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Hetero Diels–Alder Reactions of 1-Acetylamino- and 1-Dimethylamino-1-azadienes with Benzoquinones

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Abstract—Treatment of bromobenzoquinone with 2 equiv. of a 1-dimethylamino-1-azadiene afforded mixtures of the corresponding 1,8-diaza-9,10-anthraquinone and 1,5-diaza-9,10-anthraquinone. Double hetero Diels–Alder reactions between 1-dimethylamino-1-azadienes and 2,6-dibromobenzoquinone afford symmetrically substituted 1,8-diaza-9,10-anthraquinone derivatives in excellent yields. 3-Substituted 1-azadienes afford aromatic derivatives, while 4-substituted or 3,4-disubstituted 1-azadienes lead to 1,8-bis-(dimethylamino)-1,4,5,8-tetrahydro-1,8-diaza-9,10-anthraquinones, which were aromatized under thermal conditions. The hetero Diels–Alder reactions could also be controlled to give isolated 7-bromo-5,8-quinolinequinones, whose treatment with a second azadiene allowed the preparation of unsymmetrical 1,8-diaza-9,10-anthraquinones.

Introduction

Several families of antitumour natural products, including the anthracyclines (e.g. doxorubicin and daunorubicin),[1,2] the pluramycins (e.g. sapurimycin)[3,4] and some of the enediyne antibiotics, like dynemycin A and deoxydynemycin A,[5,6] contain a 9,10-anthraquinone substructure. The antitumour activity of these quinones is normally ascribed to several mechanisms, which are believed to follow DNA intercalation. Generation of free oxygen radicals concomitant with reduction of the quinone function is probably one of the main of these mechanisms.

It has been reasoned that isosteric substitution of one or both of the carbon atoms of the benzene rings in the anthraquinone unit by nitrogen atoms should lead to analogues with improved ability to generate radicals, owing to easier reduction of the quinone function, while retaining the intercalating properties.[7] For these reasons, the preparation of azaanthraquinones as potential antitumour agents is a very promising field of research. However, and in spite of this interest, many types of azaanthraquinone systems remain little studied due to limitations in the existing synthetic methodology. Thus, the unsubstituted 1,8-diazaanthraquinone parent system has been prepared in 28% yield using a sequence based on the directed *ortho*-lithiation of *N*,*N*-diethylpyridine-2-carboxamide, followed by reaction with 2-bromopyridine-3-carbaldehyde, new lithiation, cyclization and air oxidation.[8] In an alternative, potentially more flexible approach,[9,10] hetero Diels–Alder reactions[11] of quinolinequinones with 1-dimethylamino-1-azadienes[12] yield mixtures of 1,8-diazaanthraquinones and their 1,5-diaza-regioisomers, which become the major products by introduction of a halogen atom in the C-6 position of the quinolinequinone derivative.[13] We report here our research into the synthesis of 1,8-diazaanthraquinones from benzoquinone derivatives.

Methods and Results

In principle, double hetero Diels–Alder reactions of benzoquinone derivatives and suitably activated 1-azadienes should provide a very simple synthesis of symmetrically substituted 1,8-diazaanthraquinones. Unfortunately, the only literature precedent of this reaction was discouraging, since treatment of benzoquinone with excess methacrolein dimethylhydrazone afforded 6-dimethylaminoquinolinequinone as the only reaction product rather than 3,6-dimethyl-1,8-diazaanthraquinone.[9] This result can be rationalized in terms of a single hetero Diels–Alder cycloaddition, followed by a two-step aromatization to quinolinequinone with concomitant elimination of dimethylamine, addition of the latter to quinolinequinone and new oxidation (Scheme 1).

We envisaged that the problem might be solved by replacing 1-dimethylamino-1-azadienes with 1-acetylamino-1-azadienes, which, although less reactive, have the advantage of not delivering nucleophilic species into the reaction medium.[14] Indeed, treatment of benzoquinone with 2 equiv. of 1-acetylamino-3-ethyl-1-azadiene in refluxing

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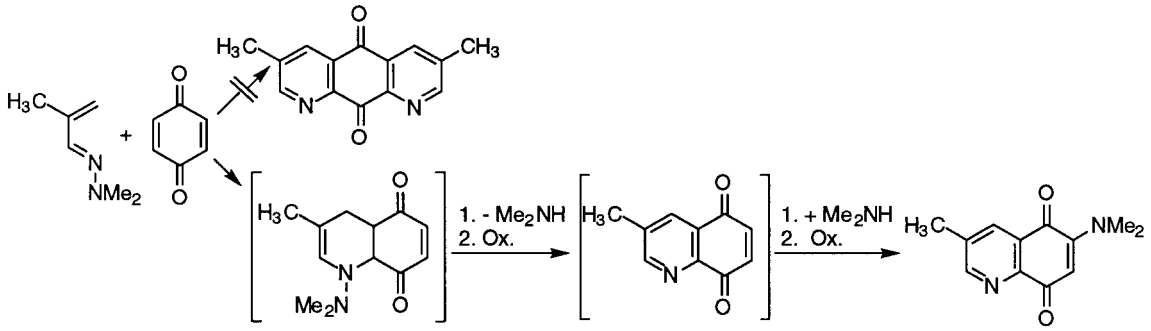
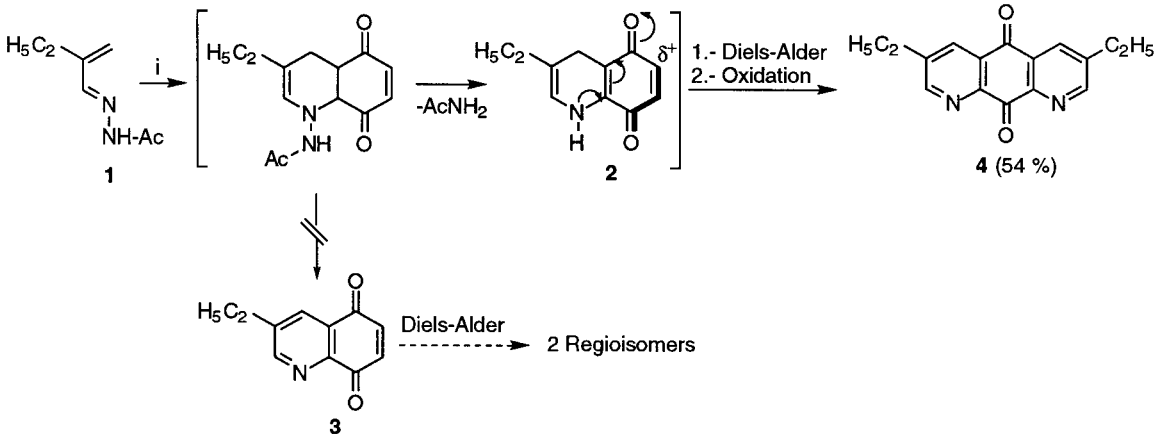


