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New Potential DNA Intercalators of the Carbazole Series from Indole-2,3-quinodimethanes: Synthesis, Crystal Structure, and Molecular Modeling with a Watson-Crick Mini-Helix

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Summary. 1-Alkylpyrano[3,4-b]indol-3-ones **3** react via a Diels-Alder step with an aryne or N-phenylmaleimide to furnish the new [b]annellated carbazoles **4–10** in a one-pot process. In an analogous procedure, the in situ generated N-benzoylindole-2,3-quinodimethane (**13**) reacted with quinones to furnish the dioxocarbazoles **14–16**. Compounds **4–8** and **14–16** with a coplanar skeleton are members of a class of potential DNA intercalators, as has been shown for **5** and **8** by X-ray structural analysis. On the basis of the geometries determined by X-ray crystallography, the intercalative binding of these molecules with a Watson-Crick mini-helix was predicted by molecular modeling methods.

Keywords. [b]annellated carbazoles; Crystal structures; Molecular modeling; DNA intercalators.

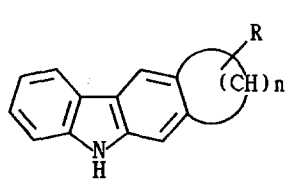
Neue potentielle DNA-Interkalatoren der Carbazol-Reihe aus Indol-2,3-chinodimethanen: Synthese, Kristallstruktur und Molecular Modeling mit einer Watson-Crick Minihelix

Zusammenfassung. 1-Alkylpyrano[3,4-b]indol-3-one **3** reagieren über einen Diels-Alder-Schritt mit Arin oder N-Phenylmaleinimid zu [b]annellierten Carbazolen **4–10** in einer Einstufenreaktion. In analoger Weise reagiert ein in situ erzeugtes N-Benzoylindol-2,3-chinodimethan **13** mit Chinonen zu den Dioxocarbazolen **14–16**. Die Verbindungen **4–8** und **14–16** gehören infolge ihrer coplanaren Struktur zur Klasse potentieller DNA-Interkalatoren. Auf der Basis von Röntgenstrukturanalysen von **5** und **8** wird die interkalative Bindung mit einer Watson-Crick Minihelix durch Molecular Modeling vorhergesagt.

Introduction

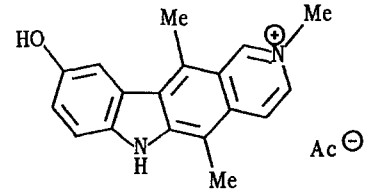
The mostly coplanar, [b]annellated carbazole derivatives **1** constitute synthetically attractive target molecules since they possess potential anti-tumour activity [1–3]. Of particular significance in this series are the pyrido[4,3-b]carbazole alkaloids of the ellipticine group such as, for example, 2-methyl-9-hydroxy-ellipticinium acetate (**2**) which is used clinically in the therapy for breast cancer, myeloblastic leukemia,

and solid tumours [3–5]; substances of this type belong to a class of new, biologically active lead compounds. Thus, the synthetic development of further analogues of **1** which may exhibit cytostatic activities is of considerable interest in medicinal chemistry. One mechanistic principle of the anti-tumour activity of these linearly annellated heterocycles is their selective complexation with the human B-DNA helix, in particular by intercalative binding [3, 4, 6].



n= 3,4

1



2

This selective interaction of coplanar polycycles with DNA has already been demonstrated by experimental studies concerned with the changes of the physical properties of the double helix in the cases of some other active principles such as, for example, triostin A, proflavine, daunomycin, dactinomycin, mitoxantrone, and amsacrine [7–10] with anti-tumour activity.

In the present paper, we report the continuation of our synthetic investigations on pericyclic six-electron processes leading to novel [b]annellated carbazoles [11–16] and on Diels-Alder reactions of the readily available pyrano[3,4-b]-indol-3-ones **3a, b** [16] with cyclic carbodienophiles. Additionally, an in situ generated indole-2,3-quinodimethane was submitted to an analogous Diels-Alder reaction. In some cases, the special structural features of the cycloadducts obtained were additionally studied with regard to their potential for intercalative binding to DNA.

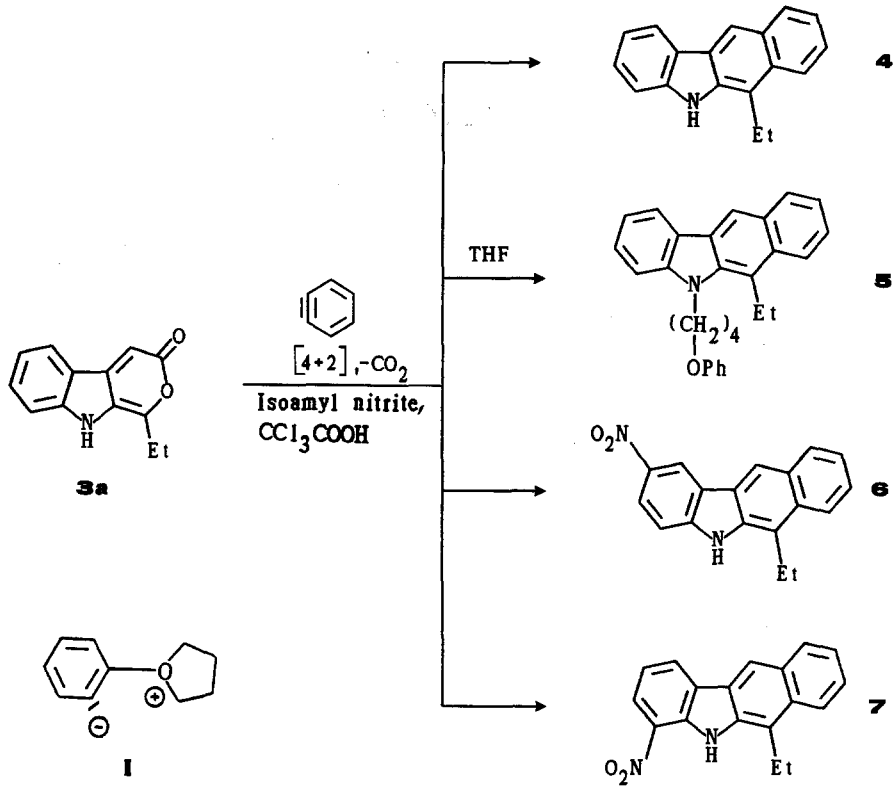
Results and Discussion

Synthetic Aspects

The procedure for the Diels-Alder reaction with pyrano[3,4-b]indol-3-ones was first reported by Plieninger and coworkers [16] and then further developed by Moody and coworkers [17] and by our group [11–15]. This methodology was recently employed for the selective synthesis of 1,2-dihydrocarbazoles [18].

Accordingly, the ethyl derivative **3a** [16] reacts as a diene component with in situ generated benzyne [11] to furnish the four new benzo[b]carbazoles **4**–**7** in dependence on the reactions conditions (Scheme 1) (see Exp. Part). Of these products, compound **4** represents the generally expected cycloadduct.

The additionally formed regioisomeric nitrobenzocarbazoles **6** and **7** are the result of a nitration reaction due to the presence of isoamyl nitrite/trichloroacetic acid in the reaction mixture for the generation of benzyne. We have previously reported such a nitration process in a related Diels-Alder reaction of pyrano[3,4-b]-indol-3-ones [11]. On the other hand, the N-substituted benzocarbazole **5** (yield 22–30%) is only formed when tetrahydrofuran is employed as the solvent.



