Pergamon

Tetrahedron, Vol. 52, No. 8, pp. 3029-3036, 1996

0040-4020/96 $15.00 + 0.00

0040-4020(95)01120-X

Diels-Alder Reactions of (Z)-Ethyl 3-[(1-ethoxycarbonyloxy-2-methoxy)ethenyl]-2-(ethoxycarbonyloxy)indole-1-carboxylate. Synthesis of the Carbazole Alkaloid Carbazomycin B.

Egle M. Beccalli*, Alessandro Marchesini

Istituto di Chimica Organica, Facolta' di Farmacia, Universita' degli Studi di Milano, via Venezian 21 20133 Milano - Italy

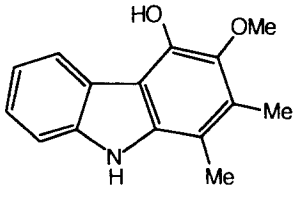
Tullio Pilati

CNR Centro Studio delle Relazioni tra Struttura e Reattivita' Chimica, via Golgi 19 20133 Milano - Italy

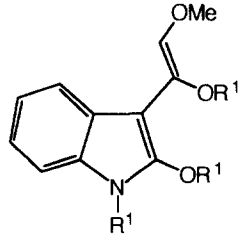
Abstract: Diels-Alder reactions of the title 3-vinylindole **2** with N-phenylmaleimide, maleimide, DEAD and DMAD are described. From Compound **10**, obtained from **2** and DMAD, Carbazomycin B (**1**) was prepared.

We have recently reported[1] a new synthesis of 3-vinylindoles starting from indol-2(3H)one. We now report the use of (Z)-ethyl 3-[(1-ethoxycarbonyloxy-2-methoxy)ethenyl]-2-(ethoxycarbonyloxy)indole-1-carboxylate (**2**)[1] as a diene in the Diels-Alder synthesis of Carbazomycin B, following the strategy by Pindur[2] for the synthesis of 4-demethoxy carbazomycin.

Carbazomycin B (**1**)[3] is an inhibitor of 5-lipoxygenase[4] and posseses weak antibacterial and antiyeast activity.[3a] It also inhibits the growth of some phytopathogenic fungi[3a] and several syntheses of the alkaloid system have been described.[5]



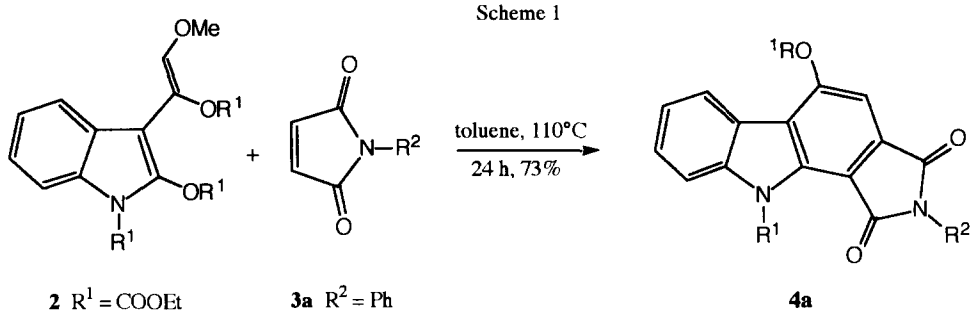
1



2 $R^1 = COOEt$

Compound **2** reacts in boiling toluene with N-phenylmaleimide **3a** (NPMI) to furnish the carbazole **4a** (Scheme 1).

