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On the [4 + 2] Cycloaddition Approach to Indolo[2,3-*a*]carbazoles

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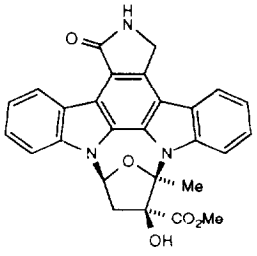
Abstract: 2,2'-Biindolyl **9** reacts with electron-deficient dienophiles at 100–110 °C to give low to moderate yields of Michael addition and formal [4 + 2] cycloaddition products, with the former predominant; the products derived from **9** and 2-(phenylsulphinyl)maleimides **14** and **15** undergo *in situ* elimination of benzenesulphenic acid, leading to 2,2'-biindolyl-substituted maleimides which can be efficiently photocyclised into indolo[2,3-*a*]carbazoles.

Dedicated with respect and affection to Professor Hans Suschitzky on the occasion of his 80th birthday.

The indolo[2,3-*a*]carbazole nucleus is incorporated in a family of natural products, typified by K-252a **1**,[1,2] staurosporine **2**[3] and its congeners **3**[4] and **4**,[5] arcyriaflavin A **5**,[6] tjipanazole J **6**,[7] and the aglycone **7** of rebeccamycin.[8] Significant biological activity has been found in this series, K-252a **1** being a potent inhibitor of protein kinase C,[9] which has been implicated in the regulation of various cellular processes including growth, differentiation, and tumour promotion.[10] Staurosporine **2** exhibits hypotensive and antimicrobial activity[11] and inhibits tyrosine-specific protein kinases at the nanomolar level;[12] 11-hydroxystaurosporine **3** also inhibits protein kinase C and is strongly cytotoxic;[4] rebeccamycin shows interesting antitumour activity.[13]



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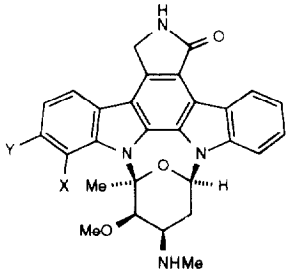
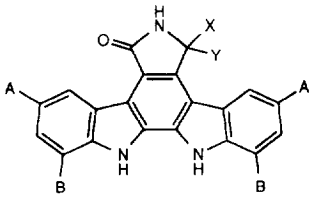
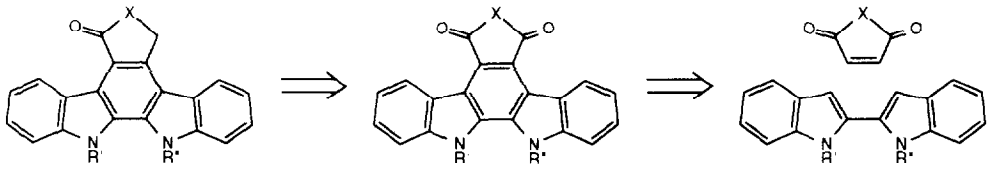


	X	Y
2	H	H
3	OH	H
4	H	OMe



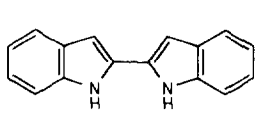
	X	Y	A	B
5	-O-		H	H
6	H	OH	Cl	H
7	-O-		H	Cl

Various approaches to this type of compound have been devised,[14,15] but we were attracted by the brevity of a [4 + 2] cycloaddition route (Scheme 1), which prior to our study[16] had received scant attention.[17-18]



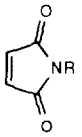
SCHEME 1

Initially we studied the cycloadditions of 2,2'-biindolyl **9**, which can be prepared in 80% yield *via* Madelung cyclisation of *N*,*N*'-bis(*o*-tolyl)oxamide **8** using potassium *t*-butoxide,[19,20] to the dienophiles **10**–**15** (Table 1). The biindolyl **9** reacted with the acetylenedicarboxylate **10** in acetonitrile at 110 °C to give the Michael addition product **16** as a single isomer in 17% yield. The same product was obtained in 37% yield by Somei and Kodama,[18] who carried out the reaction at 140 °C in the presence of 10% Pd-C. Reacting **9** with *N*-phenylmaleimide **11** in acetonitrile gave a fully aromatised product **17**[21] and the Michael adduct **18** in low yields, with no evidence for the formation of the formal [4 + 2] cycloadduct **19**. Changing the solvent to diethyl oxalate led to improved yields of both **17** and **18**. The reason for this is obscure, but we speculated that in the presence of diethyl oxalate the reaction might be enhanced *via* transient *N*-acylation of the biindolyl **9**, or through H-bonding. However, attempts to probe the latter idea using more powerful H-bond acceptor solvents (entries 5 and 6) were fruitless. *N*-Methylmaleimide **12** reacted with biindolyl **9** to give a low yield of the AT2433-B aglycone **20**,[22] the major product **21** (45%) once again being the result of Michael addition.

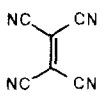


9

10



11 R = Ph
12 R = Me



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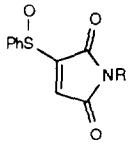
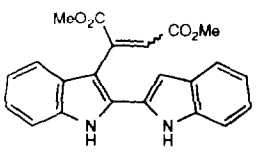


14 R = Ph
15 R = Me

Since it was possible that the putative cycloadducts (*e.g.* **19**) might be forming reversibly, we turned our attention to the use of dienophiles bearing substituents prone to thermal elimination *in situ*. The combination of 2,2'-biindolyl **9** and tetracyanoethene **13** offered a cycloadduct **22** which could eliminate HCN to give the dinitrile **23**, but in the event the reaction gave a complex mixture of products. The phenylsulphinylmaleimides **14** and **15**, prepared as shown in Scheme 2,[23] were more effective, reacting rapidly with **9** to give modest yields of the respective addition-elimination products **28** and **29**. Irradiation of these (Pyrex, medium pressure Hg lamp, ethanol) induced cyclisation to **17** (80%) and **20** (90%) respectively, making these indolocarbazoles available from *o*-toluidine in four steps.



