Design and Synthesis of Angucyclinone 5-Aza Analogues

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Abstract: A highly efficient one-pot procedure for the synthesis of phenanthridine-1,7,10-triones from acylbenzoquinones and cyclic enaminones is reported. The cycloaddition reactions of these quinones with 1-trimethylsilyloxybutadiene followed by hydrolysis and oxidative processes provide entry to a variety of angucyclinone 5-aza analogues.

Key words: Michael additions, quinones, heterocycles, Diels–Alder reactions, regioselectivity

The substitution of a nitrogen atom for an aromatic CH group in anticancer drugs (e.g. ametantrone and 11-deoxydoxorubicin),[1,2] which provides active antitumor N-analogues, has shown to be an effective strategy to design new potential antitumor compounds. These N-heterocyclic aromatic congeners could potentially retain the planar shape of the drug chromophore necessary for molecular recognition of the host. Furthermore, the basic and electron-withdrawing properties of the N-heterocycles seem to improve the affinity for the biological target and/or the cyclic redox mechanism.[3,4]

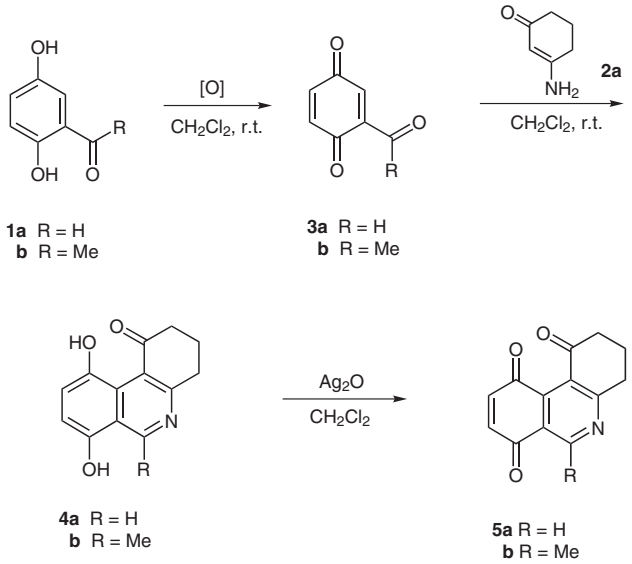
The synthesis of aza congeners of the benz[*a*]anthraquinone chromophore of angucyclines and angucyclinones[5,6] has received relatively little attention despite the antitumor activity of several members of this family of antibiotics. In this respect, Guingant et al.[7] have reported the synthesis of angucyclinone aza analogues by a method that involves cycloaddition reactions of 2-bromo-1,4-naphthoquinone derivatives with a push–pull heterodiene.

As part of our continuous interest in the synthesis and biological evaluation of quinones[8] we have recently reported studies on azaanthraquinones.[8a] The efficient and regioselective access to these compounds along with their promising antitumoral activities on several tumor cell lines encouraged us to extend our studies to the synthesis of aza analogues of benz[*a*]anthracene-1,7,12-trione, the skeleton of some angucyclines and angucyclinones.

We now report our findings which show that phenanthridine-7,10-quinone derivatives can be efficiently obtained via an ionic [3+3] process from commercially available precursors. The applications of these quinones in the synthesis of benzo[*j*]phenanthridine-7,12-quinones through highly regiocontrolled [4π+2π]-cycloaddition reactions is also described.

Based on recent results on the high-yield synthesis of a 5,8-dihydroxyisoquinoline derivative by reaction of acetylbenzoquinone **3b** with methyl aminocrotonate,[8a] we envisaged the construction of 7,10-dihydroxyphenanthridines by reaction of acyl-1,4-benzoquinones with cyclic enaminones. The following commercially available compounds were employed in this study: 2,5-dihydroxybenzaldehyde (**1a**), 2,5-dihydroxyacetophenone (**1b**), 3-amino-2-cyclohexen-1-one (**2a**), and 3-amino-5,5-dimethyl-2-cyclohexen-1-one (**2b**).

