Complex Diazaazulenones from the Reaction of *ortho*-Naphthoquinones with Ammonium Acetate

Flavio S. Emery,[a,d] Maria do Carmo F. R. Pinto,[a] Carlos A. de Simone,[b,c] Valéria R. S. Malta,[b] Eufrânio N. da Silva Júnior,*[a] Antonio V. Pinto[a]

[a] Núcleo de Pesquisas de Produtos Naturais, UFRJ, 21944-971, Rio de Janeiro, RJ, Brazil
Fax +55(21)25626512; E-mail: eufranio.junior@yahoo.com.br

[b] Instituto de Química e Biotecnologia, UFAL, 57072-970, Tabuleiro do Martins, Maceió, Al, Brazil

[c] Departamento de Física e Informática, Instituto de Física, USP, 13560-160, São Carlos, SP, Brazil

[d] Faculdade de Ciências Farmacêuticas, USP, 14040-903, Ribeirão Preto, SP, Brazil

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This paper is dedicated in the memory of our beloved Professor Antonio Ventura Pinto, who passed away on March 18th, 2010.

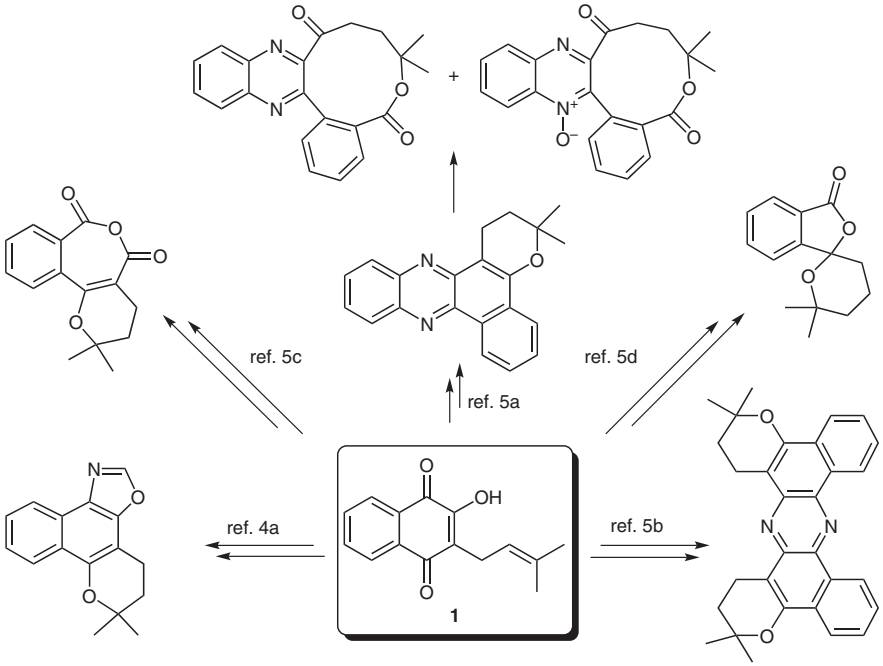
Abstract: Complex diazaazulenones compounds were obtained from *ortho*-naphthoquinones by reaction with ammonium acetate.

Key words: lapachones, heterocycles, diazaazulenone, X-ray crystallography

Heterocycles are an important class of compounds with diverse medicinal applications.[1–3] Lately, new heterocycles obtained from naphthoquinoidal compounds were developed,[4] starting from naturally occurring quinoidal compounds, such as lapachol (**1**) and β-lapachone (**2**), resulting in macrolactones, oxazoles, and other important compounds[5] (Scheme 1). In addition, some of these heterocyclic compounds showed activity against cancer cell lines,[6] the etiological agents of Chagas' disease,[2] malaria (*Plasmodium falciparum*)[3] and also against agents of other severe diseases[7] and emerge as important chemotherapeutic prototypes.

