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Synthesis of 2- and 4-Oxo-1*H*-1-Azaanthracene-9,10-diones from 2-Amino-1,4-Naphthoquinone

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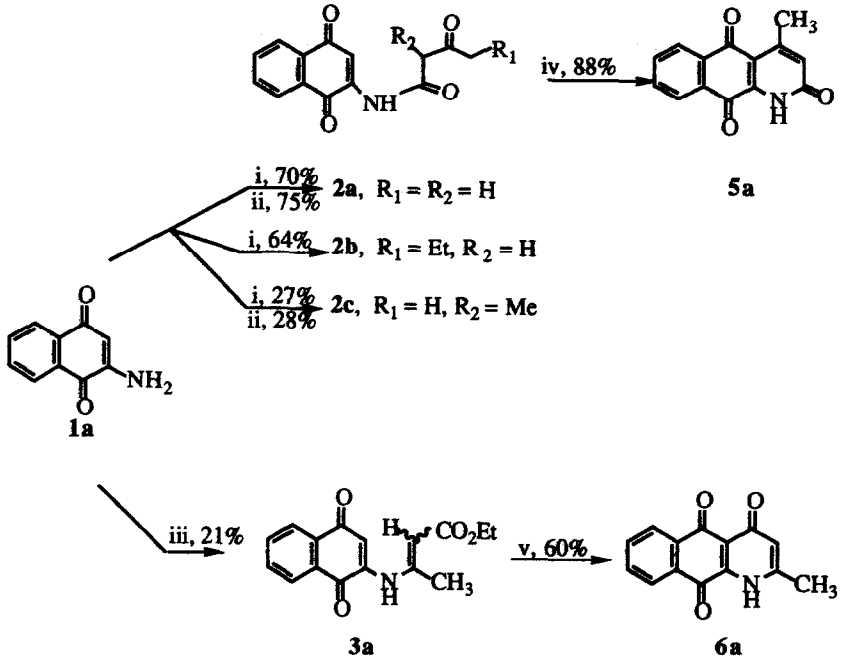
Abstract.- In spite of the poor nucleophilicity of its amino group, which is considered to have an "amide like" character, 2-amino-1,4-naphthoquinone reacts with β-dielectrophiles to give 2-oxo- or 4-oxo-1*H*-1-azaanthracene-9,10-diones.

The chemistry of heterocyclic quinones is under constant development due to growing interest in their biological properties,[1] especially as antitumor compounds.[2,3] Among natural azaanthracene-9,10-diones isolated so far, such as the alkaloids cleistopholin[4] and dielsiquinone,[5] the fungal pigments phomazarin and isophomazarin,[6] or the antibiotic diazaquinomycin,[7] some of them have not yet been synthesized and in others, the published total syntheses are not general procedures.[8] Our group has been engaged in the preparation of diazaquinomycin analogues because its potential antitumor activity,[9] and we have previously obtained simple 2-oxo-1-aza- or 1,8-diazaanthraquinones through Diels-Alder cycloaddition reactions of 1*H*-2,5,8-quinolinetriones and carbodienes or activated 1-azadienes.[10] The found antitumor activity in these series,[11] prompted us to investigate other routes. Among them, we here describe the reactions of 2-amino-1,4-naphthoquinone (**1a**) with β-dielectrophiles, as models in approaching 2-oxo and 4-oxo-1*H*-1-azaanthracene-9,10-diones.

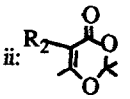
In contrast to the frequent use of 1,4-naphthoquinones as building blocks in the synthesis of fused heterocyclic systems,[1,12] the use of **1a** within this context is almost unknown.[13] The reason for this situation is presumably the "amide like" character of the amino group in **1a**, which considerably lowers its nucleophilicity.[14] For instance, intramolecular *N*-acylation of some aminonaphthoquinones has required their previous reduction to more basic aminonaphthohydroquinone derivatives,[15] and a similar three-step procedure has been used for the *N*-alkylation of **1a** with diethyl ethoxymethylenemalonate in an approach to phomazarin synthesis.[16]

The condensation of primary arylamines with β-oxoesters can be controlled to afford either ethyl β-arylaminocrotonates or β-oxoanilides, which are intermediates of 4-quinolones (Conrad-Limpach synthesis) or 2-quinolones (Knorr synthesis),[17] related reactions with **1a** were expected to give either 4-oxo- or 2-oxo-1*H*-1-azaanthraquinone derivatives. Anilide **2a** was obtained either by heating **1a**[18] with ethyl acetoacetate or using 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one as diketene equivalent[19] while, after several unsuccessful attempts,[20] **3a** was obtained according to Scheme 1. If an excess of dioxinone is present in the acetoacetylation reaction, condensation of **1a** with dehydroacetic acid[21] produces a substantial amount of 3-acetyl-6-methyl-4(1,4-dioxo-2-naphthylamino)-2*H*-pyran-2-one (**4**). Other anilides, such as **2b**, could be obtained using higher β-oxoesters but

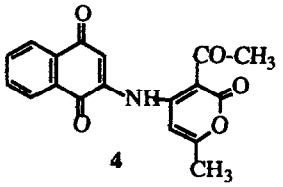
the yields were drastically reduced with α-substituted β-oxoesters such as ethyl 2-methyl-3-oxobutyrate or its equivalent 2,2,5,6-tetramethyl-1,3-dioxin-4-one[22] to give **2c**.



i: $EtO_2C\text{-}CH_2\text{-}CO\text{-}CH_2R_1$ (2 equiv.), xylene, open flask, 130 °C, 3.5-24 h

ii:  (1 equiv.), xylene, open flask, 130 °C, 1.5 h

iii: $EtO_2C\text{-}CH_2\text{-}CO\text{-}CH_3$ (3 equiv.), 160 °C, 3.5 h
iv: conc. H_2SO_4, r t, 0.5 h
v: reflux, PhOPh, 1.5 h

