DIELS-ALDER REACTION OF PYRANO[3,4-*b*]INDOLONES WITH AN ELECTRON-DEFICIENT PYRIDAZINONE: A NEW PATHWAY TO CARBAZOLE-FUSED PYRIDAZINES

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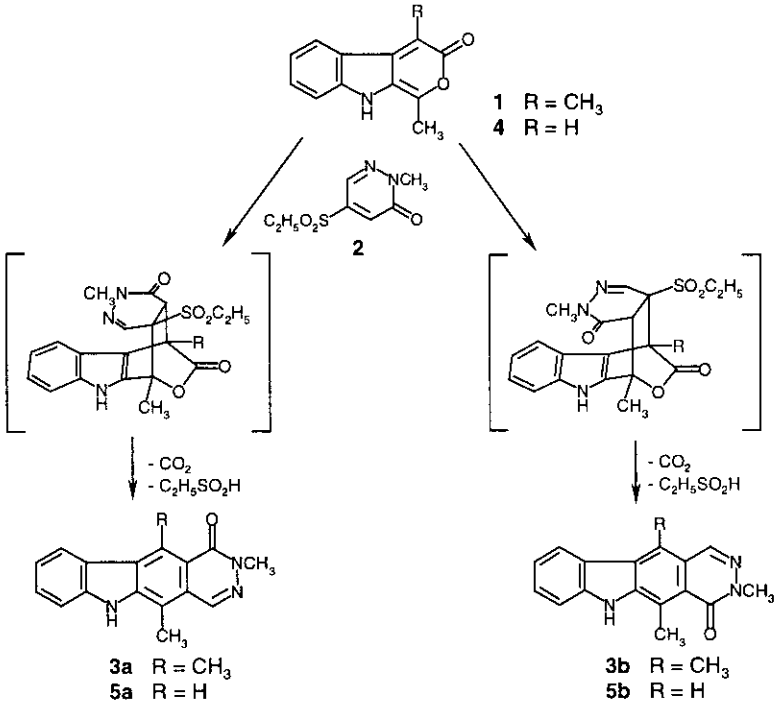
Abstract – Thermally induced [4+2] cycloaddition reactions of 5-ethanesulfonyl-2-methylpyridazin-3(2*H*)-one (**2**) with pyrano[3,4-*b*]indol-3(9*H*)-ones (**1**, **4**) affords isomeric pyridazino[4,5-*b*]carbazolones (**3a,b**, **5a,b**), the product ratio depending on the substitution pattern of the diene. Two carbazolocarbazoles (**6**, **7**) were obtained as side products.

The antineoplastic activity of *ellipticine* (5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole) has stimulated considerable interest in the field of *b*-fused carbazoles and has led to the synthesis of a large number of derivatives of the natural lead compound, some of them with superior antitumor properties.[1,2] Among those congeners, also some aza-analogous ellipticines like 6,11-dimethyl-5*H*-pyrido[3',4':4,5]pyrrolo-[2,3-*g*]isoquinoline[3] (9-azaellipticine), the drug candidate *pazelliptine*,[4] or a series of 1,4-dialkoxypyrid-azino[4,5-*b*]carbazoles[5] have been described. Whereas the latter 3-azaellipticines had been found to be almost inactive,[5] several new representatives of this ring system were prepared in our laboratory recently[6] and some of them turned out to be remarkably active in an *in-vitro* assay. In this context, the examination of alternative pathways to this tetracyclic ring system became an object of interest. In particular, a cyclo-addition reaction between a synthon with a preformed pyridazine ring and another component representing the remaining part of the tetracyclic system was considered a promising strategy. As an indole-derived diene, an appropriately substituted pyrano[3,4-*b*]indol-3(9*H*)-one should be a useful building block, as such compounds had already been employed for the construction of condensed or substituted carbazoles previously, e.g. by Plieninger,[7] Moody,[8] and Pindur.[9] As the dienophile, we chose the electron-deficient 5-ethanesulfonyl-2-methylpyridazin-3(2*H*)-one,[10] which – as well as one example of a nitro-substituted pyridazinone[11] – had been shown to react with simple butadiene derivatives in a Diels-Alder fashion to afford (tetrahydro-)phthalazinones, due to its low LUMO energy.[12,13]

