DIELS-ALDER CYCLOADDITION OF METHACROLEIN *N,N*-DIMETHYLHYDRAZONE TO 1,4-NAPHTHOQUINONE DERIVATIVES[1]

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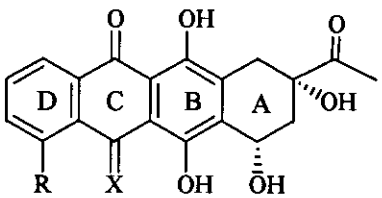
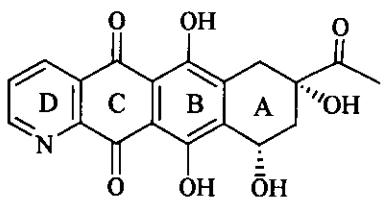
Abstract- Diels-Alder cycloadditions of naphthoquinone derivatives (**3-8**) with methacrolein *N,N*-dimethylhydrazone (**9**) have been investigated. In the reaction with the quinones (**3-4**) and (**8**) the initial cycloadducts (**10, 11** and **17a,b**) were isolated in good yields. However, the cycloaddition with quinones (**5-7**) affords directly the corresponding aromatized azaanthraquinones (**12, 15a** and **16a,b**) in good yields.

INTRODUCTION

Anthracycline antibiotics[2a] are powerful antitumor agents,[2b,c] but their utilization in cancer chemotherapy is limited due to their undesired side effects such as accumulative cardiotoxicity.[3] In the last decade considerable efforts have been devoted to develop new structurally modified anthracyclines with an improved antineoplastic activity and a low cardiotoxicity. 5-Iminodaunomycin, a quinone-modified analog, shows significantly less cardiotoxicity than daunomycin.[4] The lower cardiotoxicity has been credited to its poor redox capability for catalytic production of reactive oxygen species.[5] As part of our studies on the synthesis of anthracyclinones, the aglycones of anthracyclines, such as **1a**, we have reported recently[6] the first total synthesis of 5-iminodaunomycinone (**1b**), based on a BCD→ABCD approach. It would be of interest to synthesize heterocyclic anthracycline analogues,[7] since the heteroaromatic ring provides a useful bioisosteric replacement of the benzene ring D and it would be expected to change the redox potential. Moreover, numerous nitrogen-



1a: X= O, R= OMe
1b: X= NH, R= OMe



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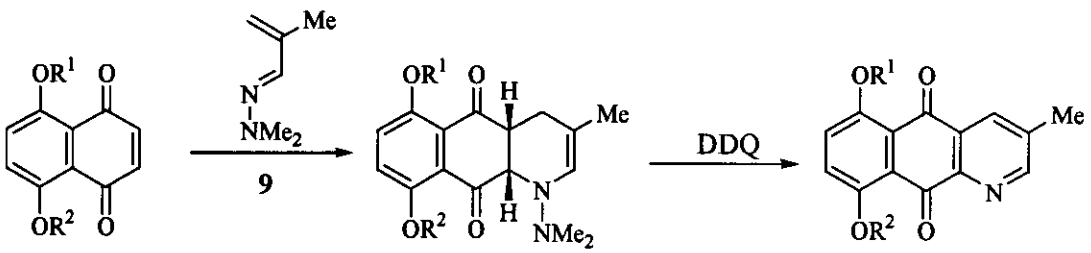
containing heterocyclic quinones also exhibit antitumor activity.[8]

Some years ago Fariña *et al.* have described[9a,b] the construction of the tetracyclic system of anthracyclinones *via* two successive Diels-Alder reactions, starting from dihydroxynaphthoquinone derivatives as BC synthons. In a similar manner, their heterocyclic analogues of type (**2**), in which the ring D is a 6-membered heterocycle, could be elaborated *via* Diels-Alder cycloaddition of naphthoquinone derivatives with an azadiene followed by a second Diels-Alder reaction with an appropriate 1,3-disubstituted buta-1,3-diene. It is well known that Diels-Alder cycloaddition reactions with azadienes provide a versatile entry to fused heterocyclic quinones[8a,10] and that the use of α,β unsaturated *N,N*-dimethylhydrazones in synthesis of aza-heterocyclic quinones has increased in the last few years due to the high reactivity and regioselectivity observed with these 1-azadienes.[11]

This paper describes the Diels-Alder cycloaddition of methacrolein *N,N*-dimethlyhydrazone (**9**) to naphthoquinone derivatives of type (**3-8**). The results obtained would provide information on the reactivity and regioselectivity of the cycloaddition and offer a possible quick entry into the pyridine ring system. The azaanthraquinones reported herein, as such or after transformation to diquinones,[12] diquinone monoimines[9c] or quinone monoimines,[9d] may allow the annelation through a second Diels-Alder reactions with suitable dienes. Therefore these compounds could be used as BCD synthons for the construction of heterocyclic analogues of anthracyclinones.

RESULTS AND DISCUSSION

The Diels-Alder cycloaddition reactions of quinones (**3-5**) with 1-dimethylamino-3-methyl-1-azabuta-1,3-diene (methacrolein *N,N*-dimethylhydrazone) (**9**) were carried out in dichloromethane at room temperature (Scheme I) and the results of the reactions are summarized in Table I.



