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Direct Amination of Naphthazarin, Juglone, and Some Derivatives

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Direct Amination of Naphthazarin, Juglone, and Some Derivatives

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Abstract: Mono- and diamino-derivatives of naphthazarin, 2-methoxynaphthazarin, juglone and their methylethers were prepared by reaction with ammonia. The structure of the products was established by NMR studies. Some compounds were tested for cytotoxic activity.

Keywords: amination, naphthazarin, naphthoquinones

INTRODUCTION

Amino or imino derivatives of quinones have been the subject of recent interest because of their occurrence as natural products and the variety of their biological activity.[1] Methods of synthesis of these compounds are known,[2] but only a few cases were reported of direct reaction of quinones

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with ammonia.[3] The structural elucidation of the products is often made difficult by the aminoquinone/iminoquinol tautomerism.[3a,4]

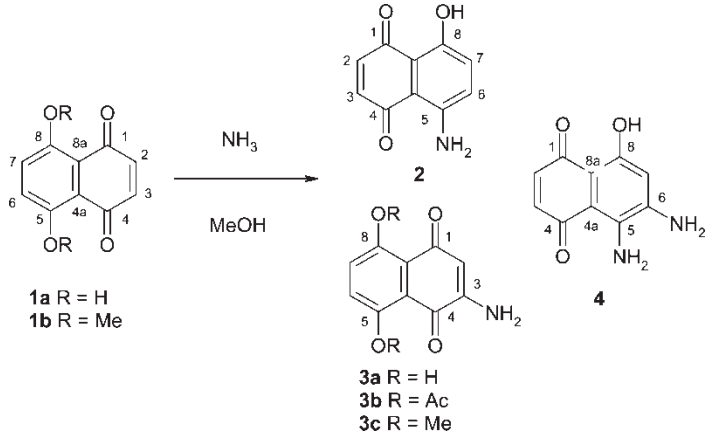
As a part of our studies of natural perylenequinones from fungi,[5] some time ago we reacted cercosporin and phleichrome with ammonia in MeOH to obtain mono- and diamino-derivatives.[6]

The amino-naphthoquinone moiety is a component of the molecular framework of several natural products and has been used as a synthetic key intermediate for the construction of several biologically important compounds.[7] As a part of a program aimed at finding new cytotoxic agents, we describe here the study on direct amination of naphthazarin (NAPH), 2-methoxy-NAPH, juglone, and their methyl ethers and the cytotoxic activity of some amino derivatives. It is interesting to note that most recently the first natural polyhydroxylated naphthazarins with an amino group, echinamines A and B, were isolated from a sea urchin,[8] and their synthesis was reported,[9] but not via direct amination.

RESULTS AND DISCUSSION

Reaction of NAPH **1a** with MeOH saturated with gaseous ammonia proceeded slowly to give, after 24 h, in moderate yields, a mixture of mono (**2**, **3a**) and diamino (**4**) derivatives, which were separated by chromatography and identified on the basis of mass and NMR spectra (Scheme 1).

Compound **2** presented a mass of m/z 189, meaning that one of the carbonyl or hydroxyl functions was substituted with an NH or NH_2 group; its ^{1}H NMR spectrum showed the presence of three exchangeable protons resonating at 13.53 (OH-8), and 7.40 ppm (NH_2-5) and two pairs of *ortho*-coupled protons resonating at 6.97 and 6.98 ppm with $^3J = 10.2$ Hz (H-2 and H-3)



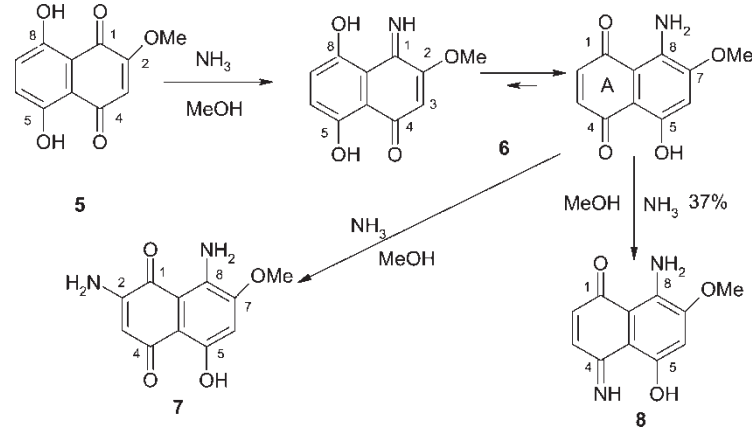
Scheme 1.

