

Synthesis of 4-Amino-substituted-6-hydroxy and 11-hydroxy-naphtho[2,3-*g*]quinoline-5,12-diones, and the Unexpected Formation of Disubstituted Imidazo[4,5,1-*i,j*]naphtho[2,3-*g*]quinolin-7-ones

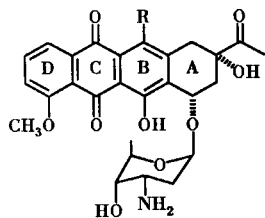
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Received August 3, 1992

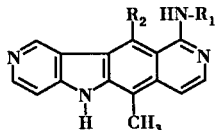
4-Chloroquinoline-5,8-dione (**8a**) and 6-bromo-4-chloroquinoline-5,8-dione (**8b**) were reacted with homophthalic anhydride to give tetracyclic compounds **10** and **11** respectively. The 6,11-dihydroxy derivative **12** was prepared in low yield by photochemical addition of benzocyclobutenedione to 4-chloroquinoline-5,8-dione (**8a**) and in better yield through a Friedel-Crafts reaction of phthalic anhydride with 4-chloro-5,8-dimethoxyquinoline (**7a**). Whereas 4-chloro-6-hydroxynaphtho[2,3-*g*]quinoline-5,12-dione (**11**) was substituted by amines in the usual way to the corresponding 4-amino-substituted derivatives, 4-chloro-11-hydroxynaphtho[2,3-*g*]quinoline-5,12-dione (**10**) led to a mixture of 4-amino derivatives and the unexpected 2,6-disubstituted-imidazo[4,5,1-*i,j*]naphtho[2,3-*g*]quinolin-7-ones, **13a-b**.

J. Heterocyclic Chem., **30**, 55 (1993).

For the last few years, a great number of heteroaromatic analogues of naturally occurring antitumor compounds have been prepared with the hope to increase their pharmacological properties or to find new derivatives with lowered side effects. In the anthracycline series, for example, the D-ring thiophene [1] and indole [2] analogues of daunomycin **1a** showed inhibitory activity against L1210 cell growth (*in vitro*) comparable to that of **1a**. The same observations were reported for D-ring pyridine and pyrazine analogues of 11-deoxydaunomycin **1b** [3]. In our laboratory, we have demonstrated that, in the ellipticine series, the replacement of an aromatic CH group by a nitrogen atom led to derivative **2a** which displayed increased antitumor activities against various neoplasms [4]. As a continuation of our studies to develop new antitumor compounds, we have prepared some naphthoisoquinoline-diones bearing dibasic side chain **3** [5]. Despite relatively weak activity of these compounds and with the aim to obtain good structure activity relationships, we looked at the influence of the nitrogen atom position, on the biological properties.

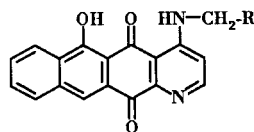
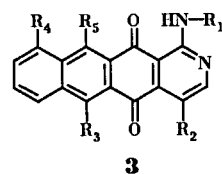


1a, R = OH
1b, R = H

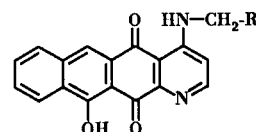


2a, R = H, R' = CH₃
2b, R₁ = NH(CH₂)₃-N(C₂H₅)₂, R₂ = H

In this paper, we report on the synthesis and biological evaluation of 4-amino-substituted-6-hydroxy and 11-hydroxynaphtho[2,3-*g*]quinoline-5,12-diones **4a-b**, **5a-b** and the unexpected disubstituted-imidazo[4,5,1-*i,j*]naphtho[2,3-*g*]quinolin-7-ones.



4a, R = CH₂-CH₂-N(C₂H₅)₂
4b, R = CH₂-N(CH₃)₂

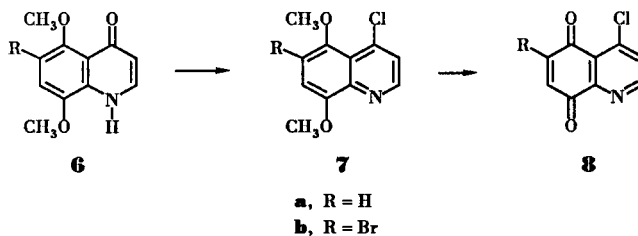


5a, R = CH₂-CH₂-N(C₂H₅)₂
5b, R = CH₂-N(CH₃)₂

Chemistry.

