First Reactions of 2,2'-Bisindolyls with Electrophilic Azo Compounds and Diethyl Mesoxalate

Ulf Pindur* and Mung-Hwa Kim

Institut für Pharmazie im Fachbereich Chemie und Pharmazie der Universität Mainz, Saarstraße 21, D-6500 Mainz 1, F.R.G.

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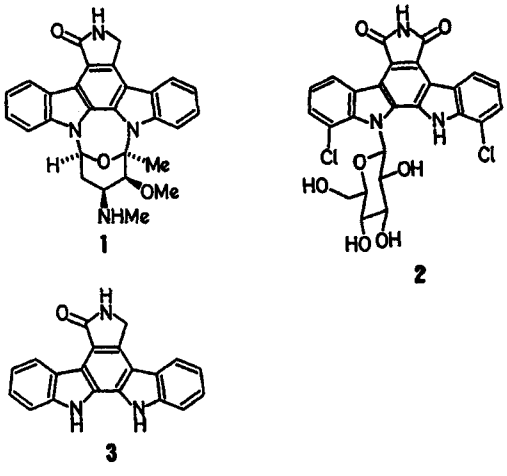
Conformations and some electronic properties of the 2,2'-bisindolyls **6** were calculated for the prediction of probable *Diels-Alder* reactivity, in analogy to previous work on 2-vinylindoles. First reactions with dienophiles revealed that compounds **6** did not participate in [4 + 2]cycloadditions but rather underwent simple electrophilic substitutions at the enamine function with, above all, some heterodienophiles.

Erste Reaktionen von 2,2'-Bisindolylen mit elektrophilen Azoverbindungen und Diethylmesoxalat

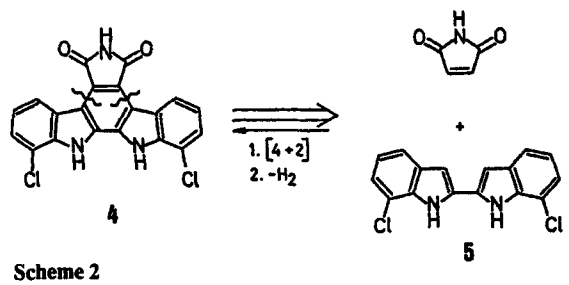
Zur Vorhersage möglicher *Diels-Alder*-Reaktionen an 2,2'-Bisindolylen **6** werden Berechnungen zur Konformation und über elektronische Eigenschaften durchgeführt. Die erstmals durchgeführten Reaktionen dieser mit 2-Vinylindolen verwandten Systeme **6** mit Dienophilen zeigen allerdings, daß keine [4 + 2]Cycloadditionen eintreten. An der Enamin-Struktur von **6** erfolgen in erster Linie einfache elektrophile Substitutionen.

The indolo[2,3-*a*]carbazole alkaloids, as exemplified by the hypotensive antibiotics staurosporine (**1**) and rebeccamycin (**2**), constitute a structurally rare class of natural products[1]. The interest in such compounds has been increased by the discovery that staurosporine (**1**) and related natural products, together with their common aglycone **3**, are potent inhibitors of protein kinase C. It is, therefore, not surprising that several approaches to the indolocarbazole ring system have been developed[1-4].



Scheme 1

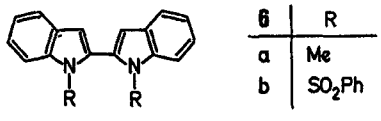
On the basis of a simple retrosynthetic analysis, the rebeccamycin aglycone **4** should be directly accessible by way of a dehydrogenative *Diels-Alder* reaction starting from the readily available 2,2'-bisindolyl **5** (Scheme 2).



Scheme 2

With this possibility in mind, we now report on the first reactions of the 2,2'-bisindolyls **6a** and **6b** with various dienophiles. In general, compounds of types **5** and **6** are also of interest as potential laser dyes[5]. These compounds contain a 2,3-diaminobutadiene moiety incorporated in two coupled indole systems. Hence, they formally possess a 2-vinylindole unit and would be expected to take part in *Diels-Alder* reactions[6].