Formylbenzoquinone **3a**, prepared by oxidation of **1a** with silver(I) oxide,[9] reacts with enaminone **2a** at room temperature to give dihydroxyphenanthridine **4a** in 87% yield. Similarly, acetylbenzoquinone **3b**, prepared from 2,5-dihydroxyacetophenone (**1b**) and manganese dioxide,[10] was reacted with **2a** in dichloromethane to yield dihydroxyphenanthridine **4b** in 68% yield. Then, dihydroxyphenanthridines **4a**,**b** were oxidized with silver(I) oxide to the corresponding quinones **5a**, **5b** in 71% and 63% yields, respectively (Scheme 1).



Scheme 1

The above results show that enaminone **2a** undergoes a Michael addition across the activated 2,3-double bond of acylquinones **3a**,**b** to give the corresponding addition products which, by further heterocyclization reactions, provide the corresponding phenanthridines **4a**,**b**.

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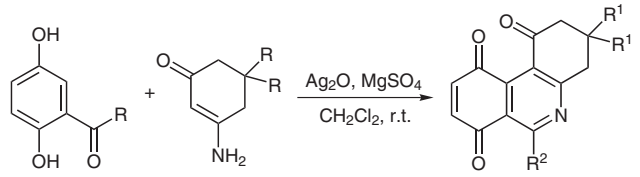
Since no intermediate products were detected in these reactions (TLC, ^{1}H NMR), it is evident that the cyclization step of the addition products to give the corresponding phenanthridines proceeds faster than the Michael addition. Based on this fact we planned to test a one-pot procedure for preparing phenanthridinequinones by oxidation of dihydroxyphenanthridines, arising from the reaction of enaminones, with the acylbenzoquinone generated in situ.

The attempts, explored with compound **1a**, enaminone **2a** and silver(I) oxide in dichloromethane, yielded the expected phenanthridinequinone **5a** (Scheme 2, Table 1). Encouraged by this result, we set out to study the scope of this one-step procedure for the synthesis of phenanthridinequinones **5b**–**d**[11] and the results are collected in Table 1.



1a,**b** **2a**,**b** **5a–d**

Scheme 2

After successfully synthesizing phenanthridinequinones **5a**–**d**, we turned our attention to carrying out the Diels–Alder reaction of these dienophiles with (*E*)-1-trimethylsilyloxybuta-1,3-diene. The cycloaddition of quinone **5a** with the diene proceeded smoothly in dichloromethane at room temperature, yielding adduct **6a** as the sole regioisomer (Scheme 3). In a similar manner, cycloaddition of quinones **5b**–**d** with the silyloxybutadiene provided access to the corresponding adducts **6b**–**d** (Scheme 3), and no regioisomers were detected (TLC, ^{1}H NMR) in the reaction mixtures. Compounds **6a**–**d** were isolated in high yields as pale yellow oils, and no purification was attempted due to their instability on silica.

The structures of adducts **6** were established from the HMBC spectra of **6a** and **6c**. In these compounds there were ^3J couplings between the C-7 carbon (δ = 197.5, 197.2) and the C-6 (δ = 4.43, 4.72) and C-8 (δ = 9.22, 9.50) protons.

The remarkable regioselectivity of the cycloaddition of quinones **5a**–**d** to the unsymmetrical diene led us to analyze the cycloaddition reaction of quinone **5a** with the diene in terms of frontier molecular orbital (FMO) theory.[12]

Theoretical calculations of the primary LUMO coefficients of dienophile **5a** (0.3967 for C-8 and 0.3141 for C-9)[13] and the primary HOMO coefficients of the diene (–0.5016 for C-4 and 0.4646 for C-1),[14] led to the prediction that adduct **6a** should be the less-favored regioisomer in this cycloaddition. Accordingly, the regiochemistry of the cycloadditions of dienophiles **5a**–**d** with trimethylsilyloxybutadiene proceeds in the opposite manner of that predicted by FMO theory. These facts can be attributed to steric and/or electronic factors associated with the fused cyclohexenone ring in compounds **5a**–**d**, which determine the regiochemical control of these cycloadditions.

Diels–Alder adducts **6a**–**d** were converted into the corresponding benzo[*j*]phenanthridinequinones **7a**–**d** (Scheme 3, Table 2, entries 1–4) by reaction with hydrochloric acid (method A). On the other hand, mild hydrolysis of adducts **6a**–**d** with hydrochloric acid followed by oxidation with pyridinium chlorochromate (PCC) of the alcohol intermediaries (method B),[15] yielded the corresponding 8-hydroxy benzo[*j*]phenanthridinequinones **7e**–**h** (Scheme 3, Table 2, entries 5–8).