In one of our publications employing quinoidal compounds, it was reported that the reaction of β-lapachone (**2**) and nor-β-lapachone (**3**) with ammonium acetate yielded complex reaction mixtures of products in both cases.[5b]

In a preliminary study, it was possible to identify fluorescent symmetric phenazines **4** and **5** from nor-β-lapachone (**3**), and compounds **6** and **7** from β-lapachone (**2**), respectively. The phenazines in each reaction were present in the more apolar fractions eluted from chromatographic columns (Scheme 2).[5b] These phenazinic compounds present very important photophysical properties.[8a] However, the more polar products from these reactions have not been studied until now. What follows is the first report of the



Scheme 1 Heterocycles obtained from lapachol (**1**) via several reactions types

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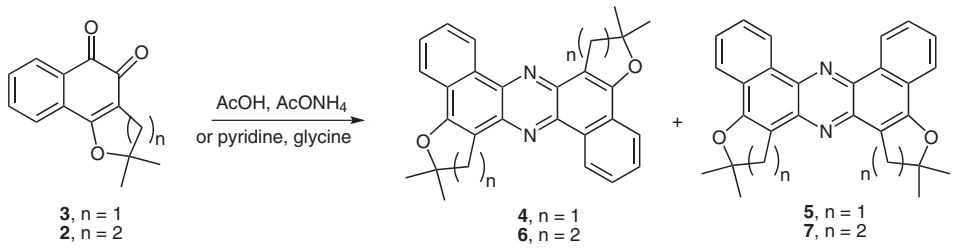


Scheme 2 Fluorescent symmetric phenazines from β-lapachone (**2**) and nor-β-lapachone (**3**)

structure of more the polar products from these two reactions.

The reactions of β-lapachone (**2**) and nor-β-lapachone (**3**) with ammonium acetate were carried out in acetic acid solution at reflux temperature. After vacuum evaporation of the solvent, the crude extract was eluted in a silica gel chromatographic column with a gradual increase of solvent polarity. In both reactions a bright yellow phenazinic fluorescent product was isolated.

In proceeding with elution, at the corresponding polarity of 2.5–3.5% (EtOAc–hexane) of the solvent system, compounds **8** and **9** were obtained from **3**. From the reaction of **2**, only **10** was isolated in the polarity corresponding to 3.5% of ethyl acetate in hexane (Scheme 3).

Only one diazaazulenic isomer was obtained from compound **2**, the transoid isomer. As a hypothesis, we suggest that the larger pyran cycles in the intermediate favors this diasteromer in relation to the cisoid one, with two pyran groups on the same side.

The proposed structures of all compounds are in agreement with their respective spectral data, such as ^{1}H NMR, ^{13}C NMR, IR, UV/vis, and MS data. Compound **9**, the transoid isomer, was reconfirmed by X-ray crystallography (Figure 1).[9–11]

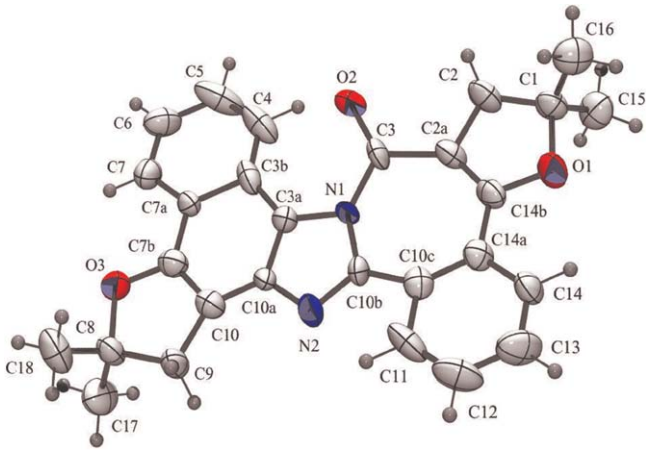
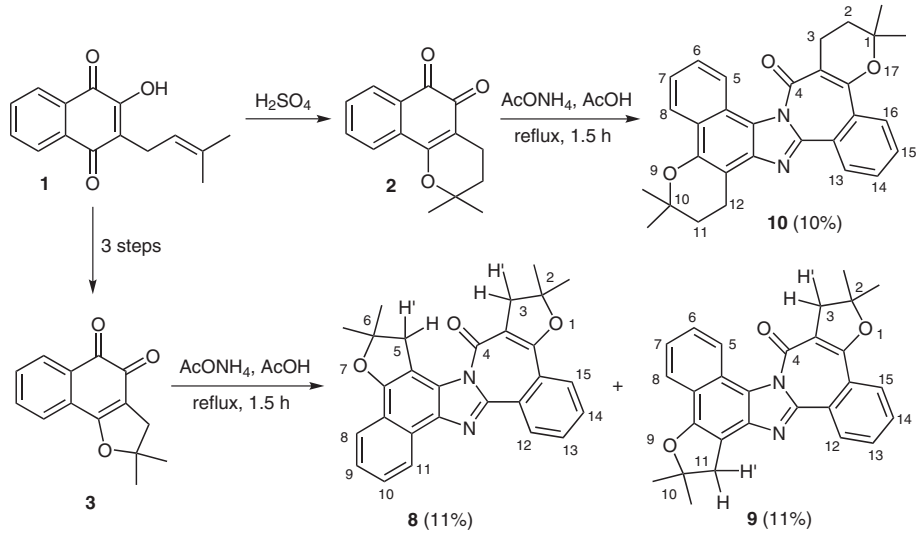