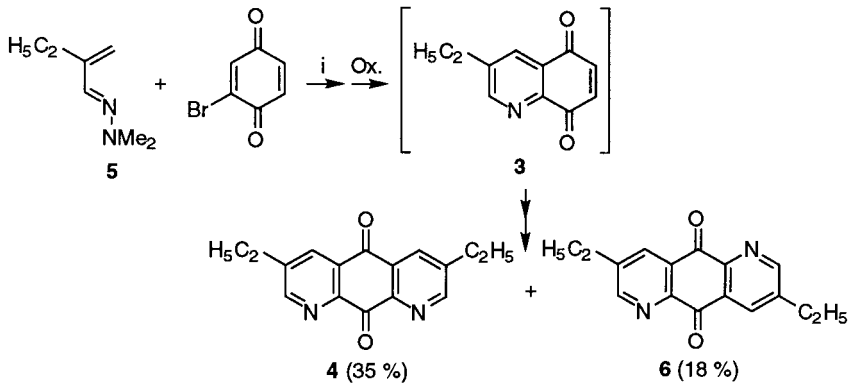
Scheme 1.

toluene for 28 h afforded a 54% yield of 3,6-diethyl-1,8-diazaanthraquinone **4** (Scheme 2). The fact that **4** was the only isolated reaction product suggests that 3-ethylquinolinequinone **3** was not an intermediate of the reaction, because in that case a mixture of both possible regioisomers should have been obtained.[15] This suggests that the second Diels–Alder reaction takes place on the non-isolated 1,4-dihydroquinoline intermediate **2**, in which conjugation between the nitrogen and the C-5 carbonyl leaves the $C_6{=}C_7{-}C_8{=}O$ portion of the molecule as a relatively isolated conjugated system with its electophilic end at C-6, leading to the observed regioselectivity.

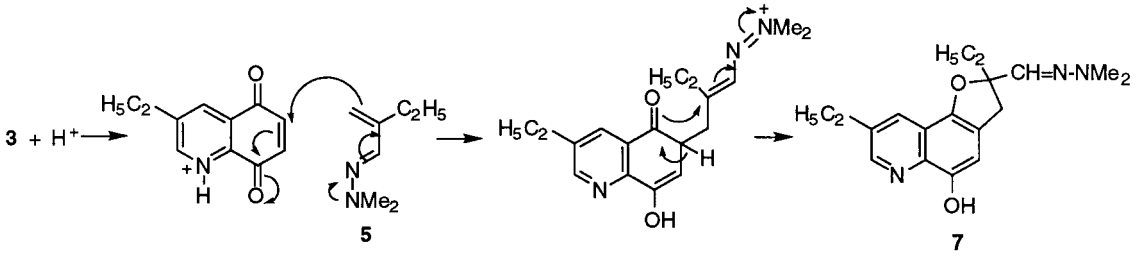
In an effort to achieve the same transformation under milder conditions, we decided to study the reactions between 1-dimethylamino-1-azadienes and halogenated benzoquinones, since we expected that liberation of the corresponding hydrogen halide from the primary Diels–Alder adduct would trap dimethylamine and prevent its undesired addition to intermediate quinolinequinones. In an initial experiment, we treated 1-dimethylamino-3-ethyl-1-azadiene **5**[16] with 2-bromobenzoquinone, and obtained a 4:1 mixture of the 1,8-diaza- and 1,5-diazaanthraquinones **4** and **6**, although the ratio changed to 2:1 after chromatography owing to partial decomposition of **4** (Scheme 3). As



Scheme 2. Reagents and conditions: (i) *p*-Benzoquinone (2 equiv.), xylene, reflux, 28 h.



Scheme 3. Reagents and conditions: (i) $CHCl_3$, rt, 3 min.