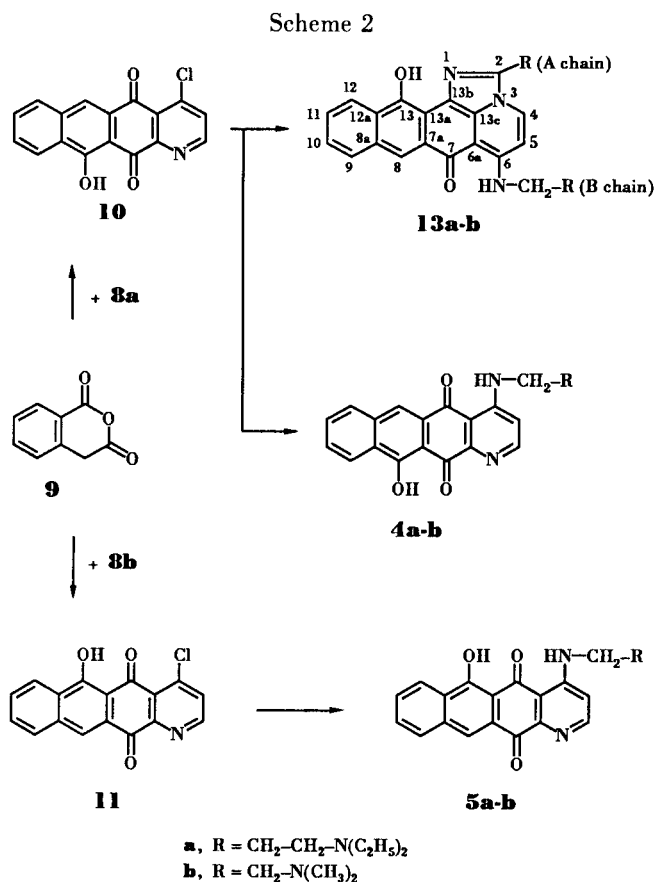
Treatment of 5,8-dimethoxy-1*H*-quinolin-4-one (**6a**) [6] with phosphorus oxychloride furnished 4-chloro-5,8-dimethoxyquinoline (**7a**). Oxidative demethylation of this compound with cerium(IV) ammonium nitrate (CAN) [7] in aqueous acetonitrile containing pyridine-2,6-dicarboxylic acid *N*-oxide at 0-5° for 1 hour afforded 4-chloroquinoline-5,8-dione (**8a**) in 84% yield. Under the same conditions 6-bromo-4-chloro-5,8-dimethoxyquinoline (**7b**) [8] was oxidized to give 6-bromo-4-chloroquinoline-5,8-dione (**8b**) in 65% yield (Scheme 1).

Scheme 1



A few years ago, it was reported that condensation of homophthalic anhydride (**9**) with halonaphthoquinone derivatives, produced the corresponding tetracyclic compound in which the nucleophilic (C-4 position) of homophthalic anhydride regioselectively attacked the unsubstituted olefinic site of the quinone [9]. Recently the same authors [3] have described a total synthesis of D-ring pyridine analogue of 11-deoxydaunomycin. In this case, attempts to obtain the intermediate tetracyclic compound failed, probably owing to the instability of the 7-halogenoquinoline-5,8-diones, under the strongly basic conditions. However, the use of the unsubstituted quinolinediones caused cycloaddition to the anhydride to give a single cycloadduct. The structure was determined unambiguously as the result of an attack on C₆ of the quinoline ring.

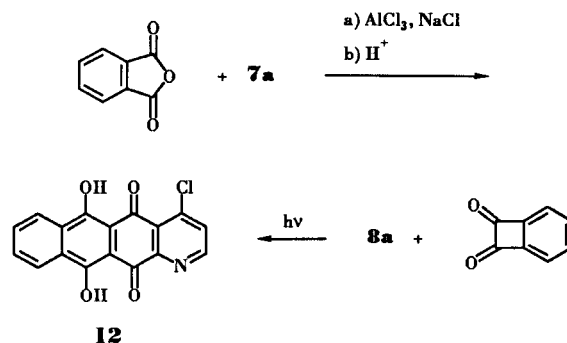
Similarly, we first used in our studies the 4-chloroquinoline-5,8-dione (**8a**). The reaction of the anion generated from homophthalic anhydride **9** and 1.1 equivalents of sodium hydride in tetrahydrofuran (THF) with **8a**, at room temperature, gave a single cycloadduct in 23% yield. The addition was thus a regioselective one but it was difficult to establish the structure of this adduct, **10** or **11**, by ¹H-nmr data, since the compound was nearly insoluble in deuteriochloroform and gave radicals in DMSO or DMF, showing only solvent peaks on the spectra.