3-5 **10, 11** **12, 13, 14**

Scheme I

Table I. Cycloadditions of diene (**9**) to naphthoquinone derivatives (**3-5**)

Quinone	R^1	R^2	Time (d)	Products	Yield (%)
3	Me	Me	17	**10**	87
4	Ac	Ac	9	**11**	64
5	Me	H	2	**12**	98

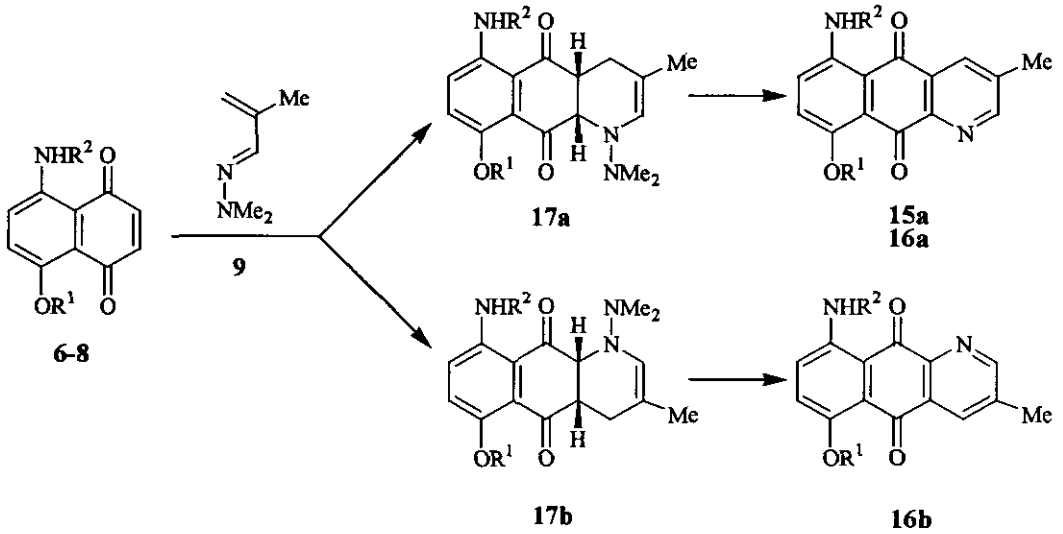
The reaction with the naphthoquinone derivatives (**3** and **4**) proceeds slowly to give the corresponding adducts (**10**) and (**11**) in good yields. Their analytical and spectral data were consistent with the expected structures. The ^{1}H-NMR spectrum reveals two singlets signals for methyl and dimethylamino group at δ 1.63 and 2.21 ppm respectively and the presence of two doubles doublets at δ 2.10 and 2.50 ppm with a *gem* coupling constant of 16.8 Hz attributable to the H-4 protons. Moreover, a coupling constant of 2.7 Hz between protons H-4a and H-9a (δ 3.30 and 4.00 respectively) is in accord with a relative *gauche* disposition, indicating a *cis* junctions at the C-4a and C-9a.

Under similar conditions the treatment of naphthoquinone (**5**) with the diene (**9**) yielded the azaanthraquinone (**12**).The formation of the azaanthraquinone was evidenced from their elemental analyses and spectral data. Thus, their ^{1}H-NMR spectra indicated the presence of two doublets at δ 8.87 and 8.36 ppm (J=2.2 Hz) are in accordance with the chemical shift values expected for H-2 and H-4 pyridine protons. Moreover, the ^{13}C-NMR spectra showed two signals at δ 187.12 and 180.92 ppm attributable to the quinonoid carbonyl groups. Taking into account the regiochemistry of cycloaddition[11d] of 5-hydroxy- and 5-methoxy-1,4-naphthoquinones with the polarized diene (**9**), the most probable that the structure of the isolated product could be (**12**). This quinone probably was generated by attack of the nucleophilic terminus of the 1-azadiene to the more electrophilic carbon atom of the 2-position in quinone (**5**), followed by elimination of dimethylamine and aromatization.

The initial cycloadducts (**10** and **11**) were oxidized with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in toluene to afford the fully aromatic azaanthraquinones (**13** and **14**), in good yield. The structure of compounds (**13**) and (**14**) was established on the basis of the spectral data, particulary their ^{1}H-NMR, in which there were no signals assignable to the H-4a and H-9a protons of the starting adducts. Moreover, the presence of two double doublets at δ 8.80 and 8.20 ppm (J=2.0 Hz) confirmed the presence of a pyridine ring system.

Next we have also studied the cycloaddition of diene (**9**) with the aminonaphthoquinones (**6-8**). The reaction was conducted in dichloromethane at room temperature (Scheme II) and the results obtained are summarized in Table II.

The reaction of the parent quinone (**6**) with the diene (**9**) proceeded slowly to give, in very good yields, the azaanthraquinone (**15a**), formed from the initial adducts by elimination of dimethylamine and subsequent



Scheme II

Table II. Cycloaddditions of diene (**9**) to naphthoquinone derivatives (**6-8**)

Quinone	R^1	R^2	Time	Products	Ratio*	Yield (%)
6	H	H	20 d	**15a**	10:0	93
7	H	Ac	8 h	**16a** + **16b**	4:1	88
8	Ac	Ac	36 h	**17a** + **17b**	1:9	79

*Relative product distribution by ^{1}H-Nmr

aromatization. The regiochemistry was established taking into account the behaviour of this quinone with polarized dienes[13] and the well known directional effect exerted by the dimethylhydrazone group in (**9**).[11a]

The reaction with naphthoquinone (**7**) proceeds fast to afford a 4:1 mixtures of the regioisomeric azaanthraquinones (**16a**) and (**16b**) and the ratios of the two regioisomers have been determined by relative integration of the well resolved chelated OH and NH protons. The two azaanthraquinones could be isolated by silica gel chromatography and the structures were assigned on the basis of their spectral data. It is noteworthy, that the sharp singlet of the chelated OH proton of azaantraquinone (**16b**) resonates at higher field (δ 13.01) than the more strong chelated OH signal of the regioisomers (**16a**) (δ 13.28).

