Chemical transformation of lapachol to dehydroiso-α-lapachone and related quinones

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Chemical transformation of lapachol to dehydroiso-α-lapachone, dehydroiso-β-lapachone, α-lapachone, β-lapachone and dehydro-α-lapachone in a single step synthesis by reaction with aqueous NaNO₂ and glacial AcOH and to di- and tri-bromo derivatives by reaction with Br₂ in CHCl₃ has been achieved. Notably dehydroiso-α-lapachone and dehydroiso-β-lapachone have been obtained from lapachol for the first time.

Dehydroiso-α-lapachone 2, a naturally occurring dihydrofuranonaphthoquinone was earlier reported from the woods of Paratecoma peroba, Tabebuia pentaphylla, Radermachera sinica and also by our group from the heartwoods of Tabebuia rosea and Markhamia platycalyx (all Bignoniaceae). Its absolute configuration as 2R was determined by using a chiral shift reagent by Inoue et al. In pursuing our interest in quinonoid constituents a number of prenylnaphthoquinone congeners such as lapachol, deoxylapachol, α- and β-lapachones, dehydro-α-lapachone, dehydroiso-α-lapachone, etc. have been isolated from the woods of various Bignoniaceae, Malvaceae and Verbenaceae plants. Lapachol 1 is a major constituent amongst congeners and a number of cyclisation reactions were studied in detail. The main striking feature of the chemistry of lapachol is the ease with which the prenyl chain cyclises into an oxygen function to give an array of pyran and furan derivatives, some of which occur naturally. As part of our study we have earlier reported the synthesis of rhinacanthin, isolated from Rhinacanthus nasutus by cyclising lapachol with MCPB. We now present conversion of lapachol to dehydroiso-α-lapachone 2, dehydroiso-β-lapachone 3 along with α-lapachone 4, β-lapachone 5 and dehydro-α-lapachone 6 by reaction with aqueous NaNO₂ and glacial AcOH and the formation of 2-hydroxy-3-(2,3-dibromo-3-methylbutyl)-1,4-naphthoquinone 7 and 2-hydroxy-3-(2,3-dibromo-3-methylbutyl)-6-bromo-1,4-naphthoquinone 8 in almost equal quantity (Scheme III).

A solution of lapachol 1 in chloroform on treatment with a solution of bromine in chloroform afforded 2-hydroxy-3-(2,3-dibromo-3-methylbutyl)-1,4-naphthoquinone 7 and 2-hydroxy-3-(2,3-dibromo-3-methylbutyl)-6-bromo-1,4-naphthoquinone 8 in almost equal quantity (Scheme III).

The characterization of products 2-8 was done on the basis of their spectral data as well as by comparison with authentic samples. Product 2 obtained as golden yellow leaflets, m p 102-3° (reported 7° m p 108-9°), [α]D 25° -31.00° (CHCl₃) was characterized as (R) dehydroiso-α-lapachone. The IR spectrum revealed absorption bands at 1675, 1650, 1640, 1600, cm⁻¹ and UV spectrum in ethanol showed
absorptions at 253, 295 and 342 nm characteristic of 1,4-naphthoquinones. The $^1$H NMR spectrum when determined in CDCl$_3$ displayed ABX splitting pattern. A pair of AB double doublets at $\delta$ 2.94 ($J$=17, 8Hz) and 3.21 ($J$=17, 10Hz) and a double doublet at $\delta$ 5.38 ($J$=10, 8Hz) corresponded to methylene and methine protons of dihydrofuran ring. A broad doublet centred at $\delta$ 5.02 assigned to vinylic protons of side chain and
an olefinic methyl appeared as singlet at δ 1.67. Aromatic region showed a set of identical multiplets at δ 7.68 and 8.07 related to two aromatic protons each. In mass spectrum it exhibited strong molecular ion peak at m/z 240 corresponding to its molecular composition C₁₃H₁₂O₃. Array of intense peaks at m/z 225, 212 and 197 in mass spectrum arrived due to the loss of methyl radical and one and two molecules of CO successively from molecular ion. It was deconvoluted by comparison with an authentic sample. The 1H NMR spectrum of its isomeric compound 3, obtained as red granules, m.p. 96°, [α]D -25° (CHCl₃) was very much similar to that of compound 2 barring the splitting pattern in aromatic region where a multiplet at δ 7.66 integrated for three aromatic protons and an another multiplet at δ 7.95 corresponded to one aromatic proton indicating the angular cyclization of side chain. The presence of an associated [M+2] ion peak of comparable intensity in the mass spectrum further supports the 1,2-naphthoquinoid nature of the compound and was characterised as dehydroiso-α-lapachone. Compounds 4, 5 and 6 were identified as α,β-lapachones, and dehydro-α-lapachone, respectively from spectral data as well as comparison with authentic samples. While compounds 7 and 8 were characterized as 2-hydroxy-3-(2,3-dibromo-3-methylbutyl)-1,4-naphthoquinone and 2-hydroxy-3-(2,3-dibromo-3-methylbutyl)-6-bromo-1,4-naphthoquinone respectively from their 1H NMR spectra.

