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N-Oxides of Azaanthraquinones

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Abstract.- A procedure is described for the efficient *N*-oxidation of heterocyclic quinones, which represents a considerable improvement over previous, multi-step methods.

The chemistry and biological activity of heterocyclic quinones is a subject of current interest.[1] We have previously reported that some azaanthraquinones analogs of the antibiotic diazaquinomycin A[2-4] show interesting antitumor activity.[5] Because of the biological properties and reactivity of aromatic *N*-oxides,[6] we have attempted the direct *N*-oxidation with MCPBA of some diazaanthraquinones with very poor results.[7]

Electron-withdrawing groups, specially in 2- or 4- positions of the ring nitrogen atom of simple azines, inhibit oxidation or lead to unpredictable results.[8] According to Fieser,[9] *N*-oxides of quinoline- and isoquinoline- quinones can not be obtained with peracids or hydrogen peroxides, due to the low basicity of the nitrogen atom. In fact, *N*-oxides of quinoline-, isoquinoline-[10] and quinoxaline-quinones[11] have been usually obtained through *N*-oxidation of reduced precursors having electron-releasing substituents in the positions 5 and 8, followed by oxidation of the carbocyclic ring.

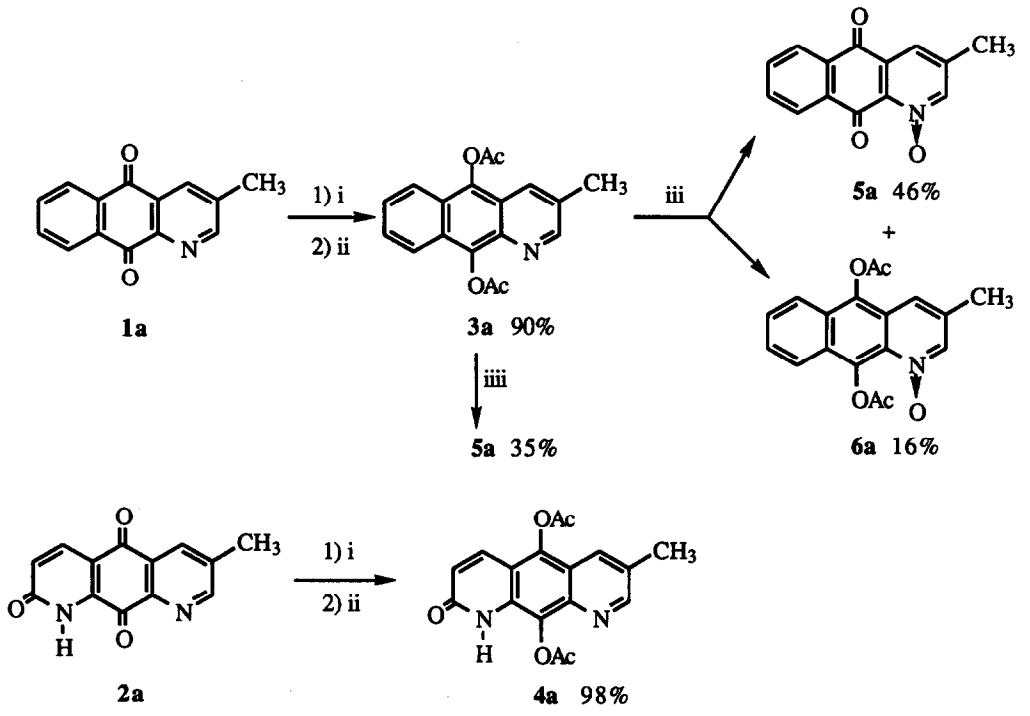
The ease of preparation of aza- and diazaanthraquinones **1** or **2** by means of hetero-Diels-Alder reactions, prompted us to study improved procedures to propare their corresponding *N*-oxides, since these compounds are convenient intermediates in the synthesis of 2,9,10-anthracenetriones and 2,7,9,10-anthracenetetraones.[6a]

