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Synthesis of 1,5- and 1,8-Diazaanthraquinones by Reaction of Aminoquinolinequinones with β-Dielectrophiles

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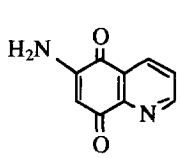
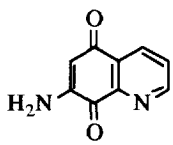
Abstract.- Easily obtained amino derivatives of quinoline-5,8-quinone (**1** and **2**) and 4-methyl-(1*H*)2,5,8-quinolinetrione (**3**) react with β-dielectrophiles, affording aminoalkylidenemalonates in a convenient procedure. These compounds cyclise thermally to 1,5-diaza-(1*H*)4,9,10-anthracenetriones (**10** and **19**), 1,8-diaza-(1*H*)4,9,10-anthracenetriones (**11** and **20**) and 1,5-diaza-(1*H*, 5*H*)2,8,9,10- anthracene-tetraones (**12** and **21**). The strategy is less convenient when applied to aromatic precursors. Knorr cyclisation of β-oxoanilides fails in both systems.

One of the strategies we focused on during our synthesis of analogues of the antifolate antibiotic diazaquinomycin A with structure of aza- and diazaanthracene-9,10-diones and potential antitumor activity[1] had as the key step the reaction of aminoquinones with β-dielectrophiles. Our first results, using 2-amino-1,4-naphthoquinone as a model compound, showed that either 1-azaanthracene-(1*H*)2,9,10- or 4,9,10-triones can be conveniently obtained, in spite of the low nucleophilicity of the amino group.[2] In order to obtain 1,5- and 1,8-diazaanthracene analogues we have extended our experiments to the amino heterocyclic quinones (**1**-**3**) as well as 2,6-diaminobenzoquinone (**5**). Among them, only 7-aminoquinoline-5,8-quinone (**2**) and its 6-methoxy-derivative have been widely studied, because they contain the AB ring system of the quinoline-5,8-quinone antitumor antibiotics lavendamycin and streptonigrin, respectively.[3]



1



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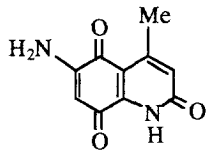

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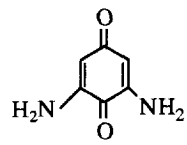
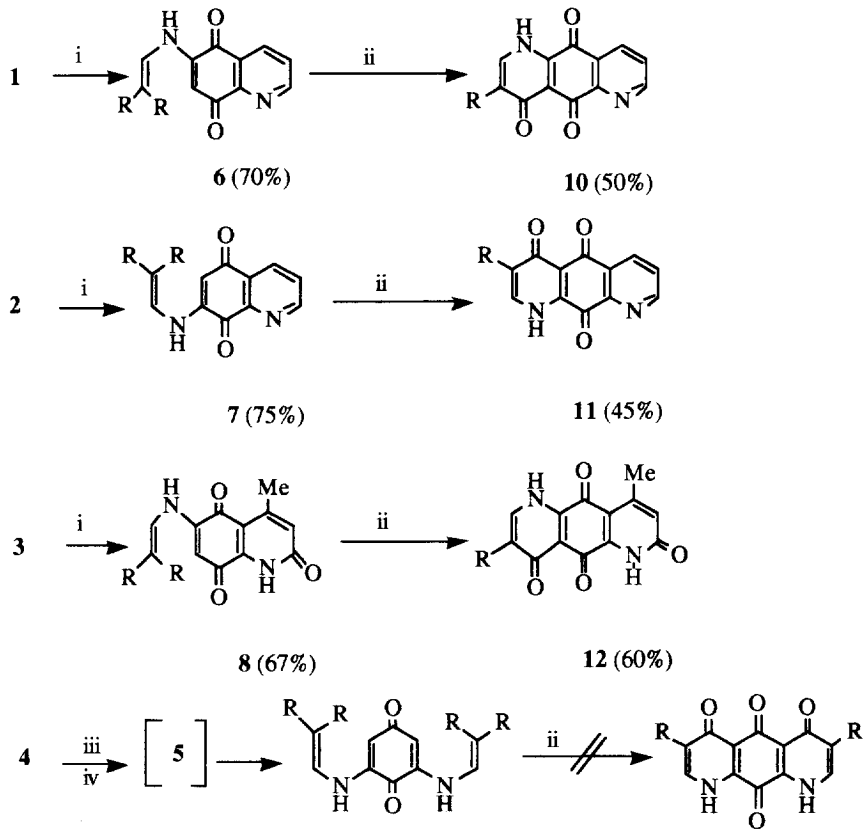


5

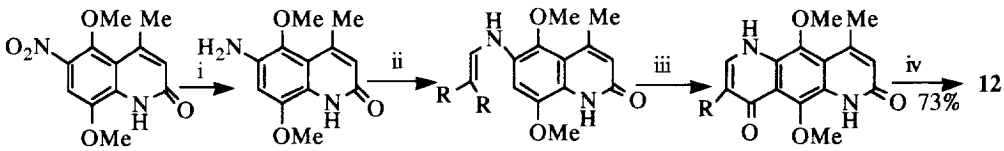
The starting reagents **1** and **3** were regioselectively prepared by addition of azidotrimethylsilane to quinoline-5,8-quinone (for **1**, 85%) or 4-methylquinoline-2,5,8-trione[4] (for **3**, 69%), while **2** can be obtained as the minor product (20%) in the reaction of quinoline-5,8-quinone with sodium azide, after chromatographic separation of the regioisomer **1** (60%) or by previously described literature procedures.[5] Compound **5** was produced *in situ* by treatment of 2,6-diaminohydroquinone bis-hydrochloride (**4**)[6] with methyloxirane and air oxidation.

Condensation with diethyl ethoxymethylenemalonate (EMME) of the aminoquinones **1-3** afforded compounds **6-8** in good yields. All of them gave the corresponding diazaanthracenetriones (**10-12**) by thermal cyclisation but, unfortunately, in the case of compound **9** derived from **5**, the expected 1,8-diaza-(1*H*, 8*H*)-4,5,9,10-anthracenetetraone was not obtained, and the starting material was recovered (Scheme 1).



