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Regiochemical control in the amination reaction of phenanthridine-7,10-quinones

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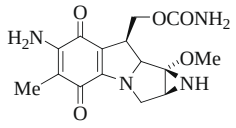
ABSTRACT

The reaction of substituted phenanthridine-7,10-quinones with amines to construct novel aminophenanthridinequinone derivatives as antitumor agents is described. The regiochemistry of the amination reaction is discussed in terms of inductive and steric effects of remote substituents to the quinone ring, which control the direction of the conjugate addition of the amines across the quinone double bond. Evidences on the significant in vitro antitumor activities of some of the obtained aminoquinones, are reported.

The molecular framework of several naturally occurring antitumoral agents contains an aminoquinonoid moiety as the key structural component, (e.g., mitomycin C **1,** cribrostatin 3 **2,** and streptonigrin **3**).[1,2] This structural array has stimulated the synthesis of novel lead compounds that exhibit significant cytotoxicity on human cancer cell lines.[3–6]



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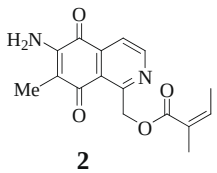

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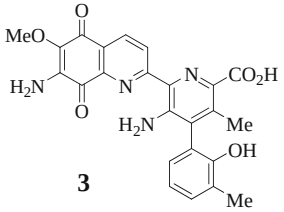

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We have recently developed a high yield synthesis of 7-substituted aminoisoquinoline-5,8-quinones **6**, using acid-induced substitution reactions of isoquinolinequinone **4** with alkyl- and arylamines.[7] These aminoquinones expressed in vitro cytotoxic activity against human lung fibroblasts, gastric adenocarcinoma, lung cancer, and bladder carcinoma cell lines. We have observed that replacement of the amino-proton of the parent compound 7-aminoisoquinoline-5,8-quinone **6** ($R^1 = R' = H$) by substituted aryl groups is more significant upon the antitumor activity than by alkyl groups. The SAR analysis of the members of the phenylaminoisoquinolinequinone derivatives reveals that the half wave potential is an important parameter determining the antitumoral activity on gastric adenocarcinoma and bladder carcinoma cells.

The high regiocontrol of the substitution reaction on quinone **4** with amines can be attributed to the C-5 carbonyl group, which is more electron deficient than the C-8 carbonyl group due to the electron-acceptor effect of the *para* nitrogen atom, as shown in structure **5**. This electron deficiency of the C-5 carbonyl is transferred to C-7 and finally leads to preferential C-7 substitution via nucleophilic attack of the amines. The regioselectivity of the 7-position is greatly increased by coordination with $CeCl_3 \cdot 7H_2O$ or $InBr_3$ to the heterocyclic nitrogen atom and/or the C-5 carbonyl group.

On the basis of these results and on the antitumor activity of some benzo- and pyridophenanthridine-7,10-quinones, prepared from **7** and **8**,[8] we decided to study their reaction with amines directed toward the synthesis of 8- (or 9)-aminophenanthridine-7,10-quinones derivatives for biological evaluation on cancer cell lines. We herein describe the reaction of phenanthridine-7,10-quinones **7** and **8** with amines, the influence of a Lewis acid catalyst on the substitution reactions. We also show preliminary results on their in vitro antitumor activity against human gastric adenocarcinoma and lung cancer cell lines.

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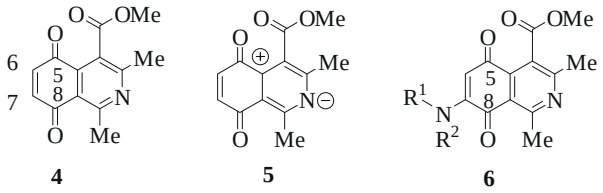
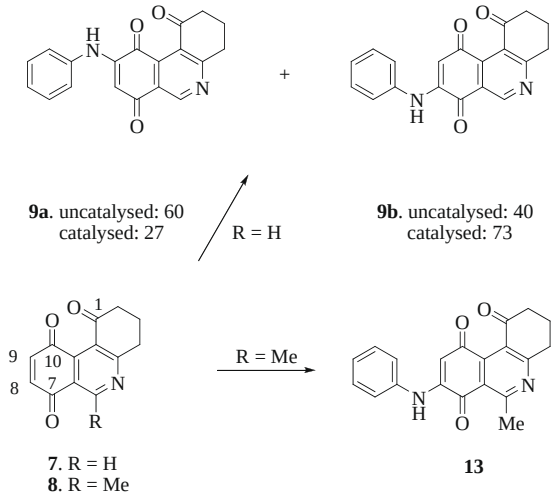


