Electrophilic Substitution and Cyclization of 2,2'-Bis(*N*-methylindolyl): A Simple Access to Potential Protein Kinase C Inhibitor [a]

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Received July 19, 1993

[a] Dedicated to Professor Dr. Bernard Unterhalt, Münster (FRG), on the occasion of his 60th birthday

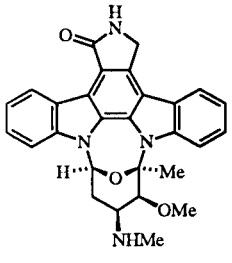
A strategy is described for the synthesis of functionalized and cyclized 2,2'-bisindolyl derivatives related to several basic systems of natural products. The starting 2,2'-bis(*N*-methylindolyl) (**8**) reacts with a variety of electrophiles and electrophilic dienophiles to furnish the novel, functionalized and cyclized bisindolyl derivatives **9-16**. In addition, some reactivity and structural aspects are discussed; an X-ray crystallographic analysis of the 2,2'-bisindolyl **8** provided valuable information for the conformational analyses.

J. Heterocyclic Chem., **31**, 377 (1994).

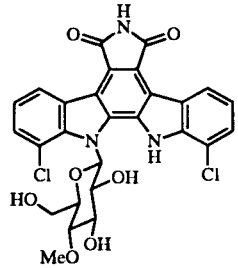
Introduction.

Indolo[2,3-*a*]carbazole alkaloids, as exemplified by the antimicrobial, hypertensive, and platelet aggregation-inhibiting antibiotic staurosporine (**1**) (*Streptomyces staurosporeus*) [1a] and the antitumor antibiotic rebeccamycin (**2**) (*Norcardia aerocolinigenes*) [1b], represent a structurally rare class of natural products [1c,1d]. However, interest in compounds of this type has increased since the discovery that staurosporine (**1**) and related natural products together with their common aglycone staurosporinone (**3**) are potent inhibitors of protein kinase C [2]. The indolo-[2,3-*a*]carbazole system constitutes the framework of some further natural products such as, for example, the pigments tjipanazole D (**4**) in blue-green algae [3] or arcyriaflavins C and D (**5a,b**) from the fungus *Arcyria denudata* [4]. From a pharmacological point of view, the related bisindolylmaleimides of the type **6** are of interest as highly active inhibitors of protein kinase C [2,4] in connection with the development of drugs with immunosuppressive and antitumor activities [2]. Furthermore, compounds of the bisindolylmaleimide series also belong to an interesting class of pigments such as, for example, the arcyriarubins A-C (**7a-c**) produced by slime molds (Myxomycetes) [5-7]. It is thus not surprising that several approaches to the indolocarbazole ring system [1c,1d,7-13] and to the bis-

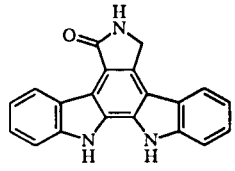
Formula Block 1



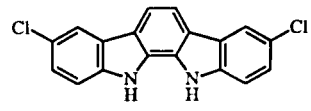
1 staurosporine



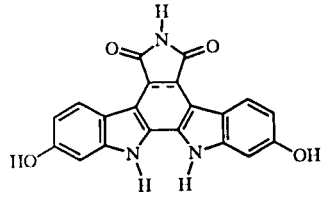
2 rebeccamycin



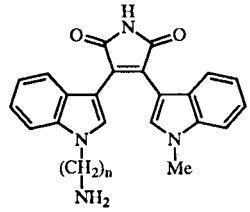
3 staurosporinone



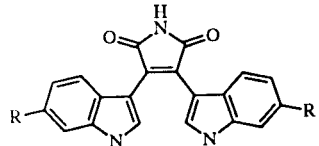
4 tjipanazole D



5a arcyriaflavin C
5b arcyriaflavin B
(with double bond)

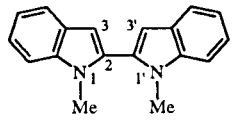


6 (n=2-5)



arcyriarubins A-C

7	R^1	R^2
a	H	H
b	OH	H
c	OH	OH



8

maleimides [2,4,6,12] have been developed in recent years and that several synthetic analogues have been described in the patent literature [14].

In the course of our current investigations, we have focussed our attention on a new strategy for the construction of the indolo[2,3-*a*]carbazole system, namely, cyclization of the 2,2'-bisindolyl system with an appropriate C_2 unit, a process which is closely related to a Diels-Alder reaction with the bisindolyl acting formally as a diene. This idea, first mentioned in ref [15], has since been realized as the basic reaction of the parent 2,2'-bisindolyl with *N*-phenylmaleimide [16]. In the light of this report and in continuation of our previous investigations [15], we now describe further synthetic results of electrophilic substitutions of 2,2'-bis(*N*-methylindolyl) (**8**) and cyclization reactions for the construction of the indolo[2,3-*a*]carbazole ring system.

Results and Discussion.

Synthetic, Reactivity, and Structural Aspects.

AM1 calculations on **8** [17] predict a high nucleophilicity for this compound. According to the frontier molecular orbital theory [18] and the net atomic charges on the indole system [17], a preferred attack of electrophiles at the indole 3,3'-position should take place. However, on consideration of our previous results [15], normal nucleophilic indole reactivity could be expected throughout. The concept of [4π + 2π] cycloaddition of the formal 2,3-diaminobutadiene moiety in **8** with dienophiles to form, in a concerted manner, the indolo[2,3-*a*]carbazole system directly should not be realizable under normal conditions because of the effect of the aromaticity of the two indole nuclei in the Diels-Alder transition state is interrupted in part; this is in complete contrast to our numerous previous reports on Diels-Alder reactions of vinylindoles [19]. However, the adoption of a fully coplanar s-*cis*-conformation - which is, in general, an essential geometrical requirement of the diene in Diels-Alder reactions - is not severely hindered sterically in **8**, as can be seen by inspection of Dreiding models. On the other hand, we have performed an X-ray crystallographic analysis of **8** which provided valuable geometrical information on the solid state conformation (see next section on the X-ray structure of **8**) and, thus, the basis for conformational analyses by molecular mechanics and quantum chemical methods. MMX molecular mechanics [20] and AM1 calculations [17] both gave rise to two minimum conformations of the (−) *anticlinal* and (+) *synclinal* types as referred to the torsional angle N1-C2-C2'-N1' (Table 1). In the solid state, the (−) *anticlinal* conformer is present exclusively. The ^{1}H nmr spectrum of **8** at room temperature revealed a single, sharp set of proton signals, which is in accord with the fast, unrestricted rotation about the central C sp^2–C sp^2 σ-bond as deduced from observations of Dreiding models.

However, should any cyclization reactions with 2,2'-bisindolyls indeed take place, a polar, multistep process has to be assumed to be operative throughout [16].

The starting material **8** was prepared in 41% yield from *N*-methylindole by a slight modification of the method of ref [21a] *via* an oxidative, copper-induced coupling reaction. With the objective of the construction of the indolo-[2,3-*a*]carbazole skeleton in mind, we first examined the reaction of **8** with the biselectrophile α-chloroacetyl chloride. However, in spite of numerous variations of the reaction conditions, an excess of this electrophile reacts first of all to yield the monosubstituted bisindolyls **9a,b** with **9a** being the major product. On the basis of AM1 charge calculations on **8**, the considerable net atomic negative charges [17] at C3, C3' and C5, C5' should additionally

Table 1
Minimum Conformations of Compound **8**

Method [a]	Torsional Angle N-N2-C2'-N1'	ΔH_f [kcal•mol^{-1}]	Type
A	-122°	–	(-) ac
B	-140°	193	(-) ac
C	-138°	124	(-) ac
B	52°	200	(+) sc
C	53°	125	(+) sc

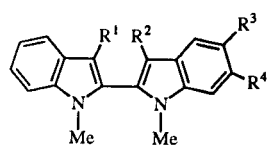
[a] A: in the crystal state (X-ray crystallography); B: MMX molecular mechanics calculations [20]; C: AM1 semiempirical quantum chemical calculations [17]. The coordinates from the X-ray crystallographic analysis were used for the starting geometry in the calculations.

Table 2
Atomic Coordinates and Equivalent Displacement Parameters (Å^2)

$$U_{eq} = (1/3)^*\Sigma\Sigma U_{ij} a_i^* a_j^* a_i a_j$$

Atom	x	y	z	U_{eq}
N1	0.3235 (2)	0.2035 (2)	0.9599 (1)	0.0348 (5)
C2	0.2112 (2)	0.1100 (2)	0.9683 (1)	0.0325 (6)
C3	0.0946 (2)	0.1576 (3)	0.9107 (1)	0.0361 (7)
C3A	0.1341 (2)	0.2826 (3)	0.8629 (1)	0.0352 (6)
C4	0.0637 (3)	0.3714 (3)	0.7945 (1)	0.0449 (8)
C5	0.1383 (3)	0.4784 (3)	0.7596 (1)	0.0539 (9)
C6	0.2814 (3)	0.5005 (3)	0.7924 (2)	0.0566 (10)
C7	0.3526 (3)	0.4174 (3)	0.8603 (1)	0.0481 (8)
C7A	0.2778 (2)	0.3075 (2)	0.8952 (1)	0.0358 (7)
C8	0.4627 (2)	0.2097 (3)	1.0141 (2)	0.0482 (8)
N1'	0.1856 (2)	-0.1818 (2)	0.99712 (9)	0.0329 (5)
C2'	0.2289 (2)	-0.0265 (2)	1.0252 (1)	0.0315 (6)
C3'	0.2912 (2)	-0.0350 (3)	1.1067 (1)	0.0363 (7)
C3A'	0.2899 (2)	-0.2011 (3)	1.1313 (1)	0.0351 (7)
C4'	0.3409 (2)	-0.2841 (3)	1.2048 (1)	0.0437 (8)
C5'	0.3237 (3)	-0.4509 (3)	1.2058 (2)	0.0503 (9)
C6'	0.2557 (3)	-0.5354 (3)	1.1355 (2)	0.0512 (9)
C7'	0.2039 (2)	-0.4576 (3)	1.0623 (1)	0.0446 (8)
C7A'	0.2225 (2)	-0.2892 (3)	1.0613 (1)	0.0340 (6)
C8'	0.1177 (3)	-0.2301 (3)	0.9140 (1)	0.0561 (9)

