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Secondary amines and unexpected 1-aza-anthraquinones from 2-methoxylapachol

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Abstract—A series of 1-aza-anthraquinones were characterized, besides the expected *N*-alkylamino derivatives, from the substitution reactions of 2-methoxylapachol with primary amines. An investigation of the reaction conditions allowed reasonable selectivity in the products distribution.

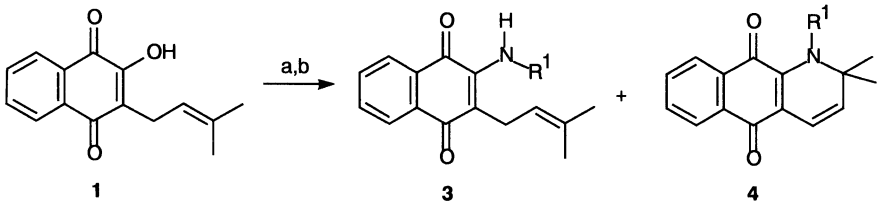
1. Introduction

The presence of a nitrogen atom in e.g. simple alkylamino derivatives[1] or in a fused heterocycle[2] is related with a wide range of biological properties in quinone compounds.[3] Potent antitumor[4] and antimalarial[5] activities have been described in both cases. In addition, the aminonaphthoquinone moiety is a component of the molecular framework of several natural products (e.g. rifamycins, kinamycins, etc.)[6] and is also present as a key synthetic intermediate for the construction of biologically important compounds.[7]

In the work described herein we were interested in using a derivative of lapachol **1**, 2-methoxylapachol **2**, to synthesize a series of 2-alkylamino derivatives **3** (Scheme 1). Nucleophilic displacement of methoxynaphthoquinone derivatives with primary amines has been investigated previously.[8] No reports on the analogous reactions of **2** were found in the literature, although the reactions of the parent compound **1** with various amines have been described.[9]

Compound **1** is a naturally occurring 3-prenylated 2-hydroxy-1,4-naphthoquinone,[10] extracted, along with its cyclic isomer β-lapachone and other naphthoquinones, from the bark of various species of the genus *Tabebuia* sp. A number of biological activities have been reported for these natural naphthoquinones and their derivatives[11] including microbicidal, cytostatic, anti-inflammatory, bactericidal, fungicidal, virucidal, anti-*Plasmodium falciparum* (the agent of malaria), anti-*Schistosoma mansoni* (agent of schistosomiasis) and anti-*Trypanosoma cruzi* (agent of Chagas disease).[12]

We found that in the presence of primary amines the prenyl side-chain in **2** undergoes further cyclization,[13] to result in novel compounds identified as 1-aza-1,2-dihydro-5,10-anthraquinones or 1,2,5,10-tetrahydro-benzo[*g*]quinoline-5,10-diones **4**.[14] The 1-aza-anthraquinone nucleus is frequently encountered in various natural products, e.g. markanyn,[15] cleistopholyn[16] and griffiazanone B.[17] Literature methods for the synthesis of 1-aza-anthraquinones are dominated by the hetero Diels–Alder cycloaddition. This method allows the construction of the structural backbone of the added heterocycle moiety.[18]



Scheme 1. *Reagents and conditions*: (a) K_2CO_3, acetone, $(CH_3)_2SO_4$, 2 h, 88%; (b) R^1NH_2 (excess).

Keywords: 1-aza-anthraquinone; lapachol; 1,4-naphthoquinone.

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Table 1. Products, methods and chemical yields of derivatives **3** and **4**