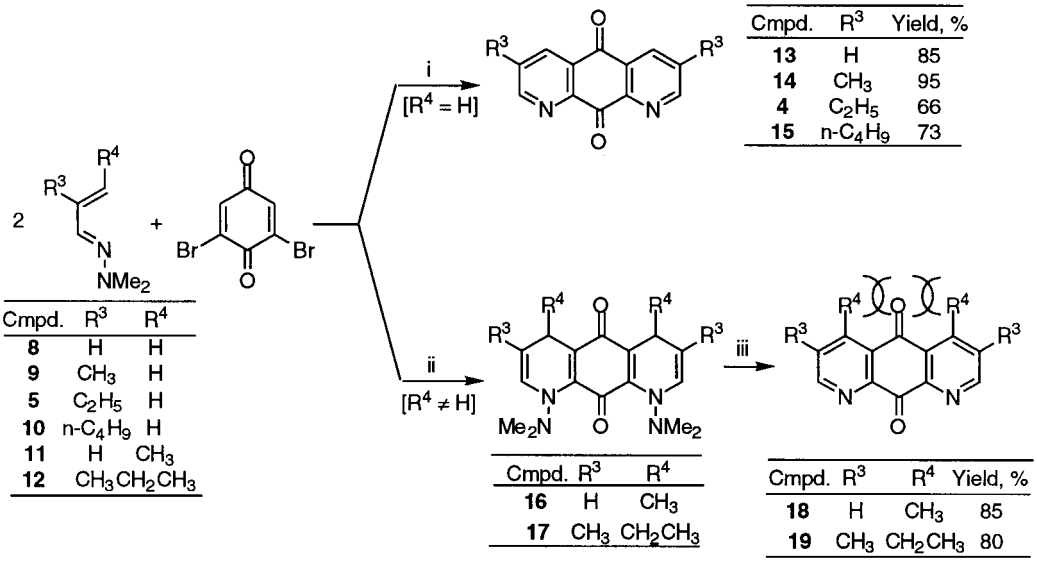


Scheme 4.

previously mentioned, this lack of regioselectivity seems to indicate that, in this case, aromatization of the primary adduct to 3-ethylquinolinequinone **3** takes place before the start of the second Diels–Alder reaction. Assignment of the 1,5- and 1,8-diazaanthraquinone structures was based on the fact that, owing to the different symmetry of both systems, the carbonyls of the 1,5-diaza derivative are equivalent, unlike those of the 1,8-diaza regioisomer. Accordingly, two clearly differentiated infrared absorptions at 1695.8 and 1668.4 cm^{-1} and two ^{13}C NMR signals at 180.3 and 182.7 ppm were observed for compound **4**, while **6** showed single IR (1682.6 cm^{-1}) and ^{13}C NMR (181.65 ppm) carbonyl signals.

In the course of the above experiments, we noticed that some reactions gave small amounts of the furo[2,3-*f*]quinoline derivative **7** together with compounds **4** and **6**. Upon closer examination, this behaviour could be attributed to the use of two different batches of bromobenzoquinone, one of which had been prepared by oxidation of 2-bromohydroquinone[17] with cerium ammonium nitrate, while for the other we had used acidic sodium dichromate for the oxidation step, and therefore the quinone might have been contaminated with traces of acid. Protonation of the quinoline nitrogen of **3** under these conditions increases the electron deficiency at the C-8 carbonyl and therefore the electrophilic character of its conjugated position, favouring a Michael addition of the azadiene to C-6.[18] The intermediate thus formed would finally lead to compound **7** through a *5-exo-trig* cyclization involving the C-5 carbonyl oxygen (Scheme 4). Similar deviations of hetero Diels–Alder reactions to formal [3+2] cycloadditions leading to furoquinolines have been previously described in situations of increased quinone polarity due to the presence of protic[19,20] or Lewis[21] acids, and also in cases where strong electron-withdrawing groups were present in the quinone[22,23] or in the azadiene.[24]

In an effort to increase the regioselectivity of the second cycloaddition, we decided to examine the reactions of 2,6-dibromobenzoquinone[25] and several 1-dimethylamino-1-azadienes (compounds **5** and **8**–**12**).[26,27] As shown in Scheme 5, the reactions involving 4-unsubstituted azadienes **5**, **8**, **9**, and **10** afforded good to excellent yields of 1,8-diazaanthraquinone derivatives, which were isolated as the fully aromatic derivatives **4** and **13**–**15**, respectively. Instead, treatment of the 4-substituted azadienes **11** and **12** with 2,6-dibromo-benzoquinone gave the 1,8-bis-(dimethylamino)-1,4,5,8-tetrahydro derivatives **16** and **17**, arising from double elimination of hydrobromic acid from the primary Diels–Alder adduct. Compounds **16** and **17** were unstable to acid, and their isolation required the addition of triethylamine to the reaction medium to trap hydrobromic acid. Steric compression between the C_4- and C_5-alkyl groups and the C-10 carbonyl presumably prevented their spontaneous aromatization through double elimination of



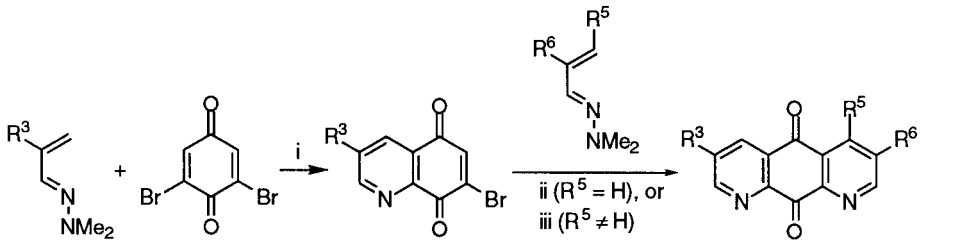
Cmpd.	R^3	R^4
8	H	H
9	CH_3	H
5	C_2H_5	H
10	n-C_4H_9	H
11	H	CH_3
12	$CH_3CH_2CH_3$	

Cmpd.	R^3	Yield, %
13	H	85
14	CH_3	95
4	C_2H_5	66
15	n-C_4H_9	73

Cmpd.	R^3	R^4
16	H	CH_3
17	CH_3	CH_2CH_3

Cmpd.	R^3	R^4	Yield, %
18	H	CH_3	85
19	CH_3	CH_2CH_3	80

Scheme 5. Reagents and conditions: (i) CH_2Cl_2, rt, 1 min; (ii) CH_2Cl_2, Et_3H, rt, 15 min; (iii) 110°C, 0.1 Torr, 2 h.