Scheme 1

Compound **12** was also obtained by an alternative procedure starting from 5,8-dimethoxy-4-methyl-6-nitro-2(1*H*)-quinolinone[7] through reduction, thermal cyclisation of the enamine (**14**) and oxidative demethylation with cerium ammonium nitrate (CAN) of **15** (Scheme 2). After considering the preparation of all starting materials, it can be concluded that this strategy is less convenient than the one shown in Scheme 1. The identity of the final product (**12**) confirms the structure of the aminoquinone **3** and thus the regiochemistry of the amination procedure employed.

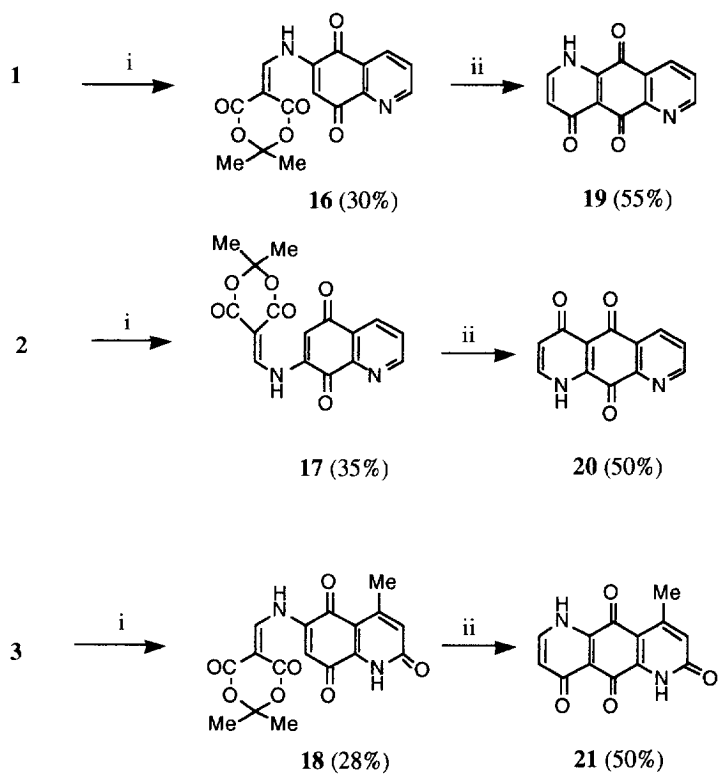


13 (56%) **14** (98%) **15** (67%)

R = CO_2Et; i:$SnCl_2$, HCl; ii: EMME, 160 °C, 2h; iii: Reflux, PhOPh; iv: CAN

Scheme 2

Although less effective from the synthetic point of view, condensation reactions of aminoquinones **1**-**3** with Meldrum's acid and trimethyl orthoformate gave compounds **16**-**18**, which cyclised to diazaanthraquinones (**19**-**21**, Scheme 3).



16 (30%) **19** (55%)

17 (35%) **20** (50%)

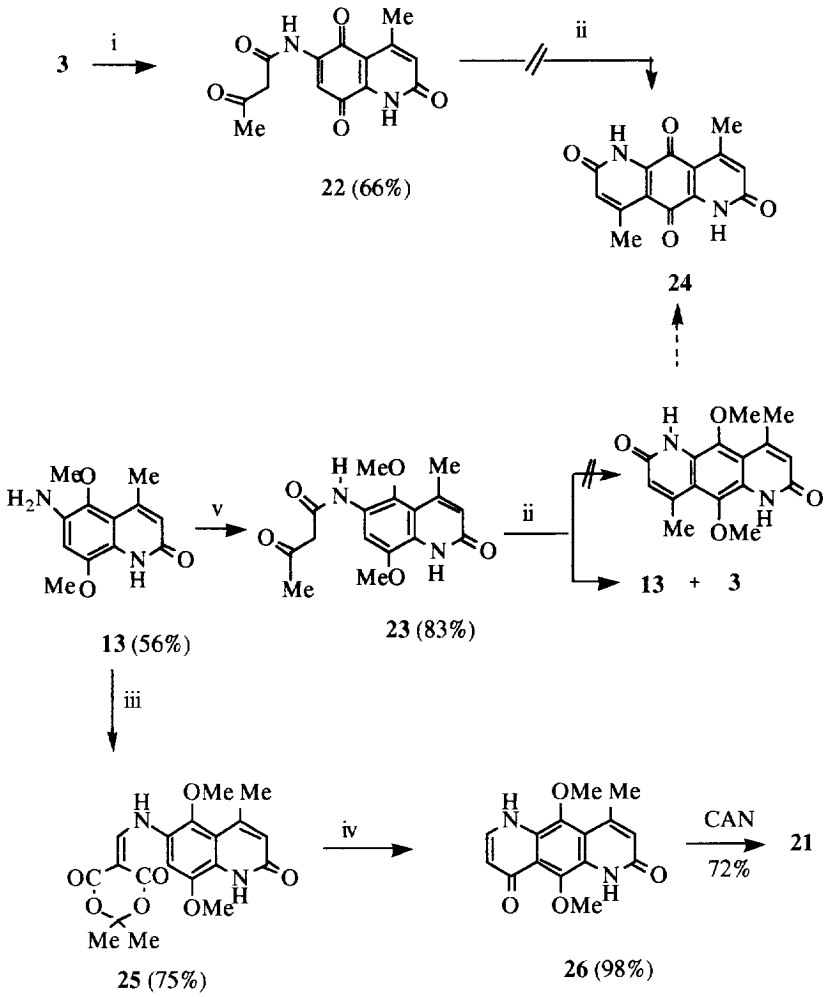
18 (28%) **21** (50%)

i: Meldrum's acid, $HC(OMe)_3$

ii: Reflux, PhOPh

Scheme 3

We also attempted the synthesis of the diazaanthracenetetraone **24** by Knorr cyclisation[8] of acetoacetamide **22** (Scheme 4).



i: 2,2,6-Trimethyl-1,3-dioxin-4-one, diglyme, open flask, 140 °C, 1.5 h
ii: conc. H_2SO_4, rt, 0.5 h
iii: Meldrum's acid, $HC(OMe)_3$
iv: Reflux, PhOPh
v: 2,2,6-Trimethyl-1,3-dioxin-4-one, xylene, open flask, 120 °C, 2h

