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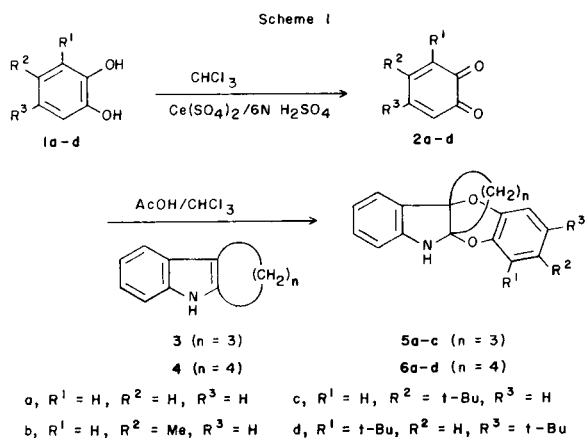
The reaction of 2,3-dihydro-1*H*-cyclopent[*b*]indole **3** and 1,2,3,4-tetrahydrocarbazole **4** with substituted *o*-benzoquinones yielded [4.3.3]- and [4.4.3]propellanes, respectively. The physical and chemical properties of the propellane compounds were investigated and a mechanism for the formation of the propellane compounds was discussed.

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During the course of the investigation of melanogenesis, we found that *o*-benzoquinones including dopaquinone can be trapped by phenylenediamine [1] or cyclopentadiene [2]. We also found that *o*-benzoquinone reacted rapidly with 2,3-disubstituted indoles, especially those having a fused ring system on the 2- and 3-positions, to afford one-to-one adducts in good yields [3].

Here, we have carried out the reaction of 2,3-disubstituted indoles having a fused ring system on the 2- and 3-positions with various *o*-benzoquinones (Scheme 1). Catechols **1a-d** were oxidized using ceric sulfate in the presence of sulfuric acid to yield a red solution of the corresponding *o*-benzoquinones **2a-d**. To these solutions indoles **3** or **4** were added in the presence of acetic acid and an immediate change in color followed by its gradual diminishing was observed. Compounds **5a-d** and **6a-d** were obtained in the yields summarized in Table 1.

The mass spectra of **5a** and **6a** showed indole units at *m/e* 157 and 171, as well as molecular ion peaks at *m/e* 265 and 279, respectively. From the elemental analytical data of **5a** and **6a**, it was found that they were one-to-one adducts. Furthermore, the propellane structures were deduced from the ir, <sup>1</sup>H-nmr and <sup>13</sup>C-nmr spectral data as shown in Scheme 1.



However, quite different patterns were observed for **5a** and **6a** in their uv spectra and a difference of about 10

Table 1

	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	<b>5</b> ( <i>n</i> = 3)	<b>6</b> ( <i>n</i> = 4)
<b>a</b>	H	H	H	28%	19%
<b>b</b>	H	H	Me	74%	69%
<b>c</b>	H	H	<i>t</i> -Bu	31%	29%
<b>d</b>	<i>t</i> -Bu	H	<i>t</i> -Bu	—	38%

Yields from catechol, except for **d** from quinone.

Table 2

<sup>13</sup>C-NMR

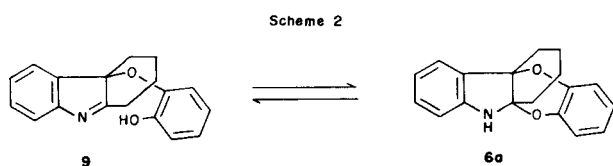
	C-1	C-2	C-3	C-4	UV
<b>5a</b>	103.9	92.8	128.8	148.7	279 (2890), 307 (2310)
<b>7</b>	103.2	54.0	134.4	144.4	297 (4600), 344 (8700)
<b>6a</b>	94.0	81.1	132.6	146.6	281 (4440), 288 (4440)
<b>8</b>	92.2	44.2	132.9	147.0	286

ppm (in deuteriochloroform)                      nm (ε) (in methanol)