Cmpd.	R^3
8	H
9	CH_3

Cmpd.	R^3
20	H
21	CH_3

Cmpd.	R^3	R^5	R^6	Yield, %
22	CH_3	H	H	91
23	CH_3	H	C_2H_5	39
24	CH_3	H	nC_4H_9	43
25	CH_3	CH_3	H	35
26	CH_2CH_3	H	H	75

Scheme 6. Reagents and conditions: (i) $(CH_2Cl)_2$, 110°C, 2 h; (ii) $CHCl_3$, rt, 12 h; (iii) $CHCl_3$, Et_3N, rt, 24 h.

dimethylamine, as observed during the preparation of compounds **2** and **13**–**15**.[28] Indeed, aromatization of **16** and **17** proved more difficult than expected, but after several unsuccessful attempts under varied literature conditions[16,29] we found that heating the neat compounds **16** and **17** under vacuum afforded excellent yields of their aromatic derivatives (compounds **18** and **19**, respectively).

Finally, and in order to extend the synthetic scope of the method, we decided to study the possibility of obtaining unsymmetrically substituted derivatives of the 1,8-diazaanthraquinone system by combination of 2,6-dibromobenzoquinone with two different azadienes. This objective required us to achieve single hetero Diels–Alder cycloadditions of 2,6-dibromobenzoquinone leading to 7-bromo-5,8-quinolinequinones, which would then be submitted to a second cycloaddition. After many unsuccessful attempts at carrying out this transformation at room temperature, we found that, in spite of the high reactivity of 2,6-dibromobenzoquinone, the best results were obtained by slow addition of the azadiene onto a diluted, refluxing solution of the starting quinone; this procedure cleanly afforded mixtures of the desired 7-bromoquinolinequinones (**20** or **21**) and dimethylamine hydrobromide.[30] Compounds **20** and **21** are relatively unstable in these mixtures since, upon standing for a few hours, dimethylamine is easily transferred from its hydrobromide to **20** or **21** leading to mixtures of dimethylamino derivatives whose structure was not investigated in detail. Since, on the other hand, compounds **20** and **21** could not be properly purified by column chromatography without extensive decomposition, the best method consisted of simple filtration through a pad of silica gel of a solution of the crude **20** or **21** in order to eliminate dimethylamine hydrobromide, followed by evaporation and immediate use for the second Diels–Alder reaction. These conditions led to the results summarized in Scheme 6, with good to excellent yields in the cases where the final product was unsubstituted at one of the pyridine rings (compounds **22** and **26**). Other substituent combinations led to less satisfactory results (35–43% yields). It is noteworthy that compound **25**, whose preparation required the use of the C-4 substituted crotonaldehyde dimethylhydrazone, was isolated as a fully aromatic derivative after 24 h at room temperature instead of the drastic conditions required for the preparation of **18** and **19**, showing the effect of a decreased steric compression in compound **26**.

Experimental

All reagents were of commercial quality (Aldrich, Fluka, SDS, Panreac) and were used as received. Solvents (SDS) were dried and purified using standard techniques. 'Petroleum ether' refers to the fraction boiling at 40–60°C. Reactions were monitored by thin layer chromatography, on aluminium plates coated with silica gel with fluorescent indicator (Macherey–Nagel Alugram Sil G/UV_{254}). Separations by flash chromatography were performed on silica gel (SDS 60 ACC, 230–40 mesh). Melting points were measured with a Reichert 723 hot stage microsope, and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer Paragon 1000 FT-IR spectrophotometer, with all compounds examined in KBr pellets or as films on a NaCl disk. NMR spectra were obtained on Bruker AC-250 (250 MHz for ^1H, 63 MHz for ^{13}C) or Varian VXR-300 (300 MHz for ^1H, 75 MHz for ^{13}C) spectrometers, with $CDCl_3$ as solvent (Servicio de Espectroscopía, Universidad Complutense). Elemental analyses were determined by the Servicio de Microanálisis, Universidad Complutense, on Perkin–Elmer 2400 CHN and Leco CHNS 932 analyzers.

Reaction of acetohydrazide (1) and *p*-benzoquinone

A solution of *N′*-(2′-ethyl-2-propenylidene)acetohydrazide **1**[14](39 mg, 0.27 mmol) and *p*-benzoquinone (30 mg, 0.27 mmol) in xylene (25 mL) was heated for 28 h at 140°C while air was bubbled through the reaction mixture, with periodic additions of fresh xylene to prevent complete evaporation. The solution was evaporated under reduced pressure and chromatographed (AcOEt), affording 20 mg (54%) of 3,6-diethyl-1,8-diaza-9,10-anthraquinone **4**, as a pale yellow solid; [Found: C, 72.50; H, 5.54; N, 10.50. $C_{16}H_{14}N_2O_2$ requires C, 72.18; H, 5.26; N, 10.53%]; mp 222–224°C; ν_{max} (KBr) 1696, 1668 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.92 (d, 2H, J=1.7 Hz, H-2,7); 8.37 (d, 2H, J=1.7 Hz, H-4,5); 2.85 (q, 4H, J=1.7 Hz, 2 CH_2–CH_3); 1,30 (t, 6H, 2 CH_2–CH_3); δ_C ($CDCl_3$, 63 MHz) 182.7 (C-9), 180.3 (C-10), 155.7 (C-2,7), 146.8 (C-8a,9a), 145.3

(C-3,6), 133.8 (C-4,5), 129.7 (C-4a,10a), 26.4 (CH_2–CH_3), 14.6 (CH_2–CH_3).