Scheme 4

Condensation of aminoquinone **3** with 2,2,6-trimethyl-1,3-dioxin-4-one (as a diketene equivalent) was easily performed, but neither **2 2** nor **2 3**, prepared from **1 3**, gave any cyclisation product, the starting material or degradation compounds being obtained instead. The combined electron-withdrawing effects of the carbonyl quinone groups and pyridone ring in **2 2** highly deactivate its 7-position. At the low pH values needed to achieve the Knorr cyclisation, both the side chain amide and pyridone functions are protonated,[9] precluding formation of the new 2-pyridone ring. In the case of the quinolinone **2 3**, it is well known that this reaction does not work for most similar ß-oxoanilides. For instance, when this approach was attempted to obtain deoxynibomycin, cyclisation of 7-(3-oxobutanoylamino)-1,4,8-trisubstituted-2(1*H*)-quinolinones to 1,8-diaza-(1*H*, 8*H*)-2,7-anthracenediones failed.[10] In fact, the total synthesis of diazaquinomycin [3,6-dimethyl-4,5-dipropyl-(1*H*, 8*H*)-2,7,9,10-anthracenetetraone] from 2,5-dihydroxy-1,3-phenylenediamine is the only known successful example of such a reaction.[11] It is noticeable that thermal cyclisation of enamine **2 5** to **2 6** proceeded almost quantitatively. Here again, the overall process to prepare **2 1** from aromatic precursors is less efficient than that starting from the aminoquinone (Scheme 3).

The insolubility of aminoquinolinequinone **1** (diglyme, xylene) lowered the yield of its β-oxobutanoyl derivative **2 7** (25%), from which the desired cyclisation to azaanthraquinone also failed.

Comparing with our previous results in 2-amino-1,4-naphthoquinone we can conclude that nucleophilic substitutions are also posible in 6- and 7-aminoquinolinequinones. However, while thermal cyclisations are efficient synthetic methods to construct a new 4-oxo-(1*H*)-pyridine ring and achieve 1,5- and 1,8-diazaanthraquinones, cyclisations that require strongly acidic media are forbidden.

ACKNOWLEDGEMENT

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EXPERIMENTAL

All melting points were obtained using a Reichart hot-stage microscope or in open capillary tubes using a Büchi immersion apparatus and are uncorrected. Infrared spectra were recorded on Perkin-Elmer 577 and Buck Scientific 500 spectrophotometers, with all compounds compressed into KBr pellets. ^{1}H-NMR and ^{13}C-NMR spectra were obtained in $CDCl_3$, DMSO-d_6 or pyridine-d_5 solutions in 5 mm tubes using TMS as internal standard 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. Elemental analyses were determined by the Servicio de Microanálisis, Universidad Complutense, on a Perkin-Elmer 2400 CHN microanalyzer. Reactions were monoritored by thin layer chromatography on aluminium plates coated with silica gel with fluorescent indicator (Scharlau Cf 530) or visualized with iodine. Separations by flash chromatography were performed on silica gel (SDS 60 ACC, 230-400 mesh and Scharlau Ge 048) with the indicated eluents.

All solvents were purified if necessary, according to standard procedures[12] and all reagents purchased from Aldrich and used without further purification unless otherwise noted. Concentration of solutions was accomplished by rotary evaporation at water aspirator pressures. The expresion "petroleum ether" refers to the fraction boiling at 40-60 °C.

6-Aminoquinoline-5,8-quinone (1).

To quinoline-5,8-quinone[13] (4.7 g, 29.55 mmol) dissolved in 150 ml of dimethylformamide, trimethyl silylazide (3.78 g, 32.83 mmol) was added. The reaction mixture was stirred at rt for 15 h. Then the reaction was purified on a column of silica gel eluting with ethyl acetate to give **1** (4.37 g, 85 %) as red crystals. Melting point: 259-60 °C. IR ν: 3450 (NH_2), 3070 (C=C), 1690 and 1620 (C=O quinone), 1585 (C=N), 1570, 1465, 1410, 1350 and 1290 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.95 (d, J=3.6 Hz, 1H, H-2); 8.32 (d, J= 7.3 Hz, 1H, H-4); 7.73 (dd, J =7.3 and 3.6 Hz, 1H, H-3); 7.31 (br s, 2H, NH_2); 5.95 (s, 1H, H-7) ppm. ^{13}C-NMR (DMSO-d_6) δ: 181.8 and 180.4 (C-5 and C-8); 154.2 (C-2); 149.9 (C-6); 148.6 (C-8a); 133.7 (C-4); 127.4 (C-4a); 126.4 (C-3); 103.5 (C-7) ppm. Analysis calc. for $C_9H_6N_2O_2$: C, 62.06; H, 3.44; N, 16.09. Found: C, 61.98; H, 3.40; N, 16.12.

7-Aminoquinoline-5,8-quinone (2).

A solution of quinoline-5,8-quinone (1.4 g, 8.8 mmol), acetic acid (8 ml) and tetrahydrofurane (20 ml) was placed in a Erlenmeyer flask which was immersed in a bath preheated to 40 °C under N_2. A solution of sodium azide (0.56 g, 8.61 mmol) in water (3.6 ml) was added. The solution was stirred for 1.5 h. The resulting mixture was cooled to rt and the solid filtered. The NMR spectrum of the crude product indicated a mixture of **1** and **2**. Separation was achieved by column chromatography on eluting with ethyl acetate. The more polar red solid compound, with Rf 0.37 (ethyl acetate) was **2** (0.30 g, 20 %). The less polar red solid compound, with Rf 0.1 (ethyl acetate) was **1** (0.91 g, 60 %). Melting point: 263 °C (ethyl acetate, lit.[5] mp 263 °C).

6-Amino-4-methyl-(1*H*)-2,5,8-quinolinetrione (3).