4 **5** **6**

Phenanthridinequinones **7** and **8** were prepared according to a recent reported procedure.[8,9] Firstly, we explored the reaction of phenantridinequinone **7** with aniline in ethanol at room temperature. The reaction went to completion in 5 h to give a 60:40 mixture of regioisomers **9a** and **9b** in 40% yield (Table 1, entry 1). Interestingly, when quinone **7** was allowed to react in ethanol in the presence of 10 mmol % of $CeCl_3{\cdot}7H_2O$, the reaction was clean and fast (90 min) to give a 27:73 mixture of regioisomers **9a** and **9b** in 88% yield (entry 2). These results clearly demonstrate that the catalyst improves the yields and changes the regiochemistry of the substitution reaction.

Then we analyzed the reactivity of quinone **8** with aniline in ethanol at room temperature. Surprisingly, in this case the result was totally different from that observed for quinone **7**, since the reaction proceeds slowly and with poor yield to give aminoquinone **13** as the unique regioisomer (entry 7). The addition of 10 mmol % of $CeCl_3{\cdot}7H_2O$ increases the reaction rate and yield of **13**, and does not change the regioselectivity (entry 8). Compounds **9a**,[10] **9b**,[11] and **13**[12] were purified by column chromatography and their structures were determined through (HMBC, HMQC) experiments (Scheme 1).



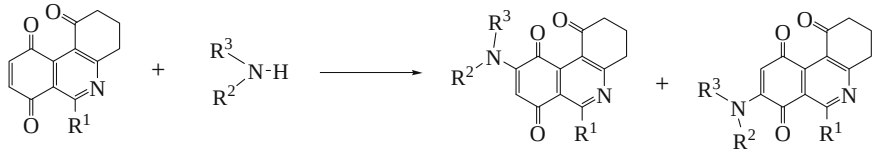
Scheme 1. Reaction of quinones **7** and **8** with aniline.

Encouraged by these results we examined the reaction of quinones **7** and **8** with *p*-anisidine, *N*-methylaniline and cyclohexylamine. The reaction of quinone **7** with *p*-anisidine in ethanol produced a 73:27 mixture of isomers **10a** and **10b** after 6 h (entry 3). In a parallel assay of this reaction with 10 mmol % of $CeCl_3{\cdot}7H_2O$, a 26:74 mixture of regioisomers **10a** and **10b** was isolated after 90 min (entry 4). *N*-Methylaniline and cyclohexylamine reacted with **7** under catalysis conditions giving aminoquinones **11a**,**b** and **12a**,**b**, respectively (entries 5 and 6). The reaction of quinone **8** with *p*-anisidine and cyclohexylamine produced the corresponding substitution products **14** and **15** (entries 10 and 11).

The results of the experiments under uncatalyzed conditions demonstrate that the C-7 carbonyl group in quinone **7** exerts a greater activation than the C-10 carbonyl group into the corresponding π-enone systems favoring the attack of the nucleophile at the 9-position. According to the resonance and FMO theories the behavior of **7** on the substitution reactions is opposite to that predicted by both the theories. In fact, the inductive effect of the heterocyclic nitrogen atom selectively increases the electron-withdrawing ability of the C-10 carbonyl group so the attack of the nucleophiles occurs at the 8-position. Concerning the polarization of the LUMO on the electrophilic quinone double bond, the 8-position is the preferred site of nucleophilic attack due to its largest LUMO coefficient.[13,14]

On the contrary, in the case of quinone **8**, the C-10 carbonyl group exerts higher activation on the quinone double bond than the C-7 carbonyl group, favoring the regiospecific attack of the

