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Hooker's 'lapachol peroxide' revisited

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ABSTRACT

The structure of 'lapachol peroxide' was published by Hooker in 1936; however, we recently discovered a mistake in the originally proposed structure; the correct structure, according to X-ray spectroscopy, is given here.

The sesquicentennial naturally occurring naphthoquinone lapachol (**1**) was isolated for the first time by Arnaudon in 1858.[1] It is the most abundant quinone obtained from the hard core of various trees of the bignoniaceous family, mainly in the tropical areas of the Western Hemisphere. In Brazil, these trees are popularly known by the name ipê. Lapachol is easily isolated from sawdust and obtained in reasonable yields (for example, almost 7.2% from the sawdust of *Tecoma arabiaceam*[2]). An interesting curiosity, noticed at sawmills, is the presence of visible yellow micro crystals of lapachol incrusted on the flat surface of recently sawed boards cut from ipê. Another curiosity is that sawmill workers commonly have their body impregnated with the very fine dust of yellow lapachol that is ejected into the air from the saws, giving them the ghostly appearance of live sculptures painted by a bright tenuous patina of gold.

The pioneering knowledge of lapachol's chemistry is largely due to a long series of careful research published by Hooker and his coworkers[3,4] during the periods 1889–1896 and 1915–1936, establishing the chemical structure of lapachol and of related bignoniaceous quinones.[2]

Prior to these investigations, Paternò[5] had shown in 1882 that lapachic acid was probably identical to Arnaudon's taiguic acid[1] and Sten's greenheart. Paternò gave the first proposed structure of lapachol, although very erroneous. In 1927 lapachol was finally synthesized by Fieser.[6]

At the present time, semi-synthetic naphthoquinones and lapachol derived by chemical conversion are compounds of great interest because of their different bio-activities.[5] Lapachol (**1**), by itself, has shown activity in several different biological screening assays, such as analgesic,[7] anti-cancer,[8] trypanocidal,[9] and leischmanicidal.[10] Very interesting also is the biological activity of heterocyclic compounds derived from lapachol,[11,12] such as β-lapachone (**2**) that acts synergistically with taxol, inducing the death of several cancer cells.[8] Lapachol is licensed in Brazil for general clinical practice as a carcinostatic drug. In addition, some semi-synthetic lapachol-derived fluorescent phenazines and imidazoles have shown interesting photophysics.[13]

In 1936 Samuel C. Hooker, in a study on the chemical reactivity of naphthoquinones, reported the oxidation of lapachol with lead dioxide in acetic acid that gives a neutral orange-yellow compound, $C_{30}H_{26}O_6$, postulated by him as being the lapachol peroxide **3**.[4]

In 1950, Ettlinger[14] showed that Hooker's peroxide compound reacts with only 1 equiv of *ortho*-phenylenediamine to give only one phenazinic compound, $C_{36}H_{30}O_4N_2$, a result that is inconsistent with the structure proposed by Hooker, (**3**), because the latter is devoid of any reactive *ortho*-quinonal moieties necessary to produce a heterocyclic phenazinic product. In spite of any additional evidence, he rejected Hooker's (**3**) structure, substituting it by proposed structure **4** (Fig. 1). The present Letter reconsiders Hooker's 'lapachol peroxide' structure, in the belief that the evidence in its favor is insufficient.

The reaction of lapachol with lead dioxide was repeated according to Hooker's methodology.[17] Lapachol in acetic acid was heated to boiling, lead dioxide was added, and the hot mixture was shaken and filtered to remove oxides of lead. Yellow crystals were obtained. In order to identify the reaction product, modern methods of structural analysis were applied. Our preliminary study, based on analyzing NMR 1D and 2D spectra, indicates that both structures **3** and **4** are equally incorrect for Hooker's 'lapachol peroxide' product.