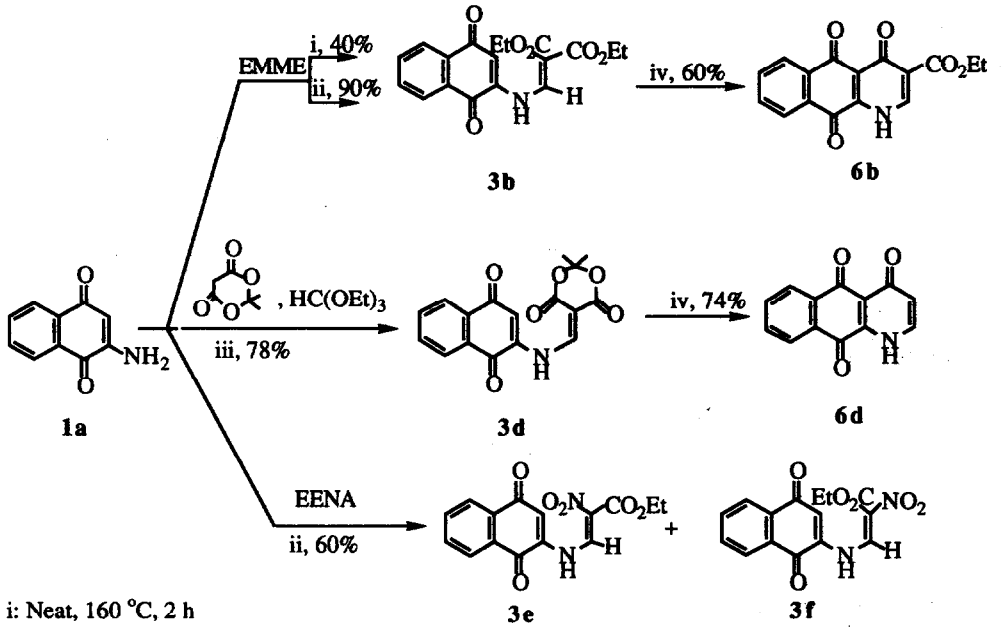


Scheme 1

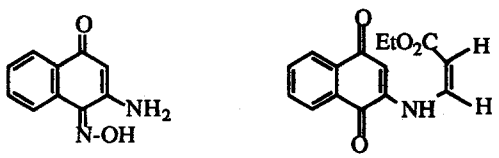
Ring closure of **2a** to 4-methyl-2-oxo-1*H*-1-azaanthraquinone (**5a**) in sulfuric acid and thermal cyclisation of **3a** to **6a** were performed in 88% and 60% yield respectively, while cyclisation of **2b** and **2c** failed, both compounds being partially degraded to **1a**. These results support that a planar conformation is sterically unfavoured in α- or γ-alkylacetoacetylaminonaphthoquinones, since the aliphatic chain of the β-oxoanilides must adopt it to facilitate the electrophilic attack by the protonated carbonyl group onto the C_2=C_3 bond.[23]

In spite of these limitations, this procedure may compete with others previously established by our group. This is the case of **5a**, which has been prepared from 2,5-dimethoxyaniline in four steps with 44% total yield[10b] and is here obtained from the easily available **1a** in two steps with a total yield of 66% .

Other studied reactions are shown in Schemes 2 and 3. Thus, thermal condensation of **1a** and diethyl ethoxymethylenemalonate (EMME) gave **3b** in moderate yield, together with traces of the degradation product (*Z*) ethyl 2(1,4-dioxo-1,4-dihydro-2-naphthylamino)acrylate (**3c**). The reaction was nearly quatitative when it was performed in trifluoroacetic acid. A similar result was found when 2-amino-1,4-naphthoquinone-1-monoxime (**1b**) was used as nucleophile. Compound **1a** also condensed with Meldrum's acid and trimethyl orthoformate[24] to yield **3d**. In the case of ethyl 3-ethoxy-2-nitroacrylate (EENA)[25] an inseparable mixture of diastereomers **3e** and **3f** in a ratio 75:25 (^{1}H-NMR analysis) was obtained. (Wolfbeys has reported a similar reaction with triethyl orthoformate and ethyl nitroacetate).[26] Subsequent ring closure of **3b** and **3d** gave 4-oxo-1-*H*-1-azaanthracene-9,10-diones (**6b** and **6d**).



i: Neat, 160 °C, 2 h
ii: F_3CCO_2H reflux, 20 min
iii: reflux 7h, overnight rt
iv: reflux, PhOPh

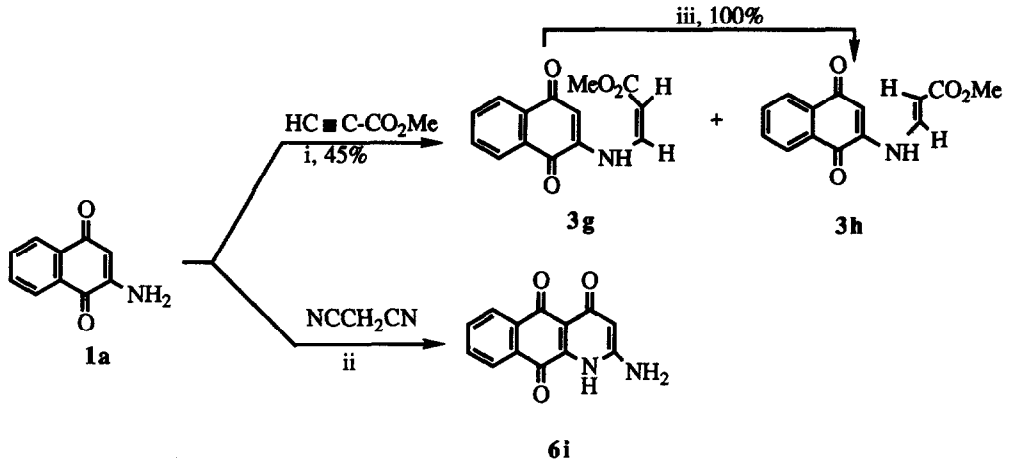


1b **3c**

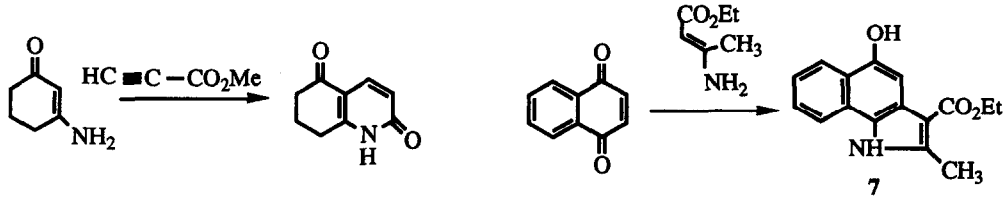
Scheme 2

In the reaction of **1a** with methyl propiolate (Scheme 3), Michael addition was not observed, either in thermal or in acid conditions nor in basic media such as sodium ethoxide,[27] but basic catalysis (triethylamine), allowed access to the *N*-adducts **3g** and **3h**, which were readily separated. However, all attempts to cyclize **3g** to **6d** failed, and quantitative isomerization to the more stable *E* -configuration took place instead. The regiochemistry of this reaction is the same to that reported in the addition of aminoquinone **1a** to DMAD,[13] which means that in the reactions of 2-aminonaphthoquinone with activated unsaturated bonds, the expected C-C bond formation is precluded, in contrast which it is known to occur in the reactions of β-amino-α,β-unsaturated carbonyl compounds and quinones as Michael substrates, or in modifications of Doebner-Miller quinoline synthesis[28] in which β-amino-α,β-unsaturated carbonyl compounds add to activated double or triple bonds. In the first case, initial formation of a C-C bond gives carbinolamines, which are intermediates of the Nenitzescu condensation to indole or carbazole derivatives.[29] For instance, naphthoquinone adds ethyl aminocrotonate to give ethyl 5-hydroxy-2-methyl-benzo[g]indole-3-carboxylate (**7**).[30] The use of 3-amino-cyclohexenones for the preparation of 4-hydroxy-2-1*H*-quinolinone precursors,[31] is an example of the second type of reaction.