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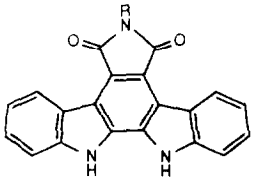

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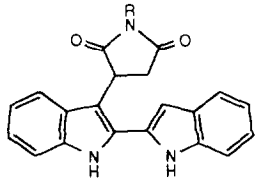
20 R = Me

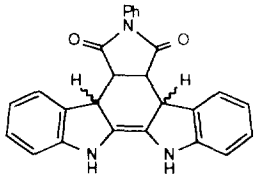


18 R = Ph
21 R = Me

TABLE 1 REACTIONS OF 2,2'-BIINDOLYLS WITH ELECTRON-DEFICIENT DIENOPHILES

Entry	*Substrate*	*Dienophile (equiv.)*	*Solvent*	*Temp. (°C)*	*Time (d)*	*Products (Yield %)**
1	**9**	**10** (5)	MeCN	110	8	**16** (17)
2	**9**	**11** (5)	MeCN	100	9	**17** (5), **18** (5)
3	**9**	**11** (10)	$(CO_2Et)_2$	105	7	**17** (10), **18** (58)
4	**9**	**11** (10)	$(CO_2Et)_2$	50–105†	9	**17** (24)‡
5	**9**	**11** (5)	Me_2SO	100	5	–¶
6	**9**	**11** (5)	$(Me_2N)_3PO$	100	5	–¶
7	**9**	**12** (5)	$(CO_2Et)_2$	100	7	**20** (7), **21** (45)
8	**9**	**13** (10)	$(CO_2Et)_2$	100	7	–¶
9	**9**	**14** (1)	MeCN	80	0.2	**28** (36)
10	**9**	**15** (1)	MeCN	80	0.2	**29** (34)
11	**30**	**11** (5)	MeCN	120	7	–¶
12	**30**	**14** (1.5)	$(CO_2Et)_2$	100	0.2	**35** (43)

* After isolation by evaporation and chromatography.
† The tube was maintained at 50 °C for 2 days, 70 °C for 5 days, and 105 °C for 2 days.
‡ No attempt was made to isolate any other product(s).
¶ A complex mixture of products was indicated by t.l.c.



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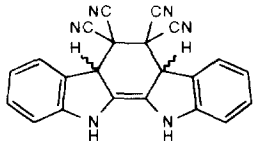

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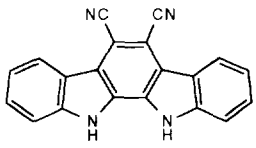

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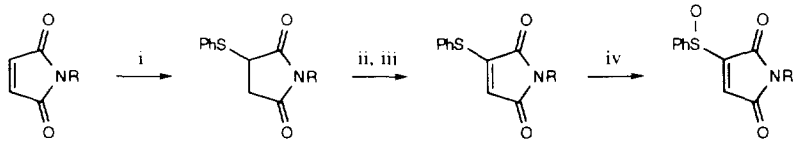


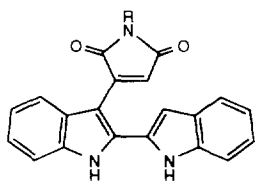
11 R = Ph
12 R = Me

24 R = Ph
25 R = Me

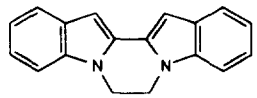
26 R = Ph
27 R = Me

14 R = Ph
15 R = Me

SCHEME 2 *Reagents:* i, PhSH, Et_3N, benzene (Ph, 89%; Me, 42%); ii, *N*-chlorosuccinimide, CCl_4, reflux (70, 93%); iii, 120–150 °C (85, 98%); iv, *m*-$ClC_6H_4CO_2H$, CH_2Cl_2 (94, 81%).



28 R = Ph
29 R = Me



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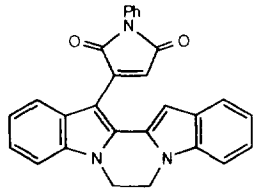
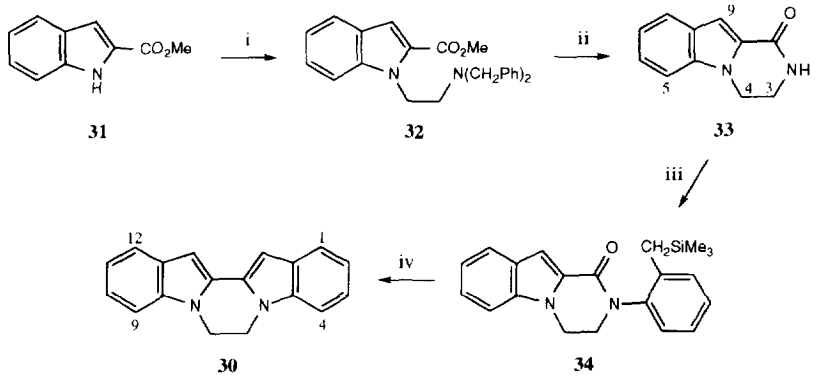


35

We also studied the behaviour of the conformationally locked biindolyl **30**, obtained *via* the reaction sequence shown in Scheme 3. Alkylation of the ester **31** using *N*-(2-chloroethyl)dibenzylamine gave **32**, which upon hydrogenation in the presence of Pearlman's catalyst afforded the fused lactam **33**. Heating **33** with 2-(trimethylsilylmethyl)bromobenzene[24] and copper(I) oxide gave a modest yield of the *N*-aryl system **34**, which was cyclised under Bartoli's conditions[25] to obtain the bridged 2,2-biindolyl **30**, m.p. 270–272 °C.