When the dimethyl-substituted pyranoindolone (**1**)[8] was heated with the pyridazinone (**2**)[10] in bromobenzene to 156°C (conditions which are suitable e.g. for the reaction of **1** with dimethyl acetylenedicarboxylate[8]), no conversion was observed. However, employment of a higher-boiling solvent (1,2,4-trichlorobenzene) turned out to effect the cycloaddition reaction at a temperature of 190°C. An excess of **1** was used (with gradual addition), and careful exclusion of air oxygen was found to be crucial. Column chromatography of the reaction mixture afforded the two isomeric cycloaddition products (**3a** and **3b**) in a ratio of 1:3 (43% combined yield; Scheme 1) as well as two side products (see Scheme 2). Obviously, compounds (**3a,b**) are formed by spontaneous elimination of carbon dioxide and ethanesulfinic acid from the initially formed, highly strained cycloadducts.[14] Structural assignment for **3a,b** is based on NOE difference spectroscopy, using the resonances of the two C-methyl groups, H-10, and/or the pyridazine proton as irradiation points (see Experimental).

Scheme 1

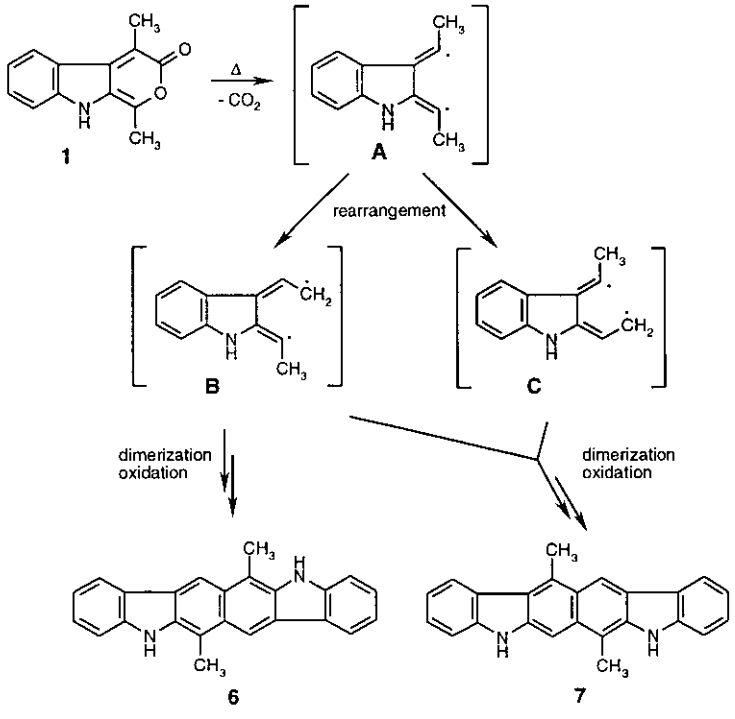


In order to examine the generality of this pathway to pyridazino[4,5-*b*]carbazoles, we also employed the 1-monosubstituted pyrano[3,4-*b*]indol-3(9*H*)-one (**4**)[7] as a diene in the Diels-Alder reaction with the pyridazinone (**2**). Not unexpectedly, the cycloaddition was found to take place at lower temperature (180°C) as compared to the transformation of **1** into **3a,b**, which may be explained by the lower degree of steric hindrance at the diene substructure. Interestingly, the product ratio of the resulting carbazole-fused pyridazinones (**5a,b**), which were separated by column chromatography (48% combined yield), was

found to be 3:1,[15] thus being reversed with respect to the **3a** : **3b** ratio of 1:3. As the electronic properties of the two pyrones (**1**, **4**) are very similar, the main reason for this observed reversal in cycloaddition regioselectivity might be associated with steric factors. In this context, not only repulsion, but also weak attractive forces between approaching subunits of the reactants should be taken into account, as discussed recently.[16]