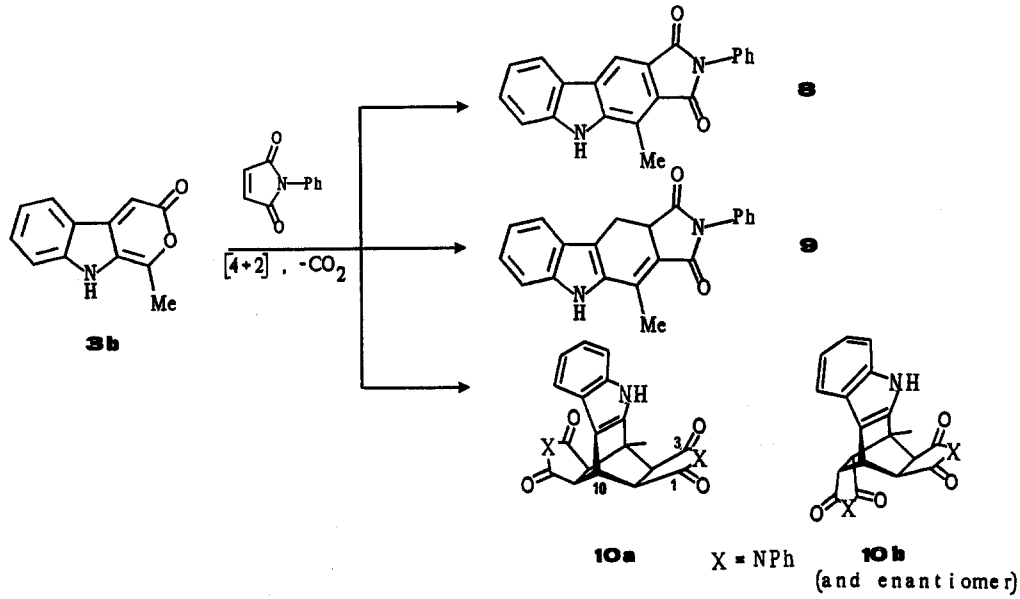
Scheme 1

For a mechanistic rationalisation of this process, we suggest that the solvent reacts with the aryne as an O-nucleophile to form the zwitterionic intermediate **I** with an oxonium centre. Subsequent N-alkylation of product **4** by the oxonium moiety of **I** and cleavage of the five-membered ring should then lead to **5**. A primary N-alkylation of **3a** via an analogous mechanism can be excluded on the basis of careful analysis of the reaction mixture.

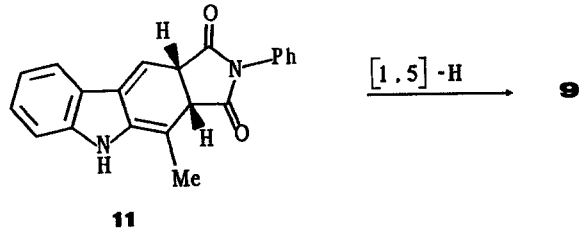
We have previously established that the Diels-Alder reaction of pyrano[3,4-b]-indol-3-ones with N-phenylmaleimide represents a convenient access to [b]pyrrolo-annellated carbazoles with a 1,3-dione functional moiety [12, 14, 15]. Complementary to our preliminary communication [12], we have now found that the reaction of **3b** with N-phenylmaleimide gives rise to the four [b]pyrrolo-annellated carbazoles **8**, **9**, **10a**, and **10b** (Scheme 2). The double Diels-Alder reaction of **3b** to furnish **10** should produce four stereoisomers (including one pair of enantiomers). However, we have only detected three isomers, namely **10a** and the racemate **10b** by HPLC analysis.

The dihydrocarbazole **9** is probably formed from the initially expected cycloadduct **11** by subsequent stabilisation through a [1,5]-H shift (Scheme 3).

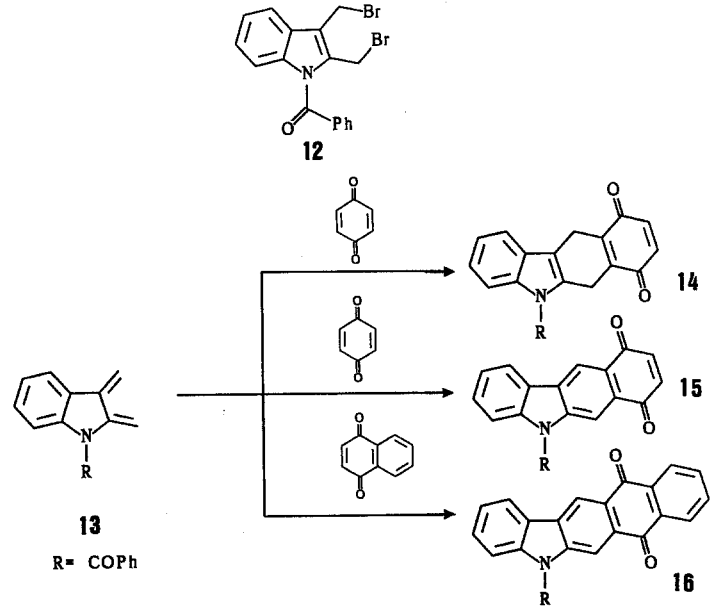
In this context, the in situ indole-2,3-quinodimethane Diels-Alder methodology represents a further variant giving rise to coplanar, [b]annellated carbazoles [14, 19]. Thus, we have extended this concept to include the generation of the diene **13** from the readily available N-benzoyl-2,3-bis(bromomethyl)indole (**12**) in the presence of sodium iodide. The in situ generated **13** was subsequently trapped with



Scheme 2



Scheme 3



Scheme 4

1,4-benzoquinone and 1,4-naphthoquinone to furnish the [b]annellated carbazoles **14–16** (Scheme 4).

Structural Investigations and Simulation of Intercalative Binding of the Carbazoles in the Base-Paired 5-Iodocytidylyl(3',5')guanosine as a DNA Mini-Helix

The constitutions of products **4–9** and **14–16** were elucidated by 400 MHz ^{1}H-NMR spectroscopy with additional ^{1}H, ^{1}H-NOE measurements. The relative configurations of the tetrahydrobarrelene isomers **10a** and **10b** were further clarified by 1D and 2D ^{1}H, ^{1}H-NOE (NOESY) experiments [12]. In the case of the carbazoles **5** and **8**, X-ray crystallography provided useful information on the geometry and conformation for the prediction of intercalative binding of this compound class with hydrogenbonded dinucleotide pairs.

Table 1. Crystallographic data and structure determination details for **5** and **8**

	5	**8**
Crystal data (Mo–$K_{\alpha 1}$, $\lambda = 0.70926$ Å)		
Formula, M_r	$C_{28}H_{27}NO$, 393.53	$C_{21}H_{14}N_2O_2 \cdot 1/2\ H_2O$, 335.37
Crystal habit (dimensions)	needle, faces somewhat irreg. ($0.16 \times 0.38 \times 2.5\,mm^3$)	wedge-shaped ($0.12 \times 0.20 \times 0.8\,mm^3$)
Crystal colour	light yellow	yellow
Crystal system, space group	orthorhombic, $Pna2_1$ (no. 33)	monoclinic, C2/c (no. 15)
Unit cell dimensions a	8.090(1) Å	15.955(2) Å
b, β	17.979(4) Å	7.077(2) Å, 91.68(1)°
c	14.905(2) Å	28.167(3) Å
Least squares fit	140 reflections $\theta = 18$–$21°$	50 reflections $\theta = 18$–$21°$
Packing: V, Z, $F(000)$	2168(1) Å^3, 4, 840	3179(1) Å^3, 8, 1400
D_{calcd}, D_{exptl} [a]	1.205, 1.203 g cm^{-3}	1.401, 1.365 g cm^{-3}
Intensity data collection (Mo–K_α, $\lambda = 0.71069$ Å, graphite monochr.)[b]		
Temperature, θ range, $\sin\theta_{max}/\lambda$	22 °C, 1.5–30°, 0.704 Å^{-1}	20 °C, 1.5–28°, 0.661 Å^{-1}
Range of hkl	0 to 11, 0 to 25, 0 to 21	0 to 21, 0 to 9, −37 to +37
Reference reflections	three, every 4000 sec	three, every 4000 sec
Loss of intens., corr., measur. time	none, no corr., 6 days	2.9%, linear, 4 days
Reflections: meas., indep. (int. R)	3568, 3568	3973, 3840 (0.0217)
Reflections used, limit	1498 with $I > 1\,\sigma(I)$	1773 with $I > 2\,\sigma(I)$
μ, absorption correction	0.38 cm^{-1}, no abs. corr.	0.51 cm^{-1}, numer. by face indices
Range of transmission		0.9904 to 0.9724
Refinement		
var., ratio ref./var., last shifts	297, 5.0, $<0.01\,\sigma$	230, 7.7, $<0.1\,\sigma$
Final R, R_w	0.0724, 0.0722[c]	0.0529, 0.81
Weighting scheme w^{-1}	$(\sigma^2(F) + 0.000635 \cdot F^2)$	$(\sigma^2(F) + 0.001113 \cdot F^2)$
Final difference Fourier maxima	0.24 e/Å^3 (near ethyl)	0.21 e/Å^3 (near methyl)