Finally, the reaction of **1a** with malonodinitrile in concentrated acetic acid gave a very complex mixture of compounds from which 2-amino-4-oxo-1*H*-1-azaanthracene-9,10-dione (**6i**) could be isolated.



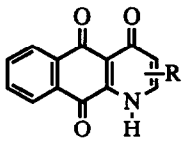
i: NEt_3, dioxane, reflux, 4h
ii: Conc. HOAc, reflux, 25 h
iii: Reflux trichlorobenzene



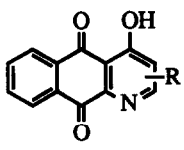
Scheme 3

In conclusion aminonaphthoquinones, although weak nucleophiles, may be conveniently exploited in heterocyclic chemistry. Moreover, the regiochemistry of the Michael additions differs from that generally found in related compounds such as 3-aminoacrylates, 2-aminocrotonates, 3-aminoenones or 6-amino-4-oxopyrimidines.

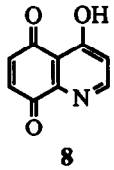
Regarding prototropic tautomerism (keto-enol tautomerism) in the pyridine ring of compounds **6** (**I** ⇄ **II**), the presence of hydrogen bond acceptors in position 4a, or in positions 4a and 3 in **6b**, suggests that intramolecular hydrogen bonding might stabilize the hydroxy forms **II**. Literature references to this problem in similar compounds are rather conflicting. Thus, an experimental and theoretical study on 4-quinolone-3-carboxylic derivatives[32] concluded that the 4-oxo tautomers became more stable in polar solvents due to the high dipole moments of such forms. On the other hand, NMR and other data of 4-hydroxy-5,8-quinolinequinone (**8**) correlate to those of 4-methoxy-5,8-quinolinequinone (**9**).[33] Furthermore, Diels-Alder reactions in non-polar solvents of methyl 4-hydroxy-5,8-quinolinequinone-2-carboxylate, are consistent with polarisation of the quinone by hydrogen-bonding involving the 4-hydroxy group,[34] while the *N*-alkyl derivatives of 1*H*-quinoline-4,5,8-trione-3-carboxylic acid, show an electronic distribution in Diels-Alder additions in which the C-8 carbonyl group is the most electron-deficient.[35] In spite of solubility problems in some cases, the comparison of ^{1}H and ^{13}C-NMR data of compounds **6** with those of 4-hydroxy-quinolinequinone and 4-methoxyquinolinequinone[33] supports the 4-oxo form **I**. However, the ^{13}C-NMR chemical shifts and the H-2 proton signal of **6b** in $CDCl_3$ would suggest the form **II** in this solvent, probably stabilized by hydrogen bonding of the 4-hydroxy group and the carbethoxy group (see Experimental).



I



II



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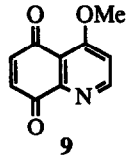

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EXPERIMENTAL

All melting points were obtained using a Reichart hot-stage microscope or a Büchi immersion apparatus and are uncorrected. Infrared spectra were recorded on Perkin-Elmer 577 and Buck Scientific 500 spectrophotometers (KBr disks). ^{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 microanalyser. Reactions were monitored 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 60ACC, 230-400 mesh and Scharlau Ge 048) with the indicated solvent. All solvents were

purified if necessary, according to standard procedures[36] 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.

2-Amino-1,4-naphthoquinone-1-monoxime (1b).

A suspension of **1a** (0.6 g, 5.5 mmol) in 15 ml of acetonitrile, was added a solution of hydroxylamine hydrochloride (0.24 g, 3.5 mmol) and sodium hydroxide (0.27 g, 6.9 mmol) in 1 ml of water. The reaction mixture was heated at 90 °C for 7 h and then cooled to rt and filtered. The residue was purified on a column of silica gel, eluting with petroleum ether/ethyl acetate (1:1) to give 300 mg (42 %) of compound **1b** as yellow crystals. Melting point, 239-240 °C. IR: 3455, 3300, 1625, 1590 cm^{-1}.^{1}H-NMR (DMSO-d_6) δ: 13.42 (s, 1H, OH); 8.92 (d, J = 7.9 Hz, 1H, H-5); 8.00 (d, J =7.9 Hz, 1H, H-8); 7.55 (m, 2H, H-6, H-7); 6.72 (s, 2H, NH_2); 5.64 (s, 1H, H-3) ppm. ^{13}C-NMR (DMSO-d_6) δ: 180.5 (CO); 155.1 (CNOH); 139.7 (C-2); 131.6 and 131.1 (C-6 and C-7); 130.0 and 129.4 (C-4a and C-8a); 126.8 and 125.2 (C-5 and C-8); 99.4 (C-3) ppm. Analysis calc. for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.25; N, 14.89. Found: C, 63.63; H, 4.42; N, 14.78.

***N*(1,4-Dioxo-1,4-dihydro-2-naphthyl)-3-oxobutanamide (2a). Method A.**

To a suspension of **1a** (960 mg, 5.5 mmol) in 15 ml of dry xylene preheated in a oil bath at 130 °C, ethyl acetoacetate (1.44 g, 11.1 mmol) was added. The reaction mixture was stirred in open flask at 130 °C (external temperature) until no starting material was detected by TLC (approximately 3.5 h) and then cooled to rt and filtered. The residue was purified on a column of silica gel eluting with petroleum ether/ethyl acetate (1:1) to give **2a** (1 g, 70 %) as brown crystals. Melting point 137-139 °C. IR: 3260 (NH), 1725 (CH_3CO), 1705 (NHCO), 1675 and 1645 (CO quinone) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 10.22 (s, 1H, NH); 8.04 (dd, J = 8.0, 1.9 Hz, H-8´); 7.96 (dd, J = 8.0, 1.9 Hz, 1H, H-5´); 7.85 (m, 2H, H-6´, H-7´); 7.69 (s, 1H, H-3´); 3.86 (s, 2H, CH_2); 2.19 (s, 3H, CH_3) ppm. ^{13}C-NMR (DMSO-d_6) δ: 202.9 (CO-3); 185.1 (CO-4´); 180.3 (CO-1´); 167.9 (CONH); 141.3 (C-2´); 134.8 (C-6´); 133.6 (C-7´); 131.2 (C-4a´); 130.1 (C-8a´); 126.3 (C-8´); 125.5 (C-5´); 116.25 (C-3´); 52.0 (CH_2); 30.2 (CH_3) ppm. Analysis calc. for $C_{14}H_{11}NO_4$: C, 65.36; H, 4.28; N, 5.44. Found: C, 65.30; H, 4.42; N, 5.33.