From the mixture obtained from the cycloaddition reaction of **2** with the monosubstituted diene (**4**), a side product was isolated and identified as 2-acetyl-3-methylindole. The formation of this compound from **4** under similar conditions had already been described by Pindur[17] and a mechanism for this transformation had been suggested which is based on hydrolysis of the pyrone structure, followed by decarboxylation of the carboxylic acid thus formed. We found that also the 1,4-disubstituted pyrano[3,4-*b*]indol-3(9*H*)-one (**1**) undergoes side reactions to some extent under the conditions employed, and we were able to isolate two interesting final products of such a process. These hexacyclic compounds (**6** and **7**), both featuring a carbazolocarbazole skeleton, were obtained in 14% and 19% yields, respectively (separation by column chromatography/MPLC).

Scheme 2



A possible mechanism for the formation of **6** and **7** could involve thermally induced extrusion of carbon dioxide from **1**,[18] affording a highly reactive species (**A**) with a diradicalic or zwitterionic structure.

Rearrangement of this intermediate, followed by a sequence of dimerization (**B+B** for **6**, **B+C** for **7**) and oxidation/dehydrogenation finally might lead to the formation of the two isomeric polycycles (Scheme 2).

The structures of compounds (**6**) and (**7**) were established by a combination of elemental analyses, MS and NMR spectroscopy, and in particular by a series of NOE difference experiments which provided full information about the substitution patterns. For compound (**7**), the key experiment enabled us to assign all four protons at ring A by a single NOE difference spectrum (Figure 1) which, in turn, made it possible to determine the position of all other Ar-H, NH, and methyl substructures by means of several consecutive NOE experiments.

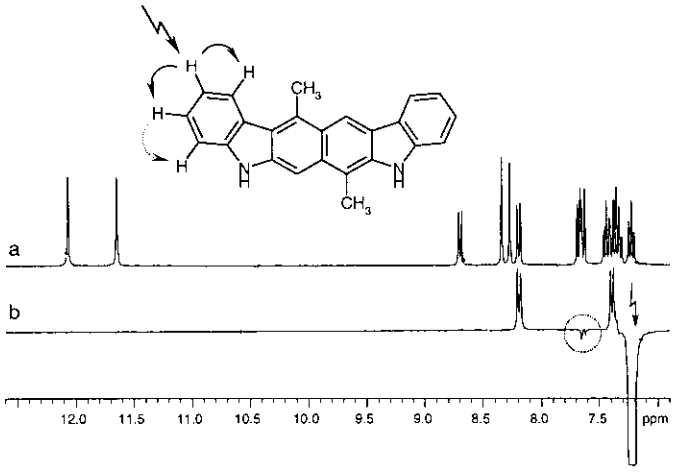


Figure 1. upper trace: downfield region of the 300 MHz ^{1}H-NMR spectrum of **7** (DMSO-d_6, 28°C);
lower trace: NOE difference spectrum of **7**; irradiation of H-11: positive effects for H-10 and H-12, negative effect for H-9 ("three-spin effect" [cf. lit.,[19]]).