Experimental Section

IR spectra were recorded in KBr on FTIR Nicolet Magna 550 spectrometer, 1H NMR spectra in CDCl₃ on JEOL FX 90Q FT NMR spectrometer, mass spectra on a JEOL JMS-D-300 instrument at 70eV direct inlet; and UV spectra in ethanol (95%) on a Perkin Elmer model 202 automatic recording spectrometer. CC was done over silica gel (BDH, 60-120 mesh) and Prep. TLC over silica gel PF₃₅₋₆F₃₅ E. Merck plates. Melting points were recorded in soft glass capillaries in an electrothermal melting point apparatus and are uncorrected. Chemical shifts are reported in δ, ppm.

Reaction of lapachol with HNO₂

To a solution of lapachol (2.0 g, 8.3 m moles) in glacial acetic acid (100 mL) in 250 mL RB flask, an aqueous solution of NaN₃ (3.208 g, 46 m moles) was added and the resulting mixture was heated at 80° for 6 hr with magnetic stirring. It was left overnight and then the reaction mixture was diluted and extracted with Et₂O. The ethereal solution was washed with 2% NaHCO₃ solution and water, respectively. The ethereal layer was dried over anhydrous Na₂SO₄ and subjected to TLC on precoated glass plates giving compounds 2-6 along with two minor components which could not be characterized owing to their meagre amounts.

Dehydroiso-α-lapachone 2: Golden yellow leaflets, mp 102-3°, yield 70 mg, [α]D -31.0° (CHCl₃); IR (KBr) : 1675 (C=O), 1650, 1640, 1600 (C=C), 1450, 1375, 1245 cm⁻¹; UV(ethOH) : 253,295,342 nm; 1H NMR(CDCl₃) : 1.67(s, 3H, =C-CH₃), 2.94(dd, 1H, J=17, 8Hz, H-3), 3.21(dd, 1H, 1=17, 10Hz, H-3'), 5.02(dbr, 2H, =CH₂), 5.38(dd, 1H, J=10, 8Hz, H-2), 7.68(m, 2H, Ar-H), 8.07(m, 2H, Ar-H); MS : m/z 240[M⁺] (C₁₃H₁₂O₃) (46.2), 221[M-Me]⁺ (94.8), 212[M-CO]⁺ (92.4), 197[225-CO]⁺ (80.9), 183[225-Ch₂=C=O]⁺ (79).
3H, Ar-H), 7.95(m, 1H, Ar-H); MS: m/z 240[M] \\
 C_{14}H_{20}O_2 (52.0), 242[M+2] \\

α-Lapachone 4: Pale yellow needles, mp 117-18°, yield 50 mg; IR(KBr): 1678(C=O), 1640, 1610, 1595(C=C) cm⁻¹; UV(EtOH): 251, 282, 332, 375 nm; 1H NMR(CDCI₃): 1.47(s, 6H, 2xCH₃), 1.87(t, 2H, J=7Hz, -CH₂-), 2.72(t, 2H, J=7Hz, -CH₂-), 7.90(m, 2H, Ar-H); MS: m/z 242[M] \\
 C_{14}H_{20}O (100), 227[M-Me] (50), 199[227-CO] (60).