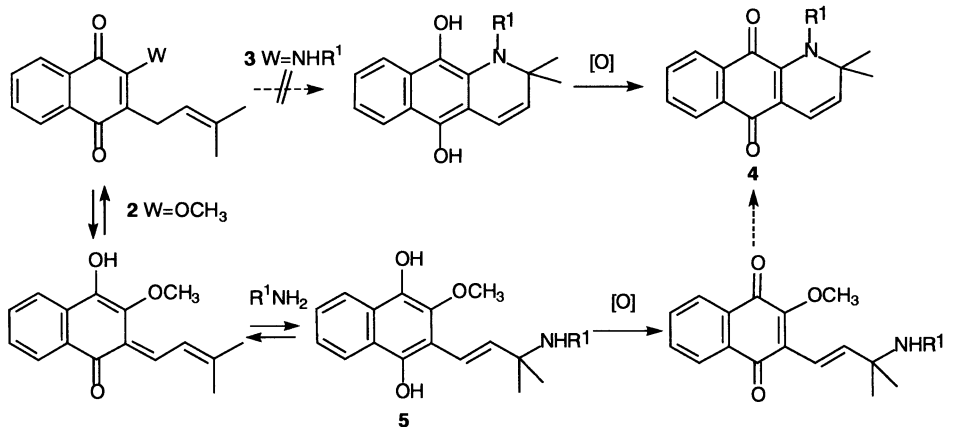
Entry	Amine	**3** (%)	**4** (%)	Time/method (see text)	Conversion (%)
1	(**a**) CH_2═$CHCH_2NH_2$	54	<1	24/A	92
2		75	20	12/B	90
3	(**b**) $PhCH_2NH_2$	59	<1	24/A	89
4		61	5	24/B	90[a]
5		52	26	4/B	82
6		(–)[b]	49	0.5/B (100°C)	100
7	(**c**) $(H_3CO)_2CHCH_2NH_2$	48	32	4/B	80
8		70	(–)[c]	24/A	63
9	(**d**) $HOCH_2CH_2NH_2$	76	(–)[c]	24/A	85
10	(**e**) $PhNH_2$	(–)[b]	57	3/A[d]	80
11		(–)	22	10 min/B (120°C)	62
12	(**f**) 4 $(H_3CO)C_6H_4NH_2$	(–)	18	10 min/B (120°C)	64
13	(**g**) 4 $(H_3C)C_6H_4NH_2$	(–)	22	10 min/B (120°C)	60

[a] Inert atmosphere (N_2).
[b] Trace.
[c] Not visible under tlc inspection.
[d] Ethanol/reflux.

2. Results and discussion

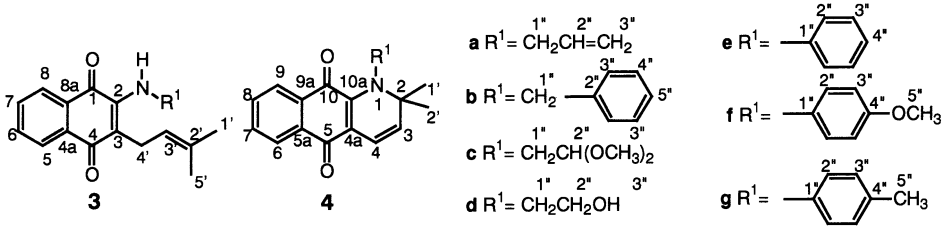
The reactions of 2-methoxylapachol **2** with allylamine (**a**), benzylamine (**b**), aminoethyl-2,2-dimethoxyacetal (**c**) and ethanolamine (**d**), in ethanol (or methanol),[19] at room temperature, for 24 h (method A) provided the corresponding substitution products **3a**–**d** in 54, 59, 70 and 76% yields, respectively (entries 1, 3, 7 and 9 of Table 1), obtained as red crystals after purification. Tlc inspection of the reaction mixtures containing **3a** and **b** before purification showed the presence of a purple-colored side-product, identified latter as the corresponding cyclic products **4a** and **b** (see Scheme 1). Interestingly, the reaction of **2** with aniline (**e**) proceeded in refluxing EtOH to give, after 3 h, only the cyclic product **4e** in 57% yield, with 80% conversion (entry 10). Aniline being less nucleophilic than the investigated alkylamines it only reacts under forcing conditions and, in this case, we believe that isomerization is thermally induced (entry 10 of Table 1). We have also investigated the reaction of **2** with the more nucleophilic *p*-methoxyaniline (**f**) (entry 12, Table 1), in the expectation that an even higher yield of the corresponding cyclized product **4f** would be formed. The reaction only gave **4f**, although in 18% yield, after 10 min at 120°C (64% conversion based on recovered **2**) and, after 30 min, only a black tar was obtained. This low yield is probably the result of an *ipso* aromatic nucleophilic substitution in the methoxyl.[20] Similar results were obtained from the reactions of **2** with aniline (entry 11) and *p*-toluidine (**g**) (entry 13) under the same conditions.

