Pergamon

Tetrahedron 55 (1999) 2363–2370

TETRAHEDRON

Synthesis of Indolo[3,2-a]pyrrolo[3,4-c]carbazole in one Step from Indole and Maleimide

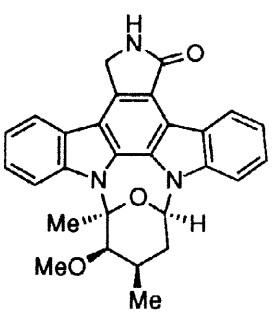
Jan Bergman*[a], Eric Desarbre[b] and Eva Koch[a]

a- Department of Chemistry, Royal Institute of Technology, SE-100 44 Stockholm, Sweden
and Department of Biosciences at Novum, SE-141 57 Huddinge, Sweden
b- Pharmacia&Upjohn, SE-751 82 Uppsala, Sweden

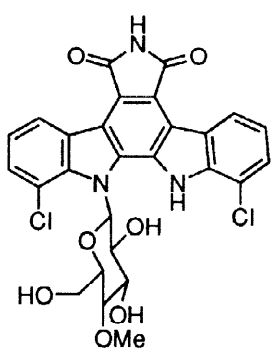
Received 11 September 1998; revised 9 December 1998; accepted 7 January 1999

Abstract: Indolo[3,2-a]pyrrolo[3,4-c]carbazole, an isomer of arcyriaflavin A, has been synthesised in a one step reaction from indole and maleimide.

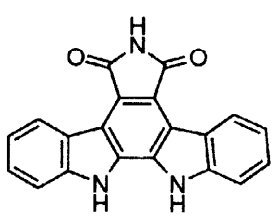
The pronounced physiological activities of the indolocarbazole alkaloids have triggered considerable synthetic efforts.[1] The active alkaloids among the sub-group indolo[2,3-a]pyrrolo[3,4-c]carbazoles include the PKC-inhibitor staurosporine **1**, which is antihypertensive[2] and inhibits platelet aggregation,[3] as well as the antitumor antibiotic rebeccamycin **2**.[4, 5] For the aglycone arcyriaflavin A **3** several syntheses have been developed[1] but surprisingly little has been done to synthesize isomeric structures such as indolo[3,2-a]pyrrolo[3,4-c]carbazole-6,8 -dione **4**[6] which now, plus a few derivatives, has been prepared in a one step reaction starting from indole **7** and the maleimides **8a-d**.



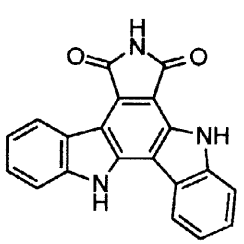
1



2



3

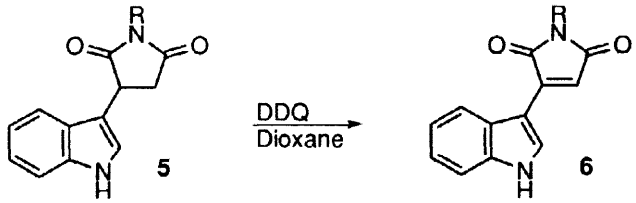


4

0040-4020/99/$ - see front matter
PII: S0040-4020(99)00029-0

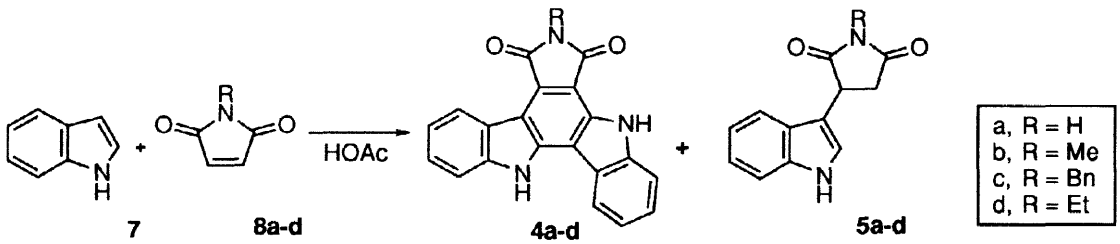
Although a few scattered examples of acid induced additions of indoles to maleimides yielding 3-(indolyl)-3-succinimide **5** had been published from 1962 and onwards, it was not until 1997, when Macor[7] published a study of this Michael type addition, that the generality of this reaction was recognised. The conditions used were refluxing glacial acetic acid, with maleimide in excess, which afforded Michael adducts such as **5** in high yields. In a related study, also published in 1997, Bogza[8] obtained similar synthetic results using $ZnCl_2$ catalysis in a nitromethane medium at 101°C.