[a] Neutral buoyancy (aqueous sodium polywolframate solution for **5**, Thoulet solution for **8**)

[b] $\omega/2\theta$-scans, CAD4 diffractometer (Enraf-Nonius)

[c] Enantiomorph: no differences in R_w and distances

a) X-Ray Crystallography of Products **5** and **8**

Compound **5** was recrystallized from methanol/water (1:1) and compound **8** from methanol. Details of the crystal parameters, intensity data collection, and structural refinement of compounds **5** and **8** are listed in Table 1. The crystal structures were

Table 2. Fractional atomic coordinates and equivalent isotropic thermal parameters for **5** (esd's in parentheses). Numbering scheme based on the nomenclature of the 6*H*-benzo[b]carbazole skeleton; groups as given in Fig. 1

Group	Atom	x	y	z	U(eq)[a] [Å^2]
Benzo	C(1)	0.3098(9)	0.2977(3)	0.0963(6)	0.087(5)
	C(2)	0.3936(10)	0.3108(4)	0.1741(6)	0.099(5)
	C(3)	0.5420(10)	0.3526(4)	0.1700(6)	0.092(5)
	C(4)	0.5999(9)	0.3788(4)	0.0908(6)	0.087(4)
Carbazole	C(4a)	0.5177(7)	0.3660(3)	0.0087(5)	0.064(3)
	C(5)	0.5770(6)	0.3939(3)	−0.0743(6)	0.066(3)
	C(5a)	0.4888(6)	0.3771(3)	−0.1512(5)	0.063(3)
	N(6)	0.5128(5)	0.3967(3)	−0.24062	0.072(3)
	C(6a)	0.3816(6)	0.3699(3)	−0.2915(5)	0.065(3)
	C(7)	0.3529(7)	0.3768(3)	−0.3835(6)	0.081(4)
	C(8)	0.2117(8)	0.3447(3)	−0.4187(6)	0.086(4)
	C(9)	0.1015(8)	0.3072(4)	−0.3633(7)	0.093(5)
	C(10)	0.1311(8)	0.2995(3)	−0.2726(6)	0.083(4)
	C(10a)	0.2704(6)	0.3320(3)	−0.2359(6)	0.064(3)
	C(10b)	0.3340(6)	0.3351(3)	−0.1461(6)	0.065(3)
	C(11)	0.2801(7)	0.3096(3)	−0.0661(6)	0.070(3)
	C(11a)	0.3658(7)	0.3235(3)	0.0129(5)	0.072(4)
Ethyl	C(51)	0.7361(6)	0.4418(4)	−0.0761(7)	0.086(4)
	C(52)	0.8921(8)	0.3964(4)	−0.0665(7)	0.104(5)
Bu–O (MC)[b]	C(61)	0.6790(11)	0.4058(5)	−0.2843(7)	0.073(6)
	C(62)	0.6965(12)	0.4852(5)	−0.3215(8)	0.076(6)
	C(63)	0.8570(24)	0.5026(9)	−0.3589(11)	0.098(10)
	C(64)	1.0044(12)	0.5041(5)	−0.2961(9)	0.067(6)
	O(65)	0.9642(8)	0.5685(4)	−0.2427(7)	0.093(5)
Phenyl	C(651)	1.0840(8)	0.5885(4)	−0.1835(6)	0.088(5)
	C(652)	1.2203(9)	0.5469(4)	−0.1513(6)	0.096(5)
	C(653)	1.3188(10)	0.5794(4)	−0.0873(7)	0.100(5)
	C(654)	1.2915(10)	0.6491(5)	−0.0592(7)	0.100(6)
	C(655)	1.1605(12)	0.6905(4)	−0.0893(7)	0.106(5)
	C(656)	1.0537(9)	0.6581(5)	−0.1513(7)	0.099(5)
Bu–O (SC)[c]	C(61a)	0.6201(26)	0.4671(13)	−0.2795(16)	0.073(5)*
	C(62a)	0.7578(28)	0.4336(14)	−0.3208(16)	0.073(5)*
	C(63a)	0.8693(39)	0.4849(14)	−0.3782(18)	0.047(6)*
	C(64a)	0.9364(42)	0.5541(20)	−0.3126(18)	0.114(9)*
	O(65a)	1.0221(32)	0.5301(15)	−0.2477(17)	0.112(8)*

[a] U(eq) defined as one third of the trace of the orthogonalized U(ij) tensor; * = isotropic U

[b] Main component of the differentiated oxybutyl group: 68%

[c] Secondary component of the differentiated oxybutyl group: 32%

solved using the programmes SHELX 86 [20] and SHELX 76 [21] for refinement according to the full matrix least squares method.

Fractional atomic coordinates of compounds **5** and **8** are listed in Tables 2 and 3**.

Both compounds **5** and **8** reveal only slight deviations in the coplanarity of the [b]annellated carbazole framework. The unit cell of **5** contains two independent molecules which differ only in the conformation of the phenoxybutyl side-chain.

Table 3. Fractional atomic coordinates and equivalent isotropic thermal parameters for **8** (esd's in parentheses). Numbering scheme based on the nomenclature of the 1,3-Dihydro-2*H*,5*H*-pyrrolo-[3,4-b]carbazole skeleton