The results of this work suggest therefore that the products distribution depends upon the nucleophilic character of the amine. In an attempt at improving the yields of the cyclic products, the reactions were reinvestigated: solvent-free mixtures of the appropriate primary amine and **2** were mixed together at room temperature (method B). The reaction with allylamine resulted in 90% conversion, after 4 h, and led to an approximate product distribution of 4:1, favoring the amino derivative **3a** over the cyclic product **4a** (entry 2). In the case of the reaction with aminoethyl-2,2-dimethoxyacetal, under the same conditions, an 80% conversion factor was observed, with a **3c**/**4c** product distribution of 3:2 (entry 7); when this reaction was carried out at 80–100°C, however, an intractable tar was obtained from which no products were identified by tlc analysis. A slightly different ratio (2:1) was encountered in the case of the room temperature solvent free reaction of **2** with benzylamine, which proceeded with an 82% conversion factor and also favored substitution product **3b** over cyclic product **4b** (entry 5). Although an improved conversion factor (89%)



Scheme 2.

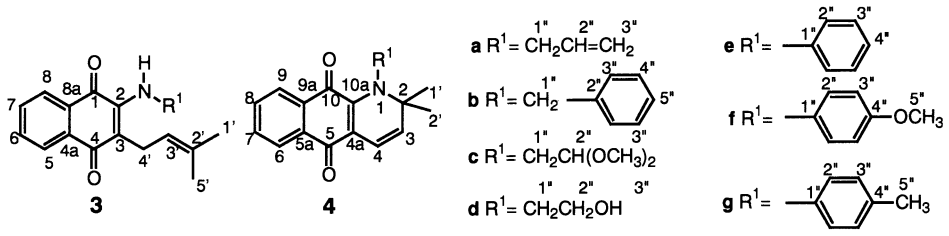
Table 2. ^{1}H NMR shift values for derivatives **3** and **4** (200 MHz, $CDCl_3$)



	δ_H (n[a], mult., J)									
	3a	**4a**	**3b**	**4b**	**3c**	**4c**	**3d**	**4e**	**4f**	**4g**
1										
2										
3		5.33 (d, 1H, 9.5)		5.39 (d, 1H, 9.4)		5.37 (d, 1H, 9.4)		5.49 (d, 1H, 9.4)	5.38 (d, 1H, 9.5)	5.37 (d, 1H, 9.3)
4		6.80 (d, 1H, 9.5)		6.88 (d, 1H, 9.4)		6.77 (d, 1H, 9.4)		6.91 (d, 1H, 9.4)	6.81 (d, 1H, 9.5)	6.82 (d, 1H, 9.3)
4a										
5	8.08 (dd, 1H, 7.7)		8.00 (d, 1H, 7.4)		8.07 (d, 1H, 7.4)		8.05 (d, 1H, 7.6)			
5a										
6	7.69 (m, 1H)	8.05 (d, 1H, 7.5)	7.54 (m, 1H)	8.05 (d, 1H, 7.6)	7.62 (m, 1H)	8.05 (d, 1H, 7.6)	7.57 (m, 1H)	8.07 (d, 1H, 7.8)	8.0 (d, 1H, 7)	8.0 (d, 1H, 7.5)
7	7.57 (m, 1H)	7.62 (m, 1H)	7.54 (m, 1H)	7.62 (m, 1H)	7.62 (m, 1H)	7.58 (m, 1H)	7.57 (m, 1H)	7.59 (m, 1H)	7.55 (m, 1H)	7.59 (m, 1H)
8	7.99 (d, 1H, 7.7)	7.62 (m, 1H)	7.91 (d, 1H, 7.4)	7.62 (m, 1H)	7.97 (d, 1H, 7.4)	7.58 (m, 1H)	7.93 (d, 1H, 7.6)	7.59 (m, 1H)	7.45 (m, 1H)	7.47 (m, 1H)
8a										
9		7.90 (d, 1H, 7.4)		7.80 (1, 1H, 7.4)		7.93 (d, 1H, 7.8)		7.76 (d, 1H, 7.6)	7.76 (d, 1H, 7.6)	7.71 (d, 1H, 7.5)
9a										
10										
10a										
1′	1.69 (s, 3H)	1.40 (s, 3H)	1.54 (s, 3H)	1.35 (s, 3H)	1.70 (s, 3H)	1.24 (s, 3H)	1.68 (s, 3H)	1.32 (s, 6H)	1.21 (s, 6H)	1.21 (s, 6H)
2′		1.40 (s, 3H)		1.35 (s, 3H)		1.24 (s, 3H)				
3′	5.09 (t, 1H, 6.2)		5.02 (m)		5.08 (t, 1H, 5.9)		5.07 (t, 1H, 5.9)			
4′	3.36 (d, 2H, 6.2)		3.26 (d, 2H, 5.7)		3.36 (2H)		3.37 (d, 2H, 5.9)			
5′	1, 73 (s, 3H)		1.62 (s, 3H)		1.76 (s, 3H)		1.74 (s, 3H)			
1″	4.13 (m, 2H)	4.46 (d, 2H, 5.0)	4.63 (s, 2H)	5.18 (s, 2H)	3.68 (t, 1H, 5.2)	4.06 (d, 2H, 5.1)	3.71 (m, 2H)			
2″	5.93 (m, 1H)	6.06 (m, 1H)			4.49 (t, 1H, 5.2)	4.39 (t, 1H, 5.1)	3.85 (m, 2H)	7.37 (m, 2H)	6.80 (d, 2H, 4.5)	6.99 (d, 2H, 6)
3″	5.24 (m, 2H)	5.18 (m, 2H)	7.24 (m)	7.25 (m)	3.41 (s, 6H)	3.33 (s, 6H)	2.3 (l, 1H)	7.20 (m, 2H)	7.02 (d, 2H, 4.5)	7.09 (d, 2H, 6)
4″			7.24 (m)	7.25 (m)				7.37 (m, 1H)		
5″			7.24 (m)	7.25 (m)					3.78 (s, 3H)	2.32 (s, 3H)
NH	5.85 (l, 1H)		5.85 (l, 1H)		5.78 (l, 1H)		6.01 (l, 1H)			