Formula Block 2

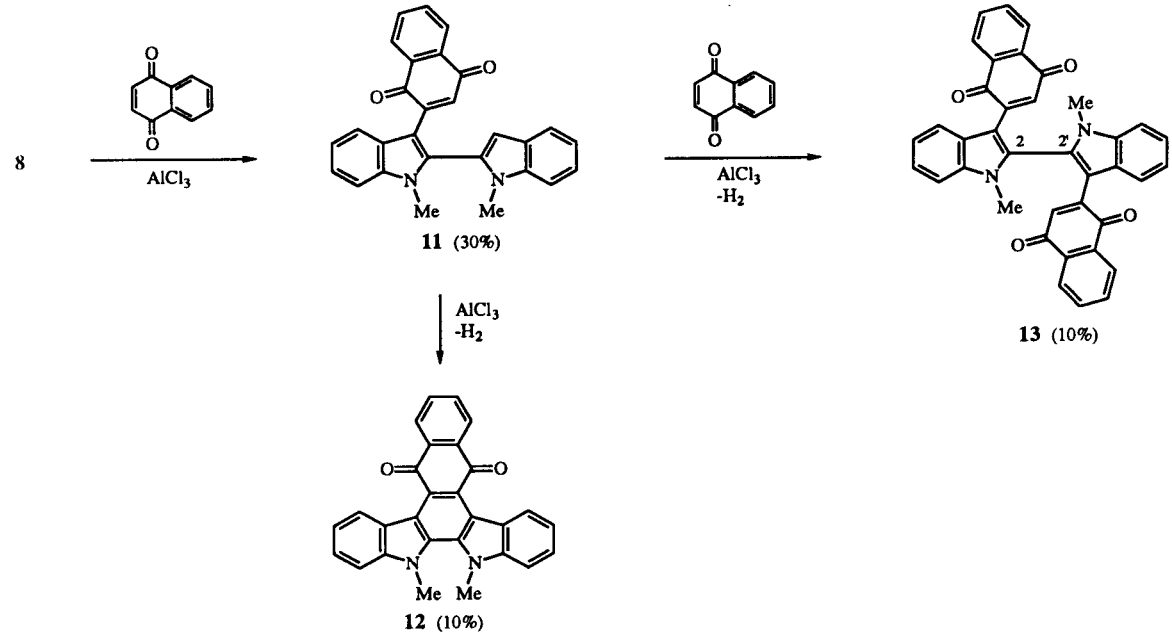


	R^1	R^2	R^3	R^4	yield (%)
9a	H	H	$COCH_2Cl$	H	40
9b	H	H	H	$COCH_2Cl$	8
10	Br	Br	H	H	90

Table 3
Anisotropic Displacement Parameters

Atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N1	0.0310 (8)	0.0333 (9)	0.0404 (9)	-0.0025 (7)	0.0094 (7)	0.0005 (7)
C2	0.034 (1)	0.031 (1)	0.0333 (10)	-0.0015 (8)	0.0107 (8)	-0.0025 (8)
C3	0.033 (1)	0.037 (1)	0.037 (1)	-0.0011 (9)	0.0087 (8)	0.0002 (9)
C3A	0.041 (1)	0.033 (1)	0.0327 (10)	0.0031 (9)	0.0122 (8)	-0.0017 (8)
C4	0.055 (1)	0.042 (1)	0.037 (1)	0.007 (1)	0.0093 (10)	0.0028 (10)
C5	0.079 (2)	0.043 (1)	0.042 (1)	0.010 (1)	0.019 (1)	0.009 (1)
C6	0.080 (2)	0.043 (1)	0.057 (1)	-0.002 (1)	0.035 (1)	0.011 (1)
C7	0.051 (1)	0.040 (1)	0.058 (1)	-0.004 (1)	0.024 (1)	0.003 (1)
C7A	0.043 (1)	0.030 (1)	0.038 (1)	0.0011 (9)	0.0161 (9)	-0.0009 (8)
C8	0.033 (1)	0.048 (1)	0.060 (1)	-0.003 (1)	0.0051 (10)	0.001 (1)
N1'	0.0383 (9)	0.0318 (9)	0.0288 (8)	-0.0033 (7)	0.0091 (7)	-0.0033 (7)
C2'	0.0329 (10)	0.0298 (10)	0.0325 (10)	-0.0011 (8)	0.0096 (8)	-0.0023 (8)
C3'	0.044 (1)	0.032 (1)	0.032 (1)	-0.0027 (9)	0.0078 (9)	-0.0040 (8)
C3A'	0.037 (1)	0.037 (1)	0.034 (1)	0.0022 (9)	0.0126 (8)	-0.0004 (9)
C4'	0.049 (1)	0.048 (1)	0.036 (1)	0.004 (1)	0.0132 (9)	0.0044 (10)
C5'	0.057 (1)	0.051 (1)	0.048 (1)	0.011 (1)	0.023 (1)	0.018 (1)
C6'	0.064 (2)	0.034 (1)	0.063 (2)	0.003 (1)	0.031 (1)	0.007 (1)
C7'	0.054 (1)	0.034 (1)	0.051 (1)	-0.004 (1)	0.022 (1)	-0.003 (1)
C7A'	0.036 (1)	0.034 (1)	0.036 (1)	0.0006 (8)	0.0145 (8)	-0.0004 (8)
C8'	0.082 (2)	0.046 (1)	0.035 (1)	-0.009 (1)	0.004 (1)	-0.009 (1)

Scheme 1



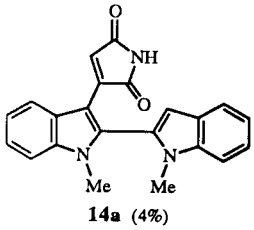
give rise to the C3, C3'-substituted products. Monitoring of the reaction by tlc revealed that the mono- or bis-3-acetylated products of **8** are probably not very stable in the reaction mixture so that only the thermodynamically more stable products **9a,b** could be isolated experimentally. Bromination of **8** (bromine, *N,N*-dimethylformamide) gave rise to bis(3,3'-bromo-*N,N'*-methylindolyl) (**10**) directly.

Although the reactions of **8** with 1,4-benzoquinone and 2-chloro- or 2-phenyl-1,4-benzoquinone were uncontrollable and yielded several uncharacteristic products, the electrophilic reaction with 1,4-naphthoquinone was successful and gave definable products (Scheme 1). Thus, **8** reacts with 1,4-naphthoquinone under aluminum trichloride catalysis to furnish the substituted bisindolyls **11** and **13**. Compound **11** can be oxidatively cyclized in a separate step to the new, bright orange-red colored indolo[2,3-*a*]-carbazole **12** [λ max (dichloromethane) = 465 nm, log ε = 3.58]. According to inspections of Dreiding models, the tetra-"*ortho*"-substituted 2,2'-bisindolyl **13** should exist as atropisomers as a consequence of the severely restricted rotation about the central C2 sp^2–C2' sp^2 σ-bond [22]. However, the ^1H nmr spectrum of **13** at room temperature revealed only one relatively sharp set of proton signals for both substituted indole systems. After addition of (*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol in deuteriochloroform as a chiral shift reagent [23] the spectrum at room temper-

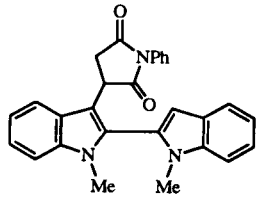
ature showed two sets of clearly separated signals of equal intensity for the *N*-methyl groups (δ = 3.94 and 3.95 ppm) and for the aromatic protons (in the range 7.22 to 7.92 ppm) as a result of complexation with **13**. Thus, we assume the existence of racemic C_2-symmetric atropisomers where the 2,2'-bisindolyl rings flip only in the range of +20 to +160° or −20 to −160° (torsional angle) on the nmr time scale according to an averaging phenomenon.

Encouraged by these results, we then examined the electrophilic reactivity of **8** with maleimide for the construction of the basic skeleton of the rebeccamycin aglycone and the arcyriaflavines B and C (**5a,b**). The reaction of **8** with maleimide occurs under aluminum trichloride catalysis to furnish only the dehydrogenated Michael-type adduct **14a** and, in spite of several attempts including other oxidative cyclization methods [16], the corresponding indolo[2,3-*a*][*c*]pyrrolocarbazole system has not yet been reached. However, the reaction of **8** with *N*-phenylmaleimide products the Michael-type adduct **14b** in 87% yield. Compound **14b** was dehydrogenated in the presence of palladium on carbon in refluxing *ortho*-dichlorobenzene to product **14c**, respectively. Also in this case no cyclization reaction was achieved.

