

A ONE-POT ACCESS TO [b]ANNELLATED CARBAZOLES AS  
 POTENTIAL DNA INTERCALATORS VIA DIELS-ALDER REACTIONS  
 WITH 1-ALYKLPYRANO[3,4-b]INDOL-3-ONES

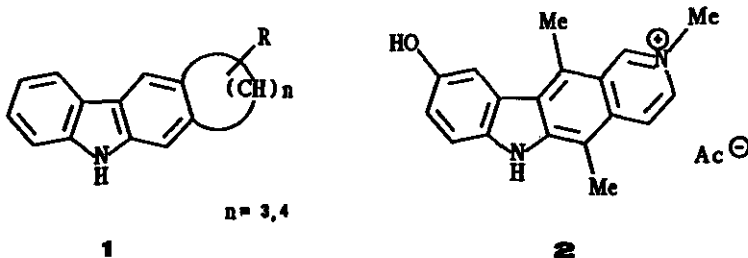
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**Abstract** — 1-Alkylpyrano[3,4-*b*]indol-3-ones (3) react via a Diels-Alder process with arynes or *N*-phenylmaleimide to furnish [b]annellated carbazoles (4-10) in a one-pot procedure. Compounds (4-8) with a coplanar framework belong to the class of potential DNA intercalators.

INTRODUCTION

The mostly coplanar, [b]annellated carbazole derivatives of the structural type (1) represent synthetically attractive target molecules since they have potential antitumor activity.<sup>1-3</sup> Prominent as biological lead substances in this respect are the pyrido[4,3-*b*]carbazole alkaloids of the ellipticine group such as, for example, 2-methyl-9-hydroxyellipticinium acetate (2) which is in clinical use for the treatment of breast cancer, myeloblastic leukemia, and solid tumors.<sup>3-6</sup> Hence, the synthetic development of further analogues with potential cytostatic activity based on structure (1) is of fundamental interest in medicinal chemistry.



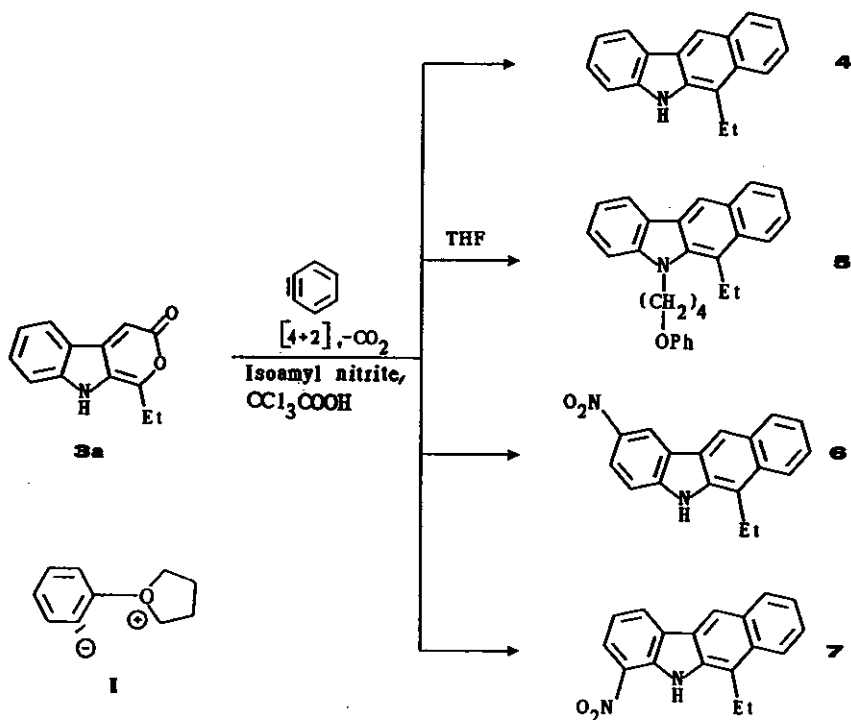
In the present paper, we report on the continuation of our synthetic investigations of pericyclic six-electron processes yielding [*b*]-annellated carbazoles<sup>7-12</sup> to include the Diels-Alder reactions of the readily available pyrano[3,4-*b*]indol-3-ones (3a) and (3b)<sup>13</sup> with cyclic carbodienophiles. The obtained experimental results constitute a convenient one-pot access to [*b*]annellated carbazoles of the type (1) (with five- and six-membered ring annellation on the carbazole skeleton) *via* a cycloaddition/cycloreversion process. This methodology was first reported by Plieninger and coworkers<sup>13</sup> and has been developed further by Moody and coworkers<sup>14</sup> as well as by our group.<sup>7-12</sup> It was recently used for a selective synthesis of 1,2-dihydrocarbazoles.<sup>15</sup> Hence, we now describe the syntheses of 2-deazaellipticine derivatives and [*b*]pyrrolocarbazoles; both types of compounds should exhibit a potential DNA intercalating activity.