SCHEME 3 *Reagents:* i, NaH, $(PhCH_2)_2NCH_2CH_2Cl.HCl$, DMF, reflux, 3 h (79%); ii, 10 atm. H_2, 10% $Pd(OH)_2/C$, EtOH-H_2O, 72 h (63%); iii, 2-$Me_3SiCH_2C_6H_4Br$, Cu_2O, *N,N*-dimethylacetamide, reflux, 48 h (28%); iv, Li 2,2,6,6-tetramethylpiperidide, THF-hexane, −10 to +20 °C (64%).

When the bridged biindolyl **30** was heated with *N*-phenylmaleimide **11** in acetonitrile, a mixture was formed but no 1:1 adducts were identified. However, the phenylsulphinylmaleimide **14** reacted cleanly and rapidly with **30** at 100 °C in diethyl oxalate to give what was believed to be the addition-elimination product **35** (43%). The preference of **30** for reaction *via* Michael addition, when it appears to be ideally arranged for Diels-Alder cycloaddition, inclines us to the view that the formal [4 + 2] cycloadducts which are obtained from the reactions of 2,2'-biindolyl **9** with dienophiles are the result of stepwise, rather than concerted, processes.

EXPERIMENTAL

All compounds are racemic. Melting points were determined using an Electrothermal apparatus and are uncorrected. Unless otherwise stated, i.r. spectra were obtained from the residues of evaporated ^1H n.m.r. samples on sodium chloride discs and were recorded on a Perkin-Elmer 1710FT instrument. ^1H N.m.r. spectra were measured for solutions in deuteriochloroform unless otherwise indicated, with tetramethylsilane as the internal standard, on a Bruker AC300 (300 MHz) instrument. Mass spectra were recorded on a Kratos MS30 instrument with 70 eV electron impact ionisation unless otherwise stated. Data for most of the peaks of intensity <20% of that of the base peak are omitted.

Starting materials and solvents were routinely purified by conventional techniques.[26] Organic solutions were dried over anhydrous magnesium sulphate or anhydrous sodium sulphate and concentrated by rotary evaporation. Analytical thin layer chromatography (t.l.c.) was carried out on Camlab Polygram SIL G/UV_{254} plates. Preparative column (flash) chromatography[27] was carried out using 60H silica gel (Merck 9385). Compositions of solvent mixtures are quoted as ratios of volume. Unless otherwise indicated, 'petroleum' refers to light petroleum, b.p. 60–80 °C. 'Ether' refers to diethyl ether.

N,N'-bis(*o-Tolyl*)*oxamide* **8**

Method A: A solution of *o*-toluidine (11.89 g, 0.11 mol) in toluene (190 ml) was treated with acetonitrile (10

ml) and oxalic acid dihydrate (7.0 g, 0.056 moles). The mixture was then heated under reflux over 4Å self-indicating molecular sieves (BDH) at 150 °C in a Soxhlet extractor under an argon atmosphere. The sieves were replaced after 2 d and the mixture heated under reflux for a further two days at 150 °C. The solvent was then removed from the reaction mixture *in vacuo*. The reddish residue was dissolved in ethyl acetate and allowed to crystallise. The crystals were collected, washed with petroleum ether and dried *in vacuo*, yielding *N,N'*-bis(*o*-tolyl)oxamide **8** (4.8 g, 32%), m.p. 215 °C; ν_{max} 3286, 1665, 1522, 1456, 753 and 711 cm^{-1}; δ 9.35 (2 H, br s, NH), 8.07 (2 H, d, *J* 7.8 Hz, 6,6'-H), 7.30–7.20 (4 H, m, 4,4',5,5'-H), 7.13 (2 H, dt, *J* 1.0, 7.5 Hz, 3,3'-H) and 2.37 (6 H, s, ArMe); m/z (ammonia CI) 286 (M + NH_4^+, 40%), 269 (M + H, 100), 108 (50) and 107 (27).

Method B: To *p*-dioxane (20 ml) under an argon atmosphere was added oxalyl chloride (6.1 ml, 8.88 g, 70 mmol) and the solution was cooled in an ice bath. Into the solution was added slowly over 30 minutes a solution of *o*-toluidine (15 g, 140 mmol) and triethylamine (19.5 ml, 14.16 g, 140 mmol) in *p*-dioxane (30 ml). The mixture was then allowed to stir for 2 h and then warm up to room temperature. To this mixture water (100 ml) was cautiously added. The resultant slurry was then dissolved in hot ethyl acetate (100 ml) and the water layer was removed. The amide **8** (16.84 g, 90%) crystallised out and was collected as in method A. The product was identical to that obtained by method A.

2,2'-Biindolyl **9**

This was prepared from the amide **8** using Bergman's procedure.[19]

Attempted Cycloadditions (Table 1)

Entry 1: 2,2'-Biindolyl **9** (0.11 g, 0.47 mmol) was dissolved in anhydrous acetonitrile (25 ml) in a dry thick-walled test tube fitted with a screw cap. To this mixture was added dimethyl acetylenedicarboxylate (DMAD) (0.07 g, 0.49 mmol). The test tube was then securely capped and left to stand in an oil bath at 110 °C. The reaction mixture was monitored by t.l.c. over 8 days, with extra portions of DMAD (total 0.36 g, 2.5 mmol) being added periodically. T.l.c. (petroleum ether-ethyl acetate 4:1) showed 6 spots. The resultant mixture was then separated by flash chromatography (elution with petroleum ether-ethyl acetate 8:1), giving 460 fractions. Fractions 131–300 were identified as *dimethyl 2-(2,2'-biindol-3-yl)but-2-ene-1,4-dioate* **16**, obtained as brown residue (0.03 g, 17%) (*M*$^+$, 374.1253. $C_{22}H_{14}N_2O_4$ requires 374.1266); ν_{max} 3403, 2925, 1739, 1704 and 1608 cm^{-1}; δ 9.27 (1 H, br s, NH), 8.02 (1 H, s, NH), 7.68 (1 H, d, *J* 7.9 Hz, 4'-H), 7.53–7.40 (3 H, m, ArH), 7.34 (1 H, s, 3"-H), 7.30–7.20 (3 H, m, ArH), 7.10 (1 H, t, *J* 7.4 Hz, 5"-H), 5.99 (1 H, s, 3-H), 3.87 (3 H, s, OMe) and 3.28 (3 H, s, OMe); m/z 374 (M$^+$, 62%), 315 (51), 283 (79), 256 (75), 255 (100) and 128 (22).

