Heterocyclics from Quinones. I - The Reaction of Lapachol with Primary Alkyl Amines

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Neste trabalho é descrito uma nova rota sintética para oxazóis substituidos, a partir de quinonas e alquilaminas. Mecanisticamente, é postulada a participação de uma forma tautomérica do lapachol, do tipo 1,2-quinoidal. β-lapachona também forma oxazóis substituídos

A new route to naphth [1,2-d] oxazoles from naphthoquinones and primary alkyl amines is described. The reaction probably proceeds through the formation of an intermediate tautomeric 1,2-naphthoquinone of an intermediate tautomeric 1,2-naphthoquinone structure of lapachol. The reaction of benzylamine with β-lapachone also gives rise to functionalized oxazole.

Key words: *lapachol, β-lapachone, naphth [1,2-d] oxazoles*

Introduction

Lapachol **1** is a natural substance extracted from the heartwood of trees belonging to the family Bignoniaceae, in particular the genus *Tabebuia (Tecoma)*. It is a prenylated hydroxyquinone which was first isolated more than a hundred years ago[1]. The great attention directed nowadays to lapachol is motivated by its anti-cancer activity and anti-viral action, inhibiting the replication of virus RNA[2,3]. Some derivatives of lapachol have cercaricidal, anti-cancer, virucide and promising activity against Chagas' disease[4-7].

The chemical reactivity of lapachol was studied at the end of the 19th century and again in the years 1915-1935 by Hooker[8]. The first synthesis of lapachol was accomplished in 1927 by Fieser[9]. The old data about the chemistry of lapachol are reported in the Thompson's book[10].

The more recent chemistry of this natural quinone concerns itself with derivatizations, giving rise to structurally related compounds, used in biological screening[11,12].

As part of a program concerned with the chemistry of abundant naturally occurring quinones from the Brazilian flora, it was decided to study their reactions with amines. The reaction of lapachol represents the first report of this series.

Previous reactions of amines with quinones were observed and amply documented, leading to Michael like addition, or to substituted aminoquinones when good leaving groups are attached to the quinoidal ring[13].

In this report it is shown that the reaction of lapachol with amines gives rise to oxazoles, representing a new entry into the synthesis os heterocyclic compounds from hydroxylated naphthoquinones.

Results and Discussion

Initial attempts to bring about the reaction of lapachol **1** with primary alkyl amines in ethanol, ethanol/HCℓ, acetic acid or toluene, under reflux, lead to recovery of the starting material. After several trials it was found that using excess of amine as solvent under reflux produced some reaction products. The course of the reactions was monitored by thin-layer-chromatography on silicagel, revealing a complex mixture of time dependent products. In all cases there appeared byproducts of higher R_f value which fluoresce under ultra-violet light. In spite of the complexity of the mixtures, isolation and identification of the byproducts was attempted. Further work-up indicated that these fluorescent products are easily isolated by column chromatography on silica gel being eluted in the first apolar fractions in an almost pure form. The other, more polar, fractions were mixtures of components which decompose with time.

The reaction is general for all amines (Scheme **I**) and allows the isolation of **2**, **5** (or **6**), and **9** from lapachol, respectively. These products represent new heterocyclic compounds of the oxazole type. The oxazole **7** is easily obtained from β-lapachone **8** in good yield. The reaction of lapachol with amines is time dependent, as shown with benzylamine.

The isopentenylphenols **2** and **5** can be transformed into **4** and **6** respectively, by oxidative cyclization in base. These cyclizations represent a new route to the chromam structure from ortho-isopentenylphenols.