In connection with a study of cycloaddition in indolic systems, indolylmaleimides of the type **6** were needed and it was found that the experiments of Macor as well as those of Bogza could be nicely reproduced and the indolosuccinimides obtained could, as expected[9] be smoothly dehydrogenated by 2, 3-dichloro-5, 6-dicyanobenzoquinone (DDQ) in dioxane.



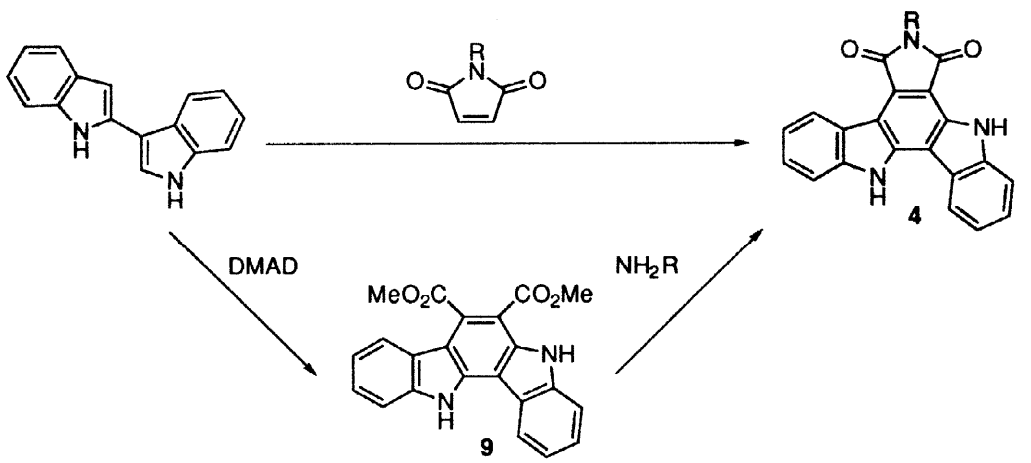
However, when the ratio of indole to maleimide was increased another product with the composition $C_{27}H_{17}N_3O_2$, not observed by the previous workers, eventually became predominant.

Thus when two equivalents of indole **7** and one equivalent of *e.g.* N-benzylmaleimide **8c**, were reacted in glacial acetic acid at 100°C, a yellow precipitate was collected after 72 h. Its structure **4c** was assigned based on the following data. The mass spectrum featured the molecular ion (m/z=415) as the base peak. The ^{1}H-NMR spectrum exhibited two different indolic NH signals and the ^{13}C-NMR data featured two carbonyl signals at 168.4 and 169.2. The previously[7] described Michael adduct **5c** was present in the mother liquor (**Scheme 1** and **Table 1**).



Scheme 1

The structure of the indolo[3,2-a]pyrrolo[3,4-c]carbazoles **4a-d** were finally confirmed by two independent[10] syntheses, both starting with 2,3-biindolyl[11] as outlined in Scheme 2.



Scheme 2

Compound **4a** (R=H) has previously been obtained as a by-product by Prabhakar[6] in a multi-step procedure involving alkylation of 3-thioloindole with 3,4-dichloromaleimide followed by desulfurization with $PdCl_2$ which gave arcyriaflavin **3** (10 % yield) and the rearranged isomer **4a** in 1 % yield. The NMR spectrum of a sample prepared in this fashion corresponded exactly to that of our product.

Further studies showed that the ratio between the indolocarbazole **4** and the Michael adduct **5** was dependent on the temperature and could also be regulated by the ratio between indole and maleimide (see **Table 1**).