Reaction of 2-ethyl-2-propenal dimethylhydrazone (5) with 2-bromobenzoquinone

(a) *Preparation of 2-bromobenzoquinone.* To a solution of 2-bromohydroquinone[17] in acetonitrile (5 mL) was added cerium ammonium nitrate (214 mg, 0.39 mmol), in small portions. The orange suspension was stirred at room temperature for 10 min, diluted with water (5 mL) and extracted with $CHCl_3$ (3×50 mL). The combined organic layers were dried over Na_2SO_4 and evaporated, yielding 40 mg (82%) of analytically pure 2-bromobenzoquinone, as yellow crystals. mp 54–55°C, lit.[31] 55–56°C; ν_{max} (KBr) 1667.1 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 7.29 (d, 1H, $J_{3,5}$=2.3 Hz, H-3); 6.81 (dd, 1H, $J_{3,5}$=2.3 Hz, $J_{5,6}$=10.1 Hz, H-5); 6.97 (d, 1H, $J_{5,6}$=10.1 Hz, H-4); δ_C ($CDCl_3$, 63 MHz) 184.7 (C-4), 179.3 (C-1), 138.2 (C-3), 137.2 (C-2), 136.8 (C-6), 135.9 (C-5).

(b) *Hetero Diels–Alder reaction.* To a solution of 2-bromobenzoquinone (40 mg, 0.2 mmol) in $CHCl_3$ (10 mL) was added 2-ethyl-2-propenal dimethylhydrazone **5**[16] (54 mg, 0.42 mmol). The solution was stirred at room temperature for 5 min and evaporated, and the residue was further heated in vacuo (water pump) at 50°C for 20 min. The residue was characterized by ^1H NMR spectroscopy as a 4:1 mixture of **4** and **6**. Chromatography (AcOEt) yielded 20 mg (35%) of **4** and 10 mg (18%) of 3,5-diethyl-1,5-diaza-9,10-anthraquinone **6**, both as pale yellow crystals. Data for **6**: [Found: C, 71.86; H, 5.50; N, 10.11. $C_{16}H_{14}N_2O_2$ requires C, 72.18; H, 5.26; N, 10.53%]; mp 218–220°C; ν_{max} (KBr) 1683 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.93 (d, 2H, *J*=2.1 Hz, H-2,6), 8.50 (d, 2H, *J*=2.1 Hz, H-4,8), 2.85 (q, 2H, *J*=7.5 Hz, C*H*$_2$–CH_3), 1.35 (t, 3H, *J*=7.5 Hz, CH_2–C*H*$_3$); δ_C ($CDCl_3$, 63 MHz) 181.6 (C-9,10), 155.7 (C-2,6), 146.50 (C-9a,10a), 145.6 (C-3,7), 135.5 (C-4,8), 130.6 (C-4a,8a), 26.6 (*C*H_2–CH_3), 14.8 (CH_2–*C*H_3).

When the starting bromobenzoquinone had been prepared by oxidation of 2-bromohydroquinone with acidic sodium dichromate, the reaction yielded a 1:1 mixture of **4** and **6** (68%) and a small amount (17%) of 2-dimethylhydrazonomethyl-2,6-diethyl-5-hydroxy-1,2-dihydrofuro[2,3-*f*]quinoline (**7**), as a pale yellow oil. [Found: C, 68.79; H, 7.22; N, 13.21. $C_{18}H_{23}N_3O_2$ requires C, 68.98; H, 7.40; N, 13.41]; ν_{max} (KBr) 3380, 1635 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.94 (d, 1H, *J*=2.2 Hz, H-7), 8.52 (m, 1H, H-9), 7.99 (s, 1H, OH), 6.94 (s, 1H, C*H*=NMe_2), 6.67 (s, 1H, H-4), 3.80 (d, 1H, *J*=15.8 Hz, H-3), 3.15 (d, 1H, *J*=15.8 Hz, H-3), 2.85 (m, 4H, 2 C*H*$_2$–CH_3), 2.76 (s, 6H, NMe_2), 1.34 (m, 6H, 2 CH_2–C*H*$_3$).

Double hetero Diels–Alder reactions of 4-unsubstituted 1-dimethylamino-1-azadienes with 2,6-dibromobenzoquinone: general procedure

To a solution of 2,6-dibromobenzoquinone (275 mg, 1.0 mmol) in $CHCl_3$ (15 mL) was added the appropriate azadiene[26] (2 equiv.). The solution was stirred for 5 min at room temperature and evaporated under reduced pressure, and the residue was further heated in vacuo (water pump) at 50°C for 20 min. The residue was washed with Et_2O (2×15 mL), yielding the aromatic derivatives **4** and **13**–**15** as off-white or pale yellow solids.

1,8-Diaza-9,10-anthraquinone (13). Yield, 184 mg (85%). Mp >300°C; lit.[8], mp >300°C. Spectral data for this compound were identical to those previously described.[8]

3,5-Dimethyl-1,8-diaza-9,10-anthraquinone (14). Yield, 233 mg (95%). [Found: C, 70.19; H, 4.46; N, 11.46. $C_{14}H_{10}N_2O_2$ requires C, 70.59; H, 4.20; N, 11.76%]; mp 263–264°C; ν_{max} (KBr) 1696, 1670 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.94 (d, 2H, *J*=1.5 Hz, H-2,7), 8.37 (d, 2H, *J*=1.5 Hz, H-4,5), 2.56 (s, 6H, 2 CH_3). δ_C ($CDCl_3$, 63 MHz) 182.6 (C-9), 180.0 (C-10), 156.2 (C-2,7), 146.6 (C-8a,9a), 139.2 (C-3,6), 134.8 (C-4,5), 129.4 (C-4a,10a), 18.9 (2 CH_3).