Next, we used, under the same conditions, 6-bromo-4-chloroquinoline-5,8-dione (**8b**) instead of **8a**. We then obtained selectively a single compound different from that obtained with the unsubstituted quinone. So, on the basis of the reported data [10] it can be concluded that this last compound corresponds to 6-hydroxynaphthoquinoline-5,12-dione **11** and structure **10** to the molecule isolated from **8a** (Scheme 2).

In order to obtain dihydroxy compound **12**, we first tried a photochemically induced cycloaddition of the bis-ketene generated from benzocyclobutenedione [11] to the 4-chloroquinolinedione **8a** as described for the synthesis of Daunomycinone derivatives [12]. This reaction took place as expected, but only a 3% yield of **12** was obtained (Scheme 3). Finally, Friedel-Crafts acylation of 4-chloro-5,8-dimethoxyquinoline (**7a**) with phthalic anhydride gave a 13% yield of the desired compound **12** which was reacted with amines giving mixtures from which we were unable to obtain a pure product. However, substitution of the chloro compounds by dialkylaminoalkylamines led us to observe that 11-hydroxy derivative **10** and the 6-hydroxynaphthoquinolinedione **11** behave differently. Thus, substitution of **11** by using a 20% excess of the required di-

Scheme 3



amine, 3-(diethylamino)propylamine or 2-(dimethylamino)ethylamine, in refluxing toluene for 4 hours, provided a 45% yield of the expected amino derivatives **5a-b**. Under the same conditions and even with a stoichiometric quantity of the diamine, **10** gives mixtures of two products: the target compounds **4a** and **4b** (20% yield), in each case accompanied by a second product. The unexpected byproducts were obtained selectively by using a large excess of amines at reflux for 24 hours. Under these conditions we isolated, after chromatography of the mixture on alumina, blue compounds **13a-b** in 45% yields (Scheme 2), the structure of which was assigned by ¹H and ¹³C nmr studies.

These nmr studies were particularly carried out with **13a**, obtained by reaction of **10** with 3-(diethylamino)propylamine. Its ¹H nmr spectra showed two unequivalent side chains, one of them with a CH₂ group missing. More-

Table 1
¹³C NMR Data

Carbon No		$\delta^{13}\text{C}$	Multiplicity	C/H correlation 2D	J coupling = Hertz
C2	Sp ²	138.21	M	α CH ₂ side chain A	
C4	Sp ² CH	128.42	dd	H4, H5	C ₄ H ₄ = 183 C ₄ H ₅ = 2.2
C5	Sp ² CH	102.80	ddd	H5, H4, NH	C ₅ H ₅ = 165 C ₅ H ₄ = 5 C ₅ NH = 6
C6	Sp ² q	125.65	d	H4	C ₆ H ₄ = 5.44
C6a	Sp ² q	98.5	M	H5, NH	C _{6a} H ₅ = 5.5 C _{6a} NH = 4
C7	Sp ² CO	179.53	d	H8	C ₇ H ₈ = 4.2
C7a	Sp ² q	117.67	S		
C8	Sp ² CH	118.48	dd	H8, H9	C ₈ H ₈ = 162.5 C ₈ H ₉ = 4.62
C8a	Sp ² q	130.09	M	H12, H10	
C9	Sp ² CH	128.61	ddd	H9, H8, H11	C ₉ H ₉ = 159
C10	Sp ² CH	124.57	dd	H10, H12	C ₁₀ H ₁₀ = 161 C ₁₀ H ₁₂ = 8.8
C11	Sp ² CH	126.06	dd	H11, H9	C ₁₁ H ₁₁ = 160 C ₁₁ H ₉ = 8.5
C12	Sp ² CH	121.30	dd	H12, H10	C ₁₂ H ₁₂ = 163 C ₁₂ H ₁₀ = 7
C12a	Sp ² q	123.79	M	H8, H11, H9	
C13	Sp ² q	147.39	d	H12	C ₁₃ H ₁₂ = 4
C13a	Sp ² q	112.64	d	H8	C _{13a} H ₈ = 7.2
C13b	Sp ² q	129.19	S		
C13c	Sp ² q	150.65	M	H4, α CH ₂ side chain B	C _{13c} H ₄ = 72