The 2,2'-bisindolyls **6a** and **6b** were prepared in 20 and 30% yields, respectively, according to a known procedure[7] comprising lithiation and copper-induced redox coupling of the appropriate *N*-substituted indoles.



6	R
a	Me
b	SO_2Ph

Scheme 3

Conformational analysis by rotation about the central σ-bond als well as MMX molecular mechanics calculations[8] revealed two energy minimum conformations for each of the compounds **6a** and **6b** in which the indole planes are twisted with respect to each other (Fig. 1). Moreover, the fully coplanar *s-cis*-conformation required for optimal *Diels-Alder* reactivity is prohibited by *van der Waals* interactions and dipole-dipole repulsions of the more or less bulky *N*-substituents. The bis-sulfonyl derivative **6b** in the synclinal (sc) conformation is more twisted than the synclinal conformation of **6a**. According to the calculated steric energy values, the (-ac)- and (-sc)-conformations of **6b** are energetically favoured over the (+sc)- and (-ac)-conformations of **6a** in the vacuum state. These calculations additionally revealed that, of the compounds **6**, the *N,N'*-bis-methyl derivative **6a** should be able to participate in a *Diels-Alder* reaction whereas, in the case of **6b**, a *Diels-Alder* reaction in a concerted step should be extremely difficult or even impossible for steric reasons.

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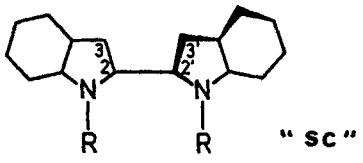
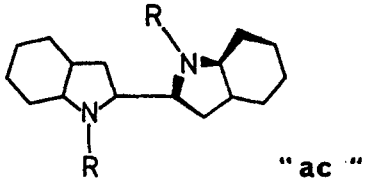
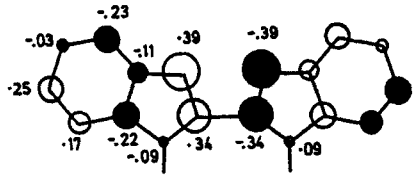


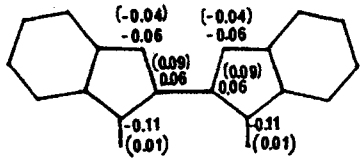


	Torsion angle N,C2,C2',N'	E_{steric} (kcal·mol^{-1})
(+sc) **6a**	52.5°	51.1
(−ac) **6a**	−138.2°	53.0
(−ac) **6b**	−94.0°	47.5
(−sc) **6b**	−60.3°	49.0

Fig. 1: Local conformations of **6a** and **6b** according to molecular mechanics calculations[8]. The *Klyne-Prelog* notation has been used (sc = synclinal, ac = anticlinal).



E_{HOMO} = -9.80 eV



Charge

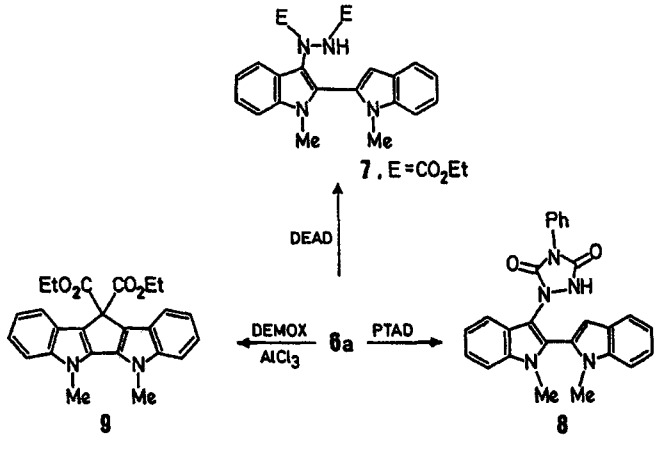
Fig. 2: HOMO[9] and π-charges (enamine structure) of **6a**[9]. π-Charges of **6b** are given in parentheses. E_{HOMO} of **6b** = -10.01 eV. 'sc'-conformations of **6a** and **6b** were calculated throughout.