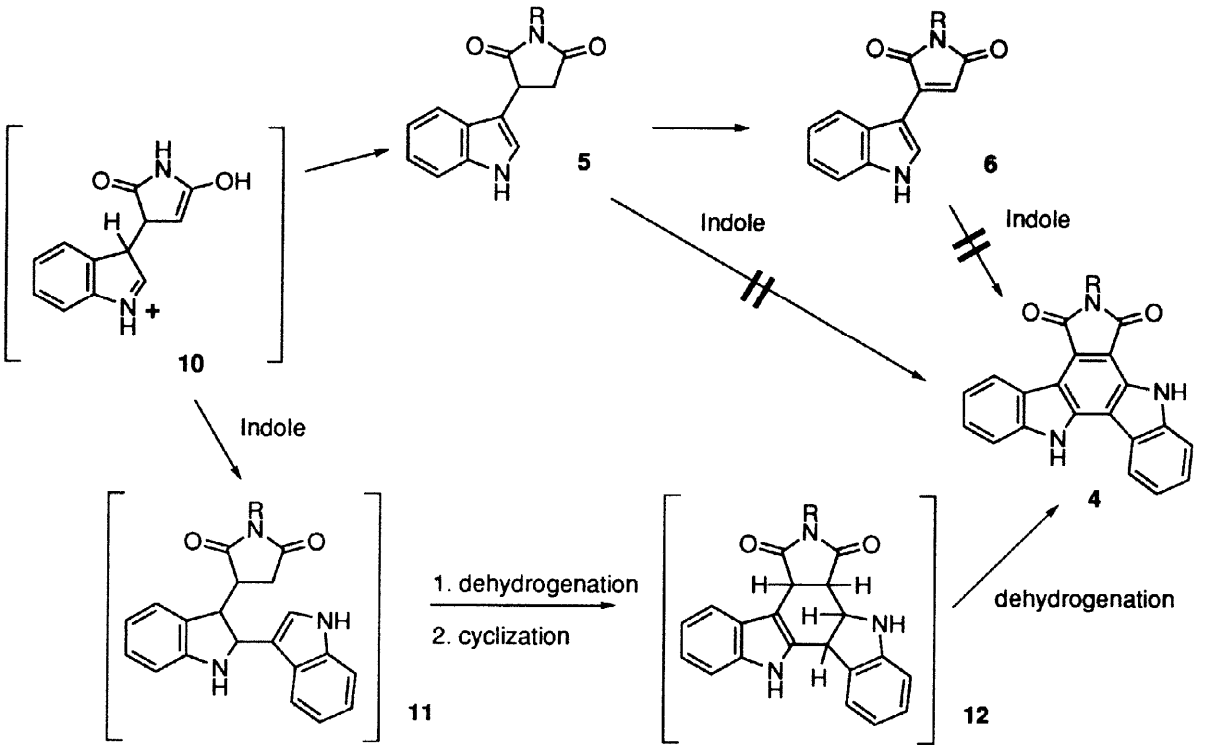
Indole (mmol)	Maleimide **8b** (mmol)	Temperature	Indolocarbazole **4b** (ratio)	Michael adduct **5b** (ratio)
1	3	90°C	1	9
1	3	117°C	1	43
2	1	90°C	1	2
2	1	117°C	1	13
3	1	100°C	1	1.6
3	1	95°C	1	0.9

Table 1

The ratios were taken from the NMR spectra of the crude reaction mixtures. The entries 1-4 illustrate the effect of the temperature on the outcome of the reactions. However at 90°C the reaction became inconveniently slow and an optimum, both in yield and ratio of indolocarbazole, was found at 95°C.

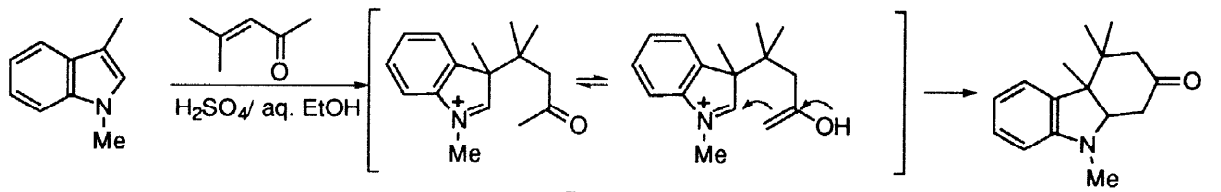
Scheme 3 is a rationalisation of the observed chemistry, wherein the two products are formed in competing reactions from a common intermediate, **10**, which can either tautomerize to the Michael adduct or react with a second molecule of indole to form the crucial 2,3-bond yielding eventually the hypothetical

intermediate **12**. The Michael adduct **5b** failed to react with indole under acidic conditions (HOAc, 100°C) indicating that the reaction is under kinetic control, i.e. the Michael adduct does not equilibrate and it is not an intermediate. The dehydrogenated maleimide **6** also failed to give the indolocarbazole **4**.



