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Unexpected transformation of quinones to spirolactones and to naturally occurring naphthalenic compounds

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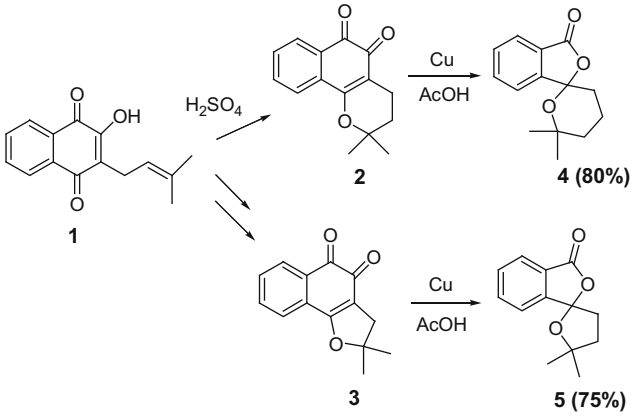
ABSTRACT

In the last few years, natural quinones of the lapachol group have been used as starting points for the preparation of several bioactive heterocyclic compounds. Herein, we announce that lapachones, derivatives of lapachol, under certain conditions in the presence of inorganic reagents give unexpected products, spirolactones and naphthalenic derivatives, nordihydrolapachenone and tetrahydrotectol, both naturally occurring compounds. Nordihydrolapachenone was identified by X-ray analysis. Lapachol itself can also be converted to tetrahydrotectol.

Lately, interest for spiro acetals and spirolactones has been stimulated by the discovery of several important pharmacological compounds endowed with these subunits in their chemical structures.[1,2] For instance, many marine toxins including the spirolides,[3–5] pinnatoxins,[6,7] and pteriatoxins[8] are naturally occurring compounds with spirocyclic subunits in their molecular skeleton. The presence of such subunits brings about pertinent challenges in organic synthesis,[2,3,9,10] as in Brimble's[11] recent article reporting the construction of the aromatic spiroketal subunits of rubromycins, a family of antibiotics isolated from Streptomyces's cultures which exhibits activity against Gram-positive bacteria.[12] Another challenging area in organic synthesis is the compounds belonging to the binaphthyl group,[13–15] which has led to the development of new synthetic methodologies of substantial importance.[16,17]

The great interest for these conspicuous classes of important compounds has motivated us to report herein unexpected reactions that lead to two of these compound classes, outcomes that proved to be of practical importance in organic synthesis and represent new chemical reactivities of the quinoidal structure not yet cited in the pertinent organic chemistry literature.

In the course of our studies on the chemical reactivity of quinones from the Brazilian flora (bignoniaceae), we hoped to carry out the reduction of the quinoidal compounds **2** and **3** to the respective quinols by using powdered copper in acetic acid, but surprisingly we observed the formation of colorless spirocyclic products **4** and **5**,[18] respectively (Scheme 1). Normally, the reaction of naphthoquinones to the respective quinols is easily conducted by using Zn/HOAc,[19] but the use of metallic copper revealed unanticipated new reactions.



Scheme 1. Synthetic route[21] to obtain the spirolactones **4** and **5.**

Another unexpected reaction in our studies emerged when we tried to cyclize lapachol (**1**) to β-lapachone (**2**) using HI as acidic agent. Usually, the cyclization of **1** to **2** is easily realized with sulfuric acid or HCl, but in this report, the acidic condition used results in the formation of colorless crystals, compound **6**,[20] Scheme 2, identified as tetrahydrotectol, a natural product that occurs in *Tabebuia avellanedae* (*bignoniaceae*).[20] This reaction course reveled a new anomalous type of reactivity of the naphthoquinonoid structure under acidic conditions. We also observed that β-lapachone (**2**) in HI/HOAc solution formed compound **6** in good yield. It was also possible to distinguish in the first crystallization step, the

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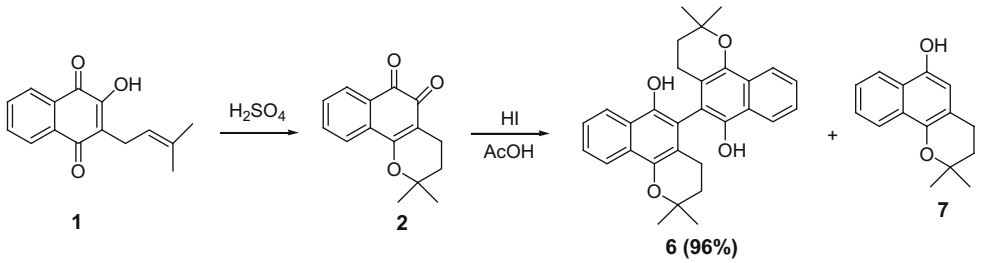