It is worth mentioning that compounds **7e**–**h** (Scheme 3, Table 2, entries 5–8) have the same relative location of the carbonyl and hydroxyl groups on the benzo[*j*]phenanthridinequinone framework as those of some angucyclinones (e.g. tetrangomycin, fujianmycin A).

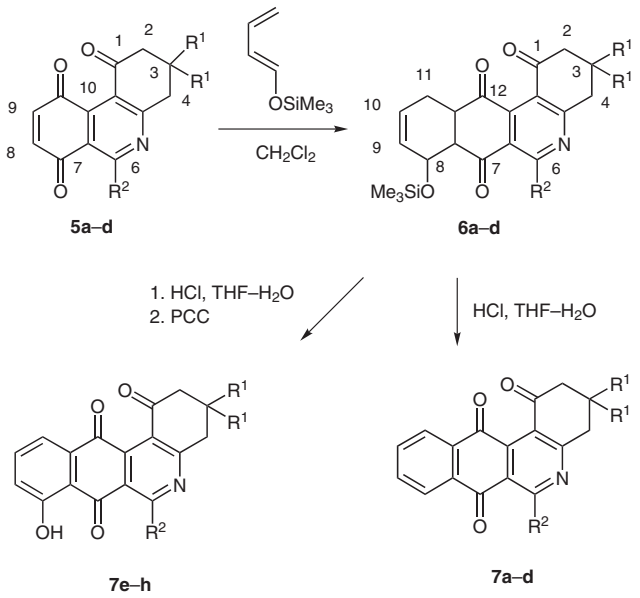
Some members of this new class of angucyclinone N-congeners and the carbocyclic analogue 6,8-dihydroxy-1,2,3,4-tetrahydrobenz[*a*]anthracene-7,12-quinone, previously reported by us,[14] were evaluated against human AGS gastric adenocarcinoma cell lines in order to get preliminary information on their cytotoxic activities.

The screening showed that compounds **7b**, **7e**, **7f**, and **7g** (entries 2 and 5–7) were more cytotoxic (IC_{50} = 9.5, 1.6, 4.5, 11.6 μm) than the carbocyclic compound (IC_{50} = 41.6 μm), thus supporting our approach to entry into new potentially cytotoxic agents based on the replacement of the nitrogen atom by CH groups in the benz[*a*]anthraquinone skeleton.

Table 1 Synthesis of Phenanthridine-7,10-quinones[a]

Substrates		Time (h)	Quinone	R^1	R^2	Yield (%)[b]
1a	**2a**	4.0	**5a**	H	H	69
1b	**2a**	3.0	**5b**	H	Me	78
1a	**2b**	2.0	**5c**	Me	H	79
1b	**2b**	2.0	**5d**	Me	Me	65

[a] Reagents: acylhydroquinone **1a**,**b** (1 equiv), enaminone **2a**,**b** (1 equiv) and silver(I) oxide (4 equiv).
[b] Isolated yields.



Scheme 3

In conclusion, we have described a simple strategy to prepare N-congeners of the angucyclinone chromophore. The reported synthesis involves commercially available precursors and an efficient Michael addition, heterocyclization, Diels–Alder reaction, and oxidative aromatization reaction sequence. This approach may be used to make a large number of such angular tetracyclic quinones from diverse acyl-1,4-quinones and cyclic enaminones. In ongoing studies, this method will be applied to the synthesis of a broad range of members of this new class of N-heterocyclic quinones and their cytotoxic activity on several cancer cells will be studied.

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Table 2 Preparation of 3,4-Dihydro-2*H*-benzo[*j*]phenanthridine-1,7,12-triones[16]

Entry	Substrate	Phenanthridine-1,7,12-triones	R^1	R^2	Yield (%)	Method[a]
1	**6a**	**7a**[b]	H	H	63	A
2	**6b**	**7b**	H	Me	72	A
3	**6c**	**7c**	Me	H	96	A
4	**6d**	**7d**	Me	Me	95	A
5	**6a**	**7e**	H	H	66	B
6	**6b**	**7f**	H	Me	82	B
7	**6c**	**7g**	Me	H	84	B
8	**6d**	**7h**	Me	Me	78	B