In contrast, the chemical shifts of the chelated NH protons of azaanthraquinone (**16a**) appears at higher field (δ 12.21) than the isomer (**16b**) in which the NH proton resonates at lower field (δ 12.37).

However, the cycloaddition to naphthoquinone (**8**), in which the OH functionality is protected as its acetate, proceeded with high regioselectivity to give a 1:9 mixture of the initial cycloadducts (**17a,b**). Adduct (**17b**) could be separated by fractional precipitation from ether. The regiochemistry of adduct (**17b**), in which the

dimethylamino substituent is adjacent to the NH-Ac group, was tentatively assigned on the expectation that the hydrogen bonding of the NH-acyl group is the dominant director of the cycloaddition.

The regiospecificity observed with naphthoquinone (**6**) may be explained in terms of the enhanced activation of the C-1 carbonyl group of the quinone by the strong intramolecular hydrogen bonding with the *peri*-OH group, which is stronger than that between the NH and the C-4 carbonyl group. This effect has been previously reported by us[13] for the cycloaddition of (*E*)-1-methoxy- and (*E*)-1-trimethylsilyloxybuta-1,3-dienes to hydroxy- and aminonaphthoquinone derivatives. However, the regioselectivity observed in the cycloaddition to 5-acetylamino-8-hydroxy-1,4-naphthoquinone (7) would be interpreted in terms of a competition between C-1 and C-4 carbonyl group. Moreover, the regiochemical reversal observed with quinone (**8**), can be attributed to the presence of the hydrogen bonding of the NHAc group with the C-4 carbonyl, which in this case is the dominant director of the cycloaddition.

However, since it was imposible to assign an unambigous regiochemistry to adducts (**17a,b**) and azaanthraquinones (**15a,16a,b**) by spectral means, it was essential to resort to chemical correlations. In order to achieve this, we have carried out the sequence of reactions as shown in Schemes III and IV.

The crude reaction mixture from cycloaddition with quinone (**6**), after deamination, *via* diazotization and treatment with hypophosphorous acid, afforded 8-hydroxy-3-methyl-1-azaanthracene-9,10-dione (**19a**) as the exclusive product, whose physical and spectral data were identical with reported ones in the literature[11d] for this compound.

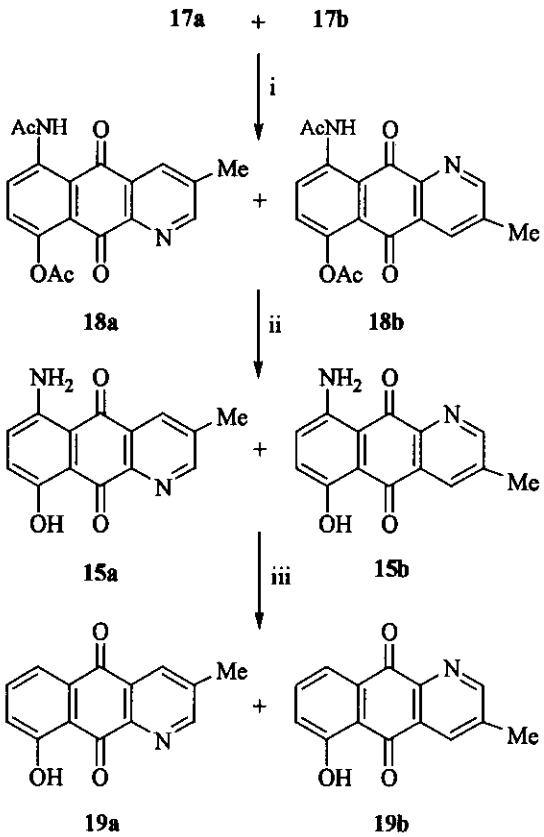
In addition, the crude mixture of the cycloadducts (**17a+17b**) was subjected to the following transformations: i) oxidation with DDO[14]; ii) hydrolysis of the protecting *N,O*-diacyl groups; and iii) deamination, *via* diazotization and subsequent treatment with hypophosphorous acid, in order to obtained a mixture of azaanthraquinones (**19a**) and (**19b**) , whose ratio was found to be approximately the same as the initial ratio of the regioisomers cycloadducts (Scheme III). Furthermore, it was possible to perform chromatographic separation of these compound to obtain pure (**19a**) and (**19b**) respectively, whose physical and spectral data were identical with those reported in the literature [11d] for these compounds.

A similar reaction sequence starting from the adduct (**17b**) gave 5-hydroxy-3-methyl-1-azaanthracene-9,10-dione (**19b**) as the exclusive product.

On the other hand, the crude mixture of the azaanthraquinones (**16a+16b**) was converted into a mixture of the azaanthraquinones (**15a+15b**), whose ratio was found to be approximately equal to the initial ratio of regioisomers, which after deamination and chromatographic separation afforded the azaanthraquinones (**19a**) and (**19b**) respectively (Scheme IV).