Figure 1 An ORTEP-3 projection, showing the atomic labelling and the 50% probability ellipsoids of compound **9**

Notably, the MS of **8** and **9** showed the same fragmentation pattern and similar *m/e* values for the molecular ions (*m/e* = 436) indicating an isomeric relationship between these two structures. The MS of **10** suggests that this compound is the next superior homologue of **9** (*m/e* = 464).

The structural correlation between **8**, **9**, and **10** are corroborated by IR spectra and these compounds have almost the same absorption band for the carbonyl groups, at 1665, 1663, and 1667 cm^{-1}, respectively.

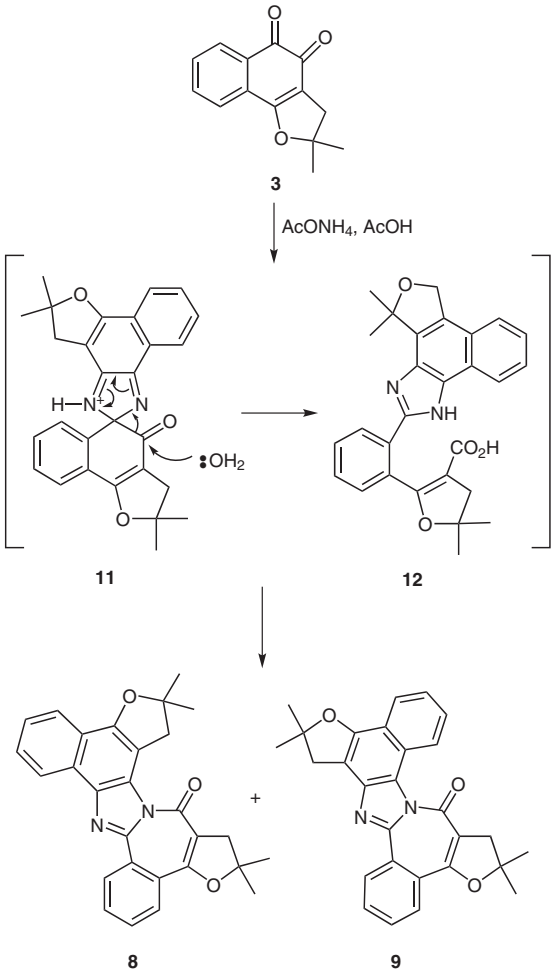


Scheme 3 Diazaazulenones obtained from β-lapachone (**2**) and nor-β-lapachone (**3**)

The ^{13}C NMR spectra of **8**, **9**, and **10** showed similar chemical shifts for the carbonyls, at δ = 160.8, 161.3, and 162.2 ppm, respectively, being compatible with carbonyl lactams from what would be expected for the proposed diazaazulenone compounds. In the ^{1}H NMR spectra for the transoid diazaazulenone **9** it was observed that the methylenic hydrogens H3 and H3′ at δ = 3.4 or 3.6 ppm and H11 and H11′ at δ = 3.4 or 3.6 ppm have similar chemical shifts. In comparison with the one cisoid isomer, compound **8**, the methylenic hydrogens H3 and H3′ at δ = 3.3 or 3.8 ppm and H5 and H5′ at δ = 3.3 or 3.8 ppm, indicating that the carbonyl group deshields the latter methylenic hydrogens in the furanic ring, supporting the interpretation of a cisoid structure.

In compound **10**, the furanic methylenes showed very similar shifts in the NMR spectra, at δ = 3.1 and 3.3 ppm for H2, H3, H11, and H10, respectively. The signals of the furanic methylenes and the aromatic hydrogen being quite comparable to the ones of **9** suggests that **10** is also a transoid diazaazulene.

For the formation of these compounds the mechanism proposed is shown in Scheme 4.[8b] The formation of diazaazulenones from naphthoquinones **3** must go on from the initial formation of intermediate **11** that then rearranges to the diazaazulenone structures. Intermediate **12** can explain the formation of cisoid and transoid derivatives for nor-β-lapachone (**3**).