Table 3

	<b>5a</b> ( <i>n</i> = 3)	<b>6a</b> ( <i>n</i> = 4)
Formation of Salt	no formation	formation
pK <sub>a</sub> <sup>1</sup>	—	(2.5), 9.4
Ferric chloride (excess sodium hydroxide)	brown-red no change	blue-black no change
(CHIRAL-PACK) [α]	separable	inseparable

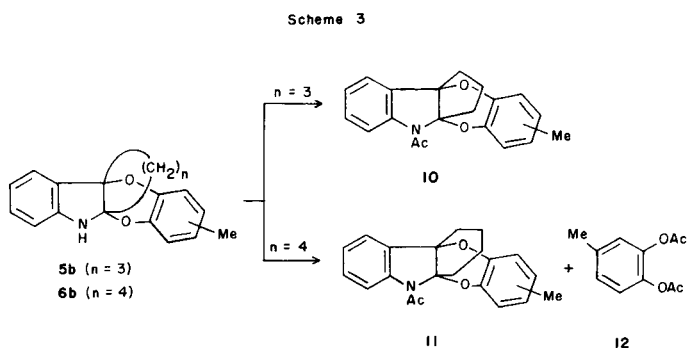
[α] A chiral stationary phase.



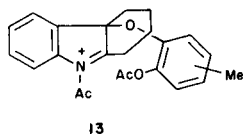
ppm was observed between both C-1 and C-2 carbons of **5a** and **6a** in the  $^{13}\text{C}$ -nmr spectra (Table 2). These differences were explained by comparing the  $^{13}\text{C}$ -nmr and uv spectral data of **5a** and **6a** with those of indole alkaloids **7** and **8** possessing similar propellane structures [4]. The results are summarized in Table 2. These same features were also observed in the case of **5b-c** and **6b-d**. From the above results it was concluded that **5** and **6** possessed the heterocyclic propellane structures illustrated.

The chemical properties of the propellane compounds were examined and the results summarized in Table 3 were obtained. The above results support the propellane structure for **5a** while suggesting the existence of a phenolic group in **6a**. It may be possible to explain these results by assuming an equilibrium between **6a** and its opened-ring tautomer **9** having a phenolic group (Scheme 2).

In order to confirm the presence of a phenolic group the acetylation of **5b** and **6b** was carried out (Scheme 3). The



reaction of **5b** and **6b** in an acetic anhydride-pyridine mixture with heating resulted in both instances in the formation of the corresponding *N*-acetyl forms **10** and **11**. However, in the case of **6b** only, a large amount of the diacetate of catechol **12** was obtained. This fact may be explained by assuming the presence of the opened-ring form **13** intermediate to the formation of **12** therefore supporting the equilibrium mentioned before.



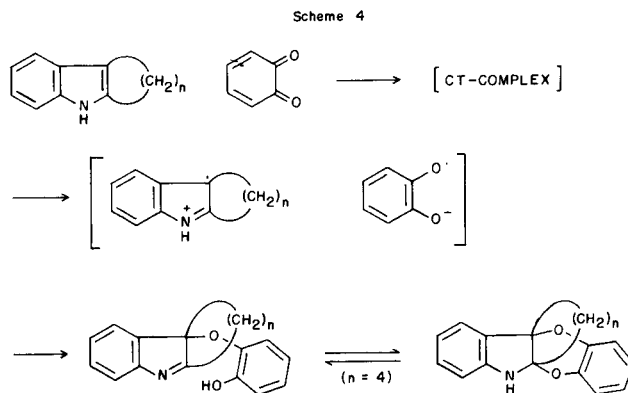
Furthermore, the thermodynamic stability of the propellane compounds and their corresponding ring-opened compounds was examined. Force field calculations of propellane compounds **14** and **15** and their corresponding

ring-opened compounds **16** and **17** were carried out and the conformational energy (corresponding the enthalpy) of the compounds was obtained (Table 4). When comparing **14** and **16** the propellane compound was obviously more stable than the ring-opened tautomer. However, in the case of **15** and **17**, very close values were obtained. From the above results it is obvious that ring-chain tautomerization occurs in the case of the [4.4.3]propellane compound while the [4.3.3]propellane compound is fixed with regard to propellane structure and could hardly tautomerize.