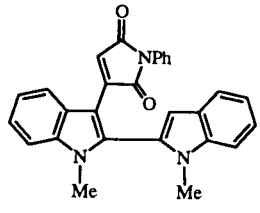
Formula Block 3



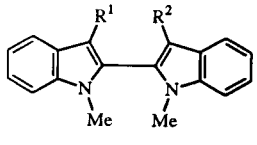
14a (4%)



14b (87%)

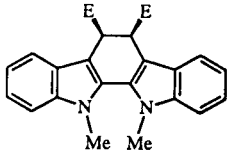


14c (20%)



15	R^1	R^2	yield (%)
a		H	10
b		H	34
c			14
d			16

E = COOMe



16 (33%)

Table 4

Final Coordinates and Isotropic Displacement Parameters for Hydrogen Atoms (Å^2)

Atom	X	Y	Z	U_{iso}
H3	0.0015 (2)	0.1072 (3)	0.9012 (1)	0.043 (6)
H4	-0.0387 (3)	0.3596 (3)	0.7730 (1)	0.048 (6)
H5	0.0993 (3)	0.5502 (3)	0.7161 (1)	0.078 (9)
H6	0.3325 (3)	0.5747 (3)	0.7639 (2)	0.067 (8)
H7	0.4534 (3)	0.4271 (3)	0.8817 (1)	0.048 (6)
H8A	0.4886 (2)	0.1091 (3)	1.0442 (2)	0.083 (5)
H8B	0.4697 (2)	0.2946 (3)	1.0557 (2)	0.083 (5)
H8C	0.5226 (2)	0.2120 (3)	0.9781 (2)	0.083 (5)
H3'	0.3278 (2)	0.0611 (3)	1.1394 (1)	0.046 (6)
H4'	0.3892 (2)	-0.2242 (3)	1.2531 (1)	0.047 (6)
H5'	0.3570 (3)	-0.5092 (3)	1.2569 (2)	0.067 (8)
H6'	0.2466 (3)	-0.6564 (3)	1.1366 (2)	0.071 (8)
H7'	0.1573 (2)	-0.5222 (3)	1.0139 (1)	0.050 (7)
H8'A	0.1474 (3)	-0.1648 (3)	0.8726 (1)	0.108 (7)
H8'B	0.1250 (3)	-0.3330 (3)	0.9075 (1)	0.108 (7)
H8'C	0.0185 (3)	-0.2093 (3)	0.9033 (1)	0.108 (7)

Table 5

Bond Lengths (Å) with Standard Deviations in Parenthesis

N1	-C2	1.396 (2)	N1'	-C2"	1.392 (3)
N1	-C7A	1.376 (3)	N1'	-C7A'	1.378 (3)
N1	-C8	1.456 (3)	N1'	-C8'	1.456 (3)
C2	-C3	1.371 (3)	C2'	-C3'	1.367 (3)
C2	-C2'	1.462 (3)	C3'	-C3A'	1.429 (3)
C3	-C3A	1.426 (3)	C3A'	-C4'	1.400 (3)
C3A	-C4	1.399 (3)	C3A'	-C7A'	1.408 (3)
C3A	-C7A	1.411 (3)	C4'	-C5'	1.383 (3)
C4	-C5	1.380 (3)	C5'	-C6'	1.397 (4)
C5	-C6	1.404 (4)	C6'	-C7'	1.377 (3)
C6	-C7	1.373 (4)	C7'	-C7A'	1.398 (3)
C7	-C7A	1.397 (3)			

Table 6

Bond Angles (°) with Standard Deviations in Parenthesis

C8	-N1	-C2	127.9 (2)	C8'	-N1'	-C2'	127.5 (2)
C8	-N1	-C7A	123.4 (2)	C8'	-N1'	-C7A'	123.8 (2)
C2'	-C2	-N1	121.8 (2)	C3'	-C2'	-C2	131.0 (2)
C2'	-C2	-C3	128.9 (2)	C3'	-C2'	-N1'	108.7 (2)
C3A	-C3	-C2	107.8 (2)	C3A'	-C3'	-C2'	108.0 (2)
C7A	-C3A	-C3	106.5 (2)	C7A'	-C3A'	-C3'	106.4 (2)
C7A	-C3A	-C4	119.3 (2)	C7A'	-C3A'	-C4'	119.3 (2)
C5	-C4	-C3A	118.7 (2)	C5'	-C4'	-C3A'	118.5 (2)
C6	-C5	-C4	121.1 (2)	C6'	-C5'	-C4'	121.1 (2)
C7	-C6	-C5	121.5 (2)	C7'	-C6'	-C5'	122.0 (2)
C7A	-C7	-C6	117.5 (2)	C7A'	-C7'	-C6'	116.8 (2)
C7	-C7A	-N1	129.7 (2)	C7'	-C7A'	-N1'	129.5 (2)
C7	-C7A	-C3A	121.9 (2)	C7'	-C7A'	-C3A'	122.4 (2)

On the other hand, **8** reacts with dimethyl acetylenedicarboxylate to furnish two monovinyl- and two divinyl-functionalized bisindolyls **15a-d**. The *Z*-configurated compound **15b** can be cyclized in the presence of aluminum trichloride to the indole[2,3-*a*]carbazole derivative **16**

Table 7
Torsional Angles (°) with Standard Deviations in Parenthesis

C7A	-N1	-C2	-C3	-1.6 (2)	N1	-C2	-C2'	-N1'	-122.2 (2)
C7A	-N1	-C2	-C2'	172.2 (2)	N1	-C2	-C2'	-C3'	53.6 (2)
C2	-N1	-C7A	-C3A	1.3 (2)	C7A'	-N1'	-C2'	-C2	175.9 (2)
C2	-N1	-C7A	-C7	-176.0 (2)	C7A'	-N1'	-C2'	-C3'	-0.8 (2)
C8	-N1	-C2	-C3	171.3 (2)	C2'	-N1'	-C7A'	-C3A'	0.2 (2)
C8	-N1	-C2	-C2'	-14.9 (2)	C2'	-N1'	-C7A'	-C7'	-178.4 (2)
C8	-N1	-C7A	-C3A	-172.0 (2)	C8'	-N1'	-C2'	-C2	-1.7 (2)
C8	-N1	-C7A	-C7	10.7 (3)	C8'	-N1'	-C2'	-C3'	-178.4 (2)
N1	-C2	-C3	-C3A	1.3 (2)	C8'	-N1'	-C7A'	-C3A'	177.9 (2)
C2'	-C2	-C3	-C3A	-171.9 (2)	C8'	-N1'	-C7A'	-C7'	-0.7 (3)
C3	-C2	-C2'	-N1'	50.2 (2)	C2	-C2'	-C3'	-C3A'	-175.1 (2)
C3	-C2	-C2'	-C3'	-134.0 (3)	N1'	-C2'	-C3'	-C3A'	1.0 (2)
C2	-C3	-C3A	-C4	176.6 (3)	C2'	-C3'	-C3A'	-C4'	177.8 (2)
C2	-C3	-C3A	-C7A	-0.5 (2)	C2'	-C3'	-C3A'	-C7A'	-0.9 (2)
C3	-C3A	-C4	-C5	-175.5 (3)	C3'	-C3A'	-C4'	-C5'	-178.2 (2)
C3	-C3A	-C7A	-N1	-0.5 (2)	C3'	-C3A'	-C7A'	-N1'	0.4 (2)
C3	-C3A	-C7A	-C7	177.0 (2)	C3'	-C3A'	-C7A'	-C7'	179.1 (2)
C7A	-C3A	-C4	-C5	1.3 (2)	C7A'	-C3A'	-C4'	-C5'	0.4 (2)
C4	-C3A	-C7A	-N1	-178.1 (2)	C4'	-C3A'	-C7A'	-N1'	-178.5 (2)
C4	-C3A	-C7A	-C7	-0.6 (2)	C4'	-C3A'	-C7A'	-C7'	0.2 (2)
C3A	-C4	-C5	-C6	-0.9 (3)	C3A'	-C4'	-C5'	-C6'	-0.7 (3)
C4	-C5	-C6	-C7	-0.3 (3)	C4'	-C5'	-C6'	-C7'	0.5 (3)
C5	-C6	-C7	-C7A	1.1 (3)	C5'	-C6'	-C7'	-C7A'	0.1 (3)
C6	-C7	C7A	-N1	176.3 (3)	C6'	-C7'	-C7A'	-N1'	178.0 (2)
C6	-C7	-C7A	-C3A	-0.7 (3)	C6'	-C7'	-C7A'	-C3A'	-0.4 (2)

which is suggested to have the *meso*-structure (*cis*-oriented ester substituents) on the basis of ^{1}H nmr data and inspection of Dreiding models of a transition state-like structure. Similar to the case with **13**, the novel bisindolyls **15c,d** also exist as true atropisomers: the ^{1}H nmr spectrum of **15d** at 20° exhibits only one set of sharp signals whereas that of **15c** under the same conditions reveals broad signals at 3.41 and 3.48 ppm for the (*E*)-alkene dimethyl ester protons and at 6.95 ppm for the vinyl protons. This dynamic process in **15c** is probably due in particular to slow rotation of the single bonds of both (*E*)-vinyl groups (the *N*-methyl protons are present as a sharp singlet for the whole molecule). Manipulations of Dreiding models demonstrated that, in addition to the basic bisindolyl atropisomerism of **15c,d**, which was confirmed by use of the above-mentioned chiral shift reagent, in the case of **15d** the rotational flexibility around all single bonds is sufficiently high in the side-chains whereas for **15c** the increased steric requirements are responsible for the retardation of the conformational flexibility of the two vinyl functions at both indole nuclei. The *E*/*Z*-configurations of the compounds **15a-d** were unambiguously elucidated by 400 MHz ^{1}H nmr nOe experiments. In the interim an X-ray crystal structure determination of **15d** unambiguously supports the *E*/*Z* configuration previously assigned by nmr spectroscopy.

X-Ray Crystallographic Structure of 2,2'-Bis(*N*-methylindolyl) (**8**).

Compound **8** crystallized from ethyl acetate in the space group $P2_1/n$ with a = 9.9694(2), b = 8.2218(1), c = 17.0058(2) Å, β = 104.909(2)°, V = 1346.98(4) Å^3, Z = 4, D_x = 1.29 g · cm^{-3}. Intensities were measured from a 0.51 x 0.8 x 0.16 mm parallelepiped crystal using an Enraf-Nonius CAD 4 diffractometer with graphite monochromatized CuKα radiation. Of the 2506 independent reflections with $1.5 \leq \theta \leq 70.0°$, 2398 had $I \geq 2\sigma(I)$ and were considered as observed. The structure was solved by direct methods [24] and refined by full matrix least squares methods [25] with 199 parameters to an R-value of 0.046 for the observed reflections. The atomic coordinates and displacement parameters are recorded in Tables 2-4, the bond lengths, bond angles, and torsional angles are given in Tables 5-7 while Figure 1 shows a view [26] of the molecule with the numbering system.