A suspension of 4-methyl-(1*H*)-2,5,8-quinolinetrione[4] (1.7 g, 9 mmol) in 20 ml of dimethylformamide was placed in a 50-ml Erlenmeyer flask. The flask was immersed in a oil bath which had been preheated to 60° C, and the solution was vigorously stirred. Trimethylsilylazide (1.2 ml, 9 mmol) was added to the hot solution. The heating and stirring was continued for a total of 1.5 h. The reaction mixture was poured into 30 ml of water. The resulting purple precipitate was collected to give **3** (1.1 g, 60 %). Melting point: >300 °C. IR ν: 3290 and 3200 (NH_2), 1676 (C=O quinone) and 1616 (C=O amide) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 11.28 (s, 2H, NH_2); 6.34 (s, 1H, H-3); 5.61 (s, 1H, H-7); 2.44 (s, 3H, CH_3) ppm. ^{13}C-NMR (DMSO-d_6) δ: 179.4 and 174.7 (C-5 and C-8); 160.4 (C-2); 151.8 (C-6); 150.3 (C-4); 143.0 (C-8a); 122.6 (C-3); 110.7 (C-4a); 96.9 (C-7); 21.6 (CH_3) ppm. Analysis calc. for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.92; N, 13.72. Found: C, 59.16; H, 4.02; N,13.80.

General procedure for the synthesis of compounds 6-8.

A mixture of aminoquinones **1-3** (7 mmol) and diethyl ethoxymethylenemalonate (1.61 g, 7.47 mmol) was solved in trifluoroacetic acid (approximately 5 ml) and refluxed for 30 min until the reaction was complete as indicated by TLC analysis. The resulting brown mixture was cooled to rt and 5 ml of ethyl ether was added. The solid was collected by filtration and was purified on a column chromatography on silica gel eluting with ethyl acetate to give **6-8**.

Diethyl 5,8-dioxo-6-quinolylaminomethylenemalonate (6).

Yield 70 %. Brown-yellow crystals. Melting point: 165-166 °C. IR ν: 1720 (C=O ester), 1690 and 1670 (C=O quinone), 1600, 1590, 1580, 1245 (C-O ester) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 11.27 (d, J =13.1 Hz, 1H, NH); 9.09 (d, J= 4.69 Hz, 1H, H-2); 8.50 (d, J = 7.89 Hz, 1H, H-4); 8.23 (d, J =13.1 Hz, 1H, NHC*H*); 7.71 (m, 1H, H-3), 6.71 (s, 1H, H-7); 4.40 and 4.29 (2q, J =7.11 Hz, 4H, CH_2); 1.42 and 1.36 (2t, J =7.11 Hz, 6H, CH_3) ppm.^{13}C-NMR ($CDCl_3$) δ: 181.8 and 179.9 (C-5 and C-8); 166.7 and 164.1 (CO_2); 155.5 (C-2); 147.9 (C-8a); 144.6 (NH*C*H); 141.9 (C-6); 134.9 (C-4); 127.4 (C-3); 110.6 (C-7); 103.6 (*C*=CH); 61.6 and

61.1 (CH_2); 14.3 and 14.2 (CH_3) ppm. Analysis calc. for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.65; N, 8.13. Found: C, 59.27; H, 4.70; N, 8.09.

Diethyl 5,8-dioxo-7-quinolylaminomethylenemalonate (7).

Yield 75 %. Brown crystals. Melting point: 175-176 °C. IR ν: 3180 (NH), 1720 (C=O ester), 1680 and 1660 (C=O quinone), 1605, 1595, 1575, 1210 (C-O ester) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 9.06 (d, *J* = 4.6 Hz, 1H, H-2); 8.46 (d, *J* = 7.93 Hz, 1H, H-4); 8.22 (d, *J* =13.18 Hz, 1H, NHC*H*); 7.74 (m, 1H, H-3), 6.61 (s, 1H, H-6); 4.40 and 4.29 (2q, *J* =6.9 Hz, 4H, CH_2); 1.42 and 1.36 (2t, *J* =6.9 Hz, 6H, CH_3) ppm.^{13}C-NMR ($CDCl_3$) δ: 182.4 and 178.4 (C-5 and C-8); 166.0 and 164.4 (CO_2); 154.3 (C-2); 146.4 (C-8a); 144.2 (NH*C*H); 142.6 (C-7); 134.5 (C-4); 129.6 (C-4a); 128.5 (C-3); 109.3 (C-6); 103.8 (*C*=CH); 61.6 and 61.2 (CH_2); 14.3 and 14.2 (CH_3) ppm. Analysis calc. for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.65; N, 8.13. Found: C, 59.36; H, 4.33; N, 8.16.

Diethyl 4-methyl-(1*H*)2,5,8-trioxo-6-quinolylaminomethylenemalonate (8).

Yield 67 %. Orange crystals. Melting point: 255-256 °C. IR ν: 3070, 3010, 1705 (C=O ester), 1655, 1576, 1260, 1225 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 11.43 (d, *J* = 13 Hz, 1H, NH); 8.11 (d, *J* = 13 Hz, 1H, C*H*-NH); 6.57 (s, 1H, H-3); 6.37 (s, 1H, H-7); 4.39 (q, *J* = 7.12 Hz, 2H, CH_2); 4.30 (q, *J* =7.18 Hz, 2H, CH_2); 2.61 (s, 3H, CH_3); 1.40 (t, *J* =7.12 Hz, 3H, CH_3); 1.35 (t, *J* =7.18 Hz, 3H, CH_3) ppm. ^{13}C-NMR (DMSO-d_6) δ: 177.7 and 177.1 (C-5 and C-8); 166.6 and 164.1 (CO_2); 160.2 (C-2); 151.4 (C-4); 143.9 (*C*H-NH); 143.0 (C-6); 139.9 (C-8a); 125.7 (C-3); 112.5 (C-4a); 105.0 (C-7); 103.9 (*C*=CH); 61.7 and 61.4 (CH_2); 22.2 (*CH_3*-C4); 14.3 and 14.1 (CH_3) ppm. Analysis calc. for $C_{18}H_{18}N_2O_7$: C, 57.75; H, 4.81; N, 7.48. Found: C, 57.69; H, 4.73; N,7.44.

2,6-Bis(2,2-diethoxycarbonylethenylamino)-1,4-benzoquinone (9).