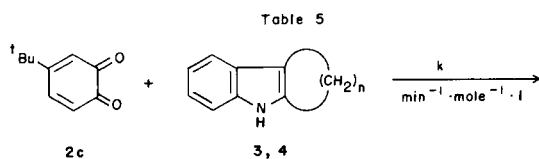
Table 4

Conformational Energy (kcal/mole)		
(14)	(16)	
42.28	84.58	( $\Delta E = 42.30$ )
(15)	(17)	
35.21	28.42	( $\Delta E = -6.79$ )

Finally the reaction mechanism was examined. As mentioned before when indoles **3** and **4** were added to *o*-benzoquinone **2** an immediate change in color was observed followed by its gradual diminution possibly indicating the formation of a charge transfer complex. Therefore the following mechanism was proposed for the formation of propellane compounds **5** and **6** (Scheme 4).



In order to examine the possibility of the formation of a charge transfer complex, the reaction rate constants of indoles **3** and **4** with 4-*t*-butyl-*o*-benzoquinone (**2c**) in various solvents were measured. Measurements were carried out under pseudo first order reaction conditions using a large excess of indoles **3** and **4**. The reactions were monitored by the uv absorbance of *o*-quinone **2c** at 386 nm.



Solvent	dielectric constant	3 (n = 3)	4 (n = 4)
Chloroform	4.81	9.50	12.8
Acetonitrile	37.5	9.59	—
Methanol	32.7	68.1	—

The results are summarized in Table 5 and it is apparent that the reaction is accelerated in accord with the order of the polarity of the solvent. This fact indicates that the reaction would proceed not through a concerted but through an ionic process, presumably *via* the formation of a charge transfer complex first as illustrated in Scheme 4.

In conclusion indoles **3** and **4** were found to react rapidly with *o*-benzoquinones to yield one-to-one adducts. The products obtained from indole **3** were very stable. These results indicate that from the viewpoint of the investigation of melanogenesis, 2,3-disubstituted indoles, especially **3** is favorable for the trapping of labile *o*-benzoquinones.

## EXPERIMENTAL

Melting points were measured on a Yanagimoto Micro Melting Point Apparatus, and uncorrected. The ir spectra were measured on a Jasco IRA-1 Infrared Spectrophotometer. The <sup>1</sup>H- and <sup>13</sup>C-nmr spectra were recorded on a Hitachi R-24 and a JEOL-100 Spectrometer using tetramethylsilane as an internal standard. The uv spectra were measured on a Shimadzu UV-365 UV-VIS-NIR Recording Spectrophotometer. Mass spectra were measured on a Hitachi M-80 Gaschromatograph Mass Spectrometer. The hplc were carried out on a Jasco Familic-100N High Pressure Liquid Chromatograph using a Jasco UVIDEC-100-II UV Spectrometer. The measurement of pK<sub>a</sub> values was carried out using a pH/Ion Meter 225 (Iwaki Glass).

### General Procedure for the Preparation of *o*-Benzoquinones.

*o*-Benzoquinones **2a-d** were prepared according to the method of Brockhaus [5] from their corresponding catechols **1a-d**. To an ice-methanol cooled solution of catechol (4.5 mmoles) in 50 ml of chloroform, 90 ml of a precooled 6*N* sulfuric acid solution of cerium (IV) sulfate (9.0 mmoles) was added and stirred vigorously for several seconds in the case of **2a** to 2 hours in the case of **2d**. The organic layer was washed with 0.01*N* sulfuric acid and dried over magnesium sulfate. The *o*-benzoquinone was isolated only in the case of **2d**. Recrystallization was from *n*-hexane.