Group	Atom	x	y	z	U(eq)[a] [Å^2]
Pyrrolo-dione	C(1)	0.6982(2)	0.3486(4)	0.5810(1)	0.040(1)
	O(11)	0.7641(1)	0.3868(3)	0.56266(8)	0.053(1)
	N(2)	0.6880(1)	0.3292(4)	0.62968(9)	0.042(1)
	C(3)	0.6040(2)	0.2871(4)	0.6402(1)	0.043(1)
	O(31)	0.5801(1)	0.2676(4)	0.68038(8)	0.064(1)
Carbazole	C(3a)	0.5583(1)	0.2737(4)	0.5942(1)	0.037(1)
	C(4)	0.4753(1)	0.2263(4)	0.5850(1)	0.037(1)
	C(4a)	0.4537(1)	0.2172(4)	0.5367(1)	0.036(1)
	N(5)	0.3758(1)	0.1709(4)	0.51622(9)	0.042(1)
	C(5a)	0.3812(2)	0.1783(4)	0.4676(1)	0.041(1)
	C(6)	0.3194(2)	0.1413(5)	0.4326(1)	0.050(2)
	C(7)	0.3408(2)	0.1627(5)	0.3864(1)	0.057(2)
	C(8)	0.4208(2)	0.2187(5)	0.3738(1)	0.056(2)
	C(9)	0.4825(2)	0.2538(5)	0.4080(1)	0.047(2)
	C(9a)	0.4623(2)	0.2336(4)	0.4558(1)	0.040(1)
	C(9b)	0.5096(1)	0.2575(4)	0.4998(1)	0.035(1)
	C(10)	0.5930(1)	0.3061(4)	0.5109(1)	0.037(1)
	C(10a)	0.6151(1)	0.3105(4)	0.5580(1)	0.035(1)
Phenyl	C(21)	0.7542(2)	0.3459(5)	0.6652(1)	0.044(2)
	C(22)	0.7503(2)	0.4876(6)	0.6985(1)	0.060(2)
	C(23)	0.8133(3)	0.5009(8)	0.7333(1)	0.080(3)
	C(24)	0.8785(2)	0.3752(10)	0.7338(1)	0.088(3)
	C(25)	0.8815(2)	0.2327(8)	0.7009(1)	0.082(3)
	C(26)	0.8185(2)	0.2169(6)	0.6653(1)	0.061(2)
Methyl	C(41)	0.4132(2)	0.1855(5)	0.6230(1)	0.054(2)
cr.w.[b]	O(20)	0.00000	0.0675(92)	0.25000	0.133(14)*

[a] U(eq) as defined in Table 2

[b] Crystal water positioned on a twofold axis

** Additional material to the structure determination can be ordered from Fachinformationszentrum Energie-Physik-Mathematik, D-W-7514 Eggenstein-Leopoldshafen 2, Federal Republic of Germany, referring to the deposition no. CSD 56452, the names of the authors and the citation of the paper.

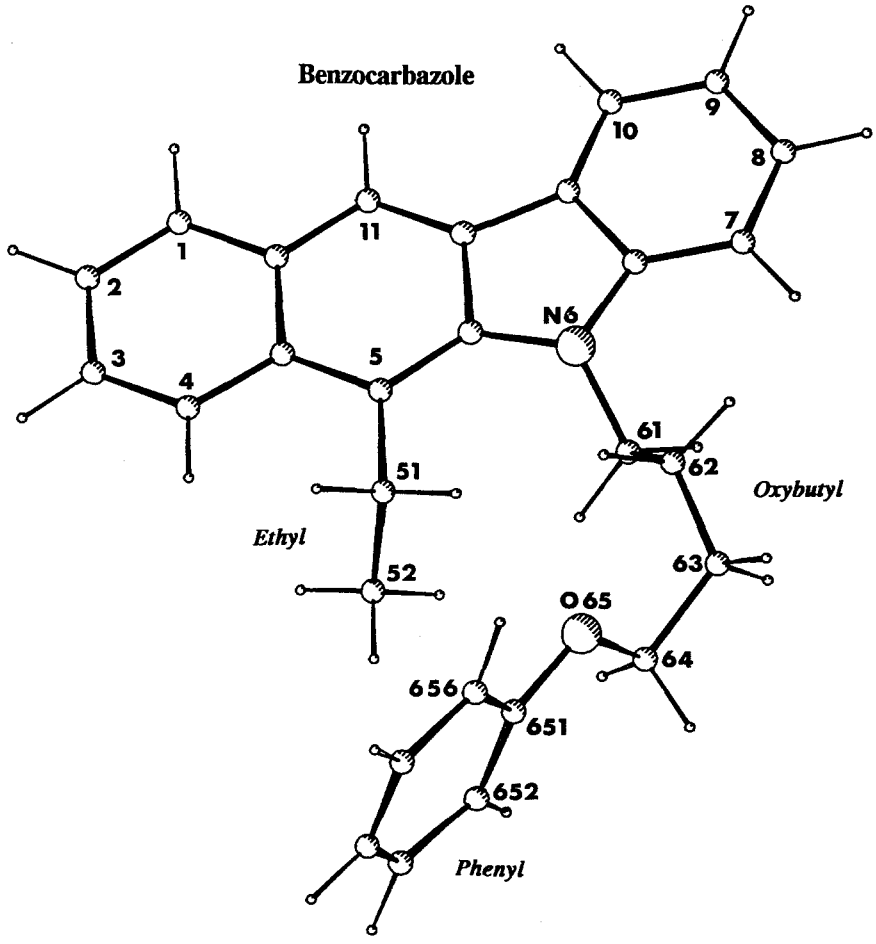


Fig. 1. PLUTO plot of the molecular structure of compound **5** (main component). View along the y axis; the numbering of the atoms does not always coincide with the IUPAC nomenclature

The structure of the main component (68%) is shown in Fig. 1. The ethyl group is orientated nearly rectangular to the ring plane (76.7°) and the phenoxybutyl side chain (the torsional angles C5a-N6-C61-C62 = 121.2° for the main component and 110.8° for the minor component) is respectively on the opposite side of the ring system in the main component and on the same side of the ring system in the minor component.

Figure 2 illustrates the torsional angles of the main and minor components of **5**. Within the limits of experimental error, the torsional angles of the main and minor components differ solely in their sign (local enantiomeric groups).

According to MMX force field calculations [22], the main component is more stable than the minor component by about 2.3 kcal mol^{-1}. Root mean square (rms) calculations for the comparison of the X-ray structure of the main component with the MMX-refined structure give a value of 0.5 Å. A global minimum conformational search by *Monte Carlo Metropolis* algorithms [22] results in an energetically most favoured conformation of the *n*-butyloxy side-chain with an *all antiperiplanar* geometry.

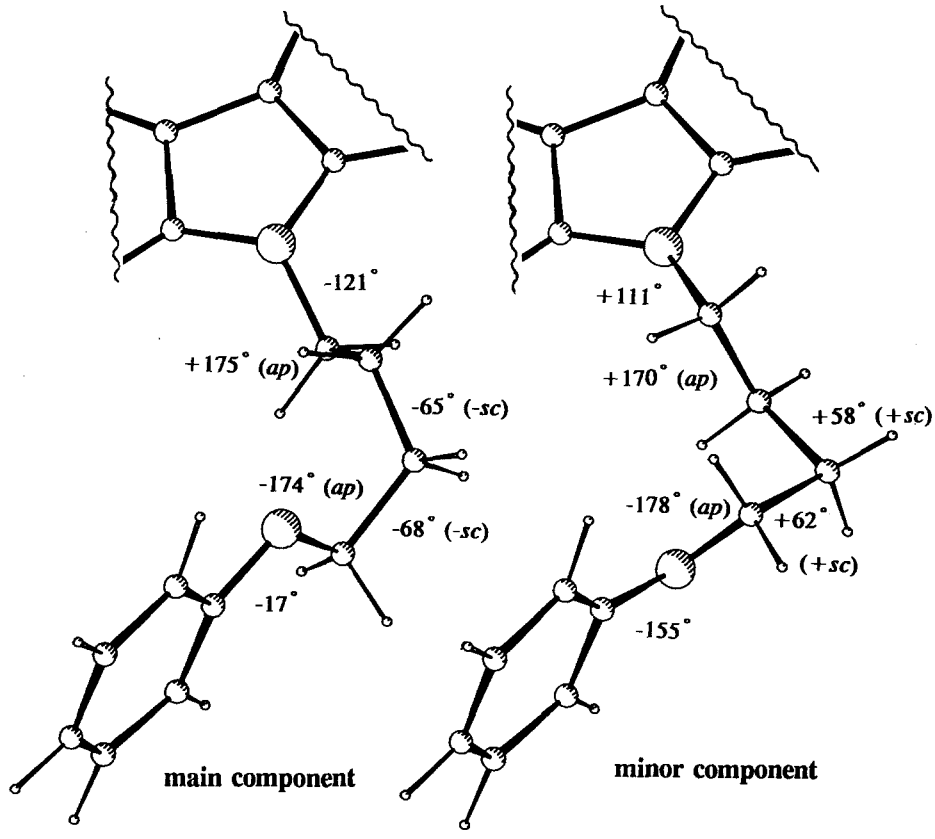


Fig. 2. Comparison of the side-chain conformations of the main and minor components of compound **5** existing in the crystal state

The molecular structure of **8** is illustrated in Fig. 3 together with the association sites in the crystal state. The N-phenyl-substituted annellated dioxopyrrole ring is of particular interest. The bond lengths of the carbonyl groups (1.216 and 1.212 Å) are in the normal range although the angles are slightly disoriented. Conspicuous is the non-symmetry of the valency angles N2-C3-O31 (123.1°) and O31-C3-C3a (130.8°). Intermolecular interactions with the molecule of water of crystallisation are in part responsible for these phenomena. The crystal packing of the molecule **8** is characterised by the formation of associates (Fig. 3).