The ^{1}H NMR spectrum of the 'lapachol peroxide' compound shows four different methyl groups and five different chemical shifts in the carbonyl region in the ^{13}C NMR spectrum, assignments that are not consistent with the proposed symmetry of structure **3**. In addition, the presence of four different long-range couplings between the carbonyl-Cs and the aromatic hydrogens (HMBC

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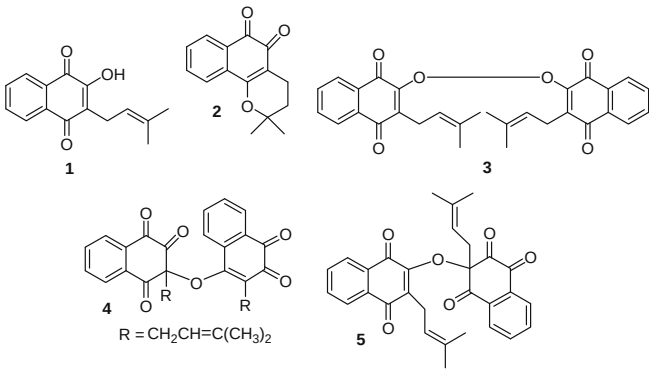


Figure 1. Lapachol (**1**), β-lapachone (**2**), Hooker's structure (**3**), Ettilinger's structure (**4**), and correct structure for the 'Hooker's peroxide' (**5**).

spectrum) is inconsistent with Ettlinger's structure **4**, which could only show a maximum of three long-range couplings. These contradictions suggested that the structure of Hooker's peroxide product should be reinvestigated.

Crystallographic data show that structures **3** and **4** are incorrect for Hooker's oxidation product and instead indicate structure **5** as the correct one for this compound, as described below. An Ortep-3 diagram of the molecule is shown in Figure 2.

Bond lengths and angles are in good agreement with the expected values reported in the literature.[15] The atoms of the naphthoquinonic ring (A–B) are coplanar and the largest deviation [0.104(2) Å] from the least-square plane is exhibited by atom C24. Atoms O1, O2, and C26 lie in the mean least-square plane of the naphthoquinonic ring with deviations of 0.062(2), 0.018(2), and 0.013(2) Å, respectively. Regarding the (C–D) rings, the atoms [C2–C10] lie in the mean least-square plane, and the largest deviation [0.043(2) Å] from the least-square plane is exhibited by atom C9, while atom C1 is 0.447(2) Å out of that plane (Figs. 2–4), thus attributing a conformation of a half-chair to the (C) ring.

The puckering parameters calculated for this conformation were $q2 = 0.253(1)$ Å, $q3 = -0.144(1)$ Å, $Q = 0.291(1)$ Å, $\theta = 119.7(3)°$, and $\varphi = 182.5(3)$.[16] The dihedral angle between the least-square plane calculated through the atoms [C2–C10] and [C16–C25] is 76.33(7)° (Fig. 3).

Crystallographic data for compound **5** have been deposited with the Cambridge Crystallographic Data Center as Supplementary Publication No. CCDC 698808. 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).

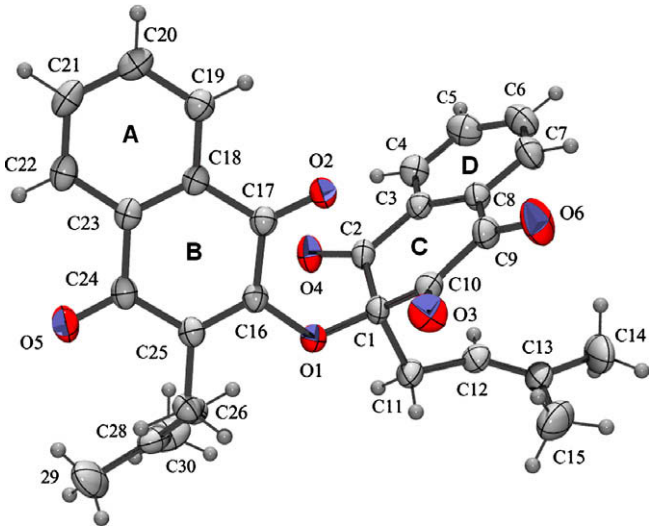


Figure 2. An ORTEP3 projection of the molecule **5**, showing the atom-numbering and displacement ellipsoids at the 30% probability level.