3,5-Diethyl-1,8-diaza-9,10-anthraquinone (4). Yield 182 mg (66%). See data above.

3,5-Di-*n*-butyl-1,8-diaza-9,10-anthraquinone (15). Yield, 241 mg (73%). [Found: C 74.14; H, 6.76; N, 8.35. $C_{20}H_{22}N_2O_2$ requires C, 74.51; H, 6.88; N, 8.69%]; mp 132–134°C; ν_{max} (KBr) 1700 and 1671 cm^{-1}. δ_H ($CDCl_3$, 250 MHz) 8.94 (d, 2H, *J*=2.2 Hz, H-2,7), 8.39 (d, 2H, *J*=2.2 Hz, H-4,5), 2.83 (t, 4H, *J*=7.6 Hz, C*H*$_2$–CH_2–CH_2–CH_3), 1.8–1.6 (m, 4H, CH_2–C*H*$_2$–CH_2–CH_3), 1.40 (m, 4H, CH_2–CH_2–C*H*$_2$–CH_3), 0.95 (t, 6H, *J*=7.3 Hz, CH_2–CH_2–CH_2–C*H*$_3$). δ_C ($CDCl_3$, 63 MHz) δ 183.0 (C-9), 180.1 (C-10), 156.2 (C-2,7), 147.1 (C-8a,9a), 144.17 (C-3,6), 134.39 (C-4,5), 129.79 (C-4a,10a), 33.1 and 32.9 (*C*H_2–CH_2–CH_2–CH_3 and CH_2–*C*H_2–CH_2–CH_3), 22.4 (CH_2–CH_2–*C*H_2–CH_3), 13.9 ($C_{3,5}$–CH_2–CH_2–CH_2–*C*H_3).

Double hetero Diels–Alder reactions of 4-substituted 1-dimethylamino-1-azadienes with 2,6-dibromobenzoquinone: general procedure

To a solution of 2,6-dibromobenzoquinone (200 mg, 0.75 mmol) in $CHCl_3$ (10 mL) was added triethylamine (2 equiv.) and the appropriate azadiene (2 equiv.). The solution was stirred at room temperature for 15 min and evaporated under reduced pressure. The residue was washed with water (3×25 mL), yielding compounds **16** or **17** as green solids, which were identified by their spectral data and used for the next step without further purification.

The appropriate 1,8-bis(dimethylamino)-1,4,5,8-tetrahydro-1,8-diaza-9,10-anthraquinone derivative **16** or **17** was heated neat at 110°C and 0.1 mm for 2 h. The cooled reaction mixture was washed with ethyl ether (2×15 mL), affording the aromatic derivatives **18** and **19** as pale yellow solids.

1,8-bis(dimethylamino)-4,5-dimethyl-1,4,5,8-tetrahydro-1,8-diaza-9,10-anthraquinone (16). δ_H ($CDCl_3$, 250 MHz) 6.14 (d, 2H, *J*=7.8 Hz, H-2,7), 5.02 (dd, 2H, *J*=7.8 and 5.1 Hz, H-3,6), 3.48 (m, 2H, H-4,5), 2.64 (s, 12H, 2 NMe_2), 1.08 (d, 6H, *J*=6.6 Hz, 2 CH_3); δ_C ($CDCl_3$, 63 MHz) 182.3 (C-9); 172.4 (C-10); 137.8 (C-4a,10a); 122.2 (C-2,7);

119.4 (C-8a,9a); 112.2 (C-3,6); 44.8 (2 NMe_2), 34.9 (C-4,5); 24.6 (2 CH_3).

1,8-bis(dimethylamino)-4,5-diethyl-3,6-dimethyl-1,4,5,8-tetrahydro-1,8-diaza-9,10-anthraquinone (17). δ_H ($CDCl_3$, 250 MHz) 6.08 (s, 2H, H-2,7); 3.47 (t, 2H, J=4.1 Hz, H-4,5); 2.60 (s, 12H, 2 NMe_2), 1.68 (s, 6H, C(3,5)–CH_3), 1.16 (m, 4H, 2 CH_2–CH_3), 0.78 (t, 6H, J=7.5 Hz, 2 CH_2–CH_3).

4,5-Dimethyl-1,8-diazaanthraquinone (18). Starting from 235 mg (0.72 mmol) of compound **16**, a yield of 146 mg (85%) of compound **18** was obtained. [Found: C, 70.67; H, 4.20; N, 11.76. $C_{14}H_{10}N_2O_2$ requires C, 70.58; H, 4.20; N, 11.76]; mp 245–247°C; ν_{max} (KBr) 1670.2 cm^{-1}. δ_H ($CDCl_3$, 250 MHz) 8.89 (d, 2H, J=4.8 Hz, H-2,7), 7.49 (d, 2H, J=4.8 Hz, H-3,5); 2.56 (s, 6H, 2 CH_3). δ_C ($CDCl_3$, 63 MHz) 186.5 (C-9); 181.1 (C-10); 153.6 (C-2,7); 151.2 (C-8a,9a); 150.4 (C-4,5); 131.7 (C-3,6); 129.9 (C-4a,10a); 22.5 (2 CH_3).