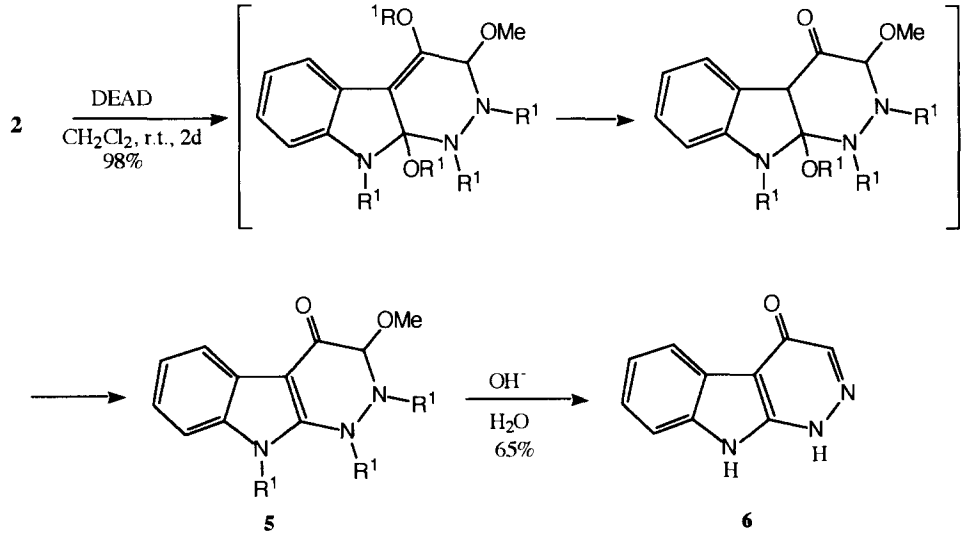
Scheme 1



2 R^1 = COOEt **3a** R^2 = Ph **4a**

Reaction with diethyl azodicarboxylate (DEAD) at room temperature gave compound **5** which on alkaline hydrolysis produces the corresponding pyridazinoindole **6.** (Scheme 2).