Table 1
Reaction of phenanthridinequinone **7** and **8** with amines



7, **8** **9a-12a** **9b-12b**, **13-15**

Entry	R^1	R^2	R^3	Time	Products	Yield[b]	Selectivity[c]
1	H	Ph–	H	5.0 h	**9a** + **9b**	40	60/40
2	H	Ph–	H	90 min[a]	**9a** + **9b**	88	27/73
3	H	4-MeO–Ph–	H	6 h	**10a** + **10b**	15	73/27
4	H	4-MeO–Ph–	H	90 min[a]	**10a** + **10b**	86	26/74
5	H	Ph–	Me	8 h[a]	**11a** + **11b**	55	32/68
6	H	Cyclohexyl–	H	6 h[a]	**12a**+**12b**	42	40/60
7	Me	Ph–	H	13 h	**13**	18	100
8	Me	Ph–	H	1h[a]	**13**	96	100
9	Me	4-MeO–Ph–	H	9 h	**14**	25	100
10	Me	4-MeO–Ph–	H	53 min[a]	**14**	79	100
11	Me	Cyclohexyl–	H	70 min[a]	**15**	45	100

[a] In the presence of 10% molar of $CeCl_3{\cdot}7H_2O$.
[b] Isolated yields.
[c] Evaluated by ^1H NMR.

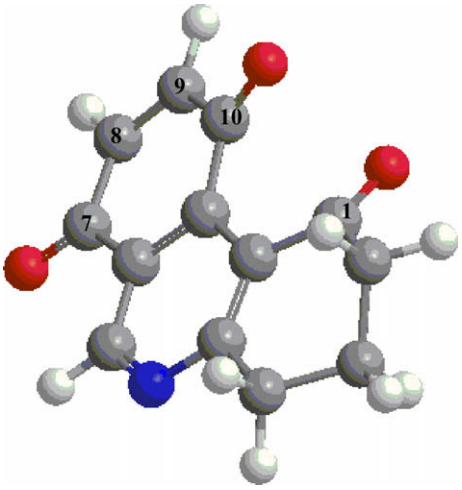


Figure 1. Minimized molecular model of quinone **7**.

nucleophile at the 8-position, which is in accordance with the theoretical predictions.[13]

Since the electron-withdrawing effect of the heterocyclic nitrogen atom in dienophile **7** does not have a significant influence on the regioselectivity of the substitution reaction apparently, the control could be determined in part by steric interactions between the C-1 and C-10 carbonyl groups into the dienophile.

An inspection of the molecular model of **7** (Fig. 1) shows an inhibition to the coplanarity of the C-10 carbonyl group with respect to the quinone double bond, due to its steric interaction with the carbonyl groups at C-1. This effect probably influences the electron-withdrawing ability of the C-10 carbonyl group so the preferential attack of the nucleophiles occurs at β-position to the C-7 carbonyl group.

The regioselectivity of the substitution reaction on quinone **8** can be explained assuming steric and electron-donor interactions between the methyl and C-7 carbonyl groups. These factors probably affect the electrophilicity of the C-9 atom and the attack of the nucleophiles occurs at β-position to the C-10 carbonyl group.

With regard to the experiments on the reactions of quinone **7** with the nucleophiles performed with $CeCl_3 \cdot 7H_2O$ catalyst, a reversal of the regioselectivity with respect to the uncatalyzed reaction is induced. However, in quinone **8** the catalyst does not change the regioselectivity of the substitution at the 8-position, as in the case of the uncatalyzed reactions.

The effect of the catalyst to promote the attack of the nucleophile at the 8-position in both quinones may be ascribed to coordination of the cerium ion to the heterocyclic nitrogen atom and/or the carbonyl group at the C-10 position. The coordination strongly enhances the electron-withdrawing capacity of the carbonyl group at the C-10 position, which is transferred to the 8-position, leading to preferential C-8 substitution via nucleophilic attack by the amines.

Some members of the aminophenanthridinequinone derivatives were evaluated in vitro against human gastric adenocarcinoma and lung cancer cell lines to get preliminary information on their cytotoxic activities. The screening showed that compounds **9a**, **9b**, **12a**, and **12b** exhibit significant antitumor activity in the range IC_{50}: 0.23–7.5 μM. It is noteworthy that compounds **9b** and **12b** exhibit higher antitumor activity (IC_{50} = 0.23 and 0.38 μM) than their corresponding regioisomers **9a** and **12a** (IC_{50} = 3.9 and 2.3 μM) on gastric cancer cells. The antitumor activity of compounds **9b** and **12b** on gastric cancer cells was comparable to that shown by the reference drug etoposide (IC_{50} = 0.36 μM).

