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TETRAHEDRON

Synthesis of 3-Alkyl- and 3-Aryl-2-aza-anthraquinones

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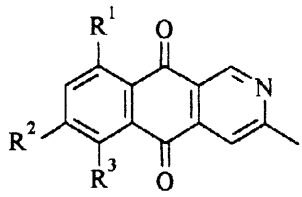
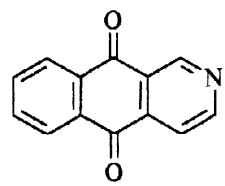
Abstract: Reaction of 2-acylated 3-phenoxymethyl-1,4-naphthoquinones with aqueous ammonium hydroxide, provides a facile entry to 3-alkyl- and 3-aryl-benz[g]isoquinoline-5,10-diones.

INTRODUCTION

Although anthraquinones represent a large class of natural products, their naturally occurring 2-aza-analogues with bostrycoidin **1**,[1] 9-O-methyl bostrycoidin **2**,[2] tolypocladin **3**[3] and benz[g]isoquinoline-5,10-dione **4**[4] as representative members, are rarely found in nature. Moreover, these 2-aza-anthraquinones possess interesting physiological activities. Bostrycoidin **1** shows an *in vitro* antibiotic activity against the tubercle bacil,[5] 9-O-methyl bostrycoidin **2** was found to have antibiotic activity against G+ bacteria[6] and benz[g]isoquinoline-5,10-dione **4** is active against the multi-drug resistant *Plasmodium falciparum*.[4]



1 $R^1 = R^3 = OH$, $R^2 = OMe$
2 $R^1 = R^2 = OMe$, $R^3 = OH$
3 $R^1 = R^2 = R^3 = OH$



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Furthermore, 2-aza-anthraquinones are of considerable interest in cancer chemotherapy. The synthetic mitoxanthrone **5** is well known as a very active anticancer drug. Mitoxanthrone **5** has been shown to be an

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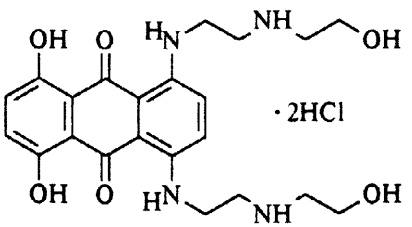
intercalating agent to DNA and on the basis of a theoretical model for intercalation, it was predicted that aza-anthraquinone analogues of mitoxanthrone would be very effective intercalating agents as well.[7]



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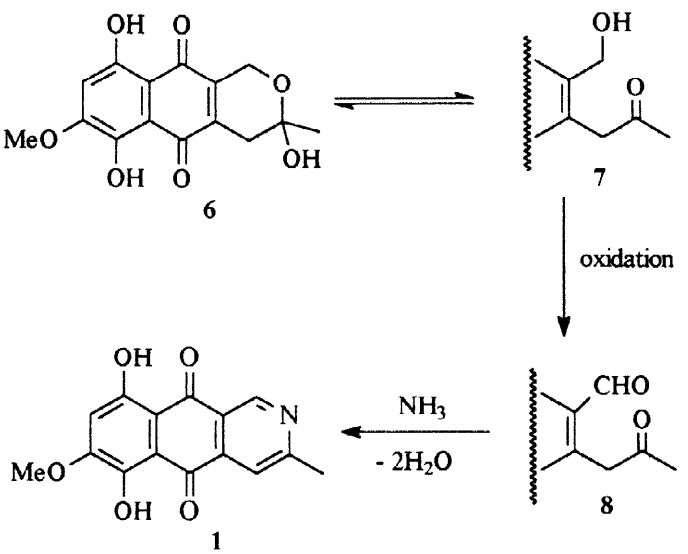
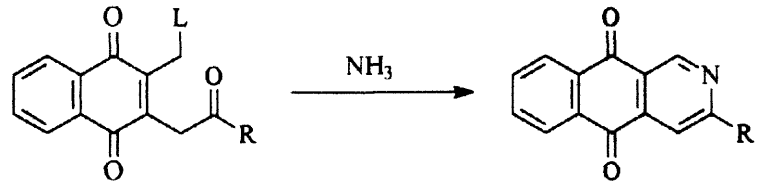
Thus, the study of new entries to aza-anthraquinones is of special interest. Several synthetic strategies have been applied in the literature. Most of them involve Diels–Alder cyclization in the formation of the heterocyclic ring or the terminal carbocyclic ring.[8-11] However, these cycloaddition reactions show only poor regioselectivity. Alternative routes of their preparation generally require a total construction of the skeleton via a multi step sequence which involves either the classical Friedel-Crafts approach[12-15] or reaction of carbanions based on a directed lithiation strategy.[7, 16, 17]

It was speculated that the naturally occurring 2-aza-anthraquinones originate *in vivo* from incorporation of ammonia into their O-analogues.[18] In addition, it was postulated that bostrycoidin **1**, which was isolated from the same fungus *Fusarium bostrycoides* as fusarubin **6**, is formed by oxidation of fusarubin **6** in the presence of ammonia as shown in Scheme 1.[5]



Scheme 1

Based on this hypothesis, we designed a novel and facile synthetic route for the synthesis of 3-alkyl- and 3-aryl-2-aza-anthraquinones **10** by reaction of a precursor of type **9** (L = leaving group) with ammonia (Scheme 2).