## RESULTS AND DISCUSSION

Accordingly, the ethyl derivative (3a)<sup>13</sup> reacts as a diene with the *in situ* generated aryne<sup>7</sup> in dependence on the selected reaction conditions (see experimental section) to furnish the four novel benzo[*b*]carbazoles (4-7) with completely coplanar frameworks (Scheme 1). Product (4) represents the generally expected cycloadduct.

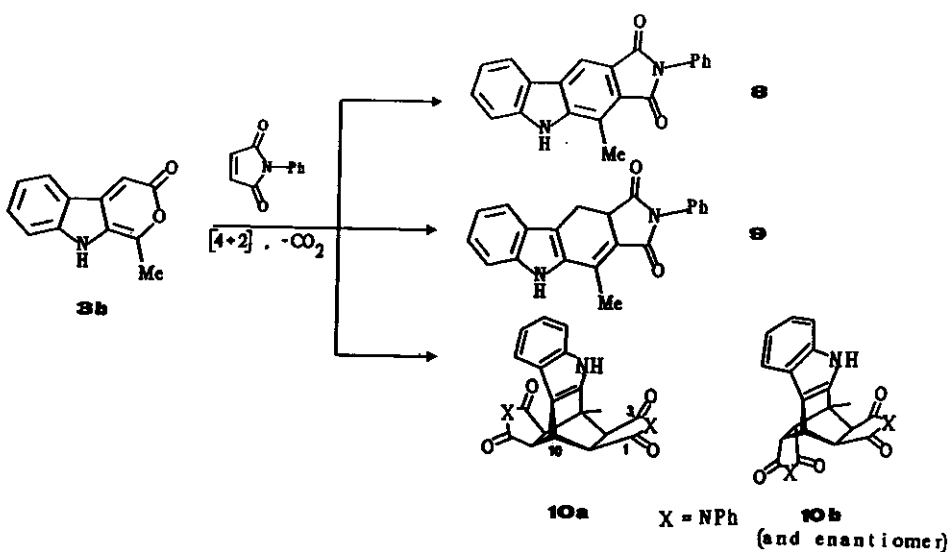
The additionally formed regioisomeric nitrobenzocarbazoles (6) and (7) are the result of a nitration reaction occurring because of the presence of isoamyl nitrite/trichloroacetic acid in the reaction medium for aryne generation. We have previously described a related nitration process in the course of Diels-Alder reactions of pyrano[3,4-*b*]indol-3-ones.<sup>7</sup> On the other hand, the *N*-substituted benzocarbazole (5) (yield: 22-30%) has, as yet, only been obtained when tetrahydrofuran was used as reaction solvent. With regard to the mechanism of formation of 5, we suggest that the solvent reacts as an *O*-nucleophile with the aryne to form the zwitterionic oxonium intermediate (I). Subsequent alkylation at the nitrogen atom of the product (4) by the oxonium moiety of I followed by cleavage of the five-membered ring of I then gives rise to product (5). An initial *N*-alkylation of 3a by an analogous mechanism can be discounted on the basis the careful analyses of the reaction mixtures carried out to date.