[a] n, number of protons.

Table 3. ^{13}C NMR shift values for derivatives **3** and **4** (50 MHz, $CDCl_3$)



	3a	4a	3b	4b	3c	4c	3d	4e	4f	4g
1	183.1		183.2		183.1		183.2			
2	145.5	59.3	145.8	59.6	146.2	58.6	146.2	59.3	59.3	59.2
3	116.8	128.1	116.2	128.0	116.6	128.5	116.2	127.5	129.3	129.1
4	182.9	117.1	183.0	117.7	183.0	118.4	183.1	118.5	118.5	118.5
4a	132.4	118.6	132.7	118.9	132.9	118.9	132.8	119.2	118.9	125.7
5	126.3	176.9	126.4	180.0	126.3	180.1	126.3	180.9	180.5	180.8
5a				133.4		133.4		132.4	135.9	137.3
6	131.8	125.6	132.0	125.6	132.0	126.9	132.0	125.8	125.7	126.4
7	134.3	132.5	134.5	132.3	134.3	132.3	134.5	132.5	132.4	132.5
8	126.0	133.7	126.1	133.7	126.1	133.5	126.1	133.7	133.7	133.6
8a	133.3		133.5		133.4		133.4			
9		126.3		126.9		126.3		126.4	126.5	129.3
9a		132.3		133.1		n.v.		132.7	130.3	132.7
10		183.3		183.0		183.5		181.6	181.7	181.6
10a		145.4		145.5		145.9		143.4	143.3	143.4
1′	18.1	28.0	18.2	27.9	18.2	27.9	18.2	28.8	28.6	28.7
2′	130.4	28.0	130.6	27.9	130.7	27.9	130.6	28.8	28.6	28.7
3′	123.2		123.1		122.7		122.7			
4′	23.6		23.8		23.8		23.8			
5′	25.6		25.8		25.8		25.8			
1″	47.1	49.6	49.3	50.5	46.4	48.0	47.2	143.1	143.8	134.8
2″	134.7	137.8	138.8	140.5	102.9	106.0	62.1	129.6	126.1	129.9
3″	115.2	116.1	127.9	126.4	54.3	55.5		128.7	113.7	129.4
4″			129.1	128.7				129.5	158.7	140.4
5″			127.3	126.2					55.5	21.4

Multiplicities were determined by DEPT or PENDANT.

was observed when the reaction was carried out with an excess benzylamine at 100°C, only the cyclic purple product **4b** was obtained, in 49%, after 0.5 h (entry 6). Table 1 summarizes the products and chemical yields obtained from the above procedures.