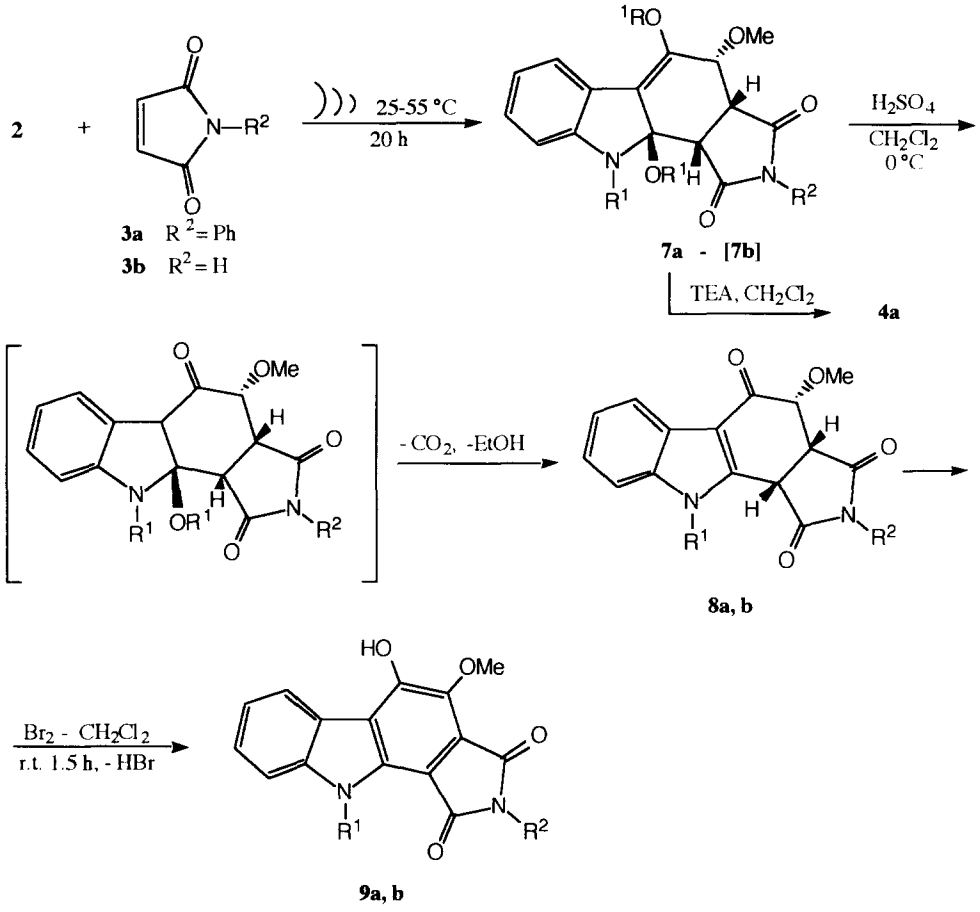
Scheme 2



Compound **5** probably arises from the Diels-Alder adduct *via* the hydrolysis of the enolcarbonate and successive CO_2 and EtOH elimination as shown in Scheme 2. This hypothesis is strongly supported by results we have obtained with Diels-Alder adducts from the diene **2** and maleimide **3a,b** under sonication conditions. Indeed, if the reaction between the diene **2** and NPMI **3a** is carried out in an ultrasound bath, the *endo* adduct **7a** is obtained in very high yield (Scheme 3). The adduct **7a** is easily obtained in a pure state by crystallization from Et_2O of the reaction mixture.

By treatment with triethylamine in CH_2Cl_2 solution at r.t. **7a** is quantitatively transformed into the carbazole **4a** (Scheme 3).

Scheme 3



When a CH_2Cl_2 solution of the compound **7a** is treated at 0 °C with a catalytic amount of H_2SO_4, the new derivative **8a** is obtained. Tlc analysis of the reaction mixture shows the presence of an intermediate which is thermally transformed into compound **8a** with elimination of CO_2 and EtOH. A possible hypothesis on the structure of this intermediate is shown in Scheme 3.

Compound **7b**, from Diels-Alder reaction with the maleimide **3b** was not isolated in pure state. The crude reaction mixture was submitted to acidic treatment to give directly **8b** in 70% yield, based on the diene **2**.

The structure of all new compounds is assigned on the basis of analytical and spectroscopic data, and in the case of **8b**, also by diffraction analysis[6]. Figure 1 shows an ORTEP view of the molecule with the atomic numbering scheme of the heavy atoms.

When compounds **8a,b** are treated with bromine in dichloromethane solution at r.t., bromination followed by HBr elimination gives the carbazole **9a,b** (Scheme 3) in very good yields. Any attempts to open, in acceptable yields, the phtalimide ring were unsuccessfully.

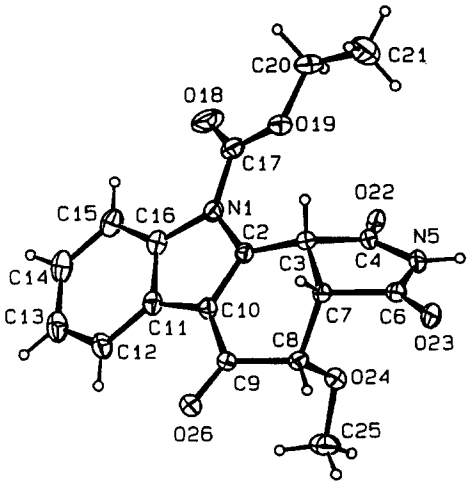
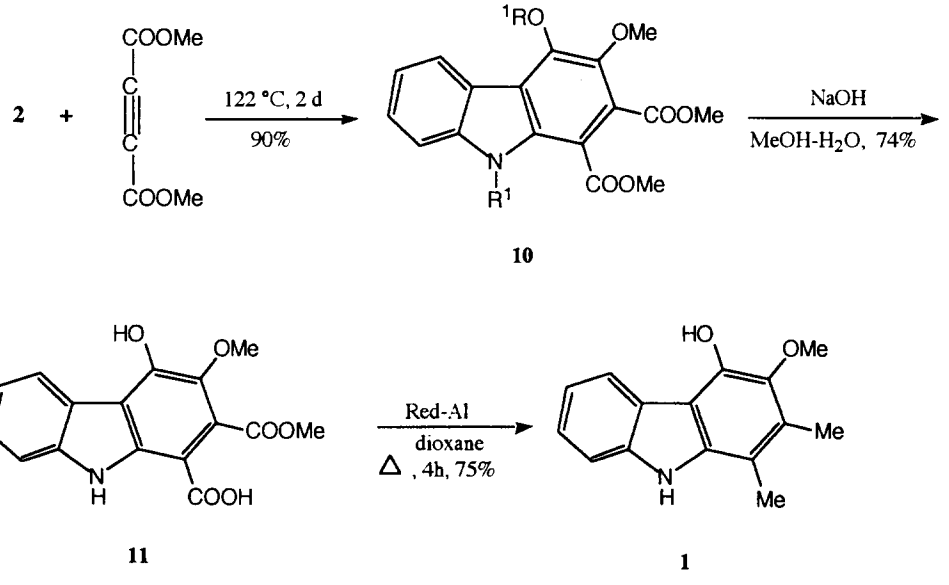