Scheme 1



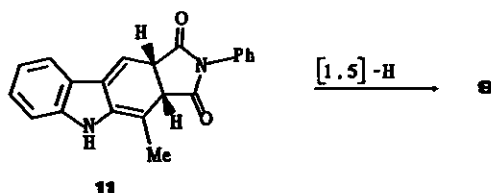
We have already demonstrated that the Diels-Alder reactions of pyrano[3,4-*b*]indol-3-ones with *N*-phenylmaleimide comprise a convenient route to [*b*]pyrrolo-annellated carbazoles possessing a 1,3-dione functionality.<sup>8,10,11</sup> In the meantime, in addition to our preliminary results,<sup>8</sup> we

Scheme 2



have found that the reaction of **3b** with *N*-phenylmaleimide in particular gives rise to the four [b]pyrrolo-annellated carbazoles (**8a**), (**9**), (**10a**), and (**10b**) (Scheme 2). The double Diels-Alder reaction of **3b** to furnish **10** should give rise to four stereoisomers (including one pair of racemates). However, hplc analysis of the reaction mixture revealed that only three isomers of the type (**10**) were formed, namely **10a** and the racemate (**10b**). The dihydrocarbazole (**9**) was presumably formed from the expected intermediate cycloadduct (**11**) which underwent stabilization by a subsequent [1,5]-H shift (Scheme 3).

Scheme 3



The constitutions of the products (**4-9**) were clarified by 400 MHz  $^1\text{H}$ -nmr spectroscopy with additional  $^1\text{H}, ^1\text{H}$ -NOE measurements. The relative configurations of the tetrahydrobarrelene isomers (**10a**) and (**10b**) were further analysed by 1D and 2D  $^1\text{H}, ^1\text{H}$ -NOE (NOESY) experiments.<sup>8</sup> In the cases of the carbazoles (**5**) and (**8**), the constitutions were unequivocally confirmed by X-ray crystallographic analyses (Figure 1).<sup>16</sup> For product (**5**), it was found that two independent molecules existed in the crystal state which differ only in the conformations of the phenoxybutyl side-chains (two "local" enantiomeric conformations).

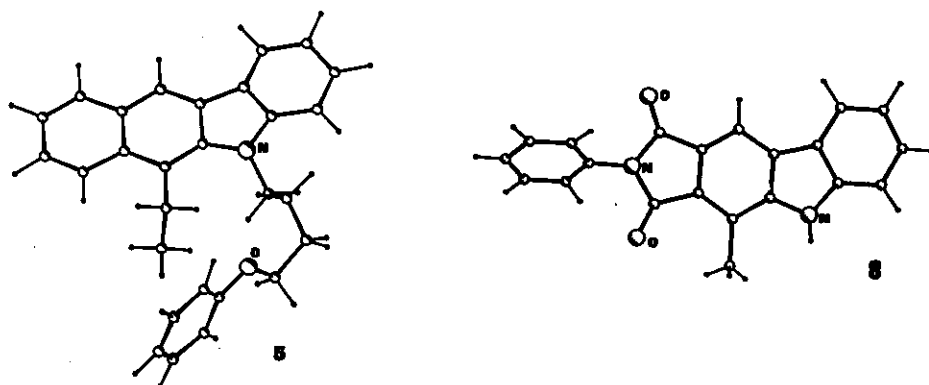


Figure 1: X-Ray crystal structures of **5** and **8** (space groups  $\text{Pna}2_1$  and  $\text{C}2/c$ ). For the carbazole (**5**), only the major component of the two independent molecules is depicted for improved clarity.