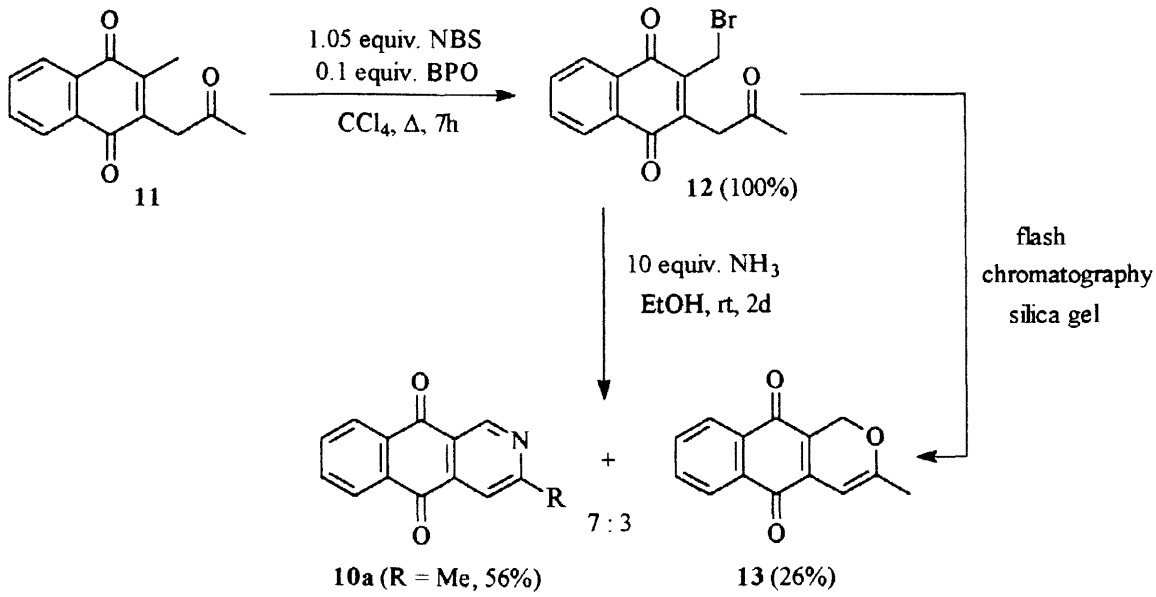


9 (L = leaving group) **10**

Scheme 2

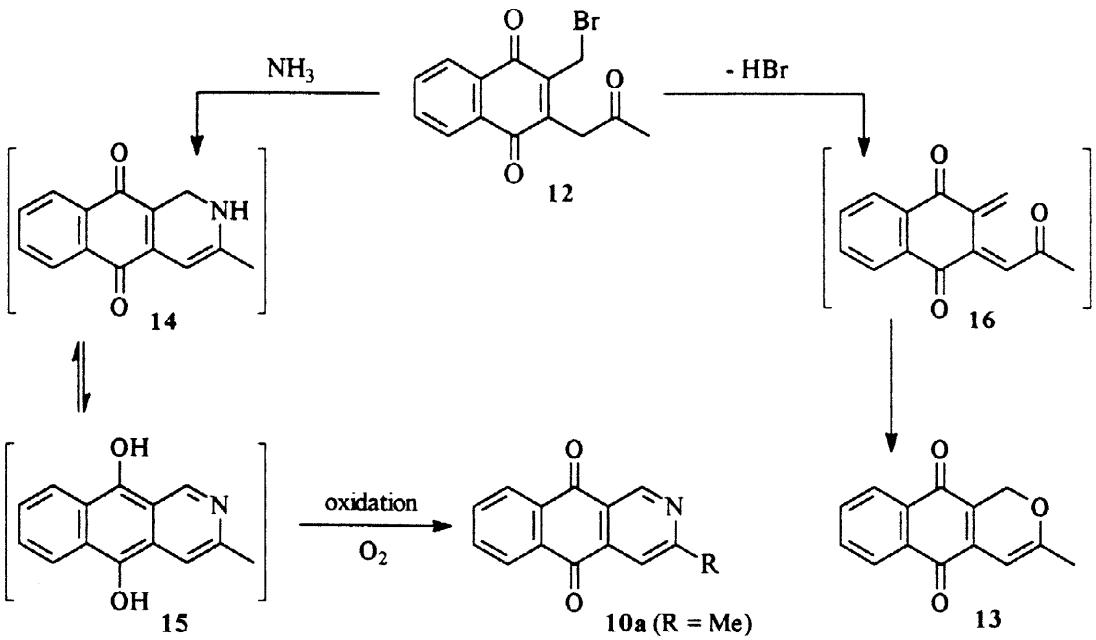
RESULTS AND DISCUSSION

To this end, in a first attempt, 2-acetonyl-3-bromomethyl-1,4-naphthoquinone **12** was prepared by selective monobromination of 1-acetonyl-2-methyl-1,4-naphthoquinone **11**[19] using 1.05 equivalents of *N*-bromosuccinimide and a catalytic amount of benzoyl peroxide in tetrachloromethane under reflux. Compound **12**, which was obtained in a crude yield of 100% (purity > 95%), could not be purified by flash chromatography as it gave rise to complete transformation into 3-methyl-1H-naphtho[2,3-c]pyran-5,10-dione **13**. Therefore, the crude 2-bromomethylnaphthoquinone **12** was treated with 10 equivalents of aqueous ammonia in ethanol at room temperature and stirred for 2 days to give a mixture of 3-methyl-2-aza-anthraquinone **10a** (R = Me) and 3-methyl-1H-naphtho[2,3-c]pyran-5,10-dione **13** in a ratio of 7 : 3 (Scheme 3). Separation of compounds **10a** and **13** by flash chromatography resulted in isolated yields of 56% and 26%, respectively.