A mixture of 2,6-diaminohydroquinone bis hydrochloride[6] (4) (0.14 g, 1.87 mmol) and diethyl ethoxymethylenemalonate (1.12 ml, 5.63 mmol) in absolute ethanol (5 ml) was stirred to rt. Then methyloxirane (0.38 ml, 5.63 mmol) was slowly added and stirring was continued for a total of 45 minutes. The reaction mixture was purified on a column of alumina eluting with petroleum ether/ethyl acetate (1:1) to give **9** (0.2 g, 21%) as crystals. Melting point: 179-180 °C. IR ν: 3465, 3235 (NH), 3085, 1745 and 1710 (C=O ester), 1690 and 1670 (C=O quinone), 1612, 1415, 1390, 1305, 1260, 1220 cm^{-1}. ^{1}H-NMR ($CDCl_6$) δ: 11.06 (d, *J* =13.1 Hz, 2H, NH); 8.13 (d, *J* =13.1 Hz, 2H, NH-*CH*); 6.29 (s, 2H, H-3 and H-5); 4.36 (2q, *J* =7.01 Hz, 4H, CH_2) and 4.27 (2q, *J* =7.06 Hz, 4H, CH_2); 1.39 (2t, *J* =7.01 Hz, 6H, CH_3) and 1.33 (2t, *J* =7.06 Hz, 6H, CH_3) ppm. Analysis calc. for $C_{22}H_{26}N_2O_{10}$: C, 55.23; H, 5.43; N, 5.85. Found: C, 55.21; H, 5.67; N, 5.53.

6-Amino-5,8-dimethoxy-4-methyl-(1*H*)2-quinolinone (13).

To a 50 ml flask a suspension of 5,8-dimethoxy-4-methyl-6-nitro-(1*H*)2-quinolinone[7] (6.3 g, 23.86 mmol), $SnCl_2.2H_2O$ (50 g, 22.16 mmol) and conc. HCl (200 ml) was added and stirred at rt for 12 h. The resulting white suspension was basified with NH_4OH and was extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure to leave a yellow solid which was crystallized from ethanol to give **13** (3.12 g 56%) as yellow crystals. Melting point: 164-165 °C. IR ν: 3500 and 3450 (NH_2), 3330, 3230, 1675 (C=O amide), 1660, 1635, 1620, 1415, 1400, 1230 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 9.03 (s, 1H, NH); 6.54 (s, 1H, H-3); 6.44 (s, 1H, H-7); 3.82 (s, 2H, NH_2); 3.87 and 3.72 (s, 6H, OCH_3); 2.65 (s, 3H, CH_3) ppm. ^{13}C-NMR ($CDCl_3$) δ: 160.7 (C-2); 148.2 (C-4); 142.4 and 136.7 (C-5 and C-8); 134.5 (C-6); 123.2 (C-3); 121.9 (C-8a); 115.3 (C-4a); 101.6 (C-7); 60.4 and 56.1 (OCH_3); 22.7 (CH_3) ppm. Analysis calc. for $C_{12}H_{14}N_2O_3$: C, 61.58; H, 5.98; N, 11.96. Found: C, 61.23; H, 5.78; N, 11.75.

Diethyl 4-Methyl-5,8-dimethoxy-(1*H*)2-oxo-6-quinolylaminomethylenemalonate (14)

A suspension of **13** (0.3 g, 1.28 mmol) and diethyl ethoxymethylenemalonate (0.77 ml, 3.84 mmol) was placed in a 50-ml botton flask inmersed in a oil bath preheated to 120 °C. The reaction mixture was stirred for 10 min. Then the reaction was cooled to rt and petroleum ether (5 ml) was added. The precipitate was collected by filtration to give **14** (0.51 g, 98 %). Melting point: 192-193 °C. IR ν: 3260 and 3180 (NH), 1670, 1666, 1658, 1632, 1592, 1416, 1380, 1268, 1236 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 11.42 (d, J=13.8 Hz, 1H, NH); 9.19 (s, 1H, NH); 8.52 (d, J=13.8 Hz, 1H, *CH*-NH); 6.90 (s, 1H, H-7); 6.51 (s, 1H, H-3); 4.31 (m, 4H, CH_2); 4.01 and 3.79 (s, 6H, OCH_3); 2.67 (s, 3H, *CH_3*-C4); 1.37 (m, 6H, *CH_3*-CH_2) ppm. ^{13}C-NMR ($CDCl_3$) δ: 168.7 and 166.4 (CO_2); 160.7 (C-2); 150.7 (*CH*-NH); 148.2 (C-4); 143.0 and 140.8 (C-5 and C-8); 127.1 (C-8a); 126.5 (C-6); 124.3 (C-3); 115.3 (C-4a); 98.9 (C-7); 94.1 (*C*=CH); 62.4 and 56.6 (OCH_3); 60.5 and 60.4 (CH_2); 22.5 (*CH_3*-C4´); 14.4 and 14.3 (*CH_3*-CH_2) ppm. Analysis calc. for $C_{20}H_{24}N_2O_7$: C, 59.40; H, 5.94; N, 6.93. Found: C, 59.38; H, 5.86; N, 6.36.

General procedure for the synthesis of compounds 10-12 and 15.

A solution of compounds **6-8** and **14** (1.45 mmol) in diphenyl ether (40 ml) was refluxed in a sand bath for 1 h. After cooling to rt, the precipitate was collected by filtration and was washed thoroughly with petroleum ether. The residue was subjected to silica gel chromatography (ethyl acetate for **10**; ethyl acetate/methanol, 1:1 for **12** and **15**) or recrystallized (ethanol for **11**).

Ethyl 1,5-diaza-(1*H*)4,9,10-trioxoanthracene-3-carboxylate (10).

Yield 50 %. Brown-yellow crystals. Melting point: >300°C (absolute ethanol). IR ν: 3440 (NH), 3090, 1740 (C=O ester), 1700 and 1685 (C=O quinone), 1630 (C=N), 1595, 1510, 1140 (C-O ester) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 9.08 (d, J= 3.0 Hz, 1H, H-6); 8.46 (d, J =6.8 Hz, 1H, H-8); 8.24 (s, 1H, H-2); 7.86 (m, 1H, H-7); 4.24 (q, J = 7.2 Hz, 2H, CH_2); 1.28 (t, J = 7.2 Hz, 3H, CH_3) ppm. ^{13}C-NMR (DMSO-d_6) δ: 180.0 and 178.4 (C-9 and C-10); 171.2 (C-4); 163.8 (CO_2); 155.3 (C-6); 148.0 (C-2); 134.0 (C-8); 127.8 (C-8a); 127.5 (C-7); 60.4 (CH_2); 14.0 (CH_3) ppm. Analysis calc. for $C_{15}H_{10}N_2O_5$: C, 60.40; H, 3.35; N, 9.39. Found: C, 60.66; H, 3.51; N, 9.50.