Molecular modeling studies of the carbazoles (4-7) and (8) with cytidyl(3',5')guanosine as the base-paired duplex (Watson-Crick minihelix) predict that these carbazole derivatives belong to a new class of potential DNA intercalators.<sup>16,17</sup>

#### EXPERIMENTAL

The <sup>1</sup>H-nmr spectra were recorded at 400 MHz and the <sup>13</sup>C-nmr spectra at 100.6 MHz. The <sup>13</sup>C-nmr shift analyses were supported by the Cnmr simulator program from the VISPER program packet (VCH, Weinheim/FRG). The mass spectra (70 eV) were obtained using a Varian MAT 7 instrument. Elemental analyses were performed with a Carlo Erba Strumentazione 1106 apparatus. Flash chromatography was performed on Merck 60 silica gel (particle size: 0.040-0.063 mm). The petroleum ether used had the boiling range 40-60 °C. All reactions were carried out in highly pure, anhydrous solvents under an argon atmosphere.

**General Procedure for Compounds (4) and (5).** Anthranilic acid (192 mg, 1.9 mmol) and trichloroacetic acid (2.5 mg, 0.015 mmol) were suspended in 10 ml of tetrahydrofuran and cooled to 0 °C. Isoamyl nitrite (0.35 ml, 305 mg, 2.6 mmol) was added to the suspension in small portions from a syringe over 2 min at the same temperature. The resultant mixture was stirred for 1.5 h at 20 °C and then added to a suspension of 1-ethylpyrano[3,4-*b*]indol-3-one (3a; 213 mg, 1 mmol) in 20 ml of tetrahydrofuran. This reaction mixture was stirred at 66 °C for 30 min and then evaporated under very mild conditions under reduced pressure. The residue obtained was separated by flash chromatography (petroleum ether/ethyl acetate, 24/1).

*6-Ethyl-5H-benzo[*b*]carbazole (4):* yield: 72 mg (29%); mp 117 °C (petroleum ether/ethyl acetate); <sup>1</sup>H-nmr (DMSO-*d*<sub>6</sub>): δ = 1.33 (t, *J* = 7.50 Hz, 3 H, CH<sub>2</sub>CH<sub>3</sub>), 3.37 (q, *J* = 7.50 Hz, 2 H, CH<sub>2</sub>CH<sub>3</sub>), 7.17 (dd, *J* = 6.78 and 7.64 Hz, 1 H, aromatic H), 7.36 (dd, *J* = 7.08 and 7.76 Hz, 1 H, aromatic H), 7.48 (m, 3 H, aromatic H), 8.05 (d, *J* = 8.21 Hz, 1 H, 2-H or 3-H), 8.13 (d, *J* = 8.66 Hz, 1 H, 3-H or 2-H), 8.23 (d, *J* = 7.67 Hz, 1 H, 10-H), 8.54 (s, 1H, 11-H), 11.10 (s, 1 H, NH); EI-*ms*: *m/z* (rel. int.) = 245 (M<sup>+</sup>, 10%), 230 (M<sup>+</sup> - CH<sub>3</sub>, 16%), 84 (100). Anal. Calcd for C<sub>18</sub>H<sub>15</sub>N: C, 88.13; H, 6.16; N, 5.71. Found: C, 88.01; H, 5.98; N, 5.44.

