Synthesis of 1-Functionalized 5-Methylnaphtho[2,3-*g*]isoquinoline-6,11-quinones

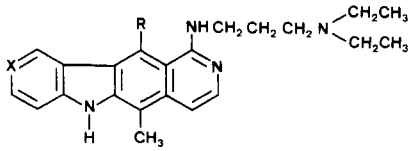
Martine Croisy-Delcey,† Marilys Rautureau,† Christiane Huel,‡ and Emile Bisagni*,†

UA 533 CNRS, Laboratoire de Synthèse Organique, and U 219 INSERM-Biophysique, Institut Curie, Section de Biologie, Bâtiments 110-112, 15, rue Georges Clêmenceau, 91405 Orsay, France

Received May 12, 1988

1-Chloro-5-methylnaphtho[2,3-*g*]isoquinoline-6,11-quinones were obtained through two independent pathways: (i) by Diels–Alder reaction of 1-chloro-5-methylbenzo[*g*]isoquinoline-6,9-quinone with 1,4-diacetoxybutadiene; (ii) by condensation of 2-formyl-1,4-dimethoxynaphthalenes with 4-acetyl-2-chloro-3-lithiopyridine ethylene glycol ketal and transformation of the resulting key intermediates by a reduction–hydrolysis–cyclization–demethylation–oxidation one-pot process. Whereas 1-substitution of 1-chloro-5-methylnaphtho[2,3-*g*]isoquinoline-6,11-quinone itself by amines took place cleanly, the corresponding 10-hydroxy derivative led to complex mixtures.

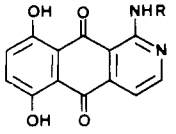
For the last few years, various studies in our laboratory have been devoted to the synthesis of antitumor drugs derived from polyheterocyclic systems and bearing a [(dialkylamino)alkyl]amino side chain.[1,2] These chains have been shown to increase strongly the antitumor properties of the corresponding unsubstituted compounds, as demonstrated by the potent activities of 1-[[3-(diethylamino)propyl]amino]-5,11-dimethyl-9-methoxy-6*H*-pyrido[4,3-*b*]carbazole (**1**, BD84),[3] which is now under clinical investigation, and 10-[[3-(diethylamino)propyl]amino]-6-methyl-5*H*-pyrido[3′,4′:4,5]pyrrolo[2,3-*g*]isoquinoline (**2**, BD40),[4] which has demonstrated high activity



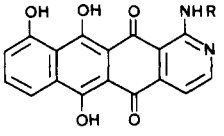
1 : R = CH_3 X = C-OCH_3

2 : R = H X = N

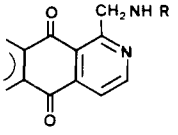
on numerous experimental tumors[5] as well as in various human cancers during phase I clinical trials.[6] We have also synthesized and screened various polycyclic quinones, which correspond to general formulas **3**, **4**,[7,8] and **5**,[9] respectively.



3



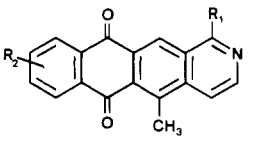
4



5

However, all these new products related to mitoxantrone, anthracyclinones, and mimocine were found inactive and our continuing interest in this area led us to design new target molecules related to both compounds **1–2** and **3–4**. Thus, maintaining the isoquinoline part of compounds **1** and **2** but replacing their indole (or 5-azaindole) nucleus by a quinone system resulted in the general structure **6**. In this paper, we describe the two ways that allowed us to prepare such polycyclic derivatives.

Cerium ammonium nitrate (CAN) oxidation of 1-chloro-5-methyl-6,9-dimethoxybenzo[*g*]isoquinoline **7**,[10] performed under the usual conditions,[11] led to the corresponding quinone **8** in 93% yield. Diels–Alder addition of 1,4-diacetoxybutadiene[12] to this quinone and subsequent elimination of acetoxy groups gave 1-chloro-5-methylnaphtho[2,3-*g*]isoquinoline-6,11-quinone **9**, which reacted with primary amines to provide the corresponding 1-amino derivatives **10** with a 31.5% overall yield. These amines were also obtained in the opposite sequence of steps (Scheme I), with a 36% overall yield.



6

However, applying this pathway to unsymmetrical dienes would probably give the two possible isomers, difficult to separate. In order to easily obtain specifically A ring substituted derivatives, another route to such compounds was then worked out, starting from 2-formyl-1,4-dimethoxynaphthalenes **13**.

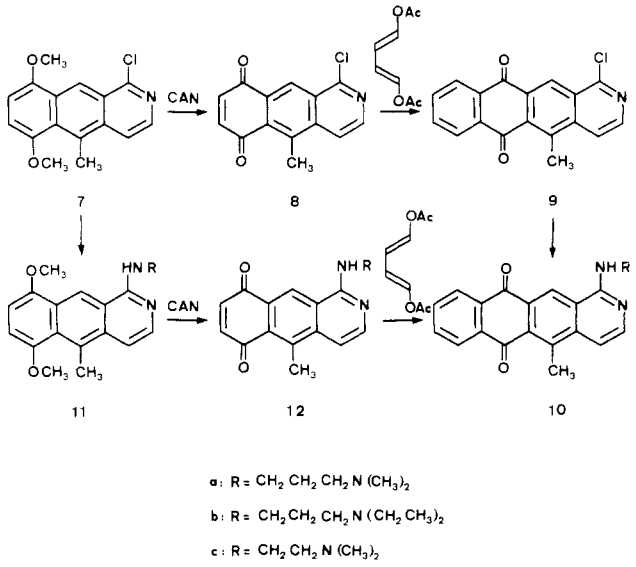
Thus, reaction of 1,4-dimethoxy-2-naphthaldehyde (**13a**)[13] with 4-acetyl-2-chloro-3-lithiopyridine ethylene glycol ketal **14**[10] afforded 4-acetyl-2-chloro-3-[hydroxy-[2-(1,4-dimethoxynaphthyl)]methyl]pyridine ethylene glycol ketal (**15a**). Reduction of this alcohol by triethyl-