Ethyl 1,8-diaza-(1*H*)-4,9,10-trioxoanthracene-3-carboxylate (11).

Yield 45 %. Melting point: 274-275 °C. IR ν: 3275 (NH), 1720 (C=O ester), 1710 and 1680 (C=O quinone), 1630 (C=N), 1590, 1560, 1510, 1300, 1140 (C-O ester) cm^1. ^{1}H-NMR (DMSO-d_6) δ: 8.94 (d, J = 4.5 Hz, 1H, H-7); 8.43 (m, 2H, H-5 and H-2); 7.82 (m, 1H, H-6); 4.18 (q, 2H, CH_2); 1.26 (t, 3H, CH_3) ppm. Analysis calc. for $C_{15}H_{10}N_2O_5$: C, 60.40; H, 3.35; N, 9.39. Found: C, 60.30; H, 3.38; N, 9.07.

Ethyl 8-Methyl-1,5-diaza-(1*H*, 5*H*)4,6,9,10-tetraoxoanthracene-3-carboxylate (12).

Yield 60 %. Melting point: 285-286 °C. IR ν: 3160 and 3090 (NH amide), 1740 (C=O ester), 1690 , 1685 and 1630 (CO quinone and C=O amide), 1515, 1140 (C-O ester) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 12.48 (s, 1H, NH) and 11.94 (s, 1H, NH); 8.12 (s, 1H, H-2); 6.52 (s, 1H, H-7); 4.21 (q, J =7.02 Hz, 2H, CH_2); 2.49 (s, 3H, CH_3); 1.25 (t, J =7.02 Hz, 3H, CH_3) ppm. ^{13}C-NMR (DMSO-d_6) δ: 177.7 and 175.0 (C-9 and C-10); 170.6 (C-4); 163.5 (CO_2); 160.8 (C-6); 149.9 (C-2); 124.7 (C-7); 60.5 (CH_2); 21.5 (*CH_3*-C8); 14.0 (CH_3) ppm. Analysis calc. for $C_{16}H_{12}N_2O_6$: C, 58.53; H, 3.65; N, 8.53. Found: C, 58.15; H, 3.26; N, 8.33.

Ethyl 9,10-Dimethoxy-8-methyl-(1*H*, 5*H*)4,6-dioxo-1,5-diazaanthracene-3-carboxylate (15)

Yield 67 %. Brown crystals. Melting point: 255-256 °C. IR ν: 3420, 3340, 3190, 1725 (C=O ester), 1665 (C=O amide), 1590, 1550, 1540, 1370, 1285, 1150 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 11.76 (s, 1H, NH); 10.93 (s,

1H, NH); 8.32 (s, 1H, H-2); 6.47 (s, 1H, H-7); 4.21 (q, J = 7.04 Hz, 2H, CH_2); 3.82 (s, 6H, OCH_3); 2.67 (s, 3H, *CH_3*-C8); 1.28 (t, J = 7.04 Hz, 3H, CH_3) ppm. ^{13}C-NMR (DMSO-d_6) δ: 172.9 (C-4); 164.5 (CO_2); 160.6 (C-6); 146.0 (C-2); 143.9 and 142.5 (C-9 and C-10); 140.8 (C-8); 129.4 (C-10a); 128.5 (C-9a); 125.8 (C-7); 122.2 (C-4a); 117.2 (C-8a); 109.5 (C-3); 63.5 and 62.3 (OCH_3); 59.4 (CH_2); 21.7 (*CH_3*-C8); 14.3 (*CH_3*-CH_2) ppm. Analysis calc. for $C_{18}H_{18}N_2O_6$: C, 60.33; H, 5.02; N, 7.82. Found: C, 60.03; H, 4.92; N, 7.55.

General procedure for the synthesis of compounds 16-18 and 25.

A suspension of Meldrum's acid (1.5 g, 10.4 mmol) in trimethyl orthoformate (38 ml, 347.34 mmol) was heated under reflux for 2h. At the end of this time, a solution of compounds **1-3** or **13** (10.3 mmol) in trimethyl orthoformate (38 ml) was added and the reflux was continued for 48 h. After cooling to rt, the formation of a crystalline yellow precipitate became noticeable. The solid was collected by filtration and subjected to silica gel chromatography by using the adecuate eluents (ethyl acetate/methanol, 9:1 for **16**, **17**; the same solvent mixture, 1:1 for **25** and ethyl acetate/petroleum ether, 2:8 for **18** .

6[5(2,2-Dimethyl-4,6-dioxo-1,3-dioxanyliden)methylamino]-5,8-quinolinequinone (16).

Yield 30 %. Yellow crystals. Melting point: >300 °C. IR ν: 3210 (NH), 3070, 1740 (C=O ester), 1695 and 1665 (C=O quinone), 1605, 1585, 1300, 1275 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 11.57 (d, J = 13.0 Hz, 1H, NH); 9.13 (d, J = 4.65 Hz, 1H, H-2); 8.55 (d, J= 13.0 Hz, 1H, NHC*H*); 8.53 (d, J = 7.73 Hz, 1H, H-4); 7.75 (m, 1H, H-3); 6.91 (s, 1H, H-7); 1.78 (s, 6H, CH_3) ppm. ^{13}C-NMR ($CDCl_3$) δ: 181.6 and 179.6 (C-5 and C-8); 162.0 (*C*OO); 155.8 (C-2), 148.3 (NH*C*H); 146.4 (C-8a); 141.7 (C-6); 135.0 (C-4); 127.7 (C-3); 127.4 (C-4a); 113.8 (C-7); 106.1 (*C*=CH); 94.6 (*C*Me$_2$); 27.5 (CH_3) ppm. Analysis calc. for $C_{16}H_{12}N_2O_6$: C, 58,53; H, 3.65; N, 8.53. Found: C, 58.41; H, 3.85; N, 8.66.

7[5(2,2-Dimethyl-4,6-dioxo-1,3-dioxanyliden)methylamino]-5,8-quinolinequinone (17).

