Synthesis of New *o*-Quinone Methides from β-Lapachone Analogues

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Abstract: In this work, we synthesized six new *o*-quinone methides from β-lapachone analogues by treating β-lapachone with acetone and a catalytic amount of iodine under thermal conditions and microwave irradiation. The yields of isolated *o*-quinone methides ranged from 20–80%. During the reactions, the formation of α-pyran naphthoquinones was observed; the yields varied depending upon the substituent. The reactions using microwave irradiation were faster, but yields and selectivities did not change significantly.

Key words: β-lapachone, *ortho*-quinone methide, microwave, isomerization

β-Lapachone (**1**) is a natural product found as a minority constituent of the heartwood of trees of the Bignoniaceae family and is known in Brazil as Ipê.[1] It is easily prepared from the natural product lapachol (**2**) or by several synthetic methods.[2] Due to the variety of microbicidal effects of this compound, it became a leading structure in medicinal chemistry, and various synthetic methods were explored, such as transformations of the carbonyls to mono- and disubstituted derivatives[3] and *ortho*-quinone methides (*o*-QM). To this effect, in our preliminary communication of this work, we reported the synthetic methodology for several stable *o*-QM **3a–e** (Figure 1) from β-lapachone (**1**),[4] which in most cases are short-lived intermediates that are involved in various biological processes and that have wide applicability in organic synthesis.[5]

Continuing our interest in the synthesis of *o*-QM, we decided to study the transformation of several β-lapachone analogues **4** into stable *ortho*-quinone methides by thermal heating and using microwave irradiation.

The preparation of the β-lapachone analogues **4a–g** was carried out in one step using an improved synthetic protocol recently reported by our group.[6] The Knoevenagel condensation of lawsone (**5**) with paraformaldehyde forms the *o*-QM intermediate **6**, which upon intermolecular hetero Diels–Alder cycloaddition with styrene derivatives **7a–g** led to α- and β-pyran naphthoquinones **8a–g** and **4a–g**, respectively, in good overall yield. The α- and β-isomers were separated by column chromatography using silica gel adsorbent in the yields outlined in Scheme 1.

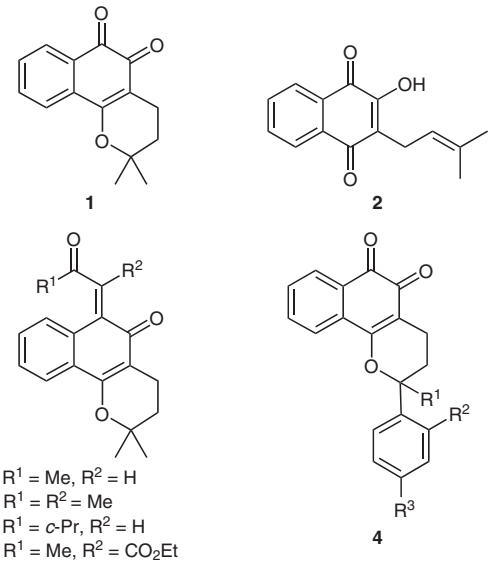

Figure 1 Structure of lapachone (**1**), its precursor lapachol (**2**), *ortho*-quinone methides **3**, and β-lapachone analogues **4**

The β-pyran naphthoquinones **4a–g** were treated with acetone, and a catalytic amount of iodine and were heated thermally and exposed to microwave irradiation to produce a mixture, which after separation on silica gel, furnished the *o*-QM **9a–g** in varying yields (Table 1). The structures of **9a–g** were assigned by infrared (IR) spectroscopy and ^{1}H NMR and ^{13}C NMR analysis. In the IR spectrum, only one absorption band corresponding to a carbonyl group (1585–1590 cm^{-1}) was observed. The structures were confirmed by ^{1}H NMR and ^{13}C NMR using 2D NMR techniques, such as COSY, HSQC, HMBC, and NOESY. For example, in **9a**, it is possible to clearly confirm that the exocyclic olefin was formed at the C-6 carbonyl due to the correlation between H-13 and H-7 in the NOESY spectrum. This result also confirms that its configuration can be securely assigned as *E*.