Entry 2: 2,2'-Biindolyl **9** (0.232 g, 1.0 mmol), *N*-phenylmaleimide **11** (0.866 g, 5.0 mmol) and anhydrous acetonitrile (10 ml) were placed in a dry screw-capped thick-walled test tube. The tube was then heated in an oil bath at *ca.* 100 °C with monitoring by t.l.c. The reaction was stopped after 9 d, at which point several products and some starting material were present. The mixture was evaporated on to silica gel and resolved by flash chromatography (202 fractions), eluting with petroleum ether-ethyl acetate (8:1, gradient to 1:1). The column was finally washed with HPLC grade acetonitrile. Fractions 29–60 were identified as 2,2'-biindolyl **9**. Fractions 61–86 contained the Michael adduct *2-(2,2'-biindol-3-yl)-N-phenylsuccinimide* **18** (20 mg, 5%), m.p. >230 °C (dec.) (*M*$^+$, 405.1475. $C_{26}H_{19}N_3O_2$ requires 405.1477); ν_{max} 3368, 2926, 1702, 1385, 1182 and 744 cm^{-1}; δ 10.7 (1 H, br s, NH), 10.6 (1 H, br s, NH), 7.64 (1 H, d, *J* 7.8 Hz, 4'-H), 7.6–7.4 (8 H, m, ArH), 7.25–7.08 (4 H, m, ArH), 6.92 (1 H, s, 3"-H), 5.01 (1 H, dd, *J* 5.3, 10.0 Hz, 2-H), 3.57 (1 H, dd, *J* 10.0, 18.3 Hz, 3-H) and 3.22 (1 H, dd, *J* 5.3, 18.3 Hz, 3-H); m/z 405 (M$^+$, 41%), 285 (29), 284 (100), 258 (21), 257 (46), 256 (62), 255 (30), 128 (50), 119 (22), 93 (40), 91 (32) and 89 (16). Fractions 127–202 contained a yellow fluorescent material identified as *6-phenylindolo[2,3-a]pyrrolo[3,4-c]carbazole-5,7-(6H)dione* **17** (20 mg, 5%), ν_{max} 3350, 1753, 1702, 1687, 1366 and 743 cm^{-1}; δ (d_6-DMSO) 11.9 (2 H, br s, NH), 9.01 (2 H, d, *J* 7.8 Hz, 4,8-H), 7.83 (2 H, d, *J* 8.1 Hz, 1,11-H), 7.6–7.4 (7 H, m, 2,10-H and Ph), 7.36 (2 H, t, *J* 7.8 Hz, 3,9-H), 7.45 (1H, t, J 8 Hz) and 7.36 (2H, t, J 8 Hz); m/z 402 (6%), 401 (M$^+$, 5), 356 (15), 103 (18), 91 (28), 77 (18) and 65 (25). The accurate mass of the molecular ion could not be measured. An identical sample of **17** was obtained using Bergman's hydrazone cyclisation method.[15]

Entry 3: A mixture of the biindolyl **9** (0.5 g, 2.16 mmol) and *N*-phenylmaleimide **11** (3.73 g, 22 mmol) in diethyl oxalate (20 ml) was heated in a screw-capped thick-walled test tube at 105 °C for 7 d and the solvent was then removed *in vacuo*. The residue was dissolved in ethyl acetate, evaporated onto silica gel, and then subjected to flash chromatography. The column was eluted with 100 ml petroleum ether, then with 100 ml of petroleum ether - ethyl acetate (19:1), and then using a solvent gradient in 10% increments of ethyl acetate up to 100% ethyl acetate. Fractions 60–78 were found to contain the Michael adduct **18** (0.51 g, 58%) and fractions 80–98 yielded the product **17** (0.09 g, 10%). Both materials were identical to those described in entry 2.

Entry 4: The procedure described in entry 3 was repeated. The temperature was varied as follows; 2 d at 50 °C, 5 d at 70 °C, and 2 d at 105 °C. The solvent was removed *in vacuo*, and flash chromatography yielded the product **17** (0.21 g, 24%).

Entry 7: A mixture of *N*-methylmaleimide **12** (0.6 g, 5.4 mmol), diethyl oxalate (10 ml) and 2,2-biindolyl **9** (250 mg, 1.08 mmol) under Ar was stirred in a sealed tube for 7 d at 100 °C. The solvent was then removed under reduced pressure and the products isolated by flash chromatography as described for entry 3. The first product isolated was the Michael adduct *2-(2,2'-biindol-3-yl)*-N-*methylsuccinimide* **21** (170 mg, 45%), a light brown solid (M^+, 313.1332. $C_{21}H_{17}N_3O_2$ requires 343.1321); ν_{max} 3353, 1691, 1438, 1384, 1331, 1282, 1248, 1119, 794, 743 and 694 cm^{-1}; δ (d_6-acetone) 10.67 (1 H, br s, NH), 10.63 (1 H, br s, NH), 7.63 (1 H, d, *J* 7.8 Hz, 4'-H), 7.50 (1 H, d, *J* 8.1 Hz, 4"-H or 7"-H), 7.49 (1 H, d, *J* 8.1 Hz, 7"-H or 4"-H), 7.27 (1 H, d, *J* 8.0 Hz, 7'-H), 7.19 (2 H, t, J 7.3 Hz, 6',6"-H), 7.09 (1 H, t, *J* 7.5 Hz, 5'-H), 7.05 (1 H, t, *J* 7.4 Hz, 5"-H), 6.88 (1 H, s, 3"-H), 4.80 (1 H, dd, *J* 5.0, 9.7 Hz, 2-H), 3.37 (1 H, dd, *J* 9.7, 18.2 Hz, 3-H), 3.07 (3 H, s, NMe) and 3.04 (1 H, dd, *J* 5.0, 18.2 Hz, 3-H); m/z 343 (M^+, 55%), 284 (20), 258 (50), 257 (55), 256 (45), 255 (20), 129 (60), 128 (100) and 114 (21). The second product isolated was *6-methylindolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7-(6*H*)dione* **20** (25 mg, 7%) (M^+ 339.1001. $C_{21}H_{13}N_3O_2$ requires 339.1008); ν_{max} 3350, 2918, 1755, 1682, 1376, 1216, 1131, 1033 and 1010 cm^{-1}; δ (d_6-DMSO) 11.8 (2 H, br s, NH), 8.99 (2 H, d, *J* 7.9 Hz, 4,8-H), 7.80 (2 H, d, *J* 8.1 Hz, 1,11-H), 7.56 (2 H, apparent t, *J* 7.2 Hz, 2,10-H), 7.35 (2 H, apparent t, *J* 7.4 Hz, 3,9-H) and 3.17 (3 H, s, NMe); m/z 339 (M^+, 85%), 254 (40), 170 (20) and 127 (80).

