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New Findings in Hetero Diels-Alder Reactions of Quinolinetriones

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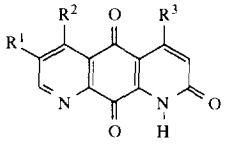
Abstract: 3-Substituted 2,5,8-(1*H*)quinolinetriones show interesting differences in their reactivity towards 1-dimethylamino-1-azadienes with respect to their 4-substituted analogues. Thus, their [4 + 2] cycloadditions with methacrolein dimethylhydrazone affording 2,9,10(1*H*)-1,8-diazaanthracenetriones gave no trace of secondary products arising from addition of dimethylamine to the starting quinone, a process that normally limits the usefulness of these hetero Diels-Alder reactions. If the C-3 substituent is strongly electron-withdrawing, a multi-step ionic mechanism involving the C_5=O carbonyl and leading to the isolation of a furo[2,3-*f*]quinolin-7-one derivative competes with the [4 + 2] cycloaddition. This process may be favoured through changes in the polarity of the reaction medium, allowing a selective, one-pot synthesis of furo[2,3-*f*]quinolin-7-ones from 5,8-dimethoxycarbostiryls.

Hetero Diels-Alder reactions[1-5] between α,β-unsaturated dimethylhydrazones, acting as 1-azadienes,[6] and electron-defficient dienophiles provide an excellent method for the preparation of a variety of heterocycles, including many biologically interesting quinones and related compounds.[7-10] In this context, we have described[11] the use of Diels-Alder reactions of 2,5,8(1*H*)-quinolinetriones[12] for the synthesis of antitumour 1,8-diazaanthracene-2,9,10-triones **1**, related to the antifolate antibiotic diazaquinomycin A **2**[13]. In our previous experience with these reactions, they were always chemoselectively directed to the C_6=C_7 bond of the substrates, and high amounts of a secondary product arising from addition of dimethylamine to the C-6 position of the starting quinone were isolated.[14]



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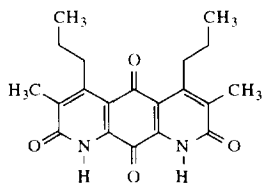
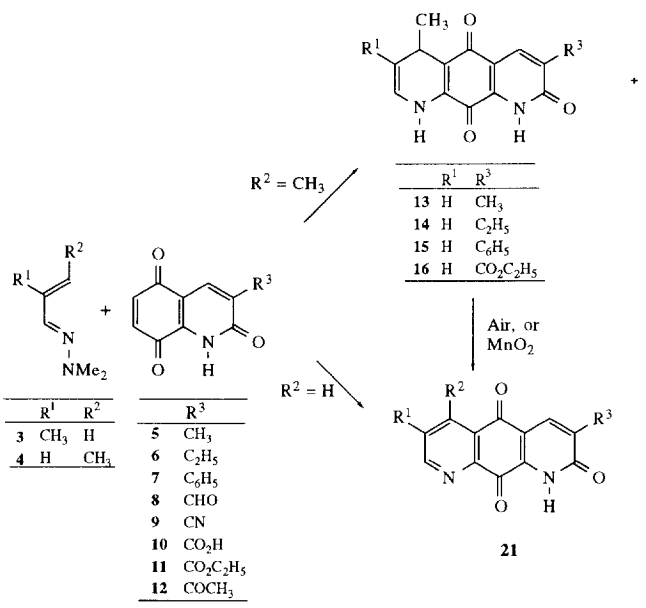


2 (Diazaquinomycin A)

In an extension of these studies, we examine here the reactions between methacrolein dimethylhydrazone **3**[15] or crotonaldehyde dimethylhydrazone **4**[15] with 3-substituted derivatives of the 2,5,8(1*H*)quinolinetrione system, available through Friedländer[12c] or Vilsmeier-Haack[12d] methodologies, which gave results that differed

from those obtained for other 2,5,8(1*H*)-quinolinetriones (Scheme 1).[11a] Thus, the reaction between quinones **5-12** and azadiene **3** in chloroform or dry tetrahydrofuran solutions gave only the aromatic 1,8-diazaanthracene-2,9,10-(1*H*)triones **21a-h** from chemo- and regioselective [4+2] cycloaddition onto the C_6=C_7 bond, with no trace of addition of dimethylamine to the starting quinones. On the other hand, treatment of compounds **5-7** and **11** with azadiene **4** under the same conditions gave mixtures of 5,8-dihydro-1,8-diazaanthracene-2,9,10-(1*H*)triones **13-16**, their aromatization products **21i-l** and 6-dimethylamino-2,5,8(1*H*)-quinolinetriones **17-20** (Scheme 1). Dihydro derivatives **13-16** tend to aromatize during silica gel chromatography and for this reason only one of them (compound **13**) was isolated and other derivatives were characterized by NMR analysis of their mixtures with the corresponding compounds **21**. These mixtures were completely aromatized by air or manganese dioxide at room temperature.