[a] Method A: 37% hydrochloric acid, THF–H_2O, r.t. Method B: (i) 5% hydrochloric acid, THF–H_2O, r.t.; (ii) PCC, NaOAc, CH_2Cl_2.
[b] The spectral properties of **7a** were in agreement with those reported in the literature.[7]

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(11) **Synthesis of 3,3,6-Trimethyl-2*H*-3,4-dihydrophenanthridine-1,7,10-trione (5d); Typical Procedure**. A suspension of 2,5-dihydroxyacetophenone (**1b**; 152 mg, 1.0 mmol), 3-amino-5,5-dimethyl-2-cyclohexen-1-one (**2b**; 139 mg, 1.0 mmol), silver(I) oxide (464 mg, 2.0 mmol), $MgSO_4$ (420 mg) and CH_2Cl_2 (20 mL) was vigorously stirred for 2 h at r.t. The mixture was filtered and the filtrate was evaporated under vacuum to give crude quinone **5d** (214 mg, 0.8 mmol, 80%). Further column chromatography of the crude product (silica; CH_2Cl_2–EtOAc, 9:1) yielded pure **5d** (175 mg, 0.65 mmol, 65%) as a yellow solid; mp 131–132 °C; R_f 0.49 (silica; CH_2Cl_2–EtOAc, 9:1). IR (KBr): 2969 (w), 1694 (s), 1668 (vs), 1610 (w), 1556 (s), 1469 (w), 1437 (w), 1391 (m), 1373 (m), 1359 (w), 1338 (s), 1311 (m), 1258 (s), 1225 (s), 1182 (w), 1155 (w), 1110 (m), 1052 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.15 (s, 6 H), 2.75 (s, 2 H), 2.97 (s, 3 H), 3.06 (s, 2 H), 6.86 (d, *J* = 10.3 Hz, 1 H), 7.05 (d, *J* = 10.3 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.22 (CH_3), 28.73 (2 × CH_3), 33.51 (C), 47.47 (CH_2), 53.28 (CH_2), 123.57 (C), 126.08 (C), 138.09 (CH), 138.48 (CH), 141.57 (C), 163.53 (C), 165.66 (C), 184.78 (C), 184.91 (C), 196.96 (C). Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.22; H, 5.50; N, 5.19.

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(16) **Synthesis of Benzo[*j*]phenanthridine-1,7,12-trione 7h; Typical Procedure for Method B**: A solution of **6d** (105 mg, 0.25 mmol), HCl acid (3 drops, 5%) in aq THF (6 mL, 90%) was left at r.t. for 1 h. The mixture was diluted with H_2O (10 mL) and then extracted with $CHCl_3$ (2 × 15 mL). The organic layer was washed with H_2O (2 × 10 mL), dried over $MgSO_4$, and evaporated under vacuum. The residue was dissolved in CH_2Cl_2 (10 mL) and the solution was added to a stirred solution of pyridinium chlorochromate (412 mg, 1.91 mmol), NaOAc (95 mg, 1.16 mmol) in CH_2Cl_2 (10 mL), and the mixture was stirred for 1.5 h at r.t. The resulting mixture was chromatographed (silica; CH_2Cl_2–EtOAc, 9:1) to give pure **7h** (65.4 mg, 0.195 mmol, 78%) as an orange solid; mp 166–167 °C (dec.); R_f 0.14 (silica; CH_2Cl_2–EtOAc, 9:1). IR (KBr): 3449 (w), 1708 (s), 1678 (s), 1636 (vs), 1571 (s), 1447 (s), 1367 (m), 1333 (s), 1283 (s), 1270 (s), 1243 (m) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.15 (s, 6 H), 2.77 (s, 2 H), 3.07 (s, 5 H), 7.28 (m, 1 H), 7.60 (m, 2 H), 12.30 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.33 (CH_3), 28.80 (2 × CH_3), 47.5 (CH_2), 53.3 (CH_2), 116.1 (C), 119.0 (CH), 124.5 (CH), 125.0 (C), 127.0 (C), 134.3 (C), 136.8 (CH), 144.4 (C), 162.0 (C), 164.5 (C), 166.0 (C), 183.6 (C), 189.0 (C), 197.0 (C). Anal. Calcd for $C_{20}H_{17}NO_4$: C, 71.63; H, 5.11; N, 4.18. Found: C, 71.45; H, 4.94; N, 4.21.