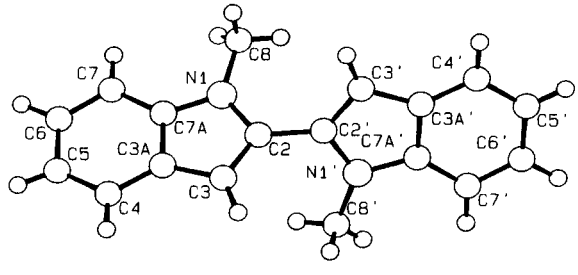


Figure 1. Molecular structure of compound **8** in the crystal state (PLUTO plot); space group: $P2_1/n$. The numbering scheme shown does not correspond to that of the IUPAC nomenclature.

In summary, the general reactivity pattern of 2,2'-bisindolyls in electrophilic substitution and/or cyclization reactions has been extended. In the special case of the investigated compound **8**, ring closure reactions are probably more difficult to achieve in comparison to the parent compound of the series [16]. Biochemical investigations of the novel functionalized and cyclized bisindolyl derivatives described in the present work as potential protein kinase C inhibitors are in progress.

EXPERIMENTAL

Materials and Techniques.

The proton magnetic resonance spectra were recorded on Bruker WM-200 and WM-400 spectrometers using tetramethylsilane as the internal standard (δ scale). The ^{13}C nmr spectra were recorded on a Bruker WM-400 spectrometer at 100.6 MHz with tetramethylsilane as an external standard (δ scale). The infrared spectra were recorded on a Beckman IR 4200 spectrophotometer. The ultraviolet spectra were recorded on an Hitachi U 2000 instrument. The ei mass spectra were measured on a Varian MAT 7 spectrometer at 70 eV. Elemental analyses were performed using a Carlo Erba Strumentazione Model 1106 apparatus. Melting points were determined on a Büchi SMP 20 apparatus and are not corrected. Merck silica gel (grain size: 0.063-0.200 mm) or alternatively Merck active neutral aluminum oxide 90 (activity state I, grain size: 0.063-0.0200 mm) was used for column chromatography and Merck silica gel (grain size: 0.040-0.063 mm) for "flash" chromatography.

All reactions were performed in highly pure and strictly anhydrous solvents under an argon atmosphere. Petroleum ether with the boiling range 40-60° was used throughout.

The constitutions and/or stereochemistries of the products **9a, 9b, 11, 14,** and **15** were clarified mainly with the help of ^1H, ^1H-nOe measurements, while for compounds **9a, 10, 11, 12,** and **13** the ^{13}C nmr APT technique was employed (symbols used for carbon atoms: C_p = primary, C_q = quaternary, C_s = secondary, C_t = tertiary).

2,2'-Bis(*N*-methylindolyl) (**8**).

To a solution of 6 g (0.046 mole) of *N*-methylindole in anhydrous diethyl ether (70 ml) 36 ml of a 1.6 *M* solution of *n*-butyllithium in *n*-hexane was slowly added dropwise using a syringe under argon atmosphere during 20 minutes. The reaction mixture was heated at reflux with stirring under an inert gas atmosphere for 4 hours and then allowed to cool to room temperature. Anhydrous copper(II) chloride (3.18 g, 0.024 mole) was then added in three portions and the mixture was again heated under reflux for 2 hours. After being allowed to cool to room temperature, the mixture was left to stand for 1 hour before being poured into ice/water. The dirty brown-green precipitate was filtered off, the organic layer was separated, and the aqueous phase was extracted twice with diethyl ether. The precipitate was washed twice with dichloromethane and the filtrate combined with the ether phase. The combined organic phases were dried with sodium sulfate, concentrated, and the residue was recrystallized from dichloromethane/ethyl acetate. The product **8** was obtained as light yellow crystals in 41% yield (2.42 g), mp 173-174° (dichloromethane/ethyl acetate), ref [21a], mp 182-184°, ref [27], mp 153-157°; ir (potassium bromide): ν 3200, 1460, 1445, 1415, 1370, 1350, 1320, 1300, 1235, 1175, 1160, 1130, 1100, 1050, 920, 810, 790, 745, 735, 675, 655 cm^{-1}; ms: m/z (%) 261 ($M^{+\cdot}$ + 1, 19), 260 ($M^{+\cdot}$, 100), 259.8 (39), 244 (10), 130 ($M^{+\cdot}$ -*N*-methylindole, 21); ^1H nmr (400 MHz, deuteriochloroform): δ 3.73 (s, 6H, N-CH_3, N'-CH_3), 6.69 (s, 2H, C3-H, C3'-H), 7.20-7.24 (mc, 2H, C6-H, C6'-H), 7.33 (mc, 2H, C5-H, C5'-H), 7.43 (d, ^3J = 8.2 Hz, 2H, C7-H, C7'-H), 7.72 (d, ^3J = 7.8 Hz, 2H, C4-H, C4'-H); ^{13}C nmr (100.6 MHz, deuteriochloroform): δ 30.6 (N-CH_3, N'-CH_3), 104.3 (C3, C3'), 109.5 (C7, C7'), 119.9 (C4, C4'), 120.6 (C5, C5'), 122.1 (C6, C6'), 127.5 (C3a, C3a'), 131.4 (C2, C2'), 137.8 (C7a, C7a').

Anal. Calcd. for $C_{18}H_{16}N_2$ (260.34): C, 83.04; H, 6.19; N, 10.76. Found: C, 82.75; H, 6.23; N, 10.78.

5-(Chloroacetyl)-1-methyl-2-(1-methylindol-2-yl)indole (**9a**).

Anhydrous aluminum trichloride (630 mg, 4.7 mmoles) was dissolved in 24 ml of anhydrous dichloromethane, the solution was stirred for 10 minutes at room temperature and for 10 minutes at 0°. α-Chloroacetyl chloride (510 mg, 44 mmoles) was then added dropwise with thorough stirring at 0° and stirring was continued for 15 minutes. Compound **8** (100 mg, 0.38 mmole) dissolved in 12 ml of anhydrous dichloromethane was then added in small portions. The resultant mixture was stirred for 1 hour at 0° and then allowed to stand at room temperature for 1 hour before being poured into 40 ml of water. The organic layer was separated and the aqueous phase was washed with two 25 ml portions of dichloromethane. The combined organic phases were dried with sodium sulfate, concentrated, and the residue separated by "flash" chromatography (eluent: petroleum ether/ethyl acetate, 3/1). Compound **9a** was obtained as yellow-colored crystals in 40% yield (51 mg), mp 171-174° (ethyl acetate); ir (potassium bromide): ν 2940, 2860, 1680, 1605, 1570, 1465, 1445, 1420, 1400, 1365, 1355, 1325, 1310, 1270, 1245, 1235, 1200, 1150, 1100, 1000, 875, 820, 810, 795, 760, 740, 710, 685, 665 cm^{-1}; ms m/z (%) 337 ($M^{+\cdot}$ + 1, 24), 336 ($M^{+\cdot}$, 100), 288 (21), 287 ($M^{+\cdot}$ -CH_2Cl, 100), 273 (11), 260 ($M^{+\cdot}$ -$OCCH_2Cl$, 7), 259 (3), 258 (17), 257 (16), 244 (11), 243 (17), 144 (30); ^1H nmr (400 MHz, deuteriochloroform): δ 3.71 (s, 3H, N'-CH_3), 3.74 (s, 3H, N-CH_3), 4.81 (s, 2H, CH_2Cl), 6.68 (s, 1H, C3'-H), 6.77 (s, 1H, C3-H), 7.20 (mc, 1H, C6'-H or C5'-H), 7.32 (mc, 1H, C5'-H or C6'-H), 7.41 (d, ^3J = 9.5 Hz, 1H, C7'-H), 7.43 (d, ^3J = 9.0 Hz, 1H, C7-H), 7.69 (d, ^3J = 7.9 Hz, 1H, C4'-H), 7.94 (dd, ^3J = 8.7 Hz, ^4J = 1.6 Hz, 1H, C6-H), 8.33 (d, ^4J = 1.4 Hz, 1H, C4-H); ^{13}C nmr (100.6 MHz, deuteriochloroform): δ 30.8 (N'-CH_3), 31.1 (N-CH_3), 46.0 (CH_2Cl), 104.9 (C_t), 106.1 (C_t), 109.7 (C_t), 110.0 (C_t), 120.2 (C_t), 120.9 (C_t), 122.7 (2 x C_t), 123.1 (C_t), 126.9 (C_q), 127.2 (C_q), 127.5 (C_q), 130.3 (C_q), 133.7 (C_q), 138.0 (C_q), 140.6 (C_q), 190.9 (CO).

Anal. Calcd. for $C_{20}H_{17}ClN_2O$ (336.82): C, 71.32; H, 5.09; N, 8.32. Found: C, 71.38; H, 5.25; N, 8.28.

6-(Chloroacetyl)-1-methyl-2-(1-methylindol-2-yl)indole (**9b**).