4,5-Diethyl-3,6-dimethyl-1,8-diazaanthraquinone (19). Starting from 286 mg (0.74 mmol) of compound **16**, an yield of 175 mg (80%) of compound **19** was obtained. [Found: C, 73.17; H, 5.98; N, 9.43. $C_{18}H_{18}N_2O_2$ requires C, 73.46; H, 6.12; N, 9.52]; mp 165–167°C; ν_{max} (KBr) 1671.3 cm^{-1}. δ_H ($CDCl_3$, 250 MHz) 8.76 (s, 2H, H-2,7), 3.13 (q, 4H, J=7.7 Hz, 2 CH_2–CH_3), 2.49 (s, 6H, 2 CH_3), 1.33 (t, 6H, J=7.7 Hz, 2 CH_2–CH_3); δ_C ($CDCl_3$, 63 MHz) 182.9 (C-9); 180.1 (C-10); 155.0 (C-2,7); 153.8 (C-8a,9a); 147.5 (C-4,5); 138.5 (C-3,6); 130.5 (C-4a,10a); 23.4 (*C*H_2–CH_3); 16.9 (C(4)–CH_3); 13.5 (CH_2–*C*H_3).

Preparation of unsymmetrical 1,8-diaza-9,10-anthraquinones: general procedures

A suspension of 2,6-dibromobenzoquinone in $(ClCH_2)_2$ (40 mL per 100 mg of dibromobenzoquinone) was stirred at 110°C for 15 min. To the solution thus obtained was added a solution of acrolein dimethylhydrazone **8** (1 equiv.) or methacrolein dimethylhydrazone **9** (1 equiv.) in $(ClCH_2)_2$ (10 mL), dropwise over 1 h. The solution was stirred at that temperature for 1 h, and an additional amount of 0.1 equiv. of the azadiene was added. After further 30 min at 110°C, the reaction mixture was cooled and evaporated. The residue was dissolved in ethyl acetate (10 mL) and filtered through a pad of silica gel. Evaporation of the solvent afforded a residue, which was characterized by ^1H NMR spectroscopy as the virtually pure 7-bromo-5,8-quinolinequinone **20** or 7-bromo-3-methyl-5,8-quinolinequinone **21**, which were immediately used without further purification.

To a solution of **20** or **21** in $CHCl_3$ (5 mL) was added the appropriate second azadiene (1.2 equiv.). The solution was stirred at room temperature for 12 h (24 h in the preparation of compound **26**) and evaporated. The residue was chromatographed (AcOEt), yielding compounds **22**–**26** as off-white, pale yellow or pale brown solids.

7-bromo-5,8-quinolinequinone (20). δ_H ($CDCl_3$, 250 MHz) 9.05 (dd, 1H, J=4.7 and 1.7 Hz, H-2), 8.46 (dd, J=7.7 and 1.7 Hz, H-4), 7.71 (dd, J=7.5 and 4.8 Hz, H-3), 7.58 (s, 1H, H-6).

7-bromo-3-methyl-5,8-quinolinequinone (21). δ_H ($CDCl_3$, 250 MHz) 8.76 (d, 1H, J=2.0 Hz, H-2), 8.10 (d, 1H, J=1.4 Hz, H-4), 6.94 (s, 1H, H-6), 2.48 (s, 3H, CH_3).

3-Methyl-1,8-diaza-9,10-anthraquinone (22). Starting from 117 mg (0.44 mmol) of 2,6-dibromobenzoquinone, 42 mg (1 equiv.) of the azadiene **8** and then 51 mg (1.2 equiv.) of the azadiene **9**, a yield of 89 mg (91%) of compound **22** was obtained, as an off-white solid. [Found: C, 69.32; H, 3.79; N, 12.29. $C_{13}H_8N_2O_2$ requires C, 69.63; H, 3.59; N, 12.49]; mp 298–301°C; ν_{max} (KBr) 1698 and 1673 cm^{-1}. δ_H ($CDCl_3$, 250 MHz) 9.16–9.12 (m, 1H, H-7), 8.95 (d, 1H, J=1.7 Hz, H-2), 8.65–8.59 (m, 1H, H-5), 8.39 (d, 1H, J=1.2 Hz, H-4), 7.80–7.72 (m, 1H, H-6), 2.56 (s, 3H, C_3–CH_3). δ_C ($CDCl_3$, 63 MHz) 182.5 (C-9), 180.1 (C-10), 156.6 and 155.70 (C-2 and C-7), 148.9 (C-8a), 146.80 (C-9a), 139.6 (C-3), 135.3 and 134.9 (C-4 and C-5), 130.04 (C-10a), 129.61 (C-4a), 128.3 (C-6), 19.1 (C_3–*C*H_3).

3-Ethyl-6-methyl-1,8-diaza-9,10-anthraquinone (23). Starting from 115 mg (0.43 mmol) of 2,6-dibromobenzoquinone, 48 mg (1 equiv.) of azadiene **9** and then 44 mg (1.2 equiv.) of azadiene **5**, a yield of 42 mg (39%) of compound **23** was obtained, as an off-white solid. [Found: C, 71.13; H, 4.68; N, 10.97. $C_{15}H_{12}N_2O_2$ requires C, 71.41; H, 4.79; N, 11.10]; mp 245–247°C; ν_{max} (KBr) 1693 and 1667 cm^{-1}. δ_H ($CDCl_3$, 250 MHz) 8.95–8.93 (m, 1H, H-2,7), 8.39–8.37 (m, 1H, H-4,5), 2.86 (q, 2H, J=7.6 Hz, C_3–CH_2–CH_3), 2.55 (s, 3H, C_6–CH_3), 1.35 (t, 3H, J=7.6 Hz, C_3–CH_2–CH_3). δ_C ($CDCl_3$, 63 MHz) 182.9 (C-9), 180.1 (C-10), 156,5 and 155.9 (C-2 and C-7), 147.0 and 146.8 (C-8a and C-9a), 145.3 (C-3), 139.4 (C-6), 135.1 and 133.9 (C-4 and C-5), 129.8 and 129.6 (C-4a and C-10a), 26.5 (C_3–*C*H_2–CH_3), 19.1 (C_6–*C*H_3), 14.7 (C_3–CH_2–*C*H_3).