Formation of the cyclic products **4** was initially rationalized in terms of a tautomerization[7e] of the amino derivatives **3**, followed by Michael addition, and then air oxidation, to form the quinone product.[13] To test this hypothesis, compound **3b** was left to react with one equivalent of benzylamine under solvent-free conditions for several hours; it was also heated under reflux in EtOH, but no cyclic product **4b** could be visualized by tlc inspection in either case.

Formation of **4** seems therefore to proceed by nucleophilic attack of the amine at an extended Michael acceptor, formed from the tautomerization of **2** that would result in **5** (Scheme 2). This compound, after air-oxidation, would undergo an intramolecular cyclization, to result in the final compound **4**. If the air-oxidation step is blocked, amines **3** would be formed instead (Scheme 2). This is in agreement with the result of the reaction of **2** with benzylamine, quoted in entry 4 (Table 1), which was carried out under N_2 and resulted only in minute amounts of **4b**. The formation of a small amount of **4b** in the absence of O_2 can be due to oxidation of the hydroquinone intermediate by any quinone present in the reaction mixture, as quinones are known oxidants.

Tables 2 and 3 summarize the NMR data for the derivatives **3** and **4**, assigned on the basis of one and two-dimensional NMR techniques (HMBC and HMQC).

3. Conclusion

New 1-aza-anthraquinones were obtained from the reactions of primary amines and methoxylapachol, which revealed an entirely novel aspect of the chemistry of an abundant naturally occurring naphthoquinone. Preliminary studies involving solvent and temperature conditions led to reasonable product selectivity. These reactions provide an entry to novel compounds with structural features which are attractive from the biological viewpoint.

4. Experimental

4.1. General

Melting points are uncorrected and were determined on a Thomas–Hoover capillary apparatus. Column chromatography was performed on silica gel G_{60} (70–230 mesh,

ASTM, Merck). Thin-layer chromatography was performed on 0.2 mm plates (Merck) and visualized with short-wavelength UV light. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ACF-200 or Bruker AMX-300 spectrometer. Values reported for coupling constants are first order. High-resolution mass spectra were obtained by electron impact (70 eV) on a VG Autospec spectrometer. Natural Lapachol **1** [2-hydroxy-3-(3-methyl-2-butenyl)-1,4-dihydro-1,4-naphthalenedione] was extracted from the bark of species of *Tabebuia* sp., by submitting wooden chips to an aqueous sodium carbonate extraction (10% w/v), followed by dilute hydrocloridric acid precipitation and then, diethyl ether crystallization of **1**, mp 137–9°C (lit. 140°C),[21] in 1–2% yield from the bark and pure enough for the next methylation step.

4.1.1. 2-Methoxylapachol (2). Lapachol **1** (484 mg, 2 mmol) was added to a stirred mixture of potassium carbonate (1.38 g, 10 mmol) in acetone (50 ml) at room temperature. Dimethyl sulfate (0.28 ml, 2.5 mmol) was slowly added to the purple mixture with stirring. After 2 h, tlc inspection showed no **1** left in the reaction media. The solvents were removed under vacuum, and solids were extracted with ethyl acetate, washed with brine and then with water and dried over anhydrous sodium sulfate. After removal of solvents under vacuum the product **2** was purified by flash chromatography with 99% hexanes/1% ethyl acetate (85–89%) and crystallized from hexane/CH_2Cl_2, as bright yellow needles (450 mg, 88%): mp 43°C (lit. 54°C);[20] IR (nujol) 1670, 1654.

4.2. Procedures for the reactions with amines

Method A. 1 mmol of 2-methoxylapachol **2** and 1.5 mmol of the appropriate amine were mixed in a beaker with a pestle. The reaction was followed by tlc and, after completion, the mixture was submitted to flash column chromatography on silica gel and ethyl acetate/hexane (15:85 for **a**, **b** and **e**; 1:9 for **c**; 3:7 for **d**).