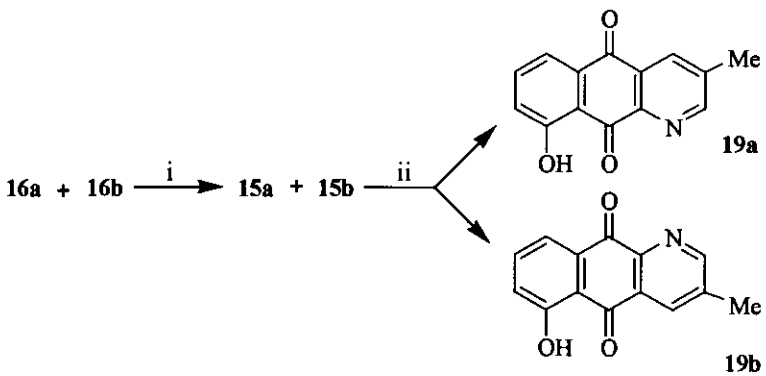
In summary, the azaanthraquinones reported here are potentially useful in natural products synthesis. Therefore, this methodology described here, could be extended to the construction of the other fused pyridine systems.

Scheme III



Reagents: i) DDQ; ii) 8% NaOH; iii) $NaNO_2$, H_3PO_2

Scheme IV



Reagents: i) 8% NaOH; ii) $NaNO_2$, H_3PO_2

EXPERIMENTAL

Mps were determined using a Kofler hot-stage apparatus and are uncorrected. Microanalyses were performed with a Heraeus analyzer. IR spectra were recorded on a Perkin-Elmer model 681 grating spectrophotometer as nujol mulls, ν values in cm^{-1}. ^{1}H-NMR spectra were determined with either a Varian Gemini 200, a Bruker AM-200 or a Varian XL-300 spectrometer, in $CDCl_3$ solution, unless otherwise

stated. ^{13}C-NMR were determined with either a Varian XL-300 or a Bruker AM-200 in $CDCl_3$ solution, unless otherwise stated. Chemical shifts were reported in ppm (δ) downfield from Me_4Si. MS spectra were determined on a VG-12-250 spectrometer. Silica gel Merck 60 (70-230 mesh) and DC-alufolien $60F_{254}$ were used for flash column chromatography and analytical TLC, respectively.

1-Dimethylamino-3-methyl-1-azabuta-1,3-diene (Methacrolein *N,N*-dimethylhydrazone) **(9)** was prepared according to the method previously reported.[15]

Cycloaddition of 1-Dimethylamino-3-methyl-1-azabuta-1,3-diene (9) to Naphtoquinone Derivatives (3-5). General Procedure

To a solution of naphthoquinone (**3-5**) (1 mmol) in dichloromethane (35 mL) was added portionwise the azadiene (**9**) (168 mg, 1.5 mmol). The mixture was allowed to stand at rt for the period of time indicated in Table I (disappearance of naphthoquinone was monitored by TLC). The solvent was removed and the residue was analyzed by ^{1}H-NMR. Analytical samples were obtained from the crude reaction mixture by crystallization.

Addition to 5,8-dimethoxy-1,4-naphthoquinone **(3)** afforded **5,8-dimethoxy-1-dimethylamino-3-methyl-1,4,4a,9a-tetrahydro-1-azaanthracene-9,10-dione (10)** (287 mg, 87%), mp 217-221°C (from dichloromethane/ethanol). Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.45, H, 6.67, N, 8.48. Found: C, 65.18, H, 6.75, N, 8.34. IR: 1710, 1685, 1590. ^{1}H-NMR: 7.21, 7.15 (AB systm., 2H, H-6, H-7, $J_{6,7}$= 9.3 Hz), 5.77 (s, 1H, H-2), 4.01 (d, 1H, H-9a, $J_{9a,4a}$= 2.7 Hz), 3.87 (s, 6H, OMe), 3.27 (m, 1H, H-4a), 2.56 (dd, 1H, H'-4, J_{gem}= 16.8 Hz, $J_{4',4a}$= 0.5 Hz), 2.21 (s, 6H, NMe_2), 2.09 (dd, 1H, H-4, J_{gem}= 16.8 Hz, $J_{4,4a}$= 4.6 Hz), 1.63 (s, 3H, Me). ^{13}C-NMR: 196.61, 194.13, 153.49, 152.23, 125.86, 123.71, 123.10, 120.07, 118.33, 109.48, 66.06, 57.46, 56.70, 49.36, 41.64, 27.25, 20.39. MS, *m/z:* 331 (M^++1) (4), 330 (M^+)(15), 286, 283, 266, 256, 241, 219, 212, 205, 190, 163, 134, 112, 97 (100), 42.

Addition to 5,8-diacetoxy-1,4-naphthoquinone **(4)** afforded **5,8-diacetoxy-1-dimethylamino-3-methyl-1,4,4a,9a-tetrahydro-1-azaanthracene-9,10-dione (11)** (246 mg, 64%), mp 134-135°C (from dichloromethane/ether). Anal. Calcd for $C_{20}H_{22}N_2O_6$: C, 62.18, H, 5.70, N, 7.25. Found: C, 61.97, H, 5.80, N, 7.25. IR: 1770, 1705, 1665, 1595. ^{1}H-NMR: 7.33, 7.28 (AB systm., 2H, H-6, H-7, $J_{6,7}$= 8.8 Hz), 5.83 (s, 1H, H-2), 4.01 (d, 1H, H-9a, $J_{9a,4a}$= 2.8 Hz), 3.28 (m, 1H, H-4a), 2.45 (dd, 1H, H'-4, J_{gem}= 16.8 Hz, $J_{4',4a}$= 3.0 Hz), 2.36 (s, 3H, OCOMe), 2.35 (s, 3H, OCOMe), 2.21 (s, 6H, NMe_2), 2.09 (dd, 1H, H-4, J_{gem}= 16.8 Hz, $J_{4,4a}$= 6.1 Hz), 1.63 (s, 3H, Me). ^{13}C-NMR: 193.06, 192.88, 169.33, 169.20, 146.92, 146.04, 130.09, 129.37, 127.49, 126.82, 123.38, 109.07, 66.79, 48.66, 41.52, 27.11, 20.87, 20.66, 20.18. MS, *m/z*: 386 (M^+) (8), 300, 274, 255, 232, 190, 162, 134, 112, 97, 43 (100).