Acetylated hydroanthraquinones **3a** and **4a** were thus obtained from **1a**[12] and **2a**[7] by reduction with sodium dithionite and subsequent acylation[13] (Scheme 1). Because of the electron-releasing acetoxy groups, these compounds should be more easily *N*-oxidized than their quinone counterparts. Actually, the reaction of **3a** with MCPBA gave **5a** in moderate yield (Scheme 2) whereas peracetic acid gave rise to a mixture of **5a** (46%) and **6a**[14] (16%). Trifluoroacetic acid, on the other hand, gave back quinone **1a** quantitatively.

On the other hand, all attempts at *N*-oxidation of **4a** with MCPBA afforded the quinone **2a** exclusively. The use of hydrogen peroxide and sodium tungstate as catalyst,[10,15] designed to avoid acidic media, also failed, and **2a** was the only compound isolated.

Since polyhalogenated azines have been reported to undergo *N*-oxidation with 90% hydrogen peroxide/ trifluoroacetic acid/ sulfuric acid[16], we decided to apply this to azaanthraquinones. To avoid the hazards associated to this reagent, Eichler and co-workers[17] succesfully applied urea hydrogen peroxide adduct[18] / trifluoroacetic acid/ sulfuric acid for the *N*-oxidation of trifluoromethyl-1,8-naphthyridine derivatives. The same

(H_2O_2/ urea) adduct in a mixture with phthalic anhydride has been recently reported as an excellent reagent for mild and safe N-oxidations.[19]



i) $Na_2S_2O_4$
ii) Ac_2O; 150°C
iii) $AcOH/H_2O_2$; 70°C
iiii) MCPBA

Scheme 1

The results of the direct *N*-oxidation of quinones **1a-1c** and **2a-2d** using procedures A-C are shown in Table I. Trifluoperacetic acid (method A) gave *N*-oxides **5a-5c** and and **7a-7d** in moderate yields. Attempts at *N*-oxidation of aza- (**1a**) and diaza-anthraquinones **2a** and **2b**[5] using urea hydrogen peroxide adduct in presence of sulfuric acid[17] gave black tars, from which no identificable compounds could be isolated. However, by simply removing the sulfuric acid, (method B), we obtained *N*-oxides **5** and **7** in good to excellent yields. The yields of **5a** drastically decrease by using UHP with phthalic anhydride (method C).[19]

In conclusion direct *N*-oxidation of azaanthraquinones by urea-hydrogen peroxide is a very useful synthetic procedure.

Acknowledgements

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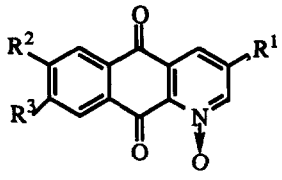
Table I. Direct *N*-Oxidation of Aza- and Diazaanthraquinones 1a-2d.



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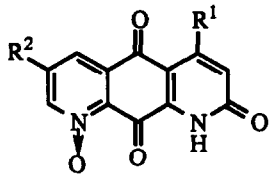

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Starting compound	Method (% Yield) A	B	C	Product
1a	65	70	15	**5a**
1b	40	80		**5b**
1c	20	67		**5c**
2a	33	73		**7a**
2b	65	87		**7b**
2c	60	72		**7c**
2d	26	85		**7d**

A) CF_3CO_2H/ 30% H_2O_2 (2:1) , 70°C , 24h.
B) CF_3CO_2H/ urea hydrogen peroxide adduct, rt, 24h.
C) Phthalic anhydride/ urea hydrogen peroxide adduct, rt, 24h.

