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Reactions of Aza- and Diazaanthraquinone *N*-oxides.

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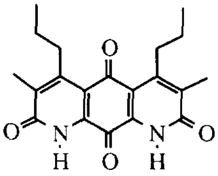
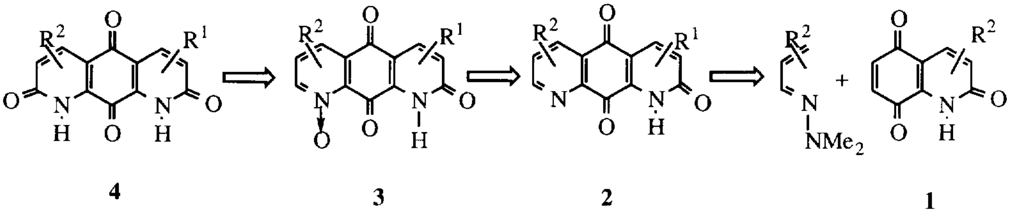
Abstract: 1-Azaanthracene-2,5,8-triones and 1,8-diazaanthracene-2,7,9,10-tetraones, which are structurally related to diazaquinomycin, are prepared by functionalization of azaanthraquinone *N*-oxides. The complete procedure implies a Diels-Alder reaction as a key step, followed by *N*-oxidation and treatment of the *N*-oxides with benzoyl or tosyl chlorides in the presence of water.

After Ochiai's systematic investigation of heteroaromatic *N*-oxides[1] the chemical behaviour and uses of these compounds in heterocyclic synthesis were established.[2] In this context, nucleophilic substitutions of heteroaromatic *N*-oxides in the presence of acylating agents are very versatile synthetic procedures. Their common feature is the initial acylation of the *N*-oxide function to *N*-acyloxy quaternary salt intermediates, which are very reactive and seldom isolated, and subsequent attack of nucleophiles to the ring carbon atoms. Conversion of *N*-oxides to oxo-derivatives, generally performed with tosyl or benzoyl chloride in an aqueous alkaline medium, is perhaps the best known of these reactions. In the case of pyridine *N*-oxides, the nucleophillic addition is usually directed to the α-position, although the presence of a 3-alkyl substituent apparently diminishes the yields of the 2-oxoderivatives.[2]

This methodology was planned to obtain 1*H*,8*H*-1,8-diazaanthracene-2,7,9,10-tetraones (**4**), which are analogues of diazaquinomycin A,[3] according to the analysis shown in Scheme 1. Diazaquinomycin is an antifolate antibiotic that failed antitumor *in vivo* tests because of its insolubility.[4] Chemical modifications of the natural product seemed to indicate that the substitution of one or both lactam rings by pyridine rings substantially reduces the biological activity.[5] In this context we have shown that some monolactam analogues **2**, obtained by cycloaddition of 2,5,8-quinolinetriones (**1**) to activated 1-azadienes[6] are very interesting antitumor compounds.[7] However the final aim of our project was to find a general procedure to obtain bislactamic structures to be biologicaly tested and compared with **2**.



Diazaquinomycin A



Scheme 1

The designed strategy was limited by the scarcity of literature references about the preparation of compounds **1**, especially the 3-substituted derivatives,[7] and by the poor results obtained in the first attempts to *N*-oxidate diazaanthracenetriones (**2**).[6] We have tried to overcome both problems by developing several routes to 3- and/or 4-substituted 2,5,8-quinolinetriones[8] and optimizing the procedures for the above mentioned *N*-oxidation, thus making *N*-oxides **3** and **6** available in good preparative yields.[9]

Diazaquinomycin itself has been synthesised by cyclization of 2,6-di(2-methyl-3-oxo-hexanoyl-amino)hydroquinone.[10] However this methodology is not reliable, the above mentioned synthesis being the only reported example of a succesful double Knorr cyclization. Consequently, the strategy shown in Scheme 1 would be a good general approach to 1,8-diazaanthracene-2,7,9,10-tetraones (**4**).