Addition to 5-hydroxy-8-methoxy-1,4-naphthoquinone **(5)** afforded **8-hydroxy-5-methoxy-3-methyl-1-azaanthracene-9,10-dione (12)** (264 mg, 98%), mp 253-255 °C (from ethanol). Anal. Calcd for $C_{15}H_{11}NO_4$: C, 66.91, H, 4.09, N, 5.20. Found: C, 66.68, H, 4.23, N, 5.17. IR: 1660, 1640, 1590. ^{1}H-NMR: 12.93 (s, 1H, OH), 8.87 (d, 1H, H-2, $J_{2,4}$= 2.2 Hz), 8.36 (d, 1H, H-4, $J_{2,4}$= 2.2 Hz), 7.44, 7.37 (AB systm., 2H, H-6, H-7, $J_{6,7}$= 9.5 Hz), 4.02 (s, 3H, OMe), 2.55 (s, 3H, Me). ^{13}C-NMR: 187.12, 180.92, 157.89, 155.35, 154.44, 145.47, 139.51, 135.04, 131.54, 127.11, 123.99, 118.35, 115.88, 56.96, 19.00. MS, *m/z*: 271 (M^++2) (3), 270 (M^++1) (18), 269 (M^+) (100), 254, 240, 226, 212, 184, 170, 141, 115, 91,

77, 65.

Oxidation of the adduct 10 and 11 with DDQ

5,8-Dimethoxy-3-methyl-1-azaanthracene-9,10-dione (13)

A mixture of the adduct (**10**) (100 mg, 0.3 mmol), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (500 mg, 2.2 mmol) and toluene (9 mL) was heated at 80°C for 48 h (disappearance of the adduct was monitored by TLC). The reaction mixture was filtered through a short column of silica gel and eluted with chloroform. The solvent was removed and the residue was crystallized from ethanol (51 mg, 72%), mp 235-238°C. Anal. Calcd for $C_{16}H_{13}NO_4$: C, 67.84, H, 4.63, N, 4.95. Found: C, 67.65, H, 4.56, N, 4.90. IR: 1680, 1670, 1660, 1595. ^{1}H-NMR: 8.83 (d, 1H, H-2, $J_{2,4}$= 2.0 Hz), 8.25 (d, 1H, H-4, $J_{2,4}$= 2.0 Hz), 7.36 (s, 2H, H-6, H-7), 3.99 (s, 3H, OMe), 3.98 (s, 3H, OMe), 2.50 (s, 3H, Me). ^{13}C-NMR: 182.68, 181.74, 155.30, 154.60, 154.19, 146.74, 138.32, 134.63, 130.20, 122.76, 121.96, 121.12, 120.58, 57.16, 56.94, 18.87. MS, *m/z:* 285 (M^++2) (1), 284 (M^++1) (3), 283 (M^+) (9), 282, 269, 266, 254, 225, 196, 115, 105, 91 (100), 77, 65.

5,8-Diacetoxy-3-methyl-1-azaanthracene-9,10-dione (14)

According to the above procedure the adduct (**11**) was converted into **14** in 30 h (43 mg, 40%), mp 250-255°C (from ethyl acetate). Anal. Calcd for $C_{18}H_{13}NO_6$: C, 63.72, H, 3.83, N, 4.13. Found: C, 63.45, H, 3.91, N, 4.27. IR: 1760, 1680, 1585. ^{1}H-NMR: 8.87 (d, 1H, H-2, $J_{2,4}$= 2.2 Hz), 8.28 (d, 1H, H-4, $J_{2,4}$= 2.2 Hz), 7.45 (s, 2H, H-6, H-7), 2.51 (s, 3H, Me), 2.48 (s, 3H, OCOMe), 2.46 (s, 3H, OCOMe). ^{13}C-NMR: 181.37, 179.79, 169.55, 169.27, 156.05, 148.73, 148.16, 146.09, 139.07, 134.74, 131.61, 131.29, 129.82, 125.93, 125.56, 21.08, 18.86. MS, *m/z:* 297 (M^+-43) (14), 255 (M^+-84) (100), 227, 170, 142, 116, 89, 77, 63, 51, 43.

Cycloaddition of 1-Dimethylamino-3-methyl-1-azabuta-1,3-diene (9) to Naphthoquinone Derivatives (6-8). General Procedure

To a solution of naphthoquinone (**6-8**)[16] (1 mmol) in dichloromethane (35 mL) was added portionwise the azadiene (**9**) (168mg, 1.5 mmol). The mixture was allowed to stand at rt for the period of time indicated in Table II (disappearance of naphthoquinone was monitored by TLC). The solvent was removed and the residue was analyzed by ^{1}H-NMR, the ratios of regioisomers being determined by the relative integration of the well resolved chelated OH and NH protons.

