base solution at 0 °C, and the resulting mixture was maintained at 0 °C for 3 h before water (0.1 mL) was added. The liquid portion of each reaction mixture was combined with ether rinses of the reaction flask, and the resulting mixture was analyzed by GC. The average values of three or more GC area determinations were corrected with predetermined response factors to give yields of **2** and **3**. The results are given in Table I. In control experiments, mixtures of **2** and **3** were found to be unchanged after treatments similar to those described above.

Effect of Amine Concentration on Rates. A stock solution of 0.20 M LDA in THF was prepared, and 2-mL portions were placed in two tubes. Diisopropylamine was added to each tube to bring the concentration to 0.20 and 0.40 M, respectively. A THF stock solution containing 0.027 M oxaziridine **1a** and *n*-hexadecane was prepared, and 2 mL of this solution was added to each of the reaction tubes at −48 °C. The reactions were quenched with 0.05 mL of water after 97 min at −48 °C and analyzed by GC. After correction for formation of **2**, **3**, and **9** from pyrolysis of unreacted **1a**, the yields given in the text were found.

Product Yields as a Function of Time. An insulated bath equipped with an overhead stirrer was brought to −32 °C (bromobenzene/CO_2). Reaction tubes were charged with 2.0-mL aliquots of a THF stock solution which contained 0.20 M LDA and 0.20 M diisopropylamine. The tubes were equilibrated at −32 °C in the bath, and a 2.0-mL portion of a THF solution which contained 0.033 mmol of oxaziridine **1a** and *n*-hexadecane was added at −32 °C to each tube. At timed intervals the solutions were quenched with 0.10 mL of water. The solutions were transferred to vials and analyzed by GC. The yields of **2** and **3** shown in Figure 1 are corrected for pyrolysis of unreacted **1a** which produces small amounts of each product.

Kinetic Isotope Effect. A THF stock solution containing 0.20 M LDA and 0.20 M diisopropylamine was prepared, and two 2.0-mL aliquots were equilibrated at 0 °C. To these solutions were added, respectively, 2.0 mL of a 0.015 M solution of **1a** with *n*-hexadecane and 2.0 mL of a 0.015 M solution of **1b** with *n*-hexadecane. After 3 h at 0 °C, the reactions were quenched with 0.05 mL of water and analyzed as described above. The reaction of **1a** gave **2** and **3** in a 69:31 ratio while the reaction of **1b** gave **2** and **3** in a 80:20 ratio.

Reaction of Nitrone 9 with LDA. A THF solution containing 0.010 M nitrone **9**, 0.21 M LDA, 0.41 M diisopropylamine, and *n*-hexadecane was equilibrated at 0 °C for 6.5 h during which time the solution became dark blue. The ESR spectrum of this solution contained a triplet with a_N = 12.5 G. The solution was quenched with water, and the resulting mixture was analyzed by GC. By comparison to the internal standard, 15% of nitrone **9** remained, and no **2** or **3** was present.

^{13}C NMR Studies. ^{1}H-decoupled ^{13}C NMR spectra were recorded on a JEOL PFT-100 instrument. Temperatures were measured with an iron–constantan thermocouple placed in an NMR tube in the instrument probe. Chemical shifts are reported relative to that of the β-carbon of THF which we define as δ 25. The experiments were performed in duplicate with an internal benzene-d_6 lock in one case and external chloroform-*d* lock in the other. The internal lock gave a better signal to noise ratio, but the benzene signals obscured the other aromatic signals. The ^{13}C NMR signals of interest at −56 °C are as follows: oxaziridine **1a**, δ 136 (aromatic C-1), 72 (ring C), 57 (quaternary C); imine **2**, δ 154 (imine C), 137 (aromatic C-1), 56 (quaternary C); LDA δ 51 (methine); diisopropylamine, δ 44 (methine).