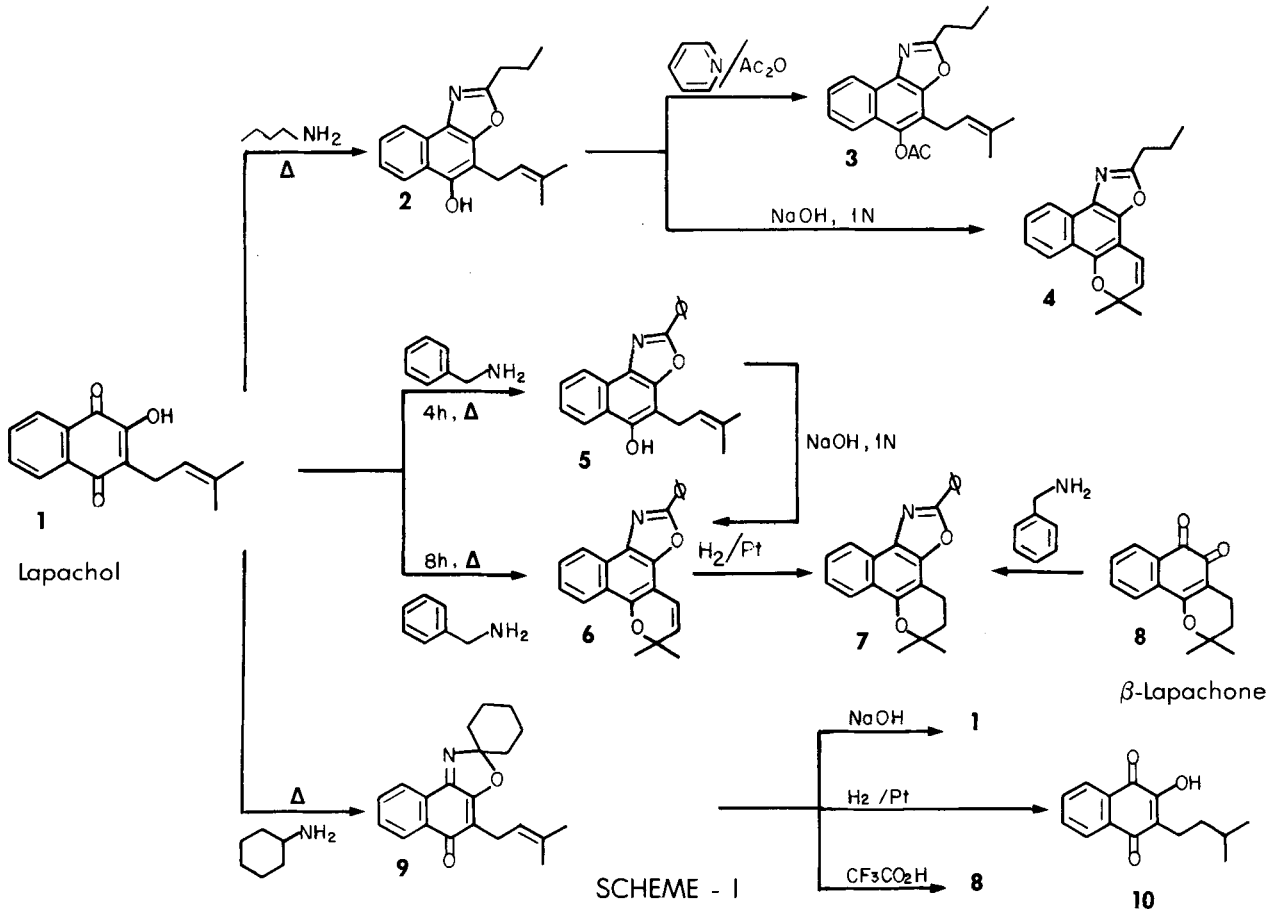
The spiro oxazole **9** on treatment with alkali gave lapachol, and with trifluoroacetic acid yielded β-lapachone **8**. As treatment of lapachol with acids also gives β-lapachone, the intermediate of this last reactions is probably also lapachol[18]. The catalytic reduction of **9**,

followed by air oxidation, affords the quinone **10**. The results with **9** are a chemical evidence that the oxazole moiety is fused to the 1,2-bond of the naphthyl ring. These reactions with **9** also reflect its quinoneimine character.