	R^1	R^2
3	CH_3	H
4	H	CH_3

	R^3
5	CH_3
6	C_2H_5
7	C_6H_5
8	CHO
9	CN
10	CO_2H
11	$CO_2C_2H_5$
12	$COCH_3$

	R^1	R^3
13	H	CH_3
14	H	C_2H_5
15	H	C_6H_5
16	H	$CO_2C_2H_5$

	R^3	Yield, %
17	CH_3	7
18	C_2H_5	6
19	C_6H_5	20
20	$CO_2C_2H_5$	8

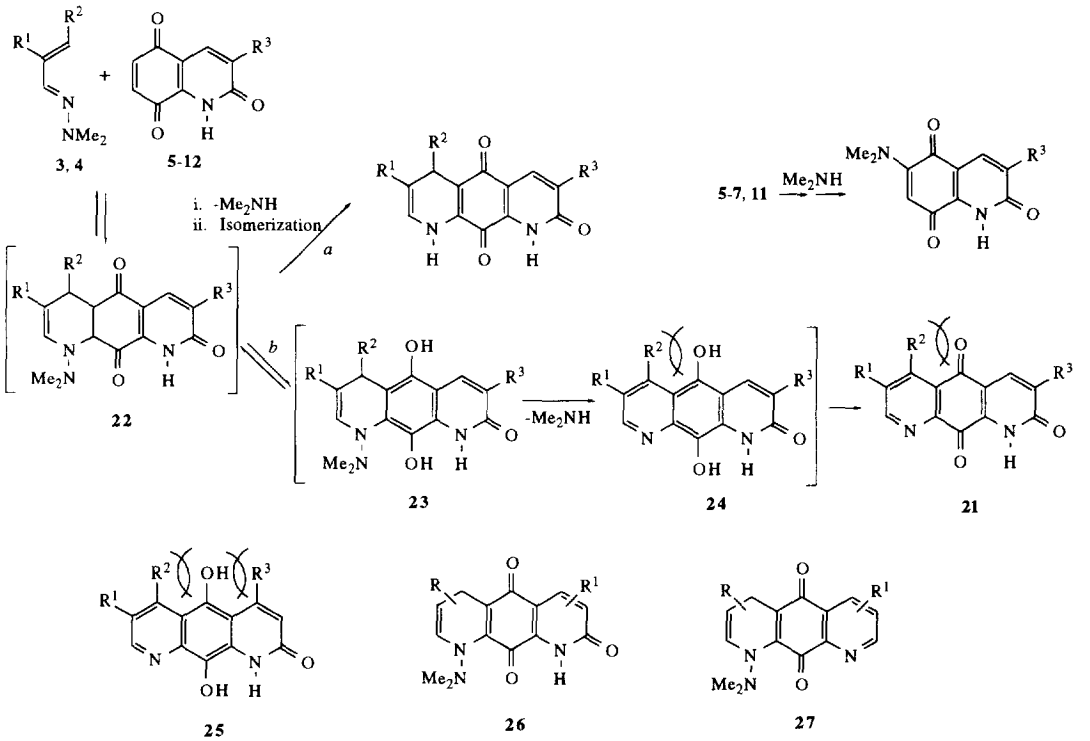
21	R^1	R^2	R^3	Yield, %
a	CH_3	H	CH_3	50
b	CH_3	H	C_2H_5	45
c	CH_3	H	C_6H_5	50
d	CH_3	H	CHO	51
e	CH_3	H	CN	63
f	CH_3	H	CO_2H	66
g	CH_3	H	$CO_2C_2H_5$	59
h	CH_3	H	$COCH_3$	62
i	H	CH_3	CH_3	46*
j	H	CH_3	C_2H_5	44*
k	H	CH_3	C_6H_5	40*
l	H	CH_3	$CO_2C_2H_5$	55*

*Overall for Diels-Alder and oxidation

Scheme 1

The different behaviour of both dienes can be explained by assuming that two alternative reaction pathways can follow the Diels-Alder cycloaddition (Scheme 2). Thus, in path *a* cycloadduct **22** evolves by elimination of a molecule of dimethylamine and subsequent isomerization yielding dihydro compounds **13-16**; addition of the liberated amine to the starting quinone followed by oxidation would afford side products **17-20**. Alternatively (path *b*), **22** can tautomerize to the corresponding hydroquinone **23** prior to dimethylamine elimination to give **24**, which would be subsequently oxidized to **21**. The lack of interaction between the R^2 substituent and the C_{10}-O oxygen atom in the hydroquinones **24** and quinones **21** when R^2 = H (*i.e.*, reactions starting with diene **3**) would favour pathway *b* in which a rapid aromatization occurs and therefore the equilibria are displaced towards the final product before the addition of dimethylamine to the starting quinone takes place. In reactions starting with diene **4** ($R^2 \neq H$), both pathways would compete and if the starting quinone bears an additional substituent

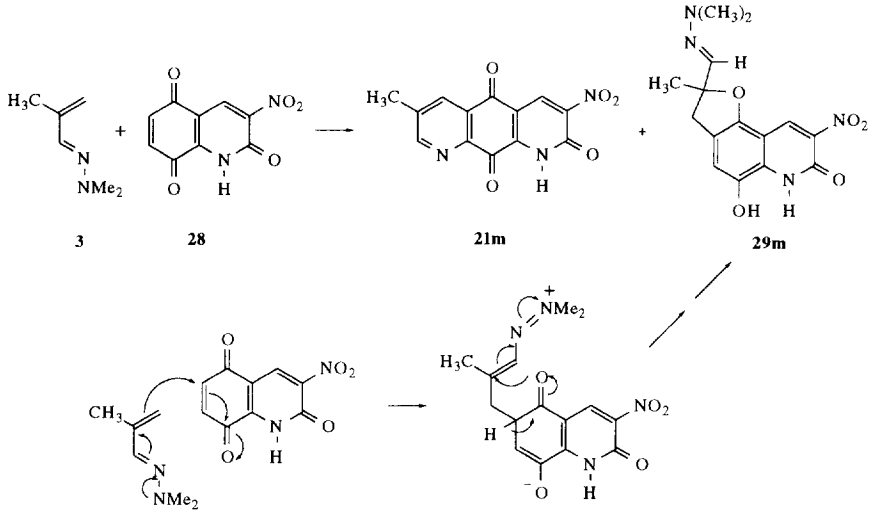
at C-4, the severe steric interactions in the intermediates **25** would preclude pathway *b*; this would explain the fact that such quinones lead only to 5,8-dihydro derivatives of the 1,8-diazaanthracenetrione system and to higher yields of dimethylamine adducts, as reported earlier.[11a] A third pathway might also be proposed involving oxidation of **22** by air or a molecule of quinone to intermediates **26**, but this alternative seems to be excluded by the isolation of several examples of the stable compounds **27** in related reactions of 1-dimethylamino-1-azadienes and bromoquinones.[16]