Scheme 3

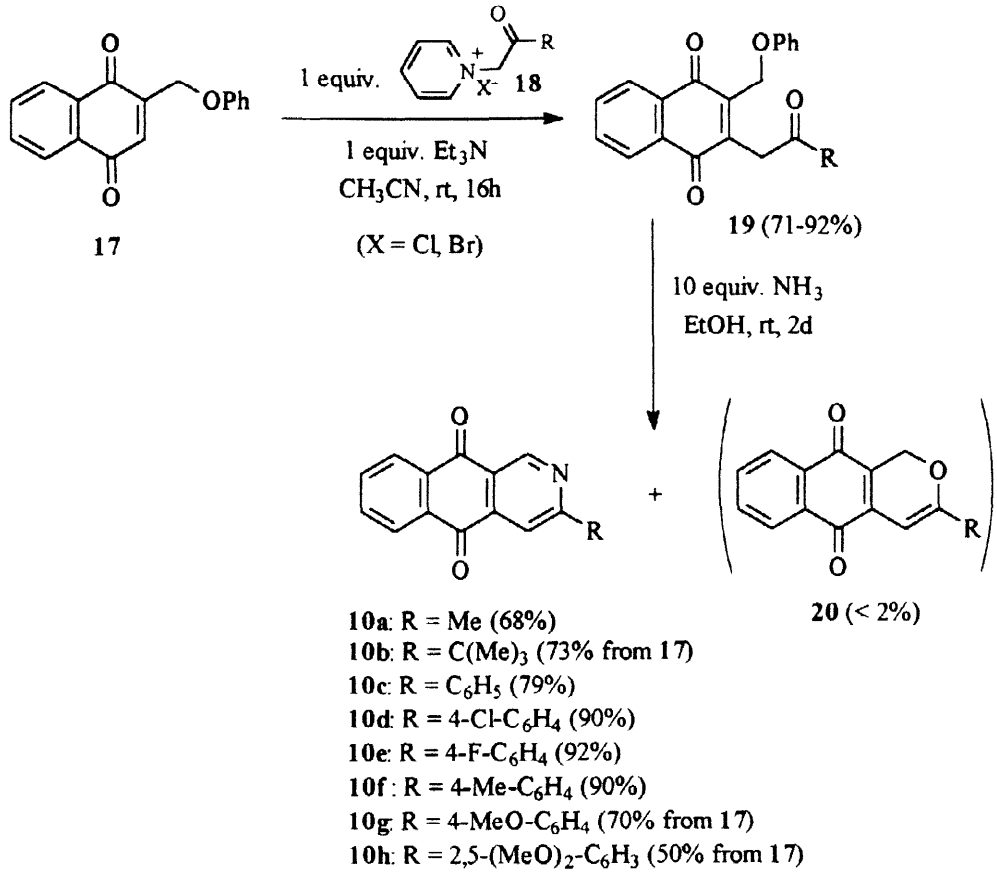
The reaction mechanism for the formation of 3-methyl-2-aza-anthraquinone **10a** is believed to proceed via condensation of the 2-bromomethylnaphthoquinone **12** with ammonia and intramolecular nucleophilic substitution to give 1,2-dihydro-2-aza-anthraquinone **14**. Double keto-enol tautomerisation leads then to the fully aromatic 2-azahydroanthraquinone **15** which is easily oxidised in the presence of air to give 3-methyl-2-aza-anthraquinone **10a**. The formation of the pyranonaphthoquinone side-product **13**, on the other hand, results from the competitive action of ammonia as a base. Via deprotonation and dehydrobromination of the 2-bromomethylnaphthoquinone **12**, the intermediate quinone methide **16** is obtained which rapidly cyclises to 3-methyl-1H-naphtho[2,3-c]pyran-5,10-dione **13** (Scheme 4).



Scheme 4

In an attempt to improve the selectivity of the 2-aza-anthraquinone synthesis, the bromine atom was replaced by phenoxide as a leaving group. A series of 2-acylated 3-phenoxymethyl-1,4-naphthoquinones **19** was prepared from the readily available 2-phenoxymethyl-1,4-naphthoquinone **17**[20] by reaction with acylated pyridinium ylides, created in situ by treatment of the corresponding pyridinium salts **18** with 1 equivalent of triethylamine.[21] When these acylated 3-phenoxymethyl-1,4-naphthoquinones **19** were treated with 10 equivalents of aqueous ammonia in ethanol at room temperature for 2 days, they were converted almost selectively into the corresponding 3-alkyl and 3-aryl-2-aza-anthraquinones **10** with only traces (< 2%) of the 3-alkyl- and 3-aryl-1H-naphtho[2,3-c]pyran-5,10-diones **20** present in the reaction mixtures. This selective transformation can be explained from the fact that with phenoxide as a poor leaving group, the formation of the pyranonaphthoquinone side-product **20**, which depends on the elimination rate of phenol, is slowed down. All

3-alkyl- and 3-aryl-2-aza-anthraquinones **10** were obtained in good yields after purification by flash chromatography (50% - 92%) (Scheme 5).



Scheme 5

In conclusion, a series of 3-alkyl- and 3-aryl-2-aza-anthraquinones **10** was synthesized by reaction of 2-acylated 3-phenoxymethyl-1,4-naphthoquinones **19** with 25% ammonium hydroxide thereby providing a new synthetic approach for the synthesis of natural and synthetic 2-aza-anthraquinones. Moreover this synthesis follows the route of the hypothesis of the *in vivo* synthesis of naturally occurring 2-aza-anthraquinones via reaction of ammonia with their corresponding O-analogues.

EXPERIMENTAL PART

General methods. ^{1}H NMR spectra (270 MHz) and ^{13}C NMR spectra (68 MHz) were run with a Jeol JNM-EX 270 NMR spectrometer. Peak assignments were performed with the aid of the DEPT technique, 2D-COSY spectra and HETCOR spectra. IR assignments were obtained from a Perkin Elmer model 1310

spectrophotometer or a Perkin Elmer 983 G infrared spectrophotometer while mass spectra were measured with a Varian MAT 112 spectrometer (70 eV). Melting points were measured with a Büchi 535 apparatus. Flash chromatography was carried out on a glass column with ACROS silica gel (particle size 0.035-0.07 mm, pore diameter ca. 6 mm). All solvents and reagents were obtained from commercial suppliers and were used without purification. All pyridinium salts were prepared according to literature methods.[19,21]