Experimental

^1H and ^{13}C NMR spectra were obtained in chloroform-*d* unless otherwise noted and TMS as internal reference. Infrared spectra were recorded as KBr pellets. Melting points are uncorrected. Elemental analysis were determinated by the Servicio de Microanálisis, Universidad Complutense, on a Perkin-Elmer 2400 CHN microanalyzer. All solvents and reagents were of reagent grade quality and used without further purification. Reactions were monitored by thin layer chromatography. Separations by flash chromatography were performed on silica gel. Compounds **1a** and **2a** were prepared according to literature procedures.[7,12] Analytical samples of azaanthraquinones **1a-2d** were obtained by sublimation. Compound **2b** was obtained in 71% yield by an improved procedure[5b]. Compound **2c** was obtained from 4-methyl-1*H*-quinoline-2,5,8-trione[20] by Diels Alder cycloadition of 2-ethyl-2-propenal-*N*,*N*-dimethylhydrazone.[21]

3-Ethyl-1-azaanthracene-9,10-dione (1b). To a solution of 1 g of naphthoquinone (6.32 mmol), in 80 ml of chloroform, were added 800 mg (6.35 mmol) of 2-ethyl-2-propenal-*N*,*N*-dimethylhydrazone. The solution was stirred at room temperature for 4 h and evaporated. The residue was refluxed in ethanol for 3 h, concentrated *in vacuo*, and washed with diethyl ether and methanol to afford 0.81 g (54 %) of **1b** as a solid: mp 165-167 °C; IR 1670, 1685 cm^{-1}; ^1H NMR δ 8.92 (s, 1H, H-2), 8.41 (s, 1H, H-4), 8.37 (m, 1H) and 8.28 (m, 1H, H-5 and H-8), 7.81 (m, 2H, H-6 and H-7), 2.86 (q, 2H, J = 7.6 Hz, CH_2), 1.36 (t, 3H, J = 7.6 Hz, CH_3) ppm. ^{13}C NMR δ 183.0, 181.7, 155.2, 146.9, 144.7, 134.6, 134.3 133.8, 133.4, 132.7, 130.3, 127.8, 127.1, 26.3, 14.7 ppm. Anal. Calcd. for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90. Found: C, 75.54; H, 4.77; N, 6.05.

6,7-Dimethyl-1zaanthracene-9,10-dione (1c). A solution of 500 mg (3.14 mmol) of quinoline-5,8-dione[13,22] and 260 mg (3.16 mmol) of 2,3-dimethyl-1,3-butadiene in 100 ml of chloroform was kept at 100

°C in an hermetically closed reactor. After evaporation of the solvent under reduced pressure, the mixture was refluxed in absolute ethanol for 30 h and then concentrated to dryness. Crude product **1c** (700 mg, 2.95 mmol, 94 %) was purified by column chromatography on silica gel (hexane/ ethyl acetate, 2:3): mp 256-257 °C; IR: 1700; 1685; 1650 cm^{-1}; ^1H NMR δ 9.10 (dd, 1H, J = 4.6 and 1.7 Hz, H-2), 8.63 (dd, 1H, J = 7.9 and 1.7 Hz, H-4), 8.17 (s, 1H) and 8.05 (s, 1H), (H-5 and H-8), 7.73 (dd, 1H, J = 7.9 and 4.6 Hz, H-3), 2.46 (s, 6H, CH_3) ppm. ^{13}C NMR δ 182.8, 181.9, 154.8, 149.1, 145.0, 144.8, 135.4, 131.4, 130.69, 130.67, 128.9, 128.2, 127.7, 20.33, 20.29 ppm. Anal. Calcd. for $C_{15}H_{11}NO_2$: C, 75.94; H, 4.67; N, 5.90. Found: C, 75.63; H, 4.94; N, 5.90.