β-Lapachone 5: Red needles, mp 154-55°, yield 40 mg; IR(KBr): 1690(C=O), 1640, 1632, 1598(C=C) cm⁻¹; UV(EtOH): 256, 282, 330, 431nm; 1H NMR(CDCI₃): 1.51(s, 6H, 2xCH₃), 1.87(t, 2H, J=7Hz, -CH₂-), 2.63(t, 2H, J=7Hz, -CH₂-), 7.74(m, 3H, Ar-H), 8.22(m, 1H, Ar-H); MS: m/z 242[M] \\
 C_{14}H_{20}O₂ (60), 227[M-Me] (40), 199[227-CO] (50), 102(100).

Dehydro-α-lapachone 6: Red needles, mp 143-44°, yield 45 mg; IR(KBr): 1681(C=O), 1640, 1590 (C=C) cm⁻¹; UV(EtOH): 267, 276, 333, 434 nm; 1H NMR(CDCI₃): 1.54(s, 6H, 2xCH₃), 5.74(d, 1H, J=10Hz, =CH), 6.66(d, 1H, J=10Hz, =CH), 7.85(m, 2H, Ar-H), 8.10(m, 2H, Ar-H); MS: m/z 240[M] \\
 C_{14}H_{18}O (98.8), 225[M-Me] (96.6), 212[M-CO] (100), 197[225-CO] (98.4), 184[212-CO] (35.6), 183[225-CH=CH=CH=O] (57.6), 169[197-CO] (62.6), 104[C,H,O] (71.4), 76[C,H₄] (62.6), 50[C,H₂] (40).

Reaction of lapachol with Br₂

A solution of lapachol (1.5 g, 6.2 m moles) in 90 mL of CHCl₃ in a stoppered conical flask was treated with a solution of bromine in CHCl₃ (4 mL of Br₂ dissolved in 15 mL of CHCl₃) and the resulting mixture was heated for 5 min on a water-bath and kept overnight at room temperature. The excess Br₂ and chloroform were removed by evaporation in fuming cupboard. It was separated by Prep. TLC using precoated glass plates with silica gel into compounds 7-9. The compound 9 could not be characterised due to its small amount.

2-Hydroxy-3-(2,3-dibromo-3-methylbutyl)-1,4-naphthoquinone 7: Violet red viscous mass, yield 75 mg; IR(nujol): 1668(C=O), 1640, 1610(C=C) cm⁻¹; 1H NMR(CDCI₃): 1.66(s, 3H, Me), 1.69(s, 3H, Me), 3.18(dd, 1H, J=18, 8Hz, -CH₂-), 3.35(dd, 1H, J=18, 6Hz, -CH₂-), 4.33(dd, 1H, J=8, 6Hz, -CHBr), 7.85(m, 2H, Ar-H), 8.17(m, 2H, Ar-H); MS: m/z 400[M] \\
 C_{13}H_{14}O,Br₂.

2-Hydroxy-3-(2,3-dibromo-3-methylbutyl)-6-bromo-1,4-naphthoquinone 8: Maroon needles, m.p. 168-69°, yield 150 mg; IR(KBr): 1670(C=O), 1630, 1610, 1580(C=C) cm⁻¹; 1H NMR(CDCI₃): 1.65(s, 6H, 2xMe), 3.12(dd, 1H, J=17, 7Hz, -CH₂-), 3.29(dd, 1H, J=17, 6Hz, -CH₂-), 4.35(dd, 1H, J=6, 7Hz, -CHBr), 7.44(d, 1H, J=8Hz, Ar-H), 7.88(d, 1H, J=8Hz, Ar-H), 8.16(m, 1H, Ar-H); MS: m/z 478[M] \\
 C_{13}H_{10}O₂,Br₂.

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References

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