Yield 35 %. Yelow crystals. Melting point: 254-255 °C. IR ν: 3300 (NH), 3070, 1730 (C=O ester), 1700 and 1670 (C=O quinone), 1595, 1580, 1390, 1280 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 11.59 (d, J = 13.74 Hz, 1H, NH); 9.10 (d, J = 4.64 Hz, 1H, H-2); 8.54 (d, J = 13.74 Hz, 1H, NH-C*H*); 8.49 (d, J = 7.93 Hz, 1H, H-4); 7.78 (m, 1H, H-3); 6.83 (s, 1H, H-6); 1.78 (s, 6H, CH_3) ppm. ^{13}C-NMR ($CDCl_3$) δ: 182.2 and 177.6 (C-5 and C-8); 163.9 and 162.2 (COO); 154.8 (C-2), 148.22 (NH*C*H); 146.8 (C-8a); 141.8 (C-7); 134.7 (C-4); 129.5 (C-4a); 128.8 (C-3); 112.7 (C-6); 106.0 (*C*=CH); 94.6 (*C*Me$_2$); 27.5 (CH_3) ppm. Analysis calc. for $C_{16}H_{12}N_2O_6$: C, 58,53; H, 3.65; N, 8.53. Found: C, 58.78; H, 3.80; N, 8.47.

6[5(2,2-Dimethyl-4,6-dioxo-1,3-dioxanyliden)methylamino]4-methyl-(1*H*)2,5,8-quinolinetrione (18).

Yield 28%. Orange crystals. Melting point > 300 °C. IR ν: 3230 (NH), 1710, 1690, 1670, 1635, 1605, 1300 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 11.48 (d, J = 13.8 Hz, 1H, NH); 8.82 (d, J = 13.8 Hz, 1H, NH-C*H*); 7.30 (s, 1H, H-7); 6.55 (s, 1H, H-3); 2.50 (s, 3H, CH_3-C4); 1.70 (s, 6H, CH_3) ppm. Analysis calc. for $C_{17}H_{14}N_2O_7$: C, 56.98; H, 3.91; N, 7.82. Found: C, 56.57; H, 3.81; N, 7.91.

5,8-Dimethoxy-6[5(2,2-dimethyl-4,6-dioxo-1,3-dioxanyliden)methylamino]-4-methyl-(1*H*)2-quinolinone (25).

Yield 75 % . Yellow crystals. Melting point: 251-252 °C. IR ν: 3300 (NH), 3090, 1735 (C=O ester), 1670 and 1630 (C=O quinone), 1440, 1400, 1345, 1290, 1210 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 11.84 (d, J = 14.1 Hz, 1H, NH); 9.29 (s, 1H, NH); 8.69 (d, J = 14.1 Hz, 1H, NH-*CH*); 7.00 (s, 1H, H-7); 6.54 (s, 1H, H-3); 4.14 and.3.83 (s, 6H, OCH_3); 2.69 (s, 3H, CH_3-C4); 1.78 (s, 6H, C-CH_3) ppm. ^{13}C-NMR ($CDCl_3$) δ: 165.6 and 163.7 (COO); 160.7.(C-2); 150.8 (NH-CH); 148.0 (C-4); 143.3 and 141.6 (C-5 and C-8); 128.1 (C-8a); 125.5

(C-6); 124.7 (C-3); 115.2 (C-4a); 105.2 (*C*=CH); 98.5 (C-7); 87.5 (*C*Me$_2$); 63.0 and 56.8 (OCH$_3$); 27.1 (CH$_3$); 22.4 (*CH$_3$*-C4) ppm. Analysis calc. for $C_{19}H_{20}N_2O_7$: C, 58.76; H, 5.15; N, 7.21. Found: C, 58.65; H, 5.17; N, 7.13.

General procedure for the synthesis of compounds 19-21 and 26.

A solution of compounds **16-18** and **25** (6.09 mmol) in diphenyl ether (70 ml) was refluxed under dry N_2 stream until the starting material had been consumed (approximately 2 h). After cooling to rt, the brown-yellow precipitate was collected by filtration and the residue was subjected to silica gel chromatography (ethyl acetate/methanol, 9:1 for **19** and **20**; ethyl acetate for **21** and petroleum ether/methanol, 9:1 for **26**.

1,5-Diaza-(1*H*)4,9,10-anthracenetrione (19).

Yield 55 %). Melting point > 300 °C. IR ν: 3455 (NH), 3080, 3050, 1690 and 1645 (C=O quinone), 1625, 1585, 1545, 1510, 1315, 1235, 1190 cm^{-1}. ^{1}H-NMR (DMSO-d$_6$) δ: 12.26 (br s, 1H, NH); 9.07 (d, 1H, H-6); 8.48 (d, *J* = 8.1 Hz, 1H, H-8); 8.01 (m, 1H, H-2); 7.85 (m, 1H, H-7); 6.71 (d, *J* = 6.3 Hz, 1H, H-3) ppm. Analysis calc. for $C_{12}H_6N_2O_3$: C, 63.71; H, 2.65; N, 12.38. Found: C, 63.73; H, 2.82; N, 12.01.

1,8-Diaza-(1*H*)4,9,10-anthracenetrione (20).

Yield 50 %. Melting point: > 300 °C. IR ν: 3460 (NH), 3100, 3050, 1700 and 1665 (C=O quinone), 1625, 1585, 1575, 1550, 1500, 1320, 1290, 1230, 1190 cm^{-1}. ^{1}H-NMR (CD$_3$OD) δ: 9.12 (d, *J* = 4.7 Hz, 1H, H-7); 8.76 (d, *J* = 7.9 Hz, 1H, H-5); 8.64 (d, *J* = 7.0 Hz, 1H, H-2); 8.03 (m, 1H, H-6); 7.53 (d, *J*= 7.0 Hz, 1H, H-3) ppm. Analysis calc. for $C_{12}H_6N_2O_3$: C, 63.71; H, 2.65; N, 12.38. Found: C, 63.69; H, 2.57; N, 12.32.

4-Methyl-1,5-diaza-(1*H*, 5*H*)2,8,9,10-anthracenetetraone (21).

Yield 50%. Melting point: >300 °C. IR ν: 1740, 1660, 1655, 1300 cm^{-1}. ^{1}H-NMR (DMSO-d$_6$) δ: 7.80 (d, *J* = 6.5 Hz, 1H, H-6); 6.44 (s, 1H, H-3); 6.36 (d, *J* = 6.5 Hz, 1H, H-7); 2.48 (s, 3H, CH$_3$) ppm. Analysis calc. for $C_{13}H_8N_2O_4$: C, 60.93; H, 3.12; N, 10.93. Found: C, 60.83; H, 3.25; N, 10.82.