*6-Ethyl-5-(4-phenoxy-n-butyl)-5H-benzo[b]carbazole* (5): yield: 87 mg (22%); mp 108 °C (petroleum ether/ethyl acetate); <sup>1</sup>H-nmr (DMSO-*d*<sub>6</sub>): δ = 1.35 (t, *J* = 7.40 Hz, 3 H, CH<sub>2</sub>CH<sub>3</sub>), 1.88 (m, 2 H, CH<sub>2</sub>), 1.96 (m, 2 H, CH<sub>2</sub>), 3.49 (q, *J* = 7.40 Hz, 2 H, CH<sub>2</sub>CH<sub>3</sub>), 4.01 (dd, *J* = 5.90 and 6.20 Hz, 2 H, N-CH<sub>2</sub>), 4.58 (dd, *J* = 8.10 and 7.10 Hz, 2 H, Ph-O-CH<sub>2</sub>), 6.90 (m, 3 H, 2'-H, 4'-H, 6'-H), 7.22 (dd, *J* = 7.43 and 7.52 Hz, 1 H, 8-H or 9-H), 7.26 (dd, *J* = 7.87 and 7.63 Hz, 2 H, 3'-H, 5'-H), 7.40 (dd, *J* = 7.15 and 7.57 Hz, 1 H, 9-H or 8-H), 7.52 (m, 2 H, 2-H, 3-H), 7.61 (d, *J* = 8.23 Hz, 1 H, 7-H), 8.04 (d, *J* = 8.17 Hz, 1 H, 10-H), 8.21 (d, *J* = 8.78 Hz, 1 H, 1-H or 4-H), 8.25 (d, *J* = 7.62 Hz, 1 H, H-4 or H-1), 8.61 (s, 1 H, NH); <sup>13</sup>C-nmr (DMSO-*d*<sub>6</sub>): δ = 15.86 (CH<sub>2</sub>CH<sub>3</sub>), 19.48 (CH<sub>2</sub>CH<sub>3</sub>), 25.89 (CH<sub>2</sub>), 26.21 (CH<sub>2</sub>), 44.47 (N-CH<sub>2</sub>), 66.71 (Ph-O-CH<sub>2</sub>), 109.17 (CH), 114.36 (2'-C, 6'-C), 117.40 (CH), 118.40 (Cq), 120.39 (4'-C, 7-C), 122.17 (Cq), 122.34 (Cq), 122.57 (Cq), 125.11 (CH), 125.50 (CH), 127.39 (CH), 128.09 (Cq), 128.79 (CH), 129.37 (3'-C, 5'-C), 130.73 (Cq), 136.79 (Cq), 143.73 (10-C), 158.40 (1'-Cq); EI-ms: *m/z* (rel. int.) = 393 (M<sup>+</sup>, 86%), 258 (M<sup>+</sup> - C<sub>9</sub>H<sub>11</sub>O, 57%), 230 (C<sub>17</sub>H<sub>12</sub>N<sup>+</sup>, 46%), 106 (100%); Anal. Calcd for C<sub>29</sub>H<sub>27</sub>NO: C, 85.46; H, 6.92; N, 3.56. Found: C, 85.20; H, 7.14; N, 3.54.

**General Procedure for Compounds (5), (6), and (7).** Anthranilic acid (384 mg, 3.8 mmol) and trichloroacetic acid (5.0 mg, 0.03 mmol) were suspended in 10 ml of tetrahydrofuran and cooled to 0 °C. Isoamyl nitrite (0.70 ml, 610 mg, 5.2 mmol) was added to the suspension in small portions from a syringe over 2 min at the same temperature. The resultant mixture was stirred for 1.5 h at 20 °C and then added in small portions over 30 min to a suspension of 3a (213 mg, 1 mmol) in 20 ml of tetrahydrofuran. This reaction mixture was stirred at 66 °C for 30 min and then evaporated under very mild conditions under reduced pressure. The residue obtained was separated by flash chromatography (petroleum ether/ethyl acetate, 7/3).

*6-Ethyl-5-(4-phenoxy-n-butyl)-5H-benzo[b]carbazole* (5): yield: 88 mg (30%).

*6-Ethyl-2-nitro-5H-benzo[b]carbazole* (6): yield: 44 mg (15%); mp 293-295 °C (petroleum ether/ethyl acetate); <sup>1</sup>H-nmr (CD<sub>3</sub>CN/DMSO-*d*<sub>6</sub>): δ = 1.36 (t, *J* = 7.52 Hz, 3 H, CH<sub>2</sub>CH<sub>3</sub>), 3.39 (q, *J* = 7.52 Hz, 2 H, CH<sub>2</sub>CH<sub>3</sub>), 7.44 (dd, *J* = 7.25 and 7.53 Hz, 1 H, 2-H or 3-H), 7.54 (d, *J* = 8.85 Hz, 1 H, 7-H), 7.55 (dd, *J* = 8.85 and 6.02 Hz, 1 H, H-3 or H-2), 8.07 (d, *J* = 8.22 Hz, 1 H, 1-H or 4-H), 8.20 (d, *J* = 8.62 Hz, 1 H, 4-H or 1-H), 8.35 (dd, *J* = 1.99 and