Scheme 2. Reaction of β-lapachone with HI. Obtaintion of tetrahydrotectol (**6**).

presence of distinct colorless crystals of a compound corresponding to **7**, as a trace by-product. After the usual workup, traces of **7** can be observed in the borders of the crystallization flask, and by careful collection with the aid of a tong, **7** can be separated from **6**. Further re-crystallization of the remaining mass gave pure **6**. The structure of **7** was determined by X-ray crystallographic analysis, and compound **7** was identified as being nordihydrolapachenole, a compound extracted from *T. avellanedae* (bignoniaceae).[20]

The assigned structure of **6** was promptly determinated by comparison with the spectroscopic and physical data reported in the literature for this compound.[21a] It is interesting to observe, inter alia, that our formal chemical sequence starting with **1**, and going through **2**, **6**, and **7**, may be considered a hypothetical chemical mimicry of the biogenetic pathway for these compounds in the bignoniaceous plants. Unfortunately, our attempts to obtain appropriate crystals of **4**, **5**, and **6** for X-ray analyses were fruitless.

Lapachol (**1**) was extracted from the heartwood of *Tabebuia sp.* (*Tecoma*) and was purified by a series of recrystallizations. The synthesis of **3** from lapachol (**1**) was made according to Hooker's methodology. [21b,c]

The spectroscopic and mass spectrometric data of the new compounds **4** and **5** and those of tetrahydrotectol (**6**) are in accordance with the proposed chemical structures. In an exploratory reaction, compounds **4** and **5** were treated with methanol/$HCl_{(g)}$ at room temperature, resulting in high yields of colorless oils. Further, as seen from analysis by ^{1}H and ^{13}C NMR spectroscopy, it was possible to conclude that these products are an equilibrium mixture of tautomers **8**/**9** (1:1) in $CDCl_3$ as a solvent[22] (Scheme 3). These results are in some way coherent with the formation of alcohol, which after ketalization generates the subsequent spirolactone as proposed in Scheme 4.

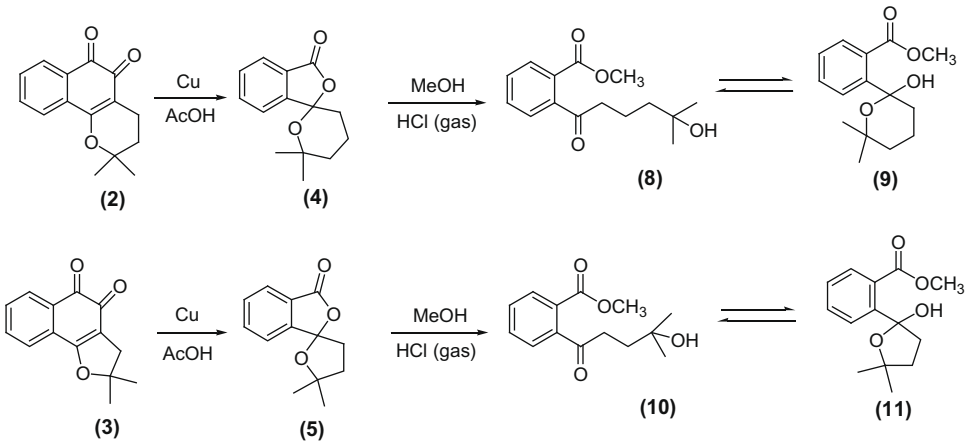
In the electron-impact mass spectrum (70 eV) for the equilibrium keto-ketal, compounds **8**/**9**, the colorless ester product does not show the presence of the inspected molecular ion fragment [M^+] at *m*/*e* 264, but clearly did show the fragment [M^+-H_2O], *m*/*e* at 246, a coherent and expected dehydration for a hemicetal/tertiary alcohol (Scheme 3). For the other equilibrium keto-ketal, compounds **10**/**11**, the results were similar.

Mechanistically, we propose that the formation of spirolactones does first occur by oxidative cleavage of the *ortho*-quinone moieties,[23] followed by hydrolysis and decarboxylation in the workup steps. The final products **4** and **5** were obtained after the lactonization as demonstrated in Scheme 4. For the formation of the binaphthyl **6**, it can be proposed that carbonyl quinoidal group after protonation with iodidric acid does suffer nucleophilic attack followed by lost of water and iodine. The formed radical intermediate suffers coupling with itself leading to the formation of binaphthyl product as described in Scheme 5.

