60% yield of 1-benzyl-2,3-diphenyl-5-hydroxyindole (**9**) and α-tetralone benzylimine a 59% yield of 1,2-benzo-9-benzyl-3,4-dihydro-6-hydroxycarbazole (**10**) with only minor contamination from the carbazole (**14**). The product from the reaction of the benzylimine of β-tetralone was predominantly that expected from reaction of the thermodynamically favored enamine. Thus, 3,4-benzo-9-benzyl-1,2-dihydro-6-hydroxycarbazole (**11**) was formed and not the alternative product **12**. There was also ^{1}H NMR and mass spectral evidence that about 15% of the product was the result of dehydrogention to the equivalent carbazole

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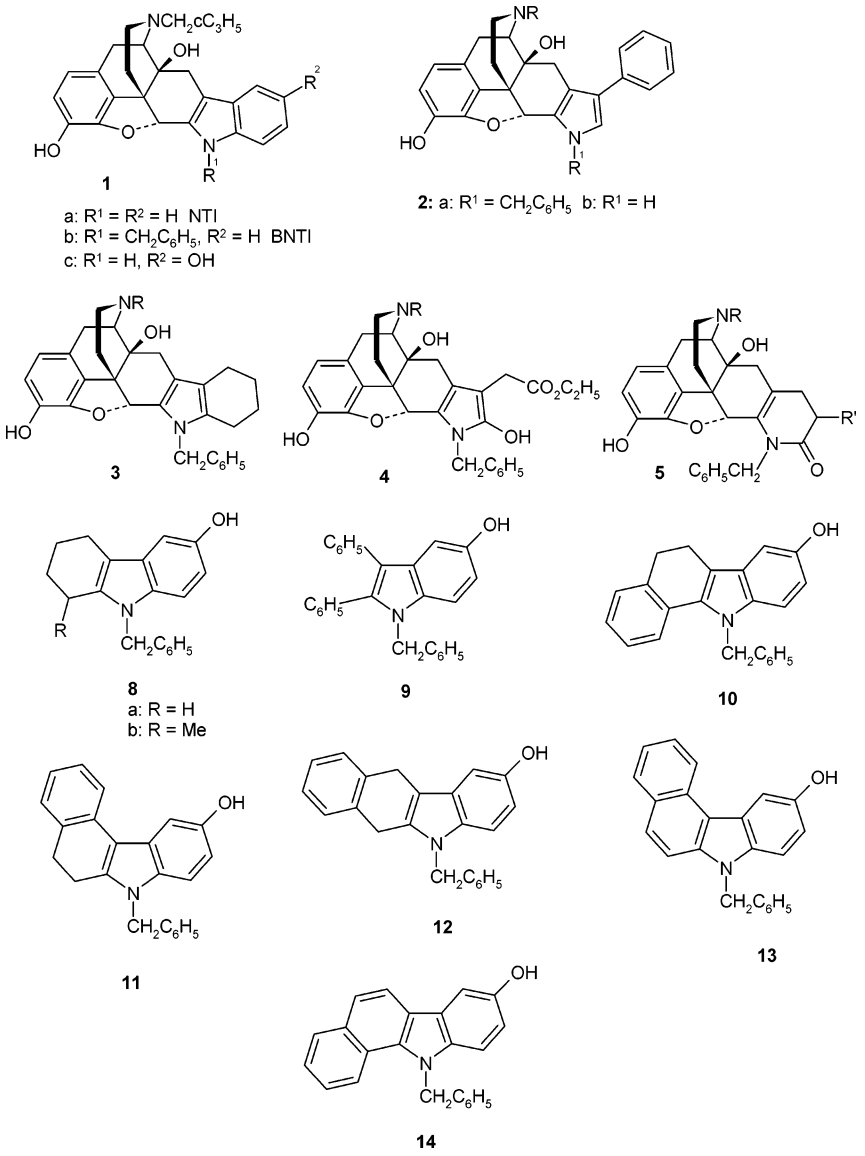
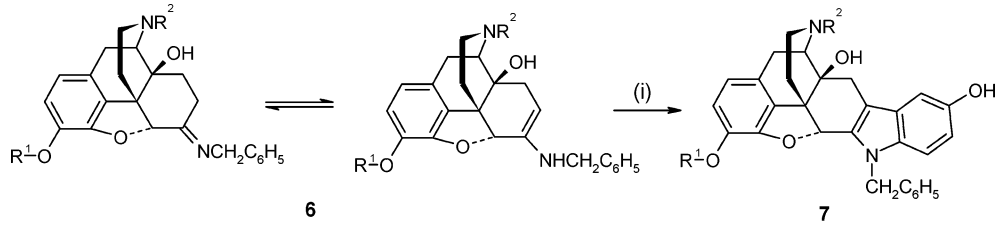
Chart 1



Scheme 1[a]



(a) R^1 = H, R^2 = $CH_2cC_3H_5$ (b) R^1 = H, R^2 = $CH_2CH{=}CH_2$ (c) R^1 = $CH_2C_6H_5$, R^2 = $CH_2cC_3H_5$

[a] (i) 1,4-Benzoquinone, $MeNO_2$ or EtOH.