over, only one exchangeable triplet signal corresponding to a NH of the chain was observed. COSY and NOESY experiments were performed pointing out one dipolar coupling between the CH₂ of the second chain and H3 pyridine proton. The proton decoupled ¹³C spectra exhibited twenty seven signals, four of them represented two carbons each. That confirmed the addition of a second chain. The DEPT spectra revealed the presence of 10 Sp² quaternary carbon atoms; 1 Sp² carbonyl, 7 Sp² CH groups, 9 Sp² methylene units and 4 methyl substituents. The disappearance of one carbonyl signal, the presence of one more Sp² quaternary carbon scalarely coupled with the CH₂ of the added chain, the loss of the aromaticity of the pyridine ring, and the multiple bond C/H 2D correlations, fully supported the proposed structure **13a** (Table I). Elemental analysis of **13a** was calculated for C₃₁H₃₉N₂O₂. Results were in good agreement with the molecular formula including one half a molecule of water. Finally the mass spectra of **13a** by electron impact showed a base peak at m/z 86 (100%) characteristic of the diethylamino-alkyl group. Molecular ion (m/z = 513) was found with a relatively high intensity (47%). The main fragmentation resulted from the cleavage of both side chains and occurred at m/z 427 (74%) and m/z 299 (7%). The transition 427 → 299 was confirmed by a metastable peak at m/z 209 (calcu-

lated = 209.37). Molecular weight was also confirmed by chemical ionization using ammonia. Under these conditions the molecular ion was obtained at M + 2 (m/z 515). As an hypothesis Scheme 4 could account for the formation of compounds **13a** and **13b**.

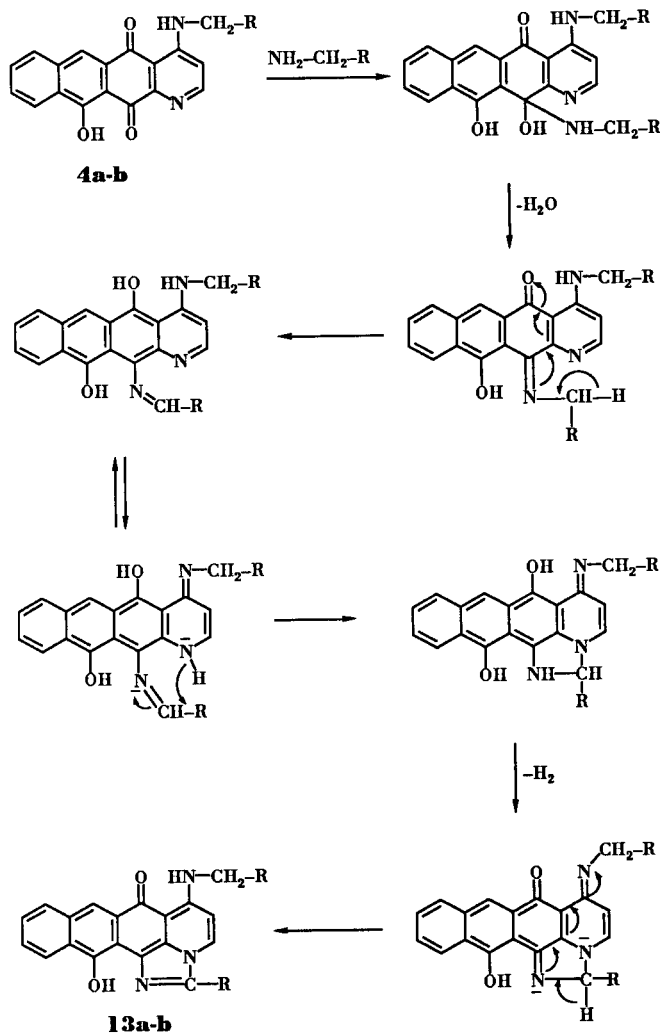
Table II

Cytostatic Activities of Alkylamino Derivatives on L1210 Cells *in vitro* after 24 Hours of Incubation

Compound	IC ₅₀ (μmoles)
4a	2.6
4b	6.2
5a	52 [a]
5b	10
13a	75
13b	19.7 [b]
BD10 (positive control)	0.02

[a] Toxic at 100 μmoles. [b] Toxic at 50 μmoles.

Scheme 4



Since recently, some (aminoalkyl)aminoimidazoacridones were reported as a novel class of antineoplastic agents [14], structures **13a-b** appeared rather interesting in the scope of our study. So, all the amino-substituted compounds were evaluated for cytostatic activity "*in vitro*" on the L1210 murine leukemia. Positive control was obtained with PZT PAZELLIPTINE, BD40 **2b**.