Despite the moderate yields, the reactions **1** → **3a,b** and **4** → **5a,b** provide a new and short synthetic pathway to pyridazine-fused carbazoles of potential pharmaceutical interest and they further demonstrate the use of pyridazine-derived synthons in Diels-Alder type cycloaddition reactions.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. IR spectra were recorded for KBr pellets on an ATI Mattson FT-IR instrument; ^{1}H-NMR spectra were recorded on a Varian Unity*plus* 300 (300 MHz) spectrometer (TMS as internal reference, δ values in ppm). MS spectra were obtained with a Shimadzu QP5000 DI 50 spectrometer. HRMS spectra were taken on a Finnigan MAT 8230 instrument at the Institute of Organic Chemistry, University of Vienna. Column chromatography was done on Merck Kieselgel 60, 0.063-0.200 mm, medium pressure liquid chromato-

graphy (MPLC) was carried out on Merck LiChroprep Si 60, 0.040-0.063 mm (detection at 280 nm). Light petroleum refers to the fraction of bp 50-70°C. Microanalyses were performed at the Institute of Physical Chemistry (Microanalytical Laboratory), University of Vienna.

Cycloaddition Reaction of 1,4-Dimethylpyrano[3,4-*b*]indol-3(9*H*)-one (**1**) with 5-Ethanesulfonyl-2-methylpyridazin-3(2*H*)-one (**2**)

A mixture of 5-ethanesulfonyl-2-methylpyridazin-3(2*H*)-one[10] (**2**) (202 mg, 1 mmol) and 1,4-dimethylpyrano[3,4-*b*]indol-3(9*H*)-one[8] (**1**) (213 mg, 1 mmol) in 1,2,4-trichlorobenzene (9 mL) was heated under an Ar atmosphere to 190°C. After 7 h, 23 h, and 31 h, further portions (107 mg, 0.5 mmol) of **1** were added. The temperature was kept at 190°C for an overall reaction time of 47 h, then the solvent was removed by Kugelrohr distillation. The dark residue was subjected to column chromatography (ethyl acetate/light petroleum, 1:1).

The *first fraction* eluted from the column contained a mixture of compounds (**6**) and (**7**), which were separated by consecutive MPLC (ethyl acetate/light petroleum, 1:2): 5,12-Dihydro-6,13-dimethylcarbazolo[3,2-*b*]carbazole (**6**) (58 mg, 14%), yellow crystals, mp >350°C (ethyl acetate/light petroleum). *Anal.* Calcd for $C_{24}H_{18}N_2 \cdot 0.5\ H_2O$: C, 83.94; H, 5.58; N, 8.16. Found: C, 83.80; H, 5.61; N, 7.93. HRMS Calcd for $C_{24}H_{18}N_2$: 334.14699. Found: 334.147±0.0017. MS: *m/z* (rel. int.) 334 (M^+, 65%), 333 (28), 239 (30), 237 (25), 225 (20), 214 (25), 213 (26), 203 (26), 194 (24), 193 (24), 121 (29), 105 (21), 98 (46), 97 (34), 96 (22), 95 (22), 91 (24), 85 (26), 84 (28), 83 (43), 82 (30), 81 (30), 71 (54), 70 (24), 69 (61), 67 (27), 60 (22), 57 (100), 56 (40), 55 (93), 45 (33). IR (cm^{-1}): 3423, 3042, 2927, 1550, 1459, 1359, 1265, 1168, 856, 743, 452. ^{1}H-NMR (DMSO-d_6) δ: 11.53 (s, 2H, NH, shows positive NOE on irradiation at 2.86 ppm), 8.70 (d, $J_{1\text{-}2,8\text{-}9}$ = 8.1 Hz, 2H, H-1, H-8, shows positive NOE on irradiation at 8.62 ppm), 8.62 (s, 2H, H-7, H-14, shows positive NOE on irradiation at 8.70 and on irradiation at 2.86 ppm), 7.67 (d, $J_{3\text{-}4,10\text{-}11}$ = 7.8 Hz, 2H, H-4, H-11, shows positive NOE on irradiation at 11.53 ppm), 7.47-7.38 (m, 2H, H-3, H-10), 7.35-7.26 (m, 2H, H-2, H-9, shows positive NOE on irradiation at 8.70 ppm), 2.86 (s, 6H, CH_3-6, CH_3-13, shows positive NOE on irradiation at 11.53 and on irradiation at 8.62 ppm). 5,8-Dihydro-6,13-dimethylcarbazolo[2,3-*b*]carbazole (**7**) (79 mg, 19%), yellow crystals, mp 319-322°C (ethyl acetate/light petroleum). *Anal.* Calcd for $C_{24}H_{18}N_2 \cdot 0.2\ H_2O$: C, 85.28; H, 5.49; N, 8.29. Found: C, 85.06; H, 5.42; N, 8.18. HRMS Calcd for $C_{24}H_{18}N_2$: 334.14699. Found: 334.147±0.0017. MS: *m/z* (rel. int.) 335 (19%), 334 (M^+, 100), 166 (88), 159 (69), 151 (28), 145 (26), 105 (15), 98 (20), 97 (16), 85 (15), 84 (15), 83 (22), 81 (17), 71 (32), 69 (32), 67 (16), 57 (70), 56 (39), 55 (56), 45 (20). IR (cm^{-1}): 3412, 3047, 1628, 1494, 1456, 1365, 1299, 1035, 739. ^{1}H-NMR (DMSO-d_6) δ: 12.07 ppm (s, 1H, NH-8, shows positive NOE on irradiation at 8.34 ppm), 11.65 (s, 1H, NH-5, shows positive NOE on irradiation at 2.80 ppm), 8.70 (d, $J_{1\text{-}2}$ = 7.8 Hz, 1H, H-1, shows positive NOE on irradiation at 8.27 ppm), 8.34 (s, 1H, H-7, shows positive NOE on irradiation at 12.07 ppm and on irradiation at 2.80 ppm), 8.27 (s, 1H, H-14, shows