and at 7.20 and 7.38 ppm with $^3J = 9.4$ Hz (H-6 and H-7). These data are consistent with structure **2** and with those reported in the literature.[10]

Compound **3a** was analyzed for $C_{10}H_7NO_4$. The presence in the ^{1}H NMR spectrum of two hydrogen bonded OH at 13.48 and 11.89 ppm, of a singlet at 5.96 ppm (H-2), and of the signals of an *ortho* system at 7.18 and 7.31 ppm ($^3J = 9.4$ Hz) proved the formation of the mono-aminoderivative. Because the sample was rather unstable, it was acetylated to give the diacetate **3b**. Again the structure of **3a** was easily identified, because it had been already synthesized from NAPH by amination with O-benzylhydroxylamine.[11]

Compound **4** exhibited a molecular peak in the mass spectrum at m/z 204, suggesting the presence of an additional amino group with respect to **2.** Accordingly, the ^{1}H NMR spectrum showed the presence of five protons resonating at 15.55, 9.35, and 7.23 ppm (OH-8, NH_2-5, and NH_2-6), which disappeared upon addition of D_2O and three aromatic protons, two of them (H-2 and H-3) *ortho*-coupled. The quaternary carbon at 105.32 ppm (C-8a) presented in the ^{13}C NMR spectrum three coupling constants ($^{>1}J_{CH}$) of 5 Hz with OH-8, H-2, and H-7, whereas the corresponding carbon at 106.68 (C-4a) presented $^{>1}J_{CH}$ of 5 Hz with H-3 and NH_2-5. Moreover, the two carbonyl carbons at 175.05 and 181.15 ppm (C-1 and C-4) presented $^{>1}J_{CH}$ of 10 Hz with H-3 and H-2 respectively. All these findings indicate the structure **4** for the compound that derives from **2** or **3a** by introduction of an additional NH_2 group. Treatment of 5,8-di-O-methylnaphthazarin (**1b**) in the same conditions with gaseous ammonia in MeOH gave aminoquinone **3c** as the main product.

A similar behavior is shown by 2-methoxy-NAPH (**5**), where the aminoquinone **6** must undergo a phenol-quinone tautomerization, followed by addition of ammonia onto carbon 4 (to give the imine **8**) or 2 (to give the aminoderivative **7**) (Scheme 2).



Scheme 2.

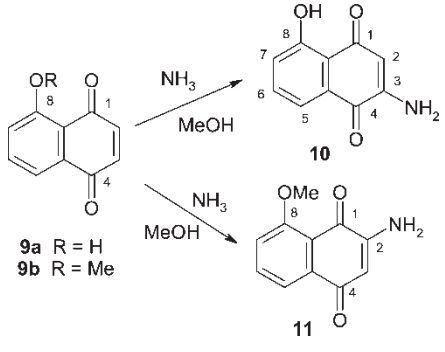
The ^{1}H NMR spectrum of **7** reveals the presence of five exchangeable protons (OH-5, NH_2-2, and NH_2-8), of one OMe group, and of two aromatic singlets (H-3 and H-6). The fact that in a nuclear overhauser effect (NOE) experiment, irradiation of OH-5 enhanced both H-3 and H-6 indicates that the first NH_2 group must be linked at C-2. Moreover the presence of a $^{>1}J_{CH}$ of 7 Hz between H-6 and the quaternary carbon at 141.18 ppm allowed us to assign this carbon as C-8, its chemical shift indicating that it must be attached to the second amino group and not to an oxygen atom. The structure of compound **6** follows from that of **7.** The aromatic pattern in its ^{1}H NMR spectrum is similar to that of the starting compound **5**, the only difference being the larger value of the *ortho* coupling constant (10.3 vs. 9.5 Hz) and the upfield chemical shift of the corresponding protons, due to the quinonoid nature of ring A. Because **6** gives **7**, the exchangeable protons must be assigned to OH-5 and NH_2-8.

The ^{1}H NMR spectrum of **8** exhibited the presence of one singlet at 6.22 ppm and of a pair of *ortho*-coupled protons resonating at different chemical shift values, indicating that one of them is adjacent to the newly entered amino group. Because the chelated hydroxy proton resonates at higher field with respect to **6** (11.66 vs. 14.34), we tentatively assigned to this compound the structure **8** in which the hydroxy proton is in *peri* position with respect to an imino group and not to a quinonoid group.

