Conversion of Lapachol to Rhinacanthin-A and other Cyclized Products

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A facile synthesis of rhinacanthin-A is achieved by the side chain cyclization of lapachol with meta-chloroperbenzoic acid along with stenocarpoquinone-A, stenocarpoquinone-B and its isomer.

Rhinacanthin-A (6), a new naturally occurring 1,4-naphthoquinone, has recently been isolated [1] from the plant Rhinacanthus nasutus (Acanthaceae). Lapachol (1) is also a naturally occurring 1,4-naphthoquinone which has been isolated by many workers [2] as well as from our laboratories [3, 4]. In pursuing our interest in the synthesis of quinones [5], we now present a synthesis of rhinacanthin-A (6) by side chain cyclization of lapachol in addition to other naturally occurring quinones (4, 5, 7). When lapachol (1) was allowed to react with meta-chloroperbenzoic acid in methylene chloride at 0 °C for 30 min a pair of dihydrofuran-nonaphthoquinones (4) and (5) and a pair of dihydroxyronaphthoquinones (6) and (7) were obtained (Scheme 1). The reaction appears [6, 7] to proceed through the initial formation of tautomeric epoxides (2) and (3). Ring opening, followed by cyclization may then afford both five membered furanoquinones-stenocarpoquinone-B (4) and β-1-(hydroxyisopropenyl)-dehydrofurano-1,2-naphthoquinone (5) and six membered pyranooquinones-rhinacanthin-A (6) and stenocarpoquinone-A (7) (Scheme 2). Characterization of all these products was done on the basis of their spectral data as well as by comparison with a PMR of an

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authentic sample. Thus, compounds 4 and 5 showed UV spectra consistent with α- and β-lapachone systems respectively [8]. The PMR spectrum of stenocarpoquinone-B (4) showed characteristic signal at δ 4.85 (t, J = 8 Hz) assignable to C-2 methine proton whereas corresponding signal in 1,2-naphthoquinone (5) also appeared at δ 4.85 (t, J = 8 Hz). Similarly for six membered quinones (6) and (7), 1,2- and 1,4-quinonoid systems were distinguished on the basis of their UV spectra. The PMR spectrum of the rhinacanthin-A (6) displayed characteristic C-3 methine proton signal at δ 3.87 (t, J = 5 Hz). It was further confirmed by comparison with PMR of an authentic sample. Its molecular formula C_{15}H_{14}O_{4} was established by taking high resolution of its parent ion peak at m/z 258.0892. The C-3 methine proton signal in stenocarpoquinone-A (7) appeared at δ 3.97 (t, J = 5 Hz).

When the reaction was carried out for a longer time (4 h) and at higher temperature (25 °C), dehydration led to the formation of dehydro-α-lapachone (8) and dehydro-β-lapachone (9) which were confirmed by comparison with authentic samples.

**Experimental**

All the melting points are uncorrected. The purity of compounds has been checked by thin layer chromatography. UV spectra (λ_{max} in nm) were recorded in ethanol on a UV(VIS)u-2000 Hitachi spectrophotometer whereas IR spectra (ν_{max} in cm^{-1}) were taken in KBr/Nujol on Perkin-Elmer 137E spectrophotometer. ¹H NMR spectra were recorded in CDCl_{3}, on a Jeol FX 90Q FT NMR and 400 MHz Bruker instruments using TMS as an internal reference (chemical shifts in δ, ppm). Mass spectra were recorded on a Hitachi model RMU 6E spectrometer at 70 eV.

Lapachol, a yellow crystalline compound, m.p. 139–140 °C, isolated from the plants *Tecomella undulata* [3] and *Haplophragma adenophyllum* [4] (Bignoniaceae), was used for these reactions; UV (λ_{max} EtOH): 251, 278, 333 nm; IR (Nujol): 3350, 1660, 1630, 1410 cm^{-1}; ¹H NMR (CDCl_{3}): δ 1.73 (s, CH_{3}), 1.82 (s, CH_{3}), 3.35 (d, J = 7.0 Hz, -CH_{2}-), 5.27 (t, J = 7.0 Hz, =CH), 7.81 (m, 2×ArH), 8.11 (m, 2×ArH) ppm.

**Reaction of lapachol (1) with meta-chloroperbenzoic acid**

To a solution of lapachol (1) (2.4 g, 10 mmol) in dry dichloromethane (30 ml) was added a solution of meta-chloroperbenzoic acid (5.1 g, 30 mmol) in dichloromethane (50 ml) at 0 °C. After 30 min workup was carried out by treating the reaction mixture with a saturated aqueous sodium hydroxide solution (100 ml) for 20 min. The organic layer was separated, washed successively with saturated aqueous sodium bicarbonate (2×25 ml), water (2×25 ml) and dried over anhydrous MgSO_{4}. The crude orange solid, 1.5 g (60%) was subjected to column chromatography over silica gel employing chloroform as solvent. The following compounds were obtained, which were further purified by preparative TLC.