### General Procedure for the Reaction of *o*-Benzoquinones and Indoles.

To the *o*-benzoquinone solutions prepared as described above, 1 ml of acetic acid and 4.5 mmoles of indole **3** or **4** were added and stirred for 1 hour in the case of **2a** to 10 hours in the case of **2d** at room temperature. The products were purified *via* silica gel chromatography with benzene-hexane (2:1) in the case of **5a,b** and **6a,b**. The eluent system, hexane-chloroform-acetone-ethanol (250:100:40:8) was used in the case of **5c** and **6c** and the eluent system, hexane-dichloromethane-acetonitrile (7:2:1) was used in the case of **6d**. The acetic acid was removed by shaking with a saturated sodium hydrogen carbonate solution, washed with water, dried and evaporated. The products were recrystallized from ethanol to yield colorless needles.

### 3a,8b-Phenylenedioxy-2,3,3a,8b-tetrahydro-1*H*-cyclopent[*b*]indole (**5a**).

This compound was obtained in 28% yield, mp 125° (from ethanol); ir (potassium bromide):  $\nu$  max 3380, 3330, 1610, 1600, 1495 cm<sup>-1</sup>; uv (methanol):  $\lambda$  max ( $\epsilon$ ) 246 (6660), 279 (2890), 307 (2310) nm; <sup>1</sup>H-nmr (deuteriochloroform):  $\delta$  1.5-2.7 (m, 6H), 4.29 (s, 1H), 6.4-7.4 (m, 8H) ppm; <sup>13</sup>C-nmr (deuteriochloroform):  $\delta$  21.8 (t), 39.6 (t), 40.2 (t), 92.9 (s), 104.0 (s), 108.5 (d), 117.8 (d), 118.1 (d), 119.2 (d), 122.3 (d), 122.5 (d), 124.1 (d), 128.7 (s), 129.8 (d), 145.1 (s  $\times$  2), 148.6 (s) ppm; ms: *m/e* 265, 157, 130.

Anal. Calcd. for C<sub>17</sub>H<sub>15</sub>NO<sub>2</sub>: C, 76.96; H, 5.67; N, 5.28. Found: C, 76.90; H, 5.74; N, 5.28.

### 3a,8b-(4-Methylphenylenedioxy)-2,3,3a,8b-tetrahydro-1*H*-cyclopent[*b*]indole (**5b**).

This compound was obtained in 74% yield, mp 140° (from ethanol); ir (potassium bromide):  $\nu$  max 3365, 1610, 1595, 1500 cm<sup>-1</sup>; uv (methanol):  $\lambda$  max ( $\epsilon$ ) 246 (6690), 283 (3460), 306 (2360) nm; <sup>1</sup>H-nmr (deuteriochloroform):  $\delta$  1.5-2.7 (m, 6H), 2.14 (s, 3H), 4.29 (s, 1H), 6.3-7.3 (m, 7H) ppm; <sup>13</sup>C-nmr (deuteriochloroform):  $\delta$  20.71 (q), 21.73 (t), 39.57 (t), 40.20 (t), 92.83 (s), 103.94 (s), 108.52 (d), 117.58 (d), 118.36 (d), 119.24 (d), 122.90 (d), 124.07 (d), 128.84 (s), 129.67 (d), 131.91 (s), 142.82 (s), 144.83 (s), 148.67 (s) ppm.

Anal. Calcd. for C<sub>18</sub>H<sub>17</sub>NO<sub>2</sub>: C, 77.39; H, 6.13; N, 5.01. Found: C, 77.48; H, 6.19; N, 4.99.