The preparation of clean base solutions has been described.[22] Stock solutions of LDEA and LDA (ca. 2 M) were prepared and added to NMR tubes, and the tubes were cooled to −78 °C. For LTMP, 1 M solutions of base in THF/hexane were used. Oxaziridine **1a** was then added as a THF solution such that the final base concentration was ca. 1.7 M and the **1a** concentration was ca. 0.4 M (for LTMP 0.8 and 0.2 M, respectively). Benzene-d_6 (200 μL) was added when required. The tubes were placed in the NMR probe at the desired temperature and ^{1}H-decoupled FT NMR spectra were recorded periodically. A small tip angle of ca. 20° was used. The methine signals of LDA and diisopropylamine were integrated for comparison; we assumed comparable relaxation times and nuclear Overhauser effects for these signals. Qualitatively, the methyl signals of LDA and diisopropylamine were present in the same ratio as the methine signals although accurate integrations of these signals were not possible due to their proximity to the large THF β-carbon signal.

Acknowledgment. Financial support of this work by the Robert A. Welch Foundation is gratefully acknowledged. R.A.R. thanks the Robert A. Welch Foundation for a Predoctoral Fellowship appointment. We appreciate useful suggestions made by an anonymous referee after reviewing an earlier draft.

Registry No. 1a, 3585-81-7; **1b**, 72918-19-5; **2**, 6852-58-0; **2**, deuterated analogue, 55103-96-3; **3**, 5894-65-5; **8**, 2564-83-2; **9**, 3376-24-7; benzoyl chloride, 98-88-4; *tert*-butylamine, 75-64-9; diisopropylamine-*N*-*d*, 25837-82-5; diisopropylamine, 108-18-9; 2,2,6,6-tetramethylpiperidine, 768-66-1.

Supplementary Material Available: Figure 2, showing ^{13}C NMR spectra of **1a**, **2**, and the reaction of **1a** with LDA at −56 °C at various times, and the material discussed in footnote 9 (3 pages). Ordering information is given on any current masthead page.

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Condensation of *p*-Benzoquinone with 4-Cyano- and 4-Nitroanilines. An Extension of the Nenitzescu Reaction

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Received July 17, 1979

A new synthesis of the 6-hydroxycarbazole ring involving the condensation of *p*-benzoquinone with various electron-withdrawing activated anilines has been presented. This procedure, an extension of the Nenitzescu reaction, gave multiple products identified on the basis of physical and spectral data. The corresponding mechanisms are described.

Among the intercalating antitumor ellipticines, 9-hydroxyellipticine (**1**) has been shown to be the most potent.[2,3] Several synthetic routes for its preparation have been described, but these require harsh experimental

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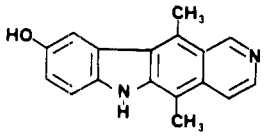


1

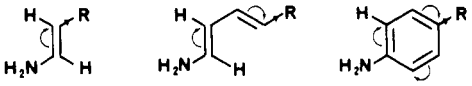
conditions.[4-9] We thought it possible that convenient access to the 6-hydroxycarbazole ring (**2**, Scheme II) might be a key step in the total synthesis of pyridocarbazoles. We have investigated the cyclization reaction leading to **2** from *p*-benzoquinone (PBQ) and the readily available aromatic amines **3**. To the best of our knowledge, this report is the first description of an extension of the Nenitzescu indole synthesis[10] to aromatic amines.

The Nenitzescu indole synthesis consists of a condensation of PBQ with an aliphatic enamine bearing an electron-withdrawing substituent. 5-Hydroxyindole derivatives can generally be obtained by using this method, in a yield of about 20%. Many byproducts which provide important information about the mechanism of the reaction have been identified.[11-19] The essential steps appear to be addition of the enamine to the electrophilic quinone followed by aromatization, oxidation, cyclization, and reduction.

Substituted aromatic amines containing electron-attracting groups, such as 4-nitro- or 4-cyanoanilines, can be considered as vinylogous enamines (Scheme I).