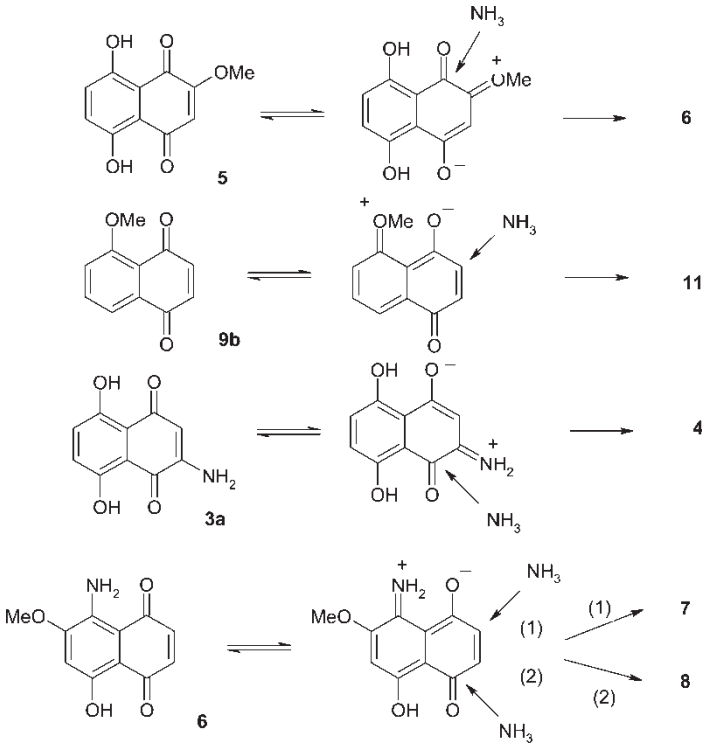
In the case of juglone (**9a**) and its methylether (**9b**), a regioselective addition of ammonia onto the quinone system occurs, with a different orientation apparently induced by the OH and the OMe group respectively (Scheme 3).

The structures of **10** and **11** were established by comparison of their NMR spectra with those reported by Parker and Sworin.[12] In all cases, a remarkable regioselectivity of the addition of ammonia is again observed. In fact, this regioselectivity can be explained by the electronic effects of the substituents (Scheme 4).

It must be observed that all the compounds here reported are in a tautomeric equilibrium of the type shown in Scheme 5, the best example being



Scheme 3.

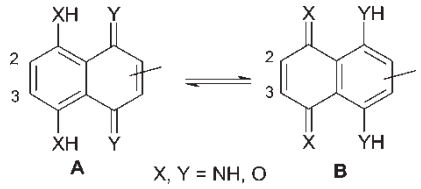


Scheme 4.

naphthazarin **1a**, where the two forms are identical. In the other compounds, the prevalent tautomeric form can be roughly estimated on the basis of the chemical shift of the ring protons that have higher δ values for the aromatic with respect to the quinonoid form.[3] If we assume the value of 7.26 ppm for naphthazarin **1a** as representative of a 1:1 situation, we can suppose that in compounds **2**, **4**, and **6**, where the δ values of the *ortho*-coupled H-2 and H-3 protons are lower (6.98 and 6.97, 6.91 and 6.77, 6.94 and 6.92 respectively) than for **1a**, form B predominates, the opposite holding for compounds **3a** and **5** (7.18 and 7.31, 7.37 and 7.30 respectively).

A further comment is deserved about the trend of the chemical shift of the hydrogen-bonded OH groups *peri* to the quinone carbonyls. There is a steady increase of the chemical shift that is known to be related to the strength of the intramolecular hydrogen bond, from **9a** (11.80), to **1a** (12.16), to **10** (13.37), to **2** (13.53), to **6** (14.34), to **7** (15.39), to **4** (15.55), clearly related to the increase of the electron density on the carbonyl carbon, due to the introduction of electron-donating groups in the rings.

Samples of compounds **4**, **6**, and **7** were tested for their cytotoxic activity in vitro against the tumor cell line H460 and showed modest activity.



Scheme 5.

In conclusion, we report a straightforward method of amination of naphthoquinones that, even if the yields are in some cases modest, could be applied successfully for the synthesis of such compounds.