Entry 9: A mixture of *N*-Phenyl-2-(phenylsulphinyl)maleimide **14** (130 mg, 0.43 mmol) and 2,2-biindolyl **9** (100 mg, 0.43 mmol) in acetonitrile (5 ml) under Ar in a sealed tube was heated for 5 h. The solvent was removed *in vacuo* and residue was absorbed onto Florisil (60–100 mesh). This mixture was then placed on top of a flash chromatography column containing Florisil (–200 mesh). Elution with petroleum - ethyl acetate (8:1) gave *2-(2,2'-biindol-3-yl)*-N-*phenylmaleimide* **28** (63 mg, 36%) as a brown powder (M^+, 403.1329. $C_{26}H_{17}O_2N_3$ requires 403.1321); ν_{max} 3369, 1704, 1598, 1500, 1447, 1383, 1338, 1150, 742 and 690 cm^{-1}; δ ($CDCl_3$ + d_6-DMSO) 11.29 (1 H, s, NH), 10.62 (1 H, s, NH), 7.21 (1 H, d, *J ca.* 8 Hz, 4'-H), 7.04 (1 H, d, *J* 7.8 Hz, 4"-H), 7.0–6.75 (7 H, m, 7',7"-H, Ph), 6.7–6.5 (4 H, m, 5',5",6',6"-H), 6.29 (1 H, br s, 3"-H) and 6.16 (1 H, s, 3-H); m/z 403 (M^+, 15%), 283 (21), 256 (29), 255 (33), 176 (20), 91 (33), 83 (20), 77 (45) and 73 (100).

Entry 10: The procedure used for entry 9 was repeated using *N*-methyl-2-(phenylsulphinyl)maleimide **15**. The quantities of materials used were as follows: **15** (328 mg, 1.39 mmol), 2,2'-biindolyl **9** (324 mg, 1.39 mmol) and acetonitrile (20 ml). The reaction mixture was allowed to stir under an argon atmosphere tor 5 h at 80 °C and the product **29** was isolated by the technique described for **28**. *2-(2,2'-Biindol-3-yl)*-N-*methylmaleimide* **29** (160 mg, 34%) was isolated as a light tan powder (M^+, 341.1172. $C_{21}H_{15}N_3O_2$ requires 341.1164); ν_{max} 3369, 3058, 2924, 1699, 1606, 1440, 1385, 1339 and 744 cm^{-1}; δ 9.64 (1 H, s, NH), 8.77 (1 H, s, NH), 7.65 (1 H, d, *J* 7.8 Hz, 4'-H), 7.60 (1 H, d, *J* 8.0 Hz, 4"-H), 7.37 (1 H, d, *J* 7.8 Hz, 7'-H), 7.36 (1 H, d, *J* 8.0, 7"-H), 7.3–7.05 (4 H, m, 5',5",6',6"-H), 6.72 (1 H, t, *J ca.* 1 Hz, 3"-H), 6.67 (1 H, s, 3-H) and 3.13 (3 H, s, Me); m/z 341 (M^+, 32%), 283 (36), 256 (50), 255 (50), 128 (100) and 114 (30).

Entry 12: *N*-Phenyl-2-(phenylsulphinyl)maleimide **14** (0.138 g, 0.5 mmol) was dissolved in diethyl oxalate (5 ml) with the bridged compound **30** (0.08 g, 0.3 mmol), the tube was then sealed and allowed to stir for 3 h

under an argon atmosphere. The solvent was removed by vacuum distillation and after isolation by flash chromatography, eluting with ethyl acetate - petroleum (1:4), the product **35** (0.057 g, 43%) was obtained as a hard red resin; ν_{max} 2925, 1713, 1598, 1502, 1447, 1386, 1329, 1266, 1199, 1152, 1114, 1083, 740 and 690 cm^{-1}; δ 7.67 (1 H, d, *J* 7.9 Hz, 12-H), 7.60 (1 H, d, *J* 8.0 Hz, 1-H), 7.45–7.20 (7 H, m, 4,9-H and Ph), 7.14 (1 H, dt, *J* 0.8, 7.9 Hz, 10-H), 7.05–6.92 (3 H, m, 2,3,11-H), 6.84 (1 H, narrow m, 14-H), 6.60 (1 H, s, COC*H*=C), 4.65 (2 H, t, *J* 6 Hz, NCH_2) and 4.5 (2 H, t, *J* 6 Hz, NCH_2); m/z 429 (M^+, 1%), 364 (1.5), 142 (16), 125 (17), 110 (38), 109 (37); the HRMS of this compound could not be determined due to the low intensity of the molecular ion peak.