Scheme 3

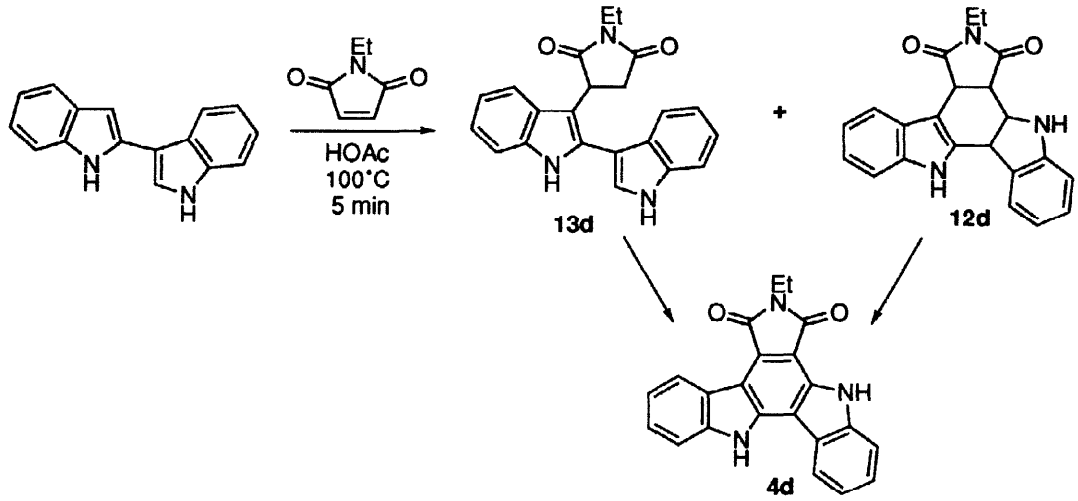
Charged intermediates analogous to **10** have been discussed previously in the literature. Thus when *e.g.* 1,3-dimethylindole is reacted with mesityloxide in the presence of sulfuric acid[12] the initial Michael reaction is followed by an intramolecular attack on the generated indolium cation (see **Scheme 4**)



Scheme 4

It is clear that the dehydrogenation of the presumed intermediate **12** is not effected by the maleimide as neither succinimide nor any other reasonable hydrogenated species thereof were found in the reaction mixture and the mass balance did not show any lack of maleimide. Here it might be added that it is known that maleimide can yield adducts (with e.g. 1,5-dihydroflavin) that subsequently disintegrate to succinimide and dehydrogenated products[13].

Attempts to isolate any of the postulated hydrogenated intermediates failed but in the much faster reaction of 2,3-biindolyl with maleimide, however, the tetrahydroindolocarbazole, **12d**, as well as the Michael adduct, **13d**, could easily be obtained. (see **Scheme 2** and **Scheme 5**)



Scheme 5

The fact that both **12d** and **13d** yielded the dehydrogenated indolocarbazole **4d** (100°C, HOAc) is in harmony with our presumed reaction mechanism in scheme 3.

EXPERIMENTAL SECTION

NMR spectra were recorded on a Bruker DPX 300 (300 MHz) spectrometer or on a Bruker AM400 (400 MHz). IR spectra were recorded with a Perkin Elmer 1600 FT-IR. Mass analyses were performed on a Micromass Platform II spectrometer and Finnigan MATSSQ710, both with a direct inlet at 70 eV. Elemental analyses were performed by H. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany. Melting points were taken on a Büchi Melting Point B-545 apparatus and are uncorrected. All solvents were purified by distillation or were HPLC grade. Chromatography was performed on Merck Silica Gel 60.