The course of the reaction has been followed by employing the simple model compound 4-nitroaniline (**3a**). In addition, we used xylidines **3b** and **3c** to investigate the range of the reaction. The use of these models led to two advantages. First, they allowed a better understanding of the mechanism of the new reaction by providing information about the influence of different substituents. Second, they afforded key hydroxycarbazole intermediates for planning the total synthesis of 9-hydroxyellipticine; the amine obtained by reduction of **2c** can be easily converted to **1** via a Pommeranz–Fritsch condensation.[20,21]

Scheme I



Results and Discussion

Unsuccessful attempts were made to carry out the reaction in several polar or aprotic solvents,[22] while acetic and trifluoroacetic acids have been found to be effective solvents. Use of the latter acid leads to more favorable kinetics (10-min reaction time, as opposed to 3 h for acetic acid). This has been demonstrated for other reactions.[23] The reaction yielded a mixture of several isolable compounds. These were detected by TLC, separated from the tarry material by medium-pressure liquid chromatography, and identified on the basis of spectral and analytical data. Three main products were systematically isolated (Scheme II): the 6-hydroxycarbazoles **2** (**2a**, 11%; **2b**, 7%; **2c**, 9%), the bis adducts **4** (**4a**, 31%; **4b**, 21%; **4c**, 29%), and the diarylamines **5** (**5a**, 12%; **5b** 17%; **5c**, 9%).

In accord with previous proposals for the mechanism of the Nenitzescu reaction, two interpretations could be advanced to account for the appearance of the carbazole ring **2**. On one hand, we suggest that **2** may arise by initial nitrogen–carbon condensation. In this case, the first step may be thought of as an attack by the amino group of the arylamine on the carbonyl moiety of PBQ. It is clear that isolation of the diarylamines **5** provides evidence that this route can be involved. On the other hand, the formation of **2** can be visualized as an initial carbon–carbon attack. The intermediate **6** must first be oxidized to the quinone **7** to permit cyclization to **8** (or **9**), which in turn requires reduction in order to convert it to carbazoles **2**. The oxidation is presumably effected by the reactant PBQ or by a more advanced adduct such as the quinone iminonium derivative **9**. The coupled reduction of **9** involves the hydroquinone (HQ). The intermediary hemiaminal adduct **8** can be postulated in accordance with the reports of Allen[11] and Kuckländer[18,19] describing the classical Nenitzescu reaction.

This latter route appears to be a major pathway and best explains the formation of the bis adduct **4**, which could arise from addition of a second molecule of aromatic amine to PBQ.

Yields of the different species **2** and **4**, to some extent, demonstrate the importance of the activating group of the aromatic amines. C–C attack is favored when a nitro group is the only substituent (**3a**). The lower reactivity of **3b** may be due to a small steric effect. The electron-withdrawing group cannot lie in the same plane because of the presence of the adjacent methyl substituent; this leads to partial hindrance of conjugation and the nitro group loses part of its activating power. Recent X-ray data related to a similar subject have clearly confirmed such an ortho effect.[8]

When a cyano group replaces the nitro group (**3c**), its coplanarity with the ring is not sterically impeded by the ortho methyl group. Therefore, it could be anticipated that the C–C attack yielding **2c** and **4c** would be favored with respect to **2b** and **4b**. However, the stronger withdrawing effect of the NO_2 outweighs the steric considerations. The

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(18) U. Kuckländer, *Tetrahedron*, **28**, 5251 (1972).

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(20) A. J. Birch, A. H. Jackson, and P. V. R. Shannon, *J. Chem. Soc., Perkin Trans. 1*, 2185 (1974).