Scheme 2

The reaction of quinone **28**[12c] with diene **3** in dry tetrahydrofuran gave small amount (10 %) of the furo[2,3-*f*]quinolinone derivative **29m** together with the expected Diels-Alder cycloadduct (compound **21m**, 48 % yield). Compound **29m** is presumably formed through a multi-step, ionic mechanism initiated by the Michael addition of the more nucleophillic end of the diene to the C-6 position of the quinone, and subsequent 5-*exo-trig* cyclization (Scheme 3), a proposal supported by the existence of a literature antecedent of a conjugate addition of the C-4 position of compound **3** onto an enone system.[17] Similar polar [3+2] cycloadditions have been described previously for reactions between α,β-unsaturated hydrazones and other quinones in cases where either the diene or the dienophile are very polarized,[18-21] normally due to catalysis by Lewis or Brönsted acids. The regiochemistry of the addition leading to **29m** can be attributed to the simultaneous conjugation of the C-8 carbonyl of quinone **28** with the C-2 carbonyl and nitro groups, leading to an increased electron deficiency at the C-6 position, and was confirmed by examination of its proton-coupled ^{13}C-NMR spectrum on the basis of the

easy assignment of the angular carbons in carbostyryl systems.[12] In compound **29m**, the signals due to C-9a and C-5a appear respectively at 103.62 ppm (clean singlet) and 120.18 ppm (triplet, ^3J = 8.0 Hz), while for the other possible regioisomer two ^3J doublets should be expected.



Scheme 3

Due to the stepwise, ionic nature of the sequence leading to **29m**, it was envisaged that changes in the polarity of the reaction medium might allow to control its outcome. In particular, very polar environments should favour compound **29m** over [4 + 2] cycloadduct **21m**. In agreement with this hypothesis, when the reaction between **3** and **28** was carried out in an acetonitrile-water mixture, compound **29m** became the major product (yields were 24 % for **21m** and 36 % for **29**). We next sought to take advantage of this improvement in the yield of furoquinolinone **29m** for the development of a simple synthesis of this class of compounds, finding eventually that oxidative demethylation of 5,8-dimethoxy-3-nitrocarbostiryl[12c] to quinone **28** with cerium ammonium nitrate in acetonitrile-water followed by *in situ* addition of azadiene **3** afforded compound **29m** as the only reaction product in 63 % overall yield. This one-pot procedure worked also for other 5,8-dimethoxycarbostiryls bearing electron acceptors in C-3 (Table 1), but failed in other cases (*e.g.*, reactions starting from 5,8-dimethoxy-3-

Table 1

R^3	Method A[a]		Method B[b]	
	% **21**	% **29**	% **21**	% **29**
NO_2	48	10	0	63
CN	63	0	0	36
CO_2CH_3	59	0	0	48
$COCH_3$	62	0	0	62

a. From quinones **9**, **11**, **12** and **28** in dry THF at 0 °C.
b. One-pot reactions from the corresponding 5,8-dimethoxycarbostiryls in CH_3CN-H_2O at room temperature.

methylcarbostiryl[12d] and 5,8-dimethoxy-3-phenylcarbostiryl[12d]). The complete selectivity in favour of the furo[2,3-*f*]quinolinone structure is probably due to the combined effects of solvent polarity and increased polarization of the quinone system under the reaction conditions owing to the presence of cerium (III) species formed[22] in the course of the oxidative demethylation.[23]

EXPERIMENTAL

All reagents were of commercial quality (Aldrich, Fluka, SDS, Probus) and were used as received. Solvents (SDS, Scharlau) were dried and purified using standard techniques. The expression "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 (Scharlau Cf 530 and Alugram Sil G/UV$_{254}$). Separations by flash chromatography were performed on silica gel (SDS 60 ACC, 230-400 mesh and Scharlau Ge 048). Melting points were measured on a Reichert 723 hot stage microsope or in open capillary tubes using a Büchi inmersion apparatus, and are uncorrected. Infrared spectra were recorded on Perkin-Elmer 577 and Perkin Elmer Paragon 1000 spectrophotometers, with solid compounds compressed into KBr pellets and liquid compounds placed between two NaCl disks. NMR spectra were obtained on Bruker AC-250 (250 MHz for ^{1}H, 63 MHz for ^{13}C) and Varian VXR-300 (300 MHz for ^{1}H, 75 MHz for ^{13}C) spectrometers with $CDCl_3$, DMSO-d_6, acetone-d_6 and pyridine-d_5 as solvents. Elemental analyses were determined by the Servicio de Microanálisis, Universidad Complutense, on a Perkin-Elmer 2400 CHN microanalyzer.

Diels-Alder Reactions of Methacrolein Dimethylhydrazone (3) and Quinones 5-12. General Procedure.

To a solution of the starting quinone (0.19 to 1.05 mmol) in chloroform (30 to 50 ml, quinones **5-7**) or dry tetrahydrofuran (3 to 5 ml, quinones **8-12**) was added the azadiene **3** (1.1 eq). The solution was stirred at room temperature for 5 to 45 min and evaporated under reduced pressure. The reaction mixture was evaporated and the residue was washed with petroleum ether and purified by column chromatography on silica gel, with the eluant indicated in each case, yielding the aromatic Diels-Alder adducts **21**. NMR data of compounds **21** can be found in Tables 2 and 3.

3,6-Dimethyl-1*H*-1,8-diazaanthracene-2,9,10-trione **21a**. Yield, 50 % after chromatography eluting with ethyl acetate. Mp > 300 °C. IR (KBr): 1650 (C=O) cm^{-1}. Anal. calcd. for $C_{14}H_{10}N_2O_3$: C, 66.14; H, 3.93; N, 11.02. Found: C, 65.86; H, 4.25; N, 11.23.

3-Ethyl-6-methyl-1*H*-1,8-diazaanthracene-2,9,10-trione **21b**. Yield, 45 % after chromatography eluting with ethyl acetate. Mp, 260-262 °C. IR (KBr): 1658 (C=O) cm^{-1}. Anal. calcd. for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.47; N, 10.44. Found: C, 67.03; H, 4.79; N, 10.08.

3-Phenyl-6-methyl-1*H*-1,8-diazaanthracene-2,9,10-trione **21c**. Yield, 50 % after chromatography eluting with ethyl acetate. Mp, 275 °C. IR (KBr): 1650 (C=O) cm^{-1}.

6-Methyl-2,9,10-trioxo-1*H*-1,8-diazaanthracene-3-carbaldehyde **21d**. Yield, 51 % after chromatography eluting with a gradient from AcOEt to EtOH. Mp > 300 °C. IR (KBr): 3240, 1654 cm^{-1}.