On the ^{1}H- or ^{13}C-NMR time scales, however, compounds **6a** and **6b** exhibit a time-averaged C_s symmetry, showing that rapid conformational exchange is taking place in solutions of both compounds. Furthermore, no preferred conformation has yet been detected by NMR analysis (e.g. by ^{1}H,^{1}H-NOE experiments).

As the next step, we performed π-SCF-MO[9] and π-charge calculations[9] on **6a** and **6b** for an analysis of the electronic structure with respect to the prediction of a [4_πs + 2_πs]cycloaddition. In both cases, the HOMO energies appear to be sufficiently high (Fig. 2) for **6a** and **6b** to participate, like the 2-vinylindoles[6], in a HOMO(*diene*)-LUMO(*dienophile*)-controlled *Diels-Alder* process. In addition, the signs of the coefficients (eigen values) predict a symmetry-allowed interaction of the frontier orbitals; this is in full agreement with previous MNDO calculations on the parent 2-vinylindole[10]. The calculated π-charges[9] at the enamine functions of **6** mirror the charge distributions of the respective *N*-methyl- and *N*-phenylsulfonylindoles (Fig. 2). Thus, the 3,3'-positions of compounds **6a** and **6b** should be attacked preferentially by electrophiles in a charge-controlled process.

The question now arises of how these theoretical considerations correlate with the experimental results obtained from reactions of **6** with dienophiles. In spite of numerous variations of the reaction conditions, **6b** did not react with carbo- or heterodienophiles of differing reactivities even in the presence of a catalyst, *e.g.* no reaction with *N*-phenylmaleimide in the presence of $EtAlCl_2$. On the other hand, the apparently more reactive 2,2'-bisindolyl **6a** only reacted with some heterodienophiles and then only in a simple electrophilic substitution step at the enamine moiety; *Diels-Alder* reactions have not yet been observed.

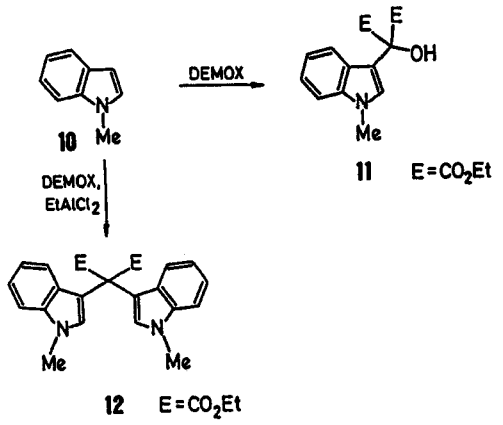
Accordingly, **6a** reacted with diethyl azodicarboxylate (DEAD) and with the highly reactive 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) to furnish the bisindolyl-hydrazine derivative **7** and the urazole **8**, respectively (Scheme 4). Diethyl mesoxalate reacted with **6a** only in the presence of a *Lewis* acid catalyst to form the pentacyclic product **9** directly (Scheme 4).



Schema 4

We have similary investigated the reactivity of *N*-methyl- and *N*-phenylsulfonylindoles towards a series of general dienophiles. This experimental screening process revealed that only *N*-methylindole (**10**) is able to react with diethyl mesoxalate in an electrophilic substitution step (Scheme 5) to furnish the diethyl α-hydroxy-α-indolylmalonate **11** in the absence of a *Lewis* acid and the diethyl bis(indolyl)malonate **12** in the presence of $EtAlCl_2$ (Scheme 5).