(**13**), though this could not be obtained free from the principal product.

The indolomorphinan derivatives **7a** and **7b** from naltrexone and naloxone were evaluated in binding assays in human recombinant opioid receptors transfected into Chinese hamster ovary (CHO) cells in which the displaced radioligands were [^{3}H]DAMGO (μ-opioid receptor, MOR), [^{3}H]Cl-DPDPE (DOR), and [^{3}H]U69593 (kappa opioid receptor, KOR);[11] the data are shown in Table 1. **7a** showed nanomolar affinity for all three opioid receptors with only marginal selectivity for DOR. The DOR affinity of **7b** was a little lower than for **7a**, but its MOR and KOR affinities were significantly lower than those of **7a**, so **7b** had significant DOR binding selectivity. In the [^{35}S]GTPγS assay[11] for opioid functional activity in the same cell lines, both **7a** and **7b** showed potent DOR antagonist activity, having K_e = 0.51 and 1.25 nM, respectively (Table 2)

. They also displayed MOR and KOR antagonist effects but of significantly lower potency than their potency as DOR antagonists, so they were significantly DOR selective. Selectivity values as DOR antagonists

Table 1. Binding Affinities of Compounds to Cloned Human Opioid Receptors Transfected into CHO Cells[a]

	K_i/nM		
ligand	DOR: [^{3}H]Cl-DPDPE	KOR: [^{3}H]U69593	MOR: [^{3}H]DAMGO
7a	2.64 ± 0.80	6.72 ± 0.66	8.68 ± 2.46
7b	4.22 ± 0.10	33.71 ± 2.25	49.0 ± 3.26
1a (NTI)	0.20 ± 0.05	10.1 ± 0.65	6.30 ± 2.30

[a] Each value represents the average of two experiments, each carried out in triplicate.

Table 2. Antagonist Potencies (K_e (nM) ± SEM) in [^{35}S]GTPγS Assays Performed in Cloned Human Opioid Receptors, versus Standard Agonists[a]

	K_e/nM		
ligand	DOR: DPDPE	KOR: U69593	MOR: DAMGO
7a	0.51 ± 0.05	8.04 ± 0.65	4.65 ± 0.59
7b	1.25 ± 0.10	64.4 ± 5.33	21.8 ± 1.87
1a (NTI)	0.11 ± 0.005	4.95 ± 0.32	4.26 ± 0.33

[a] Each value is derived from $n = 5$.

for both **7a** and **7b** were greater than in the binding assays as a result of selective increase of DOR antagonist potency over binding affinity. As in the binding assays the naloxone-derived analogue (**7b**) was substantially more DOR-selective than the naltrexone-derived analogue (**7a**). The published data on the nonbenzylated analogue (**1c**) of **7a** in isolated tissue assays show it to be a low potency nonselective opioid antagonist [K_e(DOR) = 27 nM, K_e(KOR) = 48 nM, K_e(MOR) = 19 nM].[6] Thus, the introduction of the 1′-benzyl group increased DOR antagonist potency approximately 50-fold with smaller increases in MOR (4-fold) and KOR (6-fold) potency giving more favorable DOR selectivity. A similar effect of the 1′-benzyl group was shown in the phenylpyrrolomorphinan (**2a**), which was also a potent DOR antagonist in the [^{35}S]GTPγS assay, whereas the equivalent 1′-H analogue (**2b**) in isolated tissue displayed no DOR-antagonist properties.[12]