6-Methyl-2,9,10-trioxo-1*H*-1,8-diazaanthracene-3-carbonitrile **21e**. Yield, 63 % after precipitation by addition of acetone to the petroleum ether washings, combined with chromatography of the residue eluting with

8:1 ethyl acetate-methanol. Mp > 300 °C. IR (KBr): 2320 (C=N); 1690 ($C_{9,10}$=O); 1655 (C_2=O) cm^{-1}. Anal. calcd. for $C_{14}H_7N_3O_3$: C, 63.39; H, 2.64; N, 15.84. Found: C, 63.01; H, 3.09; N, 15.87.

6-Methyl-2,9,10-trioxo-1*H*-1,8-diazaanthracene-3-carboxylic Acid **21f**. Yield, 66 % after chromatography eluting with a gradient from 9:1 ethyl acetate-ethanol to neat ethanol. Mp > 300 °C. IR (KBr): 3127 (OH); 1645 (C=O) cm^{-1}. Anal. calcd. for $C_{14}H_8N_2O_5$: C, 59.15; H, 2.81; N, 9.85. Found: C, 59.31; H, 2.96; N, 9.57.

Ethyl 6-Methyl-2,9,10-trioxo-1*H*-1,8-diazaanthracene-3-carboxylate **21g**. Yield, 59 % after chromatography eluting first with dichloromethane and then with a gradient from 8:2 dichloromethane-acetone to neat acetone. Mp > 300 °C. IR (KBr): 1755 (CO_2Et); 1650 (other C=O) cm^{-1}. Anal. calcd. for $C_{16}H_{12}N_2O_5$: C, 61.53; H, 3.84; N, 8.97. Found: C, 61.41; H, 4.13; N, 9.03.

3-Acetyl-6-Methyl-1*H*-1,8-diazaanthracene-2,9,10-trione **21h**. Yield, (62 %) after chromatography eluting with ethyl acetate. Mp > 300 °C. IR (KBr): 1680, 1645 (C=O) cm^{-1}. Anal. calcd. for $C_{15}H_{10}N_2O_4$: C, 63.83; H, 3.54; N, 9.92. Found: C, 63.49; H, 3.56; N, 9.64.

Diels-Alder Reactions of Crotonaldehyde Dimethylhydrazone (4) and Quinones 5-7, 11. General Procedures.

Method A (quinone **6**). A solution of quinone **6** (150 mg, 0.73 mmol) in chloroform (30 ml) was stirred at room temperature for 5 min and evaporated under reduced pressure. The residue was chromatographed on silica gel, eluting with ethyl acetate, affording the unstable 3-ethyl-5,8-dihydro-5-methyl-1*H*-1,8-diazaanthracene-2,9,10-trione **14** (51 mg, 27 %), 6-dimethylamino-3-ethyl-1*H*-quinoline-2,5,8-trione **18** (13 mg, 7 %) and 3-ethyl-5-methyl-1*H*-1,8-diazaanthracene-2,9,10-trione **21j** (36 mg, 18 %).

Method B (quinones **5** and **7**). A solution of the starting quinone (0.52 to 0.68 mmol) and diene **4** (1.1 to 1.3 eq) in chloroform (10 to 40 ml) was stirred at room temperature for 5 min. Without isolation of dihydro derivatives **13** and **15**, solid activated manganese dioxide (10 eq) was added and the black suspension was stirred at room temperature for 30 min and evaporated. The residue was chromatographed on silica gel, eluting with chloroform, to yield 10 mg (6 %) of 6-dimethylamino-3-methyl-1*H*-quinoline-2,5,8-trione **17** and 80 mg (46 %) of 3,5-dimethyl-1*H*-1,8-diazaanthracene-2,9,10-trione **21i**, or 6-dimethylamino-3-phenyl-1*H*-quinoline-2,5,8-trione **19** (20 %) and 5-methyl-3-phenyl-1*H*-1,8-diazaanthracene-2,9,10-trione **20k** (40 %).

Method C (quinone **11**). To a solution of quinone **11** (124 mg, 0.5 mmol) in chloroform (10 ml) was added diene **4** (84 mg, 0.75 mmol) and the solution was stirred for 2.5 h at room temperature in an open flask. The reaction mixture was evaporated under reduced pressure and the residue was chromatographed on silica gel, eluting with a gradient from 9:1 ethyl acetate-ethanol to neat ethanol. Yield, 11 mg (8 %) of ethyl 6-dimethylamino-2,5,8-trioxo-1*H*-quinonine-3-carboxylate **20** and 86 mg (55 %) of ethyl 5-methyl-2,9,10-trioxo-1*H*-1,8-diazaanthracene-3-carboxylate **21l**.

3-Ethyl-5,8-dihydro-5-methyl-1*H*-1,8-diazaanthracene-2,9,10-trione **13** Mp 98-100 °C. IR (KBr): 3400 (NH), 1650 (C=O) cm^{-1}. ^{1}H-NMR (250 MHz, d_5-pyridine) δ: 10.17 (br. s, 1H, H-8); 8.13 (s, 1H, H-4); 6.64 (dd, 1H, *J* = 4.5 and 7.6 Hz, H-7); 5.16 (m, 1H, H-6; partially hidden by the water resonance); 4.14 (m, 1H, H-5); 2.90 (q, 2H, *J* = 7.5 Hz, CH_2CH_3); 1.49 (d, 3H, *J* = 9.4 Hz, CH_3); 1.37 (t, 3H, *J* = 7.5 Hz, CH_2CH_3) ppm. ^{13}C-NMR (63 MHz, d_5-pyridine) δ: 181.98 (C-9); 176.98 (C-10); 162.54 (C-2); 141.43 (C-3); 138.65 (C-8a); 135.31 (C-9a); 129.76 (C-4); 123.10 (C-7); 115.89 (C-4a); 112.18 (C-10a); 108.29 (C-6); 30.81 (C-5); 26.36 (C_5-CH_3); 24.69 (CH_2CH_3); 12.26 (CH_2CH_3) ppm.