Two molecules of **8** (orientated about a two-fold axis) are complexed with one molecule of water of crystallisation on this two-fold axis as bridging unit through strong hydrogen bonds (O31···O20 = 2.644 Å, O31···O20···O31 = 127.6°). The angle between the intermolecular interaction partners is of similar size to the angle of a water molecule. These "complexed pairs" exist as larger units linked by somewhat weaker, almost linear hydrogen bonds from N5 to O11 (N5···O11 = 3.011 Å, H5···O11 = 2.127 Å, N5···H5···O11 = 162.4°). The thus formed chains are orientated in a stacked manner along the b axis.

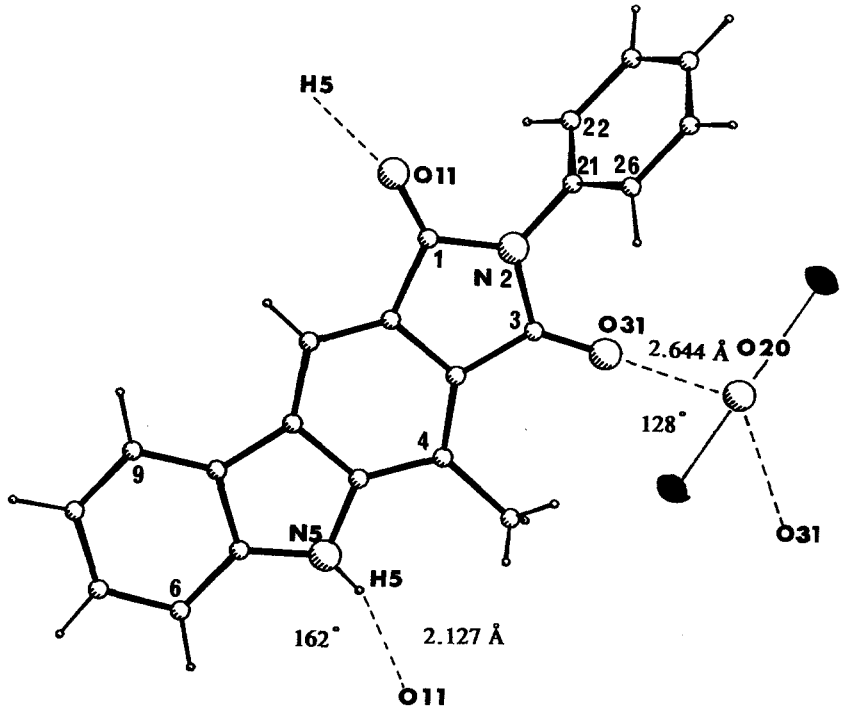


Fig. 3. Molecular structure of compound **8** with indication of the association sites; O20 = water of crystallisation located on a two-fold axis

b) Molecular Modeling of Intercalation Complexes

The Watson-Crick mini-helix, the base-paired 5-iodosubstituted cytidylyl(3',5')-guanosine (duplex molecule) was co-crystallised with ellipticine and with 3,5,6,8-tetramethyl-N-methylphenanthrolinium chloride and X-ray crystallographic analyses were performed [10, 23]. These analyses provided the necessary starting geometries for molecular modeling studies of the intercalation [24]. ^{1}H-NMR spectroscopic studies were also compatible with the calculated intercalative binding in self-complementary dinucleotides [21].

On the basis of these convincing results, we performed molecular modeling studies on the carbazoles **4–8** and **14–16** for interactive, intercalative docking in the "cleft" of the (5-iodoCpG)$_2$ dinucleotide duplex with the help of theoretical programmes in combination with real-time computer graphics. The initial geometry of the base-paired dinucleotide (dihedral angles, bond lengths) was taken from the X-ray analysis of the related ellipticine intercalator complex [10]. The same orientation as that of ellipticine in the (5-iodoCpG)$_2$ complex was assumed for the carbazoles **4–8** and **14–16** in these modeling studies. For the general preorientation of the intercalated complex, the carbazoles **4**, **6**, **7**, and **14–16** were first energy-minimised by MMX molecular mechanics calculations [22] and then previewing docking experiments were carried out with the programme ALCHEMY II [25]. In the cases of the carbazoles **5** and **8**, the initial geometries for docking experiments were taken from the X-ray analyses (Fig. 1 and 3). The energy refinements of the entire complexes of **4**, **5**, **6**, **8** with the base-paired dinucleotide