Compound **9b** was obtained in addition to **9a** by "flash" chromatographic workup as yellowish crystals in 8% yield (10 mg), mp 151° (ethyl acetate); ir (potassium bromide): ν 2960, 2940, 2860, 1680, 1605, 1465, 1420, 1400, 1365, 1340, 1325, 1310, 1265, 1235, 1200, 1180, 1100, 1020, 900, 820, 810, 800, 760, 750, 735, 625 cm^{-1}; ms: m/z (%) 337 ($M^{+\cdot}$ + 1, 21), 336 ($M^{+\cdot}$, 91), 288 (22), 287 ($M^{+\cdot}$ -CH_2Cl, 100), 273 (11), 259 (28), 258 (15), 257 (15), 244 (11), 243 (15), 144 (31); ^1H nmr (400 MHz, dideuteriodichloromethane): δ 3.74 (s, 3H, N'-CH_3), 3.82 (s, 3H, N-CH_3), 4.89 (s, 2H, $OCCH_2Cl$), 6.72 (s, 1H, C3'-H), 6.74 (s, 1H, C3-H), 7.17 (dd, ^3J = 7.5 Hz, ^4J = 0.9 Hz, 1H, C6'-H or C5'-H), 7.31 (dd, ^3J = 7.6 Hz, ^4J = 1.1 Hz, 1H, C5'-H or C6'-H), 7.44 (d, ^3J = 8.0 Hz, 1H, aromatic H), 7.68 (d, ^3J = 7.9 Hz, 1H, aromatic H), 7.74 (2 x d, 2H, 2 overlapping peaks, aromatic H), 8.11 (d, ^4J = 0.8 Hz, 1H, C7-H); ^{13}C nmr (100.6 MHz, dideuteriodichloromethane): δ 31.3 (N'-CH_3), 31.6 (N—CH_3), 47.0 ($ClCH_2CO$), 105.1 (C_t), 105.3 (C_t), 110.2 (C_t), 111.5 (C_t), 120.4 (C_t), 120.6 (C_t), 121.0 (C_t), 121.3 (C_t), 123.1 (C_t), 128.1 (C_q), 128.8 (C_q), 130.9 (C_q), 132.5 (C_q), 136.8 (C_q), 138.0 (C_q), 138.7 (C_q), 191.2 (CO).

Anal. Calcd. for $C_{20}H_{17}ClN_2O$ (336.82): C, 71.32; H, 5.09; N, 8.32. Found: C, 70.93; H, 5.27; N, 8.15.

N,N'-Dimethyl-3,3'-dibromo-2,2'-bisindolyl (**10**).

The 2,2'-bisindolyl **8** (400 mg, 1.54 mmoles) was dissolved in 20 ml of *N,N*-dimethylformamide and a solution of bromine (562 mg, 3.52 mmoles) in 13 ml of *N,N*-dimethylformamide was added dropwise with stirring at room temperature. The mixture was stirred for 15 minutes and then poured into 70 ml of ice/water containing ammonia (0.5%) and sodium metabisulfite (0.1%). The white precipitate formed was filtered, washed with cold water, dried, and crystallized from petroleum ether/ethyl acetate (4/1). The product **10** was obtained as colorless crystals in 90% yield (0.58 g), mp 204-208° (petroleum ether/ethyl acetate); ir (potassium bromide): ν 3070, 2950, 2920, 2850, 1460, 1420, 1380, 1350, 1320, 1230, 1180, 1155, 1100, 1005, 945, 735 cm^{-1}; ms: m/z (%) 418 ($M^{+\cdot}$, 90; isotope peaks: 419 and 417), 416 (45), 337 (13), 259 (14), 258 ($M^{+\cdot}$ − 2 x Br, 82), 257 (100), 256 (40), 255 (18), 243 (20), 242 (29), 241 (10), 216 (15), 214 (15), 209 (11), 130 (16), 129 (26), 128 (19), 128 (23), 121 (17), 115 (11), 114 (11), 102 (12); ^1H nmr (400 MHz, deuteriochloroform): δ 3.64 (s, 6H, N-CH_3, N'-CH_3), 7.27 (dd, ^3J = 8.0 Hz, 8.0 Hz, 2H, C6-H, C6'-H), 7.37 (mc, 2H, C5-H, C5'-H), 7.41 (d, ^3J = 8.2 Hz, 2H, C7-H, C7'-H), 7.66 (d, ^3J = 8.0 Hz, 2H, C4-H, C4'-H); ^{13}C nmr (100.6 MHz, deuteriochloroform): δ 31.3 (N-CH_3, N'-CH_3), 94.8 (C3, C3'), 110.0 (C7, C7'), 119.75 (C4, C4'), 120.75 (C5, C5'), 123.8 (C6, C6'), 126.8 (C3a, C3a'), 127.5 (C2, C2'), 137.2 (C7a, C7a').

Anal. Calcd. for $C_{18}H_{14}Br_2N_2$ (418.13): C, 51.71; H, 3.37; N, 6.70. Found: C, 51.65; H, 3.36; N, 6.56.

3-(1,4-Naphthoquinon-2-yl)-1-methyl-2-(1-methylindol-2-yl)indole (**11**).

Anhydrous aluminum trichloride (250 mg, 1.87 mmoles) and 1,4-naphthoquinone (300 mg, 1.89 mmoles) dissolved in 25 ml of anhydrous, distilled xylene were stirred at room temperature for 20 minutes. The 2,2'-bisindolyl **8** (250 mg, 0.96 mmole) was added and the resultant mixture stirred at room temperature for 2.5 hours until **8** could no longer be detected by tlc. The reaction mixture was then diluted with water (20 ml), the organic layer was separated, and the aqueous phase was washed with two 15 ml portions of dichloromethane. The combined organic phases were dried with sodium sulfate, concentrated, and the residue was purified by "flash" chromatography (eluent: petroleum ether/ethyl acetate, 2/1) to furnish red crystals comprised of compound **11** as the main product in approximately 30% yield together with compound **13**. Compound **11** was obtained in 30% yield (120 mg), mp 181° (dichloromethane/ethyl acetate); ir (potassium bromide): ν 3060, 2960, 2930, 2860, 1695, 1670, 1650, 1595, 1575, 1470, 1435, 1425, 1400, 1375, 1330, 1300, 1250, 1140, 1115, 1100, 1080, 990, 845, 785, 750, 735, 720 cm^{-1}; uv-vis (dichloromethane): λ max nm (ϵ) 490 (3395); ms: m/z (%) 417 ($M^{+\cdot}$ + 1, 33), 416 $M^{+\cdot}$, 100), 399 (14), 388 (10), 387 (12), 373 (11), 372 (12), 371 (25), 343 (10), 284 (13), 269 (11), 208 (13), ^1H nmr (400 MHz, deuteriochloroform): δ 3.66 (s, 3H, N-CH_3), 3.72 (s, 3H, N'-CH_3), 6.54 (s, 1H, C3'-H), 7.08 (s, 1H, naphthoquinone C3-H), 7.12 (dd, ^3J = 7.3 Hz, 7.3 Hz, 1H, aromatic H), 7.27-7.30 (m, 2H, aromatic H), 7.36-7.40 (m, 2H, aromatic H), 7.46 (d, ^3J = 8.2 Hz, 1H, aromatic H), 7.55 (d, ^3J = 7.8 Hz, 1H, aromatic H), 7.58 (dd, ^3J = 7.5 Hz, ^4J = 1.2 Hz, 1H, C4''-H), 7.64-7.68 (mc, 1H, aromatic H), 7.70-7.75 (mc, 2H, aromatic H), 8.04 (d, ^3J = 7.6 Hz, 1H, C4-H); ^{13}C nmr (100.6 MHz, deuteriochloroform): δ 31.0 (N-CH_3), 31.0 (N'-CH_3), 106.3 (C_t), 109.7 (C_t), 110.1 (C_t), 111.2 (C_q), 120.0 (C_t), 120.2 (C_t), 121.0 (C_t), 121.5 (C_t), 122.6 (C_t), 123.4 (C_t), 125.8 (C_t), 126.7 (C_q), 126.8 (C_t), 127.6 (C_q), 130.2 (C_q), 132.2 (C_q), 132.8 (C_q), 133.1 (C_q), 133.3 (C_t), 133.4 (C_t), 134.8 (C_t), 137.9 (C_q), 138.2 (C_q), 144.5 (C_q), 184.1 and 184.9 (2 x CO).

Anal. Calcd. for $C_{28}H_{20}N_2O_2$ (416.48): C, 80.75; H, 4.84; N, 6.73. Found: C, 80.65; H, 4.94; N, 6.82.

5,6-Dimethyl-11,16-dihydronaphtho[2,3-*c*]indolo[2,3-*a*]carbazole-11,16-dione (**12**).

Compound **11** (400 mg, 0.96 mmole) was dissolved in 100 ml of anhydrous 1,2-dichloroethane, anhydrous aluminum trichloride (350 mg, 2.6 mmoles) was added, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was subsequently heated at 50° for 15 hours, cooled, allowed to stand at room temperature for 1 hour, and then poured into water. The organic layer was separated and the aqueous phase was washed twice with 1,2-dichloroethane. The combined organic phases were dried with sodium sulfate, concentrated, and the residue purified by "flash" chromatography (eluent: petroleum ether/ethyl acetate, 1/1.5). The product was recrystallized from dichloromethane/ethyl acetate to give **12** in 10% yield (41 mg) as orange to red-colored, filmy plates, mp 229° (dichloromethane/ethyl acetate); ir (potassium bromide): ν 3030, 2905, 1660, 1640, 1590, 1580, 1510, 1465, 1435, 1395, 1345, 1325, 1270, 1245, 1155, 1135, 1105, 1080, 1020, 985, 740, 710 cm^{-1}; uv-vis (dichloromethane): λ max nm (ϵ) 465 (3835); ms: m/z (%) 415 ($M^{+\cdot}$ + 1, 31), 414 ($M^{+\cdot}$, 100), 400 (14), 399 (25), 207 (9); ^1H nmr (200 MHz, deuteriochloroform): δ 4.14 (s, 6H, 2 x N-CH_3), 7.42 (mc, 2H, C2-H, C9-H or C3-H, C8-H), 7.51-7.66 (m, 4H, aromatic H), 7.77 (dd, ^3J = 5.7 Hz, ^4J = 3.3 Hz, 2H, C13-H, C14-H), 8.34 (dd, ^3J = 5.6 Hz, ^4J = 3.3 Hz, 2H, C12-H, C15-H), 9.27 (d, ^3J = 8.2 Hz, 2H, C1-H, C10-H); ^{13}C nmr (100.6 MHz, deuteriochloroform): δ 36.50 (2 x N-CH_3), 110.2 (2 x C_t), 121.3 (2 x C_t), 122.0 (2 x C_q), 124.2 (2 x C_q), 126.4 (2 x C_t), 126.7 (2 x C_t), 127.2 (2 x C_q), 127.4 (2 x C_t), 133.2 (2 x C_t), 134.0 (2 x C_q), 134.2 (2 x C_q), 145.7 (2 x C_q), 185.2 (2 x CO).