9,10-Dimethoxy-4-methyl-1,5-diaza-(1*H*, 5*H*)2,8-anthracenedione (26)

Yield 98 %. Brown crystals. Melting point: >300 °C. IR ν: 3430 and 3240 (NH), 1670 (C=O amide), 1625, 1535 cm^{-1}. ^{1}H-NMR (CD$_3$OD) δ: 7.88 (d, *J* = 7.3 Hz, 1H, H-6); 6.54 (s, 1H, H-3); 6.22 (d, *J* = 7.3 Hz, 1H, H-7); 3.91 and 3.88 (s, 6H, OCH$_3$); 2,77 (s, 3H, CH$_3$) ppm. ^{13}C-NMR (CD$_3$OD) δ: 180.4 (C-8); 159.0 (C-2); 149.8 (C-6); 144.6 and 142.1 (C-9, C-10); 141.2 (C-4); 129.4 (C-9a); 126.3 (C-10a); 124.7 (C-3); 122.0 (C-8a); 119.4 (C-4a); 110.8 (C-7); 64.5 and 63.8 (OCH$_3$); 23.0 (*CH$_3$*-C4) ppm. Analysis calc. for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.89; N, 9.79. Found: C, 62.63; H, 4.62; N, 9.42.

4-Methyl-6(3-oxobutanoylamino)-(1*H*)-2,5,8-quinolinetrione (22).

A suspension of **3** (0.3 g, 1.47 mmol) in 5 ml of diglyme was placed in a 50-ml Erlenmeyer flask. The flask was inmersed in a oil bath which had been preheated to 140 °C, and the solution was stirred. Recently distilled 2,2,6-trimethyl-1,3-dioxin-4-one (0.19 ml, 1.47 mmol) was added to the hot solution. The evolution of acetone became apparent within several minutes and the heating was continued for a total of 5 min. Then the reaction was cooled to rt and the product was filtered and purified on a column of silica gel eluting with ethyl acetate to give **22** (0.28 g, 66 %) as orange crystals. Melting point: >300 °C. IR ν: 3310, 3180, 1725 , 1655, 1630, 1520, 1480, 1415, 1325, 1165 cm^{-1}. ^{1}H-NMR (CDCl$_3$) δ: 11.9 (s, 1H, NH); 10.30 (s, 1H, NH); 7.49 (s, 1H, H-7); 6.58 (s, 1H, H-3); 3.91 (s, 2H, CH$_2$); 2.48 (s, 3H, *CH$_3$*-C4); 2.17 (s, 3H, CH$_3$) ppm. ^{13}C-NMR (CDCl$_3$) δ: 198.3 (*C*OMe); 173.8 (C-5, C-8); 160.0 (C-2) 159.1 (RCONH); 154.0 (C-4); 146.3 (C-6); 121.2 (C-3); 106.7 (C-7); 44.6 (CH$_2$); 26.1 (CH$_3$); 24.0 (*CH$_3$*-C4) ppm. Analysis calc. for $C_{14}H_{12}N_2O_5$: C, 58.33; H, 4.16; N, 9.72. Found: C, 58.13; H, 4.29; N, 9.59.

General Procedure for the synthesis of compounds 23 and 27.

A suspension of **13** or **1** (4.27 mmol) in 25 ml of dry xylene was placed in a 50-ml Erlenmeyer flask. The flask was immersed in a oil bath than had been preheated to 120 °C, and the solution was vigorously stirred. Recently distilled 2,2,6-trimethyl-1,3-dioxin-4-one (0.56 ml, 4.27 mmol) was added to the hot solution. The evolution of acetone became apparent within several minutes and the heating was continued for a total of 30 minutes (**23**) or 2 h (**27**). Then the reaction was cooled to rt and the product was filtered and was purified on a column of silica gel eluting with ethyl acetate/methanol, 9:1 for **23** or ethyl acetate for **27**.

5,8-Dimethoxy-4-methyl-6(3-oxobutanoylamino)-(1H)2-quinolinone (23).

Yield 83 %. White crystals. Melting point: 177-178 °C. IR ν: 3420, 3260, 3190, 1730 (CH_3C=O), 1670 and 1625 (C=O quinone), 1550, 1400 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 9.72 (s, 1H, NH); 9.08 (s, 1H, NH); 8.14 (s, 1H, H-7); 6.48 (s, 1H, H-3); 3.95 and 3.78 (s, 6H, OCH_3); 3.68 (s, 2H, CH_2); 2.68 (s, 3H, CH_3-C4); 2.37 (s, 3H, $COCH_3$) ppm. ^{13}C-NMR ($CDCl_3$) δ: 205.2 (*C*OMe); 163.6 and 160.9 (RCONH and C-2); 148.2 (C-4); 141.8 and 140.3 (C-5 and C-8); 126.0 (C-8a); 125.8 (C-6); 123.6 (C-3); 114.3 (C-4a); 104.8 (C-7); 62.5 and 56.3 (OCH_3); 49.6 (CH_2); 31.4 (*C*H_3CO); 22.5 (*C*H_3-C4) ppm. Analysis calc. for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.66; N, 8.80. Found: C, 60.02; H, 5.62; N, 8.67.

6(3-Oxobutanoyl)amino-5,8-quinolinequinone (27).

Yield 25%. Brown-yellow crystals. Melting point: 150-151 °C. IR ν: 3250, 3110, 1740, 1680 and 1660 (CO quinone), 1620, 1580, 1525, 1330 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 10.15 (s, 1H, NH); 9,08 (d, J = 4.6 Hz, 1H, H-2); 8.48 (d, J = 7.9 Hz, 1H, H-4); 8.04 (s, 1H, H-7); 3.70 (s, 2H, CH_2); 2.37 (s, 3H, CH_3) ppm. ^{13}C-NMR ($CDCl_3$) δ: 203.6 (*C*OMe); 183.7 and 180.5 (C-5 and C-8); 165.0 (CONH); 155.4 (C-2); 147.5 (C-8a); 139.8 (C-6); 134.8 (C-4); 127.4 (C-3); 127.3 (C-4a); 118.5 (C-7); 49.9 (CH_2); 31.3 (CH_3) ppm. Analysis calc. for $C_{13}H_{10}N_2O_4$: C, 60.46; H, 3.87; N, 10.85. Found: C, 60.31; H, 3.90; N, 10.70.

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