Addition to 5-amino-8-hydroxy-1,4-naphthoquinone (6) afforded **5-amino-8-hydroxy-3-methyl-1-azaanthracene-9,10-dione (15a)** (237 mg, 93%), mp 299-303°C (from chloroform). Anal. Calcd for $C_{14}H_{10}N_2O_3$: C, 66.14, H, 3.96, N, 11.02. Found: C, 65.98, H, 3.97, N, 11.14. IR: 3375, 3260, 1615, 1605, 1585. ^{1}H-NMR: 13.58 (s, 1H, OH), 8.88 (d, 1H, H-2, $J_{2,4}$= 2.1 Hz), 8.44 (d, 1H, H-4, $J_{2,4}$= 2.1 Hz), 7.23, 7.06 (AB systm., 2H, H-6, H-7, J= 9.4 Hz), 7.06 (br s, 2H, NH_2), 2.55 (s, 3H, Me). MS, *m/z:* 255 (M^++1) (2), 254 (M^+) (7), 226, 168, 152, 141, 115, 95, 60, 55, 43 (100).

Addition to 5-acetylamino-8-hydroxy-1,4-naphthoquinone (7) afforded a 4:1 mixture of the azaanthraquinones **(16a)** and **(16b)** (261 mg, 88%). The products were separated from the crude mixture by preparative TLC (toluene:acetone, 3:1) to give **5-acetylamino-8-hydroxy-3-methyl-1-azaanthracene-9,10-dione (16a)** (188 mg, 62%) mp 264- 267°C (from ethanol). Anal. Calcd for $C_{16}H_{12}N_2O_4$: C, 64.86, H, 4.08, N, 9.46. Found: C, 65.03, H, 4.12, N, 9.62. IR: 1690, 1625, 1590. ^{1}H-NMR:

13.28 (s, 1H, OH), 12.21 (br s, 1H, NH), 9.12 (d, 1H, H-6, $J_{6,7}$= 9.7 Hz), 8.91 (d, 1H, H-2, $J_{2,4}$= 2.1 Hz), 8.37 (d, 1H, H-4, $J_{2,4}$= 2.1 Hz), 7.38 (d, 1H, H-7, $J_{7,6}$= 9.7 Hz), 2.57 (s, 3H, Me), 2.30 (s, 3H, NHCOMe). ^{13}C-NMR: 186.29, 185.48, 169.89, 160.31, 156.21, 145.91, 139.54, 137.08, 135.05, 131.23, 130.78, 128.43, 114.67, 114.13, 25.66, 19.04. MS, *m/z:* 297 (M^++1) (5), 296 (M^+) (38), 254 (M^+-43) (100), 226, 198, 197, 169 and **8-acetylamino-5-hydroxy-3-methyl-1-azaanthracene-9,10-dione (16b)** (27 mg, 9%) mp 275-278°C (from ethyl acetate). Anal. Calcd for $C_{16}H_{12}N_2O_4$: C, 64.86, H, 4.08, N, 9.46. Found: C, 65.05, H, 4.07, N, 9.30. IR: 1685, 1625, 1590. ^{1}H-NMR: 13.01 (s, 1H, OH), 12.37 (br s, 1H, NH), 9.12 (d, 1H, H-7, $J_{7,6}$= 9.6 Hz), 8.91 (d, 1H, H-2, $J_{2,4}$= 2.2 Hz), 8.39 (d, 1H, H-4, $J_{2,4}$= 2.2 Hz), 7.36 (d, 1H, H-6, $J_{6,7}$= 9.6 Hz), 2.56 (s, 3H, Me), 2.29 (s, 3H, NHCOMe). ^{13}C-NMR: 187.50, 184.24, 170.09, 159.71, 156.50, 146.92, 139.27, 137.71, 134.40, 131.27, 129.30, 128.16, 115.18, 113.57, 25.62, 18.96. MS, *m/z:* 297 (M^++1) (2), 296 (M^+) (20), 254 (M^+-43) (100), 225, 198, 169, 142, 115, 92, 77, 63, 43.

Addition to 5-acetylamino-8-acetoxy-1,4-naphthoquinone (8) afforded a 1:9 mixture of adducts **(17a)** and **(17b)** (305 mg, 79%). The residue was tritured with ether to give **5-acetoxy-8-acetylamino- 1-dimethylamino-3-methyl-1,4,4a,9a-tetrahydro-1-azaanthracene-9,10-dione (17b)** (274 mg, 71%), mp 142-146°C (from cyclohexane at rt). Anal. Calcd for $C_{20}H_{23}N_3O_5$: C, 62.33, H, 6.01, N, 10.90. Found: C, 62.08, H, 6.01, N, 10.86. IR: 3240, 1770, 1700, 1675, 1600. ^{1}H-NMR: 11.31 (br s, 1H, NH), 8.96 (d, 1H, H-7, $J_{7,6}$= 9.2 Hz), 7.28 (d, 1H, H-6, $J_{6,7}$= 9.2 Hz), 5.84 (s, 1H, H-2), 4.02 (d, 1H, H-9a, $J_{9a,4a}$= 2.7 Hz), 3.29 (m, 1H, H-4a), 2.45 (dd, 1H, H'-4, J_{gem}= 17.9 Hz, $J_{4',4a}$= 3.05 Hz), 2.34 (s, 3H, OCOMe), 2.24 (s, 3H, NHCOMe), 2.22 (s, 6H, NMe_2), 2.09 (dd, 1H, H-4, J_{gem}= 17.9 Hz, $J_{4,4a}$= 5.9 Hz), 1.65 (s, 3H, Me). ^{13}C-NMR: 199.64, 192.97, 169.68, 169.58, 144.14, 138.58, 131.04, 126.60, 126.12, 123.31, 119.38, 109.49, 66.54, 48.37, 41.74, 27.06, 25.48, 21.01, 20.27. MS, *m/z:* 386 (M^++1) (3), 385 (M^+) (13), 296, 273, 254, 231, 215, 189 (100), 161, 112, 97. The mother liquor was concentrated to afford a 1:1 mixture of adduct **(17b)** and **8-acetoxy-5-acetylamino-l-dimetylamino-3-methyl-1,4,4a,9a-tetrahydro-1-azaanthracene-9,10-dione (17a)** (30 mg, 8%), ^{1}H-NMR: 11.88 (br s, 1H, NH, **17a**), 11.31 (br s, 1H, NH, **17b**), 9.02 (d, 1H, H-6, $J_{7,6}$= 9.2 Hz, **17a**), 8.96 (d, 1H, H-7, $J_{7,6}$= 9.2 Hz, **17b**), 7.33 (d, 1H, H-7, $J_{6,7}$= 9.2 Hz, **17a**), 7.28 (d, 1H, H-6, $J_{6,7}$= 9.2 Hz, **17b**), 5.84 (s, 2H, H-2, **17a, 17b**), 4.02 (m, 2H, H-9a, **17a, 17b**), 3.29 (m, 2H, H-4a, **17a, 17b**), 2.59-2.41 (m, 2H, H'-4, **17a, 17b**), 2.35 (s, 3H, OCOMe, **17a**), 2.34 (s, 3H, OCOMe, **17b**), 2.24 (s, 6H, NHCOMe, **17a, 17b**), 2.23 (s, 6H, NMe_2, **17a**), 2.22 (s, 6H, NMe_2, **17b**), 2.09 (m, 2H, H-4, **17a, 17b**), 1.65 (s, 6H, Me, **17a, 17b**).