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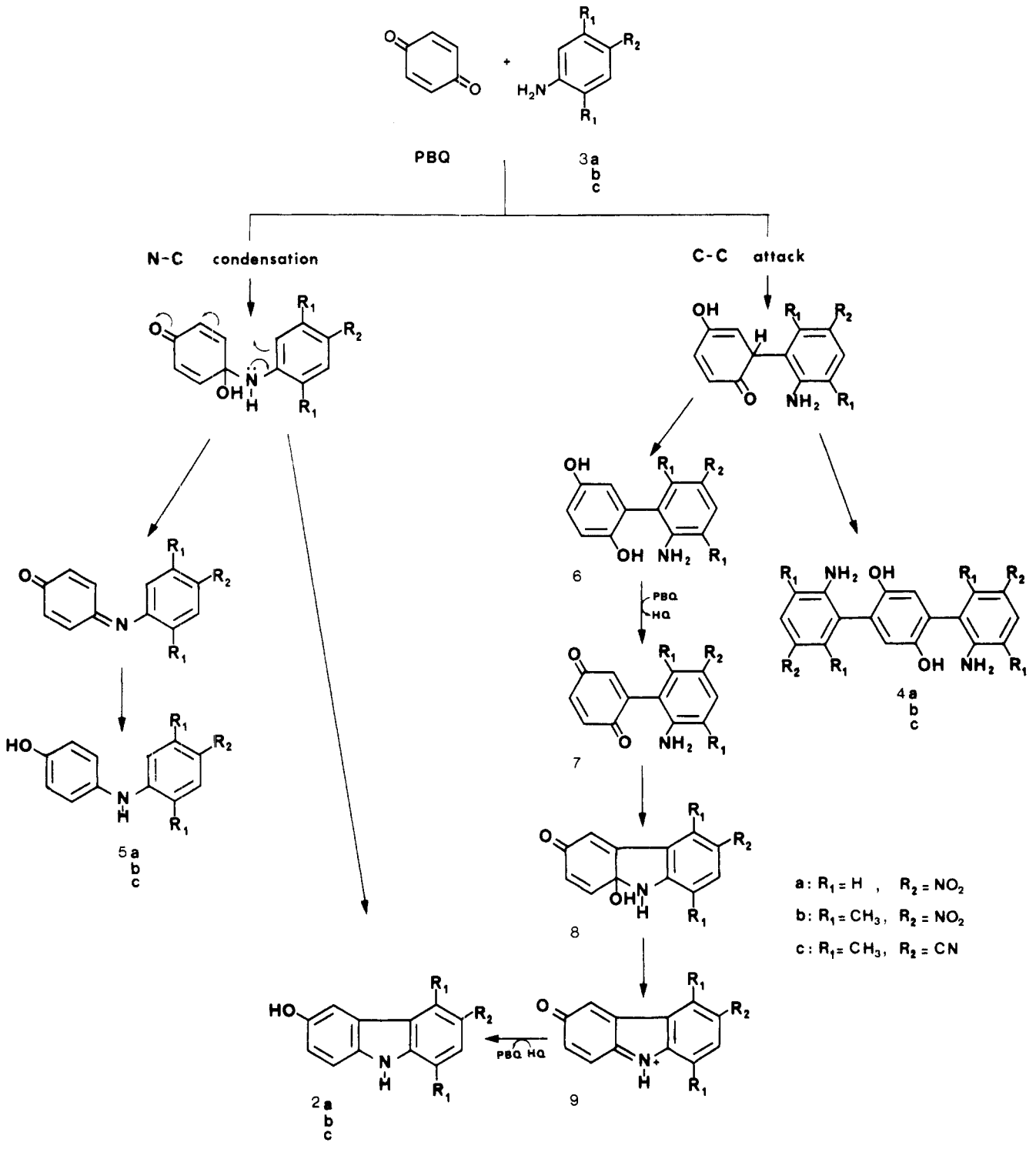
(23) M. C. Brown and R. A. Wirkkala, *J. Am. Chem. Soc.*, **88**, 1447 (1966).

Scheme II



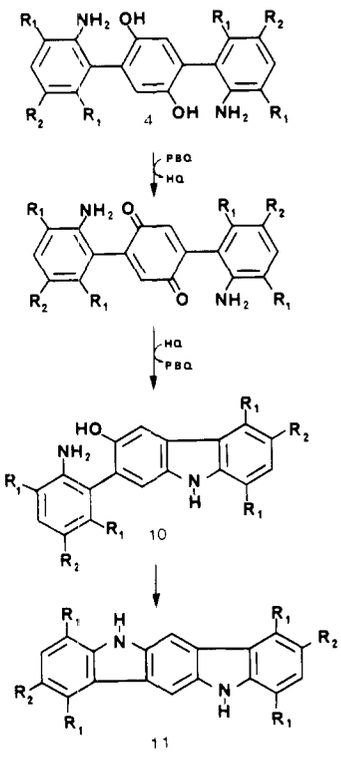
reactions were found to yield additionally a wide range of coproducts (Scheme III). Thus, a further cyclization of the bis adduct **4** led to the formation of arylcarbazole **10** (only **10b** was isolated) and indolocarbazole **11** (only **11c** was isolated). The scheme proposed to explain the formation of **10** and **11** goes well with the mechanism suggested by the isolation of **2** and **4** and takes the C–C attack to be the primary process.