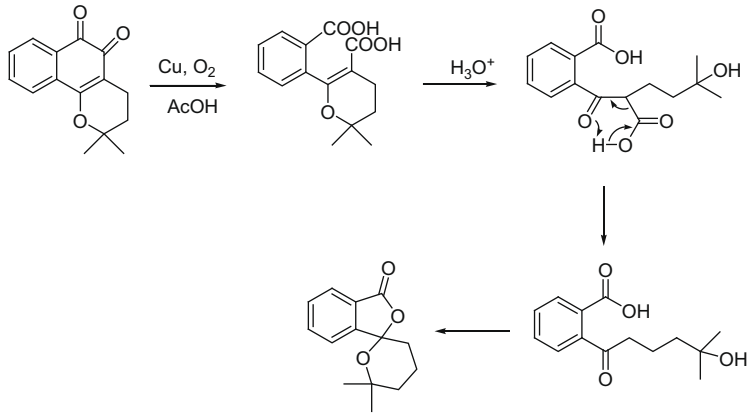
To the best of our knowledge, the two reactivates reported here for our naphthoquinones represent new reactions of the quinoidal structure which are not yet cited in the literature. We hope that these new reactions of quinones will be eventually useful for the elaboration of synthetic routes toward spirolactones and binaphthols units.

2. X-ray analysis of compound 7

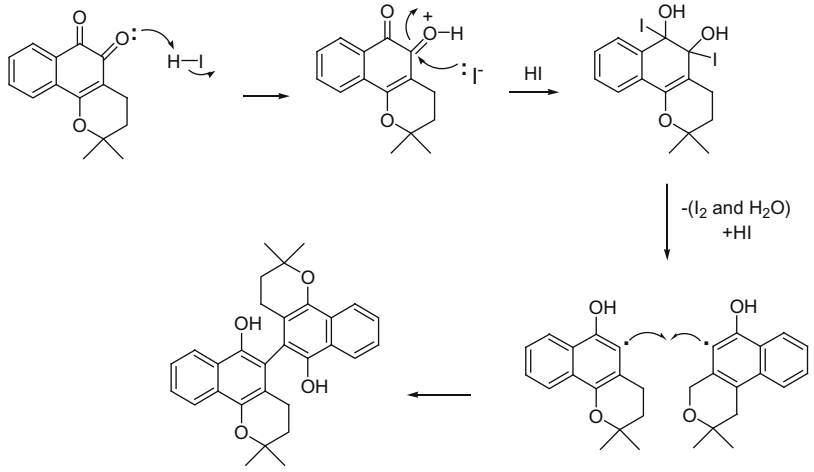
X-ray diffraction data collections were performed on an Enraf-Nonius Kappa-CCD diffractometer (95 mm CCD camera on κ-goniostat) using graphite monochromated Mo Kα radiation (0.71073 Å) at room temperature. Data collections were carried out using the COLLECT software[24] up to 50° in 2θ. Final unit cell parameters were based on 2938 reflections. Integration and scaling of the reflections, correction for Lorentz and polarization effects were performed with the HKL DENZO-SCALEPACK system of programs.[25] The structure of the compound was solved by direct methods with SHELXS-97.[26] The models were refined by full-matrix least squares on F^2 using SHELXL-97.[27] The program ORTEP-3[28] was



Scheme 3. Equilibrium keto-ketal, compounds **8**/**9** and compounds **10**/**11**.



Scheme 4. Mechanism proposed for the formation of spirolactones.



Scheme 5. Mechanism proposed for the formation of tetrahydrotectol (**6**).

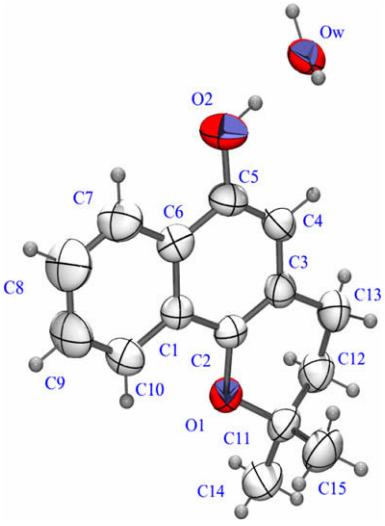


Figure 1. A projection ORTEP3 of **7**, showing the atom-numbering and displacement ellipsoids at the 50% probability level.