6-Ethyl-1*H*-1,8-diazaanthracene-2,9,10-trione (2d). To a vigorously stirred solution of 1.6 g (9 mmol) of 1*H*-quinoline-2,5,8-trione[23] in 300 ml of chloroform, 1.2 g (9.5 mmol) of 2-ethyl-2-propenal-*N,N*-dimethylhydrazone was added. After 30 min the mixture was evaporated under reduced pressure and the crude product was washed with CH_2Cl_2 and filtered to give 1.6 g of **2d** as a yellow solid in 70% yield; mp 300-302 °C; IR 1680, 1665 cm^{-1}; ^1H NMR δ 9.6 (br s, 1 H, NH), 8.91 (s, 1H, H-7), 8.38 (s, 1H, H-5), 8.15 (d, 1H, J = 9.6 Hz, H-4), 6.95 (d, 1H, J = 9.6 Hz, H-3), 2.90 (q, 2H, J = 7.5, CH_2), 1.38 (t, 3H, J = 7.5 Hz, CH_3); ^{13}C NMR δ 179.4, 176.1, 160.9, 155.0, 146.3, 144.9, 139.2, 136.0, 133.8, 129.6, 128.3, 115.9, 26.5, 14.6. Anal. Calcd. for $C_{14}H_{10}N_2O_3$: C, 66.14; H, 3.96; N, 11.02. Found: C, 65.98; H, 4.11; N, 11.10.

Synthesis of *O,O*-diacetyl aza- and diazaanthracene derivatives. General procedure. A suspension of 2 mmol of quinone **1a** or **2a** in 60 ml of an organic solvent (ethyl acetate or $CHCl_3$, respectively) was treated with a solution of 1.5 g of sodium dithionite in 15 ml of water and the mixture was stirred for 5 min. Crude hydroquinones (2 mmol) obtained by concentration of the organic layer (for **1a**) or filtration (for **2a**) were refluxed with 10 ml of acetic anhydride for 50 min for **1a** or 5 min for **2a**. The solution was concentrated under reduced pressure leaving **3a** and **4a** as yellow solids in quantitative yields (98%).

3-Methyl-9,10-diacetoxy-1-azaanthracene (3a). Mp 172-174 °C. IR 1765 cm^{-1}. ^1H NMR δ 8.82 (d, 1H, J = 1.7 Hz, H-2), 8.14 (m, 1H, H-5 or H-8) 7.90 (m, 2H, H-4 and H-8 or H-5), 7.53 (m, 2H, H-6 and H-7), 2.66 (s, 3H, CH_3COO) and 2.60 (s, 3H, CH_3-COO), 2.52 (s, 3H, CH_3). ^{13}C δ 169.6, 169.3, 154.0, 140.8, 138.7, 134.5, 130.8, 127.7, 126.9, 126.6, 125.5, 124.3, 122.0, 121.3, 119.4, 20.8, 20.5, 19.1. Anal. Calcd. for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.94; H, 4.98, 4.34.

6-Methyl-9,10-diacetoxy-1,8-diazaanthracene-2-one (4a) Mp> 300 °C (dec). IR 1770-1670 cm^{-1}. ^1H NMR (DMSO -d_6) δ 11.83 (br s, 1H, NH), 8.82 (d, 1H, J = 1.6 Hz, H-7), 8.18 (s, 1H, H-5), 8.08 (d, 1H, J = 9.9 Hz, H-4), 6.64 (d, 1H, J = 9.9, H-3), 2.62 (s, 3H, C_6-CH_3), 2.50 (s, 3H) and 2.48 (s, 3H, CH_3COO). ^{13} C NMR δ 169.8, 169.4, 161.8, 154.9, 139.9, 138.6, 133.9, 130.6, 130.3, 129.0, 128.6, 124.4, 117.1, 113.4, 21.3, 20.7, 18.3. Anal. Calcd. for $C_{17}H_{14}N_2O_5$: C, 62.57; H, 4.32; N, 8.59. Found: C, 62.77; H, 4.53; N, 8.42.