* To whom correspondance should be adressed.
† UA 533 CNRS, Laboratoire de Synthèse Organique.
‡ U 219 INSERM-Biophysique.

(1) Ducrocq, C.; Bisagni, E.; Rivalle, C.; Lhoste, J.-M., *J. Chem. Soc., Perkin Trans. 1* **1979**, 142.
(2) Bisagni, E.; Ducrocq, C.; Lhoste J.-M.; Rivalle, C.; Civier, A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1706.
(3) Ducrocq, C.; Wendling, F.; Tourbez-Perrin, M.; Rivalle, C.; Tambourin, P.; Pochon, F.; Bisagni, E.; Chermann, J. C. *J. Med. Chem.* **1980**, *23*, 1212.
(4) Chermann, J. C.; Gruest, J.; Montagnier, L.; Wendling, F.; Tambourin, P.; Perrin, M.; Pochon, F.; Ducrocq, C.; Rivalle, C.; Bisagni, E. *C. R. Acad. Sci. Ser. D* **1977**, *285*, 945.
(5) Lidereau, R.; Chermann, J. C.; Gruest, J.; Montagnier, L.; Ducrocq, C.; Rivalle, C.; Bisagni, E. *Bull. Cancer* **1980**, *67*, 1.
(6) Marty, M.; Jasmin, C.; Pouillart, P.; Gisselbrecht, C.; Gouvenia, G.; Magdelainat, H. 17th Annual Meeting of the American Society of Clinical Oncology 1981, C-108.
(7) Croisy-Delcey, M.; Bisagni, E. *J. Chem. Soc., Chem. Commun.* **1984**, 897.
(8) Croisy-Delcey, M.; Carrez, D.; Bisagni, E. *Eur. J. Med. Chem.* **1988**, *23*, 101.
(9) Croisy-Delcey, M.; Huel, C.; Bisagni, E. *J. Heterocycl. Chem.* **1988**, *22*, 661.
(10) Bisagni, E.; Rautureau, M.; Croisy-Delcey, M.; Huel, C. *Can. J. Chem.* **1987**, *65*, 2027.
(11) Kubo, A.; Kitahara, Y.; Nakahara, S., Numaka, R. *Chem. Pharm. Bull.* **1983**, *31*, 341.
(12) Echavarren, A.; Prados, P.; Del Sol, G.; Farina, F. *J. Chem. Res.* **1981**, 3675.
(13) Watanabe, M.; Maenosono, H.; Furukawa, S. *Chem. Pharm. Bull.* **1983**, *31*, 2662.

0022-3263/88/1953-5301$01.50/0

Scheme I



silane–trifluoroacetic acid mixture[14] followed by aqueous acidic treatment led directly to the corresponding quinone **9**, in a 36.5% overall yield. Accordingly, starting from 1,4,8-trimethoxy-2-naphthaldehyde (**13b**),[15] alcohol **15b**, and then 1-chloro-5-methyl-10-methoxynaphtho[2,3-*g*]-isoquinoline-6,11-quinone **16**, were obtained (24% for **15b** → **16**). The presumed intermediates in these transformations are shown in Scheme II.

Quenching the triethylsilane–trifluoroacetic acid reduction of alcohol **15b** with aqueous sodium carbonate led to ketal **17b**, which in aqueous sulfuric acid at 50 °C for 4 h gave naphthoisoquinoline-6,11-quinone **16** as the major product. Moreover, when the reaction was performed at 80 °C for 3 h, the corresponding 10-hydroxy derivative **22** was obtained in 30% overall yield.

Attempts to substitute chloroquinones **16** and **22** by primary amines, performed under various conditions, resulted in complex mixtures, from which no pure compound can be isolated. As we have already reported for hydroxylated and methoxylated 1-chloro-5-methyl-5*H*-pyrido[4,3-*b*]benzo[*f*]indole-6,11-quinones,[16] these results can be explained by substitution of hydroxy or methoxy groups.

However, refluxing of uncyclized compound **17b** with 3-(diethylamino)propylamine did lead to crude compound **23** plus recovered starting material (Scheme III). Hydrolysis of **23** (50% H_2SO_4) led to **24** in 17% yield by the transformations summarized in Scheme II. Finally, boron tribromide in methylene chloride afforded 65% of the corresponding 10-hydroxy-5-methylnaphtho[2,3-*g*]isoquinoline-6,11-quinone **25**. Although the overall yield of compound **24** is low, the sequence **17b** → **24** includes six transformations: substitution, hydrolysis, cyclization, dehydration, demethylation, oxidation (median yield = 75% for each step), and the method is a convenient one for the preparation of defined A ring substituted derivatives of 1-[[(dialkylamino)alkyl]amino]-5-methylnaphtho[2,3-*g*]isoquinoline-6,11-quinones.