2-Acetonyl-3-bromomethyl-1,4-naphthoquinone (12). A suspension of 2-acetonyl-3-methyl-1,4-naphthoquinone **11**[19] (2 mmol, 0.46 g), *N*-bromosuccinimide (2.1 mmol, 0.37 g) and benzoyl peroxide (0.2 mmol, 50 mg) in carbon tetrachloride (40 ml) was heated under reflux for 7 h. Then the reaction mixture was cooled to 0°C and the succinimide precipitate was removed by filtration. Evaporation of the filtrate at reduced pressure gave the 2-acetonyl-3-bromomethyl-1,4-naphthoquinone **12** (0.61 g, 100%) as a brown oil. The crude product (purity > 95%) could not be purified by flash chromatography (which gave complete conversion to the 3-methyl-1H-naphtho[2,3-c]pyran-5,10-dione **13**) and was used as such in the next step. An analytical sample of the 2-acetonyl-3-bromomethyl-1,4-naphthoquinone **12** was obtained as yellow needles by recrystallisation from methanol, mp 62°C. ^{1}H NMR ($CDCl_3$) : δ 2.39 (3H, s, CH_3), 3.92 (2H, s, CH_2C=O), 4.40 (2H, s, CH_2Br), 7.73-7.77 (2H, m, H-6 and H-7), 8.05-8.15 (2H, m, H-5 and H-8). ^{13}C NMR ($CDCl_3$) : δ 22.07 (CH_2Br), 30.14 (CH_3), 41.12 ($\underline{C}H_2C$=O), 126.11 and 126.24 (C-5 and C-8), 131.14 (2x =C_{quat}), 133.62 and 133.71 (C-6 and C-7), 142.32 (=C_{quat}), 143.21 (=C_{quat}), 181.56 (C=O), 183.52 (C=O), 202.37 (C=O). IR (NaCl) : ν_{max} 1715 (C=O), 1660 (C=O), 1590 (C=C) cm^{-1}. MS *m/z* (%) : no M^+, 264/6 (47), 227 (12), 226 (5), 186 (53), 185 (100), 157 (20), 128 (17), 119, (19), 117 (18), 105 (10), 77 (10), 76 (16), 43 (70). Anal. Calcd. for $C_{14}H_{11}BrO_3$: C 54.75%, H 3.61%. Found : C 54.56%, H 3.64%.

Synthesis of 3-Methyl-benz[g]isoquinoline-5,10-dione (10a) and 3-Methyl-1H-naphtho[2,3-c]pyran-5,10-dione (13) from 2-Acetonyl-3-bromomethyl-1,4-naphthoquinone (12). To a solution of 2-acetonyl-3-bromomethyl-1,4-naphthoquinone **12** (1 mmol, 0.31 g) in ethanol (20 ml) was added dropwise, a solution of aqueous ammonia (25% NH_3 in H_2O) (10 mmol, 0.68 g) in ethanol (5 ml). The solution was protected from light by aluminium foil and stirred for 2 days in an open vessel, allowing contact with the air. Then, most of the solvent was evaporated at reduced pressure and the resulting residue was dissolved in dichloromethane, washed with 1N hydrochloric acid and with an aqueous saturated sodium hydrogen carbonate solution. After drying ($MgSO_4$) and evaporation of the solvent at reduced pressure, a mixture of 3-methyl-benz[g]isoquinoline-5,10-dione **10a** and 3-methyl-1H-naphtho[2,3-c]pyran-5,10-dione **13** was obtained in a ratio of 7 : 3. Flash chromatography with 10% ethyl acetate in hexane as eluent gave first elution of 3-methyl-1H-naphtho[2,3-c]pyran-5,10-dione **13** (59 mg, 26%, R_f = 0.34) as a red powder, mp 132-133°C (from methanol). ^{1}H NMR ($CDCl_3$) : δ 2.04 (3H, d, J = 0.7 Hz, CH_3), 5.17 (2H, s, CH_2), 5.94 (1H, d, J = 0.7 Hz, CH=C-O), 7.76-7.74 (2H,

m, H-7 and H-8), 8.04-8.09 (2H, m, H-6 and H-9). ^{13}C NMR ($CDCl_3$) : δ 20.32 (CH_3), 63.22 (CH_2), 94.88 (CH=C-O), 122.10 (=C_{quat}), 125.91 and 126.45 (C-6 and C-9), 131.73 (=C_{quat}), 132.63 (=C_{quat}), 133.12 and 133.89 (C-7 and C-8), 138.06 (=C_{quat}), 165.44 (CH=C-O), 181.97 (C=O), 182.33 (C=O). IR (KBr) : ν_{max} 1660 (C=O), 1585 (C=C), 1560 (C=C) cm^{-1}. MS *m/z* (%) : 226 (M^+, 100), 225 (30), 197 (16), 183 (13), 155 (16), 141 (11), 127 (15), 77 (11), 76 (16), 43 (28). Anal. Calcd. for $C_{14}H_{10}O_3$: C 74.33%, H 4.46%. Found : C 74.13%, H 4.31%.

Elution with 20% ethyl acetate in hexane gave 3-methyl-benz[g]isoquinoline-5,10-dione **10a** (125 mg, 56%, R_f = 0.24) as a white powder, mp 173°C (from methanol). ^{1}H NMR ($CDCl_3$) : δ 2.78 (3H, s, CH_3), 7.82-7.88 (2H, m, H-7 and H-8), 7.89 (1H, s, H-4), 8.26-8.33 (2H, m, H-6 and H-9), 9.42 (1H, s, H-1). ^{13}C NMR ($CDCl_3$) : δ 25.18 (CH_3), 118.58 (C-4), 124.24 (=C_{quat}), 127.33 and 127.38 (C-6 and C-9), 133.15 (=C_{quat}), 133.21 (=C_{quat}), 134.46 and 135.02 (C-7 and C-8), 138.76 (=C_{quat}), 149.34 (C-1), 165.58 (=C_{quat}), 182.30 (C=O), 182.82 (C=O). IR (KBr) : ν_{max} 1680 (C=O), 1660 (C=O), 1585 (C=C) cm^{-1}. MS *m/z* (%) : 223 (M^+, 100), 222 (33), 195 (11), 167 (9), 166 (7), 140 (6), 139 (11), 126 (6), 77 (5), 76 (9), 75 (5), 70 (5), 63 (7), 50 (9). Anal. Calcd. for $C_{14}H_9NO_2$: C 75.33%, H 4.06%, N 6.27%. Found : C 75.52%, H 3.95%, N 6.06%.