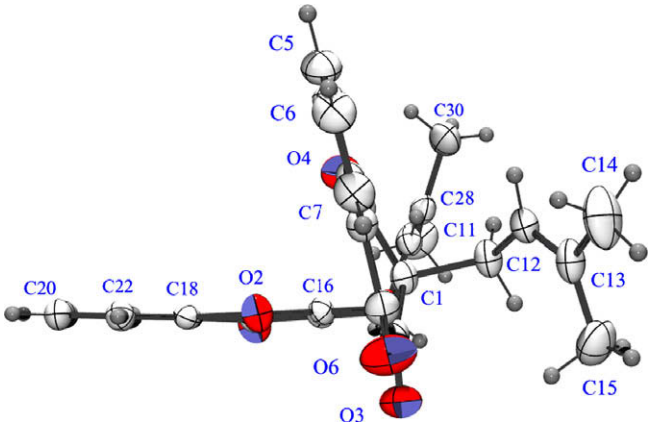


Figure 3. A view of the molecule parallel to planes of the rings (C–D).

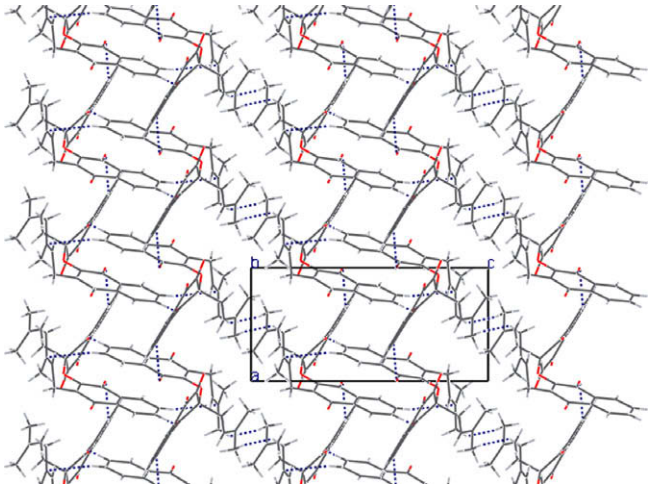
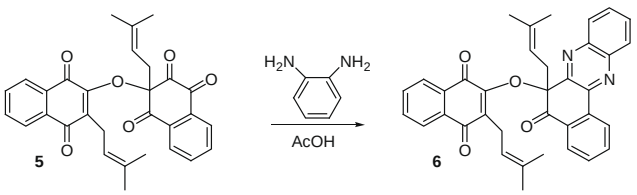


Figure 4. The packing of the molecules, viewed down the *b*-axis.

Undoubtedly, proposed structures **3** and **4** are in disagreement with the crystallographic results that indicate **5** as the correct structure for Hooker's 'lapachol peroxide'. This also allows one to indicate **6** as the correct structure for Ettlinger's phenazine.[18] The reaction of compound **5** and *ortho*-phenylenediamine is shown in Scheme 1.

Finally, the assignments in the ^{13}C and ^{1}H NMR spectral data and 2D correlated NMR spectra (*g*-COSY, *g*-HMQC, and *g*-HMBC) are all consistent with the revised structure **5**. It is worth noting that, to the best of our knowledge, Hooker's pioneering use of lead dioxide to synthesize ethers is still an unexplored reaction in the chemistry of hydroxy-substituted quinones.



Scheme 1. Phenazine **6**, obtained by the reaction of the 'lapachol peroxide' **5** and *o*-phenylenediamine.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.096.