In summary, the present results have clearly demonstrated that 2,2'-bisindolyls, in general, are not able to participate as 4π-electron systems in *Diels-Alder* reactions. Steric and electronic factors are the reason for this lack of enophilic



Schema 5

reactivity in [4 + 2]-cycloadditions. Hence, the attainment of a coplanar *s-cis*-conformation for **6** is sterically suppressed; this suppression is especially strong for **6b** and can also be demonstrated for the NH parent compound by observations of *Büchi-Dreiding* models. Inspite of suitable HOMOs for *Diels-Alder* reactions of **6a** and **6b**, the loss of resonance energy on formation of a [4 + 2] transition state involving two indole 10π-heterocyclic systems should considerably increase the activation energy; this is in complete contrast to *Diels-Alder* reactions of "normal" 2-vinylindoles[6].

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Experimental Part

Melting points: Büchi SMP-20 capillary m.p. apparatus, uncorrected.- CNH-microanalysis: Carlo Erba Strumentazione model 1106 apparatus.- ^{1}H-NMR spectra: Bruker WM 400 (400 MHz) (δ scale, tetramethylsilane as internal standard).- ^{13}C-NMR spectra: Bruker WM 400 (100.6 MHz) (δ scale, tetramethylsilane as external standard). The ^{13}C-NMR spectra were analysed using J-modulated spin echo experiments (APT technique).- EI-mass spectra: Varian MAT 7.- Flash chromatography (FC): column capacity 200 ml, Merck silica gel 60 (0.040-0.063 mm). Highly pure and strictly anhydrous solvents were used throughout and all reactions were performed under argon.

2,2'-Bis(1-methyl-1H-indolyl) (**6a**) *and*
2,2'-Bis(1-benzenesulfonyl-1H-indolyl) (**6b**)

Compounds **6a** and **6b** were prepared according to ref.[7] in yields of 20 and 30%, respectively. The physical data were in complete agreement with those cited[7].

Diethyl1-[1-Methyl-2-(1-methylindol-2-yl)-indol-3-yl]-hydrazine-1,2-dicarboxylate (**7**)

2,2'-Bisindolyl (**6a**: 0.520 g, 2 mmol) was dissolved in 30 ml of toluene and 20 ml of CH_2Cl_2 and diethyl azodicarboxylate (0.383 g, 2.2 mmol) was added slowly at room temp. The mixture was then heated at 80°C for 4 h and subsequently concentrated under vacuum. The residue was separated by FC [petrol ether (40-60°C)/ethyl acetate, 7/3]. Yield 0.765 g (88%).- M.p. 160°C [petrol ether (40-60°C)].- EI-MS (70 eV): m/z (%) = 435 [(M+1)$^+$, 31], 434 (M$^+$, 100).- ^{1}H-NMR (CD_2Cl_2): δ (ppm) = 1.21 (m, 6H, 2 x CH_2CH_3), 3.58 (s, 3H, N-CH_3), 3.59 (s, 3H, N-CH_3), 4.07 (m, 2H, 1 x CH_2CH_3), 4.08 (m, 2H, 1 x CH_2CH_3), 6.70 (s, 1H, indole 3'-H), 6.84 (s, 1H, NH), 7.21 (mc, 2H, indole 6-H and 6'-H), 7.32 (mc, 2H, indole 5-H and 5'-H), 7.43 (d, ^{3}J = 8.3 Hz, 2H, indole 7-H and 7'-H), 7.68 (d, ^{3}J = 7.9 Hz, 1H, indole 4-H and 4'-H), 7.89 (d, ^{3}J = 8 Hz, indole 4'-H or 4-H).- $C_{24}H_{26}N_4O_4$ (434.5) Calcd. C 66.3 H 6.03 N 12.9 Found C 66.5 H 5.99 N 12.8.