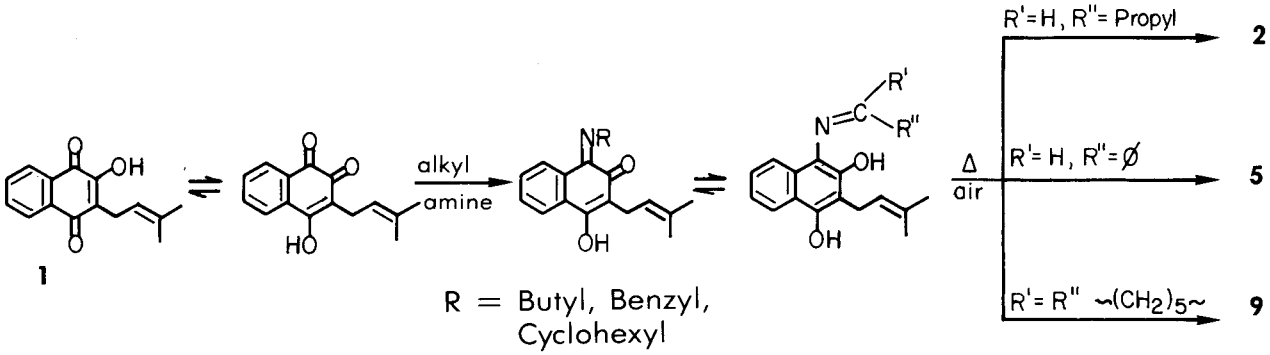
The spectroscopic data, ir, uv-vis, rmn and ms, of the products are in agreement with the structures given. Of particular support for the structure **9** was its ^{13}C NMR spectrum which showed the expected singlet (SFORD) at 184.1 ppm, indicative of a carbonyl group at C-4 position of the naphthyl ring[14]. This permits to locate the C=N double bond of the fused oxazole structure at the C-1 position of the naphthyl ring as indicated in **9**. By analogy, the nitrogen in the other oxazole structures should also be located at the same C-1 carbon of the naphthyl ring. As expected, the ^{1}H NMR spectra of these products revealed that the aromatic protons of the naphthyl moiety almost form an ABCD system, coherent with the structures given[13].

The mechanism for the formation of oxazoles from amines and lapachol can be rationalized as follows (c.f. Scheme **II**). The reaction must go through a tautomeric 1,2-naphthoquinone of lapachol, trereby favoring formation of a Schiff base, which, by prototropic rearrangement, should give a second, isomeric, Schiff base, followed by a thermodynamically favorable oxidative conversion to the fused naphth [1,2-d] oxazole structure. The chemical correlation between **6** and **7** is in support of the tautomeric 1,2-naphthoquinone structure as an intermediate in the reaction of lapachol with amines. In this respect, the ^{13}C NMR of 1,2-naphthoquinones is also relevant revealing that the carbon of the C-1 carbonyl is more deshielded than the one of the C-2 carbonyl, this being an additional support to the nucleophilic attack of amines to the carbonyl at C-1 of naphthoquinones[14].

Work is in progress for new heterocyclic compounds from β-lapachone and other naturally occurring quinones. These studies can possibly lead to a better knowledge of the chemical and physiological properties of bioactive quinones in general[15].



SCHEME - I



SCHEME - II

Materials and Methods

All melting points are uncorrected (Kofler apparatus). Proton and carbon NMR spectra were taken on a Varian XL-100-12 spectrometer. All chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane. The ir spectra were recorded on a Perkin Elmer 137-B spectrometer. The uv spectra were determined on a Beckman DB-GT spectrometer. Exact mass spectra were recorded on a Varian MAT-CH5-DF spectrometer operating at 70 eV. The low resolution mass spectra were recorded on a Micromass MM12-F spectrometer. The physical and spectral data for the heterocyclic compounds are listed in Tables 1, 2 and 3, respectively.