Cytotoxicity and antitumoral activity of compounds **10a–c** and **25** were screened following the usual NCI Protocols by F. Lavelle, Société Rhône Poulenc Santé, Vitry-sur-Seine (L1210 cultured cells and P388 leukemia system). No interesting biological property was detected for these compounds.

Experimental Section

All melting points (uncorrected) were determined with a Kofler apparatus. ^{1}H NMR spectra were recorded with a Varian XL100 spectrometer. Me_4Si was used as internal standard, and chemical shifts are reported on the δ scale, with peak multiplicities. Elemental analysis were performed by Service Central de Microanalyses du CNRS (91190 Gif-sur-Yvette, France).

1-Chloro-5-methylbenzo[*g*]isoquinoline-6,9-quinone (8). A solution of cerium ammonium nitrate (CAN, 4.76 g, 8.68 mmol) in acetonitrile–water (1:1, 20 mL) was added dropwise to a stirred ice-cooled suspension of compound **7**[10] (1 g, 3.48 mmol) in acetonitrile (400 mL) containing a solution of pyridine-2,6-dicarboxylic acid *N*-oxide (1.6 g, 8.74 mmol) in acetonitrile–water (2:1, 45 mL). After completion of addition and removal of the cooling bath, the mixture was stirred for an additional 20-min period below 20 °C and then diluted with water and extracted with chloroform (3 × 100 mL). The combined extract was washed with brine until obtention of a colorless aqueous solution, and the organic layer was dried over magnesium sulfate and evaporated. The residue was taken up in hexane (10 mL) to give the crude quinone (850 mg, 93%), which was sufficiently pure to be used in the subsequent reaction. Flash chromatography on silica gel, eluting with methylene chloride, afforded yellow needles, mp 208 °C, which rapidly turned brown. ^{1}H NMR ($CDCl_3$): δ 3.21 (s, 3 H, 5-CH_3), 7.08 (s, 2 H, 7-H + 8-H), 8.04 (dd, 1 H, 4-H, J_{4-3} = 6 Hz), 8.5 (d, 1 H, 3-H), 9.05 (d, 1 H, 10-H, J_{10-4} = 0.8 Hz).

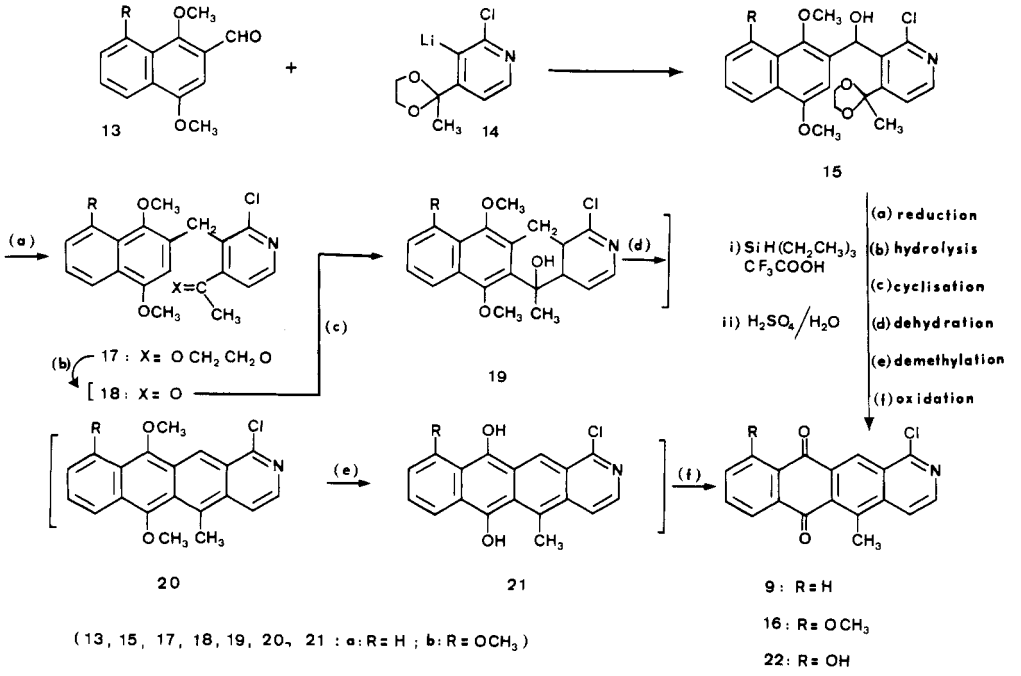
1-Chloro-5-methylnaphtho[2,3-*g*]isoquinoline-6,11-quinone (9). Method A. The crude quinone **8** (0.8 g, 3.1 mmol) and *trans,trans*-1,4-diacetoxybutadiene (0.640 g, 3.72 mmol) were dissolved in toluene–dimethylformamide (7:3, 50 mL). The mixture was stirred in a sealed flask for a 10-day period at ambient temperature and a further day in the presence of air. After evaporation of the solvent, the residue was taken up in toluene to give 420 mg (44%) of yellow needles, mp 262 °C. ^{1}H NMR ($CDCl_3$): δ 3.22 (s, 3 H, CH_3), 7.84 (m, 2 H, 7-H + 10-H), 8.08 (dd, 1 H, 4-H, J_{4-12} = 1 Hz), 8.35 (m, 2 H, 8-H + 9-H), 8.52 (d, 1 H, 3-H, J_{3-4} = 6 Hz), 9.33 (d, 1 H, 12-H). Anal. Calcd for $C_{18}H_{10}ClNO_2$: C, 70.24; H, 3.25; N, 4.55. Found: C, 70.52; H, 3.56; N, 4.74.