### 3a,8b-(4-*t*-Butylphenylenedioxy)-2,3,3a,8b-tetrahydro-1*H*-cyclopent[*b*]indole (**5c**).

This compound was obtained in 179-180° [from hexane:chloroform (2:1)]; ir (potassium bromide):  $\nu$  max 3380, 1615, 1595, 1505 cm<sup>-1</sup>; <sup>1</sup>H-nmr (deuteriochloroform):  $\delta$  1.3-2.7 (m, 6H), 1.21 (s, 9H), 4.20 (br s, 1H), 6.2-7.4 (m, 7H) ppm; <sup>13</sup>C-nmr (deuteriochloroform):  $\delta$  21.72 (t), 31.38 (q), 34.13 (s), 39.60 (t), 40.31 (t), 92.26 (s), 103.33 (s), 108.67 (d), 114.80 (d), 117.07 (d), 119.18 (d), 119.29 (d), 124.11 (d), 129.10 (s), 129.64 (d), 142.32 (s), 144.05 (s), 145.46 (s), 148.60 (s) ppm; ms: *m/e* 322, 157, 130.

Anal. Calcd. for C<sub>21</sub>H<sub>23</sub>NO<sub>2</sub>: C, 78.47; H, 7.21; N, 4.35. Found: C, 78.41; H, 7.27; N, 4.35.

### 4a,9b-Phenylenedioxy-1,2,3,4,4a,9b-hexahydrocarbazole (**6a**).

This compound was obtained in 19% yield, mp 173° (from ethanol); ir (potassium bromide):  $\nu$  max 3320, 1610, 1600, 1495 cm<sup>-1</sup>; uv (methanol):  $\lambda$  max ( $\epsilon$ ) 281 (4440), 288 (4440) nm; <sup>1</sup>H-nmr (deuteriochloroform):  $\delta$  1.6-2.3 (m, 8H), 4.37 (s, 1H), 6.5-7.2 (m, 8H) ppm; <sup>13</sup>C-nmr (deuteriochloroform):  $\delta$  20.37 (t), 23.03 (t), 31.29 (t), 36.81 (t), 81.14 (s), 93.94 (s), 111.43 (d), 116.60 (s), 116.83 (d), 120.24 (d), 120.94 (d), 121.12 (d), 122.24 (d), 128.24 (d), 132.51 (s), 141.49 (s), 142.55 (s), 146.54 (s) ppm; ms: *m/e* 279, 171, 143.

Anal. Calcd. for C<sub>18</sub>H<sub>17</sub>NO<sub>2</sub>: C, 77.39; H, 6.13; N, 5.01. Found: C, 77.15; H, 6.17; N, 4.98.

### 4a,9b-(4-Methylphenylenedioxy)-1,2,3,4,4a,9b-hexahydrocarbazole (**6b**).

This compound was obtained in 69% yield, mp 144° (from ethanol); ir (potassium bromide):  $\nu$  max 3345, 1620, 1600, 1505 cm<sup>-1</sup>; uv (methanol):  $\lambda$  max ( $\epsilon$ ) 285 (5980) nm; <sup>1</sup>H-nmr (deuteriochloroform):  $\delta$  1.6-2.2 (m, 8H), 2.16 (s, 3H), 4.40 (s, 1H), 6.5-7.2 (m, 7H) ppm; <sup>13</sup>C-nmr (deuteriochloroform):  $\delta$  20.37 (t), 20.61 (q), 23.13 (t), 31.29 (t), 36.93 (t), 81.08 (s), 93.99 (s), 11.43 (d), 116.54 (d), 116.95 (d), 120.24 (d), 121.47 (d), 122.17 (d), 128.87 (d), 130.67 (s), 132.62 (s), 139.14 (s), 142.25 (s), 146.60 (s) ppm; ms: *m/e* 294, 171, 143.

Anal. Calcd. for C<sub>19</sub>H<sub>19</sub>NO<sub>2</sub>: C, 77.78; H, 6.52; N, 4.77. Found: C, 77.75; H, 6.54; N, 4.73.