N-*Phenyl-2-(phenylthio)succinimide* **24**

A solution of *N*-phenylmaleimide **11** (3 g, 17.3 mmol) in benzene (30 ml) containing triethylamine (0.17 ml, 0.12 g, 1.2 mmol) was treated dropwise over 30 min with a solution of thiophenol (1.8 ml, 1.9 g, 17.5 mmol) in benzene (30 ml). A white precipitate was observed within 5 min. The reaction mixture was diluted with benzene (20 ml) and allowed to stir overnight. The solvent was removed *in vacuo* and the residue crystallised from petroleum - ethyl acetate (5:1) to give the *title compound* **24** (4.5 g, 89%) as off-white needles, m.p. 140–142 °C (*M*$^+$, 283.0680. $C_{16}H_{13}NO_2S$ requires 283.0667); ν_{max} 1778, 1708, 1498, 1393, 1199, 1158, 1069, 942, 778, 765, 747, 737 and 695 cm^{-1}; δ 7.60–7.55 (2 H, m, 2',6'-H), 7.45–7.30 (6 H, m, ArH), 7.05–7.00 (2 H, m, ArH), 4.13 (1 H, dd, *J* 3.8, 9.4 Hz, 2-H), 3.32 (1 H, dd, *J* 9.4, 19.0 Hz, 3-H) and 2.89 (1 H, dd, *J* 3.8, 19.0 Hz, 3-H); m/z 283 (M^+, 57%), 136 (100), 135 (41), 109 (20) and 91 (33).

N-*Methyl-2-(phenylthio)succinimide* **25**

To a solution of *N*-methylmaleimide **12** (5 g, 45.0 mmol) in benzene (100 ml) containing triethylamine (0.7 ml, 0.5 g, 5 mmol) was added dropwise a solution of thiophenol (4.6 ml, 4.95 g, 95 mmol) in benzene (25 ml). The reaction was followed by t.l.c. and when all the thiophenol had been consumed the solution was washed with water and the solvent removed *in vacuo*. Crystallisation of the residue from ethyl acetate - petroleum (40–60°) (1:4) gave the *title compound* **25** (4.17 g, 42%) as white crystals, m.p. 64–65 °C (*M*$^+$, 221.0507. $C_{11}H_{11}O_2NS$ requires 221.0510); ν_{max} 1779, 1699, 1436, 1382, 1282, 1118, 747 and 692 cm^{-1}; δ 7.49–7.43 (2 H, m, 2',6'-H), 7.35–7.25 (3 H, m, 3',4',5'-H), 4.00 (1 H, dd, *J* 3.9, 9.0 Hz, 2-H), 3.11 (1 H, dd, *J* 9.0, 18.8 Hz, 3-H), 2.86 (3 H, s, Me) and 2.67 (1 H, dd, *J* 3.9, 18.8 Hz, 3-H); m/z (ammonia CI) 239 ($M + NH_4^+$, 100%).

N-*Phenyl-2-(phenylthio)maleimide* **26**

A mixture of the imide **24** (3.0 g, 10.6 mmol) and *N*-chlorosuccinimide (NCS) (1.46 g, 10.9 mmol) in tetrachloromethane (50 ml) under Ar was heated under reflux for 12 h. An extra portion of NCS (0.1 g, 0.75 mmol) was added after 11 h to complete the reaction. The reaction mixture was cooled in an ice bath and then filtered. The solvent was removed *in vacuo*, giving a yellow powder which was crystallised from ethyl acetate - petroleum ether (40–60°) to give 2-chloro-*N*-phenyl-2-(phenylthio)succinimide (2.36 g, 70%) as fine yellow crystals which decomposed above 120 °C; ν_{max} 1729, 1500, 1379, 1196, 750 and 692 cm^{-1}; δ 7.68–7.64 (2 H, m, 2',6'-H), 7.55–7.35 (6 H, m, ArH), 7.25–7.20 (2 H, m, ArH), 3.49 (1 H, d, *J* 18.9 Hz, 3-H) and 3.45 (1 H, d, *J* 18.9 Hz, 3-H). The chloro compound (2.04 g, 6.4 mmol) was heated at 110–150 °C for 10 min. The evolution of white fumes occurred at 120 °C. The reaction mixture was then allowed to cool to a yellow cake (1.81 g). This solid was dissolved in hot ethyl acetate (25 ml) and diluted with petroleum ether (40–60°; 20 ml). Upon cooling, the *title compound* **26** (1.54 g, 85%) was formed as yellow needles, m.p. 150–152 °C (*M*$^+$, 299.0863. $C_{16}H_{11}NO_2S$ requires 299.0854); ν_{max} 1702, 1562, 1397, 1147, 1059, 831, 695, 667 and 624 cm^{-1}; δ 7.61–7.55 (2 H, m, 2',6'-H), 7.50–7.40 (5 H, m, ArH), 7.35–7.30 (2 H, m, ArH) and 5.77 (1 H, s, 3-H); m/z (ammonia CI) 299 ($M + NH_4^+$, 100%).

N-*Methyl-2-(phenylthio)maleimide* **27**

A mixture of the imide **25** (1.89 g, 8.6 mol) and NCS (1.15 g, 8.6 mmol) in tetrachloromethane (75 ml) under Ar was heated under reflux for 48 h. Extra portions of NCS (4 x 0.5 g, 4 x 3.7 mmol) were added at intervals to complete the reaction. The reaction mixture was cooled in an ice bath and then filtered. The solvent was removed *in vacuo*, and the residue purified by flash chromatography over Florisil (60–100 mesh), eluting with petroleum ether (40–60°) - ethyl acetate (10:1), which afforded 2-chloro-*N*-methyl-2-(phenylthio)succinimide

(2.04 g, 93%) as a yellow oil; ν_{max} 1770, 1704, 1562, 1474, 1441, 1386, 1258, 1116, 1024, 972, 856, 821, 753, 704, 692, and 658 cm^{-1}; δ 7.63–7.28 (5 H, m, ArH), 3.30 (1 H, d, *J* 18.9 Hz, 3-H), 3.24 (1 H, d, *J* 18.9 Hz, 3-H) and 3.00 (3 H, s, Me). The chloro compound (1.85 g, 7.24 mmol) was heated at 120–160 °C for 15 min, during which the evolution of white fumes occurred. The residue gave the *title compound* **27** (1.55 g, 98%) as a red oil (*M*$^+$, 219.0345. $C_{11}H_9NO_2S$ requires 219.0354); ν_{max} 1770, 1702, 1561, 1441, 1386, 1258, 972, 821, 752 and 691 cm^{-1}; δ 7.55–7.50 (2 H, m, 2',6'-H), 7.45–7.40 (3 H, m, 3',4',5'-H), 5.60 (1 H, s, 3-H) and 2.97 (3 H, s, Me); m/z (ammonia CI) 237 (M + NH_4^+, 100%), 219 (M^+, 6), 155 (10) and 134 (20).