Method B.

A suspension of **1a** (1g, 5.8 mmol) in 20 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 (0.8 ml, 5.8 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 1.5 h. Then the reaction was cooled to rt and the product was filtered and recrystallized in xylene to give 1.1 g (75%) of **2a**.

***N*(1,4-Dioxo-1,4-dihydro-2-naphthyl)-3-oxohexanamide (2b).**

To **1a** (0.7 g, 4.0 mmol) dissolved with stirring in 20 ml of dry xylene in a oil bath at 140 °C ethyl 3-oxohexanoate (1.3 ml, 8.1 mmol) was added. The reation mixture was heated under reflux for 24 h and then cooled to rt and filtered to give **2b** (0.73 g, 64 %) as yellow crystals. Melting point 176-177 °C. IR : 3230 (NH), 1725 (CO-3), 1700 (CO-1), 1665 and 1640 (m, CO-1´and CO-4´) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 10.12 (s, 1H, NH); 8.13 (m, 2H, H-5´, H-8´); 7.84 (s, 1H, H-3´); 7.76 (m, 2H, H-6´, H-7´); 3.65 (s, 2H, $COCH_2CO$); 2.50 (t, J = 7.1 Hz, 2H, CH_2CO); 1.69 (m, 2H, CH_2); 0.98 (t, J = 7.4 Hz, 3H, CH_3) ppm. ^{13}C-NMR ($CDCl_3$) δ: 205.8 (CO-3); 185.5 (CO-4´); 181.0 (CO-1´); 165.1 (CO-1); 140.0 (C-2´); 134.9 (C-6´); 133.4 (C-7´); 132.0

(C-4a'); 130.3 (C-8a'); 126.8 (C-8'); 126.3 (C-5'); 117.9 (C-3'); 49.5 (C-2); 46.0 (C-4); 16.8 (C-5); 13.5 (CH_3) ppm. Analysis calc. for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.04; N, 4.91. Found: C, 67.14; H, 5.04; N, 4.92.

***N*(1,4-Dioxo-1,4-dihydro-2-naphthyl)-2-methyl-3-oxobutanamide (2c).**

To **1a** (1 g, 5.8 mmol) dissolved in 15 ml of dry xylene was added ethyl 2-methyl-3-oxobutirate (1.63 ml, 11.5 mmol). The reaction mixture was stirred in open flask for 2h at 130 °C (external temperature). After cooling to rt, the precipitate was collected by filtration and was purified on a column of silica gel eluting with petroleum ether/ ethyl acetate (1:1) to give 0.76 g of starting material and **2c** (0.1 g, 27 %) as orange crystals. Melting point 146-147 °C. IR: 3320 (NH), 1720 (CO-3), 1700 (CO-1), 1675 and 1655 (s, CO-1', CO-4') cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 9.38 (s, 1H, NH); 8.11 (m, 2H, H-5', H-8'); 7.83 (s, 1H, H-3'); 7.76 (m, 2H, H-6', H-7'); 3.67 (q, *J* = 7.2 Hz, 1H, H-2); 2.34 (s, 3H, CH_3CO); 1.55 (d, *J* = 7.2 Hz, 3H, CH_3) ppm. Analysis calc. for $C_{15}H_{13}NO_4$: C, 66.42; H, 4.79; N, 5.16. Found: C, 66.23; H, 4.96; N, 4.98.

Ethyl 3(1,4-dioxo-1,4-dihydro-2-naphthylamino)crotonate (3a).

A mixture of **1a** (5 g, 28.9 mmol) and ethyl acetoacetate (11.3 g, 86.7 mmol) was stirred in a bath at 160 °C until the starting material was consumed (approximately 3.5 h). After cooling to rt, the precipitate was collected by filtration and the residue was purified by column chromatography on silica gel eluting with petroleum ether/ethyl acetate (7:3) to yield comound **3** (1.8 g, 21 %) as orange crystals. Melting point 70-71 °C. IR: 1680, 1630, 1605, 1575 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.13 (m, 1H, H-8'); 8.10 (m, 1H, H-5'); 7.73 (m, 2H, H-6', H-7'); 6.53 (s, 1H, H-3'); 5.09 (s, 1H, H-2); 4.24 (q, *J* =7.2 Hz, 2H, CH_2); 2.36 (3H, H-4); 1.31 (t, *J* =7.2 Hz, 3H, CH_3) ppm. ^{13}C-NMR ($CDCl_3$) δ: 184.0 (CO-4'); 181.2 (CO-1'); 168.5 (CO-1); 152.5 (C-3); 142.5 (C-2'); 134.6 (C-6'); 132.9 (C-7'); 132.1 (C-4a'); 130.1 (C-8a'); 126.8 (C-8'); 125.9 (C-5'); 110.6 (C-3'); 98.5 (C-2); 59.4 (CH_2); 21.9 (C-CH_3), 14.2 (CH_2-CH_3) ppm. Analysis calc. for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.26; N, 4.91. Found: C, 67.65; H, 5.44; N, 4.85.

3-Acetyl-6-methyl-4(1,4-dioxo-2-naphthylamino)-2*H*-pyran-2-one (4).

A solution of **1a** (1.5 g, 8.7 mmol) in 20 ml of dry xylene was placed in a Erlenmeyer flask and was immersed in a oil bath preheated to 130 °C. The solution was vigorously stirred and freshly distilled 2,2,6-trimethyl-1,3-dioxin-4-one (4.53 ml, 34.7 mmol) was added. The heating was continued for a total of 2.5 h. After cooling to rt, the product (**4**) was collected and recrystallized in ethyl acetate/chloroform (1:1) (0.9 g, 32 %) as a yellow solid. Melting point 226-227 °C. IR: 1700, 1665, 1650, 1620, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 12.74 (s, 1H, NH); 7.98 (m, 2H, H-5', H-8'); 7.83 (s, 1H, H-5); 7.60 (m, 2H, H-6', H-7'); 6.21 (s, 1H, H-3'); 2.70 (s, 3H, $COCH_3$); 2.21 (s, 3H, CH_3) ppm. ^{13}C-NMR ($CDCl_3$) δ: 185.0 (*C*O-CH_3); 180.8 (CO-4'); 178.7 (CO-1'); 175.8 (CO-2); 165.1; 163.4 and 141.5 (C-2'', C-4 and C-6); 134.9 (C-6'); 133.0 (C-7'); 132.0 (C-4a')'; 130.3 (C-8a'); 126.7 (C-8'); 126.0 (C-5'); 117.9, 116.1 and 114.9 (C-3, C-5 and C-3'); 21.5 (CO-*C*H_3); 11.4 (CH_3) ppm. Analysis calc. for $C_{18}H_{13}NO_5$: C, 66.87; H, 4.02; N, 4.33. Found: C, 66.77; H, 3.97; N, 4.21.