***N*-oxidation of 3a:**

1) A solution of 0.42 g (1.4 mmol) of **3a** and 0.60 g (3.4 mmol) of MCPBA in 150 ml of CH_2Cl_2 was refluxed for 4 h with hourly additions of 0.1 g of MCPBA. The mixture was purified by a gradient column chromatography eluting with diethyl ether, ethyl acetate, acetone and ethanol to give **5a** (0.12 g, 35% yield) (see below for its description).

2) A solution of 0.5 g (1.6 mmol) of **3a** in 2.1 ml of acetic acid and 0.7 ml of 30% H_2O_2 was stirred for 17 h at 70 °C. The mixture was neutralized in an ice bath with concentrated NH_4OH to give **5a** (46%) and **6a** (16%).

***N*-oxidation of aza- and diazaanthraquinones:**

Method A: A solution of 0.8 mmol of quinone in 2 ml of trifluoroacetic acid and 1 ml of 30% H_2O_2 was stirred for 17 h at 70 °C. The mixture was cooled to room temperature and 50 ml of water was added. Unless otherwise noted, the precipitate *N*-oxide was filtered and washed with water and methanol. The aqueous phases were extracted with CH_2Cl_2 to yield further amounts of *N*-oxide.

Method B: A solution of 0.4 mmol of quinone and 65 mg of urea hydrogen peroxide adduct (the equivalent of 0.34 mmol of H_2O_2) in 0.7 ml of trifluoroacetic acid was stirred at room temperature for 24 hours with hourly additions of 30 mg of urea hydrogen peroxide adduct in the first 4 hours. Unless otherwise stated, water was then added and the precipitated *N*-oxide was filtered and washed with water and methanol. The filtrate was extracted with CH_2Cl_2 to obtain further amounts of *N*-oxide.

Method C: According to the procedure of Kaczmarec ,[19] urea hydrogen peroxide adduct(95 mg, i. e. the equivalent of 0.50 mmol of H_2O_2) and 0.49 mmol of phthalic anhydride in 10 ml of acetonitrile were stirred at room temperature for 15 min. Then 100 mg (0.45 mmol) of **1a** was added and the mixture was stirred at room temperature for 24 h. The mixture was neutralized with saturated aqueous K_2CO_3 and extracted with CH_2Cl_2.

3-Methyl-1-azaanthracene-9,10-dione-1-oxide (5a).

Method A: The *N*-oxide **5a** was prepared from **1a** according to general procedure and isolated in 65% yield by column chromatography on silica gel eluting with ethyl acetate/ CH_2Cl_2 9:1, orange solid mp 182-183 °C; IR : 1680 cm^{-1}; ^1H NMR δ 8.41 (s, 1H, H-2), 8.37 (dd, 1H, J = 7.4 and 1.2 Hz) and 8.24 (dd, 1H, J = 7.4 and 1.2 Hz, H-5 and H-8), 7.95 (s, 1H, H-4), 7.84 (m, 2H, H-6 and H-7), 2.47 (s, 3H, CH_3) ppm. ^{13}C NMR δ 180.8, 175.2, 146.5, 145.1, 140.0, 135.3, 134.3, 134.0, 133.5, 131.4, 128.1, 127.0, 124.3, 18.8 ppm. Anal. Calcd. for $C_{14}H_9NO_3$. $2H_2O$: C, 61.09; H, 4.76; N, 5.05. Found: C, 60.89; H, 4.61; N, 4.84.

Method B: The *N*-oxide **5a** was prepared according to the general procedure.

Method C: After the usual workup, the residue was purified by chromatography as in methods A and B.

3-Ethyl-1-azaanthracene-9,10-dione-1-oxide (5b). Orange solid mp 194-195 °C; IR 1675 cm^{-1}; ^1H NMR δ (DMSO-d_6) 8.55 (s, 1H, H-2), 8.12 (m, 2H, H-5 and H-8), 7.94-7.81 (m, 3H, H-4, H-6 and H-7), 2.69 (q, 2H, J = 7.5 Hz, CH_2), 1.20 (t, 3H, J = 7.5 Hz CH_3) ppm. ^{13}C NMR δ 180.8, 174.8, 145.6, 145.4, 137.9, 135.1, 134.2, 133.7, 133.6, 131.4, 126.9, 126.2, 122.2, 25.0, 14.1 ppm. Anal. Calcd. for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. Found: C, 70.99; H, 4.24; N, 5.44.