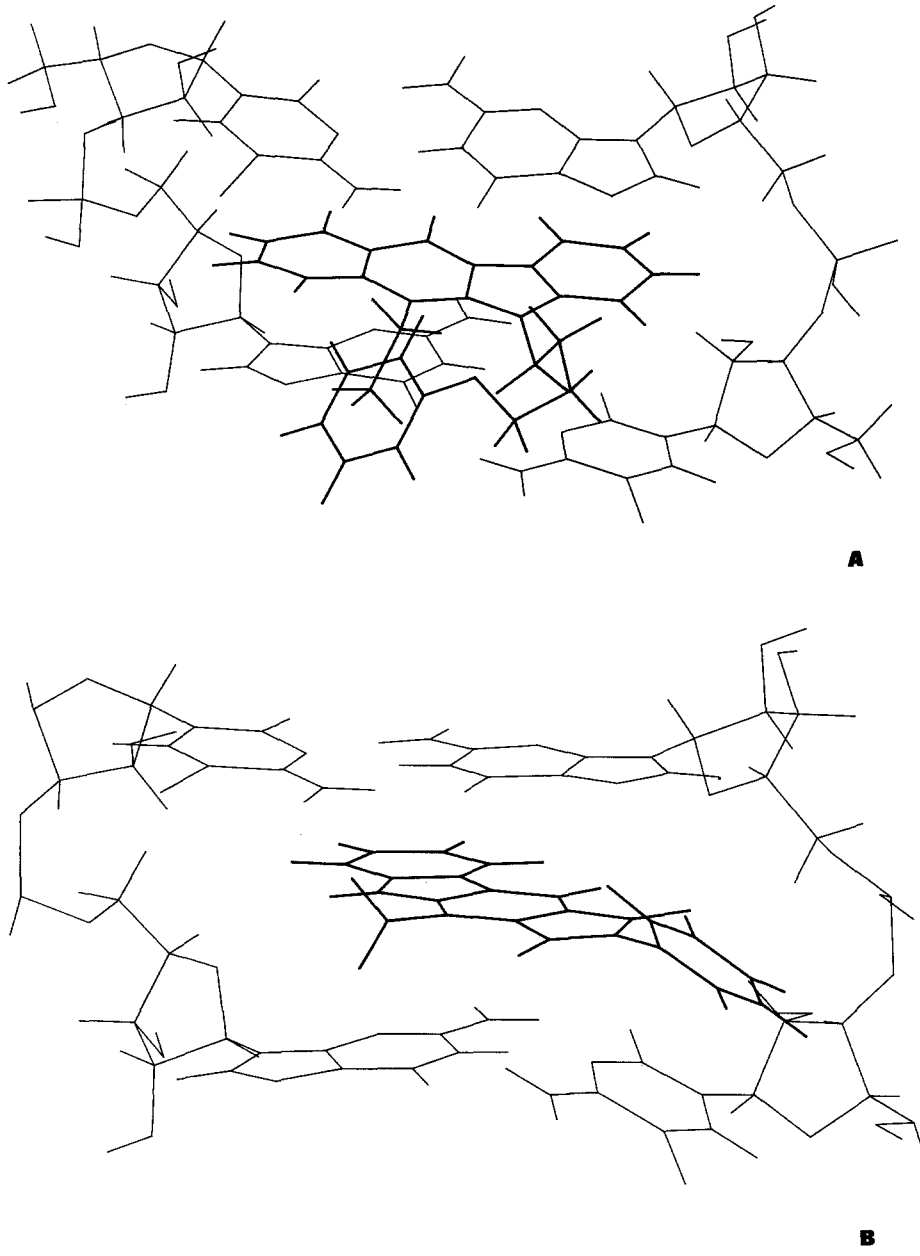


Fig. 4. Molecular graphic representation of the energy minimised and energetically favoured complexes (MAXIMIN 2) of **5** (**A**) and **8** (**B**) (geometries of the major component in the crystal were used for **5**) with (5-iodoCpG)$_2$ [26]. View approximately along the helical axis. Minimum overlap of the van der Waals surface between intercalator and dinucleotide was realised. (Interaction energy for **A** = -39.2 kcal mol^{-1}; interaction energy for **B** = -40.1 kcal mol^{-1})

were then performed exemplarily by MAXIMIN 2 molecular mechanics calculations using the TRIPOS basis set of force field parameters in the SYBYL programme packet [26–28]. For the analysis of complexes of lower energies, an automatic docking programme in the SYBYL environment was developed. For compounds

Table 4. Characteristic torsional angles of dinucleotides and intercalated complexes with ellipticine, **5** (MC)[i], and **8**

Dinucleotide/ intercalated complex	χ	χ'[f]	β[g]
$(dCpG)_2$ in B-DNA[a]	−98°	−98°	−146°
$(dCpG)_2$ in B-DNA[b]	−95°	−95°	209°
dCpG-dinucleotide[b]	–	–	174°
$(5\text{-iodoCpG})_2$[c,h]	−155°	−75°	−136°
	−158°	−75°	−157°
$(5\text{-iodoCpG})_2$/ellipticine[d,h]	−162°	−85°	−155°
	−164°	−91°	−165°
$(5\text{-iodoCpG})_2$/**5**[d,h] (MC)[i]	−163°	−79°	−160°
	−170°	−100°	−176°
$(5\text{-iodoCpG})_2$/**8**[d,h]	−158°	−84°	−162°
	−175°	−88°	−165°

[a] From the biopolymer module in SYBYL [26, 29]

[b] From Ref. [29]

[c] From X-ray analysis [10]

[d] Energy minimised complexes from MAXIMIN 2 molecular mechanics calculations; for definition of torsional angles and numbering in nucleotides, see Ref. [29]

[e] O4′–C1′–N1–C2

[f] O4′–C1′–N9–C4

[g] P–O5′–C5′–C4′

[h] The different values represent the different chains in the dinucleotide duplex

[i] MC = main component

4–6, an edge-on alignment orientation in the dinucleotide duplex cleft is energetically favoured. On the other hand, the relatively "long" molecules **8** (longitudinal axis 14.7 Å) and **16** (docking with ALCHEMY programme) intercalate in the duplex in nearly the same way as daunomycin in the base-paired d(CpGpTpApCpG) nucleotide [29]. In this case, the chromophore is inserted "head-on" between adjacent base pairs. The base pair hydrogen bonds are fully intact in all cases so far simulated. The typical intercalation is illustrated in more detail for the intercalation with compounds **5** and **8** (Fig. 4, Table 4). In the framework of the dinucleotide backbone in both cases, the pyrimidine sugar is held in the C3′-*endo* conformation and the purine sugar in the C2′-*endo* conformation (sugar puckering) [29]. These results are in accord with X-ray and NMR results for dinucleoside monophosphate duplexes [24, 29]. In addition to the unwinding of the helical twist of two stacked base pairs on going from the non-intercalated duplex to the intercalated form, the change in the glycosidic torsional angle χ (χ') and the change of the torsional angle β in the phosphate backbone are significant parameters for the generation of an intercalation site in a dinucleotide duplex [29]. Some characteristic torsional angles of the intercalated nucleotide duplex $(5\text{-iodoCpG})_2$ together with those of the non-complexed form, the relevant B-DNA duplex, and the simple dCpG dinucleotide are given in Table 4. In comparison to the

non-complexed (5-iodoCpG)$_2$ duplex, the relevant torsional angles in the intercalative duplex with the anti-tumour alkaloid ellipticine or the carbazoles **5** and **8** are, in part, significantly increased with the consequence of a partial unwinding of the overall helical structures [29]. The hydrophobic aryloxyalkyl sidechain of **5** in the complex (**A**) is orientated approximately perpendicular to the stacked base pair lines and is directed in the major groove (Fig. 4, **A**). In the complex (5-iodoCpG)$_2$/**8** (**B**), the conformation of **8** has changed only slightly in comparison to its starting conformation (from X-ray analysis). The N-phenyl group is similarly oriented in the major groove. The distance between the stacked base pairs in the non-intercalated dinucleotide increases in general from 3.4 Å to about 7 Å [26] when a carbazole chromophore is inserted in the dinucleotide duplex.

Experimental Part

The ^{1}H-NMR spectra were recorded at 400 MHz and the ^{13}C-NMR spectra at 100.6 MHz. The ^{13}C-NMR shift analyses were supported by the C-NMR simulator programme from the VISPER programme 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. The molecular modeling computations were performed on IBM PS/2 386 and MicroVAX 310 computers and the Evans & Sutherland Computation Graphic System PS 390.

General Procedure for the Preparation of **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%), m.p. 117 °C (petroleum ether/ethyl acetate). ^{1}H-NMR (*DMSO-d*$_6$): δ (ppm) 1.33 (t, ^3J = 7.50 Hz, 3 H, $CH_2\mathbf{CH_3}$), 3.37 (q, ^3J = 7.50 Hz, 2 H, $\mathbf{CH_2}CH_3$), 7.17 (dd, ^3J = 6.78 and 7.64 Hz, 1 H, aromatic H), 7.36 (dd, ^3J = 7.08 and 7.76 Hz, 1 H, aromatic H), 7.48 (m$_c$, 3 H, aromatic H), 8.05 (d, ^3J = 8.21 Hz, 1 H, C2–H or C3–H), 8.13 (d, ^3J = 8.66 Hz, 1 H, C3–H or C2–H), 8.23 (d, ^4J = 7.67 Hz, 1 H, C10–H), 8.54 (s, 1 H, C11–H), 11.10 (s, 1 H, NH). EI-MS: *m/z* (%) = 245 (M^+, 10), 230 (M^+–CH_3, 16), 84 (100). $C_{18}H_{15}N$ (245.3): calcd. C 88.13, H 6.16, N 5; 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%), m.p. 108 °C (petroleum ether/ethyl acetate). ^{1}H-NMR (*DMSO-d*$_6$): δ (ppm) 1.35 (t, ^3J = 7.40 Hz, 3 H, $CH_2\mathbf{CH_3}$), 1.88 (m$_c$, 2 H, CH_2), 1.96 (m$_c$, 2 H CH_2), 3.49 (q, ^3J = 7.40 Hz, 2 H, $\mathbf{CH_2}CH_3$), 4.01 (dd, ^3J = 5.90 and 6.20 Hz, 2 H, N–$\mathbf{CH_2}$), 4.58 (dd, ^3J = 8.10 and 7.10 Hz, 2 H, *Ph*–O–$\mathbf{CH_2}$), 6.90 (m$_c$, 3 H, C2′–H, C4′–H, C6′–H), 7.22 (dd, ^3J = 7.43 and 7.52 Hz, 1 H, C8–H or