The results reported here suggest that extension of the Nenitzescu reaction to aromatic amines can be useful for a one-step preparation of 6-hydroxycarbazoles. However, the procedure, applied in an attempt to obtain a key intermediate in the synthesis of 9-hydroxyellipticine, suffers from the formation of many byproducts.

Experimental Section

Thin-layer chromatograms were run on 5 × 10 cm glass plates precoated with silica gel F_{254} (Merck), 0.25 mm; the solvent system was chloroform/methanol (4:1) in a saturated ammonia atmosphere. Separation was achieved through column chromatography on silica gel 40 (Merck; 70–230 mesh ASTM) or/and by medium-pressure medium-performance liquid chromatography on Lichroprep Si60 (Merck, 25.40 μm) at a flow rate of 260 mL/h and a pressure of 50 bars with a Milton-Roy Minipump. Infrared spectra were recorded with a Perkin-Elmer 177 infrared spectrometer by using a potassium bromide pellet. NMR spectra were recorded on a Jeol-JNM-MH60 spectrometer with tetramethylsilane as an internal standard. Mass spectra were recorded on a AEI-MS-30 spectrometer. Combustion analyses were performed on a Perkin-Elmer CHN240 apparatus.

Scheme III



General Procedure. PBQ (0.01 mol) was refluxed with the aromatic amine[24] (0.01 mol) in acetic acid for 4 h or in trifluoroacetic acid for 0.5 h. After the solution was cooled, the precipitate was washed successively with ether, acetone, and ethanol to afford the pure bis adduct 4. Filtrate and washings were collected and solvents removed under reduced pressure. The crude residue was submitted to column chromatography with CH_2Cl_2 as eluant.

1,4-Dihydroxy-2,5-bis(2-amino-5-nitrophenyl)benzene (4a). **4a** was obtained as a brown product in 31% yield: mp >300 °C; mass spectrum, *m/e* 382 ($M^{+\cdot}$), 381, 380, 363, 351, 334, 305, 244; IR 3480 (NH), 3660 (OH), 1500, 1300 (NO_2), 1485 (C–N), 1620 (aromatic) cm^{-1}. Anal. Calcd for $C_{18}H_{14}N_4O_6$: C, 56.54; H, 3.70; N, 14.65. Found: C, 56.32; H, 3.65; N, 14.81.

1,4-Dihydroxy-2,5-bis(2-amino-3,6-dimethyl-5-nitrophenyl)benzene (4b). **4b** was obtained as a brown product in 21% yield: mp >300 °C; mass spectrum, *m/e* 438 ($M^{+\cdot}$), 419, 406, 391, 243, 191, 158; IR 3660 (OH), 3480 (NH), 1520, 1320 (NO_2), 1590, 1620, 1640 (aromatic) cm^{-1}. Anal. Calcd for $C_{22}H_{22}N_4O_6$: C, 60.27; H, 5.06; N, 12.78. Found: C, 60.42; H, 5.15; N, 12.69.

1,4-Dihydroxy-2,5-bis(2-amino-3,6-dimethyl-5-cyanophenyl)benzene (4c). **4c** was obtained as a brown product in 29% yield: mp >300 °C; mass spectrum, *m/e* 398 ($M^{+\cdot}$), 381, 380, 379, 351, 251, 223; IR 3660 (OH), 3480 (NH), 2220 (C≡N), 1590, 1620, 1640 (aromatic) cm^{-1}. Anal. Calcd for $C_{24}H_{22}N_4O_2$: C, 72.35; H, 5.56; N, 14.06. Found: C, 72.17; H, 5.68; N, 14.13.