6-Dimethylamino-3-methyl-1*H*-quinoline-2,5,8-trione **17**. IR (KBr): 3420 (NH); 1652 (C=O) cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 9.60 (s, 1H, NH); 7.72 (s, 1H, H-4); 5.65 (s, 1H, H-7); 3.29 (s, 6H, NMe_2); 2.80 (s, 3H, CH_3) ppm.

6-Dimethylamino-3-ethyl-1*H*-quinoline-2,5,8-trione **18**. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 9.57 (s, 1H, NH); 7.70 (s, 1H, H-4); 5.66 (s, 1H, H-7); 3.30 (s, 6H, NMe_2); 2.62 (q, 2H, J = 7.5 Hz, CH_2); 1.24 (t, 3H, J = 7.5 Hz, CH_3) ppm.

6-Dimethylamino-3-phenyl-1*H*-quinoline-2,5,8-trione **19**. IR (KBr): 3409, 3191 (NH); 1654 (C=O) cm^{-1}. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 9.65 (s, 1H, NH); 8.02 (s, 1H, H-4); 7.75 (m, 2H, C_6H_5); 7.43 (m, 3H, C_6H_5); 5.71 (s, 1H, H-7); 3.32 (s, 6H, NMe_2) ppm. ^{13}C-NMR (63 MHz, $CDCl_3$) δ: 181.83 (C-9); 176.24 (C-10); 161.34 (C-2); 153.04 (C-6); 138.76 (C-8a); 135.04 (C-1'); 133.17 (C-4); 128.82 (C-4'); 128.52 and 128.37 (C-2',6' and C-3',5'); 113.69 (C-4a); 101.94 (C-7); 43.66 (NMe_2) ppm.

Ethyl 6-dimethylamino-2,5,8-trioxo-1*H*-quinoline-3-carboxylate **20**. ^{1}H-NMR (250 MHz, $CDCl_3$) δ: 8.54 (s, 1H, H-4); 5.70 (s, 1H, H-7); 4.30 (q, 2H, J = 7.3 Hz, CH_2CH_3); 2.82 (s, 3H, NMe_2); 1.18 (t, 3H, J = 7.3 Hz, CH_2CH_3) ppm.

3,5-Dimethyl-1*H*-1,8-diazaanthracene-2,9,10-trione **21i** Mp > 300 °C. IR (KBr): 3415 (NH), 1643 (C=O) cm^{-1}. Anal. calcd. for $C_{14}H_{10}N_2O_3$: C, 66.14; H, 3.93; N, 11.02. Found: C, 66.24; H, 4.09; N, 10.89.

3-Ethyl-5-methyl-1*H*-1,8-diazaanthracene-2,9,10-trione **21j** Mp 223-225 °C. IR (KBr): 3420 (NH); 1641 (C=O) cm^{-1}. Anal. calcd. for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.47; N, 10.44. Found: C, 66.86; H, 4.84; N, 10.73.

5-Methyl-3-phenyl-1*H*-1,8-diazaanthracene-2,9,10-trione **21k** Mp 285-287 °C. IR (KBr): 3421 (NH); 1653 (C=O) cm^{-1}. Anal. calcd. for $C_{19}H_{12}N_2O_3$: C, 72.15; H, 3.79; N, 8.86. Found: C, 72.32; H, 4,12; N, 8.58.

Ethyl 5-Methyl-2,9,10-trioxo-1*H*-1,8-diazaanthracene-3-carboxylate **21l** Mp, 212 °C. IR (KBr): 1766 (CO_2Et); 1680 ($C_{9,10}$=O); 1651 (C_2=O) cm^{-1}.

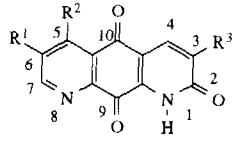
Reaction of Diene 3 and 3-nitro-1*H*-quinoline-2,5,8-trione 28.

Method A. A solution of 3-nitro-1*H*-quinoline-2,5,8-trione **28** (37 mg, 0.16 mmol) and methacrolein dimethylhydrazone **3** (121 mg, 1.08 mmol) in dry tetrahydrofuran (5 ml) was stirred at room temperature for 15 min, under an argon atmosphere. The solution was evaporated under reduced pressure and the residue was washed with petroleum ether (3 x 10 ml) and chromatographed on silica gel, eluting with a gradient from 7:1 ethyl acetete-ethanol to neat ethanol. Yield, 23 mg (48 %) of **21m**.

Method B. To a solution of 3-nitro-1*H*-quinoline-2,5,8-trione **28** (35 mg, 0.15 mmol) in a mixture of water (4 ml) and acetonitrile (6 ml) was added methacrolein dimethylhydrazone **3** (35.6 mg, 0.31 mmol). The solution was stirred at room temperature for 15 min, diluted with water (10 ml) and extracted with chloroform (3 x 15 ml). The combined chloroform layers were dried (sodium sulphate) evaporated under reduced pressure and the residue was chromatographed on silica gel, eluting with a gradient from neat ethyl acetete to neat ethanol. Yield, 19 mg (36 %) of 2-dimethylhydrazono-5-hydroxy-2-methyl-8-nitro-6*H*-furo[2,3-*f*]quinolin-7-one (**29m**) (see data below) and 11 mg (24 %) of compound **21m**.

6-Methyl-3-nitro-1*H*-1,8-diazaanthracene-2,9,10-trione **21m**. Mp > 300 °C. IR (KBr): 1680 (C=O); 1630, 1380 (NO_2) cm^{-1}. Anal. calcd. for $C_{13}H_7N_3O_5$: C, 54.73; H, 2.45; N, 14.73. Found: C, 55.75; H, 2.56; N, 15.19.