Cytostatic results are reported in Table II. As it can be seen, all tested compounds displayed IC₅₀ between 1 and 10 μM , more of them showing toxic effects above 10 μM . Taken with our preceding reported results, this allowed us to conclude that various amino-substituted quinolines and isoquinolines [5] fused to the hydroxynaphthoquinone systems do not indicate further interest in the field of anti-neoplastic agents.

EXPERIMENTAL

All melting points were taken with a Reichert hot-stage microscope and are uncorrected. Microanalytical results were obtained

from C.N.R.S. Institut des Substances Naturelles, Gif-sur-Yvette. Mass spectra were recorded on a A.E.I. MS50, operating at 70 ev, using direct introduction (200°). Molecular weights were confirmed by chemical ionisation with ammonia using a Delsi-Nermag 30 apparatus. The ¹H and ¹³C nmr spectra were taken on a Bruker 200 AC (200 MHz). Chemical shifts are reported as δ values (ppm) down-field from internal tetramethylsilane. The nmr abbreviations used are as follows: br (broad), s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet).

4-Chloro-5,8-dimethoxyquinoline (**7a**).

5,8-Dimethoxy-1*H*-quinolin-4-one [6] (2.4 g, 10.7 mmoles) was heated in phosphorus oxychloride (60 ml) for 2 hours. After being cooled to room temperature, phosphorus oxychloride was evaporated. The residue was poured into cold water and the solution filtered. The filtrate was basified with potassium carbonate and the precipitate was filtered off and washed with water. Recrystallization from cyclohexane gave 2.2 g (85%) of colorless needles, mp 111°; ¹H nmr (deuteriochloroform): δ 3.83 (s, 3H, OCH₃), 3.96 (s, 3H, OCH₃), 6.78 (d, 1H, H₇, J_{H₇-H₆} = 8.7 Hz), 6.90 (d, 1H, H₆), 7.38 (d, 1H, H₃, J_{H₃-H₂} = 4.7 Hz), 8.64 (d, 1H, H₂).

Anal. Calcd. for C₁₁H₁₀ClNO₂: C, 59.07; H, 4.51; N, 6.28. Found: C, 59.08; H, 4.35; N, 6.25.

4-Chloroquinoline-5,8-dione (**8a**).

4-Chloro-5,8-dimethoxyquinoline (**7a**) (1.9 g, 8.5 mmoles) dissolved in acetonitrile (60 ml) was added to pyridine-2,6-dicarboxylic acid *N*-oxide (7.7 g, 42 mmoles) suspended in acetonitrile-water (1:1, v/v, 77 ml). The mixture was stirred at 0-5°, then a solution of CAN (23 g, 42 mmoles) in acetonitrile-water (1:1, v/v, 64 ml) was added dropwise over 1 hour. After 1 hour at 0-5°, it was adjusted to pH 8 with saturated aqueous sodium bicarbonate solution and extracted with dichloromethane (3 x 300 ml). The extract was washed with water, dried, and evaporated. The crystals were collected by filtration and washed with diethyl ether. Recrystallization from cyclohexane gave 1.4 g (85%) of yellow crystals, mp 150°.

Anal. Calcd. for C₉H₄ClNO₂: C, 55.84; H, 2.08; N, 7.24. Found: C, 55.59; H, 2.10; N, 7.38.

6-Bromo-4-chloroquinoline-5,8-dione (**8b**).

This compound was obtained using 6-bromo-4-chloro-5,8-dimethoxyquinoline (**7b**) [8] (2 g, 6.6 mmoles) in the same reaction described above. Compound **8b** was recrystallized from cyclohexane to give 1.1 g (61%) of yellow crystals, mp 163°; ¹H nmr (deuteriochloroform): δ 7.65 (s, 1H, H₇), 7.70 (d, 1H, H₃, J_{H₃-H₂} = 5.2 Hz), 8.86 (d, 1H, H₂).

Anal. Calcd. for C₉H₃BrClNO₂: C, 39.67; H, 1.11; N, 5.14. Found: C, 39.61; H, 1.41; N, 5.1.

4-Chloro-11-hydroxynaphtho[2,3-*g*]quinoline-5,12-dione (**10**).