3-Nitro-6-hydroxycarbazole (2a). **2a** was obtained as a red product in 11% yield: mp 164 °C; TLC R_f 0.42; mass spectrum, *m/e* 228 ($M^{+\cdot}$), 214, 200, 184, 183, 167, 154, 128; IR 3400 (NH band characteristic of a carbazole ring), 1510, 1310 (NO_2) cm^{-1}; ^1H NMR[25] (Me_2SO-d_6) δ 6.72 (d, 1 H, H-1), 7.92 (d, 1 H, H-2, $J_{H_1-H_2}$ = 8 Hz), 7.88 (s, 1 H, H-4), 6.90 (s, 1 H, H-5), 6.75 (d, 1 H, H-7), 7.00 (d, 1 H, H-8, $J_{H_7-H_8}$ = 8 Hz), 8.95 (s, 1 H, exchangeable by D_2O, NH), 8.80 (s, 1 H, exchangeable by D_2O, OH). Anal. Calcd for $C_{12}H_8N_2O_3$: C, 63.16; H, 3.53; N, 12.27. Found: C, 63.21; H, 3.47; N, 12.35.

1,4-Dimethyl-3-nitro-6-hydroxycarbazole (2b). **2b** was obtained as a brown product in 7% yield: mp 160 °C; TLC R_f 0.89; mass spectrum, *m/e* 256 ($M^{+\cdot}$), 228, 191, 165, 155, 151, 137; IR 3400 (NH) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.85 (s, 1 H, H-2), 7.10 (s, 1 H, H-5), 6.75 (d, 1 H, H-7), 7.15 (d, 1 H, H-8, $J_{H_7-H_8}$ = 8 Hz), 2.10 (s, 3 H, CH_3-1), 2.22 (s, 3 H, CH_3-4), 8.90 (s, 1 H, NH), 8.75 (s, 1 H, OH). Anal. Calcd for $C_{14}H_{12}N_2O_3$: C, 65.63; H, 4.72; N, 10.93. Found: C, 65.34; H, 4.58; N, 10.45.

1,4-Dimethyl-3-cyano-6-hydroxycarbazole (2c). **2c** was obtained as a red product in 9% yield: mp 152 °C; TLC R_f 0.80; mass spectrum, *m/e* 236 ($M^{+\cdot}$), 219, 207, 205, 191, 177, 165, 151, 149; IR 3400 (NH) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.45 (s, 1 H, H-2), 6.80 (s, 1 H, H-5), 6.64 (d, 1 H, H-7), 6.90 (d, 1 H, H-8, $J_{H_7-H_8}$ = 8 Hz), 2.13 (s, 3 H, CH_3-1), 2.18 (s, 3 H, CH_3-4), 8.95 (s, 1 H, NH), 8.80 (s, 1 H, OH). Anal. Calcd for $C_{15}H_{12}N_2O$: C, 76.27; H, 5.12; N, 11.86. Found: C, 75.83; H, 5.32; N, 11.69.

4-Hydroxy-4′-nitrodiphenylamine (5a). **5a** was obtained as a red product in 12% yield: mp 185 °C (lit.[26] mp 183 °C); TLC R_f 0.44; mass spectrum, *m/e* 230 ($M^{+\cdot}$), 221, 200, 193, 191, 165, 141, 137; IR 3360, 3480 (NH) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 6.95 (d, 2 H, H-2, H-6), 6.65 (d, 2 H, H-3, H-5, $J_{H_2-H_3}$ = $J_{H_5-H_6}$ = 8 Hz), 6.67 (d, 2 H, H-2′, H-6′), 7.85 (d, 2 H, H-3′, H-5′; $J_{H_2'-H_3'}$ = $J_{H_5'-H_6'}$ = 8 Hz). Anal. Calcd for $C_{12}H_{10}N_2O_3$: C, 62.61; H, 4.38; N, 12.17. Found: C, 62.68; H, 4.42; N, 12.25.