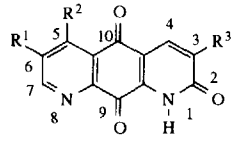
Table 2. ^{1}H-NMR Data of Compounds **21**[a]



Cmpd.	H-1	H-4	H-5	H-6	H-7	R^1	R^2	R^3
21a	9.65	7.98	8.35 (s)	---	8.87 (s)	2.58	---	2.32 (s, 3H)
21b	9.70	7.96	8.36 (s)	---	8.89 (s)	2.58	---	2.71 (q, 2H, J = 7.4); 1.30 (t, 3H, J = 7.4)
21c	9.84	8.27	8.37 (s)	---	8.90 (s)	2.59	---	7.71 (dd, 2H, $J_{2'3'}$ = 7.1; $J_{2'4'}$ = 1.6; H-2',6') 7.47 (m, 3H, H-3',4',5')
21d	b	8.32	8.68 (s)	---	8.90 (s)	2.50	---	10.20 (s, 1H)
21e	8.58	8.25	8.25 (d, J = 1.7)	---	8.83 (d, J = 1.7)	2.61	---	---
21f	b	8.64	8.30 (s)	---	8.88 (s)	2.50	---	b
21g	b	8.82	8.40 (s)	---	8.93 (s)	2.60	---	4.44 (q, 2H, J = 7.3); 1.42 (t, 2H, J = 7.3)
21h	12.85	8.45	8.32 (d, J = 1.7)	---	8.90 (d, J = 1.7)	2.60	---	2.51 (s, 3H)
21i	9.83	7.96	---	7.52 (d, J = 5.1)	8.85 (d, J = 5.1)	---	2.87	2.31 (s, 3H)
21j	9.69	7.91	---	7.50 (d, J = 4.8)	8.83 (d, J = 4.8)	---	2.86	2.69 (dq, 2H, J = 7.4, 1.1); 1.22 (t, 3H, J = 7.2)
21k	9.74	8.26	---	7.54 (d, J = 4.9)	8.87 (d, J = 4.9)	---	2.90	7.81 (dd, 2H, $J_{2'3'}$ = 7.9; $J_{2'4'}$ = 2.5; H-2',6') 7.46 (m, 3H, H-3',4',5')
21l	12.74	8.47	---	7.72 (d, J = 4.8)	8.85 (d, J = 4.8)	---	2.78	4.30 (q, 2H, J = 7.0); 1.31 (t, 3H, J = 7.0)
21m	b	8.96	8.43 (d, J = 2.0)	---	8.97 (d, J = 2.0)	2.50	---	---

a. At 250 or 300 MHz in $CDCl_3$ (compounds **21a-c** and **21i-k**) or d_6-DMSO (all other compounds). b. Signal not detected

Table 3. ^{13}C-NMR Data of Compounds **21**[a,b]



Cmpd.	C_2	C_3	C_4	C_{4a}	C_5	C_6	C_7	C_{8a}	C_9	C_{9a}	C_{10}	C_{10a}	R^1	R^2	R^3
21a	162.75	139.24	132.68	116.00	134.19	140.18	155.39	144.87	179.87	137.50	176.12	129.33	19.15	---	17.47
21b	161.37	144.90	130.30	116.26	134.94	140.16	155.52	144.52	179.91	137.25	176.20	129.35	19.15	---	23.93, 12.00
21c	160.34	139.30	132.60	116.44	135.02	140.31	155.51	144.89	179.71	137.71	175.88	129.48	19.17	---	134.35, 129.69, 128.70, 128.56
21d	161.47	139.53	128.82	114.00	134.00	141.95	154.81	145.64	179.72	137.47	173.03	128.09	18.26	---	188.88
21e	168.80	114.47	139.13	102.93	134.15	142.54	154.52	152.15	181.57	146.57	180.53	129.80	18.50	---	118.32
21f	165.34	128.98	138.93	116.86	134.03	139.26	154.77	145.96	180.03	139.26	177.26	131.49	18.22	---	166.90
21g	158.82	126.26	139.74	113.94	134.25	138.95	154.96	145.81	179.85	143.97	175.89	129.06	18.53	---	163.65, 61.38, 14.22
21h	160.30	131.99	137.84	103.73	134.15	137.23	154.76	143.99	179.99	141.53	175.69	128.92	18.25	---	191.07, 30.46
21i	161.65	139.64	132.17	117.31	151.49	132.36	153.15	148.32	181.77	136.26	176.49	127.92	---	22.70	17.56
21j	161.45	145.06	130.59	117.46	151.59	132.27	153.24	148.24	182.03	136.14	176.60	128.03	---	24.07	22.81, 12.09
21k	160.26	139.66	132.26	117.50	151.61	132.83	153.25	148.22	181.62	136.46	176.17	129.68	---	22.85	134.45, 129.68, 128.71, 128.55
21l	160.03	126.77	138.92	112.22	149.21	131.56	152.60	148.62	180.79	136.92	173.32	126.52	---	21.90	163.25, 61.08, 13.99

a. At 250 or 300 MHz, in $CDCl_3$ (compounds **21a-c** and **21i-k**) or d_6-DMSO (all other compounds). b. Data for compound **21m** could not be obtained due to its very low solubility. c. Signal not detected.

One-pot Synthesis of 6*H*-furo[2,3-*f*]quinolin-7-ones 29. General Procedure.

To a suspension of the suitable 3-substituted 5,8-dimethoxy-1*H*-quinolin-2-one[12c] (0.44 mmol) in a mixture of acetonitrile (17 ml) and water (17 ml) was added solid cerium ammonium nitrate (550 mg, 1.0 mmol); complete dissolution of the reagents was achieved within 5 min. The reaction was stirred at r.t. for further 10 min. After confirming complete consumption of the starting material by TLC analysis, diene **3** (535 mg, 4.77 mmol) was added and the reacting mixture was vigorously stirred for 10 min, diluted with water (15 ml) and extracted with chloroform (3 x 50 ml). The organic layers were dried over sodium sulphate and evaporated, and the residue was chromatographed on silica gel eluting with a gradient from dichloromethane to ethyl acetate.