Hydroxylation of *N*-acyloxy quaternary salts derived from **3** and **6** was expected to afford the α-oxo compounds **4** and **7**, although a related approach aimed at the synthesis of a nybomycin analogue through conversion of 4-acetyloxymethyl-1,5-dimethyl-1*H*-1,8-diazaanthracene-2,9,10-trione methotriflate salt to the corresponding α-pyridone by treatment with potassium hydroxide and potassium ferricyanide failed, because the nucleophilic attack took place at the γ-position.[11]

On the other hand, *N*-oxides **6**, obtained from 1-aza-anthracene-9,10-diones (**5**), would give 1-aza-2,9,10-anthracenetiones (**7**), in an interesting synthetic alternative to our current procedure to obtain these compounds through Diels-Alder cycloadditions of carbostyrilquinones to carbodienes[12] or by cyclization of 3-unsubstituted 2(β-oxoacylamino)naphtoquinones.[13] In fact, compounds **5** are readily available by Diels-Alder reactions of simple dienophiles such as naphthoquinone or quinolinequinone with 1-azadienes or carbodienes respectively.[14]

Conversion of **6a** to **7a** was initially employed for screening the best experimental conditions (Table 1). Acetic anhydride and NaOH pellets at high temperature gave a complex reaction mixture from which **7a** was isolated in low yield. By treatment with benzoyl chloride and 2*N* NaOH, 1-benzoyloxy-3-methyl-9,10-dioxo-1-azoniaanthracene hydroxide (**8a**) precipitated, but by using water as nucleophile the desired α-oxo-compound was obtained.

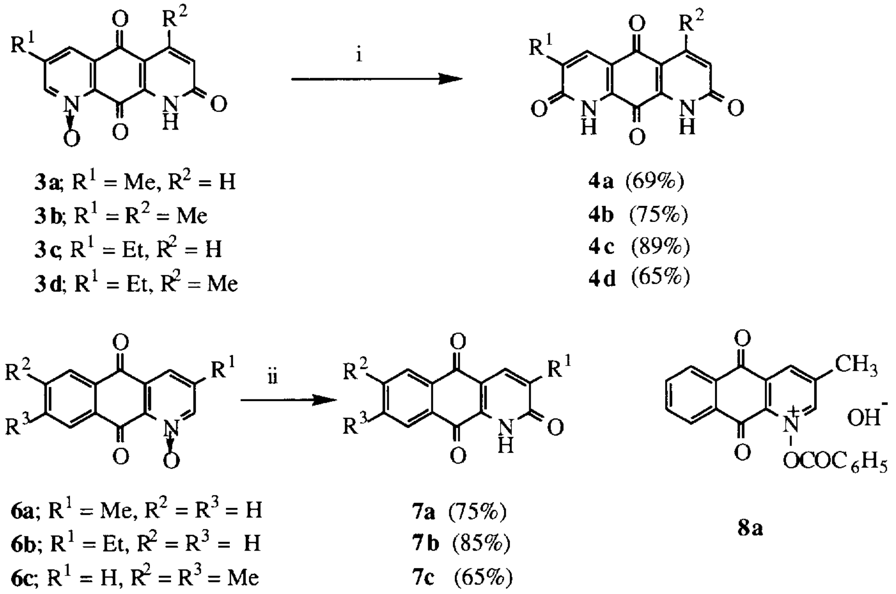
Table 1. Nucleophilic substitutions in **6a**.

Acylating agent	Solvent/nucleophile	Product	% Yield
Ac_2O	Ac_2O/NaOH	**7a**	21
PhCOCl	THF/2*N* NaOH	**8a**	46
PhCOCl	$HCCl_3/H_2O$	**7a**	64
TosCl	CH_3CN/H_2O	**7a**	65

The use of tosyl chloride as acylating agent, acetonitrile as solvent and water as nucleophile afforded **7a** in similar yields. Therefore, variations of method D were used in the conversion of *N*-oxides **6b, 6c,** and **3a-3d** to azaanthracenetriones **7b** and **7c** and diazaanthracenetetraones **4a-4d** (Scheme 2).

Isolation and NMR study of **8a** allowed to discard the other possible structure for the addition compound (3-methyl-2-hydroxy-1-benzoyloxy-1,2-dihydro-1-azaanthraquinone).[15]

Structural assignment of compounds **4** and **7** as α-oxo-derivatives instead of the alternative γ-oxo-structure is based on carbonyl group δ values of their ^{13}C NMR spectra. It is known in the quinolone series that the ^{13}C NMR chemical shift values of the 2-oxo-compounds (at about 160 ppm) are lower than those of their 4-oxo-analogues (at about 180 ppm).[16] Our own data for other 2-oxo- and 4-oxo-1-azaanthracene-9,10-diones obtained by alternative strategies[6,7,13] confirm this criterium. Many quaternary carbon signals are not observed in the ^{13}C NMR spectra of **4** and **7** because the low solubility of these compounds.