Scheme 4 Mechanism proposed for the formation of diazaazulenone compounds from lapachones

In conclusion, we have described a new chemical reaction path of quinoidal compounds for the formation of diazaazulenone structures.[12] The easy preparation of the complex heterocycles in one step using simple substrates and reagents clearly demonstrates the importance of this line of attack.

Acknowledgment

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(9) A orange crystal (0.086 × 0.150 × 0.240) mm^3 of compound **9** was selected for X-ray diffraction. Intensity data were collected at r.t. (T = 298K) using a diffractometer Kappa CCD of Enraf Nonius with MoKα monochromatic radiation

(λ = 0.71073 Å) and using the Collect[10a] software, as well as Scalepack[10b] for cell refinement. The compound **9** was measured a total of 4349 reflections to a maximum 2θ of 27.42°. No significant absorption effect (μ = 0.088 mm^{-1}) for compound **9** was revealed, so no absorption correction was applied. The crystal structure for compound **9** was solved by direct methods and refined anisotropically with full matrix least square on F^2 using SHELXL-97 program.[10c] H atoms attached to C atoms were located on stereochemical grounds placed (C–H = 0.93–0.98 Å) and refined as riding with $U_{iso}(H) = 1.5\ U_{eq}$ (C-methyl) or $1.2\ U_{eq}$(other) times the value of the equivalent isotropic displacement parameter of atoms to which they are bonded. The software used were: data collection: COLLECT;[10a] cell refinement: HKL SCALEPACK;[10b] data reduction: HKL DENZO and SCALEPACK.[10b] The program (s)used to solve structure: SHELXS-97.[10d] The program (s)used to refine structure: SHELXL-97.[10c] molecular graphics: ORTEP-3, software used to prepare material for publication: WinGX.[10e] Crystallographic data for compounds **9** have been deposited with the Cambridge Crystallographic Data Center as Supplementary Publication No. CCDC 739857. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CH21EZ, UK (fax:+44 1223 336 033 or e-mail: deposit@ccdc.cam.ac.uk).

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(11) **Crystal Data and Structure Refinement for Compound 9**
Empirical formula: $C_{28}H_{24}N_2O_3$; formula weight: 436.49; temperature: 295 (2) K; wavelength: 0.71073 Å; crystal system: monoclinic; space group: Pn; unit cell dimensions: a = 5.32360 (10) Å, b = 9.9426 (3) Å, β = 95.6930 (10)°, c = 20.1385 (7) Å; volume: 1060.68 (5) $Å^3$; Z: 2; density(calcd): 1.367 mg/m^3; absorption coefficient: 0.088 mm^{-1}; F(000): 460; crystal size: (0.086 × 0.150 × 0.240) mm^3; θ range for data collection: 2.29–27.42°; index ranges: $-6 \le h \le 6$, $-12 \le k \le 11$, $-26 \le l \le 25$; reflections collected: 4349; independent reflections: 4219 [R(int) = 0.060]; completeness to θ = 27.42°: 98.7%; absorption correction: none; refinement method: full-matrix least-squares on F^2; data/restraints/parameters: 4219/2/365; goodness-of-fit on F^2: 1.077; final R indices [$I > 2\sigma(I)$]: $R1$ = 0.0562, $wR2$ = 0.1403; R indices (all data): $R1$ = 0.0803, $wR2$ = 0.1662; largest diff. peak and hole: 0.305 and –0.343 e $Å^{-3}$.

(12) Melting points were obtained on Thomas Hoover and are uncorrected. Analytical grade solvents were used. Column chromatography was performed on silica gel (Acros Organics 0.035–0.070 mm, pore diameter ca 6 nm). Infrared spectra were recorded on a Perkin-Elmer FT-IR spectrometer. ^1H and ^{13}C NMR were recorded at r.t. using a Varian Gemini 200, in the solvents indicated, with TMS as internal standard. Chemical shifts (δ) are given in ppm. Electron-impact mass spectra (70 eV) were obtained using a VG Autospec apparatus (Micromass, Manchester, UK). The main fragments were described as a relation between atomic mass units and the charge (m/e) and the relative abundance in percentage of the base peak intensity. Lapachol(**1**) was extracted from the hardwood *Tabebuia sp.* (*Tecoma*) and purified by a series of recrystallizations with the appropriate solvent.[13a] β-lapachone (**2**) was obtained by acid cyclization from lapachol (**1**) by Hooker's methodology.[13b]