Under a nitrogen atmosphere, a solution of homophthalic anhydride (0.977 g, 6 mmoles) in dry THF (65 ml) was added to a stirred suspension of NaH (97%, 167 mg, 6.9 mmoles) in dry THF (65 ml) at 0°, and the mixture was stirred for 3 minutes. A solution of 4-chloroquinoline-5,8-dione (**8a**) (1.4 g, 7.2 mmoles) in dry THF (65 ml) was added to the mixture, and the whole was stirred at room temperature for 3 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride (60 ml). The mixture was concentrated *in vacuo* and the residue was dissolved in DMF and filtered. Recrystallization from DMF gave

510 mg (23%) of orange needles, mp 304°; ¹H nmr (deuteriochloroform): δ 7.70 (m, 3H, H₈ + H₉ + H₃, J_{H₃-H₂} = 5.1 Hz), 8.01 (dd, 1H, H₇, J_{H₇-H₉} = 2.2 Hz, J_{H₇-H₈} = 7 Hz), 8.29 (s, 1H, H₆), 8.55 (m, 1H, H₁₀), 8.93 (d, 1H, H₂), 14.32 (s, 1H, OH).

Anal. Calcd. for C₁₇H₈ClNO₃: C, 65.93; H, 2.6; N, 4.52. Found: C, 65.86; H, 2.3; N, 4.64.

4-Chloro-6-hydroxynaphtho[2,3-*g*]quinoline-5,12-dione (**11**).

By a similar procedure to that described for the preparation of **10**, **11** was obtained from bromoquinone **8b** (717 mg, 2.63 mmoles) and homophthalic anhydride (356 mg, 2.2 mmoles). Recrystallization from DMF gave 170 mg (25%) of red needles, mp 302°; ¹H nmr (deuteriochloroform): δ 7.72 (m, 3H, H₈ + H₉ + H₃, J_{H₃-H₂} = 5 Hz), 8.00 (m, 1H, H₁₀), 8.40 (s, 1H, H₁₁), 8.55 (m, 1H, H₇), 8.90 (d, 1H, H₂), 14.31 (s, 1H, OH).

Anal. Calcd. for C₁₇H₈ClNO₃: C, 65.93; H, 2.6; N, 4.52. Found: C, 65.86; H, 2.89; N, 4.47.

4-Chloro-6,11-dihydroxynaphtho[2,3-*g*]quinoline-5,12-dione (**12**).

Method A.

4-Chloroquinoline-5,8-dione (300 mg, 1.55 mmoles) and benzocyclobutenedione [**11**] (410 mg, 3.10 mmoles) were dissolved in deoxygenated dichloromethane (50 ml). The solution was placed in 2 test tubes of 15 mm diameter, then cautiously deaerated, stoppered and left at room temperature in the daylight (but not in sunlight) for 8 days. After evaporation of the solvent, the residue was washed with acetone and crystallized from toluene to give 16 mg (3%) of red needles, mp 314°; ¹H nmr (deuteriochloroform): δ 7.72 (d, 1H, H₃, J_{H₃-H₂} = 4.9 Hz), 7.89 (m, 2H, H₈ + H₉), 8.50 (m, 2H, H₁₀ + H₇), 8.96 (d, 1H, H₂), 14.92 (s, 1H, OH), 15.81 (l, 1H, OH).

Anal. Calcd. for C₁₇H₈ClNO₄: C, 62.69; H, 2.48; N, 4.3. Found: C, 62.47; H, 2.81; N, 4.32.

Method B.

To a magnetically stirred melt of aluminum chloride (12.5 g, 94 mmoles) and sodium chloride (2.5 g, 42.8 mmoles) at 180° were added in portion, an intimate mixture of 4-chloro-5,8-dimethoxyquinoline (2.3 g, 10 mmoles) and phthalic anhydride (1.48 g, 10 mmoles). The reaction mixture was stirred at this temperature for 10 minutes, cold water (100 ml) was added cautiously and after cooling, it was basified by addition 20% sodium hydroxide. The purple precipitate was collected by filtration and dried overnight. The dry precipitate was treated with concentrated sulfuric acid (10 ml) and the mixture was diluted to 100 ml with water. After filtration, the dry solid was crystallized from DMF to give 250 mg (13%) of red needles, identical to compound **12** obtained in the method A.

General Procedure for Obtaining Amino Derivatives **4a-b** and **5a-b**.

A mixture of the required chloro derivative (50 mg, 0.16 mmole) and the appropriate amine (1.2 molar equivalents) was refluxed in toluene (20 ml). The substitution was followed by tlc and a drop of triethylamine was added at the end of the reaction (ca. 4 hours). The solvent was removed under reduced pressure, and the residue was washed with hexane and recrystallized.

4-[[3-(Diethylamino)propyl]amino]-6-hydroxynaphtho[2,3-*g*]quinoline-5,12-dione (**5a**).