positive NOE on irradiation at 8.70 ppm and on irradiation at 3.08 ppm), 8.19 (d, $J_{11\text{-}12}$ = 7.8 Hz, 1H, H-12, shows positive NOE on irradiation at 7.27-7.19 ppm and on irradiation at 3.08 ppm), 7.68 (d, $J_{3\text{-}4}$ = 7.8 Hz, 1H, H-4, shows positive NOE on irradiation at 11.65 ppm), 7.64 (d, $J_{9\text{-}10}$ = 8.1 Hz, 1H, H-9, shows positive NOE on irradiation at 12.07 ppm and shows *negative* NOE on irradiation at 7.27-7.19 ppm), 7.48-7.29 (m, 3H, H-3 [downfield part of multiplet], H-10 [center part of multiplet, shows positive NOE on irradiation at 7.27-7.19 ppm], H-2 [upfield part of multiplet, shows positive NOE on irradiation at 8.70 ppm]), 7.27-7.19 (m, 1H, H-11, shows positive NOE on irradiation at 8.19 ppm), 3.08 (s, 3H, CH_3-13, shows positive NOE on irradiation at 8.27 ppm and on irradiation at 8.19 ppm), 2.80 (s, 3H, CH_3-6, shows positive NOE on irradiation at 11.65 ppm and on irradiation at 8.34 ppm).