8-Cyano-2-dimethylhydrazono-5-hydroxy-2-methyl-6*H*-furo[2,3-*f*]quinolin-7-one **29e**. Yield, 36 %. Mp 109 °C. IR (KBr): 3420 (OH); 2250 (CN); 1682 (C=O); 1654 (C=N) cm^{-1}. ^{1}H-NMR (250 MHz, d_6-DMSO) δ: 11.26 (br. s, 1H, NH); 9.83 (br. s, 1H, OH); 8.68 (s, 1H, H-9); 7.00 (s, 1H, CH=N); 6.68 (s, 1H, H-4); 3.58 (d, 1H, *J* = 15.6 Hz, H-3); 2.99 (d, 1H, *J* = 15.6 Hz, H-3); 2.73 (s, 6H, NMe_2); 1.54 (s, 3H, C_2-CH_3) ppm. ^{13}C-NMR (63 MHz, d_6-DMSO) δ: 158.04 (C-7); 147.52 (C-9b); 143.47 (C-9); 136.98 (C-5); 134.59 (CH=N); 127.73 (C-3a); 118.49 (C-5a); 116.20 (C-4); 115.88 (CN*); 115.46 (C-8*); 98.21 (C-9a); 90.37 (C-2); 42.35 (N-CH_3); 39.14 (C_2); 25.27 (C_2-CH_3) ppm. Anal. calcd. for $C_{16}H_{16}N_4O_3$: C, 61.56; H, 5.12; N, 17.94. Found: C, 61.23; H, 5.41; N, 17.64.

Ethyl 2-dimethylhydrazono-5-hydroxy-2-methyl-7-oxo-6*H*-furo[2,3-*f*]quinolin-8-carboxylate **29g**. Yield, 48 %. Mp 136 °C. IR (KBr): 3387 (OH); 1731 (CO_2Et); 1645 (C_7=O); 1610 (C=N) cm^{-1}. ^{1}H-NMR (250 MHz, d_6-DMSO) δ: 10.62 (br. s, 1H, NH); 9.69 (br. s, 1H, OH); 8.23 (s, 1H, H-9); 6.93 (s, 1H, CH=N); 6.71 (s, 1H, H-4); 4.23 (q, 2H, *J* = 7.1 Hz, CH_2CH_3); 3.58 (d, 1H, *J* = 15.5 Hz, H-3); 2.97 (d, 1H, *J* = 15.6 Hz, H-3); 2.73 (s, 6H, NMe_2); 1.54 (s, 3H, C_2-CH_3); 1.27 (t, 3H, J = 7.1 Hz, CH_2CH_3) ppm. ^{13}C-NMR (63 MHz, d_6-DMSO) δ: 164.15 (CO_2CH_2-CH_3); 157.96 (C-7); 147.88 (C-9a); 137.97 (C-9); 136.76 (C-5); 135.21 (CH=N); 128.39 (C-8); 122.00 (C-3a); 117.87 (C-5a); 115.22 (C-4); 104.05 (C-9a); 90.30 (C-2); 60.84 (CO_2CH_2-CH_3); 42.65 (NMe_2); 25.64 (C_2-CH_3); 14.37 (CO_2CH_2-CH_3). Anal. calcd. for $C_{18}H_{21}N_3O_5$: C, 60.19; H, 5.84; N, 11.69. Found: C, 59.99; H, 6.05; N, 11.45.

8-Acetyl-2-dimethylhydrazono-5-hydroxy-2-methyl-6*H*-furo[2,3-*f*]quinolin-7-one **29h**. Yield, 62 %. Mp 105 °C. IR (KBr): 3290 (OH); 1680, 1636 (C=O, C=N) cm^{-1}. ^{1}H-NMR (250 MHz, d_6-DMSO) δ: 10.73 (br. s, 1H, NH); 9.70 (br. s, 1H, OH); 8.24 (s, 1H, H-9); 6.95 (s, 1H, CH=N); 6.71 (s, 1H, H-4); 3.60 (d, 1H, *J* = 15.5 Hz, H-3); 2.97 (d, 1H, *J* = 15.5 Hz, H-3); 2.73 (s, 6H, NMe_2); 2.59 (s, 3H, $COCH_3$); 1.55 (s, 3H, C_2-CH_3) ppm. ^{13}C-NMR (63 MHz, d_6-DMSO) δ: 196.91 ($COCH_3$); 159.71 (C-7); 148.30 (C-9b); 137.02 (C-9); 136.50 (C-5); 134.95 (CH=N); 128.43 (C-8); 127.88 (C-3a); 117.63 (C-5a); 115.24 (C-4); 104.33 (C-9a); 90.06 (C-2); 42.38 (N-CH_3); 39.07 (C_2); 30.56 ($COCH_3$); 25.43 (C_2-CH_3) ppm. Anal. calcd. for $C_{17}H_{19}N_3O_4$: C, 62.00; H, 5.77; N, 12.75. Found: C, 61.79; H, 6.08; N, 12.56.

2-Dimethylhydrazono-5-hydroxy-2-methyl-8-nitro-6*H*-furo[2,3-*f*]quinolin-7-one **29m**. Yield, 63 %. Mp 125 °C. IR (KBr): 3400 (OH); 1680 (C=O and C=N); 1470, 1260 (NO_2) cm^{-1}. ^{1}H-NMR (250 MHz, d_6-DMSO) δ: 11.44 (br. s, H-6); 9.90 (s, 1H, OH); 8.52 (s, 1H, H-9); 7.03 (s, 1H, CH=N); 6.70 (s, 1H, H-4); 3.61 (d, 1H, *J* = 15.6 Hz, H-3); 3.00 (d, 1H, *J* = 15.6 Hz, H-3); 2.73 (s, 6H, NMe_2); 1.56 (s, 3H, C_2-CH_3) ppm. ^{13}C-NMR (63 MHz, d_6-DMSO) δ: 153.28 (br. s, C-7); 148.38 (br. s, C-9b); 139.20 (br. s, C-5); 136.94 (s, C-8); 134.56 (d, *J* = 160.1 Hz, CH=N); 132.17 (d, *J* = 167.8 Hz, C-9); 127.66 (br. s, C-3a); 118.72 (t, *J* = 8.0 Hz, C-5a); 116.31 (d, *J* = 160.3 Hz, C-4); 102.41 (s, C-9a); 90.58 (br. s, C-2); 42.64 (q, *J* = 135.5 Hz, N-CH_3);

39.83 (t, J = 158.4 Hz, C_2); 25.62 (q, J = 127.7 Hz, C_2-CH_3) ppm. Anal. calcd. for $C_{15}H_{16}N_4O_5$: C, 54.21; H, 4.81; N, 16.86. Found: C, 54.66; H, 4.87; N, 16.66.