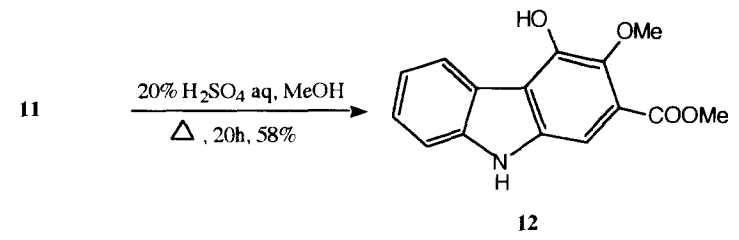
Figure 1. ORTEP of **8b**.

Very good yields (90%) were also obtained in the Diels-Alder reaction of the diene **2** with dimethyl acetylendicarboxylate (DMAD), giving the carbazole **10**. Using from **10**, carbazomycin B **1** may be obtained in three steps from **2** in an overall yield of 50% (Scheme 4). The spectral data for the synthetic carbazomycin B agree with those described in the literature.[3,5] Attempted acidic hydrolysis of the acid **11** gives raise to decarboxylation and the ester **12** is obtained in 58% yield, confirming the structure of compound **11** (Scheme 4).

Scheme 4



Scheme 4



EXPERIMENTAL

Melting points were determined on a Buchi apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 298 instrument, in nujol mull for solids and as liquid film for oils. ^{1}H-NMR were recorded on a Varian Gemini 200 spectrometer in $CDCl_3$ solution unless otherwise stated; chemical shifts are expressed in ppm (δ) relative to TMS, coupling constants (J) in Hz. Colomn chromatography was performed on Kieselgel Merck 60, 0.063-0.2 mm. Evaporation was carried out under vacuum in a rotary evaporator.

5-Ethoxycarbonyloxy-1,3-dioxo-2-phenyl-2,3-dihydro-1H-pyrrolo[3,4-a]carbazole-10-carboxylic acid ethyl ester **4a**.

Compound **2** (1 mmol, 421 mg) and **3a** (1.2 mmol, 207 mg) were dissolved in toluene (30 mL). After heating to reflux for 48h, the mixture was evaporated and the residue purified by silica gel column chromatography (hexane-dichloromethane, 2:1) affording compound **4a** (345 mg, 73%); mp 180-181 °C (CH_2Cl_2-Et_2O); ^{1}H NMR δ 1.36 (3H, t, 7.2), 1.48 (3H, t, 7.1), 4.46 (2H, q, 7.1), 4.55 (2H, q, 7.2), 7.39-7.54 (5H, m), 7.62 (1H, t, 8.8), 7.92 (1H, s), 8.19 (2H, d, 8.8); IR 1775, 1738, 1714 cm^{-1}; Anal. Calcd. for $C_{26}H_{20}N_2O_7$: C, 66.10; H, 4.27; N, 5.93. Found C, 66.28; H 4.19; N, 5.81.

1,2,9-Tri-ethoxycarbonyl-3-methoxy-4-oxo-1,2,3,4-tetrahydro-pyridazino[3,4-b]indole **5**.