4-Methyl-1*H*-1-aza-2,9,10-anthracenetrione (5a).

A solution of **2a** (0.4 g, 0.39 mmol) in 4.5 ml of sulfuric acid was vigorously stirred at rt until the starting material disappeared (30 minutes approximately). The reaction mixture was poured into ice and the resulting yellow precipitate was dissolved in ammonium hydroxide until pH 6-7. Compound **5a** was isolated by suction and washed thoroughly with cold water. Recrystallization from chloroform gave green crystals (0.08 g, 88 %). Melting point > 300 °C. IR: 1685, 1650, 1590 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 9.80 (s, 1H, NH); 8.21 (m, 2H, H-5, H-8); 7.83 (m, 2H, H-6 , H-7); 6.70 (s, 1H, H-3); 2.72 (s, 3H, CH_3) ppm. ^{13}C-NMR (DMSO-d_6) δ: 181.9

and 178.3 (CO-9 and CO-10); 161.1 (CO-2); 151.0 and 150.9 (C-3 and C-4); 135.4 (C-6); 133.9 (C-7); 132.9 (C-10a); 130.7 (C-8a); 126.7 (C-8); 126.2 (C-5); 121.0 and 120.0 (C-4a and C-9a); 22.1 (CH_3) ppm. Analysis calc. for $C_{14}H_9NO_3$: C,70.29; H, 3.76; N, 5.85. Found: C, 70.10; H, 3.88; N, 5.78.

2-Methyl-1*H*-1-aza-4,9,10-anthracenetrione (6a).

A solution of **3a** (0.4 g, 1.40 mmol) in 5 ml of diphenyl ether was refluxed until the starting material was consumed (approximately 1.5 h). After cooling to rt, the precipitate was collected by filtration and the residue was purified by column chromatography of silica gel eluting with ethyl acetate/petroleum ether (2:8) to yield **6a** (0.2 g, 60 %) as yellow crystals. Melting point: 261-262 °C. IR: 3530, 1720, 1700, 1665, 1635 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 8.12 (m, 2H, H-5, H-8); 7.91 (m, 2H, H-6, H-7); 6.86 (s, 1H, H-3); 2.44 (s, 3H, CH_3) ppm. Analysis calc. for $C_{14}H_9NO_3$: C, 70.29; H, 3.76; N, 5.85. Found: C, 70.13; H, 3.91; N, 5.69.

Diethyl 1,4-dioxo-1,4-dihydro-2-naphthylaminomethylenemalonate (3b). Method A.

To a 50 ml flask equipped with a reflux condenser a suspension of **1a** (1g, 5.8 mmol) and diethyl ethoxymethylenemalonate (4.7 ml, 23.1 mmol) was added and stirred at 170 °C (external temperature) for 2h until the reaction was complete as indicated by TLC analysis. The resulting brown mixture was cooled to rt and the solid filtered. The NMR spectrum of the crude product indicated a mixture of **3b** and traces of **3c**. Fine separation was achieved by column chromatography on eluting with petroleum ether/ethyl acetate (9:1). The more polar pale light orange solid compound was **3b** (790 mg, 40%). Melting point: 151-152 °C (lit.[16] 151.5-152.5 °C). IR: 3060, 1710 (CO_2Et), 1680 and 1660 (CO quinone) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 11.21 (d, *J* =13.2 Hz, 1H, NH); 8.20 (d, *J* =13.2 Hz, 1H, NHCH); 8.16 (dd, *J* =7.1, 1.5 Hz, 1H, H-8'); 8.13 (dd, *J* =7.08, 1.47 Hz, 1H, H-5'); 7.77 (m, 2H, H-6', H-7'); 6.50 (s, 1H, H-3'); 4.39 (q, *J* =7.1 Hz, 2H, CH_2); 4.29 (q, *J* =7.1 Hz, 2H, CH_2); 1.42 (t, *J* =7.1 Hz, 3H, CH_3); 1.36 (t, *J* =7.1 Hz, 3H, CH_3) ppm.^{13}C-NMR ($CDCl_3$) δ: 183.5 (CO-4'); 180.0 (CO-1'); 166.7 and 164.3 (CO_2); 145.0 (NHCH); 142.1 (C-2'); 135.0 (C-6'); 133.4 (C-7'); 132.3 (C-4a'); 130.2 (C-8a'); 126.9 (C-8'); 126.5 (C-5'); 110.1 (C-3'); 102.7 (C-2); 61.4 and 61.0 (CH_2); 14.3 and 14.2 (CH_3) ppm. Analysis calc. for $C_{18}H_{17}O_6N$: C, 62.97; H, 4.95; N, 4.08. Found: C, 63.00; H, 4.81; N, 4.08.

Method B.

A mixture of **1a** (1.5 g, 8.7 mmol) and diethyl ethoximethylenemalonate (1.87 ml, 9.3 mmol) in 10 ml of trifluoroacetic acid was refluxed for 20 min to give **3b** that was chromatographed (silica gel, petroleum ether/ethyl acetate, 7:3) to give 2.67 g (90% yield).

Ethyl (*Z*)-3(1,4-dioxo-1,4-dihydro-2-naphthylamino)acrylate (3c)

Light yellow crystalls, with R_f 0.76 (petroleum ether/ ethyl acetate, 2:8). Melting point: 168-170 °C. IR: 3220 (NH), 1735 (CO ester), 1700 and 1630 (CO quinone) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 10.75 (d, *J* =12.2 Hz, 1H, NH); 8.12 (m, 2H, H-5', H-8'); 7.74 (m, 2H, H-6', H-7'); 7.04 (dd, *J*= 12.2, 8.7 Hz, 1H, H-3); 6.27 (s, 1H, H-3'); 5.28 (d, *J* = 8.7 Hz, 1H, H-2); 4.27 (q, *J* =7.1 Hz, 2H, CH_2); 1.35 (t, *J* =7.1 Hz, 3H, CH_3) ppm. ^{13}C-NMR ($CDCl_3$) δ: 183.6 (CO-4'); 180.0 (CO-1'); 168.5 (CO_2); 142.7 (C-2'); 136.7 (C-3); 134.8 (C-6'); 132.9 (C-7'); 132.6 (C-4a'); 130.3 (C-8a'); 126.7 (C-8'); 126.2 (C-5'); 106.4 (C-3); 98.3 (C-2); 60.4 (CH_2); 14.3 (CH_3) ppm. Analysis calc for $C_{15}H_{13}NO_4$: C, 66.42; H, 4.79; N, 5.16. Found: C, 66.23; H, 4.68; N, 5.35.