N-*Phenyl-2-(phenylsulphinyl)maleimide* **14**

To a stirred solution of the maleimide **26** (0.15 g, 0.5 mmol) in dichloromethane (10 ml) under Ar at −10 °C was added over 30 min a solution of 3-chloroperoxybenzoic acid (mCPBA) (65% w/w; 141 mg, 0.5 mmol) in dichloromethane (10 ml). The reaction was stirred overnight and monitored by t.l.c. A further portion of mCPBA (100 mg, 0.36 mmol) was added after 14 h, and after 18 h the reaction mixture was washed with 10% aq. sodium sulphite followed by 10% aq. sodium hydrogen carbonate, and then dried and evaporated *in vacuo*, affording the *title compound* **14** (0.149 g, 94%) as a light cream paste (*M* + H, 298.0507. $C_{16}H_{12}NO_3S$ requires 298.0538); ν_{max} 1718, 1502, 1384, 1142, 1087, 1057, 751, 707, 690 and 601 cm^{-1}; δ 7.9–7.8 (2 H, m, 2',6'-H), 7.6–7.5 (3 H, m, 3',4',5'-H), 7.45–7.25 (5 H, m, Ph) and 7.22 (1 H, s, 3-H); m/z (ammonia CI) 315 (M + NH_4^+, 100%) and 298 (M + H, 39).

N-*Methyl-2-(phenylsulphinyl)maleimide* **15**

To a stirred solution of the maleimide **27** (400 mg, 1.83 mmol) in dichloromethane (40 ml) under Ar at −10 °C was added over 30 min a solution of mCPBA (65% w/w; 485 mg, 1.83 mmol) in dichloromethane (20 ml). The reaction was stirred and monitored by t.l.c. A further portion of mCPBA (100 mg, 0.36 mmol) was added after 4 h, and after 6 h the reaction mixture was washed with 10% aq. sodium sulphite followed by 10% aq. sodium hydrogen carbonate, and then dried and evaporated *in vacuo*, affording the *title compound* **15** (350 mg, 81%) as a yellow solid, m.p. 65 °C (*M* + NH_4, 253.0640. $C_{11}H_{13}N_2O_3S$ requires 253.0647); ν_{max} 1708, 1445, 1383, 1160, 1083, 1055, 751 and 686 cm^{-1}; δ 7.85–7.75 (2 H, m, 2',6'-H), 7.55–7.50 (3 H, m, 3',4',5'-H), 7.13 (1 H, s, 3-H) and 2.93 (3 H, s, Me); m/z (ammonia CI) 253 (M + NH_4^+, 100%).

Photocyclisation of **28**

A solution of the substituted maleimide **28** (100 mg, 0.25 mmol) in ethanol (75 ml) in a Pyrex immersion well photochemical reactor was simultaneously purged with argon and irradiated using a 125-watt medium pressure mercury lamp in a water jacket. The reaction was monitored by t.l.c. and after 5 h the reaction was complete. The solvent was then removed yielding **17** (80 mg, 80%) as an orange powder, whose spectroscopic properties were identical to the product obtained previously.

Photocyclisation of **29**

A solution of the substituted maleimide **29** (100 mg, 0.29 mmol) in ethanol (75 ml) was irradiated as described for **28**. The reaction was monitored by t.l.c. and after 3 h the reaction was complete. The solvent was then removed yielding **20** (90 mg, 90%) as an orange powder, whose spectroscopic properties were identical to the product obtained previously.

Methyl indole-2-carboxylate **31**

A solution of indole-2-carboxylic acid (25 g, 155 mmol) in methanol (820 ml) under nitrogen was treated with acetyl chloride (41 ml) and the mixture was heated under reflux for 4 h. The solvent was removed *in vacuo* and the crude product was dissolved in hot ethyl acetate. When the solution was cooled the ester **31** (15.8 g, 58%) was obtained as colourless needles, m.p. 147–150 °C [lit.[28] 151 °C (MeOH)]; ν_{max} 3334 and 1697 cm^{-1}; δ (d_6-DMSO) 11.9 (1 H, br s, NH), 7.60 (1 H, d, 4-H), 7.50 (1 H, d, 7-H), 7.25 (1 H, t, *J ca.* 8 Hz, 6-H), 7.15 (1 H, s, 3-H), 7.05 (1 H, t, *J ca.* 8 Hz, 5-H) and 3.80 (3 H, s, OMe).

Methyl N-*(2-dibenzylaminoethyl)indole-2-carboxylate* **32**

A solution of methyl indole-2-carboxylate **31** (1 g, 5.7 mmol) in dry DMF (50 ml) under argon was treated

with *N*-(2-chloroethyl)dibenzylamine hydrochloride (1.69 g, 5.7 mmol). To this solution was carefully added sodium hydride (80% oil dispersion; 0.375 g, 12.5 mmol). The mixture was then heated under reflux for 3 h, and then poured into water. The product was extracted into ethyl acetate, and the extract dried and evaporated, affording the *title compound* **32** (1.8 g, 79%) as a colourless oil that solidified below 5 °C (*M*$^+$, 398.1993. $C_{26}H_{26}N_2O_2$ requires 398.1994); ν_{max} 1713, 1462, 1250, 1202, 747 and 699 cm^{-1}; δ 7.7 (1 H, d, *J* 8 Hz, 4-H), 7.5–7.1 (13 H, m, ArH and 3-H), 7.0 (1 H, d, *J ca.* 8 Hz, 7-H), 4.75 (2 H, t, *J ca.* 6 Hz, 1'-CH_2), 3.8 (3 H, s, OMe), 3.7 (4 H, s, 2 x PhCH_2) and 2.9 (2 H, t, *J ca.* 6 Hz, 2'-CH_2); m/z 398 (M$^+$, 3%), 210 (70) and 91 (100). When this reaction was carried out on larger scales, flash chromatography was used to remove residual DMF.