Compound **2** (1 mmol, 421 mg) and diethyl azodicarboxylate (DEAD) (1.2 mmol, 207 mg) were dissolved in CH_2Cl_2 (20 mL). After 48h at r.t., the mixture was purified by silica gel column chromatography (hexane-dichloromethane, 2:1) affording compound **5** (oil, 410 mg, 98%); ^{1}H-NMR δ 1.32 (6H, m), 1.47 (3H, t, 7.2), 3.60 (3H, s), 4.33 (4H, m), 4.51 (2H, q, 7.2), 5.54 (1H, bs), 7.35 (2H, m), 8.12 (2H, m); IR 1745, 1727, 1718 cm^{-1}; Anal. Calcd. for $C_{20}H_{23}N_3O_8$: C, 55.42; H, 5.35; N, 9.70. Found C, 55.30; H, 5.40; N, 9.89.

1,4-Dihydro-4-oxo-9H-pyridazino[3,4-b]indole **6**.

Compound **5** (1 mmol, 433 mg) was dissolved in MeOH (20 mL) and H_2O (20 mL) and NaOH (6 mmol, 240 mg) was then added. The mixture was heated under reflux for 30 min. MeOH was evaporated and the solid filtered and crystallized gave compound **6** (120 mg, 65%); mp 227-230 °C (CH_2Cl_2-Et_2O); ^{1}H-NMR (DMSO-d_6) δ 6.15 (1H, bs, exchange with D_2O), 7.34 (1H, t, 6.7), 7.60 (2H, m), 8.18 (1H, d, 7.8), 8.26

(1H, s), 12.55 (1H, bs, exchange with D_2O); IR 3200, 3150, 1605 cm^{-1}; Anal. Calcd. for $C_{10}H_7N_3O$: C, 64.86; H, 3.81; N, 22.69. Found: C, 64.70; H, 3.90; N, 22.70.

5,10aβ-Bis-ethoxycarbonyloxy-4α-methoxy-1,3-dioxo-2-phenyl-2,3,3aβ,4,10a,10bβ-hexahydro-1H-pyrrolo[3,4-a]carbazole-10-carboxylic acid ethyl ester **7a**.

A mixture of compound **2** (5 mmol, 2.1 g) and N-phenylmaleimide **3a** (6 mmol, 1.03 g) in CH_2Cl_2 (3 mL) was sonicated in a sonication bath at 25-50 °C for 20h. After this time the evaporation of the solvent gives a solid residue that, was taken up in Et_2O (50 mL) and filtered giving pure **7a** (2.67 g, 90%); mp 179-180 °C (CH_2Cl_2-Et_2O); ^{1}H-NMR δ 1.23 (3H, t, 7.2), 1.38 (3H, t, 7.2), 1.46 (3H, t, 7.1), 3.39 (3H, s), 4.03 (1H, dd, 3.4, 8.3), 4.14 (2H, m), 4.34 (2H, m), 4.52 (2H, m), 5.07 (1H, d, 8.3), 5.28 (1H, d, 3.4), 7.24-7.38 (5H, m), 7.40-7.52 (2H, m), 8.09 (1H,m), 8.21 (1H, m); IR 1762, 1748, 1730, 1715 cm^{-1}; Anal. Calcd. for $C_{30}H_{30}N_2O_{11}$: C, 60.60; H, 5.09; N, 4.71. Found: C, 60.80; H, 4.91; N, 4.90.

The compound **7b** was prepared in a similar procedure using maleimide **3b** (6 mmol, 582 mg) as a dienophile. In this case the product **7b** was used without purification.

5-Ethoxycarbonyloxy1,3-dioxo-2-phenyl-2,3-dihydro-1H-pyrrolo[3,4-a]carbazole-10-carboxylic acid ethyl ester **4a** from **7a**.

Compound **7a** (1 mmol, 595 mg) was dissolved in CH_2Cl_2 (10 mL) and then TEA was added (0.05 mL). Evaporation of the solvent and crystallization afforded pure **4a** (448 mg, 95%).