Method B. Alcohol **15** (4.15 g, 10 mmol) was mixed with triethylsilane (3.2 mL, 20 mmol), and while the temperature was maintained below 20 °C, trifluoroacetic acid (20 mL) was added dropwise, with stirring. After a further 5-h period with stirring at ambient temperature, the mixture was evaporated to dryness under reduced pressure, and water (10 mL) and then sulfuric acid (40 mL, d = 1.86) were successively added to the residue. The resulting new mixture was heated at 55–60 °C with stirring for 6 h and poured in ice–water. The precipitate was filtered, taken up in cold aqueous ammonia, and extracted with methylene chloride. The residue obtained after evaporation of solvent was chromatographed on silica gel, with methylene chloride as eluent. Evaporation and subsequent recrystallization of the residue (toluene) gave 1.12 g (36%) of yellow needles, mp 261–262 °C. This compound was identical (^{1}H NMR, R_f) with that obtained by method A.

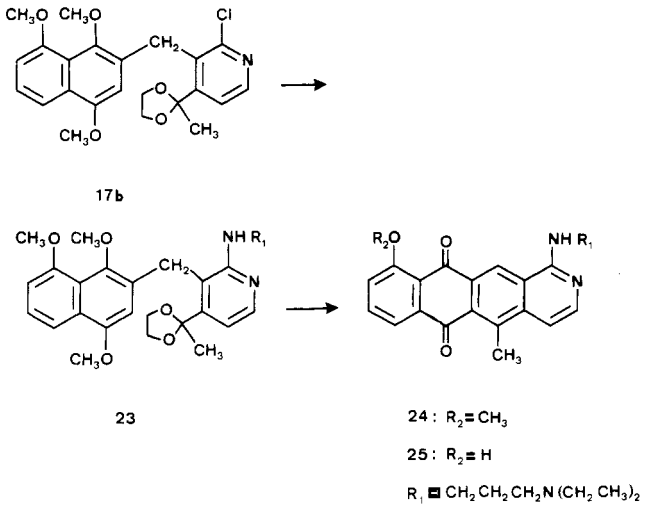
1-[[3-(Dimethylamino)propyl]amino]-5-methyl-6,9-dimethoxybenzo[*g*]isoquinoline (11a). 1-Chloro-5-methyl-6,9-dimethoxybenzo[*g*]isoquinoline **7**[10] (500 mg, 1.74 mmol) was heated at reflux (150 °C) in 3-(dimethylamino)propylamine (15 mL) for 4 h, and excess amine was evaporated in vacuo. After addition of 3 N sodium hydroxide (50 mL), the amino-substituted derivative was extracted with methylene chloride (3 × 50 mL), and solvent was evaporated. The crude oily residue was dissolved in boiling acetone (50 mL), filtered, and added at once to a solution of maleic acid (605 mg, 5.22 mmol) in acetone (50 mL). The resulting precipitate was collected, taken up in boiling acetone (60 mL), and filtered to give 950 mg (93.4%) of the dimaleate of the title compound as pale yellow microcrystals, mp 220 °C. ^{1}H NMR (D_2O): δ 2.28 (m, 2 H, β-CH_2), 2.6 (s, 3 H, 5-CH_3), 3.02 (s, 2 × 3 H, $N(CH_3)_2$), 3.4 (m, 2 H, γ-CH_2), 3.6 (m, 2 H, α-CH_2),

(14) Kursanow, D. N.; Parnes, Z. N.; Louin, N. M. *Synthesis* **1974**, 633.
(15) Keude, A. S.; Gesson, J. P.; Demuth, T. P. *Tetrahedron Lett.* **1981**, *22*, 1667.
(16) Robaut, C.; Rivalle, C.; Rautureau, M.; Lhoste, J.-M.; Bisagni, E.; Chermann, J. C. *Tetrahedron* **1985**, *41*, 1945.

Scheme II



Scheme III



3.86 + 3.98 (2 s, 2 × 3 H, 6-OCH_3 + 9-OCH_3), 6.12 (s, 4 H, 2 × CH=CH maleate), 6.66 + 6.83 (2 d, 2 H, 7-H + 8-H, J_{7-8} = 8.5 Hz), 6.98 (d, 1 H, 4-H, J_{4-3} = 6.1 Hz), 7.11 (d, 1 H, 3-H), 8.3 (s, 1 H, 10-H). Anal. Calcd for $C_{29}H_{25}N_3O_{10}$: C, 59.48; H, 6.03; N, 7.18. Found: C, 59.10; H, 5.98; N, 7.23.