3a; R^1 = Me, R^2 = H
3b; R^1 = R^2 = Me
3c; R^1 = Et, R^2 = H
3d; R^1 = Et, R^2 = Me

4a (69%)
4b (75%)
4c (89%)
4d (65%)

6a; R^1 = Me, R^2 = R^3 = H
6b; R^1 = Et, R^2 = R^3 = H
6c; R^1 = H, R^2 = R^3 = Me

7a (75%)
7b (85%)
7c (65%)

8a

i) See experimental
ii) See experimental

Scheme 2

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EXPERIMENTAL

Ir spectra were recorded on Perkin-Elmer 577 and Buck Scientific 500 spectrophotometers, with all compounds compressed into KBr pellets. Nmr spectra were obtained on Bruker AC-250 (250 MHz for ^{1}H and

63 MHz for ^{13}C) spectrometer; $CDCl_3$ and DMSO-d_6 were used as solvents and TMS was added as an internal standard for proton and carbon spectra. Elemental analyses were determined by the Servicio de Microanálisis, Universidad Complutense, on a Perkin-Elmer 2400 CHN microanalyzer. Melting points were measured in open capillary tubes using a Büchi immersion apparatus, and are uncorrected. Reactions were monitored by thin layer chromatography on aluminium plates coated with silica gel (SDS 60ACC, 230-240 mesh and Scharlau Ge 048). All reagents were of commercial quality (Aldrich, Merk, SDS, Probus) and were used as received. The expression "petroleum ether" refers to the fraction boiling at 40-60 °C.

3-Methyl-1*H*-1-azaanthracene-2,9,10-trione (7a).

Method A. A solution of 190 mg (0.79 mmol) of **6a**[9] and 2 ml of acetic anhydride was refluxed and stirred for 5 h. The mixture was cooled, basified with 2.4 g of NaOH pellets and stirred at 120 °C for 2 h. The mixture was extracted with chloroform to eliminate 3-methyl-1-azaanthracene-9,10-dione which is produced by thermal decomposition of **6a**. Dilute 2*N* chlorhydric acid (30 ml) was added to the aqueous layer, which was lately extracted with chloroform. The organic residue was chromatographed on silica gel eluting with $CHCl_3$/MeOH (10:0.5) to yield **7a** as a yellow solid (21% yield).

Method C. To a stirred solution of 125 mg (0.52 mmol) of **6a** in 12 ml of chloroform at 60 °C were added 3 portions of 1 ml (0.86 mmol) of benzoyl chloride in hourly intervals. Then 0.4 ml of water were added and the mixture was stirred for 1h at 60 °C and for further 12 h at room temperature. The mixture was evaporated to dryness and the residue was treated with diethyl ether (60 ml) and petroleum ether (40 ml) and filtered to yield 80 mg (64 %) of pure **7a**.

Method D. To a stirred suspension of 100 mg (0.42 mmol) of **6a** and 50 mg (0.26 mmol) of tosyl chloride in 25 ml of acetonitrile at 60 °C was added 1 ml of water. The resulting solution was stirred for 16 h at 60 °C with hourly addition of 4 portions of 50 mg of tosyl chloride. The cooled mixture was filtered to yield 50 mg of **7a**. An additional amount was obtained by evaporation of the aqueous solution followed by chromatographic purification of the residue as in method A. Total yield 65%. Mp >300 °C. IR 3640-3300, 1680, 1670 and 1640 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ. 8.25 (dd, 1H, J = 7.3 and 1.47 Hz, H-8), 8.20 (dd, 1H, J = 7.3 and 1.47 Hz, H-5), 8.00 (q, 1H, J = 1.20 Hz, H-4), 7.82 (m, 2H, H-6 and H-7), 2.31 (d, 3H, J =1.20 Hz, CH_3). Anal. Calcd. for $C_{14}H_9NO_3$. 1/2 H_2O: C, 67.74; H, 4.06; N, 5.64. Found: C, 67.49; H, 3.90; N, 5.77.