The synthesis of 2-Acetonyl-3-phenoxymethyl-1,4-naphthoquinone (19a) is representative for the synthesis of 2-Acylated 3-phenoxymethyl-1,4-naphthoquinones (19). Under a N_2 atmosphere, a solution of 2-phenoxymethyl-1,4-naphthoquinone **17**[20] (1.9 mmol, 0.50 g) and 1-acetonylpyridinium chloride (1.9 mmol, 0.33g) in acetonitrile (50 ml) was heated at 50°C to dissolve all starting material. At the same temperature, a solution of triethylamine (1.9 mmol, 0.19 g) in acetonitrile (5 ml) was added dropwise and the reaction mixture was stirred for 16 h at room temperature. Then, the solvent was evaporated at reduced pressure and the residue was dissolved in ethyl acetate, washed with 2N hydrogen chloride and then with an aqueous saturated sodium hydrogen carbonate solution. Drying ($MgSO_4$) and evaporation of the solvent at reduced pressure gave 2-acetonyl-3-phenoxymethyl-1,4-naphthoquinone **19a** (0.58 g, 96%) which was pure enough (purity > 95%) to be used in the next step. An analytical sample was obtained as a white powder after recrystallisation from methanol, mp 74°C. ^{1}H NMR ($CDCl_3$) : δ 2.29 (3H, s, CH_3), 3.98 (2H, s, CH_2C=O), 5.09 (2H, s, CH_2O), 6.91-7.01 (3H, m, 3x =CH), 7.25-7.32 (2H, m, 2x =CH), 7.71-7.74 (2H, m, H-6 and H-7), 8.05-8.14 (2H, m, H-5 and H-8). ^{13}C NMR ($CDCl_3$) : δ 30.31 (CH_3), 41.51 (CH_2C=O), 61.13 (CH_2O), 114.57 (2x =CH), 121.62 (=CH), 126.59 and 126.68 (C-5 and C-8), 129.67 (2x =CH), 131.73 (=C_{quat}), 131.86 (=C_{quat}), 133.87 and 134.03 (C-6 and C-7), 142.06 (=C_{quat}), 144.56 (=C_{quat}), 158.02 (=C-O), 183.52 (C=O), 184.36 (C=O), 203.30 (C=O). IR (KBr) : ν_{max} 1660 (C=O), 1590 (C=C) cm^{-1}. MS *m/z* (%) : 320 (M^+, 9), 249 (8), 227 (36), 226 (51), 186 (11), 185 (79), 157 (13), 128 (13), 94 (79), 77 (13), 76 (12), 65 (8), 43 (100). Anal. Calcd. for $C_{20}H_{16}O_4$: C 74.99%, H 5.03%. Found : C 74.62%, H 4.81%.

3-Phenoxymethyl-2-phenacyl-1,4-naphthoquinone (19c)

Recrystallisation from methanol : yield 71%, mp 84.0-84.5°C. ^{1}H NMR ($CDCl_3$) : δ 4.57 (2H, s, CH_2C=O), 5.13 (2H, s, CH_2O), 6.82-7.02 and 7.19-7.63 (8H, m, 8x =CH), 7.71-7.82 (2H, m, H-6 and H-7), 8.00-8.08 (2H, m, 2x =CH), 8.09-8.18 (2H, m, H-5 and H-8). ^{13}C NMR ($CDCl_3$) : δ 36.80 ($\underline{C}H_2C$=O), 61.30 (CH_2O), 114.52 (2x =CH), 121.40 (=CH), 126.58 (C-5 and C-8), 128.28 (2x =CH), 128.64 (2x =CH), 129.45 (2x =CH), 131.77 (=C_{quat}), 131.84 (=C_{quat}), 133.42 (=CH), 133.75 (=CH), 133.89 (=CH), 136.35 (=C_{quat}), 142.25 (=C_{quat}), 145.14 (=C_{quat}), 157.92 (=C-O), 183.50 (C=O), 184.22 (C=O), 195.13 (C=O). IR (KBr) : ν_{max} 1660 (C=O), 1590 (C=O) cm^{-1}. MS *m/z* (%) : 382 (M^+, 7), 290 (6), 289 (20), 288 (42), 287 10), 284 (14), 264 (34), 248 (19), 247 (100), 235 (12), 231 (13), 171 (11), 143 (33), 115 (45), 105 (95), 104 (13), 94 (54), 89 (15), 77 (51), 76 (22), 66 (14), 65 (24), 63 (12), 51 (19), 50 (14). Anal. Calcd. for $C_{25}H_{18}O_4$: C 78.52%, H 4.74%. Found : C 78.18%, H 4.55%.

2-(4-Chlorophenacyl)-3-phenoxymethyl-1,4-naphthoquinone (19d)

Recrystallisation from ethyl acetate : yield 92%, mp 98.5-99.4°C. ^{1}H NMR ($CDCl_3$) : δ 4.50 (2H, s, CH_2C=O), 5.12 (2H, s, CH_2O), 6.81 (1H, d, J = 7.9 Hz, H-4"), 6.92-6.99 and 7.16-7.32 (each 2H, each m, H-2", H-3", H-5" and H-6"), 7.42 (2H, d, J = 8.4 Hz, H-3' and H-5'), 7.69-7.73 (2H, m, H-6 and H-7), 7.93 (2H, d, J = 8.4 Hz, H-2' and H-6'), 8.04-8.10 (2H, m, H-5 and H-8). ^{13}C NMR ($CDCl_3$) : δ 36.80 ($\underline{C}H_2C$=O), 61.37 (CH_2O), 114.50 (2x =CH), 121.53 (=CH), 126.63 and 126.66 (C-5 and C-8), 129.00 (2x =CH), 129.54 (2x =CH), 129.74 (2x =CH), 131.71 (=C_{quat}), 131.83 (=C_{quat}), 133.85 and 133.97 (C-6 and C-7), 134.73 (C_{quat}), 139.91 (=C_{quat}), 142.37 (=C_{quat}), 144.77 (=C_{quat}), 157.90 (=C-O), 183.47 (C=O), 184.18 (C=O), 194.01 (C=O). IR (KBr) : ν_{max} 1686, 1657, 1587, 1322, 1292, 1246, 753, 687 cm^{-1}. MS *m/z* (%) : no M^+, 101 (19), 86 (100). Anal. Calcd. for $C_{25}H_{17}O_4Cl$: C 72.03%, H 4.01%. Found : C 72.23%, H 3.81%.