4-Hydroxy-2′,5′-dimethyl-4′-nitrodiphenylamine (5b). **5b** was obtained as a brown product in 17% yield: mp 240 °C; TLC R_f 0.90; mass spectrum, *m/e* 258 ($M^{+\cdot}$), 228, 197, 191, 179, 167, 153, 149, 139, 121; IR 3360, 3380 (NH) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.05 (d, 2 H, H-2, H-6), 6.70 (d, 2 H, H-3, H-5, $J_{H_2-H_3}$ = $J_{H_5-H_6}$ = 8 Hz), 7.70 (s, 1 H, H-3′), 6.60 (s, 1 H, H-6′), 2.10 (s, 3 H, CH_3-2′), 2.48 (s, 3 H, CH_3-5′). Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.84. Found: C, 65.28; H, 5.59; N, 10.96.

4-Hydroxy-2′-5′-dimethyl-4′-cyanodiphenylamine (5c). **5c** was obtained as a brown product in 9% yield: mp 195 °C; TLC R_f 0.92; mass spectrum, *m/e* 238 ($M^{+\cdot}$), 222, 218, 206, 197, 183, 179, 156; IR 3360, 3380 (NH) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 6.92 (d, 2 H, H-2, H-6), 6.60 (d, 2 H, H-3, H-5, $J_{H_2-H_3}$ = $J_{H_5-H_6}$ = 8 Hz), 7.43 (s, 1 H, H-3′), 6.55 (s, 1 H, H-6′), 2.40 (s, 3 H, CH_3-2′), 2.15 (s, 3 H, CH_3-5′). Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.60; H, 5.92; N, 11.75. Found: C, 75.32; H, 6.09; N, 11.50.

1,4-Dimethyl-3-nitro-6-hydroxy-7-(2-amino-3,6-dimethyl-5-nitrophenyl)carbazole (10b). **10b** was obtained as a red product in 3% yield: mp 193 °C; TLC R_f 0.94; mass spectrum, *m/e* 420 ($M^{+\cdot}$), 418, 402, 388, 372, 255, 208, 166, 148, 76; IR 3350, 3380 (NH), 3500 (OH) cm^{-1}.

5,11-Dihydro-2,8-dicyano-1,4,7,10-tetramethylindolo[3,2-*b*]carbazole (11c). **11c** was obtained as a brown product in 2% yield: mp 160 °C; TLC R_f 0.69; mass spectrum, *m/e* 362 ($M^{+\cdot}$), 360, 341, 238, 172, 167, 105, 77, 44; IR 3400 (NH), 2200 (C≡N) cm^{-1}.

Acknowledgment. This investigation was supported by funds from the Institut National de la Santé et de la Recherche Médicale, Grant CRL INSERM 79 5 163 3.

Registry No. 2a, 72917-34-1; **2b**, 72917-35-2; **2c**, 72917-36-3; **3a**, 100-01-6; **3b**, 3460-29-5; **3c**, 72917-37-4; **4a**, 72917-38-5; **4b**, 72917-39-6; **4c**, 72917-40-9; **5a**, 16078-86-7; **5b**, 72917-41-0; **5c**, 72917-42-1; **10b**, 72917-43-2; **11c**, 72917-44-3; PBQ, 106-51-4.

(24) (a) 4-Nitroaniline (**3a**) is a commercially available compound. (b) **3b** was prepared in 60% yield from xylidine; mp 145 °C (ethanol). See R. Adams and A. S. Nagarkaffi, *J. Am. Chem. Soc.*, **72**, 4601 (1950). (c) **3c** was prepared in 35% overall yield from **3b** by the Sandmeyer–Gatterman method; mp 158–160 °C (benzene). See T. R. Govindachari, S. Rajappa, and V. Sudarsanam, *Indian J. Chem.*, 1, 247 (1963).

(25) NMR spectra were recorded in Me_2SO-d_6. Chemical shifts of protons are reported in parts per million (ppm) downfield from tetramethylsilane; s and d designate singlet and doublet, respectively. The intensities are shown in parentheses.

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