In conclusion, we have described the reaction of two representative phenanthridinequinones with amines that provides a regioselective access to potentially antitumor aminophenanthridinequinone derivatives. The effect of remote substituents and the catalysis on the control of the regioselectivity of the studied reaction, together with the significant anticancer activity observed on the 8-regioisomers, appears as valuable precedents toward the development of new aminophenanthridinequinone-containing antitumor drugs. The scope of the amination reaction on phenanthridinequinone directed to prepare a variety of new members of this class of *N*-heterocyclic quinones, and their biological evaluation on representative cancer cell lines, are in progress in our laboratory.

Acknowledgment

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10. *Compound* **9a**: purple solid, mp 182–184 °C; IR (KBr): ν_{max} 3447 (N–H), 1703 (C=O), 1607 and 1590 (C=O quinone); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.22 (t, *J* = 6.5 Hz, 2H, 3-H), 2.89 (t, *J* = 6.5 Hz, 2H, 2-H), 3.18 (t, *J* = 6.5 Hz, 2H, 4-H), 6.31 (s, 1H, 8-H), 7.23 (m, 3H, arom.), 7.25 (m, 2H, arom.), 7.41 (s, 1H, NH), 9.33 (s, 1H, 6-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.50, 33.39, 39.26, 102.24, 122.67, 124.25 (2C), 126.25, 128.89 (2C), 129.83,136.93, 140.44, 143.75, 150.75, 167.65, 180.79, 181.97, 197.62. The HMBC spectrum of **9b** shows $^3J_{C,H}$ coupling of the C-10 carbon (δ 180.79 ppm) with the protons at: δ 7.41 and 6.31.HRMS (M+): *m/z* calcd for $C_{19}H_{14}N_2O_3$ [M+]: 318.10044; found: 318.10005.
11. *Compound* **9b**: red solid, mp 179–182 °C; IR (KBr): ν_{max} 3441 (N-H),1668 (C=O),1610 and 1566 (C=O quinone); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.21 (t, *J* = 6.5 Hz, 2H, 3-H), 2.89 (t, *J* = 6.5 Hz, 2H, 2-H), 3.13 (t, *J* = 6.5 Hz, 2H, 4-H), 6.43 (s, 1H, 9-H), 7.23 (m, 3H, arom.), 7.25 (m, 2H, arom.), 7.41 (s, 1H, NH), 9.24 (s, 1H, 6-H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.37, 33.40, 39.13, 104.99, 122.67, 124.25 (2C), 126.09, 128.90 (2C), 129.84, 136.92, 140.45, 143.74, 149.66, 169.79, 180.80, 181.42, 198.00. The HMBC spectrum of **9a** shows $^3J_{C,H}$ coupling of the C-7 carbon (δ 181.42 ppm) with the protons at: δ 9.24; 7.41 and 6.43 ppm.HRMS (M+): *m/z* calcd for $C_{19}H_{14}N_2O_3$: 318.10044; found: 318.10012.
12. *Compound* **13**: dark red solid, mp 180–183 °C; IR (KBr): ν_{max} 3443 (N-H), 1696 (C=O), 1591 and 1564 (C=O quinone), ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.20 (t, *J* = 6.7 Hz, 2H, 3-H), 2.85 (t, *J* = 6.7 Hz, 2H, 2-H), 2.92 (s, 3H, 6-CH_3), 3.05 (t, *J* = 6.7 Hz, 2H, 4-H), 6.35 (s, 1H, 9-H), 7.22 (m, 3H, arom.), 7.38 (m, 2H, arom.), 7.74 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.39, 26.33, 33.18, 39.12, 103.27, 122.58 (2C), 125.82, 128.07, 129.71 (2C), 137.17, 143.43, 144.74, 146.54, 162.27, 167.64, 181.42, 181.99, 198.64. The HMBC spectrum of **13** shows $^3J_{C,H}$ coupling of the C-7 carbon (δ 181.99 ppm) with the protons at δ 7.74 and 6.35 ppm, and $^4J_{C,H}$ coupling of the C-7 carbon (δ 181.99 ppm) with the protons of the methyl group at δ 2.92 ppm.HRMS (M^+): *m/z* calcd for $C_{19}H_{14}N_2O_3$ [M+]: 332.11609; found: 332.11552.
13. The LUMO eigenvector coefficients were obtained with DFT level in B3LYP/6-31G using the package GAUSSIAN 03. Compound **7**: C8 = −0.20625, C9 = 0.19330 eV. Compound **8**: C8 = −0.20483, C9 = 0.19584 eV.
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