Anal. Calcd. for $C_{28}H_{18}N_2O_2$ (414.46): C, 81.14; H, 4.38; N, 6.76. Found: C, 80.68; H, 4.47; N, 6.67.

N,N'-Dimethyl-3,3'-bis(1,4-naphthoquinon-2-yl)-2,2'-bisindolyl (**13**).

This product was formed together with compound **11** as described above as red-violet colored crystals in 10% yield (55 mg), mp 333-334° (dichloromethane/ethyl acetate); ir (potassium bromide): ν 3050, 1670, 1645, 1600, 1575, 1465, 1445, 1420, 1380, 1335, 1300, 1250, 1140, 1110, 1080, 985, 900, 885, 840, 780, 745, 715 cm^{-1}; vis (dichloromethane): λ max nm (ϵ) 482 (12,800); ms: m/z (%) 573 ($M^{+\cdot}$ + 1, 46), 572 ($M^{+\cdot}$, 100), 416 (16), 415 ($M^{+\cdot}$ -naphthoquinone, 51), 400 (16); ^1H nmr (400 MHz, deuteriochloroform): δ 3.96 (s, 6H, N-CH_3, N'-CH_3), 6.37 (s, 2H, naphthoquinone C3-H, C3'-H), 7.22 (d, ^3J = 7.7 Hz, 2H, aromatic H), 7.26 (d, ^3J = 7.8 Hz, 2H, aromatic H), 7.4 (ddd, ^3J = 8.3 Hz, 7.2 Hz, ^4J = 1.0 Hz, 2H, aromatic H), 7.48 (dd, ^3J = 7.6 Hz, ^4J = 1.3 Hz, 2H, aromatic H), 7.51-7.55 (mc, 4H, aromatic H), 7.63-7.67 (mc, 2H, aromatic H), 7.92 (dd, ^3J = 7.8 Hz, ^4J = 0.9 Hz, 2H, C4-H, C4'-H); ^{13}C nmr (100.6 MHz, deuteriochloroform): δ 31.7 (N-CH_3, N'-CH_3), 110.4 (2 x C_t), 113.2 (2 x C_q), 119.6 (2 x C_t), 121.7 (2 x C_t), 123.9 (2 x C_t), 125.8 (2 x C_t), 125.9 (2 x C_q), 126.1 (2 x C_t), 131.7 (2 x C_q), 132.4 (2 x C_q), 132.8 (2 x C_t), 133.1 (2 x C_q), 133.2 (2 x C_t), 133.8 (2 x C_t), 138.7 (2 x C_q), 144.5 (2 x C_q), 184.1 and 184.3 (each 2 x CO).

Anal. Calcd. for $C_{38}H_{24}N_2O_4$ (572.62): C, 79.71; H, 4.22; N, 4.89. Found: C, 78.94; H, 4.31; N, 4.99.

3-(Maleimido-2-yl)-1-methyl-2-(1-methylindol-2-yl)indole (**14a**).

Anhydrous aluminum trichloride (400 mg, 3.0 mmoles) and maleimide (480 mg, 4.9 mmoles) were dissolved in 40 ml of anhydrous, distilled xylene and the solution was stirred for 30 minutes at room temperature. The 2,2'-bisindolyl **8** (360 mg, 1.38 mmoles) was then added and the mixture heated at 57° for 1 hour. After being allowed to cool to room temperature, the reaction mixture was poured into 50 ml of water. The organic layer was separated and the aqueous phase was washed with two 30 ml portions of dichloromethane. The combined organic phases were concentrated under reduced pressure whereupon a colorless precipitate formed. This precipitate was filtered, dried, and then dissolved in 15 ml of toluene and the resultant solution heated under reflux for 1 hour. A 0.03 *M* solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in toluene (15 ml) was added dropwise to the hot reaction mixture and heating was continued for 1 hour. After 1 hour further 15 ml of the DDQ solution were added and the mixture was stirred and heated under reflux for 5 hours. After being allowed to cool to room temperature, the reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography on active neutral aluminum oxide 90 (eluent:petroleum ether/ethyl acetate, 1/3). Product **14a** was obtained as yellow-orange crystals in 4% yield (18 mg), mp 218-220° (petroleum ether/ethyl acetate); ms: m/z (%) 355 ($M^{+\cdot}$, 100), 338 (12), 284 (22), 283 (17), 269 (21), 268 (18); ^{1}H nmr (400 MHz, deuteriochloroform): δ 3.61 (s, 3H, N-CH_3 or N'-CH_3), 3.63 (s, 3H, N'-CH_3 or N-CH_3), 6.17 (s, 1H, maleimide C3-H), 6.60 (s, 1H, C3-H), 7.16-7.20 (mc, 1H, aromatic H), 7.21 (br s, 1H, maleimide NH), 7.30-7.35 (m, 2H, aromatic H), 7.38-7.45 (m, 3H, aromatic H), 7.65 (d, ^{3}J = 7.9 Hz, 1H, C7-H or C4'-H), 7.97 (d, ^{3}J = 8.0 Hz, 1H, C4-H); ^{13}C nmr (100.6 MHz, deuteriochloroform): δ 30.8 and 31.0 (2 x N-CH_3), 106.2 (C3'), 107.1 (C3), 109.9 (C_t), 110.18 (C_t), 120.4 (C_t), 121.2 (C_t), 122.1 (C_t), 123.0 (C_t), 123.1 (C_t), 123.9 (2 x C_t, one C_t overlapping), 125.9 (C_q), 127.6 (C_q), 129.3 (C_q), 134.2 (C_q), 138.0 (C_q), 138.2 (C_q), 142.2 (C_q), 170.0 and 170.7 (2 x CO).

Anal. Calcd. for $C_{22}H_{17}N_3O_2$ (355.40): C, 74.35; H, 4.82; N, 11.82. Found: C, 74.00; H, 4.81; N, 11.57.

3-(1,4-Dioxo-5-phenyl-2,3-dihydromaleimido)-1-methyl-2-(1-methylindol-2-yl)indole (**14b**).

A suspension of 420 mg (2.43 mmoles) of *N*-phenylmaleimide and 480 mg aluminum trichloride in 40 ml of anhydrous xylene was stirred at room temperature for 30 minutes. The 2,2'-bisindolyl **8** (520 mg, 2.00 mmoles) was then added, the reaction mixture was heated under reflux for 10 minutes, and then allowed to cool to room temperature. The cooled mixture was poured into water, the organic layer was separated, and the aqueous phase washed with dichloromethane. The combined organic layers were dried with sodium sulfate, concentrated, and the residue purified by "flash" chromatography (eluent:petroleum ether/ethyl acetate, 1.5/1). Compound **14b** was obtained in 87% yield (754 mg), mp 203-204° (petroleum ether/ethyl acetate); ir (potassium bromide): ν 3050 (aryl-H), 2930 (CH valency vibration), 1710 (CO bands), 1495, 1465 (CH deformation bands), 1385, 1325, 1180, 1050, 1000, 955, 820, 795, 750, 730, 690, 670, 610 cm^{-1}; ms: m/z (%) 433 ($M^{+\cdot}$, 100), 286 (33), 285 (26), 271 (29), 270 (31), 256 (14), 255 (12); ^{1}H nmr (200 MHz, deuteriochloroform) AB spin system: δ 3.1 (dd, ^{2}J = $J_{A,B}$ = 18.5 Hz, ^{3}J = J_A = 5.5 Hz, 1H, 3''-H), 3.34 (dd, ^{2}J = $J_{A,B}$ = 18.5 Hz, ^{3}J = J_A = 9.8 Hz, 1H, 3''-H), 3.52 (s, 3H, N-CH_3), 3.56 (s, 3H, N-CH_3), 4.48 (dd, ^{3}J = J_B = 9.8 Hz, ^{3}J = J_A = 5.6 Hz, 1H, 2''-H), 6.63-6.68 (m, 2H, 2 x phenyl H), 6.76 (s, 1H, C3-H), 7.15-7.23 (m, 3H, 2 x and 1 x phenyl H), 7.25-7.31 (m, 1H, aromatic H), 7.32-7.47 (m, 5H, aromatic H), 7.56 (d, ^{3}J = 7.8 Hz, 1H, aromatic H), 7.68 (d, ^{3}J = 7.8 Hz, 1H, C4-H).

Anal. Calcd. for $C_{28}H_{23}N_3O_2$ (433.51): C, 77.58; H, 5.35; N, 9.69. Found: C, 77.87; H, 5.31; N, 9.70.

3-(1,4-Dioxo-5-phenylmaleimido)-1-methyl-2-(1-methylindol-2-yl)-indole (**14c**).

Compound **14b** (150 mg, 0.25 mmole) was dissolved in 15 ml of anhydrous *o*-dichlorobenzene and stirred at room temperature for 10 minutes. The solution was treated with 10% Pd/C (105 mg) and then refluxed for 48 hours. The reaction mixture was then allowed to cool to room temperature before being filtered off. The filtrate was concentrated and the residue was separated by "flash" chromatography (eluent:petroleum ether/ethyl acetate, 3/1). Compound **14c** was obtained as orange-red crystals in 20% yield (29 mg), mp 180-185° (petroleum ether/ethyl acetate); ms: m/z (%) 432 ($M^{+\cdot}$ + 1, 28), 431 ($M^{+\cdot}$, 87), 414 (11), 339 (11), 312 (18), 311 (69), 310 (10), 297 (13), 285 (17), 284 (67), 283 (74), 282 (14), 281 (11), 271 (10), 270 (27), 269 (100), 268 (83), 267 (28), 266 (10), 254 (10), 253 (13), 241 (16); ^{1}H nmr (400 MHz, deuteriochloroform): δ 3.63 (s, 3H, N-CH_3), 3.64 (s, 3H, N-CH_3), 6.27 (s, 1H, phenylmaleimido-H), 6.65 (s, 1H, C3-H), 7.17-7.23 (m, 2H, aromatic H), 7.26-7.46 (m, 10H, aromatic H), 7.67 (d, ^{3}J = 7.9 Hz, 1H, C4-H).