**Stenocarpoquinone-B (4)**

It was obtained as yellow needles, crystallized from benzene, 0.21 g (9%); m.p. 160–161 ºC; UV (λ_{max} EtOH): 250, 284, 331, 372 nm; IR (KBr): 3450, 1670, 1630, 1585, 1560, 1520, 1125 cm^{-1}; ¹H NMR (CDCl_{3}, 400 MHz): δ 1.21 (s, CH_{3}), 1.34 (s, CH_{3}), 2.98 (d, J = 8 Hz, -CH_{2}), 4.85 (t, J = 8 Hz, =CH), 7.7 (m, 2×ArH) and 8.05 (m, 2×ArH) ppm.

**β-(1-Hydroxyisopropenyl)-dehydrofurano-1,4-naphthoquinone (5)**

It was separated as red needles, 0.26 g (11%); m.p. 132 ºC; UV (λ_{max} EtOH): 253, 280, 332, 430 nm; IR (KBr): 3460, 1690, 1630, 1590, 1560, 1520, 1125, 1115 cm^{-1}; ¹H NMR (CDCl_{3}, 90 MHz): δ 1.21 (s, CH_{3}), 1.34 (s, CH_{3}), 2.98 (d, J = 8 Hz, -CH_{2}), 4.85 (t, J = 8 Hz, =CH), 7.55 (m, 3×ArH) and 7.90 (m, 1×ArH) ppm; MS (m/z): 258 [M^+], 240 [M^+–H_{2}O], 230 [M^+–CO], 212 [2×H_{2}O]^{+}.

**Rhinacanthin-A (6)**

It was separated as orange solid, 0.1 g (4%); m.p. 186–187 ºC; UV (λ_{max} EtOH): 245, 251, 282, 330 nm; ¹H NMR (CDCl_{3}, 90 MHz): δ 1.38 (s, CH_{3}), 1.46 (s, CH_{3}), 2.67 (dd, J = 5, 18 Hz, =CH),
2.83 (dd, J = 5, 18 Hz, -CH-), 3.87 (t, J = 5 Hz, -CH-\text{-OH}), 7.60 (m, 2×ArH) and 8.00 (m, 2×ArH) ppm; MS (m/z): 258 [M+] (C_{15}H_{14}O_4) (100%), 243 [M-Me]+ (18%), 225 (29%), 159 (29%).

**Stenocarpoquinone-A (7)**

It was separated as red needles, crystallized from benzene, 0.6 g (25%); m.p. 170–171 °C; UV (\(\lambda_{\text{max}}\) EtOH): 250, 282, 331, 431 nm; IR (KBr): 3450, 1690, 1650, 1590, 1565 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 1.45 (s, CH\(_3\)), 1.50 (s, CH\(_3\)), 2.61 (dd, J = 5, 18 Hz, -CH-), 2.77 (dd, J = 5, 18 Hz, -CH-), 3.97 (t, J = 5 Hz, -CH-\text{-OH}), 7.5 and 7.65 (t, J = 7.5 Hz, each, 2×ArH), 7.84 and 8.05 (d, J = 7.5 Hz, each, 2×ArH) ppm; MS (m/z): 258 [M+] (C_{15}H_{14}O_4).

**Dehydro-\(\alpha\)-lapachone (8)**

It was isolated as orange needles, m.p. 143 °C; \(^1\)H NMR (CDCl\(_3\), 90 MHz): \(\delta\) 1.56 (s, 2×CH\(_3\)), 5.76 (d, J = 10.5 Hz, =CH), 6.87 (d, J = 10.5 Hz, =CH), 7.82 (m, 2×Ar-H) and 8.15 (m, 2×Ar-H) ppm.

**Dehydro-\(\beta\)-lapachone (9)**

It was separated as red mass; \(^1\)H NMR (CDCl\(_3\), 90 MHz): \(\delta\) 1.56 (s, CH\(_3\)), 1.60 (s, CH\(_3\)), 6.20 (d, J = 10.5 Hz, =CH), 7.07 (d, J = 10.5 Hz, =CH), 7.64 (m, 3×ArH), 7.86 (m, 1×ArH) ppm; IR (Nujol): 1690, 1637, 1621, 1587 cm\(^{-1}\).

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