1-Benzoyloxy-3-methyl-9,10-dioxo-1-azoniaanthracene hydroxide (8a).(Method B) To a preheated solution (60 °C) of 0.27 g (1.1 mmol) of **6a** , 0.2 ml (1.7 mmol) of benzoyl chloride and 25 ml of tetrahydrofurane, was added 1ml of 2*N* NaOH. The reaction mixture was evaporated under reduced pressure and the solid residue was washed with absolute ethanol, to give 0.18 g of **8a** as a yellow solid (46% yield).Mp 225-227 °C (dec). IR 1740, 1685 and 1670 cm^{-1}. ^{1}H-NMR (DMSO-d_6). δ 8.65 (s, 1H, H-2), 8.22 (m, 5H, H-4, H-5, H-8, H-2′ and H-6′), 7.95 (m, 2H, H-6 and H-7), 7.84 (t, 1H, J = 7.3 Hz H-4′), 7.68 (m, 2H, H-3′and H-5′), 2.42 (s, 1H, CH_3). ^{13}C-NMR δ 182.1, 180.6, 163.9, 160.0, 146.5, 139.9, 135.1, 135.0, 134.8, 133.6, 132.7, 132.4, 130.4 (2), 130.2, 129.6 (2), 127.9, 127.2, 126.9 and 16.0. Anal. Calcd. for $C_{21}H_{15}NO_5$: C, 69.80; H, 4.18; N, 3.88. Found: C, 69.44; H, 3.82; N, 3.89.

3-Ethyl-1*H*-1-azaanthracene-2,9,10-trione (7b). To a stirred solution of 100 mg (0.39 mmol) of **6b** in 25 ml of acetonitrile and 1 ml of water at 60 °C were added 4 portions of 50 mg (1 mmol) of tosyl chloride in hourly intervals. The mixture was stirred for 4 h at 60 °C. To the cooled solution, 4 ml of water were added. The yellow precipitate obtained, was filtered and washed with a small amount of acetonitrile, to yield 60 mg of pure **7b**. The filtrates were combined and evaporated and the residue was purified by chromatography, eluting with ethyl acetate-dichloromethane (1:1) to yield 25 mg of **7b**. Total yield 85%. Mp. 253-255 °C. IR 3700-3400, 1690, 1670 and 1640 cm^{-1}. ^{1}H-NMR (DMSO *d*$_6$) δ 12.08 (s, 1H, NH), 8.04 (m, 2H, H-5 and H-8), 7.86 (m, 2H, H-6 and H-7), 7.80 (s, 1H, H-4), 2.50 (q, 2H, *J* = 7.3 Hz, CH_2), 1.13 (t, 3H, *J* = 7.3 Hz, CH_3); ^{13}C-NMR δ 180.4, 177.7, 161.8, 141.4, 138.8, 134.8, 133.9, 131.6, 131.3, 130.1, 126.2 (2C), 115.8, 23.2 and 12.1. Anal. Calcd. for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 70.99; H, 4.45; N, 5.42.

6,7-Dimethyl-1*H*-1-azaanthracene-2,9,10-trione (7c). Application of method D as described above for **7b** to 106 mg (0.42 mmol) of **6c**^{9} gave 69 mg (65%) of **7c** after stirring at 60 °C for 20 h. Mp. >300 °C. IR 3630-3400, 1685, 1665 and 1650 cm^{-1}. ^{1}H-NMR (Pyridine-*d*$_6$) δ 8.22 (d, 1H, *J* = 9.5 Hz, H-4), 8.09 (s, 1H, H-8), 8.04 (s, 1H, H-5), 7.01 (d, 1H, *J* = 9.5 Hz, H-3), 2.22 (s, 3H, CH_3), 2.20 (s, 3H, CH_3). ^{13}C-NMR δ 180.6, 178.8, 163.0, 145.1, 129.9, 128.0, 127.9, 126.9, 117.0, 19.9 and 19.8. Other signals are mixed with those of the solvent . Anal. Calcd. for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 70.96; H, 4.39; N, 5.45.