Experimental Section

Column chromatography was performed under gravity, over silica gel 60 (35−70 μm) purchased from Merck. Preparative TLC was performed on plates made with Kieselgel 60 $PF_{254+366}$ for preparative TLC, obtained from Merck. The thickness of the silica layer was approximately 1 mm. Analytical TLC was performed using aluminum-backed plates coated with Kieselgel 60 F_{254}, from Merck. The chromatograms were visualized using either UV light (UVGL-58, short wavelength), ninhydrin (acidic), or potassium permanganate (basic). Melting points were carried out using a Reichert-Jung Thermo Galen Kopfler block or a Gallenkamp MFB-595 melting point apparatus and are uncorrected. High- and low-resolution fast atom bombardment (FAB) mass spectra were recorded on a Fisons VG AutoSpec Q instrument, with a matrix of *m*-nitrobenzyl alcohol. High- and low-resolution electron impact (EI) mass spectra were recorded using EI ionization at 70 eV, on a VG AutoSpec instrument, equipped with a Fisons autosampler. ^{1}H NMR and ^{13}C NMR spectra were recorded using JEOL EX 400 (operating at 400 MHz for ^{1}H and 101 MHz for ^{13}C) or JEOL GX270 (operating at 270 MHz for ^{1}H and 68 MHz for ^{13}C) spectrometers. Chemical shifts (δ) are measured in ppm relative to TMS. Coupling constants (J) are expressed in hertz. Microanalysis was performed with a Perkin-Elmer 240C analyzer. Anhydrous THF, DMF, DCM, and MeOH were purchased from Aldrich. All other solvents used were GPR grade, purchased from Merck or Fisher Scientific. Chemicals were purchased from Aldrich, Fluka, Lancaster, and Acros chemical companies.

General Methods. 1′-Benzyl-17-cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-3,14,5′-trihydroxyindolo[2′,3′:6,7]-morphinan (7a). A solution of naltrexone (0.5 g, 1.47 mmol) and benzylamine (0.18 mL, 1.5 mmol) in EtOH was refluxed in the presence of molecular sieves (4 Å) under nitrogen for 3 h. A solution of 1,4-benzoquinone (0.16 g, 1.5 mmol) in EtOH (2.5 mL) was added and allowed to reflux overnight. On completion of the reaction, the mixture was then cooled, filtered, washed with ethanol, evaporated to dryness, and purified by column chromatography using 5% MeOH:DCM as eluent: yield 0.42 g (55%); R_f (10% MeOH:DCM) 0.70; mp (HCl) 238−240 °C; ^{1}H NMR (270 MHz, $CDCl_3$) 7.15 (m, 3H, ArH), 6.94 (d, 1H, J = 8.6, ArH), 6.85 (m, 2H, ArH), 6.48 (m, 3H, ArH), 6.22 (m, 1H, ArH), 5.64 (s, 1H, H-5), 4.94 (d, 1H, J = 17.2, benzylic proton), 4.81 (d, 1H, J = 17.2, benzylic proton), 3.36 (d, 1H, J = 6.3, H-9), 3.10 (d, 1H, J = 18.4, H-10), 2.70 (m, 4H), 2.28 (m, 4H), 1.72 (m, 1H), 0.87 (m, 1H, H-19), 0.55 (m, 2H, H-20 and H-21), 0.15 (m, 2H, H-20 and H-21); ^{13}C NMR (68 MHz, $CDCl_3$) 152.75, 142.59, 138.74, 138.30, 130.85, 128.37, 128.30, 126.89, 126.15, 125.10, 120.56, 119.26, 118.84, 116.83, 115.97, 110.88, 109.70, 95.57, 84.97, 73.41, 62.16, 59.37, 48.05, 46.31, 43.56, 31.20, 28.63, 23.06, 9.36, 4.06, 3.77; EI-MS *m/z* (% rel int) 520 (M^+, 100), 91 (55). Anal. ($C_{33}H_{32}N_2O_4$·HCl·0.75H_2O) C, H, N.

17-Allyl-1′-benzyl-6,7-didehydro-4,5α-epoxy-3,14,5′-trihydroxyindolo[2′,3′:6,7]morphinan (7b). Naloxone (1.0 g, 3.0 mmol), benzylamine (0.35 mL, 3.0 mmol), *p*-toluenesulfonic acid monohydrate (2 mg), 1,4-benzoquinone (0.32 g, 3.0 mmol), and ethanol (10 mL) were reacted as described under **7a**. Purification was by column chromatography using 5% MeOH:DCM as eluent: yield 0.30 g (20%); R_f (10% MeOH:DCM) 0.6; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.73 (d, 1H, J = 12 Hz), 2.55−2.68 (m, 2H), 2.75−2.87 (m, 2H), 3.12−3.21 (m, 4H), 4.85 (d, 1H, J = 16 Hz), 4.96 (d, 1H, J = 16 Hz), 5.18−5.29 (m, 2H), 5.65 (s, 1H, H-5), 6.22 (d, 1H, J = 2.2 Hz), 6.40−6.54 (m, 2H, Ar), 6.82−6.89 (m, 2H, Ar), 6.97 (d, 1H, J = 8.3 Hz), 7.14−7.23 (m, 5H, Ar); ^{13}C NMR (101 MHz, $CDCl_3$) δ 23.0, 26.5, 30.9, 40.0, 43.0, 46.0, 48.1, 57.9, 62.5, 73.4, 85.0, 95.0, 109.0, 110.0, 116.5, 118.0, 119.0, 119.5, 121.0, 125.0, 126.0, 127.0, 128.0, 135.0, 138.5, 138.0, 142.0, 152.5; MS *m/z* (M^+) 506. Anal. ($C_{32}H_{30}N_2O_4$·HCl) C, H, N.