8.85 Hz, 1 H, 8-H), 8.65 (s, 1 H, 11-H), 9.10 (d,  $J = 1.99$  Hz, 1 H, 10-H), 11.37 (s, 1 H, NH); EI-*ms*:  $m/z$  (rel. int.) = 290 ( $M^+$ , 100%), 244 ( $M^+ - NO_2$ , 65%). Anal. Calcd for  $C_{18}H_{14}N_2O_2$ : C, 74.47; H, 4.86; N, 9.65. Found: C, 74.31; H, 4.77; N, 9.65.

*6-Ethyl-4-nitro-5H-benzo[b]carbazole (7)*: yield: 20 mg (7%); the product was obtained as a 1:1 mixture with **5**, further purification even by mpc resulted in decomposition; however, the structure was confirmed unambiguously by high resolution  $^1H$ -nmr spectroscopy.  $^1H$ -Nmr ( $CD_3CN$ ):  $\delta = 1.40$  (t,  $J = 7.53$  Hz, 3 H,  $CH_2CH_3$ ), 3.54 (q,  $J = 7.53$  Hz, 2 H,  $CH_2CH_3$ ), 7.27 (dd,  $J = 7.64$  and 7.84 Hz, 1 H, 9-H), 7.40 (dd,  $J = 7.42$  and 7.47 Hz, 1 H, 2-H or 3-H), 7.50 (m, 1 H, 3-H or 2-H), 8.01 (d,  $J = 7.49$  Hz, 1 H, 1-H or 4-H), 8.03 (d,  $J = 8.20$  Hz, 1 H, 4-H or 1-H), 8.20 (d,  $J = 7.66$  Hz, 1 H, 8-H or 10-H), 8.25 (m, 2 H, 11-H and 10-H or 8-H), 10.05 (s, 1 H, NH).

**General Procedure for Compounds (8), (9), and (10b)**. 1-Methylpyrano[3,4-*b*]indol-3-one (**3b**; 1 g, 5 mmol) was suspended in 250 ml of bromobenzene, the suspension was heated at 156 °C, and a solution of *N*-phenylmaleimide (865 mg, 5 mmol) in the minimum amount of bromobenzene was added. Heating under reflux was continued for 13 h, the mixture was allowed to cool, and then evaporated under reduced pressure. The obtained residue was separated by flash chromatography (acetone/chloroform, 1/12). Product (**8**) was further purified by several fractional crystallizations from methanol, attempts to separate product (**9**) from **8** even by mpc were unsuccessful and resulted in decomposition.

*4-Methyl-2-phenyl-1H,3H,5H-pyrrolo[3,4-*b*]carbazole-1,3-dione (8)*: yield: 82 mg (5%); mp 297-298 °C (methanol);  $^1H$ -nmr ( $DMSO-d_6$ ):  $\delta = 2.90$  (s, 3 H,  $CH_3$ ), 7.28 (dd,  $J = 7.51$  and 0.8 Hz, 1 H, 6-H or 7-H), 7.45 (m, 2 H, aromatic H), 7.52 (m, 3 H, aromatic H), 7.61 (d,  $J = 8.20$  Hz, 1 H, 6-H), 8.34 (d,  $J = 7.93$  Hz, 1 H, 9-H), 8.62 (s, 1 H, 10-H), 12.12 (s, 1 H, NH);  $^{13}C$ -nmr ( $DMSO-d_6$ ):  $\delta = 12.10$  ( $CH_3$ ); C- $sp^2$ : 111.83, 114.57, 120.17, 121.46, 121.54, 121.86, 122.56, 124.38, 125.32 (2'-C, 6'-C or 3'-C, 5'-C), 127.38, 127.57, 128.62 (3'-C, 5'-C or C-2', C-6'), 132.30, 141.04, 142.05, 167.13 (CO), 167.97 (CO); EI-*ms*:  $m/z$  (rel. int.) = 326 ( $M^+$ , 100%). Anal. Calcd for  $C_{21}H_{14}N_2O_2$ : C, 77.27; H, 4.33; N, 8.59. Found: C, 76.74; H, 4.55; N, 8.50.