C9–H), 7.26 (dd, ^3J = 7.87 and 7.63 Hz, 2 H, C3′–H, C5′–H), 7.40 (dd, ^3J = 7.15 and 7.57 Hz, 1 H, C9–H or C8–H), 7.52 (m_c, 2 H, C2–H, C3–H), 7.61 (d, ^3J = 8.23 Hz, 1 H, C7–H), 8.04 (d, ^3J = 8.17 Hz, 1 H, C10–H), 8.21 (d, ^3J = 8.78 Hz, 1 H, C1–H or C4–H), 8.25 (d, ^3J = 7.62 Hz, 1 H, C4–H or C1–H), 8.61 (s, 1 H, NH). ^{13}C-NMR (*DMSO-d*$_6$): δ (ppm) 15.86 (CH_2CH_3), 19.48 (CH_2CH_3), 25.89 (CH_2), 26.21 (CH_2), 44.47 (N–CH_2), 66.71 (*Ph*–O–CH_2), 109.17 (CH), 114.36 (C2′, C6′), 117.40 (CH), 118.40 (Cq), 120.39 (C4′, C7), 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 (C3′, C5′), 130.73 (Cq), 136.79 (Cq), 143.73 (C10), 158.40 (Cq–1′). EI-MS: *m/z* (%) = 393 (M^+, 86), 258 (M^+–$C_9H_{11}O$, 57), 230 ($C_{17}H_{12}N^+$, 46), 106 (100). $C_{28}H_{27}NO$ (393.5): calcd. C 85.46, H 6.92, N 3.56; found C 85.20, H 7.14, N 3.54.

General Procedure for the Preparation of **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%), m.p. 293–295 °C (petroleum ether/ethyl acetate). ^{1}H-NMR (CD_3CN/*DMSO-d*$_6$): δ (ppm) 1.36 (t, ^3J = 7.52 Hz, 3 H, CH_2CH_3), 3.39 (q, ^3J = 7.52 Hz, 2 H, CH_2CH_3), 7.44 (dd, ^3J = 7.25 and 7.53 Hz, 1 H, C2–H or C3–H), 7.54 (d, ^3J = 8.85 Hz, 1 H, C7–H), 7.55 (dd, ^3J = 8.85 and 6.02 Hz, 1 H, C3–H or C2–H), 8.07 (d, ^3J = 8.22 Hz, 1 H, C1–H or C4–H), 8.20 (d, ^3J = 8.62 Hz, 1 H, C4–H or C1–H), 8.35 (dd, ^4J = 1.99 Hz, ^3J = 8.85 Hz, 1 H, C8–H), 8.65 (s, 1 H, C11–H), 9.10 (d, ^4J = 1.99 Hz, 1 H, C10–H), 11.37 (s, 1 H, NH). EI-MS: *m/z* (%) = 290 (M^+, 100), 244 (M^+–NO_2, 65). $C_{18}H_{14}N_2O_2$ (290.3): calcd. 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 MPLC resulted in decomposition; however, the structure was confirmed unambiguously by high resolution ^{1}H-NMR spectroscopy. ^{1}H-NMR (CD_3CN): δ (ppm) 1.40 (t, ^3J = 7.53 Hz, CH_2CH_3), 3.54 (q, ^3J = 7.53 Hz, 2 H, CH_2CH_3), 7.27 (dd, ^3J = 7.64 and 7.84 Hz, 1 H, C9–H), 7.40 (dd, ^3J = 7.42 and 7.47 Hz, 1 H, C2–H or C3–H), 7.50 (m_c, 1 H, C3–H or C2–H), 8.01 (d, ^3J = 7.49 Hz, 1 H, C1–H or C4–H), 8.03 (d, ^3J = 8.20 Hz, 1 H, C4–H or C1–H), 8.20 (d, ^3J = 7.66 Hz, 1 H, C8–H or C10–H), 8.25 (m_c, 2 H, C11–H and C10–H or 8–H), 10.05 (s, 1 H, NH).

General Procedure for the Preparation of **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 crystallisation from methanol, attempts to separate product **9** from **8** even by MPLC 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%), m.p. 297–298 °C (methanol). ^{1}H-NMR (*DMSO-d_6*): δ (ppm) 2.90 (s, 3 H, CH_3), 7.28 (dd, $^3J = 7.51$ Hz, $^5J = 0.8$ Hz, 1 H, C6–H or C7–H), 7.45 (m_c, 2 H, aromatic H), 7.52 (m_c, 3 H, aromatic H), 7.61 (d, $^3J = 8.20$ Hz, 1 H, C6–H), 8.34 (d, $^3J = 7.93$ Hz, 1 H, C9–H), 8.62 (s, 1 H, C10–H), 12.12 (s, 1 H, NH). ^{13}C-NMR (*DMSO-d_6*): δ (ppm) 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 (C2′, C6′, or C3′, C5′), 127.38, 127.57, 128.62 (C3′, C5′ or C2′, C6′), 132.30, 141.04, 142.05, 167.13 (C), 167.97 (CO). EI-MS: *m/z* (%) = 326 (M^+, 100). $C_{21}H_{14}N_2O_2$ (326.4): calcd. 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 characterised by ^{1}H-NMR and EI-mass spectroscopy. ^{1}H-NMR (*DMSO-d_6*): δ (ppm) 2.60 (d, $^5J = 1.97$ Hz, 3 H, CH_3), 2.81 (dd, $^2J = 16.30$ Hz, $^3J = 8.66$ Hz, 1 H, C10α–H) 3.40 (dd, $^3J = 8.66$ Hz, $^2J = 15.82$ Hz, 1 H, C10β–H), 4.06 (ddd, $^5J = 2.06$ Hz, $^3J = 8.58$ Hz, $^2J = 16.70$ Hz, 1 H, C10aβ–H), 7.05 (dd, $^3J = 7.56$ and 7.37 Hz, 1 H, C7–H or C8–H), 7.18 (dd, $^3J = 7.25$ and 7.62 Hz, 1 H, C8–H or C7–H), 7.45 (m_c, 6 H aromatic H), 7.62 (d, $^3J = 7.84$ Hz, 1 H, C9–H), 11.58 (s, 1 H, NH). EI-MS: *m/z* (%) = 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}H-NMR). Further purification of **10b** even by MPLC led to decomposition of the product; **10b** was therefore characterised by ^{1}H-NMR spectroscopy. ^{1}H-NMR (*DMSO-d_6*): δ (ppm) 2.11 (s, 3 H, CH_3), 3.17 (d, $^3J = 7.32$ Hz, 1 H, C3a–H or C12–H), 3.24 (d, $^3J = 7.64$ Hz, 1 H, C12–H or C3a–H), 3.35 (overlapping with solvent signal, $^3J_{10aH,10H}$ or $^3J_{11H,10H} = 3.05$ Hz, $^3J_{10aH,3aH}$ or $^3J_{11H,12H}$ overlapped by solvent signal, 2 H, 10a–H or 11–H), 4.38 (dd, $^3J = 3.22$ and 3.17 Hz, 1 H, C10–H), 6.14 (d, $^3J = 7.64$ Hz, 2 H, C2′–H, C6′-*exo*-phenyl-H), 7.03 (dd, $^3J = 7.03$ and 7.65 Hz, 1 H, aromatic H), 7.10 (dd, $^3J = 7.26$ and 7.04 Hz, 1 H, aromatic H), 7.18 (m_c, 2 H, aromatic H), 7.42 (m_c, 3 H, aromatic H), 7.53 (m_c, 5 H, aromatic H), 11.49 (s, 1 H, NH). ^{13}C-NMR (*DMSO-d_6*): δ (ppm) 16.22 (CH_3), 32.42 (C10), 40.00 (C4), 43.19, 46.75, 47.00, 50.14 (C3a, C12, C10a, C11), 174.96, 175.49, 175.89, 176.22 (CO).