General procedures (from amine) for the preparation of: 4-(3-methyl-2-butenyl)-2-Propylnaphth[1,2-d]oxazol-5-ol, **(2)**; 4-(3-methyl-2-butenyl)-2-Phenylnaphth[1,2-d]oxazol-5-ol, **(5)**; 6,6-Dimethyl-2-phenyl-6H-pyrano[3,2:3,4]naphth[1,2-d]oxazole, **(6)**; 4,5-Dihydro-6,6-dimethyl-2-phenyl-6H-pyrano[3',2':4]naphth[1,2-d]oxazole, **(7)**; 4'-(3-methyl-2-butenyl)spiro[cyclohexane-1,2(5'H)-naphth[1,2-d]oxazol]-5'-one, **(9)**.

Lapachol **1**, (1mmol), (or β-lapachone **8** to prepare **7**), was dissolved in the appropriate amine (8 mℓ) and refluxed during the indicated time in Scheme I. The mixture of the reaction products was then concentrated under reduced pressure. The residue was dissolved in ether and washed

Table 1. - *Physical data for compounds* **2**, **3**, **4**, **5**, **6**, **7** *and* **9**

Compound	Yield(%)	Mp (°C) (recrustallized in Hexane-Ethylacetate)	Molecular Fórmula *	(Calcd)	(Found)
2	24	150-151	$C_{19}H_{21}NO_2$	(295.1572),	(295.1579)
3	86	oil	$C_{21}H_{23}NO_3$	(337.1679),	(337.1691)
4	90	oil	$C_{19}H_{19}NO_2$	(293.1416),	(293.1428)
5	25	164	$C_{22}H_{19}NO_2$	(329.1416),	(329.1421)
6	27	159	$C_{22}H_{17}NO_2$	(327.1259),	(327.1254)
7	90(from 6) 60(from 8)	158-160	$C_{22}H_{19}NO_2$	(329.1416),	(329.1423)
9	27	110-111	$C_{21}H_{23}NO_2$	(321.1729),	(321.1735)

* *Exact mass spectra*

Table 2. - *Mass, I.R. and U.V. data for compounds* **2**, **3**, **4**, **5**, **6**, **7** *and* **9**

Compound	Mass (M^+) (relat. int. %)	IR (cm^{-1}) (KBr)[a]	U.V.(ethanol) (λ max/nm) (log ϵ)
2	295 / 278 / 239 / 211 (40) (8) (100) (20)	3040(OH), 2857 1593(C=N), 1100	242(4.48), 316(3.73), 329(3.75), 221(4.47), 258(4.49), 290(4.18), 345(4.20)[b]
3	337 / 295 / 239 / 211 (22) (75) (100) (19)	3030, 1767 (C=O) 1677, 1594 (C=N), 1206	324(3.35), 320(3.34), 292(3.82), 280(3.84), 236(4.02)
4	293 / 278 /249 (23) (100) (11)	2944, 1636 (C=C) 1582 (C=N), 1217	249(4.01), 258(4.09), 345(3.29)
5	329 / 273 / 105 (32) (100) (46)	3226 (OH), 2940 1576 (C=N), 1549 1102	240(4.42), 242(14.52), 312(4.06) 344(4.31)[b]
6	327 / 312 / 105 (48) (100) (17)	2956, 1628 (C=C) 1568 (C=N), 1445 1232	228(4.39), 272(4.36), 281(4.29) 321(3.95), 345(3.95), 363(4.09), 381(4.05)
7	329 / 273 / 105 (67) (100) (70)	2910, 1575 (C=N) 1451, 1412, 1236	242(4.38), 312(4.07), 342(4.32) 354(4.17)
9	321 / 306 / 292 / 278 (100) (68) (9) (70)	2941, 1660 (C=O) 1616 (C=C), 1562 (C=N) 1100	216(3.92), 248(3.98), 284(3.76) 370(3.35)

[a] *film for 3 and 4*

[b] *modified by base*

first with a 2% HCℓ solution, and then water. The ether solution was dryed over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was chromatographed on a column of silica gel, using hexane/ethyl acetate (19:1) as eluant. In all reactions the desired heterocyclic compounds were obtained from the first eluting fractions.