**4-Methyl-2-phenyl-10,10a-dihydro-1H,3H,5H-pyrrolo[3,4-b]carbazole-1,3-dione (9):** yield: 273 mg (as a 3:1 mixture of 9 and 8); compound (9) was characterized by  $^1\text{H}$ -nmr and EI-mass spectroscopy.  $^1\text{H}$ -Nmr (DMSO- $d_6$ ):  $\delta$  = 2.60 (d,  $J$  = 1.97 Hz, 3 H,  $\text{CH}_3$ ), 2.81 (dd,  $J$  = 16.30 and 8.66 Hz, 1 H,  $10\alpha\text{-H}$ ), 3.40 (dd,  $J$  = 8.66 Hz and 15.82 Hz, 1 H,  $10\beta\text{-H}$ ), 4.06 (ddd,  $J$  = 2.06, 8.58, and 16.70 Hz, 1 H,  $10a\beta\text{-H}$ ), 7.05 (dd,  $J$  = 7.56 and 7.37 Hz, 1 H, 7-H or 8-H), 7.18 (dd,  $J$  = 7.25 and 7.62 Hz, 1 H, 8-H or 7-H), 7.45 (m, 6 H aromatic H), 7.62 (d,  $J$  = 7.84 Hz, 1 H, 9-H), 11.58 (s, 1 H, NH); EI- $m/z$  (rel. int.) = 328 ( $M^+$ , 50%), 58 (100%).

**2,14-Diphenyl-4-methyl-3a,5,10,10a-tetrahydro-(3acH,10acH,11synH)-4t,10t-epipyrrolopyrrolo[3,4-b]carbazole-1,3,13,15-tetraone (10b):** product (10b) was contaminated by 8 (10b:8 = 1:4 by  $^1\text{H}$ -nmr). Further purification of 10b even by *mplc* led to decomposition of the product; 10b was therefore characterized by  $^1\text{H}$ -nmr spectroscopy.  $^1\text{H}$ -Nmr (DMSO- $d_6$ ):  $\delta$  = 2.11 (s, 3 H,  $\text{CH}_3$ ), 3.17 (d,  $J$  = 7.32 Hz, 1 H, 3a-H or 12-H), 3.24 (d,  $J$  = 7.64 Hz, 1 H, 12-H or 3a-H), 3.35 (overlapping with solvent signal,  $J_{10a\alpha,10a\beta}$  or  $J_{11\alpha,10\alpha}$  = 3.05 Hz,  $J_{10a\alpha,3a\alpha}$  or  $J_{11\alpha,12\alpha}$  overlapped by solvent signal, 2 H,  $10a\text{-H}$  or  $11\text{-H}$ ), 4.38 (dd,  $J$  = 3.22 and 3.17 Hz, 1 H,  $10\text{-H}$ ), 6.14 (d,  $J$  = 7.64 Hz, 2 H, 2'-H, 6'-*exo*-phenyl-H), 7.03 (dd,  $J$  = 7.03 and 7.65 Hz, 1 H, aromatic H), 7.10 (dd,  $J$  = 7.26 and 7.04 Hz, 1 H, aromatic H), 7.18 (m, 2 H, aromatic H), 7.42 (m, 3 H, aromatic H), 7.53 (m, 5 H, aromatic H), 11.49 (s, 1 H, NH);  $^{13}\text{C}$ -nmr (DMSO- $d_6$ ):  $\delta$  = 16.22 ( $\text{CH}_3$ ), 32.42 (10-C), 40.00 (4-C), 43.19, 46.75, 47.00, 50.14 (3a-C, 12-C,  $10a\text{-C}$ , 11-C), 174.96, 175.49, 175.89, 176.22 (CO).