3-(3,5-Dioxo-4-phenyl-[1,2,4]triazolidin-1-yl)-1-methyl-2-(1-methylindol-2-yl)indole (**8**)

2,2'-Bisindolyl (**6a**; 0.520 g, 2 mmol) was dissolved in 20 ml of toluene + 20 ml of CH_2Cl_2 and 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD; 0.385 g, 2.2 mmol) was added in small portions at room temp. The mixture was heated under reflux for 7 h at 110°C whereupon a colourless precipitate formed. The precipitate was separated by filtration and purified by FC (petrol ether/ethyl acetate, 1/1). Yield 0.420 g (48%).- M.p. 242°C (petrol ether).- EI-MS (70 eV): m/z (%) = 435 (M$^+$, 100), 274 (77).- ^{1}H-NMR (CD_2Cl_2): δ (ppm) = 3.85 (s, 3H, N-CH_3), 3.63 (s, 3H, N-CH_3), 6.78 (s, 1H, 3'-H), 7.14-7.50 (m, 11 H, aromatic H), 7.63 (2 x d, ^{3}J = 7.8 Hz, 2H, 4-H and 4'-H), 8.48 (s, 1H, NH).- ^{13}C-NMR (CD_2Cl_2): δ (ppm) = 31.13 (N-CH_3), 31.24 (N-CH_3), 106.62 (C-3'), 110.30 and 110.83 (C-7 and C-7'), 112.63 (C-3), 118.36 and 120.48 (C-4 and C-4'), 121-41 and 121.63 (C-5 and C-5'), 123.17 and 124.01 (C-6 and C-6'), 123.80 (C-2'), 126.40 (phenyl C-2/C-6), 127.74 and 128.04 (C-3a and C-3a'), 128.69 (phenyl C-4), 129.38 (phenyl C-3/C-5), 131.65 (C-2'), 131.87 (phenyl C-1), 136.61 and 131.87 (C-7a and C-7a'), 152.65 (C=O), 153.76 (C=O).- $C_{26}H_{21}N_5O_2$ (435.5) Calcd. C 71.7 H 4.86 N 16.1 Found C 71.5 H 4.9 N 15.9.

Diethyl5,6-Dimethyl-5H,6H-cyclopentano[2,1-b:3,4-b] diindole-11,11-dicarboxylate (**9**)

$AlCl_3$ (0.270 g, 2.00 mmol) and diethyl mesoxalate (0.348 g, 2.00 mmol) were dissolved in 25 ml of toluene and the solution was stirred for 20 min at room temp. 2,2'-Bisindolyl (**6a**; 0.400 g, 1.54 mmol) dissolved in 20 ml of CH_2Cl_2 was added and the resultant mixture was heated at 100°C for 4 h. It was then poured into water (50 ml), the org. layer was separated, and the aqueous phase was washed with two 30-ml portions of CH_2Cl_2. The combined org. phases were dried (Na_2SO_4), concentrated, and the residue recrystallized from CH_2Cl_2/diethyl ether. Yield 0.147 g (23%).- M.p. 286°C (CH_2Cl_2/diethyl ether).- EI-MS (70 eV): m/z (%) = 416 (M$^+$, 80), 343 (100).- ^{1}H-NMR (CD_2Cl_2): δ (ppm) = 1.30 (t, ^{3}J = 7.0 Hz, 6H, 2 x CH_2CH_3), 4.06 (s, 6H, 2 x N-CH_3), 4.25 (q, ^{3}J = 7.0 Hz, 4H, 2 x CH_2CH_3), 7.20 (m, 4H, 2-H, 3-H, 8-H, 9-H), 7.38 (m, 2H, 4-H, 7-H), 7.74 (m, 2H, 1-H, 10-H).- ^{13}C-NMR (CD_2Cl_2): δ (ppm) = 14.39 (2 x CH_2CH_3), 33.42 (2 x N-CH_3), 60.21 (C-11), 62.49 (2 x CH_2CH_3), 110.60 (C-4 and C-7), 119.58 (C-1 and C-10), 121.11 (C-2 and C-9), 121.59 (C-3 and C-8), 122.20 (C-10b and C-11a), 124.85 (C-10a and C-11b), 138.97 (C-5a and C-5b), 141.31 (C-4a and C-6a), 169.08 (2 x C=O).- $C_{25}H_{24}N_2O_4$ (416.5) Calcd. C 72.1 H 5.81 N 6.7 Found C 72.1 H 5.69 N 6.4.