5-Acetylamino-8-acetoxy- and 8-acetylamino-5-acetoxy-3-methyl-1-azaanthracene-9,10-diones (18a) + (18b)

A 1:9 mixture of the crude adducts **(17a)** and **(17b)** (513 mg, 1.33 mmol), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (273 mg, 1.2 mmol) and toluene (12 mL) was heated at 80°C until no starting material remained (30 min)(disappearance of the adducts was monitored by TLC). The reaction mixture was filtered through a short column of silica gel and eluted with chloroform. The solvent was removed and the residue was estimated by ^{1}H-NMR to be a 1:9 mixture of the azaanthraquinone **(18a)** and **(18b)** (55 mg, 13%). ^{1}H-NMR: 12.44 (s, 0.9H, NH, **18b**), 12.26 (s, 0.1H, NH, **18a**), 9.20 (d, 1H, H-7, **18b**, H-6, **18a**, $J_{7,6}$= 9.3 Hz), 8.90 (d, 0.9H, H-2, $J_{2,4}$= 1.8 Hz, **18b**), 8.87 (d, 0.1H, H-2, $J_{2,4}$=2.1 Hz, **18a**), 8.32 (d, 0.1H, H-4, $J_{2,4}$=2.1 Hz, **18a**), 8.29 (d, 0.9H, H-4, $J_{2,4}$= 1.8 Hz, **18b**), 7.43 (d, 1H, H-6, **18b**, H-7, **18a**, $J_{6,7}$= 9.3

Hz), 2.57 (s, 2.7H, Me, **18b**), 2.54 (s, 0.3H, Me, **18a**), 2.47 (s, 3H, OCOMe, **18a**, **18b**), 2.35 (s, 2.7H, NHCOMe, **18b**), 2.32 (s, 0.3H, NHCOMe, **18a**).

8-Acetylamino-5-acetoxy-3-methyl-1-azaanthracene-9,10-dione (18b)

According to the above procedure, the adduct (**17b**) (486 mg, 1.26 mmol) was converted into **18b** (90 mg, 21%), mp 232-236°C (from ethyl acetate). Anal. Calcd for $C_{18}H_{14}N_2O_5$: C, 63.90, H, 4.17, N, 8.28. Found: C, 63.85, H, 4.27, N, 8.56. IR: 3160, 1755, 1695, 1670, 1645, 1590. ^{1}H-NMR: 12.44 (s, 1H, NH), 9.20 (d, 1H, H-7, $J_{7,6}$= 9.3 Hz), 8.90 (d, 1H, H-2, $J_{2,4}$= 1.8 Hz), 8.29 (d, 1H, H-4, $J_{2,4}$= 1.8 Hz), 7.43 (d, 1H, H-6, $J_{6,7}$= 9.3 Hz), 2.57 (s, 3H, Me), 2.47 (s, 3H, OCOMe), 2.35 (s, 3H, NHCOMe). ^{13}C-NMR: 185.18, 181.29, 169.91, 169.32, 155.95, 145.95, 145.30, 141.01, 139.01, 134.54, 132.54, 129.76, 127.88, 123.96, 118.01, 25.54, 20.94, 18.87. MS, *m/z:* 339 (M^++1) (0.3), 338 (M^+) (1), 296, 254 (100), 225, 199, 169, 142, 117, 89, 43.