### 4a,9b-(4-*t*-Butylphenylenedioxy)-1,2,3,4,4a,9b-hexahydrocarbazole (**6c**).

This compound was obtained in 29% yield, mp 188-189° [from hexane:chloroform:acetone:ethanol (250:100:40:8)]; ir (potassium bromide):  $\nu$  max 3320, 1620, 1520, 1500 cm<sup>-1</sup>; uv (methanol):  $\lambda$  max ( $\epsilon$ ) 284 (6850), 289 (6710) nm; <sup>1</sup>H-nmr (deuteriochloroform):  $\delta$  1.4-2.4 (m, 8H), 1.23 (s, 9H), 4.34 (s, 1H), 6.6-7.3 (m, 7H), ppm; <sup>13</sup>C-nmr (deuteriochloroform):  $\delta$  20.42 (t), 23.13 (t), 31.42 (q), 34.08 (s), 36.89 (t), 81.05 (s), 93.72 (s), 111.49 (d), 113.82 (d), 116.10 (d), 118.00 (d), 120.27 (d), 122.38 (d), 129.00 (d), 132.89 (s), 139.12 (s), 141.67 (s), 144.32 (s), 146.65 (s) ppm.

*Anal.* Calcd. for  $C_{22}H_{25}NO_2$ : C, 78.77; H, 7.51; N, 4.17. Found: C, 78.67; H, 7.52; N, 4.13.

4a,9b-(3,5-Di-*t*-butylphenylenedioxy)-1,2,3,4,4a,9b-hexahydrocarbazole (**6d**).

This compound was obtained in 38% yield, mp 117-119° (from ethanol); ir (potassium bromide):  $\nu$  max 3340, 1610, 1595  $cm^{-1}$ ; uv (methanol):  $\lambda$  max ( $\epsilon$ ) 286 (5460) nm;  $^1H$ -nmr (deuteriochloroform):  $\delta$  0.7-3.1 (m, 8H), 1.19 (s, 9H), 1.38 (s, 9H), 4.20 (s, 1H), 6.4-7.3 (m, 6H) ppm;  $^{13}C$ -nmr (deuteriochloroform):  $\delta$  20.66 (t), 22.85 (t), 29.82 (q), 31.53 (q), 32.06 (t), 34.31 (s), 34.94 (s), 35.77 (t), 80.11 (s), 93.32 (s), 111.20 (d), 112.08 (d), 115.49 (d), 120.17 (d), 122.46 (d), 128.89 (d), 132.59 (s), 136.59 (s), 138.25 (s), 141.41 (s), 142.58 (s), 146.97 (s) ppm.

*Anal.* Calcd. for  $C_{26}H_{29}NO_2$ : C, 79.75; H, 8.49; N, 3.57. Found: C, 79.51; H, 8.48; N, 3.56.

#### Salt Formation of **6a** with D-(10)-Camphorsulfonic Acid.

Compounds **5a** or **6a** along with D-(10)-camphorsulfonic acid was dissolved in ethanol with heating. The solution was allowed to stand and the salt was obtained as crystals in the case of **6a**.

#### The Salt of **6a**.

This compound had mp 244-245°; ir (potassium bromide):  $\nu$  max 3260, 1735, 1610, 1595  $cm^{-1}$ ; uv (methanol):  $\lambda$  max ( $\epsilon$ ) 281 (7400);  $^1H$ -nmr ir (deuteriochloroform):  $\delta$  0.8-3.5 (m, 17H), 0.78 (s, 3H), 1.07 (s, 3H), 6.4-7.9 (m, 8H), 9.59 (s, 2H) ppm.

*Anal.* Calcd. for  $C_{28}H_{33}NO_5S$ : C, 65.73; H, 6.50; N, 2.73. Found: C, 65.67; H, 6.55; N, 2.70.

#### Resolution of **5a** and **6a**.

Compounds **5a** and **6a** were dissolved in methanol and applied to hplc using a chiral stationary phase (Jasco CHIRAL PACK).