2-(4-Fluorophenacyl)-3-phenoxymethyl-1,4-naphthoquinone (19e)

Recrystallisation from ethyl acetate : yield 83%, mp 116.-118°C. ^{1}H NMR ($CDCl_3$) : δ 4.53 (2H, s, CH_2C=O), 5.14 (2H, s, CH_2O), 6.82 (2H, d, J = 8.9 Hz, H-3' and H-5'), 6.94 (1H, t, J = 7.3 Hz, H-4"), 7.11-7.25 (4H, m, H-2", H-3", H-5"and H-6"), 7.70-7.78 (2H, m, H-6 and H-7), 8.04 (2H, dd, J = 8.9 Hz, 5.3 Hz, H-2' and H-6'). 8.08-8.17 (2H, m, H-5 and H-8). ^{13}C NMR ($CDCl_3$) : δ 36.75 ($\underline{C}H_2C$=O), 61.38 (CH_2O), 114.54 (2x =CH), 115.70 (=CH), 116.00 (=CH), 121.54 (=CH), 126.68 and 126.72 (C-5 and C-8), 129.56 (2x =CH), 130.96 (=CH), 131.10 (=CH), 131.80 (=C_{quat}), 131.93 (=C_{quat}), 132.85 (=C_{quat}), 132.88 (=C_{quat}),133.89 and 134.05 (C-6 and C-7), 142.41 (=C_{quat}), 144.40 (=C_{quat}), 157.73 (=C-O), 165.99 ($^1J_{CF}$ = 255 Hz, =CF), 183.56 (C=O), 184.31 (C=O), 193.65 (C=O). IR (KBr) : ν_{max} 1682, 1658, 1595, 1326, 1290, 1243, 1227, 838, 751 cm^{-1}. MS *m/z* (%) : 400 (M^+, 4), 306 (48), 123 (42), 94 (100). Anal. Calcd. for $C_{25}H_{17}O_4F$: C 74.99%, H 4.28%. Found : C 74.99%, H 4.21%.

2-(4-Methylphenacyl)-3-phenoxymethyl-1,4-naphthoquinone (19f)

Recrystallisation from ethyl acetate: yield 88%, mp 107-109°C. ^{1}H NMR ($CDCl_3$) : δ 2.43 (3H, s, CH_3), 4.55 (2H, s, CH_2C=O), 5.14 (2H, s, CH_2O), 6.86 (2H, d, J = 8.6 Hz, H-3' and H-5'), 6.94 (1H, t, J = 7.4 Hz, H-4"), 7.21-7.29 (4H, m, H-2", H-3", H-5" and H-6"), 7.71-7.76 (2H, m, H-6 and H-7), 7.93 (2H, d, J = 8.6 Hz, H-2' and H-6'), 8.07-8.17 (2H, m, H-5 and H-8). ^{13}C NMR ($CDCl_3$) : δ 21.69 (CH_3), 36.75 ($\underline{C}H_2C$=O), 61.35 (CH_2O), 114.61 (2x =CH), 121.44 (=CH), 126.65 (C-5 and C-8), 128.48 (2x =CH), 129.40 (2x =CH), 129.52 (2x =CH), 131.88 (=C_{quat}), 131.92 (=C_{quat}), 133.80 and 133.94 (C-6 and C-7), 142.24 (=C_{quat}), 144.36 (=C_{quat}), 145.42 (=C_{quat}), 158.04 (=C-O), 183.59 (C=O), 184.33 (C=O), 194.80 (C=O). IR (KBr) : ν_{max} 1662, 1627, 1592, 1494, 1323, 1290, 1244, 1180, 814, 755, 691 cm^{-1}. MS *m/z* (%) : 396 (M^+, 8), 302 (23), 119 (100), 94 (45), 91 (25). Anal. Calcd. for $C_{26}H_{20}O_4$: C 78.77%, H 5.08%. Found : C 78.42%, H 5.03%.

The 2-acylated 3-phenoxymethyl-1,4-naphthoquinones **19b, 19g** and **19h** could not be purified due to decomposition and they were used immediately in the next step.

The synthesis of 3-Methyl-benz[g]isoquinoline-5,10-dione (10a) from 2-Acetonyl-3-phenoxymethyl-1,4-naphthoquinone 19a is representative for the synthesis of 3-Alkyl- and 3-Aryl-benz[g]isoquinoline-5,10-diones (10). To a solution of 2-acetonyl-3-phenoxymethyl-1,4-naphthoquinone **19a** (1.5 mmol, 0.48 g) in ethanol (30 ml) was added dropwise a solution of aqueous ammonia (25% NH_3 in H_2O) (15 mmol, 1.02 g) in ethanol (5 ml). The solution was protected from light by aluminium foil and stirred for 2 days in an open vessel, allowing contact with the air. Then, most of the solvent was evaporated at reduced pressure and the resulting residue was dissolved in dichloromethane, washed with 1N hydrochloric acid and then with 2N sodium hydroxide. After drying ($MgSO_4$) and evaporation of the solvent at reduced pressure, 3-methyl benz[g]isoquinoline-5,10-dione **10a** (170 mg, 68%) was obtained as a white powder after recrystallisation from methanol. For spectrometric data of compound **10a**, vide supra.