3,1′-Dibenzyl-17-cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-14,5′-dihydroxyindolo[2′,3′:6,7]morphinan (7c). 3-*O*-Benzylated naltrexone (1 g, 2.3 mmol), *p*-toluenesulfonic acid monohydrate (2 mg), and benzylamine (0.27 mL, 2.3 mmol) were stirred under reflux in toluene for 4 h using a Dean−Stark trap to remove H_2O. The reaction mixture was cooled to 10 °C and filtered to remove insoluble materials, and the solvent was removed in vacuo and directly used in the subsequent transformation. This crude imine was dissolved in nitromethane (10 mL) and added to a solution of 1,4-benzoquinone (0.27 g, 2.3 mmol) in nitromethane (10 mL) over 30 min. The initial dark green solution became dark brown red, and a precipitate was formed after 48 h of stirring at room temperature. The reaction mixture was cooled in an ice bath, filtered, and washed with fresh nitromethane. The filtrate thus

obtained was concentrated and purified through flash column chromatography: yield 0.77 g (55%); R_f (5% MeOH:DCM with 1% NH_4OH) 0.5; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.07−0.15 (m, 2H), 0.15−0.34 (m, 2H), 0.57−0.69 (m, 1H), 2.22−2.98 (m, 8H), 3.12 (d, 1H, J = 18.9 Hz, H-10), 3.39 (d, 1H, J = 8.0 Hz), 4.47 (d, 2H, J = 16.8 Hz, benzylic protons), 4.66 (d, 2H, J = 16.8 Hz, benzylic protons), 4.79 (bs, 2H), 5.62 (s, 1H, H-5), 6.01 (bs, 1H, Ar), 6.32−7.43 (m, 15H, Ar); ^{13}C NMR (68 MHz, $CDCl_3$) δ 7.6, 7.8, 13.2, 26.9, 32.7, 35.3, 47.3, 50.2, 51.6, 63.2, 66.0, 75.1, 77.0, 88.4, 99.6, 113.2, 114.3, 83.0, 119.0, 119.9, 122.2, 123.1, 125.0, 130.1, 130.2, 130.5, 131.3, 131.5, 132.0, 132.2, 132.6, 136.0, 141.0, 141.8, 142.1, 146.0, 149.0, 156.6; FAB-MS *m/z* 611 $[M + 1]^+$. Anal. ($C_{40}H_{38}N_2O_4$·HCl·1.5H_2O) C, H, N.

1-Benzyl-4-hydroxy-6,7,8,9-tetrahydrocarbazole (8a). By the analogous procedure as described for **7c**, compound **8a** was prepared with cyclohexanone (0.5 mL, 5.3 mmol), benzylamine (0.6 mL, 5.3 mmol), and 1,4-benzoquinone (0.55 g, 5.3 mmol): yield 0.85 g (60%); R_f (0.3% MeOH:CH_2Cl_2) 0.60; mp 58−60 °C; ^{1}H NMR (270 MHz, $CDCl_3$) 7.24 (m, 4H, ArH), 6.99 (m, 3H, ArH), 6.63 (m, 1H, ArH), 5.18 (d, 2H, J = 12.8, benzylic proton); ^{13}C NMR (68 MHz, $CDCl_3$) 21.1, 22.1, 22.2, 23.2, 46.3, 95.4, 102.7, 108.3, 108.9, 109.5, 109.9, 118.3, 126.1, 127.1, 128.7; EI-MS *m/z* (% rel int) 277 (M^+, 100), 186 (50). Anal. ($C_{19}H_{19}NO$·0.5H_2O) C, H, N.