4-(3-methyl-2-butenyl)-2-Propylnaphth[1,2-d]oxazol-5-il, acetate, (**3**): a solution of **2**, (22mg), in pyridine (1 mℓ) and 1 mℓ of acetic anhydride was refluxed for 5 hours. The reaction mixture was evaporated *in vacuo* and the residue was purified by filtration through a thick pad of silica gel eluting with hexane/ethyl acetate (19:1) to yield **3**, 22mg, as a pale yellow oil.

6,6-Dimethyl-2-propyl-6H-pyrano[3',2':3,4]naphth[1,2-d] oxazole, (**4**): to a solution of **2** (20mg) in ethanol (15 mℓ) was added 8 mℓ of a 1N sodium hydroxide solution and refluxed for 12 hours. The reaction mixture was cooled, acidified with acetic acid and extracted with ether. The ether solution was washed with cold water, dryed over anhydrous sodium sulfate and evaporated *in vacuo*. The liquid residue was purified by filtration through a thick pad of silica gel, eluting with hexane/ethyl acetate (19:1), to yield **4**, 18 mg, as a pale yellow oil.

Preparation, of **7** *from* **6**: from 22mg of **6**, the transformation was carried out over palladium on charcoal (10%), using ethyl acetate as solvent. The reaction was run at room temperature and 50psi under hydrogen pressure. The product was purified by silica gel column chromatography, eluting with hexane/ethyl acetate (19:1). The product of this reaction had physical and spectral data identical to **7**.

The degradation reactions of **9**:

a) by sodium hydroxide — to an ethanol solution of **9** (20mg), was added 10 mℓ of a 1N sodium hydroxide solution. The reaction mixture was refluxed during 3 hours. After cooling, it was acidified with acetic acid and extracted with ether. The ether solution was washed with water and dryed over anhydrous sodium sulfate. It was evaporated *in vacuo*. The residue was purified by chromatography using a short column of silica gel (hexane/ethyl acetate) to give lapachol **1** as the main product[10], mp=140°C;

b) by trifluoroacetic acid — to a solution of **9** (20mg) in THF was added trifluoroacetic acid (1mℓ). The mixture was kept at room temperature for 12 hours, followed by evaporation *in vacuo*. The residue was recrystallized from

Table 3. - *^1H and ^{13}C NMR spectral data for compounds* **2, 3, 4, 5, 6, 7** *and* **9**