The *second fraction* eluted from the column contained a 1:3 mixture of compounds (**3a**) and (**3b**) (120 mg, 43%), which were separated by consecutive MPLC (dichloromethane/methanol, 98:2): 2,6-Dihydro-2,5,11-trimethyl-1*H*-pyridazino[4,5-*b*]carbazol-1-one (**3a**), brownish crystals, mp 342-343°C (ethyl acetate/light petroleum). *Anal.* Calcd for $C_{17}H_{15}N_3O \cdot 0.4\ H_2O$: C, 71.76; H, 5.60; N 14.77. Found: C 71.98 H 5.63 N 14.32. HRMS Calcd for $C_{17}H_{15}N_3O$: 277.1215. Found: 277.1215±0.0015. MS: *m/z* (rel. int.) 278 (20%), 277 (M^+, 100), 250 (12), 249 (65), 234 (10), 206 (49), 205 (11), 204 (21), 191 (20), 103 (13), 102 (12), 57 (13). IR (cm^{-1}): 3270, 2944, 1627, 1589, 1407, 1369, 1332, 1251, 730. ^{1}H-NMR (DMSO-d_6) δ: 11.74 ppm (s, 1H, NH, shows positive NOE on irradiation at 2.78 ppm), 8.49 (d, J = 1.5 Hz, 1H, H-4, shows positive NOE on irradiation at 2.78 ppm), 8.35 (d, $J_{9\text{-}10}$ = 7.8 Hz, 1H, H-10), 7.62 (d, $J_{7\text{-}8}$ = 8.1 Hz, 1H, H-7), 7.57-7.49 (m, 1H, H-8), 7.32-7.23 (m, 1H, H-9), 3.67 (s, 3H, NCH_3), 3.46 (s, 3H, CH_3-11) 2.78 (s, 3H, CH_3-5). 3,6-Dihydro-3,5,11-trimethyl-4*H*-pyridazino[4,5-*b*]carbazol-4-one (**3b**), yellow crystals, mp 342°C (ethyl acetate). *Anal.* Calcd for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.37; H, 5.35; N, 14.95. MS: *m/z* (rel. int.) 277 (M^+, 38%), 249 (18), 206 (16), 139 (14), 111 (13), 103 (14), 102 (16), 98 (15), 97 (28), 96 (29), 95 (24), 85 (21), 84 (22), 83 (43), 82 (28), 81 (20), 71 (39), 70 (19), 69 (38), 67 (29), 57 (100), 56 (28), 55 (95), 45 (69). IR (cm^{-1}): 3281, 2942, 1615, 1587, 1497, 1364, 1319, 1263, 956, 744, 665. ^{1}H-NMR (DMSO-d_6) δ: 11.70 ppm (br s, 1H, NH), 8.58 (d, J = 1.2 Hz, 1H, H-1), 8.33 (dd, $J_{9\text{-}10}$ = 7.9 Hz, ^4J = 0.75 Hz, 1H, H-10), 7.63 (dd, $J_{7\text{-}8}$ = 8.4, ^4J = 0.75 Hz, 1H, H-7), 7.58-7.50 (m, 1H, H-8), 7.31-7.23 (m, 1H, H-9, shows positive NOE on irradiation at 8.33 ppm), 3.65 (s, 3H, NCH_3), 3.10 (s, 3H, CH_3-5), 3.05 (s, 3H, CH_3-11, shows positive NOE on irradiation at 8.58 ppm and on irradiation at 8.33 ppm).

Cycloaddition Reaction of 1-Methylpyrano[3,4-*b*]indol-3(9*H*)-one (**4**) with 5-Ethanesulfonyl-2-methyl-pyridazin-3(2*H*)-one (**2**)

A mixture of 5-ethanesulfonyl-2-methylpyridazin-3(2*H*)-one[10] (**2**) (202 mg, 1 mmol) and 1-methyl-pyrano[3,4-*b*]indol-3(9*H*)-one[7] (**4**) (199 mg, 1 mmol) in 1,2,4-trichlorobenzene (9 mL) was heated under an Ar atmosphere to 180°C. After 7 h, 23 h, and 31 h, further portions (100 mg, 0.5 mmol) of **4** were

added. The temperature was kept at 180°C for an overall reaction time of 47 h, then the solvent was removed by Kugelrohr distillation. The dark residue which contained the two main products (**5a,b**) in a ratio of **5a** : **5b** = 3:1 (according to ^{1}H-NMR spectroscopy[15]) was subjected to column chromatography (ethyl acetate/light petroleum, 2:1).

The *first fraction* was recrystallized twice from ethyl acetate/light petroleum to afford 2-acetyl-3-methyl-indole[20] (50 mg, 12%) as colorless crystals, mp 145-147°C (lit.,[20] mp 147-148°C).