Anal. Calcd. for $C_{28}H_{21}N_3O_2$ (431.49): C, 77.94; H, 4.91; N, 9.74. Found: C, 77.98; H, 4.90; N, 9.72.

3-(2-Dimethoxyfumaroyl)-1-methyl-2-(1-methylindol-2-yl)indole (**15a**).

A suspension of 200 mg (1.5 mmoles) of anhydrous aluminum trichloride in 12 ml of bromobenzene was stirred at room temperature for 10 minutes, 120 µl (142 mg, 1.0 mmole) of dimethyl acetylenedicarboxylate were added dropwise, and stirring was continued for 10 minutes. The 2,2'-bisindolyl **8** (200 mg, 0.77 mmole) dissolved in 10 ml of bromobenzene was then added, the resultant mixture was stirred for 40 minutes at room temperature before being diluted with 20 ml of water. The organic layer was separated, the aqueous phase was extracted with dichloromethane, the combined organic phases were dried with sodium sulfate, and concentrated. The residue was purified by column chromatography (eluent:petroleum ether/ethyl acetate, 5/1). Product **15a** was obtained as yellow crystals in 10% yield (30 mg), mp 150-153° (petroleum ether/ethyl acetate); ms: m/z (%) 403 ($M^{+\cdot}$ + 1, 13), 402 ($M^{+\cdot}$, 44), 343 (33), 342 (19), 312 (24), 311 (100), 287 (28), 285 (50), 284 (93), 283 (28), 282 (11), 270 (15), 269 (43), 268 (28), 267 (11), 245 (17), 243 (19), 203 (18), 201 (21), 165 (13), 123 (23), 57 (10), 55 (11), 43 (69), 42 (10), 41 (23); ^{1}H nmr (400 MHz, dideuteriodichloromethane): δ 3.45 (s, 3H, NCH_3 or OCH_3), 3.54 (s, 3H, NCH_3 or OCH_3), 3.61 (s, 3H, NCH_3 or OCH_3), 3.70 (s, 3H, NCH_3 or OCH_3), 6.60 (s, 1H, C3'-H), 6.91 (s, 1H, vinyl H), 7.15-7.22 (m, 2H, aromatic H), 7.28-7.32 (m, 1H, aromatic H), 7.34-7.38 (mc, 2H, aromatic H), 7.40 (d, ^{3}J = 8.2 Hz, 1H, aromatic H), 7.46 (d, ^{3}J = 8.2 Hz, 1H, aromatic H), 7.66 (d, ^{3}J = 7.9 Hz, 1H, C4-H).

Anal. Calcd. for $C_{24}H_{22}N_2O_4$ (402.45): C, 71.63; H, 5.51; N, 6.96. Found: C, 71.40; H, 5.64; N, 6.88.

3-(2-Dimethoxymaleoyl)-1-methyl-2-(1-methylindol-2-yl)indole (**15b**).

The 2,2'-bisindolyl **8** (400 mg, 1.8 mmoles) was dissolved in 40 ml of dry bromobenzene and the solution was stirred for 5 minutes before the dropwise addition of 240 µl (284 mg, 2.0 mmoles) of dimethyl acetylenedicarboxylate followed by 400 mg of aluminum trichloride. The resultant mixture was stirred for 2 hours at room temperature, allowed to stand for 2 hours at room temperature, and was then poured into water. The organic layer was separated, the aqueous layer was washed with dichloromethane, and the combined organic phases were dried with sodium sulfate and concentrated. The residue was purified by column chromatography (eluent:petroleum ether/ethyl acetate, 3/1). The product **15b** was obtained as yellow crystals in 34% yield (210 mg), mp 159-161° (petroleum ether/ethyl acetate); ms: m/z (%) 403 ($M^{+\cdot}$ + 1, 12), 402 ($M^{+\cdot}$, 44), 343 (33), 342 (16), 312 (23), 311 (100), 285 (12), 284 (51), 283 (17), 269 (26), 268 (17), 171 (11); ^{1}H nmr (400 MHz, dideuteriodichloromethane): δ 3.12 (s, 3H, NCH_3 or OCH_3), 3.52 (s, 3H, NCH_3 or OCH_3), 3.55 (s, 3H, NCH_3 or OCH_3), 3.68 (s, 3H, NCH_3 or OCH_3), 6.32 (s, 1H, vinyl H), 6.68 (s, 1H, C3'-H), 7.16-7.21 (mc, 1H, aromatic H), 7.26-7.44 (m, 5H, aromatic H), 7.67 (d, ^3J = 7.8 Hz, 1H, aromatic H), 7.88 (d, ^3J = 7.4 Hz, 1H, aromatic H).

Anal. Calcd. for $C_{24}H_{22}N_2O_4$ (402.45): C, 71.63; H, 5.51; N, 6.96. Found: C, 71.60; H, 5.56; N, 6.96.

3,3'-Bis(2-dimethoxyfumaroyl)-2,2'-bisindolyl (**15c**).

Anhydrous aluminum trichloride (300 mg, 2.25 mmoles) was suspended in 15 ml of anhydrous bromobenzene and the suspension was stirred for 30 minutes before 30 ml (24 mmoles) of dimethyl acetylenedicarboxylate were added dropwise. Stirring was continued for 15 minutes and then 300 mg (1.15 mmoles) of the 2,2'-bisindolyl **8** dissolved in 15 ml of bromobenzene were added dropwise. The resultant mixture was stirred for 2 hours at room temperature and subsequently poured into water. The organic layer was separated, the aqueous phase was extracted with dichloromethane, the combined organic phases were dried, and concentrated. The residue was purified by column chromatography (eluent:petroleum ether/ethyl acetate, 3/1) to furnish compound **15c** together with **15d**. Product **15c** was obtained as yellow crystals in 14% yield (87 mg), mp 148-150° (petroleum ether/ethyl acetate); ms: m/z (%) 544 ($M^{+\cdot}$, 100), 485 (36), 453 (18), 425 (26), 400 (38), 369 (35), 367 (11), 343 (14), 342 (49), 329 (29), 307 (11), 298 (12), 294 (12), 293 (20), 292 (14); ^{1}H nmr (400 MHz, dideuteriodichloromethane): δ 3.41 (br, 6H, 2 x OCH_3), 3.48 (br, 6H, 2 x OCH_3), 3.72 (s, 6H, 2 x NCH_3), 6.95 (br, 2H, 2 x vinyl H), 7.15 (dd, ^3J = 7.4 Hz, 7.4 Hz, 2H, aromatic H), 7.30-7.34 (mc, 4H, aromatic H), 7.45 (d, ^3J = 8.2 Hz, 2H, C4-H, C4'-H); ^{13}C nmr (100.6 MHz, dideuteriodichloromethane): δ 31.6 (2 x NCH_3), 51.6 (2 x OCH_3), 52.7 (2 x OCH_3), 110.2 (2x), 120.3 (2 x 2, two overlapping peaks), 120.7 (2x), 123.1 (2x), 127.7 (2x), 129.7 (2x), 130.6 (2x), 137.4 (2x), 138.1 (2x), 165.6 and 166.6 (each 2x, CO).

Anal. Calcd. for $C_{30}H_{28}N_2O_8$ (544.56): C, 66.17; H, 5.18; N, 5.14. Found: C, 66.17; H, 5.32; N, 5.09.

3-(2-Dimethoxyfumaroyl)-3'-(2-dimethoxymaleoyl)-1-methyl-2-(1-methylindol-2-yl)indole (**15d**).

Compound **15d** was obtained in the preparation of **15c** as described above and separated by column chromatography as yellow crystals in approximately 16% yield (101 mg), mp 185-189° (petroleum ether/ethyl acetate); ms: m/z (%) 545 ($M^{+\cdot}$ + 1, 21), 544 ($M^{+\cdot}$, 64), 486 (10), 485 (32), 453 (22), 426 (15), 425 (36), 401 (22), 400 (42), 370 (10), 369 (42), 367 (15), 366 (12), 353 (10), 352 (13), 351 (14), 343 (13), 342 (47), 329 (36), 327 (13), 308 (14), 307 (16), 298 (13), 295 (11), 294 (13), 293 (22), 292 (15), 283 (11), 268 (14); ^{1}H nmr (400 MHz, dideuteriodichloromethane): δ 3.33 (s, 3H, NCH_3 or OCH_3), 3.46 (s, 3H, NCH_3 or OCH_3), 3.55 (s, 3H, NCH_3 or OCH_3), 3.68 (s, 3H, NCH_3 or OCH_3), 3.75 (s, 3H, NCH_3 or OCH_3), 3.76 (s, 3H, NCH_3 or OCH_3), 5.73 (s, 1H, vinyl H of maleoyl type), 6.87 (s, 1H, vinyl H of fumaroyl type), 7.16-7.27 (m, 2H, aromatic H), 7.30-7.42 (m, 3H, aromatic H), 7.57 (d, ^3J = 8.3 Hz, 1H, aromatic H), 7.59 (d, ^3J = 8.2 Hz, 1H, aromatic H), 7.67 (d, ^3J = 8.3 Hz, 1H, C4-H); ^{13}C nmr (100.6 MHz, dideuteriodichloromethane): δ 31.2 (NCH_3), 31.3 (NCH_3), 51.8 (OCH_3), 52.0 (OCH_3), 52.6 (OCH_3), 52.8 (OCH_3), 110.8, 111.9, 112.8, 117.9, 120.0, 120.2, 121.1, 122.1, 123.6, 124.0, 126.1, 127.2, 128.6, 129.1, 130.7, 137.9, 138.0, 138.5, 142.1, and 165.9, 166.3, 167.3, 169.0 (each one peak, 4 x CO), one signal is overlapped (120.9 or 129.1 ppm).

Anal. Calcd. for $C_{30}H_{28}N_2O_8$ (544.56): C, 66.17; H, 5.18; N, 5.14. Found: C, 65.85; H, 5.35; N, 5.04.