1-[[3-(Diethylamino)propyl]amino]-5-methyl-6,9-dimethoxybenzo[g]isoquinoline (11b). As mentioned above for obtaining **11a** but with 3-(diethylamino)propylamine, the dimaleate salt of **11b** was obtained in a 68% yield, mp 205 °C. ^{1}H NMR (D_2O): δ 1.38 (t, 2 × 3 H, $(CH_2CH_3)_2$), 2.3 (m, 2 H, β-CH_2), 2.74 (s, 3 H, 5-CH_3), 3.38 (m, 3 × 2 H, $(CH_2CH_3)_2$ + γ-CH_2), 3.65 (t, 2 H, α-CH_2), 3.91 + 4.02 (2 s, 2 × 3 H, 6-OCH_3 + 9-OCH_3), 6.15 (s, 4 H, 2 × CH=CH maleate), 6.76 + 6.93 (2 d, 2 H, 7-H + 8-H, J_{7-8} = 8.5 Hz), 7.14 (d, 1 H, 4-H), 7.22 (d, 1 H, 3-H), 8.42 (s, 1 H, 10-H). Anal. Calcd for $C_{31}H_{39}N_3O_{10}$: C, 60.67; H, 6.41; N, 6.85. Found: 60.54; H, 6.47; N, 6.98.

1-[[3-(Dimethylamino)propyl]amino]-5-methylbenzo[g]isoquinoline-6,9-quinone (12a). Oxidation of **11a** (260 mg, 0.68 mmol) in acetonitrile (20 mL) was performed as for obtention of chloroquinone **8**, with pyridine-2,6-dicarboxylic acid *N*-oxide (304 mg, 1.66 mmol) in acetonitrile–water (2:1, 7 mL) and dropwise addition of CAN (901 mg, 1.63 mmol) in acetonitrile–water (1:1, 4 mL) at 0 °C with stirring. Stirring was continued for 10 min at 0 °C and 10 min further without cooling. The mixture was poured in water, basified with ammonia, and extracted (3 × 20 mL) with chloroform. The organic layer was washed with brine, dried over sodium sulfate, and evaporated, and the residue was recrystallized from cyclohexane to afford 170 mg (71.5%) of red needles, mp 148 °C. ^{1}H NMR ($CDCl_3$): δ 1.90 (m, 2 H, β-CH_2), 2.5 (s, 2 × 3 H, $N(CH_3)_2$), 2.66 (m, 2 H, γ-CH_2), 2.99 (s, 3 H, 5-CH_3), 3.70 (m, 2 H, α-CH_2), 6.98 (s, 2 H, 6-H + 7-H), 7.15 (dd, 1 H, 4-H, J_{4-10} = 0.8 Hz), 8.18 (d, 1 H, 3-H, J_{3-4} = 6.2 Hz), 8.55 (s, 1 H, 10-H), 9.26 (br s, 1 H, NH). Anal. Calcd for $C_{19}H_{21}N_3O_2$: C, 70.56; H, 6.55; N, 13.00. Found: C, 70.30; H, 6.47; N, 12.71.

1-[[3-(Diethylamino)propyl]amino]-5-methylbenzo[g]isoquinoline-6,9-quinone (12b). Use the above mentioned technique but starting from **11b**, **12b** (red needles, mp 136 °C) was obtained in 47% yield. ^{1}H NMR ($CDCl_3$): δ 1.16 (t, 2 × 3 H, $(CH_2CH_3)_2$), 1.91 (m, 2 H, β-CH_2), 2.80 (m, 3 × 2 H, γ-CH_2 + $(CH_2CH_3)_2$), 2.99 (s, 3 H, 5-CH_3), 3.73 (m, 2 H, α-CH_2), 6.98 (s, 2 H, 6-H + 7-H), 7.16 (dd, 1 H, 4-H, J_{4-10} = 1 Hz), 8.19 (d, 1 H, 3-H, J_{3-4} = 6.2 Hz), 8.59 (s, 1 H, 10-H), 9.17 (br s, 1 H, NH). Anal. Calcd for $C_{21}H_{25}N_3O_2 \cdot 0.33H_2O$: C, 70.56; H, 7.23; N, 11.75. Found: C, 70.57; H, 7.12; N, 12.17.

1-[[3-(Dimethylamino)propyl]amino]-5-methylnaphtho[2,3-g]isoquinoline-6,11-quinone (10a). Method A. Chloroquinone **9** (307 mg, 1 mmol) was heated in 3-(dimethylamino)-propylamine (10 mL) at 100 °C for 6 h. The cooled mixture was poured in water (100 mL) and allowed to stand at room temperature for 18 h. The resulting solid was filtered, air-dried, and recrystallized from cyclohexane to give 286 mg (77%) of red needles, mp 172 °C. ^{1}H NMR ($CDCl_3$): δ 1.92 (m, 2 H, β-CH_2), 2.55 (s, 2 × 3 H, $N(CH_3)_2$), 2.66 (m, 2 H, γ-CH_2), 3.08 (s, 3 H, 5-CH_3), 3.74 (m, 2 H, α-CH_2), 7.18 (dd, 1 H, 4-H, J_{4-3} = 6.3 Hz, J_{4-12} = 0.7 Hz), 7.78 (m, 2 H, 8-H + 9-H), 8.18 (d, 1 H, 3-H), 8.32 (m, 2 H, 7-H + 10-H), 8.80 (d, 1 H, 12-H), 9.25 (br s, 1 H, NH). Anal. Calcd for $C_{23}H_{23}N_3O_2$: C, 73.97; H, 6.21; N, 11.25. Found: C, 74.17; H, 6.41; N, 10.97.