5-Acetylamino-8-acetoxy-3-methyl-1-azaanthracene-9,10-dione (18a)

A mixture of azaanthraquinone (**16a**) (156 mg, 0.53 mmol), acetic anhydride (34 mL) and pyridine (7 drops) was heated at 70°C for 4 h. The resulting solution was poured into ice/water and extracted with chloroform. The chloroform extract was dried over $MgSO_4$ and the solvent was removed to afford **18a** (133 mg, 74%), mp 233-238°C (from ethyl acetate). Anal. Calcd for $C_{18}H_{14}N_2O_5$: C, 63.90, H, 4.17, N, 8.28. Found: C, 64.31, H, 4.18, N, 8.52. IR: 3240, 1765, 1705, 1685, 1640, 1590. ^{1}H-NMR: 12.26 (s, 1H, NH), 9.19 (d, 1H, H-6, $J_{6,7}$= 9.3 Hz), 8.87 (d, 1H, H-2, $J_{2,4}$= 2.1 Hz), 8.32 (d, 1H, H-4, $J_{2,4}$= 2.1 Hz), 7.44 (d, 1H, H-7, $J_{7,6}$= 9.3 Hz), 2.54 (s, 3H, Me), 2.47 (s, 3H, OCOMe), 2.32 (s, 3H, NHCOMe). ^{13}C-NMR: 186.80, 180.00, 169.88, 169.79, 156.41, 146.18, 146.06, 140.78, 139.05, 134.81, 132.87, 129.74, 127.87, 124.54, 117.65, 25.74, 21.09, 18.94. MS, *m/z:* 339 (M^++1) (0.6), 338 (M^+) (0.7), 296, 281, 254 (100), 226, 197, 169, 142, 115, 89, 43 (96).

5-Amino-8-hydroxy- and 8-amino-5-hydroxy-3-methyl-1-azaanthracene-9,10-diones (15a)+ (15b)

A 1:9 mixture of the crude azaanthraquinones (**18a**) and (**18b**) (308 mg, 0.91 mmol) and 8% aqueous sodium hydroxide (98 ml) was heated at 80°C until no starting material remained (7 h). Then the reaction mixture was acidified with 8% hydrochloric acid and extracted with chloroform and the extract was dried over $MgSO_4$ and the solvent was removed. The residue was estimated by ^{1}H-NMR to be a 1:9 mixture of azaquinones (**15a**) and (**15b**) (141 mg, 65%).

8-Amino-5-hydroxy-3-methyl-1-azaanthracene-9,10-dione (15b)

According to the above procedure, azaquinone (**18b**) (338 mg, 1 mmol) was converted into azaquinone (**15b**) (186 mg, 73%), mp 298-300°C (from chloroform). Anal. Calcd for $C_{14}H_{10}N_2O_3$: C, 66.14, H, 3.96, N, 11.02. Found: C, 66.03; H, 3.90; N, 11.12. IR: 3360, 3260, 3175, 1610, 1590. ^{1}H-NMR: 13.35 (s, 1H, OH), 8.91 (d, 1H, H-2, $J_{2,4}$= 2.1 Hz), 8.42 (d, 1H, H-4, $J_{2,4}$= 2.1 Hz), 7.22, 6.98 (AB systm., 2H, H-6, H-7, J= 9.3 Hz), 7.19 (br s, 2H, NH_2), 2.54 (s, 3H, Me).

8-Hydroxy-3-methyl-1-azanthracene-9,10-dione (19a)

Sodium nitrite (290 mg, 4.2 mmol) was added to a magnetically stirred solution of **15a** (261 mg, 1.02 mmol) in 0.5% aqueous sodium hydroxide (400 mL) and dioxane (20 mL). The mixture was then added to

a solution of hypophosphorous acid (37 mL) in ice (700 g). After 15 min, positive test for free nitrous acid was observed, the mixture was warmed at 70 °C for 3 h and allowed to stand at rt for 10 h. Then the mixture was extracted with chloroform, and the extract was dried over $MgSO_4$ and the solvent was removed under vacuum. The residue was crystallized from ethyl acetate to give **19a** (106 mg, 44%), mp 224-225 °C (lit.,[11d] 225-226°C). The spectral data were also identical with those reported in the literature.[11d]

8-Hydroxy- and 5-hydroxy-3-methyl-1-azaanthracene-9,10-diones (19a)+(19b)

a) According to the above procedure, 1:9 crude mixture of **15a** and **15b** was converted into 1:9 mixture of **19a** and **19b**, (92 mg, 40%). The products were separated by preparative TLC (chloroform) to give **8-hydroxy-3-methyl-1-azaanthracene-9,10-dione (19a)** (8 mg, 3%), mp 224-226°C (from ethyl acetate) (lit.,[11d] 225-226°C) and **5-hydroxy-3-methyl-1-azaanthracene-9,10-dione (19b)** (80 mg, 35%), mp 259-261°C (from ethyl acetate) (lit.,[11d] 261-263°C). The spectral data were also identical with those reported in the literature.[11d]

b) According to the above procedures a 4:1 mixture of **16a** and **16b** (296 mg, 1 mmol), was converted into 4:1 mixture of **19a** and **19b** (92 mg, 49%). The mixture of azaanthraquinones was separated by preparative TLC (chloroform) to give **8-hydroxy-3-methyl-1-azaanthracene-9,10-dione (19a)** (75 mg, 40%), mp 224-225°C (from ethyl acetate) (lit.,[11d] 225-226°C) and **5-hydroxy-3-methyl-1-azaanthracene-9,10-dione (19b)** (9 mg, 5%), mp 259-261°C (from ethyl acetate) (lit.,[11d] 261-263).

5-Hydroxy-3-methyl-1-azaanthracene-9,10-dione (19b)

According to the above procedure, a sample of the pure anthraquinone (**15b**) was converted into **19b** mp 259-261°C (from ethyl acetate) (lit.,[11d] 261-263°C) (30%). The spectral data was also identical with those reported in the literature.[11d]

ACKNOWLEDGMENT

We thank the Secretaría de Estado de Universidades e Investigación (DGICYT grant PB93-0156) for financial support and J. A. Esteban for technical assistance.

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Received, 11th May, 1998