Compound	^1H NMR (100 MHz) δ (ppm)[a]	^{13}C NMR (25,2 MHz) δ (ppm) (sford)[a]
2	1.2(t, 3 H, CH_3), 1.8(s, 3 H, CH_3), 1.9(s, 3 H, CH_3), 2.0(m, 2 H, CH_2), 3.0(t, 3 H, CH_2), 3.8(d, 2 H, CH_2), 5.5(t, 1H, olefinic), 6.3(bs, 1H, OH)[b], 7.56(m, 2H, arom.), 8.36(m, 2H, arom.).	13.7(q), 17.9(q), 20.7(t), 24.0(t), 125.7(q), 30.6(t), 107.0(s), 120.4(d), 121.5(d), 122.3(d), 123.3(s), 124.2(d), 124.6(s), 126.4(d), 135.8(s), 147.5(s), 147.7(s), 164.5(s).
3	1.2(t, 3 H, CH_3), 1.72(s, 3 H, CH_3), 1.85(s, 3 H, CH_3), 2.0(m, 2 H, CH_2), 2.5(s, 3 H, $COCH_3$), 3.0(t, 2 H, CH_2), 3.64(d, 2 H, CH_2), 5.3(t, 1H, olefinic), 7.55 (m, 2 H, arom.), 7.8(dd, 1H, arom., J = 7Hz, J' = 2Hz), 8.46(dd, 1H, arom., J = 7Hz, J' = 2 Hz).	
4	1.2(t, 3 H, CH_3), 1.5(s, 6H, 2 CH_3), 1.9(m, 2 H, CH_2), 3.0(t, 2 H, CH_2), 5.75(d, 1H, olefinic, J = 10 Hz), 6.75(d, 1H, olefinic, J = 10 Hz), 7.5(m, 2 H, arom.), 8.36(m, 2 H, arom.).	
5	1.86(s, 3 H, CH_3), 1.98(s, 3 H, CH_3), 3.82(d, 2 H, CH_2), 5.9(bs, 1H, OH)[b], 7.5(m, 5H, arom.), 8.2(m, 3H, arom.), 8,4(dd, 1H, arom., J = 7 Hz, J' = 2 Hz).	
6	1.58(s, 6 H, 2 CH_3), 5.8(d, 1H, olefinic, J = 10 Hz), 6.9(d, 1H, olefinic, J = 10 Hz), 7.5(m, 5 H, arom.), 8.3(m, 3H, arom.), 8.5(dd, 1H, arom., J = 7Hz, J' = 2 Hz).	27.6(q), 77.1(s), 103.1(s), 116.3(d), 121.9(d), 122.8(d), 123.1(s), 124.5(d), 125.9(s), 126.6(d), 126.9(d), 128.5(d), 129.1(d), 130.1(d), 130.8(s), 144.5(s), 146.6(s), 160.5(s).
7	1.5(s, 6 H, 2 CH_3), 2.0(t, 2 H, CH_2), 3.14(t, 2 H, CH_2), 7.5(m, 5 H, arom.), 8.24(m, 3 H, arom.), 8.46(dd, 1H, arom., J = 7 Hz, J' = 2 Hz).	
9	1.7(s, 3 H, CH_3), 1.8(s, 3H, CH_3), 1.9-2.2(m, 10 H, 5 CH_2), 3,25(d, 2 H, CH_2), 5.3(t, 1H, olefinic), 7.65(m, 2 H, arom.), 8.2(m, 2H, arom.).	17.9(q), 24.7(q), 22.5(t), 23.3(t), 25.6(t), 35.6(t), 112.9(s), 117.7(s), 120.8(d), 124.3(d), 126.9(s), 126.9(d), 131.3(d), 132.4(s), 132.8(s), 154.9(s), 160.1(s), 184.1(s).

[a] *Deuteriochloroform was used as the solvent. TMS as internal standard; s = singlet, bs = broad singlet; d = doublet; dd = double doublet; t = triplet; q = quartet; m = multiplet.*

[b] *Disappear with deuterium oxide*

ethanol, to yield orange red crystals. mp = 155°C, exhibiting the same physical and spectral data as **8**[10];

c) by hidrogenolysis — compound **9** (20mg), was hydrogenated over palladium on charcoal (10%) in ethyl acetate as solvent, at room temperature and 50psi under hydrogen for 6 hours. The catalyst was filtered and the solution evaporated *in vacuo*. The residue was purified by TLC (silica gel, 5% ethyl acetate in hexane), to give a major band which, after extraction, yielded yellow crystals, mp = 87-88°C, identical with all aspects with **10**.

Lapachol, **1**; β-Lapachone, **8** and Dihydrolapachol, **10**: the quinone 1, lapachol, was isolated from the core of a *Tabebuia* sp[1]. β-Lapachone **8** and dihydrolapachol **10**, were obtained from lapachol by the methods described in the literature[8,16].

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