3,4-Dihydropyrazino[1,2-a]indol-1(2H)-one **33**

A solution of the ester **32** (26.36 g, 66 mmol) in ethanol (475 ml) and water (25 ml) was treated with palladium dihydroxide (20% on charcoal) (3 g) and the mixture was stirred under an atmosphere of hydrogen (10 atm) for 3 d. The reaction mixture was then heated, filtered while hot to remove the catalyst, and then heated under reflux for 30 min. On cooling the *title compound* **33** (7.82 g, 63%) was deposited as small needles, m.p. 240–242 °C (*M*$^+$, 186.0797. $C_{11}H_{10}N_2O$ requires 186.0793); ν_{max} 1655, 1418, 1345 and 732 cm^{-1}; δ (d_4-acetic acid + d_6-acetone) 9.6 (1 H, s, NH), 7.75 (1 H, t, 9-H), 7.50 (1 H, d, 6-H), 7.40 (1 H, t, *J ca.* 8 Hz, 7-H), 7.32 (1 H, s, 10-H), 7.20 (1 H, t, *J ca.* 8 Hz, 8-H), 4.40 (2 H, t, 4-H_2) and 3.90 (2 H, t, 3-H_2); m/z 186 (M$^+$, 90%), 157 (25), 129 (100), 128 (20), 102 (24) and 89 (20).

3,4-Dihydro-2-(2-trimethylsilylmethylphenyl)pyrazino[1,2-a]indol-1(2H)-one **34**

A solution of the tricycle **33** (5 g, 27 mmol) and 2-trimethylsilylmethylbromobenzene[24] (8.43 g, 34.7 mmol) in dimethyl acetamide (100 ml) under argon was vigorously stirred with copper(I) oxide (19.2 g, 134 mmol) and maintained under reflux in a Woods metal bath (*ca.* 200 °C) for 48 h. The solvent was removed by distillation, and the residue was then adsorbed on to Florisil 60–100 mesh (4 g) and loaded on to a column of Florisil (–200 mesh). Elution of the column with ethyl acetate - petroleum (b.p. 40–60°) (1:4) afforded the *title compound* **34** (2.6 g, 28%) as white fluffy crystals, m.p. 194–196 °C (Found: C, 72.44; H, 6.62; N, 8.02. $C_{21}H_{24}N_2OSi$ requires 72.37; H, 6.94; N, 8.04%); ν_{max} 1651, 1544, 1425, 1346, 1244, 840, 765 and 738 cm^{-1}; δ 7.75 (1 H, d, *J* 7.9 Hz, 9-H), 7.38–7.36 (3 H, m, ArH), 7.26–7.14 (5 H, m, ArH), 4.5–4.2 (3 H, m, 3-H_2 and 4-H), 3.94–3.84 (1 H, dt, *J* 4.4, 12.4 Hz, 4-H), 2.15 (2 H, s, CH_2TMS) and 0.0 (9 H, s, $SiMe_3$); m/z (FAB), 349 (MH$^+$, 100%), 333 (32), 259 (18), 93 (25), 93 (24), 73 (67) and 72 (54).

6,7-Dihydropyrazino[1,2-a:4,3-a']diindole **30**

A solution of the tricycle **34** (420 mg, 1.21 mmol) in anhydrous THF (10 ml) was stirred under Ar and cooled with a salt/ice bath (–10 °C). The flask was fitted with an Ar-purged self-equalising dropping funnel containing a magnetic stirrer was charged with anhydrous THF (5 ml) and 2,2,6,6-tetramethylpiperidine (0.2 ml, 0.17 g, 1.2 mmol), and agitated magnetically. To this solution was added *n*-butyl lithium in *n*-hexane (1.35 M, 0.9 ml, 1.22 mmol), producing a yellow solution of lithium 2,2,6,6-tetramethylpiperidide, which was then dripped into the solution of **34** during 20 min. The solution was observed to change to a violet colour and allowed to warm to room temperature, whereupon it became a beige colour. The reaction was quenched with 10% aq. ammonium chloride (10 ml) and the products extracted into ether. The extract was dried and the solvent removed *in vacuo*. Flash chromatography of the residue, eluting with petroleum ether (40–60°) - ethyl acetate (4:1), yielded the *title compound* **30** (200 mg, 64%), m.p. 270–272 °C (Found: C, 83.48; H, 5.84; N, 10.86. $C_{18}H_{14}N_2$ requires 83.69; H, 5.46; N, 10.84%) (*M*$^+$, 258.1166. $C_{18}H_{14}N_2$ requires 258.1157); ν_{max} 2952, 1489, 1446, 1398, 1374, 1334, 1321, 1249, 843, 785, 767 and 740 cm^{-1}; δ (CF_3CO_2D) [as unsymmetrical salt?] 7.9 (1 H, dd, *J* 1.8, 7.9 Hz), 7.81 (1 H, dd, *J* 1.8, 7.1 Hz), 7.78–7.66 (4 H, m), 7.57 (1 H, d, *J* 8.8 Hz), 7.4 (1 H, t, *J* 7.1 Hz) and 4.85 (4 H, m, NCH_2), signals due to 13,14-H not visible, possibly due to deuterium exchange with solvent; m/z 258 (M+, 100%), 129 (30) and 128 (27).

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