**Direct Preparation of 8 by a Dehydrogenative Diels-Alder Reaction of 3b.** Compound (3b; 500 mg, 2.5 mmol) and 10% palladium on carbon (310 mg, 0.25 mmol, calculated as PdO) were suspended in 125 ml of bromobenzene. The suspension was heated under reflux and a solution of *N*-phenylmaleimide (433 mg, 2.5 mmol) in 10 ml of bromobenzene was added slowly. Heating under reflux was continued for 20 h, the reaction mixture was then filtered, and the filtrate was evaporated under reduced pressure. The residue obtained was separated by flash chromatography (petroleum ether/ethyl acetate, 7/3); yield: 90 mg (11%).

**2,14-Diphenyl-4-methyl-3a,5,10,10a-tetrahydro-(3acH,10acH,11antiH)-4t,10t-epipyrrolopyrrolo[3,4-b]carbazole-1,3,13,15-tetraone (10a).** A mixture of 3b (200 mg, 1 mmol) and *N*-phenylmaleimide (346 mg, 2 mmol) in 60 ml of



tetrahydrofuran was stirred at 20 °C for 25 h. The resultant yellow solution was concentrated under reduced pressure to a volume of 2 ml and 10 ml of benzene were added. The immediately formed precipitate was filtered off, washed five times with benzene, and dried; yield: 401 mg (80%); mp 315 °C (acetone, *n*-hexane), [lit.,<sup>13</sup> mp, 315-316 °C]; <sup>1</sup>H-nmr (acetone-*d*<sub>6</sub>): δ = 2.27 (s, 3 H, CH<sub>3</sub>), 3.47 (d, *J* = 8.01 Hz, 2 H, 3a-H, 12-H), 3.72 (dd, *J* = 8.01 and 3.02 Hz, 2 H, 10a-H, 11-H), 4.60 (t, *J* = 3.02 Hz, 1 H, 10-H), 6.43 (m, 4 H, 2'/6'-phenyl-H), 7.04 (dd, *J* = 7.13 and 7.90 Hz, 1 H, 7-H or 8-H), 7.10 (dd, *J* = 8.02 and 7.13 Hz, 1 H, 8-H or 7-H), 7.17 (m, 6 H, 3'/4'/5'-phenyl-H), 7.38 (d, *J* = 7.98 Hz, 1 H, 6-H), 7.49 (d, *J* = 8.85 Hz, 1 H, 9-H), 10.60 (s, 1 H, NH); <sup>13</sup>C-nmr (DMSO-*d*<sub>6</sub>): δ = 15.85 (CH<sub>3</sub>), 33.07 (10-C), 40.68 (4-C), 45.06, 49.03 (3a-C, 12-C, 10a-C, 11-C), 111.52, 117.09, 119.30, 120.73 (6-C, 7-C, 8-C, 9-C), 126.30, 128.50 (2'-C, 3'-C, 5'-C, 6'-C), 128.04 (4'-C), 131.74 (1'-C), 107.19, 124.68, 135.89, 136.73 (9a-C, 9b-C, 5a-C, 4a-C), 175.03, 175.96 (CO); EI-ms: *m/z* (rel. int.) = 501 (M<sup>+</sup>, 40%), 181 (100%). Anal. Calcd for C<sub>21</sub>H<sub>23</sub>N<sub>3</sub>O<sub>4</sub>: C, 74.24; H, 4.62; N, 8.38. Found: C, 74.51; H, 4.95; N, 7.95.

#### ACKNOWLEDGEMENTS

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16. Full details of the X-ray analyses together with molecular modeling studies will be submitted to *Liebigs Ann. Chem.* for publication.
17. For molecular modeling studies, quantum chemistry and molecular mechanics programs (AM1, Tripos force field) were used in combination with the SYBYL 5.2 program packet from Evans and Sutherland; Tripos Associates, Inc., St. Louis, MO, USA.

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