4α-Methoxy-1,3,5-trioxo-2-phenyl-2,3,3aβ,4,5,10bβ-hexahydro-1H-pyrrolo[3,4-a]carbazole-10-carboxylic acid ethyl ester **8a** *and 4α-methoxy-1,3,5-trioxo-2,3,3aβ,4,5,10bβ-hexahydro-1H-pyrrolo[3,4-a]carbazole-10-carboxylic acid ethyl ester* **8b**.

Compound **7** (5 mmol) was dissolved in CH_2Cl_2 (60 mL) and after cooling at 0 °C two drops H_2SO_4 conc. were added. The mixture was then neutralized with $NaHCO_3$ and the product purified by silica gel column chromatography (dichloromethane-ethyl ether, 30:1) affording from **7a** compound **8a** (1.94 g, 90%); mp 230-232 °C (CH_2Cl_2-Et_2O); ^{1}H-NMR δ 1.51 (3H, t, 7.1), 3.36 (3H, s), 3.39 (1H, dd, 4.2, 8.0), 4.14 (1H, d, 4.2), 4.59 (2H, m), 5.33 (1H, d, 8.0), 7.27 (1H, m), 7.38-7.50 (6H, m), 8.11 (1H, m), 8.26 (1H, m); IR 1749, 1729, 1715 cm^{-1}; Anal. Calcd. for $C_{24}H_{20}N_2O_6$: C, 66.66; H, 4.66; N, 6.48. Found: C, 66.50; H, 4.66; N, 6.42. From **7b** compound **8b** was obtained (1.28 g, 72% based on **2**); mp 248-250 °C (CH_2Cl_2-Et_2O); ^{1}H-NMR δ 1.52 (3H, t, 7.2), 3.32 (3H, s), 3.82 (1H, dd, 4.2, 8.0), 4.04 (1H, d, 4.2), 4.61 (2H, m), 5.21 (1H, d, 8.0), 7.42 (2H, m), 7.97 (1H, bs, exchange with D_2O), 8.13 (1H, m), 8.23 (1H, m); IR 3180, 3070, 1782, 1740, 1720 cm^{-1}; Anal. Calcd. for $C_{18}H_{16}N_2O_6$: C, 60.67; H, 4.53; N, 7.86. Found: C, 60.59; H, 4.55; N, 7.90.

5-Hydroxy-4-methoxy-1,3-dioxo-2-phenyl-2,3-dihydro-1H-pyrrolo[3,4-a]carbazole-10-carboxylic acid ethyl ester **9a** *and 5-hydroxy-4-methoxy-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-a]carbazole-10-carboxylic acid ethyl ester* **9b**.

Compound **8** (1 mmol) was dissolved in CH_2Cl_2 (30 mL) and then Br_2 (2 mmol, 0.11 mL) was added under stirring. After 1.5 h at r.t. the solution was evaporated and the residue purified by silica gel column chromatography (dichloromethane-ethyl ether, 40:1), affording, from **8a**, compound **9a** (409 mg, 95%); mp

177-178 °C (CH_2Cl_2-Et_2O); ^{1}H-NMR δ 1.38 (3H, t, 7.1), 4.30 (3H, s), 4.54 (2H, q, 7.1), 7.09 (1H, s, exchange with D_2O), 7.39-7.61 (7H, m), 8.14 (1H, d, 7.4), 8.31 (1H, dd, 1.5, 7.7); IR 3450, 1758, 1722, 1704 cm^{-1}; Anal. Calcd. for $C_{24}H_{18}N_2O_6$: C, 66.97; H, 4.22; N, 6.51. Found: C, 67.03; H, 4.17; N, 6.40. From **8b**, compound **9b** was obtained (315 mg, 89%); mp 313-314 °C; ^{1}H-NMR (DMSO-d_6) δ 1.27 (3H, t, 7.1), 4.00 (3H, s), 4.42 (2H, q, 7.1), 7.48 (1H, t, 7.5), 7.61 (1H, m), 8.02 (1H, d, 8.0), 8.31 (1H, d, 6.9), 11.10 (1H, s, exchange with D_2O), 11.42 (1H, s, exchange with D_2O); IR 3390, 3160, 1740, 1735, 1690 cm^{-1}; Anal. Calcd. for $C_{18}H_{14}N_2O_6$: C, 61.02; H, 3.98; N, 7.91. Found: C, 60.94; H, 4.01; N, 8.01.