1-[[3-(Diethylamino)propyl]amino]-5-methylnaphtho[2,3-g]isoquinoline-6,11-quinone (10b). A solution of quinone **12b** (40 mg, 0.114 mmol) and 1,4-diacetoxybutadiene (22 mg, 0.13 mmol) in toluene (2.5 mL) was stirred at room temperature for 15 days. Then, evaporation of toluene, addition of water, basification with *N*-sodium hydroxide solution, chloroform extraction, and evaporation of solvent gave a residue, which was chromatographed on alumina, eluting with chloroform. The fractions were evaporated, and recrystallization of the residue from cyclohexane gave 25 mg (55%) of red needles, mp 138 °C. ^{1}H NMR ($CDCl_3$): δ 1.21 (t, 2 × 3 H, $(CH_2CH_3)_2$), 1.96 (m, 2 H, β-CH_2), 2.86 (m, 3 × 2 H $(CH_2CH_3)_2$ + γ-CH_2), 3.07 (s, 3 H, 5-CH_3), 3.75 (m, 2 H, α-CH_2), 7.19 (dd, 1 H, 4-H, J_{4-12} = 1 Hz), 7.78 (m, 2 H, 7-H + 10-H), 8.18 (d, 1 H, 3-H, J_{3-4} = 6.5 Hz), 8.31 (m, 2 H, 8-H + 9-H), 8.84 (s, 1 H, 12-H), 8.96 (br s, 1 H, NH). Anal. Calcd for

$C_{25}H_{27}N_3O_2$: C, 74.78; H, 6.78; N, 10.47. Found: C, 74.81; H, 6.81; N, 10.25.

1-[[2-(Dimethylamino)ethyl]amino]-5-methylnaphtho[2,3-*g*]isoquinoline-6,11-quinone (10c). By substitution of chloroquinone **9** with 2-(dimethylamino)ethylamine at 120 °C for 2 h and treatment according to method A described for obtention of its analogue **10a**, **10c** was obtained in 66% yield: red needles (cyclohexane), mp 190 °C. ^{1}H NMR ($CDCl_3$): δ 2.49 (s, 2 × 3 H, $N(CH_3)_2$), 2.84 (t, 2 H, β-CH_2), 3.06 (s, 3 H, 5-CH_3), 3.78 (m, 2 H, α-CH_2), 7.23 (d, 1 H, 4-H), 7.75–7.85 (m, 2 H, 8-H + 9-H), 8.13 (d, 1 H, 3-H, J_{3-4} = 6.1 Hz), 8.25–8.31 (m, 2 H, 7-H + 10-H), 8.88 (s, 1 H, 12-H). Anal. Calcd for $C_{22}H_{21}N_3O_2$: C, 73.51; H, 5.89; N, 11.69. Found: C, 73.53; H, 5.96; N, 11.49.

4-Acetyl-2-chloro-3-[hydroxy[2-(1,4-dimethoxynaphthyl)]methyl]pyridine Ethylene Glycol Ketal (15a). Dry tetrahydrofuran (100 mL) was introduced in a moisture-protected three-necked flask, and after cooling at 0 °C, *n*-butyllithium (15 mL of a 1.6 N solution in hexane, 24 mmol) and then diisopropylamine (3.36 mL, 24 mmol) were successively added, with stirring. The mixture was stirred for 1 h further, cooled at −70 °C, and 4-acetyl-2-chloropyridine ethylene glycol ketal (4 g, 20 mmol) was added at once. The mixture progressively turned to orange yellow, and a slurry appeared. After 4 h at −70 °C, finely powdered aldehyde **13a**[13] (4.32 g, 20 mmol) was added, stirring was pursued for 1 h at −70 °C and then for 15 h at ambient temperature, and the resulting heterogeneous mixture was poured in water. Extraction with methylene chloride and evaporation of solvent gave a residue, which was crystallized in hexane. The collected solid was recrystallized from ethyl acetate to afford 4.81 g (57.9%) of colorless crystals, mp 224 °C. ^{1}H NMR ($CDCl_3$): δ 1.80 (s, 3 H, CH_3), 3.77 + 3.84 (2 s, 1′-OCH_3 + 4′-OCH_3), 3.66–4.12 (m, 2 × 2 H, CH_2CH_2), 4.58 (d, 1 H, OH, J_{OH-H} = 8.7 Hz), 6.58 (s, 1 H, 3′-H), 6.99 (d, 1 H, C*H*OH), 7.52 (m, 2 H, 6′-H + 7′-H), 7.62 (d, 1 H, 5-H, J_{5-6} = 5.1 Hz), 8.12 (m, 2 H, 5′-H + 8′-H), 8.36 (d, 1 H, 6-H). Anal. Calcd for $C_{22}H_{22}ClNO_5$: C, 63.53; H, 5.29; N, 3.36; Cl, 8.54. Found: C, 63.81; H, 5.37; N, 3.57; Cl, 8.87.