3-Methyl-1*H*,8*H*-1,8-diazaanthracene-2,7,9,10-tetraone (4a). Application of method D to 108 mg (0.42 mmol) of **3a**^{6,9} gave 74 mg (69%) of **4a**, after stirring at 60 °C for 20 h. Mp. >300 °C. IR 3650-3300, and 1650 cm^{-1}. ^{1}H-NMR (DMSO-*d*$_6$) δ 12.35 (s, 2H, NH), 7.98 (d, 1H, *J* = 9.1 Hz, H-5), 7.87 (s, 1H, H-4), 6.77 (d, 1H, *J* = 9.1 Hz, H-6), 2.14 (s, 3H, CH_3). ^{13}C-NMR δ Anal. Calcd. for $C_{13}H_8N_2O_4$. H_2O: C, 60.94; H, 3.15; N, 10.93. Found: C, 60.69; H, 3.59; N, 10.53.

3,5-Dimethyl-1*H*,8*H*-1,8-diazaanthracene-2,7,9,10-tetraone (4b). Application of method D (as described above for **7b**) to 114 mg (0.42 mmol) of **3b**^{9} gave 85 mg (75%) of **4b**, after stirring at 60 °C for 20 h. Mp. >300 °C. IR 3650-3350, 1680 and 1650 cm^{-1}. ^{1}H-NMR (DMSO-*d*$_6$) δ 12.17 (s, 2H, NH), 7.80 (s, 1H, H-4), 6.56 (s, 1H, H-6), 2.47 (s, 3H, C_5-CH_3), 2.10 (s, 3H, C_3-CH_3). ^{13}C-NMR δ 180.9, 173.8, 162.4, 162.5, 150.9, 136.8, 132.2, 22.2 and 17.3. Anal. Calcd. for $C_{14}H_{10}N_2O_4$. H_2O: C, 58.33; H, 4.20; N, 9.72. Found: C, 57.95; H, 4.13; N, 9.44.

3-Ethyl-1*H*,8*H*-1,8-diazaanthracene-2,7,9,10-tetraone (4c). Application of method D to 114 mg (0.42 mmol) of **3c**^{9} gave 101 mg (89%) of **4c**, after stirring at 60 °C for 20 h. Mp. >300 °C (dec.). IR 3680-3360, 1690 and 1670 cm^{-1}. ^{1}H-NMR (DMSO-*d*$_6$) δ 12.30 (s, 2H, NH), 7.93 (d, 1H, *J* = 9.4 Hz, H-5) 7.73 (s, 1H, H-4), 6.72 (d, 1H, *J* = 9.4 Hz, H-6), 2.45 (q, 2H, *J* = 7.4 Hz, CH_2), 1.10 (t, 3H, *J* = 7.4 Hz, CH_3). ^{13}C-NMR δ 179.0, 173.3, 162.2, 161.8, 141.3, 137.7, 135.6, 129.9, 114.2, 23.3 and 12.1. Anal. Calcd. for $C_{14}H_{10}N_2O_4$. H_2O: C, 58.33; H, 4.20; N, 9.72. Found: C, 58.60 ; H, 3.99 ; N, 9.82.

3-Ethyl-5-methyl-1*H*,8*H*-1,8-diazaanthracene-2,7,9,10-tetraone (4d). To a stirred solution of 85 mg (0.30 mmol) of **3d**^{9} in 25 ml of acetonitrile and 4 ml of water at 70 °C, were added 4 portions of 50 mg (1 mmol) of tosyl chloride in hourly intervals. The mixture was stirred for 20h at 70 °C. After addition of 2.5 ml of diethyl ether, a red solid was obtained. The precipitate was filtered and washed with a small amount of diethyl ether to yield 55 mg (65%) of pure **4d**. Mp. >300 °C. (dec). IR 3700-3300, 1680 and 1655 and 1645 cm^{-1}. ^{1}H-NMR (DMSO-*d*$_6$) δ 12.15 (s, 2H, NH), 7.73 (s, 1H, H-4), 6.55 (s, 1H, H-6), 2.47 (m, 5H, CH_2 and C_5-CH_3), 1.11 (t, 3H, *J* = 7.4 Hz, CH_3). ^{13}C-NMR δ 180.6, 173.8, 161.7, 161.0, 151.5, 141.3, 136.3, 130.1, 23.3, 21.9. Anal. Calcd. for $C_{15}H_{12}N_2O_4$. H_2O: C, 59.60; H, 4.67; N, 9.27. Found: C, 59.78; H, 4.90 ; N, 9.42.

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