3-*tert*-Butyl-benz[g]isoquinoline-5,10-dione (10b)

Flash chromatography (ethyl acetate/hexane 10/90, R_f = 0.19) : yield 73% as yellow needles, mp 98°C (from methanol). ^{1}H NMR ($CDCl_3$) : δ 1.47 (9H, s, $C(CH_3)_3$), 7.83-7.87 (2H, m, H-7 and H-8), 8.10 (1H, d, J = 0.7 Hz, H-4), 8.29-8.34 (2H, m, H-6 and H-9), 9.49 (1H, d, J = 0.7 Hz, H-1). ^{13}C NMR ($CDCl_3$) : δ 29.81 ($C(\underline{C}H_3)_3$), 38.58 ($\underline{C}(CH_3)_3$), 114.14 (C-4), 123.67 (=C_{quat}), 127.01 and 127.13 (C-6 and C-9), 133.03 (2x =C_{quat}), 134.16 and 134.69 (C-7 and C-8), 138.51 (=C_{quat}), 148.75 (C-1), 176.51 (C-3), 182.21 (C=O), 182.91 (C=O). IR (KBr) : ν_{max} 1670 (C=O), 1580 (C=C) cm^{-1}. MS *m/z* (%) : 265 (M^+, 34), 264 (16), 251 (17), 250 (100), 223 (29). Anal. Calcd. for $C_{17}H_{15}NO_2$: C 76.96%, H 5.70%, N 5.28%. Found : C 76.56%, H 5.59%, N 5.15%.

3-Phenyl-benz[g]isoquinoline-5,10-dione (10c)

Flash chromatography (chloroform, R_f = 0.33) : yield 79% as yellow needles, mp 199.7-201.6°C (from methanol). ^{1}H NMR ($CDCl_3$) : δ 7.52-7.58 (3H, m, H-3' and H-4' and H-5'), 7.85-7.89 (2H, m, H-7 and H-8), 8.20-8.23 (2H, m, H-2' and H-6'), 8.33-8.38 (2H, m, H-6 and H-9), 8.51 (1H, d, J = 0.7 Hz, H-4), 9.62 (1H, d, J = 0.7 Hz, H-1). ^{13}C NMR ($CDCl_3$) : δ 115.34 (C-4), 124.60 (=C_{quat}), 127.31 and 127.44 (C-6 and C-9), 127.60 (C-2' and C-6'), 129.09 (C-3' and C-5'), 130.74 (C-4'), 133.21 (=C_{quat}), 133.33 (=C_{quat}), 134.43 and 135.04 (C-7 and C-8), 137.66 (=C_{quat}), 139.26 (=C_{quat}), 150.02 (C-1), 162.84 (C-3), 182.30 (C=O), 182.82 (C=O). IR (KBr) : ν_{max} 1674, 1634, 1613, 1581, 1325, 1298, 1283, 711 cm^{-1}. MS *m/z* (%) : 285 (M^+, 100), 256 (8), 229 (7), 228 (12), 202 (7), 114 (8), 101 (11), 77 (6). Anal. Calcd. for $C_{19}H_{11}NO_2$: C 79.99%, H 3.89%, N 4.91%. Found : 79.68%, H 3.87%, N 4.56%.

3-(4-Chlorophenyl)-benz[g]isoquinoline-5,10-dione (10d)

Flash chromatography (ethyl acetate/hexane 10/90) : yield 90% as an orange powder, mp 213-214°C (from ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$) : δ 7.52 (2H, d, J = 8.9 Hz, H-3' and H-5'), 7.86-7.90 (2H, m, H-7 and H-8), 8.17 (2H, d, J = 8.3 Hz, H-2'and H-6'), 8.33-8.38 (2H, m, H-6 and H-9), 8.47 (1H, d, J = 0.7 Hz, H-4), 9.60 (1H, d, J = 0.7 Hz, H-1). ^{13}C NMR ($CDCl_3$) : δ 115.11 (C-4), 124.74 (=C_{quat}), 127.36 and 127.47 (C-6 and C-9), 128.83 (C-2' and C-6'), 129.43 (C-3' and C-5'), 133.15 (=C_{quat}), 133.29 (=C_{quat}), 134.49 and 135.11 (C-7 and C-8), 136.06 (=C_{quat}), 137.12 (=C_{quat}), 139.36 (=C_{quat}), 150.09 (C-1), 161.48 (C-3), 182.17 (C=O), 182.62 (C=O). IR (KBr) : ν_{max} 1667, 1587, 1551, 1584, 1488, 1408, 1372, 1265, 1130, 924, 843, 746, 702 cm^{-1}. MS *m/z* (%) : 319/21 (M^+, 100), 256 (10), 228 (7). Anal. Calcd. for $C_{19}H_{10}NO_2Cl$: C 71.37%, H 3.15%, N 4.38%. Found : C 71.23%, H 3.02%, N 4.58%.

3-(4-Fluorophenyl)-benz[g]isoquinoline-5,10-dione (10e)

Flash chromatography (ethyl acetate/hexane 10/90) : yield 92% as an orange powder, mp 199-202°C (from ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$) : δ 7.22 (2H, t, J = 8.9 Hz, H-3' and H-5'), 7.85-7.90 (2H, m, H-7 and H-8), 8.23 (2H, dd, J = 8.9 Hz, 5.3 Hz, H-2'and H-6'), 8.33-8.36 (2H, m, H-6 and H-9), 8.46 (1H, d, J = 0.7 Hz, H-4), 9.60 (1H, d, J = 0.7 Hz, H-1). ^{13}C NMR ($CDCl_3$) : δ 114.98 (C-4), 116.02 and 116.35 (C-2' and C-6'), 124.54 (=C_{quat}), 127.36 and 127.47 (C-6 and C-9), 129.59 and 129.73 (C-3' and C-5'), 133.20 (=C_{quat}), 133.34 (=C_{quat}), 133.92 (=C_{quat}), 134.48 and 135.11 (C-7 and C-8), 139.37 (=C_{quat}), 150.09 (C-1), 161.80 (C-3), 164.50 (d, $^1J_{CF}$ = 245 Hz, =CF), 182.26 (C=O), 182.80 (C=O). IR (KBr) : ν_{max} 1683, 1664, 1648, 1598, 1584, 1551, 1296, 1153, 925, 844 cm^{-1}. MS *m/z* (%) : 303 (M^+, 100), 274 (4), 75 (12). Anal. Calcd. for $C_{19}H_{10}NO_2F$: C 75.24%, H 3.22%, N 4.64%. Found : C 75.17%, H 3.23%, N 4.36%.