5H,7H,13H-Indolo[3,2-a]pyrrolo[3,4-c]carbazole-6,8-dione (4a)

Indole (0.705 g, 6 mmol) and maleimide (0.194 g, 2 mmol) were heated in glacial acetic acid (15 ml) at 95°C for 64 hours. The orange precipitate was collected and washed with diisopropyl ether to give 0.145 g (22%) of **4a** as a orange solid. An additional small amount (1-2%) was present in the mother liquor.
mp: sublimes around 375°C. IR (KBr, cm^{-1}): 3342, 3302, 3240, 1740, 1716, 1690, 1254, 1038, 748. NMR (DMSO-d_6): δ 7.30-7.42 (2H, m), 7.51-7.53 (2H, m), 7.70-7.77 (2H, m) 8.76 (1H, d, J = 7.8 Hz), 8.93 (1H, d, J =8.9 Hz), 11.00 (1H, s, broad), 12.12 (1H, s), 12.28 (1H, s). ^{13}C-NMR (DMSO-d_6): δ 107.5 (s), 110.9 (s), 111.6(d), 111.9 (s), 112.3 (d), 120.1 (d) 120.2 (s), 120.4 (d), 121.3 (s), 121.8 (d), 123.8 (d), 124.7 (s), 126.3 (d), 126.3 (s), 132.5 (s), 138.3 (s), 141.1 (s), 141.1 (s), 170.3 (s), 171.1 (s).

MS: m/z= 325 (100%).

7-Methyl-5H,13H-indolo[3,2-a]pyrrolo[3,4-c]-6,8 -dione (4b)

Indole (0.705 g, 6 mmol) and N-methylmaleimide (0.225 g, 2 mmol) were heated in glacial acetic acid (15 ml) at 95°C for 96 h. The reaction mixture was filtered and the yellow crystals thus obtainedwere washed with diisopropyl ether to give 0.120 g (18%) of **4b**. The filtrate was evaporated and purified by column chromatography on silica gel with 20% EtOAc in hexane as eluant to give 0.026g of **4b** and a final yield of 21%.

mp: sublimes around 350°C. IR (KBr, cm^{-1}) : 3429, 3359, 1732, 1682, 1380, 1254, 752, 731. ^{1}H-NMR (DMSO-d6): δ 3.08 (3H, s), 7.27 (1H, t, J = 6.5 Hz) 7.37 (1H, t, J = 6.0 Hz), 7.45-7.53 (2H, m), 7.67 (1H, d, J= 7.7 Hz), 7.73 (1H, d, J = 6.0 Hz), 8.71 (1H, d, J = 7.3 Hz), 8.84 (1H, d, J = 7.7 Hz). ^{13}C-NMR (DMSO-d6):δ 23.4 (q), 106.1 (s), 110.5 (s), 11.3 (d), 111.9(s), 112.0 (d), 119.9 (d), 120.1 (d), 120.1(s), 121.0 (s), 121.7 (d), 123.5 (d), 123.5 (s), 126.0 (d), 126.1 (d), 132.3 (s), 138.0 (s), 141.0 (s), 141.0 (s), 168.7 (s), 169.4 (s). MS: m/z=339 (100%). Anal. Calculated for $C_{21}H_{13}N_3O_2$:C, 74.33; H, 3.86; N, 12.38. Found: C, 74.19; H, 3.74; N, 12.30.

7-Benzyl- 5H,13H-indolo[3,2-a]pyrrolo[3,4-c]-6,8-dione (4c)

Indole (0.702g, 6 mmol) and N-benzylmaleimide (0.374g, 2 mmol) were heated in glacial acetic acid (15 ml) at 95°C for 72h. The reaction mixture were allowed to cool and the yellow crystals formed were filtered,washed with acetic acid and dried to give 0.214g (26%) of **4c**. An additional small amount (1-2%) of **4c** was present in the mother liquor.

mp:319-320°C. IR (KBr, cm^{-1}): 3463, 3370, 1749, 1682, 1387, 1251, 726. ^{1}H-NMR (DMSO-d6): δ 4.91 (2H, s), 7.28-7.57 (10H, m), 7.75 (2H, dd), 8.78 (1H, d), 8.92 (1H, d), 12.23 (1H, s), 12.34 (1H, s). ^{13}C-NMR (DMSO-d6):δ 40.6 (t), 106.0 (s), 110.9 (s), 111.6 (d), 112.2 (d), 112.2 (s), 120.1 (s), 120.1 (d), 120.3 (d), 121.0 (s), 121.8 (d), 123.3 (s), 123.6 (d), 126.3 (d), 126.4 (d), 127.3 (d), 127.4 (d), 128.6 (d), 132.6 (s), 137.4 (s), 138.3 (s), 141.2 (2s), 168.4, (s) 169.2 (s).