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REFERENCES

1. a) Boger, D. L. *Tetrahedron* **1983**, *39*, 2869-2939. b) Boger, D. L. *Chem. Rev.* **1986**, *86*, 781-793. c) Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*. Academic Press, 1987. d) Boger, D. L.; Patel, M. *Progress Heterocycl. Chem.* **1989**, *1*, 31. e) Boger, D. L. in Paquette, L. A. (ed.), *Comprehensive Organic Synthesis*, vol. 5, p. 451 (Trost, B. M. and Fleming, I. general editors). Pergamon Press, 1991.
2. Barluenga, J. and Tomás, M. *Adv. Heterocycl. Chem.* **1993**, 57, 1.
3. Kametani, T.; Hibino, S. *Adv. Heterocycl. Chem.* **1987**, *42*, 246.
4. Tietze, L. F. *J. Heterocycl. Chem.* **1990**, *27*, 47.
5. a) Weinreb, S. M.; Scola, P. M. *Chem. Rev.* **1989**, *89*, 1525. b) e) Weinreb, S. M. in Paquette, L. A. (ed.), *Comprehensive Organic Synthesis*, vol. 5, p. 401 (Trost, B. M. and Fleming, I. general editors). Pergamon Press, 1991.
6. a) Serckx-Poncin, B.; Hesbain-Frisque, A.-M.; Ghosez, L. *Tetrahedron Lett.* **1982**, *23*, 3261. b) Ghosez, L.; Serckx-Poncin, B.; Rivera, M.; Bayard, P.; Sainte, F. Demoulin, A.; Hesbain-Frisque, A.-M.; Mockel, A.; Muñoz, L.; Bernard-Henriet, C. *Lect. Heterocycl. Chem.* **1985**, *8*, 69.
7. For reviews on the chemistry and some biological aspects of heterocyclic quinones, see: a) Middleton, R. W. and Parridge, J. In Patai, S. and Rappoport, Z. (eds.), *The Chemistry of the Quinonoid Compounds*, vol. 2, p. 1019. John Wiley and Sons, 1988. b) Thomson, R. H. In ApSimon, J. (ed.), *The Total Synthesis of Natural Products*, vol. 8, p. 312. Academic Press, 1992. c) Itoh, S. and Ohshiro, Y. *Nat. Prod. Rep.*, **1995**, *12*, 45.
8. a) Bracher, F. *Liebigs Ann. Chem.* **1989**, 87-88. b) Gómez-Bengoa, E.; Echavarren, A. M. *J. Org. Chem.* **1991**, *56*, 3497.
9. a) Potts, K. T.; Walsh, E. B.; Bhattacharjee, D. *J. Org. Chem.* **1987**, *52*, 2285. b) Kitahara, Y. and Kubo, A. *Heterocycles* **1992**, *34*, 1089.
10. Behforouz, M.; Gu, Z.; Cai, W.; Horn, M. A.; Ahmadiam, M. *J. Org. Chem.* **1993**, *58*, 7089.
11. a) J. M. Pérez, C. Avendaño, J. C. Menéndez, *Tetrahedron* **1995**, *51*, 6573. For biological data, see: b) Gesto, C., de la Cuesta, E., Avendaño, C.; Emling, F., *J. Pharm. Sci.*, **1992**, *81*, 815. c) Avendaño, C.; Alonso, M. A.; Espada, M.; García-Grávalos, D.; Menéndez, J. C.; Ocaña, B.; Pérez, J. M., *Eur. Pat. Appl.* EP 574,195 (15-12-93). *Chem. Abstr.*, **1994**, *120*, 270358e.
12. a) Pettit, G. R.; Fleming, W. C.; Paull, K. D. *J. Org. Chem.* **1968**, *33*, 1089. b) Avendaño, C.; de la Cuesta, E.; Gesto, C. *Synthesis* **1991**, 727. c) Blanco, M. M.; Avendaño, C.; Cabezas, N.; Menéndez, J.

C. *Heterocycles*, **1993**, *36*, 1387. d) Alonso, M. A.; Blanco, M. M.; Avendaño, C.; Menéndez, J. C. *Heterocycles*, **1993**, *36*, 2315. e) Kitahara, Y.; Nakahara, S.; Shimizu, M.; Yozenawa, T.; Kubo, A. *Heterocycles* **1993**, *36*, 1909. f) Martín, O.; de la Cuesta, E.; Avendaño, C. *Tetrahedron* **1995**, *51*, 7547.

13. a) Omura, S.; Iwai, Y.; Hinotozawa, K.; Tanaka, H.; Takahashi, Y.; Nakagawa, A. *J. Antibiotics* **1982**, *35*, 1425. b) Tsuzuki, K.; Yokozuka, T.; Murata, M.; Tanaka, H.; Omura, S. *J. Antibiotics* **1989**, *42*, 727.
14. Other workers have noticed similar problems associated with the use of 1-dimethylamino-1-azadienes in Diels-Alder chemistry. See, for example, reference 9a and: Nebois, P.; Cherkaoui, L.; Fillion, H. *Tetrahedron* **1994**, *50*, 8457.
15. Waldner, A. *Helv. Chim. Acta*, 1988, **71**, 486.
16. M. M. Blanco, J. M. Pérez, C. Avendaño, J. C. Menéndez, unpublished results.
17. Hegedus, L. S.; Sestrick, M. R.; Michaelson, E. T.; Harrington, P. J., *J. Org. Chem.*, **1989**, *54*, 4141.
18. Nebois, P. and Fillion, H., *Tetrahedron Lett.*, **1991**, *32*, 1307.
19. Valderrama, J. A. and González, M. F. *Heterocycles* , **1993**, *36*, 1553.
20. Echavarren, A. M., *J. Org. Chem.* **1990**, *55*, 4255.
21. Nebois, P.; Fillion, H; Benameur, L., *Tetrahedron*, **1993**, *49*, 9767.
22. Tanoue, Y. and Terada, A., *Bull. Chem. Soc. Jpn.*, **1988**, *61*, 2039.
23. Cerium (III) derivatives are well-known Lewis acids. See, for example: a) Molander, G. A., *Chem. Rev.*, **1992**, *92*, 29. b) Imamoto, T., *Lanthanides in Organic Synthesis*, chapter 5. Academic Press, 1994.

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