Diethyl α-Hydroxy-α-(1-methylindol-3-yl)-malonate (**11**)

N-Methylindole (**10**; 0.262 g, 2 mmol) and diethyl mesoxalate (0.385 g, 2.2 mmol), dissolved in 30 ml of toluene, were heated under reflux for 3 h. The resultant mixture was concentrated under vacuum and the residue was recrystallized from CH_2Cl_2/petrol ether. Yield 0.598 g (98%).- M.p. 78°C (CH_2Cl_2/diethyl ether).- EI-MS (70 eV): m/z (%) = 305 (M$^+$, 12), 159 (100).- ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1.15 (t, ^{3}J = 7.0 Hz, 6H, 2 x CH_2CH_3), 3.63 (s, 3H, N-CH_3), 4.18 (m, 4H, 2 x CH_2CH_3), 4.21 (s, 1H, OH), 6.97 (dd, ^{3}J = 8.0 Hz, 1H, indole 6-H), 7.08 (dd, ^{3}J = 7.9 Hz and 9.0 Hz, 1H, indole 5-H), 7.16 (d, ^{3}J = 8.2 Hz, 1H, indole 7-H), 7.23 (s, 1H, indole 2-H), 7.57 (d, ^{3}J = 7.9 Hz, 1H, indole 4-H).- $C_{16}H_{19}NO_5$ (305.3) Calcd. C 62.9 H 6.27 N 4.6 Found C 62.8 H 6.21 N 4.4.

Diethyl α,α-Bis(1-methylindol-3-yl)-malonate (**12**)

A 25% solution of $EtAlCl_2$ in toluene (1.8 ml, 3.3 mmol) was slowly added from a syringe to a solution of diethyl mesoxalate (0.570 g, 3.3 mmol) in 30 ml of dichloromethane during 20 min at room temp. The indole **10** (0.393 g, 3.3 mmol), dissolved in 20 ml of CH_2Cl_2, was then added and the mixture stirred for 5 h at room temp. The resultant mixture was concentrated under vacuum and the residue was purified by FC (petrol ether/ethyl acetate, 9/1). Yield 0.470 g (68%).- M.p. 172°C (petrol ether).- EI-MS (70 eV): m/z (%) = 418 (M^+, 21), 345 (100).- ^{1}H-NMR (CD_2Cl_2): δ (ppm) = 1.22 (t, ^3J = 7.2 Hz, 6H, 2 x CH_2CH_3), 3.75 (s, 6H, 2 x N-CH_3), 4.23 (q, ^3J = 7.2 Hz, 4H, 2 x CH_2CH_3), 6.96 (dd, ^3J = 7.9 Hz and 8.0 Hz, 2H, 2 x indole 6-H), 7.17 (dd, ^3J = 8.0 Hz, 2H, 2 x indole 5-H), 7.26 (s, 2H, 2 x indole 2-H), 7.32 (d, ^3J = 8.2 Hz, 2H, 2 x indole 7-H), 7.37 (d, ^3J = 8.2 Hz, 2H, 2 x indole 4-H).- ^{13}C-NMR (CD_2Cl_2): δ (ppm) = 14.23 (2 x CH_2CH_3), 33.16 (2 x N-CH_3), 60.01 (quaternary C of malonate), 62.02 (2 x CH_2CH_3), 109.62 (2 x indole C-7), 111.76 (2 x indole C-3), 119.23 (2 x indole C-4), 121.73 (2 x indole C-5 and 2 x indole C-6), 127.20 (2 x indole C-3a), 130.03 (2 x indole C-2), 137.61 (2 x indole C-7a), 170.39 (2 x C=O).- $C_{25}H_{26}N_2O_4$ (418.5) Calcd. C 71.8 H 6.26 N 6.7 Found C 71.6 H 6.37 N 6.6.

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