MS: m/z=415 (100%). Anal. calculated for $C_{27}H_{17}N_3O_2$: C, 78.06; H, 4.12; N, 10.11. Found: C, 77.89; H, 4.18; N, 10.04.

7-Ethyl- 5H,13H-indolo[3,2-b]pyrrolo[3,4-c]-6,8-dione (4d)

Indole (0.702g, 6 mmol) and N-ethylmaleimide (0.250g, 2mmol) were heated in glacial acetic acid (15 ml) at 95°C for 72h. The reaction mixture was filtered and the yellow crystals formed were washed with acetic acid and dried to give 0.114g (17%) of **4d**. An additional small amount (1-2%) of **4d** was present in the mother liquor.

mp: sublimes around 300°C. IR (KBr, cm^{-1}): 3459.8, 3386.1, 1739.6, 1678.5, 1387.5, 1253.5, 751.2, 727.8. ^{1}H-NMR (DMSO-d6): δ 1.27 (3H, t, J = 7 Hz), 3.69 (2H, q, J = 7 Hz), 7.30 (1H, t, J = 8 Hz), 7.38 (1H, t, J = 8 Hz), 7.47-7.55 (2H, m), 7.69 (1H, d, J = 8 Hz), 7.87 (1H, d, J= 8 Hz), 8.72 (1H, d, J = 8 Hz), 8.88 (1H, d, J = 8 Hz). ^{13}C-NMR (DMSO-d6):δ 14.2 (q), 32.2 (t), 106.3 (s), 110.8 (s), 111.6 (d), 112.2 (s), 112.3 (d), 120.2 (d), 120.3 (d), 120.4,(s), 121.2 (s), 121.9 (d), 123.6 (s), 123.7 (d), 126.3 (d), 126.4 (d), 132.6 (s)138.3 (s), 141.2 (s), 141.2 (s)168.7 (s), 169.4 (s). Anal calculated for $C_{22}H_{15}N_3O_2$: C, 74.78; H, 4.28; N, 11.89. Found: C, 74.55; H, 4.30; N, 11.79.

Synthesis of 4d, the tetrahydro indolocarbazole (12d) and the Michael adduct (13 d) from

2,3-biindolyl.

2,3-Biindolyl (0.200g, 0.86 mmol) and N-ethylmaleimide (0.249g, 2 mmol) were heated in acetic acid (15 ml) at 100°C for 5 minutes. The resulting mixture was allowed to cool and then it was poured into saturated aquous $NaHCO_3$. The residue was dissolved in EtOAc and washed with water and brine. The combined EtOAc extracts were dried with $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography on silica gel using 30% EtOAc in hexane as eluant gave 0.037 g (12%) **4d**, 0.078g (25%) **12d** and 0.170g (55%) **13d** as solids.

The isomeric structure of **12d** was assigned based on the coupling between indolinic NH with the multiplet at 4.53 ppm. The coupling constants for the peak at 4.53 ppm were resolved with homo-decoupling. The NMR-experiment also showed that the small coupling J = 1 Hz at 4.53 ppm is a long-range coupling to the broad doublet at 4.43. mp: 255-256°C. ^{1}H-NMR (DMSO-d_6): δ 1.17 (3H, t, J = 7 Hz), 3.42-3.50 (3H, m), 4.34 (1H, dd, J = 8 Hz, J = 1 Hz), 4.43 (1H, d, J = 7 Hz), 4.53 (ddd, J = 7 Hz, J = 4 Hz, J = 3 Hz), 5.53 (1H, d, J = 3 Hz), 6. 46 (1H, d, J = 8 Hz) 6. 66 (1H, t, J = 7 Hz) 6.92-7.02 (3H, m), 7.27 (1H, d, J = 8 Hz) 7.62 (2H, d), 10.72 (1H, s). ^{13}C-NMR (DMSO-d_6) :δ 12.9 (q), 33.0 (t), 37.4 (d), 39.1 (d), 42.4 (d), 59.9 (d), 101.4 (s), 110.5 (d), 110.9 (d), 118.3 (d), 118.7 (d), 119.6 (d), 121.1 (d), 124.7 (d), 126.7 (s), 127.8 (d), 129.9 (s), 132.9 (s), 136.6 (s), 150.3 (s), 176.9 (s), 177.8 (s). IR (KBr, cm^{-1}): 3457, 3334, 1685, 1458, 1404, 1346, 1216, 744. No correct elemental analysis could be obtained of this compound, due to ease of dehydrogenation.