used for graphic representation and the program WINGX[29] was used to prepare materials for publication. All H atoms were located by geometric considerations placed (C–H = 0.93–0.98 Å) and were refined as riding with $U_{iso}(H) = 1.5U_{eq}$(C-methyl) or $1.2U_{eq}$(other). An

Table 1
Crystallographic parameters

Empirical formula	$C_{15}H_{16}O_2 \cdot H_2O$
Formula weight (g mol^{-1})	238.29
Temperature (K)	293(2)
Crystal dimensions (mm)	0.19 × 0.13 × 0.11
Crystal system	Tetragonal
Space group	*P*42
Unit cell dimensions	
a (Å)	12.6820(1)
b (Å)	12.6820(8)
c (Å)	8.0840(3)
V (Å^3)	1300.17(1)
Z	2
λ (Mo Kα) radiation (Å)	0.71073
Calcd density (mg m^{-3})	1.22
μ (Mo Kα) (mm^{-1})	0.081
F_{000}	512
θ Range for data collection (°)	2.9–27.5
Index range	$-16 \leqslant h \leqslant 12$
	$-10 \leqslant k \leqslant 13$
	$-10 \leqslant l \leqslant 8$
Reflections collected	5223
Independent reflections [R_{int}]	2838 [0.033]
Reflections with $I > 2\sigma(I)$	2030
Number of parameters refined	160
R [$F^2 > 2\sigma(F^2)$]	0.06
Goodness-of-fit on F^2	1.12
Residual electron density (e Å^{-3})	0.14

Ortep-3 diagram of the molecule is shown in Figure 1, and Table 1 shows the main crystallographic parameters.