4-Ethoxycarbonyloxy-3-methoxy-carbazole-1,2,9-tricarboxylic acid 9-ethyl ester 1,2-dimethyl ester **10**.

Compound **2** (7 mmol, 2.95 g) and DMAD (21 mmol, 2.58 mL) were heated in a sealed tube at 125 °C for 2d. After this time the reaction mixture was purified by silica gel column chromatography (hexane-ethyl ether, 1:1), giving pure compound **10** (2.98 g, 90%); mp 93-96 °C (hexane-Et_2O); ^{1}H-NMR δ 1.43 (6H, m), 3.91 (3H, s), 3.95 (3H, s), 3.97 (3H, s), 4.44 (4H, m), 7.40 (1H, t, 7.6), 7.55 (1H, m), 8.01 (1H, d, 7.7), 8.16 (1H, d, 8.3); IR 1758, 1730, 1718 cm^{-1}; Anal. Calcd. for $C_{23}H_{23}NO_{10}$: C, 58.35; H, 4.90; N, 2.96. Found: C, 58.26; H, 4.93; N, 2.99.

4-Hydroxy-3-methoxy-9H-carbazole-1,2-dicarboxylic acid 2-methyl ester **11**.

Compound **10** (4 mmol, 1.89 g) was dissolved in MeOH (50 mL) and H_2O (50 mL). NaOH (60 mmol, 3 g) was then added and the mixture heated under reflux for 3 h. MeOH was evaporated and the solution acidified with 18% HCl. The mixture was extracted with AcOEt (3 x 30 mL). the organic layer was dried, filtered and evaporated to give, after crystallization, pure compound **11** (0.934 g, 74%); mp 255-257 °C (CH_2Cl_2-Et_2O); ^{1}H-NMR δ 3.83 (3H, s), 3.91 (3H, s), 7.20 (1H, m), 7.38 (2H, m), 8.27 (1H, d, 7.7), 9.11 (1H, bs, exchange with D_2O), 9.93 (1H, bs, exchange with D_2O), 12.30 (1H, bs, exchange with D_2O). IR 3200-3450br, 1710 cm^{-1}; Anal. Calcd. for $C_{16}H_{13}NO_6$: C, 60.95; H, 4.16; N, 4.44. Found: C, 61.10; H, 4.20; N, 4.51.

Carbazomycin B **1**.

Red-Al (5 mL, 3.5 M solution) was added to a solution of compound **11** (1 mmol, 315 mg) in anhydrous dioxane (30 mL), under nitrogen. After 4h undr reflux, the solution was cooled, MeOH (3 mL) added and evaporated. The residue was taken up with 15% HCl (50 mL) and extracted with CH_2Cl_2 (2 x 50 mL). The organic layer was dried, filtered and evaporated. Silica gel column chromatography (hexane-dichloromethane, 1:1) of the residue afforded pure **1** (180 mg, 75%); mp 160-161 °C (pentane-Et_2O); in ref. 3a reported 158.5-160 °C, in ref. 5d reported 162-164 °C.

4-Hydroxy-3-methoxy-9H-carbazole-2-carboxylic acid methyl ester **12**.

Compound **11** (2 mmol, 630 mg) was dissolved in MeOH (30 mL) and 10% H_2SO_4 (20 mL). Th solution was heated under reflux for 20h. MeOH was evaporated and the residue extracted with CH_2Cl_2 (2 x 20 mL). The organic layer was dried, filtered and evaporated and the residue purified by silica gel column chromatography (dichloromethane-ethyl ether, 1:1) gave compound **12** (314 mg, 58%); mp 142-146 °C (CH_2Cl_2-Et_2O); ^{1}H-NMR δ 3.96 (3H, s), 3.99 (3H, s), 6.51 (1H, s, exchange with D_2O), 7.25 (1H, m),

7.43 (2H, m), 7.56 (1H,s) 8.16 (1H, bs, exchange with D_2O), 8.33 (1H, d, 7.7); IR 3480, 3340, 1698 cm^{-1}; Anal. Calcd. for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.43; H, 4.80; N, 5.11.