3-*n*-Butyl-6-methyl-1,8-diaza-9,10-anthraquinone (24). Starting from 75 mg (0.28 mmol) of 2,6-dibromobenzoquinone, 32 mg (1 equiv.) of azadiene **9** and then 35 mg (1.2 equiv.) of azadiene **10**, a yield of 34 mg (43%) of compound **24** was obtained, as an off-white solid. [Found: C, 72.60; H, 5.58; N, 9.66. $C_{17}H_{16}N_2O_2$ requires C, 72.84; H, 5.75; N, 9.99; mp 168–170°C; ν_{max} (KBr) 1694 and 1665 cm^{-1}; δ_H ($CDCl_3$, 250 MHz) 8.92 (br. s, 2H, H-2,7), 8.36 (br. s, 2H, H-4,5), 2.80 (t, 2H, J=7.6 Hz, C_3–CH_2–CH_2–CH_2–CH_3), 2.55 (s, 3H, C_6–CH_3), 1.68 (m, 2H, C_3–CH_2–CH_2–CH_2–CH_3), 1.38 (m, 2H, C_3–CH_2–CH_2–CH_2–CH_3), 0.93 (t, 3H, J=7.3 Hz, C_3–CH_2–CH_2–CH_2–CH_3); δ_C ($CDCl_3$, 63 MHz) 182.9 (C-9), 180.1 (C-10), 156,4 and 156.2 (C-2 and C-7), 147.0 and 146.9 (C-8a and C-9a), 144.15 (C-3), 139.4 (C-6), 135.1 and 134.3 (C-4 and C-5), 129.7 and 129.6 (C-4a and C-10a), 33.1 (C_3–*C*H_2–CH_2–CH_2–CH_3), 32.8 (C_3–CH_2–*C*H_2–CH_2–CH_3), 22.35 (C_3–CH_2–CH_2–*C*H_2–CH_3), 19.09 (C_6–*C*H_3), 13.88 (C_3–CH_2–CH_2–CH_2–*C*H_3).

3,5-Dimethyl-1,8-diaza-9,10-anthraquinone (25). Starting from 117 mg (0.44 mmol) of 2,6-dibromobenzoquinone, 49 mg (1 equiv.) of azadiene **9** and then 59 mg (1.2 equiv.) of azadiene **11**, a yield of 36 mg (35%) of compound **25**

was obtained, as a pale brown solid. [Found C, 70.39; H, 4.53; N, 11.50. $C_{14}H_{10}N_2O_2$ requires C, 70.58; H, 4.23; N, 11.76]; mp 177–179°C. ν_{max} (KBr) 1697 and 1667 cm^{-1}. δ_H ($CDCl_3$, 250 MHz) 8.90–8.81 (m, 2H, H-2,7), 8.36 (br. s, 1H, H-4), 7.51 (d, 1H, *J*=4.8 Hz, H-6), 2.89 (s, 3H, C_4–C*H*$_3$), 2.56 (s, 3H, C_3–C*H*$_3$). δ_C ($CDCl_3$, 63 MHz) 185.1 (C-9), 181.1 (C-10), 157.2 and 156.3 (C-2 and C-7), 153.7 and 151.6 (C-5 and C-9a), 146.5 (C-8a), 139.4 (C-3), 134.9 (C-4), 131.3 (C-6), 130.5 (C-4a), 128.1 (C-10a), 22.9 (C_5–*C*H$_3$), 19.18 (C_3–*C*H$_3$).

3-Ethyl-1,8-diaza-9,10-anthraquinone (26). Starting from 117 mg (0.44 mmol) of 2,6-dibromobenzoquinone, 49 mg (1 equiv.) of azadiene **9** and then azadiene **5** (1.2 equiv.), a yield of 78 mg (80%) of compound **26** was obtained, as a pale yellow solid. [Found C, 70.42; H, 4.48; N, 11.56. $C_{14}H_{10}N_2O_2$ requires C, 70.58; H, 4.23; N, 11.76]; mp 292–293°C; ν_{max} (KBr) 1694.6 and 1670.1 cm^{-1}. δ_H ($CDCl_3$, 250 MHz) 9.11 (dd, 1H, *J*=4.6 and 1.7 Hz, H-7), 8.94 (d, 1H, *J*=2.2 Hz, H-2), 8.61 (dd, 1H, *J*=7.9 and 1.7 Hz, H-5), 8.38 (d, 1H, *J*=2.2 Hz, H-4), 7.74 (dd, 1H, *J*=7.9 and 4.6 Hz, H-6), 2.89 (q, 2H, *J*=7.8 Hz, C*H*$_2$–CH$_3$), 1.33 (t, 3H, *J*=7.8 Hz, CH$_2$–C*H*$_3$), δ_C ($CDCl_3$, 63 MHz) 182.6 (C-9), 180.1 (C-10), 156.2 and 155.9 (C-2 and C-7), 148.9 (C-8a), 146.9 (C-9a), 145.5 (C-3), 135.5 (C-4), 133.9 (C-5), 130.0 (C-4a), 129.1 (C-10a), 128.7 (C-6), 26.5 (*C*H$_2$–CH$_3$), 14.7 (CH$_2$–*C*H$_3$).

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