#### Measurement of $pK_a'$ Values.

Known amounts of **5a** or **6a** (0.15 mmole) and sulfamic acid or D-(10)-camphorsulfonic acid (0.20 mmole) were dissolved in aqueous acetonitrile and titrated with a previously standardized sodium hydroxide solution (0.03 mole/l) and measuring the pH value after every addition of 0.1 ml.

#### Acetylation of **5b** and **6b**.

Propellane compounds **5b** and **6b** (3 mmoles) were dissolved in an acetic anhydride-pyridine mixture (1:1, 15 ml) and refluxed for one hour. The reaction mixture was extracted with dichloromethane, washed with hydrochloric acid and a saturated sodium hydrogen carbonate solution, dried and evaporated. The products were purified with hexane-ethyl acetate (5:1) on silica gel.

*N*-Acetyl-3a,8b-(4-methylphenylenedioxy)-2,3,3a,8b-tetrahydro-1*H*-cyclopent[*b*]indole (**10**).

Compound **10** was afforded from **5b** in 28% yield; ir (potassium bromide):  $\nu$  max 1660, 1595, 1495  $cm^{-1}$ ;  $^1H$ -nmr (deuteriochloroform):  $\delta$  2.09 (s, 3H), 2.53 (s, 3H), 1.2-3.0 (m, 6H), 6.4-7.5 (m, 6H), 8.12 (d, 1H,  $J = 8.0$  Hz);  $^{13}C$ -nmr (deuteriochloroform):  $\delta$  20.72 (q), 22.78 (t), 24.25 (q), 40.04 (t), 41.51 (t), 93.94 (s), 105.09 (s), 116.30 (d), 117.66 (d), 118.33 (d), 123.47 (d), 124.29 (d), 129.28 (s), 130.10 (d), 132.62 (s), 143.19 (s), 143.37 (s), 143.90 (s), 169.85 (s) ppm.

*Anal.* Calcd. for  $C_{20}H_{19}NO_3$ : C, 74.61; H, 5.97; N, 4.41. Found: C, 74.74; H, 5.96; N, 4.36.

*N*-Acetyl-4a,9b-(4-methylphenylenedioxy)-1,2,3,4,4a,9b-hexahydrocarbazole (**11**).

Compound **11** was afforded from **6b** in 31% yield; ir (potassium bromide):  $\nu$  max 1660, 1605, 1595, 1510  $cm^{-1}$ ;  $^1H$ -nmr (deuteriochloroform):  $\delta$  0.7-2.8 (m, 8H), 2.33 (s, 3H), 6.4-7.7 (m, 6H), 8.28 (d, 1H,  $J = 8$  Hz);  $^{13}C$ -nmr (deuteriochloroform):  $\delta$  20.5 (q), 20.8 (t), 22.3 (t), 24.2 (q), 27.2 (t), 35.6 (t), 78.0 (s), 93.8 (s), 116.8 (d), 118.3 (d), 121.8 (d), 123.2 (d), 123.8 (d), 128.8 (s), 130.6 (d), 131.0 (s), 138.0 (s), 142.1 (s), 169.3 (s) ppm.

*Anal.* Calcd. for  $C_{21}H_{21}NO_3$ : C, 75.10; H, 6.35; N, 4.12. Found: C, 75.20; H, 6.31; N, 4.17.

#### *O,O*-Diacyetyl-4-methylcatechol (**12**).

Compound **12** was obtained from **6b** in 42% yield and its identity confirmed by comparison with an authentic sample.

#### Measurement of the Reaction Rate Constants.

*t*-Butyl-*o*-benzoquinone (**2c**) solution with a concentration of about  $10^{-4}$  mole/l was prepared. Solutions of indoles **3** and **4** with a concentration of about  $10^{-2}$  mole/l and containing 6% acetic acid were prepared. The solutions of *o*-benzoquinone (2 ml) and the indole (2 ml) were mixed and placed immediately in a uv cell. The decrease of the absorption at 386 nm was measured with time. The reaction rate constants were calculated by means of the least square method.

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