13d: mp: 142-143°C. ^{1}H-NMR (DMSO-d_6): δ 1.13 (3H, t, J = 7 Hz), 2.79 (1H, dd, J =18.2 Hz, J = 4.9 Hz), 3.22 (1H, dd, J = 18.2 Hz, J = 9.7 Hz), 3.52 (2H, q, 7 Hz), 4.40 (1H, dd, J = 9.7 Hz, J = 4.9 Hz) 6.97 (1H, t), 7.06-7.15 (3H, m), 7.18 (1H, t), 7.41 (1H, t), 7.50 (1H, d), 7.62 (1H, d), 7.77 (1H, d), 11.25 (1H, s), 11.54 (1H, s). ^{13}C-NMR (DMSO-d_6) :δ 12.8 (q), 33.2 (t), 36.0 (t), 38.7 (d), 106.6 (s), 106.7(s), 111.6(d), 111.9 (d), 117.0 (d), 119.0 (d), 119.6 (d), 119.7 (d), 120.8 (d), 121.9 (d), 125.3 (d), 126.1 (s), 126.1 (s), 132.4 (s), 136.3 (s), 136.3 (s), 176.6 (s), 178.9 (s). IR (KBr, cm^{-1}):3450-3150 (br), 1691, 1402, 1223, 1124, 743. Anal. calculated for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76. Found: C, 73.84; H, 5.44; N, 11.70.

3-(Indol-3-yl)-succinimide (5, R=H)

Indole (4.38g, 40 mmol) and maleimide (3.92, 40 mmol) in acetic acid (35 ml) were refluxed for 36h. Upon cooling, crystals of **5** (**R=H**) were obtained, 4.75g (55%) (concentration of the mother liquor gave a second crop of 1.1 g) mp:196-197°C (lit[14, 15] 197-198°C). IR (KBr, cm^{-1}): 3392, 3370, 1696, 1184, 740, 701. ^{1}H-NMR (DMSO-d_6): δ 2.78 (1H, dd, J = 18.0 Hz, J = 5.3 Hz), 3.18 (1H, dd, J = 18.0 Hz, J = 9.5 Hz), 4.33 (1H, dd, J = 9.5 Hz, J = 5.3 Hz)7.00, (1H, t, J = 7 Hz), 7.10 (1H, t, J = 7 Hz), 7.33 (1H, d, J = 2.3 Hz), 7.38 (1H, d, J = 8 Hz), 7.42 (1H, d, J = 8 Hz). ^{13}C-NMR (DMSO-d_6) :δ 37.5 (t), 39.1 (d), 11.0 (s), 111.8 (d), 118.5 (d), 118.9 (d), 121.5 (d), 123.5 (d), 126.0 (s), 136.6 (s), 178.2 (s), 180. 1 (s).

N-Methyl-3-(indol-3-yl)-maleimide (6, R=Me)

DDQ (0.346g, 1.5 mmol) dissolved in dioxane (20 ml) was slowly (1h) added to a solution of N-methyl-3-(indol-3-yl)- succinimide **5** (**R=Me**)[16] (0.348g, 1.5 mmol) in dioxane (20 ml). The reaction was left over night. DDQ-2H was filtered off and the dioxane was evaporated, yielding 0.248g (72%) of N-methyl-3-(indol-3-yl)-maleimide **6**. mp: 195-196°C. IR (KBr, cm^{-1}): 3190, 1682, 1607, 1442, 798, 747.