Method B. 1 mmol of **2** in MeOH or EtOH (10 ml) was slowly added to 1.5 mmol of the appropriate amine in the same solvent (40 ml) with stirring. After reaction completion, the solvent was removed under vacuum and the residue submitted to flash chromatography on silica gel and ethyl acetate/hexane (as stated before).

4.2.1. 2-Allylamino-3-(3-methyl-2-butenyl)-1,4-dihydro-1,4-naphthalene-dione (3a). Obtained as red crystals, mp 55°C, IR (nujol) (ν max., cm^{-1}) 3346, 1669; Anal. found: C, 77.04; H, 6.79; N, 4,74. Calcd for $C_{18}H_{19}NO_2$: C, 76.87; H, 6.76; N, 4.98.

4.2.2. 2,2-Dimethyl-1-(2-propenyl)-1,2,5,10-tetrahydrobenzo[*g*]quinoline-5,10-dione (4a). Purple crystals, mp 88–89°C, IR (KBr) (ν max., cm^{-1}) 1666, 1624, 1593; MS (rel int) *m/z* 279 (M^+, 10), 264 (100), 246 (8), 224 (24); HRMS found: 279.12593. Calcd for $C_{18}H_{17}NO_2$: 279.12592.

4.2.3. 2-Benzylamino-3-(3-methyl-2-butenyl)-1,4-dihydro-1,4-naphthalenedione (3b). Orange crystals, mp 93–95°C; IR (KBr) (ν max., cm^{-1}) 3296, 1677, 1618, 1568; MS (rel int) *m/z* 331 (M^+, 10), 275 (6), 256 (20), 241 (30), 226 (100), 91 (15), 77 (14); Anal. found: C, 80.48; H, 6.19; N, 4.22; Calcd for $C_{22}H_{21}NO_2$: C, 79.76; H, 6.34; N, 4.23.

4.2.4. 1-Benzyl-2,2-dimethyl-1,2,5,10-tetrahydrobenzo-[*g*]quinoline-5,10-dione (4b). Obtained as purple crystals, mp 125–127°C; IR (KBr) (ν max., cm^{-1}) 1660, 1616, 1589, 1530; M/S (rel int) *m/z* 329 (M^+, 14), 314 (M−15, 62), 225 (58), 91 (100). HRMS found: 329.14158. Calcd for $C_{22}H_{19}NO_2$: 329.14157.

4.2.5. 2-(2,2-Dimethoxyethylamino)-3-(3-methyl-2-butenyl)-1,4-dihydro-1,4-naphthalenedione (3c). Obtained as red oil. IR (KBr) (ν max., cm^{-1}) 3343, 1699, 1625, 1604, 1571; MS (rel int) *m/z* 329 (M^+, 2), 297 (5), 282 (20), 75 (100). HRMS found 329.16271. Calcd for $C_{19}H_{23}NO_4$ 329.16270.

4.2.6. 1-(2,2-Dimethoxyethyl)-2,2-dimethyl-1,2,5,10-tetrahydrobenzo[*g*]quinoline-5,10-dione (4c). Obtained as a purple oil. IR (KBr) (ν max., cm^{-1}) 1668, 1626, 1593,1529; MS (rel int) *m/z* 327 (M^+, 3), 312 (28), 75 (100). HRMS found: 327.14706. Calcd for $C_{19}H_{21}NO_4$: 327.14705.

4.2.7. 2-(2-Hydroxyethylamino)-3-(3-methyl-2-butenyl)-1,4-dihydro-1,4-naphthalenedione (3d). Obtained as red crystals, mp 80–81°C; IR (KBr) (ν max., cm^{-1}) 3391, 3321, 1678, 1599, 1555, 1513; MS (rel int) *m/z* 285 (M^+, 57), 270 (100), 198 (70). HRMS found: 285.13649. Calcd for $C_{17}H_{19}NO_3$: 285.13649.

4.2.8. 2,2-Dimethyl-1-phenyl-1,2,5,10-tetrahydro-benzo-[*g*]quinoline-5,10-dione (4e). Obtained as purple crystals, mp 145–6°C; IR (KBr) (ν max., cm^{-1}) 1672, 1627, 1591, 1536; M/S (rel int) *m/z* 315 (M^+, 3), 300 (100), 77 (7). HRMS found: 315.12593. Calcd for $C_{21}H_{17}NO_2$: 315.12592.