The *second fraction* was further purified by MPLC (dichloromethane/methanol, 98:2) and then by recrystallization from ethyl acetate to give 3,6-dihydro-3,5-dimethyl-4*H*-pyridazino[4,5-*b*]carbazol-4-one (**5b**) (25 mg, 9%) as almost colorless crystals, mp 301-302°C. *Anal.* Calcd for $C_{16}H_{13}N_3O \cdot 0.15\ H_2O$: C, 72.25; H, 5.04; N, 15.80. Found: C, 72.48; H, 5.02; N, 15.51. *HRMS* Calcd for $C_{16}H_{13}N_3O$: 263.1059. Found: 263.106±0.0013. MS: *m/z* (rel. int.) 264 (18%), 263 (M^+, 100), 236 (13), 235 (73), 234 (12), 192 (52), 191 (28), 190 (16), 179 (12), 132 (11), 96 (26). IR (cm^{-1}): 3345, 3055, 2919, 1619, 1593, 1495, 1474, 1366, 1244, 852, 744, 655. ^{1}H-NMR (DMSO-d_6) δ: 11.74 ppm (s, 1H, NH), 8.51 (s, 1H, H-11), 8.33 (s, 1H, H-1, shows positive NOE on irradiation at 8.51 ppm), 8.26 (dd, $J_{9\text{-}10}$ = 7.8 Hz, ^4J = 0.9 Hz, 1H, H-10, shows positive NOE on irradiation at 8.51 ppm), 7.62 (dd, $J_{7\text{-}8}$ = 7.0 Hz, ^4J = 0.75 Hz, 1H, H-7), 7.59-7.52 (m, 1H, H-8), 7.31-7.24 (m, 1H, H-9), 3.67 (s, 3H, NCH_3), 3.15 (s, 3H, CH_3-5).

Evaporation of the *third fraction* afforded 2,6-dihydro-2,5-dimethyl-1*H*-pyridazino[4,5-*b*]carbazol-1-one (**5a**) (102 mg, 39%) as brownish crystals, mp 328-329°C (ethyl acetate/light petroleum). *Anal.* Calcd for $C_{16}H_{13}N_3O$: C, 72.99; H, 4.98; N, 15.96. Found: C, 72.71; H, 4.90; N, 15.75. MS: *m/z* (rel. int.) 263 (M^+, 50%), 235 (33), 192 (23), 191 (19), 190 (33), 162 (15), 117 (15), 98 (15), 97 (21), 96 (56), 92 (23), 91 (55), 89 (25), 84 (16), 83 (32), 82 (29), 81 (29), 76 (19), 73 (19), 71 (43), 70 (19), 69 (61), 67 (26), 63 (25), 57 (79), 56 (29), 55 (100), 50 (19), 45 (56). IR (cm^{-1}): 3225, 2944, 1606, 1590, 1412, 1373, 1255, 947, 732. ^{1}H-NMR (DMSO-d_6) δ: 11.78 ppm (s, 1H, NH, shows positive NOE on irradiation at 2.84 ppm), 8.94 (s, 1H, H-11), 8.61 (d, J = 0.3 Hz, 1H, H-4, shows positive NOE on irradiation at 2.84 ppm), 8.38 (d, $J_{9\text{-}10}$ = 8.1 Hz, 1H, H-10), 7.60 (d, $J_{7\text{-}8}$ = 8.1 Hz, 1H, H-7), 7.57-7.50 (m, 1H, H-8), 7.30-7.23 (m, 1H, H-9), 3.74 (s, 3H, NCH_3), 2.84 (s, 3H, CH_3-5).

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14. For the sake of clarity, the representation of other possible *endo/exo* isomers of the cycloadducts was omitted in Scheme 1.
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18. Also in the absence of dienophile (**2**), formation of **6** and **7** from **1** under analogous conditions could be detected by TLC and ^{1}H-NMR.
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