3-(4-Methylphenyl)-benz[g]isoquinoline-5,10-dione (10f)

Flash chromatography (ethyl acetate/hexane) : yield 90% as a yellow powder, mp 192-193°C (from ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$) : δ 2.44 (3H, s, CH_3), 7.34 (2H, d, J = 8.1 Hz, H-3' and H-5'), 7.83-7.88 (2H, m, H-7 and H-8), 8.11 (2H, d, J = 8.1 Hz, H-2' and H-6'), 8.33-8.34 (2H, m, H-6 and H-9), 8.46 (1H, d, J = 0.7 Hz, H-4), 9.58 (1H, d, J = 0.7 Hz, H-1). ^{13}C NMR ($CDCl_3$) : δ 21.43 (CH_3), 114.82 (C-4), 124.25 (=C_{quat}), 127.23 and 127.36 (C-6 and C-9), 127.45 (C-2' and C-6'), 129.80 (C-3' and C-5'), 133.16 (=C_{quat}), 133.31 (=C_{quat}), 134.80 (=C_{quat}), 134.31 and 134.93 (C-7 and C-8), 139.09 (=C_{quat}), 141.18 (=C_{quat}), 149.93 (C-1), 162.67 (C-3), 182.20 (C=O), 182.81 (C=O). IR (KBr) : ν_{max} 1666, 1636, 1613, 1584, 1544, 1326, 1284, 1129, 1039, 924, 820, 742, 704 cm^{-1}. MS *m/z* (%) : 299 (M^+, 100). Anal Calcd. for $C_{20}H_{13}NO_2$: C 80.25%, H 4.38%, N 4.68%. Found: C 79.86%, H 4.34%, N 4.30%.

3-(4-Methoxyphenyl)-benz[g]isoquinoline-5,10-dione (10g)

After flash chromatography (ethyl acetate/hexane 10/90), compound **10g** was further purified by extraction from ether with 12N hydrochloric acid. The organic phase was discarded and the aqueous phase was treated with 2N sodium hydroxide until pH 14 and extracted again with ether. After drying ($MgSO_4$) and evaporation at reduced pressure, the pure compound **10g** was obtained as a yellow powder in 70% yield, mp 199-200°C (from ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$) : δ 3.89 (3H, s, OCH_3), 7.04 (2H, d, J = 8.9 Hz, H-3' and H-5'), 7.83-7.88 (2H, m, H-7 and H-8), 8.18 (2H, d, J = 8.9 Hz, H-2'and H-6'), 8.31-8.36 (2H, m, H-6 and H-9), 8.41 (1H, d, J = 0.7 Hz, H-4), 9.55 (1H, d, J = 0.7 Hz, H-1). ^{13}C NMR ($CDCl_3$) : δ 55.47 (OMe), 114.34 (C-4), 114.50 (C-2' and C-6'), 123.95 (=C_{quat}), 127.27 and 127.40 (C-6 and C-9). 129.19 (C-3' and C-5'), 130.27 (=C_{quat}), 133.25 (=C_{quat}), 133.45 (=C_{quat}), 134.30 and 134.96 (C-7 and C-8), 139.17 (=C_{quat}), 150.02 (C-1), 161.99 and 162.42 (C-3 and C-4'), 182.26 (C=O), 182.98 (C=O). IR (KBr) : ν_{max} 1675, 1659, 1613, 1581, 1515, 1388, 1298, 1277, 1020, 959, 925, 830, 749 cm^{-1}. MS *m/z* (%) : 315 (M^+, 100), 300 (25), 272 (11). Anal. Calcd. for $C_{20}H_{13}NO_3$: C 76.18%, H 4.16%, N 4.44%. Found : C 75.98%, H 4.03%, N 4.36%.

3-(2,5-Dimethoxyphenyl)-benz[g]isoquinoline-5,10-dione (10h)

After flash chromatography (ethyl acetate/hexane 10/90), compound **10h** was further purified by extraction from ether with 12N hydrochloric acid. The organic phase was discarded and the aqueous phase was treated with 2N sodium hydroxide until pH 14 and extracted again with ether. After drying ($MgSO_4$) and evaporation at reduced pressure, the pure compound **10h** was obtained as red needles in 50% yield, mp 198-200°C (from ethyl acetate/hexane).

^{1}H NMR ($CDCl_3$) : δ 3.86 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 7.01 (2H, d, J = 2.4 Hz, H-3' and H-4'), 7.58 (1H, d, J = 2.4 Hz, H-6'), 7.82-7.90 (2H, m, H-7 and H-8), 8.31-8.37 (2H, m, H-6 and H-9), 8.73 (1H, s, H-4), 9.61 (1H, s, H-1). ^{13}C NMR ($CDCl_3$) : δ 55.86 (OMe), 56.20 (OMe), 112.90 and 117.71 (C-3'and C-4'), 115.57

(C-6'), 120.48 (C-4), 124.09 (=C_{quat}), 127.18 and 127.31 (C-6 and C-9), 127.63 (=C_{quat}), 133.29 (2x =C_{quat}), 134.33 and 134.84 (C-7 and C-8), 138.27 (=C_{quat}), 149.26 (C-1), 152.07 and 153.88 (C-2' and C-5'), 161.38 (C-3), 182.40 (C=O), 182.94 (C=O). IR (KBr) : ν_{max} 1669, 1657, 1578, 1567, 1487, 1447, 1291, 1180, 1048, 923, 892 cm^{-1}. MS *m/z* (%) : 345 (M^+, 100), 328 (30), 316 (36), 315 (12), 314 (24). Anal. Calcd. for $C_{21}H_{15}NO_4$: C 73.04%, H 4.38%, N 4.06%. Found : C 72.79%, H 4.35%, N 3.86%.

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