2,2-Dimethyl-5(1,4-dioxo-2-naphthylaminometylen)dioxan-4,6-dione (3d).

A suspension of Meldrum's acid (0.48 g, 5.8 mmol) in trimethyl orthoformate (22 ml, 201.1 mmol) was heated under reflux for 2h. At the end of this time, a solution of **1a** (1 g, 5.8 mmol) in trimethyl orthoformate (60

ml) was added and the reflux was continued for 7 h. After cooling to rt, the formation of a crystalline yellow-orange precipitate became noticeable. Filtration and removal of the solvent left a yellow solid that was subjected to silica gel chromatography by using a mixed solvent system of petroleum ether/ethyl acetate (8:1) to afford pure **3d** (1.40 g, 78 % yield). Melting point: 243-245 °C. IR: 3250 (NH), 1735 (CO ester), 1690 and 1660 (CO quinone) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 11.60 (d, J = 13.9 Hz, 1H, NH); 8.54 (d, J = 13.9 Hz, 1H, N-CH); 8.17 (m, 2H, H-5´,H-8´); 7.83 (m, 2H, H-6´, H-7´); 6.75 (s, 1H, H-3´); 1.78 (s, 6H, CH_3) ppm. ^{13}C-NMR ($CDCl_3$) δ: 183.1 (CO-4´); 179.3 (CO-1´); 164.0 (CO-4 and CO-6); 148.6 (NHCH); 141.1 (C-2´); 135.4 (C-6´); 133.9 (C-7´); 132.1 (C-4a´); 130.0 (C-8a´); 1267.1 (C-8´); 126.7 (C-5´); 113.5 (C-2); 105.9 (C-3´); 93.9 (C-5); 27.4 (CH_3) ppm. Analysis calc. for $C_{17}H_{13}NO_6$: C, 62.38; H, 3.97; N, 4.28. Found: C, 62.17; H, 4.08; N, 4.23.

Z/E-Ethyl 3(1,4-dioxo-1,4-dihydro-2-naphthylamino)2-nitroacrylates (3e and 3f).

To a suspension of **1a** (0.68 g, 3.9 mmol) in trifluoroacetic acid (3 ml) ethyl 3-ethoxy-2-nitroacrylate (EENA)[25] (0.8 g, 4.2 mmol) was added. The solution was heated at reflux for 20 minutes. After cooling at rt, the solid was removed by filtration and washed with methanol to give a brown faded to a yellow product as a *E*/*Z* = 3:1 mixture estimated by ^{1}H-NMR of **3e** and **3f** (0.7 g, 60 % yield). IR: 3350 (NH), 1720 (CO-1), 1670 and 1645 (CO-1´and CO-4´) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 10.96 (d, J = 13.7 Hz, 1H, NH), 8.73 and 8.27 (2d, J = 13.7 Hz, 1H, H-3); 8.16 (m, 2H, H-5´, H-8´); 7.81 (m, 2H, H-6´, H-7´); 6.69 and 6.67 (2s, 1H, H-3´); 4.45 and 4.39 (2q, J = 7.1 Hz, 2H, CH_2-*E* isomer and CH_2-*Z* isomer); 1.45 and 1.39 (2t, J = 7.1 Hz, 3H, CH_3-*E* isomer and CH_3-*Z* isomer) ppm. Analysis calc. for $C_{15}H_{12}N_2O_6$: C, 56.90; H, 3.79; N, 8.86. Found C, 56.86; H, 3.83; N, 8.77.

Ethyl 1*H*-1-aza-4,9,10-trioxoanthracene-3-carboxylate (6b).

A solution of **3b** (0.6 g, 1.7 mmol) in trichlorobenzene (40 ml) was refluxed in a sand bath for 7 h. After cooling to rt, the precipitate was collected by filtration and was purified on a column of silica gel (ethyl acetate as eluent) to give **6b** (0.31 g, 60 %) of as yellow crystals. Melting point: 226-227 °C (hexane/absolute ethanol, 9:1) (lit. 224-226.5 °C[16]). IR: 3430, 1720, 1680 and 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 13.7 (br s, 1H, NH); 9.29 (s, 1H, H-2);[37] 8.34 (m, 2H, H-5 and H-8); 7.89 (m, 2H, H-6 and H-7); 4.75 (q, J = 7.2 Hz, 2H, CH_2); 1.44 (t, J = 7.2 Hz, 3H, CH_3) ppm. ^{13}C-NMR ($CDCl_3$) d: 180.4 (CO-9 and CO-10); 167.9(C-4); 157.6 (CO_2); 151.5 (C-2); 135.6, 134.9, 128.1 and 127.1(C-6 - C-8); 134.9 and 132.8 (C-9a and C-8a); 118.2 (C-4a); 116.0 (C-3); 62.0 (CH_2) and 14.1 (CH_3) ppm. ^{13}C-NMR (DMSO-d_6) δ: 179.7 (CO-9 and CO-10); 171.2 (C-4); 163.7 (CO_2); 143.8 (C-2); 135.5, 133.5, 132.9, 130.4; 126.4, 125.9 and 124.2 (C-5 - C-8, C-9a, C-5a, C-4a); 120.0 (C-3), 60.5 (CH_2) and 14.1 (CH_3) ppm. ^{13}C-NMR (pyridine-d_5) d: 183.3 and 180.6 (C-9 and C-10); 171.0 (C-4); 164.6 (CO_2)146.8 (C-2); 133.9, 133.4, 131.7, 127.0 and 126.5 (C-5 -C-8 and C-9a); 120.3 (C-3); 61.3 (CH_2) and 14.2 (CH_3) ppm. Analysis calc. for $C_{16}H_{11}NO_5$: C, 64.64; H, 3.70; N, 4.71. Found: C, 64.51; H, 3.84; N, 4.54.

1*H*-1-Aza-4,9,10-anthracenetrione (6d).