5,6-Dimethyl-11,12-dimethoxycarbonyl-11,12-dihydroindolo[2,3-*a*]carbazole (**16**).

Compound **15b** (140 mg) was dissolved in 40 ml of anhydrous dichloromethane and 100 mg of anhydrous aluminum trichloride were added. The mixture was stirred at room temperature for 2 hours, allowed to stand for 20 minutes, and was then poured into water. The organic phase was separated, the aqueous phase was extracted with dichloromethane, the combined organic phases were dried with sodium sulfate and concentrated. The residue was purified by "flash" chromatography (eluent:petroleum ether/ether acetate, 2/1) to furnish compound **16** in 33% yield (20 mg), mp 187-189° (ethyl acetate); ms: m/z (%) 403 ($M^{+\cdot}$ + 1, 26), 402 ($M^{+\cdot}$, 100), 344 (15), 343 (63), 330 (13), 329 (54), 285 (15), 284 (66), 269 (22), 268 (14), ^{1}H nmr (400 MHz, deuteriochloroform): δ 3.15 (s, 2H, C11-H, C12-H), 3.71 (s, 6H, 2 x NCH_3 or 2 x OCH_3), 4.05 (s, 6H, 2 x OCH_3 or 2 x NCH_3), 7.15-7.20 (m, 4H, aromatic H), 7.32-7.34 (mc, 2H, aromatic H), 7.76 (mc, 2H, aromatic H).

Anal. Calcd. for $C_{24}H_{22}N_2O_4$ (402.45): C, 71.63; H, 5.51; N, 6.96. Found: C, 71.31; H, 5.64; N, 6.87.

Acknowledgements.

We thank the Deutsche Forschungsgemeinschaft (Bonn, FRG, project Pi 135/10-1) and the Fonds der Chemischen Industrie (FRG) for financial support of this work.

REFERENCES AND NOTES

[1a] S. Omura, Y. Iwai, A. Hirano, A. Nakagawa, J. Awaya, H. Tsushiya, Y. Takahashi and R. Masuma, *J. Antibiot.*, **30**, 275 (1977); S. Oka, M. Kodama, H. Takeda, N. Tomizuka and H. Suzuki, *Agric. Biol. Chem.*, **50**, 2723 (1986); [b] T. Kaneka, H. Wong, K. T. Okamoto and J. Clardy, *Tetrahedron Letters*, **26**, 4015 (1985); D. E. Nettleton, T. W. Doyle, B. Krishnan, G. K. Matsumoto and J. Clardy, *Tetrahedron Letters*, **26**, 4011 (1985); [c] J. Bergman, in Studies in Natural Products Chemistry, Vol **1**, Part A, Stereoselective Synthesis, Atta-ur-Rahman, ed, Elsevier, Amsterdam, 1988, p 3 ff; [d] R. P. Joyce, J. A. Gainer and S. M. Weinreb, *J. Org. Chem.*, **52**, 1177 (1986).

[2a] P. D. Davis, L. H. Elliott, W. Harris, C. H. Hill, S. A. Hurst, E. Keech, M. K. H. Kumar, G. Lawton, J. S. Nixon and S. E. Wilkinson, *J. Med. Chem.*, **35**, 994 (1992); [b] P. D. Davis, C. H. Hill, W. A. Thomas and I. W. A. Whitcombe, *J. Chem. Soc., Chem. Commun.*, 182 (1991); [c] W. Sato, K. Yusa, M. Naito, T. Tsuruo, *Biochem. Biophys. Res. Commun.*, **173**, 1252 (1990); [d] Reviews on protein kinase C (PKC): Y. Nishizuka, *Nature*, **334**, 661 (1988); Y. Nishizuka, *Science*, **233**, 305 (1986).

[3a] R. Bonjouklian, T. A. Smitka, L. E. Doalin, R. M. Molloy, M. Debono, S. A. Shaffer, J. B. Stewart and G. M. Patterson, *Tetrahedron*, **47**, 7739 (1991); [b] G. W. Gribble and B. Pelcman, *J. Org. Chem.*, **57**, 3636 (1992).

[4] H. Barth, J. Hartenstein, C. Rudolph, C. Schaechtele, H. J. Betche, H. Osswald and R. Reck, European Patent Appl. EP 397.060 (1990); *Chem. Abstr.*, **114**, 228726z (1991).

[5] W. Steglich, B. Steffan, L. Kopanski and G. Eckhardt, *Angew. Chem., Int. Ed. Engl.*, **19**, 459 (1980).

[6] M. Brenner, H. Rexhausen, B. Steffan and W. Steglich, *Tetrahedron*, **44**, 2887 (1988).

[7] For reviews on naturally occurring indolo[2,3-*a*]carbazoles and bisindolylmaleimides, see ref [1c] and M. Gill and W. Steglich, *Progr. Chem. Org. Nat. Prod.*, **51**, 216 (1987); W. Steglich, *Pure Appl. Chem.*, **61**, 281 (1989).

[8] J. Bergman and B. Pelcman, *J. Org. Chem.*, **54**, 824 (1989).

[9] C. J. Moody and K. J. Rahimtoola, *J. Chem. Soc., Chem. Commun.*, 1667 (1990).

[10] I. Hughes, W. P. Nolan and R. A. Raphael, *J. Chem. Soc., Perkin Trans. 1*, 2475 (1990).

[11] Ref [3d] and G. W. Gribble and S. J. Berthel, *Tetrahedron*, **48**, 8869 (1992).

[12] B. Sarstedt and E. Winterfeldt, *Heterocycles*, **20**, 469 (1983).

[13] M. Gallant, J. T. Link and S. J. Danishefsky, *J. Org. Chem.*, **58**, 343 (1993); J. T. Link, M. Gallant, S. J. Danishefsky, *J. Am. Chem. Soc.*, **115**, 3782 (1993).

[14] Patent literature: T. Hirata, M. Takahashi, T. Muragata, H. Kase, K. Yamada and K. Iwahashi, *Chem. Abstr.*, **107**, 236750 (1987); T. Hirata and M. Tak, *Chem. Abstr.*, **107**, 236751 (1987); T. Hirata, K. Mochida, T. Muragata, M. Tokahashi, H. Kase, K. Yamada, K. Iwahashi, A. Sato, M. Kasai, *Chem. Abstr.*, **111**, 194456 (1989); J. Kleinschroth, J. Hartenstein, H. Barth, C. Schaechtele, C. Rudolph and G. Weinheimer, *Chem. Abstr.*, **112**, 55832 (1990); J. Kleinschroth, C. Schaechtele, J. Hartenstein and C. Rudolph, *Chem. Abstr.*, **115**, 159123 (1991); J. Kleinschroth, J. Hartenstein, C. Schaechtele, C. Rudolph, D. J. Dooley and G. Weinheimer, *Chem. Abstr.*, **113**, 191154 (1990); H. Barth, J. Hartenstein, H. J. Betche, C. Schaechtele, C. Rudolph, H. Osswald, *Chem. Abstr.*, **114**, 185264 (1991); H. Barth, J. Hartenstein, C. Rudolph, H. J. Betche, H. Osswald and R. Rech, *Chem. Abstr.*, **114**, 228726 (1991); P. D. Davis, C. H. Hill and G. Lawton, *Chem. Abstr.*, **112**, 98378 (1990); P. D. Davis, C. H. Hill and G. Lawton, *Chem. Abstr.*, **114**, 81582 (1991).

[15] U. Pindur and M.-H. Kim, *Arch Pharm. (Weinheim)*, **325**, 353 (1991).

[16] M. Somei and A. Kodama, *Heterocycles*, **34**, 1285 (1992).

[17] The MOPAC 6.0 program (QCPE 504) was used for AM1 calculations: M. J. S. Dewar, E. G. Zoebisch, E. F. Healy and J. J. Stewart, *J. Am. Chem. Soc.*, **107**, 3902 (1985); HOMO data of the geometry-optimized structure (torsional angle N1-C2-C2'-N1' = 52°) of compound **8** (starting geometry from the X-ray analysis): E*(HOMO)* = −8.17 eV; HOMO coefficients at C2,2' = −0.37; +0.30; C3,3' = −0.32; +0.19; net atomic charge at N1,N1' = −0.11; C2,2' = −0.01; C3,3' = −0.16; C5,5' = −0.16; C6,6' = +0.11.

[18] I. Fleming, Frontier Orbitals and Organic Chemical Reactions, John Wiley and Sons, New York, 1976.

[19] U. Pindur, Cycloaddition Reactions of Indole Derivatives, in Advances in Nitrogen Heterocycles, C. J. Moody, ed, JAI Press Inc., Greenwhich, Connecticut, 1994, in press.

[20] The MMX molecular mechanics program is an enhanced MM2 variant: J. J. Gajewski, K. E. Gilbert and J. McKelvey, Advances in Molecular Modeling Vol **2**, JAI Press Inc., Greenwich, Connecticut, 1990, pp 66-90.

[21a] J. Bergman and N. Eklund, *Tetrahedron*, **36**, 1439 (1980); [b] for other concepts for the syntheses of 2,2'-bisindolyls and their applications as chelate complexing ligands, see D. S. Black, *Synlett*, 246 (1993).

[22] M. Oki, *Angew. Chem., Int. Ed. Engl.*, **15**, 87 (1976), M. Oki *Top. Stereochem.*, **14**, 1-81 (1983).

[23] H. Pirkle and D. J. Hoover, *Top. Stereochem.*, **13**, 362 (1982).

[24] G. M. Sheldrick, SHELXS-86, Program for the Solution of Crystal Structures, University of Göttingen, Germany, 1986.

[25] G. M. Sheldrick, SHELX-76, Program for Crystal Structure Determination, University of Cambridge, England, 1976.

[26] W. D. S. Motherwell and W. Clegg, PLUTO, Program for Plotting Molecular and Crystal Structures, University of Cambridge, England, 1978.

[27] J. Fraenkel, Thesis, University of Aachen, Germany, 1965.