EXPERIMENTAL

UV absorptions were measured for solutions in 95% EtOH. Mass spectra were obtained with a Finnigan-MATT-TSQ 70-ev spectrometer; NMR spectra were measured on a Bruker spectrometer operating at 400 MHz with Me_4Si as internal standard; HPLC analysis were performed using a LiChroCARTcolumn RP-18 (Merck) on an Agilent 1100 instrument. Flash-column chromatography was performed on Merck silica gel, thin-layer chromatography (TLC) and preparative layer chromatography (PLC) with Merck HF_{254} silica gel. The purity of products was checked by TLC, NMR, and MS and deemed sufficient for the purpose of structural determination.

Compounds **1b**[13] and **9b**[14] were obtained by methylation of NAPH **1a** and juglone **9a** respectively with MeI, Ag_2O, and acetone dry at rt for 3 days in the dark.

2-Methoxy-5,8-dihydroxy-[1,4]naphthoquinone (5)

NAPH (**1a**, 300 mg) was dissolved in 75 ml of CH_3CN; the solution was saturated with Cl_2 and exposed to daylight in a Pyrex® container for 15 min. The solvent was evaporated, and a saturated solution of MeONa in MeOH (200 mg of Na in 55 ml MeOH) was added; the mixture was refluxed for 3 days. The residue was chromatographed on silica gel containing 4% of K_2HPO_4 with CH_2Cl_2 (30:1) as eluent to yield 80 mg of **5**: red crystals, mp 190–195°C, m/z 220 (M^+); ^1H NMR ($CDCl_3$): δ 12.66 and 12.19 (2H, s, OH-5 and -8), 7.30 and 7.22 (2H, d, $J = 9.5$ Hz, H-6 and -7), 6.18 (1H, s, H-3), 3.95 (3H, s, OMe).

General Procedure for Amination

To 100 mg each of compounds **1a**, **1b**, **5**, **9a**, and **9b** dissolved in MeOH (20 ml), a saturated solution of NH_3 in MeOH (5 ml) was added; after 24 h

the solvent was evaporated, and the residue was chromatographed on a column of silica gel (with added 4% KH_2PO_4) with CH_2Cl_2-MeOH as eluent (gradient) and purified further by preparative TLC using a mixture of CH_2Cl_2-MeOH-HCOOH (15:1:0.5 *v*/*v*) as eluant to give compounds **2**, **3a**, **3c**, **4**, **6**, **7**, **8**, **10**, and **11** respectively.

Data

5-Amino-8-hydroxy-[1,4]naphthoquinone (2). Yield 10%, mp 245–250°C dec., ^{1}H NMR (250.1 MHz, acetone-d_6): δ 13.53 (br s, 1H, OH-8), 7.40 (br signal, 2H, NH_2-5), 7.38 and 7.20 (d, $J = 9.4$ Hz, 2H, H-7 and -6), 6.98 and 6.97 (d, $J = 10.2$ Hz, 2H, H-2 and -3).

3-Amino-5,8-dihydroxy-[1,4]naphthoquinone (3a). Yield 13%, mp >270°C dec., ^{1}H NMR (acetone-d_6): δ 13.48 (s, 1H, OH-8), 11.89 (s, 1H, OH-5), 7.31 and 7.18 (d, $J = 9.4$ Hz, H-7 and -6), 6.85 (br signal, 2H, NH_2-3), 5.96 (s, 1H, H-2), m/z 205(M^+). Found: C, 58.83; H, 3.25; N, 6.67; $C_{10}H_7NO_4$ requires C, 58.54; H, 3.44; N, 6.83.

3-Amino-5,8-diacetoxy-[1,4]naphthoquinone (3b). ^{1}H NMR ($CDCl_3$): δ 7.36 and 7.27 (d, $J = 9.8$ Hz, 2H, H-7 and -6), 5.84 (s, 1H, H-2), 5.03 (br signal, 2H, NH_2-3), 2.43 and 2.42 (s, 6H, 2xOAc).

3-Amino-5,8-dimethoxy-[1,4]naphthoquinone (3c). Yield 68%, mp 216–220°C, m/z 233 (M^+); ^{1}H NMR ($CDCl_3$): δ 7.34 and 7.23 (d, $J = 9.8$ Hz, 2H, H-7 and -6), 5.88 (s, 1H, H-2), 4.98 (br signal, 2H, NH_2-3), 3.96 and 3.93 (s, 6H, 2xOMe).