4-Acetyl-2-chloro-3-[hydroxy[2-(1,4,8-trimethoxynaphthyl)]methyl]pyridine Ethylene Glycol Ketal (15b). According to the preceding technique but starting from 1,4,8-trimethoxy-2-naphthaldehyde **13b**,[15] **15b** was obtained in 65% yield. It was recrystallized from cyclohexane, giving colorless crystals, mp 188 °C. ^{1}H NMR ($CDCl_3$): δ 1.80 (s, 3 H, CH_3), 3.71 + 3.80 + 3.99 (3 s, 3 × 3 H, 1′ + 4′ + 8′-(OCH_3)), 3.68–4.05 (m, 2 × 2 H, CH_2CH_2), 4.62 (d, 1 H, OH, J_{OH-H} = 8 Hz), 6.57 (s, 1 H, 3′-H), 6.93 (dd, 1 H, 7′-H), $J_{7'-6'}$ = 8.5 Hz, $J_{7'-5'}$ = 1 Hz), 7.02 (d, 1 H, C*H*OH), 7.38 (t, 1 H, 6′-H), 7.61 (d, 1 H, 5-H, J_{5-6} = 5 Hz), 7.85 (dd, 1 H, 5′-H, $J_{5'-6'}$ = 8.2 Hz), 8.35 (d, 1 H, 6-H). Anal. Calcd for $C_{23}H_{24}ClNO_6$: C, 61.95; H, 5.43; N, 3.14; Cl, 7.95. Found: C, 61.81; H, 5.38; N, 3.37; Cl, 7.85.

1-Chloro-5-methyl-10-methoxynaphtho[2,3-*g*]isoquinoline-6,11-quinone (16). By use of method B described for obtention of chloroquinone **9** but by starting from alcohol **15b**, this compound was obtained with a 24% overall yield. It was recrystallized from toluene, giving orange microcrystals, mp 309 °C. ^{1}H NMR ($CDCl_3$): δ 3.14 (s, 3 H, 5-CH_3), 4.08 (s, 3 H, OCH_3), 7.34 (dd, 1 H, 9-H, J_{9-8} = 8 Hz, J_{9-7} = 0.5 Hz), 7.74 (t, 1 H, 8-H), 7.92 (dd, 1 H, 7-H, J_{7-8} = 8 Hz), 8.02 (dd, 1 H, 4-H, J_{4-3} = 6.1 Hz, J_{4-12} = 1 Hz), 8.47 (d, 1 H, 3-H), 9.22 (d, 1 H, 12 H). Anal. Calcd for $C_{19}H_{12}ClNO_3$: C, 67.55; H, 3.55; N, 4.14; Cl, 10.51. Found: C, 67.48; H, 3.82; N, 3.81; Cl, 10.24. *Remark*: chromatography of **16** was performed on a silica gel column, eluting with methylene chloride. Beside **16**, a less mobile compound was isolated (1.1%, mp 261 °C), which corresponded to hydroxy quinone **22**.

4-Acetyl-2-chloro-3-[[2-(1,4,8-trimethoxynaphthyl)]methyl]pyridine Ethylene Glycol Ketal (17b). To the mixture of alcohol **15b** (891 mg, 2 mmol) and triethylsilane (0.36 mL, 2.2 mmol) was added trifluoroacetic acid (4 mL) dropwise, maintaining temperature at +5 °C. One hour later, the mixture was poured in water, alcalinized with solid potassium carbonate, and extracted with methylene chloride. After evaporation, the residue was chromatographed on silica gel, with methylene chloride as eluent. The pure fractions were evaporated, and the solid residue was recrystallized from hexane, to give 575 mg (67%) of colorless microcrystals, mp 150 °C. ^{1}H NMR ($CDCl_3$): δ 1.60 (s, 3 H, CH_3), 3.66 + 3.94 + 4.04 (3 s, 3 × 3 H, 1′ + 4′ + 8′-(OCH_3), 3.57–4.05 (m, 2 × 2 H, CH_2CH_2), 4.70 (s, 2 H, CH_2), 5.95 (s, 1 H, 3′-H), 6.92 (dd, 1 H, 7′-H, $J_{7'-6'}$ = 7.5 Hz, $J_{7'-5'}$ = 1 Hz), 7.34 (t, 1 H, 6′-H), 7.60 (d, 1 H, 5-H, J_{5-6} = 5 Hz), 7.81 (dd, 1 H, 5′-H, $J_{5'-6'}$ = 8.4 Hz), 8.36 (d, 1 H, 6-H). Anal. Calcd for $C_{23}H_{24}ClNO_5$: C, 64.26; H, 5.58; N, 3.25; Cl, 8.26. Found: C, 64.25; H, 5.60; N, 3.41; Cl, 8.43.

1-Chloro-5-methyl-10-hydroxynaphtho[2,3-*g*]isoquinoline-6,11-quinone (22). Method A. The preceding ketal **17b** (200 mg) was suspended in water (1.5 mL), and sulfuric acid (*d* = 1.86, 5 mL) was added dropwise without cooling. The temperature, which reached 80 °C, was maintained for 3 h further with stirring, and the mixture was poured in water and then alcalinized with ammonia. The resulting solid was filtered, air-dried, and chromatographed on silica gel, with methylene chloride as eluent. Evaporation of solvent afforded a solid residue, which was recrystallized from toluene to give 45 mg (30%) of yellow needles, mp 261 °C. ^{1}H NMR ($CD_3)_2SO$): δ 3.6 (s, 3 H, 5-CH_3), 7.47 (dd, 1 H, 9-H, J_{9-8} = 8 Hz, J_{9-7} = 0.5 Hz), 7.81 (m, 1 H, 8-H), 7.94 (d, 1 H, 7-H), 8.40 (d, 1 H, 4-H, J_{4-3} = 6.1 Hz), 8.64 (d, 1 H, 3-H), 9.09 (s, 1 H, 12-H), 12.31 (s, 1 H, OH). Anal. Calcd for $C_{18}H_{10}ClNO_3$: C, 66.78; H, 3.11; N, 4.53. Found: C, 66.50; H, 3.10; N, 4.27.