4.2.9. 2,2-Dimethyl-1-(4-methoxy)-phenyl-1,2,5,10-tetrahydro-benzo[*g*]quinoline-5,10-dione (4f). Obtained as purple crystals, mp 145–6°C; IR (KBr) (ν max., cm^{-1}) 1667, 1621, 1587, 1530; M/S (rel int) *m/z* (M^+, 3), 330 (100). HRMS found: 345.1364. Calcd for $C_{22}H_{19}NO_3$: 345.1365.

4.2.10. 2,2-Dimethyl-1-(4-methyl)-phenyl-1,2,5,10-tetrahydro-benzo[*g*]quinoline-5,10-dione (4g). Obtained as a purple oil. IR (KBr) (ν max., cm^{-1}) 1670, 1626, 1598, 1540; M/S (rel int) *m/z* (M^+, 5), 314 (100),. HRMS found: 329.14158. Calcd for $C_{22}H_{19}NO_2$: 329.14157.

4.3. Attempts to obtain 4b from 3b

Compound **3b** (0.2 mmol) and excess benzylamine (1 ml) or triethylamine (1 ml) were stirred at ambient temperature for three days without any change, by inspection by tlc. The mixture with excess benzylamine was also refluxed in absolute ethanol for up to 24 h, and no trace of **4b** could be visualized by tlc inspection. In order to investigate the proposal made by Weider and cols (see Ref. 13), we submitted the mixture of compound **3b** (0.2 mmol) and chloranil (146.15 mg, 0.6 mmol) in toluene under N_2 to a 36 h reflux period, and, among the various decomposition

products formed, no trace of the corresponding cyclic product **4b** could be observed by tlc inspection.