5,6-Diamino-8-hydroxy-[1,4]naphthoquinone (4). Yield 30%, mp 191–195°C, ^{1}H NMR (DMSO-d_6): δ 15.55 (s, 1H, OH-8), 9.35 (br signal, 2H, NH_2-5), 7.23 (br s, 2H, NH_2-6), 6.91 and 6.77 (d, $J = 9.8$ Hz, H-2 and -3), 6.05 (s, 1H, H-7). ^{13}C NMR (62.9 MHz, DMSO-d_6): δ 181.15 (C-4); 175.05 (C-1); 168.37 (C-8); 149.97 (C-6); 142.02 (C-5); 137.75 (C-3); 135.86 (C-2); 106.68 (C-4a); 105.32 (C-8a); 101.05 (C-7).

5-Hydroxy-7-methoxy-8-amino-[1,4]naphthoquinone (6). Yield 15%, mp 218–222°C, m/z 219 (M^+); ^{1}H NMR ($CDCl_3$): δ 14.34 (s, 1H, OH-5), 9.20 (br signal, 2H, NH_2 -8), 6.94 and 6.92 (d, $J = 10.3$ Hz, 2H, H-2 and -3), 6.50 (s, 1H, H-6), 4.00 (s, 3H, OMe-7).

2,8-Diamino-5-hydroxy-7-methoxy-[1,4]naphthoquinone (7). Yield 25%, mp 214–220°C, m/z 234 (M^+); ^{1}H NMR (DMSO-d_6): δ 15.39 (s, 1H, OH-5), 9.11 (br signals, 2H, NH_2-8), 7.25 (br signals, 2H, NH_2-2), 6.62 (s, 1H, H-6), 5.72 (s,1H, H-3), 3.92 (s, 3H, OMe-7). ^{1}H NMR (NOE_s, DMSO-d_6):

irradiation of H-6 enhanced OH-5 (2%) and OMe-7 (4%); irradiation of OH-5 enhanced H-3 (1.5%) and H-6 (2%); irradiation of OMe-7 enhanced H-6 (8.5%). ^{13}C NMR (DMSO-d_6): δ 184.20 (C-4); 178.04 (C-1); 157.88 (C-5); 153.59 (C-7); 152.56 (C-2); 141.18 (C-8); 106.02 (C-6); 105.79 (C-8a); 103.71 (C-4a); 100.24 (C-3); 56.44 (OMe). HREIMS, m/z 234.0654 ($C_{11}H_{10}N_2O_4$ requires 234.0640).

8-Amino-5-hydroxy-4-imino-7-methoxy-4H-naphthalene-1-one (8). Compound **8** was obtained by treating **6** with NH_3 37% at 50°C for 30 min. Yield 55%. M/z 218 (M^+), ^{1}H NMR (acetone-d_6): δ 11.66 and 7.48 (br signals, 4H, NH_2, NH and OH), 7.24 and 6.77 (d, $J = 9.8$ Hz, 2H, H-2 and -3), 6.22 (s, 1H, H-6), 3.97 (s, 3H, OMe-7). HREIMS, m/z 218.0663 ($C_{11}H_{10}N_2O_3$ requires 218.0691).

3-Amino-8-hydroxy-[1,4]naphtoquinone (10). Yield 20%, mp 180–186°C, m/z 189 (M^+); ^{1}H NMR (DMSO-d_6): δ 13.37 (s, 1H, OH-8), 7.90 and 7.52 (br signals, 2H, NH_2-3), 7.56 (dd, $J = 8.5$ and 8.2 Hz, 1H, H-6), 7.48 (br,$J = 8.2$ Hz, 1H, H-5), 7.27 (br, $J = 8.5$ Hz, 1H, H-7). ^{13}C NMR (DMSO-d_6): δ 188.79 (C-1); 181.65 (C-4); 160.54 (C-8); 152.31 (C-3); 134.53 (C-6); 130.99 (C-4a); 125.41 (C-7); 118.75 (C-5); 114.95 (C-8a); 101.03 (C-2).

2-Amino-8-methoxy-[1,4]naphtoquinone (11). Yield 60%, mp 154–158°C, m/z 203 (M^+); ^{1}H NMR ($CDCl_3$): δ 7.75 (br d, $J = 8.2$ Hz, 1H, H-5), 7.67 (dd, $J = 8.4$ and 8.2 Hz, 1H, H-6), 7.21 (br d, $J = 8.4$ Hz, 1H, H-7), 5.94 (s, 1H, H-3), 5.29 (br signal, 2H, NH_2-2), 4.02 (s, 3H, OMe-8).

Cytotoxicity Assay

Some compounds were tested for their cytotoxicity against the non-small cell lung tumor cell line H460 and showed modest activity [IC_{50} (μM): 16.5 for **4**, 26.5 for **6** and 72.0 for **7**].

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