Direct Preparation of **8** *by a Dehydrogenating 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%), m.p. 315 °C (acetone, *n*-hexane), (Ref. [13] m.p. 315–316 °C). ^{1}H-NMR (acetone-d_6): δ (ppm) 2.27 (s, 3 H, CH_3), 3.47 (d, $^3J_{3aH,10aH} = {}^3J_{12H,11H} = 8.01$ Hz, 2 H, C3a–H, C12–H), 3.72 (dd, $^3J_{10aH,3aH} = {}^3J_{11H,12H} = 8.01$ Hz, $^3J_{10aH,10H} = {}^3J_{11H,10H} = 3.02$ Hz, 2 H, C10a–H, C11–H), 4.60 (t, $^3J_{10H,10aH} = {}^3J_{10H,11H} = 3.02$ Hz, 1 H, C10–H), 6.43 (m_c, 4 H, C2′/C6′-phenyl-H), 7.04 (dd, $^3J = 7.13$ and 7.90 Hz, 1 H, C7–H or C8–H), 7.10 (dd, $^3J = 8.02$ and 7.13 Hz, 1 H, C8–H or C7–H), 7.17 (m_c, 6 H, C3′/C4′/C5′-phenyl-H) 7.38 (d, $^3J = 7.98$ Hz, 1 H, C6–H), 7.49 (d, $^3J = 8.85$ Hz, 1 H, C9–H), 10.60 (s, 1 H, NH). ^{13}C-NMR (*DMSO-d*$_6$): δ (ppm) 15.85 (CH_3), 33.07 (C10), 40.68 (C4), 45.06, 49.03 (C3a, C12, C10a, C11), 111.52, 117.09, 119.30, 120.73 (C6, C7, C8, C9), 126.30, 128.50 (C2′, C3′, C5′, C6′), 128.04 (C4′), 131.74 (C1′), 107.19, 124.68, 135.89, 136.73 (C9a, C9b, C5a, C4a), 175.03, 175.96 (CO). EI-MS: *m/z* (%) = 501 (M^+, 40), 181 (100). $C_{31}H_{23}N_3O_4$ (501.5): calcd. C 74.24, H 4.62, N 8.38; found C 74.51, H 4.95, N 7.95.

General Procedure for the Preparation of **14**, **15**, *and* **16**

Compound **12** (100 mg, 0.25 mmol) and the respective dienophile (0.25 mmol) were dissolved in 50 ml of *DMF* and then heated at 50–55 °C. Powdered sodium iodide (10 mg) was added to the mixture which was then stirred at 50 °C for 1.5–3 h. The solvent was evaporated under reduced pressure and the crude product was treated with aqueous sodium thiosulphate solution. The residue was dried, purified by flash chromatography (petroleum ether/ethyl acetate), and recrystallised from ethyl acetate.

6-Benzoyl-5,11-dihydro-6H-benzo[b]carbazole-1,4-dione (**14**)

Prepared from **12** (325 mg, 0.8 mmol) and 1,4-benzoquinone (86 g, 0.8 mmol). Yield: 55%. ^{1}H-NMR (*DMSO-d*$_6$): δ (ppm) 3.72 (br. s, 2 H, C5–H_2 or C11–H_2), 3.82 (br. s, 2 H, C11–H_2 or C5–H_2), 6.53 (d, $^3J = 10.76$ Hz, 1 H, C2–H or C3–H), 6.56 (d, $^3J = 10.69$ Hz, 1 H, C3–H or C2–H), 6.91 (m_c, 2 H, aromatic H), 7.17 (dd, $^3J = 7.49$ Hz and 7.71 Hz, 1 H, C8–H or C9–H), 7.52 (m_c, 3 H, aromatic H), 7.71 (m_c, 3 H, aromatic H). MS: *m/z* (%) = 353 (M^+, 32), 105 (100). $C_{23}H_{15}NO_3$) (353.09): calcd. C 78.16, H 4.25, N 3.97; found C 77.81, H 4.31, N 4.03.

6-Benzoyl-6H-benzo[b]carbazole-1,4-dione (**15**)

Prepared from **12** (325 mg, 0.8 mmol) and 1,4-benzoquinone (86 mg, 0.8 mmol) Yield: 22%. ^{1}H-NMR (*DMSO-d*$_6$): δ (ppm) 7.06 (d, $^3J = 10.27$ Hz, 1 H, C2–H or C3–H), 7.10 (d, $^3J = 10.23$ Hz, 1 H, C3–H or C2–H), 7.34 (d, $^3J = 8.64$ Hz, 1 H, C7–H), 7.48 (m_c, 2 H, aromatic H), 7.63 (dd, $^3J = 7.66$ Hz and 7.81 Hz, 2 H, aromatic H), 7.78 (m_c, 3 H, aromatic H), 7.99 (s, 1 H, C5–H), 8.50 (d, $^3J = 6.97$ Hz, 1 H, aromatic H), 8.84 (s, 1 H, C11–H). ^{13}C-NMR (*DMSO-d*$_6$): δ (ppm) 112.9, 115.3, 119.0, 121.9, 124.2, 124.3, 127.3, 128.9, 129.1, 129.3, 129.9, 133.1, 134.5, 139.0, 140.2, 140.95, 168.9 (benzoyl-CO), 184.2 (C1 or C4), 184.3 (C4 or C1). MS: *m/z* (%) = 351 (M^+, 10), 105 (100). $C_{23}H_{13}NO_3$ (351.09): calcd. C 78.61, H 3.73, N 3.99; found C 78.45, H 3.81, N 4.03.

7-Benzoyl-7H-naphtho[2,3-b]carbazole-5,13-dione (**16**)

Prepared from **12** (400 mg, 1 mmol) and 1,4-naphthoquinone (158 mg, 1 mmol). Yield: 32%. ^{1}H-NMR (*DMSO-d*$_6$): δ (ppm) 7.44 (d, $^3J = 8.10$ Hz, 1 H, C8–H), 7.52 (m_c, 2 H, aromatic H), 7.65 (dd, $^3J = 7.91$ Hz and 7.72 Hz, 2 H, aromatic H), 7.81 (dd, $^3J = 8.12$ Hz and 8.89 Hz, 3 H, aromatic H), 7.93 (m_c, 2 H, aromatic H), 8.20 (dd, $^3J = 8.17$ Hz and 8.17 Hz, 1 H, aromatic H), 8.22 (s, 1 H, C6–H), 8.27 (d, $^3J = 8.50$ Hz, 1 H, aromatic H), 8.58 (d, $^3J = 8.02$ Hz, 1 H, aromatic H), 9.10 (s, H, C12–H). MS: *m/z* (%) = 401 (M^+, 17), 105 (100). $C_{27}H_{15}NO_3$ (401.1): calcd. C 80.00, H 3.74, 3.49; found C 80.61, H 3.83, N 3.34.

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