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17. *Synthesis of lapachol peroxide as described by Samuel C. Hooker*:[4] A solution of 10 g of lapachol in 100 cc. of glacial acetic acid was heated to boiling, the source of heat was removed, and 10 g of lead dioxide was added. The hot mixture was shaken for a minute or two and filtered to remove oxides of lead, and the filtrate on cooling very slowly deposited large yellow crystals of the peroxide. Collected after six days this amounted to 2.7 g, and an additional 0.6 g of crystalline material separated after diluting the mother liquor with 40 cc of water. Lapachol peroxide crystallizes from glacial acetic acid as heavy, orange-yellow prisms Hooker's melting at 154–155 °C. Some decomposition occurs on crystallization from alcohol or benzene. 90% yield, Mp uncorrected found by us 152–153 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.47–8.35 (m, H_7), 8.25–8.17 (m, H_4), 8.01 (dd, J = 8.3 and 1.6 Hz, H_{22}), 7.97–7.83 (m, H_5 and H_6), 7.69–7.55 (m, H_{19} and H_{21}), 7.49 (td, J = 7.6 and 1.5 Hz, H_{20}), 5.39 (tt, J = 7.2 Hz and 1.4 Hz, H_{27}), 4.89 (tt, J = 8.0 and 1.4 Hz, H_{12}), 3.52 (d, J = 7.5 Hz, H_{26}), 2.95 (dd, J = 15.1 and 8.9 Hz, H_{11}), 2.81 (dd, J = 15.1 and 7.7 Hz, H_{11}), 1.85 (s, H_{29} or H_{30}), 1.74 (s, H_{29} or H_{30}), 1.50 (s, H_{14} or H_{15}), 1.41 (s, H_{14} or H_{15}). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 189.5 (C_2), 185.3 (C_{10}), 184.2 (C_{24}), 182.4 (C_{17}), 179.6 (C_9), 150.8 (C_{16}), 139.4 (C_{13}), 135.6 (C_5 or C_6), 134.7 (C_5 or C_6), 134.5 (C_3), 134.4 (C_{19} or C_{21}), 133.8 (C_{28}), 133.6 (C_8), 132.9 (C_{20}), 131.9 (C_{25}), 131.7 (C_{23}), 130.5 (C_{18}), 128.8 (C_7), 128.2 (C_4), 126.6 (C_{19} or C_{21}), 126.2 (C_{22}), 119.3 (C_{27}), 114.7 (C_{12}), 92.8 (C_1), 37.9 (C_{11}), 25.8 (C_{29} or C_{30}), 25.6 (C_{14} or C_{15}), 23.5 (C_{26}), 18.1 (C_{29} or C_{30}), 17.6 (C_{14} or C_{15}). Elemental Anal. Calcd for $C_{30}H_{26}O_6$: C, 74.68; H, 5.39. Found: C, 74.33; H, 5.38.
18. *Synthesis of Ettlinger's phenazine*:[14] A mixture of 0.5 g of lapachol peroxide, 0.25 g of *o*-phenylenediamine, and 10 cc of acetic acid was heated on the steam-bath for half an hour, cooled, and filtered. The solid, crystallized from acetic acid (100 cc per g), Ettlinger's phenazine melting at 184–185 °C. 86% yield, Mp uncorrected found by us at 186–187 °C ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.93 (dd, J = 7.3 and 0.4 Hz, 1H), 8.22 (dd, J = 7.8 and 1.2 Hz, 1H), 8,16 (dd, J = 8.0 and 0.9 Hz, 1H), 7.95 (dd, J = 7.5 and 0.7 Hz, 2H), 7.87 (tt, J = 8.5 and 1.2 Hz, 1H), 7.77–7.62 (m, 3H), 7.52 (tt, J = 7.5 and 1.4 Hz, 1H), 7.46–7.30 (m, 2H), 5.70–5.62 (m, 1H), 4.96–4.87 (m, 1H), 3.67 (d, J = 6.3 Hz, 2H), 3.09–2.89 (m, 2H), 1.95 (s, 3H), 1.84 (s, 3H), 1.39 (s, 3H), 1.10 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 192.8 (C=O), 184.7 (C=O), 181.3 (C=O), 152.9 (C), 152.4 (C), 144.4 (C), 141.4 (C), 141.1 (C), 137.2 (C), 135.6 (C), 134.4 (CH), 133.6 (CH), 133.0 (C), 132.4 (CH), 131.9 (C), 131.8 (C), 131.5 (C), 131.0 (CH), 130.4 (C), 129.9 (CH), 129.8 (CH), 129.3 (CH), 128.9 (CH), 127.3 (CH), 126.1 (CH), 125.7 (CH), 120.1 (CH), 115.5 (CH), 88.1 (C), 41.9 (CH_2), 25.9 (CH_3), 25.4 (CH_3), 23.4 (CH_2), 18.1 (CH_3), 17.2 (CH_3).