General Procedure for the Synthesis of the Compounds 8–10

To 1.0 mmol of β-lapachone (**2**) or nor-β-lapachone (**3**) in a solution of glacial AcOH (10.0 mL), was added NH_4OAc (14.4 mmol), followed by reflux for 2.5 h. After cooling, the reaction medium was poured in H_2O, and the solid residue was filtered under vacuum, washed with water for neutralization and soon after the solid was chromatographed in a silica gel column starting with hexane as eluent. In preparing **8**, the compound was found in a polarity corresponding to 2.5% of the EtOAc–hexane gradient. In obtention of **9**, the compound was chromatographed in the EtOAc–hexane gradient corresponding to 3.5%. Compound **10** was obtained in the EtOAc–hexane gradient corresponding to 3.5%. The orange solids were recrystallized in a mixture of hexane–acetone (1:1).

Spectroscopic Data of Compound 8

Orange crystals; mp 244–245 °C; yield 11.2%. IR (KBr): 3064, 2963, 2924, 2851, 1665, 1629, 1499, 1388, 1284, 1172, 1074, 1062, 1020, 870, 759, 703 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 9.4 (dd, 1 H), 8.8 (dd, 1 H), 8.1 (dd, 2 H), 7.6 (m, 4 H), 3.8 (s, 2 H), 3.3 (s, 2 H), 1.6 (s, 12 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 160.8, 159.5, 153.6, 144.2, 133.5, 131.3, 129.0, 127.2, 126.4, 125.7, 125.3, 123.2, 122.7, 122.2, 120.1, 108.4, 107.4, 86.2, 85.7, 47.7, 45.1, 29.6, 28.4, 28.2. UV (EtOH): λ_{max} (log ε) = 373.0 (4.09), 328.5 (4.29), 315.5 (4.27), 264.5 (4.36), 228.0 (4.49), 205.5 (4.40) nm. MS (70 eV): m/z (%) = 437 (33), 436 (100), 421 (15), 393 (8,0), 341 (8,0), 325 (20), 297 (6), 218 (5).

Spectroscopic Data of Compound 9

Orange crystals; mp 265–268 °C; yield 11.2 (%). IR (KBr): 3074, 3058, 2976, 2928, 2856, 1663, 1630, 1601, 1531, 1460, 1385, 1276, 1250, 1117, 1069, 867, 752, 710 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 9.3 (dd, 1 H), 8.4 (dd, 1 H), 8.1 (m, 2 H), 7.6 (m, 4 H), 3.6 (s, 2 H), 3.4 (s, 2 H), 1.6 (s, 12 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 161.3, 158.8, 154.5, 148.8, 139.7, 131.4, 131.0, 129.6, 128.2, 127.2, 126.6, 125.0, 124.0, 123.2, 122.5, 120.3, 109.7, 108.1, 88.3, 86.0, 45.3, 41.8, 28.4, 28.2. UV (EtOH): λ_{max} (log ε) = 373.0 (3.99), 328.5 (4.19), 315.5 (1.32), 265.0 (1.62), 228.5 (2.21), 203.0 (2.03) nm. MS (70 eV): m/z (%) = 436 (100), 421 (34), 393 (10,6), 341 (8.7), 325 (42), 297 (10), 218 (9), 140 (11), 41 (22).

Spectroscopic Data of Compound 10

Orange crystals; mp 243–245 °C; yield 10%. IR (KBr): 3094, 2973, 2920, 2850, 1667, 1611, 1597, 1584, 1529, 1459, 1446, 1365, 1348, 1316, 1282, 1255, 1158, 1117, 1087, 760, 720, 701 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 9.0 (d, 1 H), 8.3 (d, 1 H), 8.1 (m, 2 H), 7.6 (m, 4 H), 3.3 (t, 2 H), 3.1 (t, 2 H), 2.0 (m, 4 H), 1.6 (s, 12 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 168.2, 155.2, 147.8, 147.2, 141.5, 130.7, 129.6, 129.6, 126.5, 125.8, 125.4, 125.0, 123.9, 123.0, 122.8, 121.7, 121.3, 109.5, 106.9, 76.8, 74.7, 32.2, 31.7, 26.6, 26.3, 22.8, 18.4. UV (EtOH): λ_{max} (log ε) = 364 (4.01), 306 (4.62), 230 (4.67) nm. MS (70 eV): m/z (%) = 464 (5), 408 (2), 352 (2), 44 (13), 40 (100).

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