Method B. A solution of methoxy quinone **16** (102 mg, 0.3 mmol) in dry methylene chloride (25 mL) was cooled at −70 °C, and boron trichloride (1.2 mL of a 1 N solution in dichloromethane, 1.2 mmol) was added at once. The mixture was stirred at −70 °C for 3 h and at −40 °C for a further 3-h period. After conventional treatment and chromatography as above mentioned, pure hydroxy quinone **22**, mp 261 °C, was obtained (49 mg, 50%) beside a fraction (40 mg) of the mixture **16** + **22**.

1-[[3-(Diethylamino)propyl]amino]-5-methyl-10-methoxynaphtho[2,3-*g*]isoquinoline-6,11-quinone (24). The mixture of compound **17b** (480 mg) and 3-(diethylamino)propylamine (10 mL) was heated at reflux in an oil bath at 190 °C for a 85-h period, and the excess of amine was evaporated under reduced pressure.

The residue was taken up in methylene chloride and chromatographed on silica gel column, eluting with methylene chloride for elimination of starting material (80 mg, 16.6%). Eluting the column with ethanol–triethylamine mixture (97/3, v/v) and evaporation of solvent afforded an oily residue of **23** (not pure, TLC, Al_2O_3 and SiO_2). It was treated with aqueous sulfuric acid (10 mL, 50%, v/v) and the mixture was heated at 60 °C for 4 h. The mixture was then poured in water (75 mL), alcalinized with potassium carbonate, and extracted with methylene chloride. The solid residue from solvent evaporation was chromatographed on silica gel, eluting with methanol. Evaporation of the fractions provided a solid, which was recrystallized from cyclohexane to give orange red crystals (80 mg, 16.5%), mp 138 °C. Anal. Calcd for $C_{26}H_{29}N_3O_3{\cdot}H_2O$: C, 69.46; H, 6.95; N, 9.35; Cl, 14.24. Found: C, 69.60; H, 6.65; N, 9.35; Cl, 14.24. ^{1}H NMR ($CDCl_3$): δ 1.24 (t, 2 × 3 H, $(CH_3CH_2)_2$), 2.05 (m, 2 H, β-CH_2), 2.92 (m, 3 × 2 H, $(CH_3CH_2)_2$ + γ-CH_2), 3.02 (s, 3 H, 5-CH_3), 3.78 (m, 2 H, α-CH_2), 4.04 (s, 3 H, OCH_3), 7.19 (dd, 1 H, 4-H, J_{4-3} = 6.3 Hz; J_{4-12} = 0.8 Hz), 7.3 (dd, 1 H, 9-H, J_{9-8} = 8.2 Hz, J_{9-7} = 1.2 Hz), 7.71 (dd, 1 H, 8-H, J_{8-7} = 7.5 Hz), 7.91 (dd, 1 H, 7-H), 8.15 (d, 1 H, 3-H), 8.74 (br s, 2 H, 12-H + NH).

1-[[3-(Diethylamino)propyl]amino]-5-methyl-10-hydroxynaphtho[2,3-*g*]isoquinoline-6,11-quinone (25). The stirred solution of the preceding compound (75 mg, 0.17 mmol) in dry methylene chloride (10 mL) was maintained under argon, cooled to −70 °C, and treated by boron tribromide (1.74 mL of the 1 M Aldrich solution). The cooling bath was removed, stirring was maintained for 15 h further at ambient temperature, and the mixture was evaporated to dryness. Water (20 mL) was added, and the homogeneous mixture was alcalinized with ammonia. The solid was collected, air-dried, and recrystallized from cyclohexane to give red microcrystals (45 mg, 62%), mp 158 °C. Anal. Calcd for $C_{25}H_{27}N_3O_3$: C, 71.92; H, 6.52; N, 10.07. Found: C, 71.62; H, 6.69; N, 9.79. ^{1}H NMR ($CDCl_3$): δ 1.23 (t, 2 × 3 H, $(CH_3CH_2)_2$), 2.01 (m, 2 H, β-CH_2), 2.89 (m, 3 × 2 H, $(CH_3CH_2)_2$ + γ-CH_2), 3.05 (s, 3 H, 5-CH_3), 3.77 (m, 2 H, α-CH_2), 7.19 (dd, 1 H, 4-H, J_{4-3} = 6.5 Hz, J_{4-12} = 0.7 Hz), 7.26 (dd, 1 H, 9-H, J_{9-8} = 7.7 Hz, J_{9-7} = 1.5 Hz), 7.67 (dd, 1 H, 8-H, J_{8-7} = 7.9 Hz), 7.82 (dd, 1 H, 7-H), 8.19 (d, 1 H, 3-H), 8.93 (br s, 2 H, 12-H + NH), 9.32 (br s, 1 H, OH).