Orange needles (31 mg, 48%) were obtained from toluene, mp 184°; ¹H nmr (deuteriochloroform): δ 1.05 (t, 6H, N-(CH₂-CH₃)₂), 1.56 (H₂O), 1.90 (m, 2H, β CH₂), 2.58 (q, 6H, N-(CH₂-CH₃)₂ + γ CH₂, J = 7 Hz), 3.43 (q, 2H, α CH₂), 6.83 (d, 1H, H₃, J_{H₃-H₂} = 6.1 Hz), 7.70 (m, 2H, H₈ + H₉), 7.98 (m, 1H, H₁₀), 8.37 (s, 1H, H₁₁), 8.50 (m, 1H, H₇), 8.51 (d, 1H, H₂), 9.73 (br s, 1H, NH), 14.32 (s, 1H, OH).

Anal. Calcd. for C₂₄H₂₅N₃O₃·0.5H₂O: C, 69.88; H, 6.35; N, 10.19. Found: C, 69.99; H, 5.97; N, 10.03.

4-[[2-(Dimethylamino)ethyl]amino]-6-hydroxynaphtho[2,3-*g*]quinoline-5,12-dione (**5b**).

Orange needles (25 mg, 43%) were obtained from toluene, mp 229°; ¹H nmr (deuteriochloroform): δ 1.65 (H₂O), 2.36 (s, 6H, N-(CH₃)₂), 2.68 (t, 2H, β CH₂, J = 6.2 Hz), 3.40 (q, 2H, α CH₂), 6.76 (d, 1H, H₃, J_{H₃-H₂} = 6.1 Hz), 7.68 (m, 2H, H₈ + H₉), 7.96 (m, 1H, H₁₀), 8.34 (s, 1H, H₁₁), 8.49 (m, 1H, H₇), 8.51 (d, 1H, H₂), 9.71 (br s, 1H, NH), 14.31 (s, 1H, OH).

Anal. Calcd. for C₂₁H₁₉N₃O₃·0.5H₂O: C, 68.10; H, 5.44; N, 11.34. Found: C, 68.27; H, 5.23; N, 11.28.

4-[[3-(Diethylamino)propyl]amino]-11-hydroxynaphthoquinoline-5,12-dione (**4a**).

After 3 recrystallizations from cyclohexane **4a** was obtained, (10 mg, 15%) as orange needles, mp 130°; ¹H nmr (deuteriochloroform): δ 1.06 (t, 6H, N-(CH₂CH₃)₂), 1.72 (H₂O), 1.92 (m, 2H, β CH₂), 2.59 (m, 6H, γ CH₂ + N-(CH₂CH₃)₂), 3.43 (q, 2H, α CH₂, J = 6.7 Hz), 6.83 (d, 1H, H₃, J_{H₃-H₂} = 5.9 Hz), 7.70 (m, 2H, H₈ + H₉), 7.97 (m, 1H, H₇), 8.20 (s, 1H, H₆), 8.50 (m, 1H, H₁₀), 8.52 (d, 1H, H₂), 9.95 (br s, 1H, NH), 14.25 (br s, 1H, OH).

Anal. Calcd. for C₂₄H₂₅N₃O₃·0.5H₂O: C, 69.88; H, 6.35; N, 10.19. Found: C, 69.98; H, 6.07; N, 10.03.

4-[[2-(Dimethylamino)ethyl]amino]-11-hydroxynaphtho[2,3-*g*]quinoline-5,12-dione (**4b**).

After repeated crystallizations from cyclohexane **4b** was obtained (13 mg, 24% yield) as orange needles, mp 214°; ¹H nmr (deuteriochloroform): δ 1.68 (H₂O), 2.36 (s, 6H, N-(CH₃)₂), 2.67 (t, 2H, β CH₂), 3.40 (q, 2H, α CH₂, J = 6.1 Hz), 6.77 (d, 1H, H₃, J_{H₃-H₂} = 6.1 Hz), 7.70 (m, 2H, H₈ + H₉), 7.95 (m, 1H, H₇), 8.24 (s, 1H, H₆), 8.51 (m, 1H, H₁₀), 8.53 (d, 1H, H₂), 10.03 (m, 1H, NH), 14.49 (br s, 1H, OH).

Anal. Calcd. for C₂₁H₁₉N₃O₃·0.5H₂O: C, 68.10; H, 5.44; N, 11.34. Found: C, 68.56; H, 5.32; N, 11.42.