Bond lengths and angles are in good agreement with the expected values reported in the literature.[30] The atoms of the naphthoquinonic ring are coplanar, and the largest deviation [0.028(2) Å] from the least-square plane is exhibited by atom C4. Atom O2 lies in the mean least-square plane of the naphthoquinonic ring with deviations of 0.062(2), while atom O1 is 0.125(2) Å out of that plane. The pyrano ring has a half chair conformation, and the puckering parameters calculated for this conformation were $q_2 = 0.3500(3)$ Å, $q_3 = 0.3157(2)$ Å, $Q = 0.4713(3)$ Å, $\theta = 47.9(3)^\circ$ and $\varphi = -149.9(5)$.[31] The compound crystallized with one solvent water molecule that forms OW–H1W···O1^{i} and OW–H2W···O1^{ii} [i = x, y, $z-1$; ii = $-x+1$, $-y$, $z-1$] hydrogen-bonding interactions where H1W···O1^{i} = 2.260(2) Å; OW–H1W···O1^{i} = 110° and H2W···O1^{ii} = 1.906(2) Å; OW–H2W···O1^{ii} = 165°. Crystallographic data for compound **7** have been deposited with the Cambridge Crystallographic Data Center as Supplementary Publication No. CCDC 697642. 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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18. ^{1}H and ^{13}C NMR were recorded at room temperature using a Varian Gemini 200 (Varian, Palo Alto, CA, USA) in the solvents indicated, with TMS as internal standard. Chemical shifts (δ) are given in ppm and coupling constants (J) in Hertz. IR spectra were recorded using Perkin–Elmer and Nicolet IRFT. The mass spectra were obtained at 70 eV in a VG-autospec. The fragments were described as a relation between atomic mass units and the charge (m/z) and the relative abundance in percentage of the base peak intensity. General procedure for the synthesis of the spirolactones **4** and **5**: 3 g of finely divided metallic copper, under strong agitation, was added to 1 mmol of the corresponding quinone dissolved in 10 mL of acetic acid. The reaction mixture was stirred at 60 °C for 20 h. After the end of the reaction was confirmed by TLC, the mixture was added to H_2O and extracted with CH_2Cl_2 (3 × 50 mL) and washed several times with H_2O. After the organic phase was dried with Na_2SO_4, the solvent was evaporated under reduced pressure. The residue was chromatographed over silica gel and eluted with mixtures of hexane/EtOAc of increasing polarity. With 3% EtOAc/hexane, the colorless oils were isolated and characterized as being the corresponding spirolactone **4** (80% yield) or **5** (75% yield). Spirolactone **4** λ_{max} (EtOH) nm ($\log\varepsilon$): 221 (4.10). MS [70 eV, m/z (%)]: 217(15), 204(10), 188(12), 174(9), 159(50), 149(100), 105(45), 84(90), 77(30), 56(80). IR (KBr) cm^{-1}: 2970, 2940, 1770, 1620, 1610, 1280, 1100, 770, 750, 700. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.8 (1H, dt, J = 0.8, 8.0 Hz), 7.7 (1H, ddd, J = 2.0, 8.0, 7.9 Hz), 7.6 (1H, m), 7.5 (1H, m), 2.4–1.6 (6H, m), 1.5 (3H, s), 1.3 (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 168.5 (C=O), 150.0 (C_0), 134.0 (CH), 129.9 (CH), 126.4 (C_0), 124.9 (CH), 121.9 (CH), 107.4 (C_0), 75.7 (C_0), 35.1 (CH_2), 33.6 (CH_3), 31.7 (CH_2), 26.3 (CH_3), 16.0 (CH_2). Spirolactone **5** λ_{max} (EtOH) nm ($\log\varepsilon$): 223 (4.07). MS [70 eV, m/z (%)]: 203(20), 185(15), 174(60), 160(50), 149(40), 105(100), 77(30). IR (KBr) cm^{-1}: 2964, 1754, 1615, 1284, 1123, 1087, 774, 756, 731. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.8 (1H, d), 7.7 (1H, t), 7.6 (1H, t), 7.5 (1H, d), 2.6–2.0 (4H, m), 1.5 (3H, s), 1.4 (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 168.0 (C=O), 146.7 (C_0), 134.2 (CH), 130.2 (CH), 127.3 (C_0), 124.9 (CH), 122.0 (CH), 114.3 (C_0), 86.3 (C_0), 37.9 (CH_2), 36.9 (CH_2), 29.1 (CH_3), 28.1 (CH_3).
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22. *General procedure for the synthesis of the compounds* **8**/**9** *and* **10**/**11**: 200 mg of the spirolactone **4** or **5** was dissolved in 20 mL of CH_3OH, then dry $HCl_{(gas)}$ was bubbled for 20 min under constant agitation. After addition, the mixture was maintained under agitation in room temperature for an additional 4 h. The end of the reaction was monitored by TLC. After the solvent was evaporated under reduced pressure, the obtained residue was chromatographed over silica gel and eluted with mixtures of hexane/AcOEt of increasing polarity. With a mixture of 4% EtOAc/hexane, colorless oil was isolated in 95% yield. Compound **8**/**9** MS [70 eV, m/z (%)]: 246(5), 214(10), 163(100), 146(25), 104(20). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.0–7.2 (8H, m), 3.9 (3H, s), 3.0 (3H, s), 2.8 (2H, t), 2.3–1.6 (10H, m), 1.6 (6H, s), 1.5 (3H, s), 1.4 (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 204.9 (C_0), 167.9 (C_0), 166.8 (C_0), 146.3 (C_0), 142.9 (C_0), 134.4 (CH), 131.9 (CH), 130.5 (CH), 129.7 (CH), 129.6 (CH), 128.2 (C_0), 127.8 (C_0), 126.0 (CH), 125.4 (CH), 122.3 (CH), 110.3 (C_0), 70.6 (C_0), 70.3 (C_0), 52.3 (CH_3), 50.9 (CH_3), 45.5 (CH_2), 44.9 (CH_2), 42.3 (CH_2), 38.4 (CH_2), 32.2 (CH_3), 32.1 (CH_3), 19.5 (CH_2), 18.8 (CH_2). Compound **10**/**11** MS [70 eV, m/z (%)]: 232(3), 200(12), 87(100), 105(22). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.0–7.3 (8H, m), 3.9 (3H, s), 3.1 (3H, s), 3.2 (2H, s), 2.5–1.6 (4H, m), 1.6 (6H, s), 1.5 (3H, s), 1.45 (3H, s). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 204.7 (C_0), 167.8 (C_0), 166.8 (C_0), 146.1 (C_0), 142.9 (C_0), 134.5 (CH), 132.1 (CH), 130.6 (CH), 129.7 (CH), 129.6 (CH), 128.1 (C_0), 127.6 (C_0), 126.0 (CH), 125.4 (CH), 122.3 (CH), 110.1 (C_0), 69.9 (C_0), 69.6 (C_0), 52.4 (CH_3), 50.9 (CH_3), 39.3 (CH_2), 38.9 (CH_2), 38.7 (CH_2), 34.3 (CH_2), 32.4 (CH_3), 32.1 (CH_3).
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