X-ray structure determination of ***8b.***

Single crystal of **8b** was obtained from acetone-ethyl ether: the crystals are stable in sealed glass capillary. Data were collected on a SIEMENS-P4 diffractometer using $K\alpha$ radiation (λ = 0.71069 Å).

The structure were solved by SIR92[7] and refined by full-matrix least squares based on I (SHELXL-93)[8]. **8b** contains ethylic ether with **8b**/solvate ratio 2:1; the ether molecule is disordered around a centre. Only H atoms of N-H and of quaternary C-H refined. The disordered ether molecule in **8b** was introduced as a planar all trans model (whitout H atoms) and then refined anisotropically with some constraints (SAME and SIMU instructions of SHELX-93). Figure 1 shows the molecule in **8b.** As can be see from the Figure H3 and H7 are syn each to the other. $C_{18}H_{16}N_2O_6$. 1/2 $C_4H_{10}O$, F_W = 393.40, triclinic, space group $P\bar{1}$, a = 7.888(1), b = 9.844(2), c = 12.519(2), α = 97.99(1), β = 94.99(1), γ = 93.76(1), V = 956.0(3), Z = 2, D_{calc} = 1.367 $g.cm^{-3}$, data collection: $4.5 < 2\theta < 50.0°$, *hkl* range 0,9; -11,11; -14,14, No. independent data 3328, 2117 observed [$I > 2\sigma(I)$]. Refinement on I, R_1 = 0.056, wR_2 (all reflections) 0.175, goodness-of-fit = 1.034, $|\Delta\rho|$ min = 0.35, Δ/σ max= 0.042.

REFERENCES

1. Beccalli, E.M.; Marchesini, A. *Synth. Commun.* **1993**, *23*, 2945.
2. Pindur, U.; Pfeuffer, L. *Heterocycles* **1987**, *26*, 325.
3. (a) Sakano, K.-I.; Ishimaru, K.; Nakamura, S. *J. Antibiot.* **1980**, *33*, 683. (b)Sakano, K.-I.; Nakamura, S. *J. Antibiot.* **1980**, *33*, 961. (c) Kaneda, M.; Sakano, K.-I.; Nakamura, S.; Kushi, Y.; Litaka, Y. *Heterocycles* **1981**, *15*, 993.
4. Hook, D.J.; Yacobucci, J.J.; O'Connor, S.; Lee, M.; Kerns, E.; Krishnan, B.; Matson, J.; Hesler, G. *J. Antibiot.* **1990**, *53*, 1347.
5. (a) Knolker, H.-J.; Bauermeister, M.; Blaser, D.; Boese, R.; Pannek, J.-B. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 223. (b) Knolker, H.-J.; Bauermeister, M. *J. Chem. Soc. Chem. Comm.* **1989**, 1648. (c) Moody, C.-J.; Shah, P. *J. Chem. Soc. Perkin Trans I* **1989**, 376. (d) Moody, C.J.; Shah, P. *J. Chem. Soc. Perkin Trans I* **1989**, 2463. (e) Clive, D.L.J.; Eltkin, N.; Joseph, T.; Lown, J.W. *J. Org. Chem.* **1993**, *58*, 2442.
6. Crystallographic details have been deposited with Cambridge Crystallographic Data Centre, Lensfield, Cambridge CB 2 1EW, England.
7. Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M.C.; Polidori, G.; Camalli, M. *J. Appl. Cryst.* **1994**, *27*, 435.
8. Shedrick, G.M. (1993) SHEXL93 *Program of the refinement of crystal structures* Univ. of Gottingen, Germany.

(*Received in UK* 3 *October* 1995; *revised* 18 *December* 1995; *accepted* 20 *December* 1995)