A solution of **3d** (1.2 g, 3.6 mmol) in diphenyl ether (35 ml) was refluxed until the starting material had been consumed (approximately 3 h). After cooling to rt, the precipitate was collected by filtration and the residue was subjected to silica gel chromatography (ethyl acetate) to give **6d** (0.6 g, 74 %). Melting point > 300 °C. IR: 3500, 1690, 1645 and 1615 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 12.67 (br s, 1H, NH); 8.82 (d, J = 5.5 Hz, 1H, H-2); 8.40 and 8.33 (dd, J = 8.9, 3.0, 2H, H-5 and H-8), 7.9 (m, 2H, H-6 and H-7), 7.19 (d, J = 5.5 Hz, 1H, H-3) ppm. Analysis calc. for $C_{13}H_7NO_3$: C, 69.33; H, 3.11; N, 6.22. Found: C, 69.18; H, 3.26; N, 6.19.

Z and E-Methyl 3(2-naphthylamino)propenoate (3g and 3h).

A solution of **1a** (1.8 g, 10.4 mmol) in dioxane (30 ml) was placed in a 50-ml botton-flask immersed in a oil bath preheated to 100 °C. Methyl propiolate (1.7 ml, 20.8 mmol) and three drops of triethylamine were added and the reaction mixture was stirred and refluxed for 4 h . Then the reaction was cooled to rt and filtered. The crude material was purified by column chromatography on silica gel (ethyl acetate/ petroleum ether, 2:8) to give the *E*-isomer **3h** 0.8 g (30%) and the *Z*-isomer **3g** (0.4, 15 %). Compound **3h** was recrystallized from chloroform and was obtained as red crystals. Melting point: 244-245 °C. IR: 3180 (NH); 1725 (CO ester); 1680 and 1640 (CO quinone) cm^{-1}.^{1}H-NMR ($CDCl_3$) δ: 8.11 (m, 2H, H-5´,H-8´); 7.73 (m, 3H, H-3, H-6´, H-7´); 6.34 (s, 1H, H-3´); 5.65 (d, *J* = 13.1 Hz, 1H, H-2); 3.77 (s, 3H, CH_3) ppm. ^{13}C-NMR (DMSO-d_6) δ: 182.8 (CO-4´); 181.2 (CO-1´); 167.0 (CO-1); 143.9 (C-2´); 139.4 (C-3); 134.8 (C-6´); 133.1 (C-7´); 132.0 (C-4a´); 130.3 (C-8a´); 126.2 (C-8´); 125.4 (C-5´); 107.1 (C-3´); 98.8 (C-2); 50.9 (CH_3) ppm. Analysis calc. for $C_{14}H_{11}NO_4$: C, 65.36; H, 4.28; N, 5.44. Found: C, 65.18; H, 4.34; N, 5.28. Compound **7f** was obtained as dark-red crystals. Melting point: 200-201 °C. IR: 3180 (NH), 1725 (CO ester), 1680 and 1640 (CO quinone) cm^{-1}.^{1}H-NMR ($CDCl_3$) δ: 10.74 (d, *J* = 12Hz, 1H, NH); 8.1 (m, 2H, H-5´, H-8´); 7.72 (m, 2H, H-6´, H-7´); 7.05 (dd, *J* = 12.0, 8.5 Hz, H-3); 6.27 (s, 1H, H-3´); 5.3 (d, *J* = 8.5, 1H, H-2); 3.80 (s, 3H, CH_3) ppm. ^{13}C-NMR ($CDCl_3$) δ: 183.6 (CO-4´); 180.4 (CO-1´); 168.9 (CO-1); 142.7 (C-2´); 137.0 (C-3); 134.8 (C-6´); 133.0 (C-7´); 132.6 (C-4a´); 130.3 (C-8a´); 126.8 (C-8´); 125.3 (C-5´); 106.6 (C-3´); 97.8 (C-2); 51.3 (CH_3) ppm. Analysis calc. for $C_{14}H_{11}NO_4$: C, 65.36; H, 4.28; N, 5.44. Found: C, 65.32; H, 4.35; N, 5.28.

2-Amino-1*H*-1-aza-4,9,10-anthracenetrione (6i).

A solution of **1a** (5 g, 28.9 mmol) and malonodinitrile (2.84 g, 43 mmol) in glacial acetic acid (30 ml) was refluxed for 25 h. The reaction mixture was cooled, and the precipitate was purified by column chromatography to afford **6i** (0.14 g, 2 %) as brown crystals. Melting point: 150-151 °C. IR: 3250 (NH_2), 1765, 1710, 1690 and 1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.37 (br s, 1H, NH); 8.12 (m, 2H, H-5, H-8); 7.86 (s, 1H, H-3); 7.76 (m, 2H, H-6, H-7) ppm. ^{13}C-NMR ($CDCl_3$) δ: 185.0 (C-10); 181.0 (C-9); 169,4 (C-4); 139.9 (C-2); 135.0 (C-6); 133.3 (C-7); 132.1 (C-4a); 130 (C-8a); 126.7 (C-8); 126.4 (C-5); 117.2 (C-3) ppm. Analysis calc for $C_{13}H_8N_2O_3$: C, 65.00; H, 3.33; N, 11.66. Found: C, 65.13; H, 3.41; N, 11.54.

Ethyl 5-hydroxy-2-Methyl-1*H*-benzo[g]indole-3-carboxilate (7).

A solution of 1,4-naphthoquinone (1 g, 6.3 mmol) of in xylene (15 ml) was placed in a Erlenmeyer flask and immersed in a oil bath that had been preheated at 120 °C. Ethyl 3-aminocrotonate (0.81 g, 6.3 mmol) was added. The solution was stirred and the heating was continued for 1 h. The reaction was cooled to rt and the product was collected and recrystallized in ethyl acetate to give **7** (0.5 g, 28 %). Melting point: 266-267 °C (reported 261-262 °C[30]). IR: 3580 (OH), 1665 cm^{-1}. ^{1}H-NMR (DMSO) δ: 12.26 (s, 1H, OH); 9.64 (s, 1H, NH); 8.26 and 8.18 (m, 2H, H-6 and H-9); 7.59 (dd, *J* = 7.3, 7.5 Hz, 1H) and 7.40 (dd, *J* = 7.9, 7.2 Hz, 1H) (H-7 and H-8); 4.30 (q, *J* = 7.1 Hz, 2H, CH_2); 2.72 (s, 3H, C-CH_3); 1.39 (t, *J* = 7.1 Hz, 3H, CH_2CH_3) ppm. ^{13}C-NMR (DMSO-d_6) δ: 165.3 (CO); 148.0 (C-5); 141.3 (C-1); 125.8; 123.4; 123.3; 122.7; 121.7,;120.2; 103.9 (C-3); 101.5 (C-4); 58.6 (CH_2); 14.5 (CH_3); 13.8 (CH_3) ppm. Analysis calc. for $C_{16}H_{15}NO_3$: C, 71.37; H, 5.57; N, 5.20. Found: C, 71.20; H, 5.66; N, 5.13.