1-Benzyl-4-hydroxy-9-methyl-6,7,8,9-tetrahydrocarbazole (8b). Methylcyclohexanone (1.1 mL, 8.9 mmol), benzylamine (1.0 mL, 8.9 mmol), and 1,4-benzoquinone (1.0 g, 9.0 mmol) were reacted as described under **7c**: yield 1.12 g.(40%); R_f (1% MeOH:DCM with 1% NH_4OH) 0.6; ^{1}H NMR (400 MHz,$CDCl_3$) δ 1.15 (d, 3H, J = 6.4 Hz), 1.68−1.78 (m, 1H), 1.80−1.92 (m, 3H), 2.57−2.65 (m, 1H), 2.74−2.79 (m, 1H), 2.89−2.94 (m, 1H), 5.18 (dd, 2H, J = 17.2 Hz, benzylic protons), 6.48 (d, 1H, J = 2.4 Hz, Ar), 6.57 (dd, 1H, J = 8.8 Hz), 6.89−6.93 (m, 2H, Ar), 7.14−7.23 (m, 3H, Ar), 7.28 (d, 1H, J = 8.4 Hz, Ar); ^{13}C NMR (400 MHz, $CDCl_3$) δ 16.4, 21.4, 25.2, 25.7, 25.8, 29.7, 52.6, 52.9, 54.4, 55.3, 56.9, 57.9, 59.6, 62.2, 62.5, 62.6, 104.3, 126.0; EI-MS *m/z* (M^+) 291. Anal. ($C_{20}H_{21}NO$·0.5H_2O) C, H, N.

1-Benzyl-2,3-diphenyl-5-hydroxyindole (9). Deoxybenzoin (0.5 g, 2.47 mmol), benzylamine (0.28 mL, 2.47 mmol), and 1,4-benzoquinone (0.27 g, 2.47 mmol) were reacted as described under **7c**: yield 0.57 g (60%); R_f (CH_2Cl_2) 0.40; ^{1}H NMR (270 MHz, $CDCl_3$) 7.7−6.8 (m, 18H, ArH), 5.29 (s, 2H, benzylic proton); EI-MS *m/z* (% rel int) 375 (M^+, 100), 284 (60); ^{13}C NMR (68 MHz, $CDCl_3$) 47.7, 104.1, 104.9, 111.3, 111.6, 111.9, 113.3, 125.5, 126.1, 126.9, 127.1, 127.6, 128.2, 128.4, 128.7, 129.0, 129.1, 129.6, 129.7, 130.9. Anal. ($C_{27}H_{21}NO$·HCl) C, H, N.

1,2-Benzo-9-benzyl-3,4-dihydro-6-hydroxycarbazole (10). α-Tetralone (2 g, 0.013 mol), benzylamine (1.6 mL, 0.013 mol), and 1,4-benzoquinone (1.9 g, 0.018 mol) were reacted as described under **7a**: yield 2.6 g (59%); R_f (1% MeOH:DCM With 1% NH_4OH) 0.5; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.8−3.0 (m, 4H), 5.40 (s, 2H, benzylic protons), 6.55 (s, 1H, Ar), 6.67 (d, 1H, J = 8 Hz), 6.80−6.84 (m, 1H, Ar), 7.0−7.4 (m, 7H, Ar), 7.95−8.2(m, 2H, Ar); ^{13}C NMR (101 MHz, $CDCl_3$) δ 20.2, 30.5, 48.6, 96.0, 109.7, 118.6, 119.5, 121.5, 125.3, 125.8, 125.9, 126.7, 127.2, 127.4, 128.5, 128.9, 128.99, 129.3; FAB-MS *m/z* 326 $[M + 1]^+$. Anal. ($C_{23}H_{19}NO$·0.5H_2O) C, H, N.

3,4-Benzo-9-benzyl-1,2-dihydro-6-hydroxycarbazole (11). β-Tetralone (2 g, 0.013 mol), benzylamine (1.6 mL, 0.013 mol), and 1,4-benzoquinone (1.9 g, 0.018 mol) were reacted as described under **7c**: yield 1.1 g (25%); R_f (1% MeOH:DCM with 1% NH_4OH) 0.5; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.7−3.0 (m, 4H), 5.58 (bs, 2H), 6.72 (dd, 1H, J = 9.4 Hz), 6.9−7.4 (m, 4H), 7.4−7.6 (m, 3H), 7.74 (m, 1H), 7.76−7.83 (m, 2H), 7.96 (d, 1H, J = 8.0 Hz), 8.04 (d, 1H, J = 2.2 Hz), 8.67 (d, 1H, J = 8 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.1, 29.4, 46.5, 107.4, 109.9, 110.8, 113.3, 122.6, 122.7, 125.8, 126.0, 126.8, 127.3, 128.63, 128.65, 129.0, 138.6; FAB-MS *m/z* 325 [M^+, 100]. Anal. ($C_{23}H_{19}NO$) C, H, N.

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Supporting Information Available: Microanalysis data for **7a**−**c**, **8a**, **8b**, and **9**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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