Analyses of the secondary product in these reactions prove that they are α-pyran naphthoquinones **8a–g**, a product that originates from the isomerization of β-pyran naphthoquinones **4a–g**, as shown in Scheme 2.

The formation of the *o*-QM **9a–g** and the α-isomers **8a–g** were quantified by ^{1}H NMR analysis of that crude mixtures that were obtained by thermal heating and micro-

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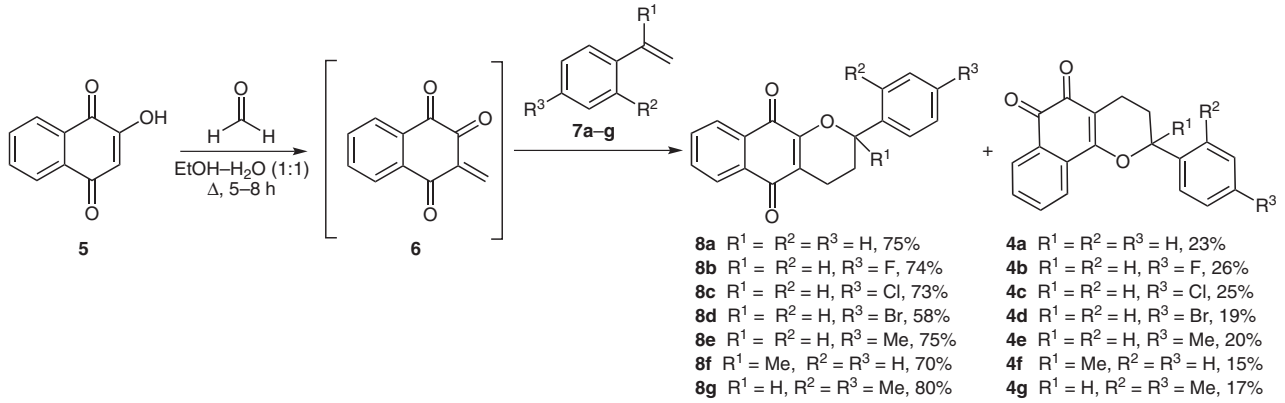


Scheme 1 Preparation of α- and β-pyranaphthoquinones **8a–g** and **4a–g**

Table 1 *o*-QM **9a–g** Obtained under Thermal and Microwave Reactions

Entry	Product **9**	R^1	R^2	R^3	Yield (%)[a]	Yield (%)[b]
1	**9a**	H	H	H	70	80
2	**9b**	H	H	F	60	65
3	**9c**	H	H	Cl	45	58
4	**9d**	H	H	Br	45	52
5	**9e**	H	H	Me	20	40
6	**9f**	Me	H	H	40	48
7	**9g**	H	Me	Me	0	0

[a] Conventional heating, reaction time: 12 h.
[b] Microwave irradiation, reaction time: 10 min.

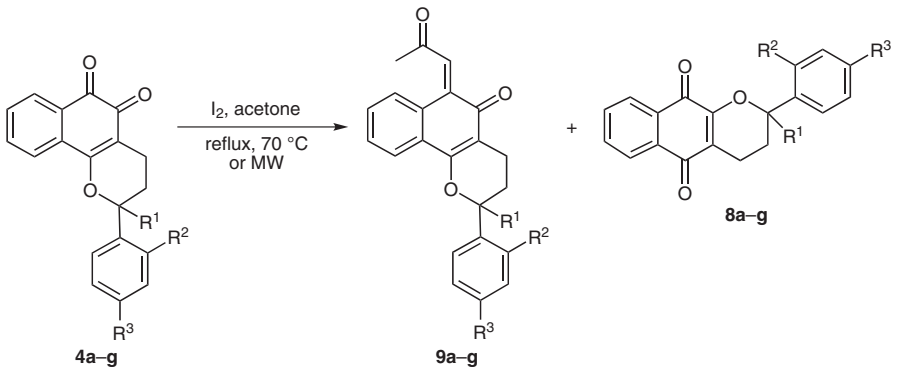
Table 2 Analysis of Crude Mixtures by ^{1}H NMR of the Reactions Carried on Thermal and Microwave Conditions