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References

1. Middleton, R. W.; Patrick, J. Heterocyclic Quinones. *The Chemistry of Quinonoid Compounds*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1988; Vol. 2, p. 1019.
2. (a) Couladouros, E. A.; Plyta, Z. F.; Papageorgiou, V. P. *J. Org. Chem.* **1996**, *61*, 3031. (b) Chu, K.; Griffiths, J. *J. Chem. Res. (M)* **1978**, 2319. (c) Shaikh, I. A.; Johnson, F.; Grollman, A. P. *J. Med. Chem.* **1986**, *29*, 1329.
3. (a) Bouziz, Z.; Nebois, P.; Fillion, H.; Luche, J.; Jenner, G. *Tetrahedron* **1995**, *51*, 4057. (b) Yoon, E. Y.; Choi, H. Y.; Shin, K. J.; Yoo, K. H.; Chi, D. Y.; Kim, D. J. *Tetrahedron Lett.* **2000**, *41*, 7475. (c) Germeraad, P.; Weyler, Jr., W.; Moore, H. W. *J. Org. Chem.* **1974**, *39*, 781.
4. (a) Porter, T. H.; Bowman, C. M.; Folkers, K. *J. Med. Chem.* **1973**, *16*, 115. (b) Lin, T.-S.; Xu, S.-P.; Zhu, L.-Y.; Cosby, L.; Sartonelli, A. *J. Med. Chem.* **1989**, *32*, 1467. (c) Stefanska, J. B.; Dzieduszycka, M.; Martelli, S.; Antonini, I.; Borowski, E. *J. Org. Chem.* **1993**, *58*, 1568. (d) Konoshima, T.; Kozuka, M.; Koyama, J.; Okatani, T.; Tagahara, K.; Tokuda, H. *J. Nat. Prod.* **1989**, *52*, 987.
5. (a) Lin, T.-S.; Xu, S.-P.; Zhu, L.-Y.; Divo, A.; Sartonelli, A. *J. Med. Chem.* **1991**, *34*, 1634. (b) Boger, D. L.; Yasuda, M.; Mitscher, L. A.; Drake, S. D.; Kitos, P. A.; Thompson, S. C. *J. Med. Chem.* **1987**, *30*, 1918.
6. (a) Nagaoka, K.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3783. (b) Furusaki, A.; Watanabi, T. *Chem. Pharm. Bull.* **1973**, *21*, 931.
7. (a) Aristoff, P.; Johnson, P. *J. Org. Chem.* **1992**, *57*, 6234. (b) Kesteleyn, B.; Puyvelde, L. V.; Kimpe, N. D. *J. Org. Chem.* **1999**, *64*, 438. (c) Kesteleyn, B.; Puyvelde, L. V.; Kimpe, N. D. *J. Org. Chem.* **1999**, *64*, 1173. (d) Panetta, C. A.; Fan, P. W.-J.; Fattah, R.; Greever, J. C.; He, Z.; Hussey, C. L.; Sha, D.; Wescott, L. D. *J. Org. Chem.* **1999**, *64*, 2919. (e) Kesteleyn, B.; Kimpe, N. D. *J. Org. Chem.* **2000**, *65*, 640.
8. (a) Joshi, B. S.; Kamat, V. N. *J. Chem. Soc., Perkin Trans. 1* **1975**, 327. (b) Fieser, L. F. *J. Am. Chem. Soc.* **1926**, *48*, 2922.
9. (a) Pinto, A. V.; Pinto, C. N.; Pinto, M. C. F. R.; Emery, F. S.; DeMoura, K. C. G.; Carvalho, C. E. M.; Brinn, I. M. *Heterocycles* **1997**, *45*, 2431. (b) Chavés, J. P.; Pinto, M. C. F. R.; Pinto, A. V. *J. Braz. Chem. Soc.* **1990**, *1*, 22.
10. Spyroudis, S. *Molecules* **2000**, 1291.
11. Oliveira, C. G. T.; Miranda, F. F.; Ferreira, V. F.; Freitas, C. C.; Rabello, R. F.; Carballido, J. M.; Correa, L. C. D. *J. Braz. Chem. Soc.* **2001**, *12*, 339.
12. DeMoura, K. C. G.; Emery, F. S.; Neves-Pinto, C.; Pinto, M. C. F. R.; Dantas, A. P.; Salomão, K.; Castro, S. L.; Pinto, A. V. *J. Braz. Chem. Soc.* **2001**, *12*, 325 and references cited therein.
13. (a) Weider, P. R.; Hegedus, L. S.; Asada, H.; D'Andreq, S. V. *J. Org. Chem.* **1985**, *50*, 4276 and references cited therein. (b) Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. *J. Am. Chem. Soc.* **1978**, *100*, 5800.
14. Naruta, Y.; Maruyama, K. Recents Advances in the Synthesis of Quinonoid Compounds. *The Chemistry of Quinonoid Compounds*; Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1988; Vol. 1, p. 242.
15. Soonthornchareonnon, N.; Swanborirux, K.; Bavovada, R.; Patarapanich, C.; Cassady, J. M. *J. Nat. Prod.* **1999**, *62*, 1390.
16. Hsien, T.; Chang, F.; Wu, Y. *J. Chin. Chem. Soc.* **1999**, *46*, 607; *Chem. Abstr.* 131 297609.
17. Zhang, Y.; Kong, M.; Chen, R. Y.; Yu, Q.-D. *Chin. Chem. Lett.* **1998**, *9*, 1029; *Chem. Abstr.* 131 308836.
18. (a) Serckx-Poncin, B.; Hesbain-Frisque, A.-M.; Ghosez, L. *Tetrahedron Lett.* **1982**, *23*, 3261. (b) Potts, K. T.; Walsh, E. B.; Bhattachargee, D. *J. Org. Chem.* **1987**, *52*, 2285. (c) Ocaña, B.; Espada, M.; Avendaño, C. *Tetrahedron* **1994**, *50*, 9505. For an example that does not involve a Diels–Alder cyclization step in the construction of the aza-anthraquinone nucleus see (d) Molina, P.; Pastor, A.; Vilaplana, M. J.; Foces, C.-F. *Tetrahedron* **1995**, *51*, 1265.
19. (a) Rosa, M. A. MSc Thesis, Instituto de Química, 2000, UNICAMP, 82 p. (b) See Ref. 3b for a discussion of solvent effects in quinone substitution by amines.
20. Corbett, J. F. *J. Chem. Soc., Perkin Trans. 2* **1972**, 539.
21. Thomson, R. H. *Naturally Occurring Quinones*; 2nd ed; Academic Press: London, 1971.