Synthesis of lapachol derivatives and their antibacterial activity

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Several lapachol derivatives were synthesized from lapachol and tested for their antibacterial activity.

The root bark of \textit{Stereospermum sueovelens} DC (Bignoniaceae), commonly known as \textit{Pathiri} in Tamil and \textit{Patala} in Sanskrit finds application in traditional medicine. It is one of the ten root constituents of \textit{Dasamula} used in Ayurveda\textsuperscript{1}. Lapachol, a 1,4-naphthaquinone, the main constituent of this plant, is reported to exhibit antiulcerogenic, antiviral, anticancer and antimalarial activities\textsuperscript{2}.

The present communication deals with the isolation of lapachol (1) from this plant and its conversion to 2-benzoyllapachol (2), 2-acetyllapachol (3), 2-methoxylapachol (4), 2-(p-nitrobenzoyl)lapachol (5), 2-(p-chlorobenzoyl)lapachol (6), diacetate of hydroxylapachol (7), hydroxylapachol (8) and cyclized derivative (9) by standard procedure\textsuperscript{3} (Chart 1). These compounds were studied for their antibacterial activity against \textit{Psuedomonas prutidi}, \textit{Pseudomonas} (non-fluorescent), \textit{Xanthomonas citri}, \textit{X. oryzae} and \textit{Escherichia coli} using chloramphenicol as standard (30 \textmu g/disc) by disc-diffusion method\textsuperscript{4}. The objective of the work was to study the substituent effect at 2-position of the quinone, the importance of the side-chain and also the quinone system against these bacterial strains.

Lapachol was found to be active against \textit{X. oryzae}, \textit{Psuedomonas} (non-fluorescent) and \textit{E. coli} at 750 ppm but inactive to others even at 1500 ppm. 2-Benzoyllapachol was the only active compound towards \textit{P. prutidi} and \textit{X. citri}. Hydroxylapachol and its diacetate were inactive towards all the bacterial strains. The cyclized derivative was effective to four strains except \textit{X. citri}. It seemed to exhibit a better activity than lapachol: (i) good zone exhibition at same concentration and (ii) good activity at lower concentration, indicating that cyclization of the hydroxy group of lapachol leads to good activity.

The zone of inhibition against \textit{X. oryzae} at 475 ppm for 2-benzoyl, 2-nitrobenzoyl, 2-acetyl, is around 13 mm as against no activity for parent compound. At the same concentration, for \textit{Pseudomonas} (non-fluorescent), the inhibition of the cyclized derivative is more than twice (16 mm) and 2-benzoyl- and 2-(p-nitro)benzoyllapachols are more effective (11 mm) than lapachol (6 mm). For \textit{P. prutidi}, \textit{X. citri} and \textit{E. coli}, the inhibition was only at 750 ppm, exhibiting only marginal activity (6 mm).
Experimental

M.ps. were taken in open capillary tubes and are uncorrected. IR spectra (KBr) were recorded on Perkin-Elmer 1600 FTIR and UV spectra (MeOH) on Perkin-Elmer λ-3 instruments.

The root was procured from local market and identified at the Botany Department of Central Research Institute (Siddha), Chennai.

The root (1 kg) was cut, coarsely powdered and extracted with boiling n-hexane using Soxhlet apparatus. Hexane extract was concentrated to a syrupy mass which on column chromatography over silica gel and elution with hexane : benzene (1 : 1) yielded a solid on concentration and cooling (3 g). It was filtered and crystallized from hexane-ether, m.p. 145–46°, and identified as lapachol (1), viz. 2-hydroxy-(3-methyl-2-butenyl)-1,4-naphthoquinone by m.p., m.m.p. and co-TLC with authentic sample.

This material was used for synthesis of other derivatives.

2-Benzoyllapachol (2) : To lapachol (1; 320 mg, 1.3 mmol) dissolved in NaOH solution (2%; 4 ml), benzoyl chloride (182 mg, 1.3 mmol) dissolved in NaOH was added dropwise. The flask was stoppered and shaken vigorously until the odour of benzoyl chloride disappeared (10–15 min). The solid product was then extracted with ether (2 x 150 ml), washed with water and dried. The residue after evaporation was crystallized from hexane:ether, washed with water, dried and evaporated to yield 2 (6.38 mg), crystallized from EtOH, (455 mg), m.p. 135°, \( \nu_{\text{max}} \) 1768, 1686, 1654 cm\(^{-1} \), \( \lambda_{\text{max}} \) 384, 330 nm.

2-(p-Chlorobenzoyl)lapachol (6) : A mixture of p-chlorobenzoic acid (200 mg, 1.27 mmol) and thionyl chloride (4 ml) was heated on a boiling water-bath (5 h) with occasional shaking till the evolution of HCl ceased. It was then cooled in ice and crystallized from CCl\(_4\), (217 mg).

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To 1 (280 mg, 1.14 mmol) dissolved in NaOH solution (5%; 4 ml), p-nitrobenzoyl chloride (195.50 mg, 1.14 mmol) was added and shaken vigorously (5–10 min). It was then extracted with ether (2 x 150 ml), washed with water, dried and evaporated to yield a solid. It was crystallized from EtOH, (96 mg), m.p. 210°, \( \nu_{\text{max}} \) 1756, 1684, 1560, 1353 cm\(^{-1} \), \( \lambda_{\text{max}} \) 384, 330 nm.

Hydroxylapachol (8) : The diacetate of lapachol (7; 100 mg, 0.3 mmol) was refluxed (1 h) with NaOH (10%; 4 ml). The residue was acidified with dil. HCl, extracted with ether (2 x 150 ml), washed with NaHCO\(_3\) and then with water, dried and evaporated to yield 8 (64 mg), m.p. 135°, \( \nu_{\text{max}} \) 3296, 2942, 1617 cm\(^{-1} \), \( \lambda_{\text{max}} \) 323 nm.

Cyclized lapachol (9) : To 1 (200 mg, 0.82 mmol) was added conc. H\(_2\)SO\(_4\) (3 ml) and the mixture heated on a boiling water bath with stirring at 100–120°. Cold water (50 ml) was added and stirred well to complete the reaction. It was extracted with ether (2 x 150 ml), washed with water, dried, evaporated and crystallized, m.p. 125°, \( \nu_{\text{max}} \) 2942, 1583, 1617, 1094 cm\(^{-1} \), \( \lambda_{\text{max}} \) 425, 328 nm.
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