6,7-Dimethyl-1-azaanthracene-9,10-dione-1-oxide (5c). Yellow solid, mp 210 °C (dec.); IR: 1675 cm^{-1}; ^1H NMR δ 8.53 (d, 1H, J = 6.3 Hz, H-2), 8.10 (m, 2H) and 7.99 (s, 1H), (H-4, H-5 and H-8), 7.54 (t, 3H, H-3), 2.46 (s, 3H, CH_3), 2.44 (s, 3H, CH_3). ^{13}C NMR δ 180.3, 175.6, 146.7, 146.6, 145.8, 144.3, 134.3,, 132.1, 129.2, 128.9, 127.9, 127.7, 122.8, 20.5, 20.2 ppm. Anal. Calcd. for $C_{15}H_{11}NO_3.H_2O$: C, 66.41; H, 4.83; N, 5.16 Found: C, 66.63; H, 4.48; N, 4.87.

3,5-Dimethyl-8*H*-1,8-diazaanthracene-7,9,10-trione-1-oxide (7b). Mp >300 °C (dec.); IR 3200-2800, 1680, 1660, 1650 cm^{-1}. ^1H NMR δ (DMSO-d_6) 12.0 (s, 1H, NH) 8.52 (s, 1H, H-2), 7.77 (s, 1H, H-4), 6.56 (s, 1H, H-6) 2.54 (s, 3H, CH_3-5), 2.38 (s, 3H, CH_3-3). Anal. Calcd. for $C_{14}H_{10}N_2$)4.H_2O: C, 58.33; H, 4.20; N, 9.72. Found: C, 58.56; H, 3.99; N, 9.69.

3-Ethyl-5-methyl-8*H*-1,8-diazaanthracene-7,9,10-trione-1-oxide (7c). Orange solid, mp> 300 °C (dec.); IR 3550-3300, 1665, 1650 cm^{-1}; ^1H NMR δ NH was not observed, 8.37 (s, 1H, H-2), 7.93 (s, 1H, H-4), 6.66 (s, 1H, H-6), 2.78 (q, 2H, J = 7.4 Hz, CH_2), 2.67 (s, 3H, CH_3-5), 1.37 (t, 3H, J = 7.4 Hz, CH_2-CH_3). ^{13}C NMR δ 177.7, 169.1, 160.2, 151.5, 147.4, 145.0, 140.8, 134.4, 133.4, 127.4, 124.2, 114.7, 26.5, 22.6, 13.7. Anal. Calcd. for $C_{15}H_{12}N_2O_4$: C, 63.38; H, 4.25; N, 9.85. Found: C, 63.26; H, 4.35; N, 9.68.

3-Ethyl-8*H*-1,8-diazaanthracene-7,9,10-trione-1-oxide (7d). Orange solid Mp> 300 °C (dec.); IR 1650 cm^{-1}; ^1H NMR δ (DMSO-d_6) 12.24 (br s, 1H, NH), 8.55 (s, 1H, H-2), 7.99 (d, 1H, J = 9.5 Hz, H-5), 7.83 (s, 1H, H-4), 6.73 (d, 1H, *J* = 9.5 Hz, H-6), 2.71 (q, 2H, *J* = 7.5 Hz, CH_2), 1.21 (t, 3H, *J* = 7.5 Hz, CH_3). Anal. Calcd. for $C_{14}H_{10}N_2O_4.H_2O$: C, 58.33; H, 4.20; N, 9.72. Found: C, 58.54; H, 4.13; N, 9.51.

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