Entry	R^1	R^2	R^3	Ratio of **9/8**[a]	Ratio of **9/8**[b]
1	H	H	H	95:5	98:2
2	H	H	F	96:4	99:1
3	H	H	Cl	87:13	95:5
4	H	H	Br	44:56	52:48
5	H	H	Me	40:60	48:52
6	Me	H	H	45:55	56:44
7	H	Me	Me	0:100	0:100

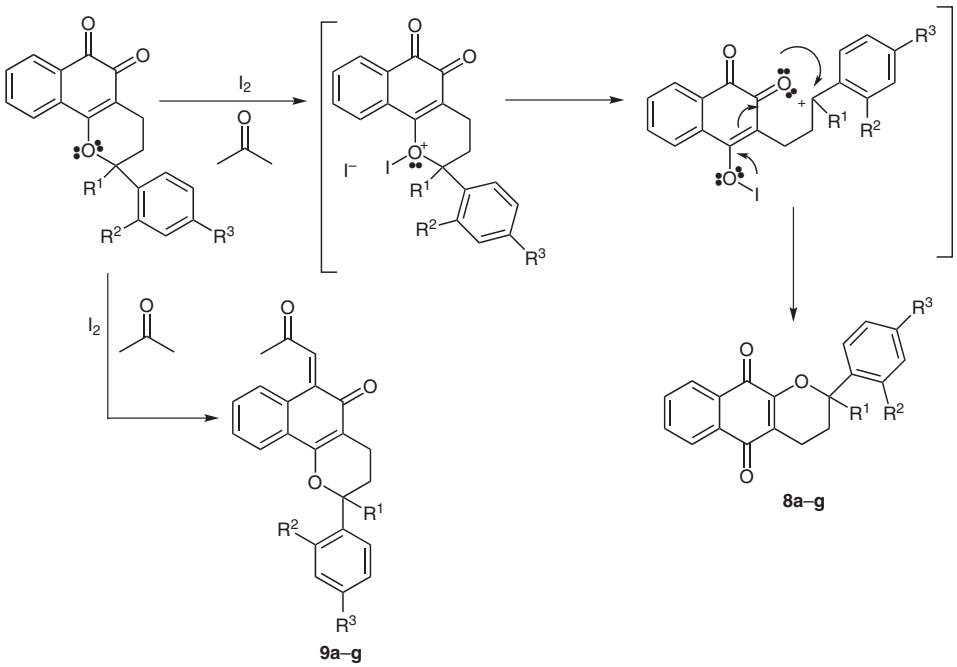
[a] Conventional heating.
[b] Microwave irradiation, reaction time: 10 min.

wave irradiation. The aromatic proton signals of H-7 and H-10 that corresponded with the *o*-QM (**9**) and the α-isomer byproducts **8**, respectively, were selected for this analysis, and ratios of 10:8 for compounds are described in Table 2.

The overall yields of the reactions under microwave irradiation were higher than the thermal reactions and run for a shorter time period, but ratios 11:9 of the products remained comparatively the same. These results can be rationalized considering that the addition of acetone and catalytic iodine to the C-6 carbonyl leads to the formation of the *o*-QM **9a–g** and competes with the pyran ring opening to a benzylic carbenium ion and then closing to the α-isomers **8a–g** (Scheme 3). This hypothesis is confirmed by observing the stabilization of the carbenium ion intermediate caused by the electronic effects of the aromatic ring. A more stable carbenium ion leads to increased formation of the α-isomer (entries 4–7 in Table 2). In the case of entry 7 (Table 2), **8g** was obtained quantitatively. Electron-withdrawing groups increased the yield of the *o*-QM (entries 2–4).



Scheme 2 Reaction of β-pyran naphthoquinones **4a–g** with acetone catalyzed by iodine



Scheme 3 Proposed mechanism for formation of **9a–g** and **8a–g**

This study showed that other analogues of β-lapachone could be used for the synthesis of a new stable *o*-QM. However, in the studied reactions, it was observed that the pyran ring is not stable and can be opened to produce the α-pyran naphthoquinone isomers. The results clearly show that the stabilization of the carbenium ion intermediates increases the formation of α-isomers. The reactions under microwave irradiation were faster, but the yields and selectivities did not change significantly.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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