REFERENCES AND NOTES

1. Middelton, R. W.; Parrick, J. *Heterocyclic Quinones*, in *The chemistry of Quinonoid Compounds*; Patai, S.; Rappoport, Z., eds, Wiley, New York, 1988, Vol. 2 (part 2), pp 1019-1066.
2. Lin, A. J.; Corby, L. A.; Shausky, C. W.; Sartorelly, A.C. *J. Med. Chem.* **1972**, *15*, 1247.
3. Moore, H. W.; West, K. F.; Srinivasacher, K.; Czerniak, R. in *Structure-Activity Relationships of Antitumor Agents*, Reinhoudt, D. N.; Connors, T. A.; Pinedo, H. M.; van de Poll, K. W., eds, Martinus Nijhoff Publishers, The Hague, 1983, pp 93-110.
4. Waterman, P.G.; Muhamed, I. *Phytochemistry* **1985**, *24*, 523.
5. Soulart, M.O.F.; Santane, A.E.G.; de Oliveira, A. B.; de Oliveira, G. D.; Maia, J. G. *Phytochemistry*, **1985**, *25*, 1691.
6. Cameron, D. W.; Deutscher, K. R.; Feutrill, G. I.; Hunt, D. E. *Aust. J. Chem.***1982**, *35*, 1451.
7. Omura, S.; Iwai, Y.; Hinotozawa, K.; Tanaka, H.; Takahashi, Y.; Nakagawa, A. *J. Antibiotics* **1982**, *35*, 1425.
8. Kelly, T. R.; Field, J. A.; Li, Q. *Tetrahedron Lett.*. **1988**, *29*, 3545.
9. a) Omura, S.; Iwai, Y; Hinotozawa, K.; Tanaka, H; Takahashi, Y.; Nakagawa, A. *J. Antibiotics* **1989**, *42*, 727. b) Omura, S. *Microbiological Reviews* **1986**, *50*, 259. c) Tsuzuki, K.; Yokuzuka, T.; Murata, M.; Tanaka, H.; Omura, S. *J. Antibiotics* **1989**, *42*, 727.
10. a) Gesto, C.; de la Cuesta, E.; Avendaño, C. *Tetrahedron* **1989**, *45*, 4477. b) Pérez, J.M.; Vidal, L.; Grande, M.T.; Menéndez. J.C.; Avendaño, C. *Tetrahedron* **1994**, *50*, 7923.
11. Gesto, C.; de la Cuesta, E.; Avendaño, C; Emling, F. *J. Pharm. Sci* . **1992**, *81*, 815. c) Avendaño, C.; Alonso, M. A.; Espada, M.; Garcia Grávalos, D.; Menéndez, J. C.; Ocaña, B.; Pérez, J. M. *Eur. Pat. Appl.* 93304354.9 (15-12-1993).
12. Tisler, M. *"Heterocyclic Quinones"* in *Adv. Heterocyclic Chem.* **1989**, *45*, 38.
13. Pinto, A. V.; Ferreira, V. F.; Pinto, M. C. F. R.; Mayer, L. U. *Synthetic Cmmun.* **1985**, *15*, 1181.
14. Fieser, L.; Fieser, M. *J. Am. Chem. Soc.* **1934**, *56*, 1565.
15. Corey, E. J.; Clark, D. A. *Tetrahedron Lett.* **1980**, *21*, 2045.
16. Dudley, K. H.; Mckee, R. L. *J. Org. Chem.* **1967**, *32*, 3210.
17. Jones, G. in Boulton, A. J. and McKillop, A. *Comprehensive Heterocyclic Chemistry* Vol. 2, pp 425 (Katritzky, A. R.; Rees, C. W., general editors) Pergamon Press, 1984.
18. Fieser, L. F., Hartawel, J. L. *J. Am. Chem. Soc.* **1935**, 1482.
19. Clemens, R. J.; Hyatt, J. A. *J. Org. Chem.* **1985**, *50*, 2431.
20. Hauser, Ch. R.; Reynolds, G. A. *J. Am. Chem. Soc.* **1948**, *70*, 2402.
21. Clemens, R. J.; Witzeman, J.S. *J. Am. Chem. Soc.* **1989**, *111*, 2186.
22. Sato, M.; Ogasawara, H.; Oi, K.; Kato, T. *Chem. Pharm. Bull.* **1983**, *31*, 1896.
23. Staskum, B. *J. Org. Chem.* **1964**, *29*, 1153.
24. McNab, H. *Chem. Soc. Rev.* **1978**, *7*, 345.
25. Kamlet, M. J. *J. Org. Chem.*. **1959**, *24*, 714.
26. Wolfbeis, O. S. *Chem. Ber.*. **1977**, *110*, 2480.
27. Anderson, G. L. *J. Heterocyclic Chem.* **1985**, *22*, 1469.

28. a) Doebner, O.; von Miller, W. *Chem. Ber.* **1883**, *16*, 1664; b) Blaise, E. E.; Maire, M. *Bull. Soc. Chim. France* **1908**, *3*, 658; c) Wepplo, P. J., Princeton, N. J. *USS Patent* 4,460,77. Jul, 1984.
29. Littel, R., Morton, G. O.; Allen, G. R. *J. Am. Chem. Soc.* **1970**, *92*, 3740.
30. Teuber, H.-J.; Thaler, G. *Chem. Ber.* **1959**, *92*, 667.
31. a) Pettit, G. R.: Fleming, W. C.; Paull, K. D. *J. Org. Chem.* **1968**, *33*, 1089; b) Sluyter, M. A. T.; Pandit, U. K.; Speckamp, W. N.; Huisman, H. O. *Tetrahedron Lett.* **1966**, 87.
32. De la Cruz, A.; Elguero, J.; Goya, P.; Martínez, A. *Tetrahedron* **1992**, *48*, 6135.
33. Withopf, P.; Lackuer, H. *Tetrahedron* **1987**, *43*, 4549.
34. Baxter, I.; Phillips, W. *J. Chem. Soc. Perkin I* **1973**, 2374.
35. Link, H.; Bernauer, K.; Englert, G. *Helv. Chim. Acta* **1982**, 65, 2645.
36. Perrin D. D. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon: New York, 1987.
37. δ H-2 (DMSO-d_6): 8.18 ppm; δ H-2 (F_3CCO_2H)[16]: 9.54 ppm.

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