2-[(Diethylamino)ethyl]-6-[(diethylamino)propyl]amino-13-hydroxy-7*H*-imidazo[4,5,1-*i*']naphtho[2,3-*g*]quinolin-7-one (**13a**).

A mixture of compound **10** 100 mg (0.323 mmole) and 252 mg (1.95 mmoles) of 3-(diethylamino)propylamine were dissolved in toluene (30 ml) and refluxed for 24 hours. After cooling, the solvent was evaporated to dryness *in vacuo*. The residue was chromatographed on alumina, grade III, and eluted with dichloromethane and ethyl alcohol (9/1). Collection of the blue fraction gave 68 mg (41%) of **13a** as a blue solid, which was recrystallized from cyclohexane to give blue needles, mp 195°; ¹H nmr (deuteriochloroform): δ 1.02 (m, 12H, N-(CH₂-CH₃)₂ chain A + chain B), 1.86 (m, 2H, β CH₂ chain B), 2.54 (m, 10H, N-(CH₂-CH₃)₂ chain A + γ CH₂-N-(CH₂-CH₃)₂ chain B), 2.92 (m, 2H, β CH₂ chain A), 2.99 (m, 2H, α CH₂ chain A), 3.33 (q, 2H, α CH₂ chain B), 5.95 (d, 1H, H₅, J_{H₅-H₄} = 7.7 Hz), 7.41 (d, 1H, H₄), 7.52 (m, 2H, H₁₀ + H₁₁), 7.99 (m, 1H, H₉, J_{H₉-H₁₀} = 7.9 Hz), 8.34 (m, 1H, H₁₂), 8.44

(s, 1H, H8), 9.67 (br s, 1H, OH), 10.11 (t, 1H, NH); ms: (ie) m/z 513, (ic, NH_3) $M + 2$ m/z 515.

Anal. Calcd. for $\text{C}_{31}\text{H}_{39}\text{N}_5\text{O}_2 \cdot 0.5\text{H}_2\text{O}$: C, 71.24; H, 7.71; N, 13.40; O, 7.65. Found: C, 71.32; H, 7.44; N, 13.48; O, 7.61.

2-[(Dimethylamino)methyl]-6-[(dimethylamino)ethyl]amino-13-hydroxy-7*H*-imidazo[4,5-*i,j*]naphtho[2,3-*g*]quinolin-7-one (**13b**).

Under the conditions as for **13a** but using 2-(dimethylamino)ethylamine **13b** was obtained (39%), as blue needles from cyclohexane, mp 221°; ^1H nmr (deuteriochloroform): δ 2.27 (s, 6H, N-(CH_3)₂ chain A), 2.35 (s, 6H, N-(CH_3)₂ chain B), 2.69 (t, 2H, β CH_2 chain B), 3.54 (q, 2H, α CH_2 chain B), 3.92 (s, 2H, α CH_2 chain A), 6.37 (d, 1H, H5, $J_{\text{H5-H4}} = 7.5$ Hz), 7.53 (m, 2H, H10 + H11), 8.03 (m, 1H, H9, $J_{\text{H9-H10}} = 8.05$ Hz), 8.26 (d, 1H, H4, $J_{\text{H4-H5}} = 7.5$ Hz), 8.39 (m, 1H, H12, $J_{\text{H12-H11}} = 8.9$ Hz), 8.61 (s, 1H, H8), 9.74 (br s, 1H, OH), 10.36 (t, 1H, NH); ms: (ic, NH_3) $M + 2$ m/z 431.

Anal. Calcd. for $\text{C}_{25}\text{H}_{27}\text{N}_5\text{O}_2 \cdot 0.5\text{H}_2\text{O}$: C, 68.47; H, 6.44; N, 15.97; O, 9.12. Found: C, 68.55; H, 6.21; N, 15.91; O, 9.01.

Biological Testing.

L1210 (ATCC-CCL 219) cells were cultivated in Dulbecco's MEM Supplemented with 10% fetal calf serum at 37° in a water-jacketed carbon dioxide incubator (5% carbon dioxide). Cells were seeded at 10^5 cells/ml in 1 ml microwell plates. After 24 hours (usually 3 to 4 x 10^5 cells/ml), the tested compounds were added in duplicate in various concentrations and incubated for 24 hours. Cells were counted with a Coulter-Counter 2M (Coultronics Inc). The dose inhibiting the growth by 50% (IC50) was extrapolated from regression curves obtained with experimental points without significant toxicity.

Acknowledgements.

Nathalie Frey is greatly acknowledged for editorial assistance.

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