^{1}H-NMR (DMSO-d$_6$): δ 2.92 (3H, s), 6.87 (1H, s), 7.20 (1H, t, J = 8 Hz), 7.25 (1H, t, J = 8 Hz), 7.51 (1H, d, J = 8 Hz), 7.96 (1H, d, J = 8 Hz), 8.38 (1H, d, J =3.0 Hz), 12.02 (1H, s, br). ^{13}C-NMR (DMSO-d$_6$) :δ 23.5 (q), 105.5 (s), 112.7 (d), 114.1 (d), 120.5 (d), 121.5 (d), 123.1(d), 125.5 (s), 131.1 (d), 136.7 (s), 139.1 (s), 171.7 (s), 172.1 (s).

3-(Indol-3-yl)-maleimide (6, R=H)

The procedure given above was used, using 3-(indol-3-yl) succinimide **5 (R=H)** (0.428g, 2 mmol).The crude product was treated with hot 2-propanol and the product was collected by filtration after cooling. Yield: 0.360g, 85%.

mp:259-260°C. IR (KBr, cm^{-1}):3349, 3231, 1754, 1697, 1592, 1346, 1227, 814, 687, 669. ^{1}H-NMR (DMSO-d$_6$): δ 6.77 (1H, s), 7.14-7.28 (2H, m), 7.51 (1H, d, J = 7 Hz), 7.94 (1H, d, J = 7 Hz) 8.36 (1H, d, J = 3 Hz). ^{13}C-NMR (DMSO-d$_6$):δ 105.4 (s), 112.6 (d), 115.3 (d), 120.4 (d), 121.4 (d), 123.0 (d), 125.6 (s), 131.0 (d), 136.7 (s), 139.5 (s), 173.3 (s), 173 5 (s).

Acknowledgements. Financial support from the Swedish Natural Science Council is gratefully acknowledged. We also thank Prof. S. Prabhakar, Univ. Nova, Lisbon, Portugal, for kind provision of a sample of compound **4a** for comparison.

REFERENCES AND NOTES

1. Gribble, G. W. *Stud. Nat. Prod. Chem.*, **1993**, 12, 365.
2. Omura, S.; Iwai, Y.; Hirano, A.; Nakagana, A.; Awaya, J.; Tsuchiya, Y.; Takahshi, Y.; Masums, R. *J. Antibiotics*, **1977**, 30, 275.
3. Oka, S.; Kodama, M.; Taheda, H.; Tomizuka, N.; Suzuki, H. *Agric. Biol. Chem.*, **1986**, 50, 2723.
4. Kaneko, T.; Wong, H.; Okamoto, K. T.; Clardy, J. *Tetrahedron Lett.*, **1985**, 26, 4015.
5. Nettleton, D. E.; Doyle, T. W.; Krishnan, B.; Matsumoto, G. K.; Clardy, J. *Tetrahedron Lett.*, **1985**, 26, 4011.
6. Fonseca, A. P.; Lobo, A. M.; Prabhakar, S. *Tetrahedron Lett.*, **1995**, 36, 2689.
7. Macor, J. E.; Blank, D. H.; Ryan, K.; Post, R. J. *Synthesis*, **1997**, 443.
8. Bogza, S. L.; Kobrakov, K. I.; Zubritskii, M. Y.; Suikov, S. Y.; Dulenko, V. I. *Khim. Geterosikl. Soedin.*, **1997**, 85.
9. Bergman, J.; Carlsson, R.; Misztal, S. *Acta Chem. Scand.*, **1976**, 30 B, 853.
10. The experimental details of the DMAD-reactions are not included in this publication. See: Janosik, T.; Bergman, J. *following paper*
11. Bergman, J. *J. Het. Chem*, **1973**, 10, 121.
12. Robinson, B.; Smith, G. F. *J. Chem. Soc.*, **1960**, 4574.
13. Venkataram, U. V.; Bruice, T. C. *J. Am. Chem. Soc.*, **1984**, 106, 5703.
14. Perron, Y. G.; Minor, W. F. *J. Org. Chem*, **1959**, 24, 1165.
15. Julia, M.; Bagot, J. *Bull. Soc. Chim. Fr.*, **1964**, 1924.
16. Prepared according to Macor's procedure.[7]