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NEW SYNTHESIS OF 4-PHENYL COUMARINS: DALBERGIN AND NORDALBERGIN

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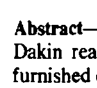
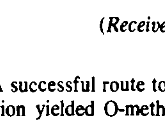
Abstract—A successful route to the synthesis of 4-phenylcoumarins in good yield has been developed. Vanillin on Dakin reaction yielded O-methoxyhydroquinone which on subsequent condensation with ethyl benzoyl acetate furnished dalbergin (overall yield, 65%). The latter on demethylation afforded nordalbergin (overall yield, 62%). This procedure is applicable to the synthesis of other 4-phenylcoumarins.

The interest in the synthesis of 4-phenyl coumarins occurring in the heartwood of various timbers has been created by their insect and termite repellant properties. During the past two decades more than a dozen of novel highly substituted 4-phenylcoumarins,[1-9] 4-phenyl dihydrofuranocoumarins (angular)[5-10] and 4-phenyl chromeno-α-pyrones (angular)[5,11-13] have been discovered in plants.

From the heartwood of *Dalbergia sissoo*,[1-4] known to produce good timber, dalbergin (1), nordalbergin (2), isodalbergin (3) and methyl dalbergin (4) have been isolated. In addition two more compounds, viz. dalberginone (5) and dalbergichrome (6) have been reoported.



1, R=H, $R_1=CH_3$
2, $R=R_1=H$
3, $R=CH_3$, $R_1=H$
4, $R=R_1=CH_3$



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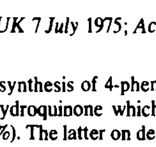

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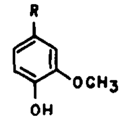
In connection with the studies on naturally occurring pesticides it was necessary to develop an economic process for the synthesis of dalbergin and nordalbergin as the existing method for its synthesis[4] is not satisfactory. A new total synthesis of dalbergin and nordalbergin from readily available vanillin has now been achieved in appreciably high yield (65% and 62%). The method developed provides a general procedure for the synthesis of related 4-phenylcoumarins, like isodalbergin,[2] stevenin[14] and melannein.[8,15]

Vanillin (7) when subjected to Dakin reaction[16,17] furnished O-methoxyhydroquinone (8) which on condensation with freshly distilled ethyl benzoyl acetate[18,19] yielded dalbergin.



7, R= –CHO
8, R= –OH

Dalbergin, $C_{16}H_{12}O_4$ (M^+ 268), m.p. 209° thus obtained gave a single spot on chromatoplate (TLC) in different solvent systems. The IR spectrum [3240 cm^{-1} (–OH) and 1710, 1680 cm^{-1} (>C=O)] was exactly the same as that of naturally occurring dalbergin.[2] In the NMR spectrum which has not been reported the conspicuous absence of the characteristic coumarin doublets and the appearance of a singlet (1H) at δ6.2 suggested the presence of an olefinic proton at C_3 and a substituent at C_4. The C_4-phenyl nucleus exhibited a five-proton singlet[20] at δ7.53. Another diagnostic signal appeared at δ7.21 (1H, s, D_2O-exchangeable, phenolic OH) while two aromatic para-protons and an aromatic methoxyl function were clearly discernible at δ6.96 (2H, d, J = 2 Hz) and δ4.00 (3H, s) respectively.

Mass spectrum of dalbergin is hitherto unreported. Ion fragments of both natural and synthetic dalbergin (M^+ 268, 100%) exhibited significant peaks at *m/e* 240, 225, 197, 168, 155, 141, 127. The spectrum was interpreted as outlined in Chart 1.

The molecular ion (M^+ 268) lost the stable neutral carbon monoxide molecule to give a benzofuran cation (*m/e* 240). This was confirmed from the metastable peak at m* 214.9. Subsequent loss of $-CH_3$ from this ion particle generated the fragment *m/e* 225, the corresponding metastable peak being discernible at m* 211.0. Further loss of carbon monoxide molecule from the ion *m/e* 225 yielded the cation *m/e* 197 with the metastable peak at m* 172.5. The lower mass fragments were not intense and no metastable peaks were apparent to support the fragmentation pattern.

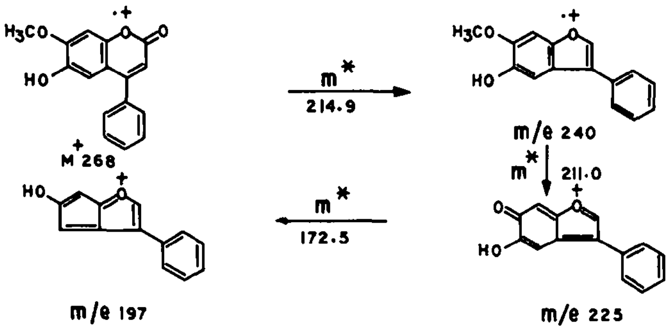
Synthetic dalbergin (1) could easily be demethylated to nordalbergin (2) in nearly 62% yield by boron tribromide.[21] Spectral data of synthetic nordalbergin were the same as that of dalbergin except for the absence of -OMe signal and the appearance of a new peak for phenolic -OH in the NMR spectrum.

EXPERIMENTAL

Microanalyses were performed by Mr. S. K. Ray, Chemistry Department, University of Calcutta.

M.ps and b.ps are uncorrected. UV spectra were measured in Carl-Zeiss Universal Spectrophotometer (Model VSU-1) using 95% aldehyde-free EtOH and IR spectra with Beckman IR-20 Infrared Spectrophotometer in Nujol Mull. The NMR spectra were recorded with Varian A 60 D instrument with TMS as the internal standard. The analytical samples were routinely dried *in*

CHART-I



vacuo at 80° over P_2O_5 for 24 hr. For TLC experiments silica gel (Gouri Chemicals) was used.

Conversion of vanillin (7) *to* O-*methoxyhydroquinone* (**8**). Vanillin (20 g) was dissolved in 2N NaOH (200 ml) through which N_2 was passed for 10 min. The soln turned yellow. It was cooled in an ice bath. An ice-cold H_2O_2 (3%; 150 ml) was added to the mixture when the colour of the soln gradually changed to deep yellow, brown and finally to wine-red (in about 15 min). N_2 atmosphere was maintained for further 30 min. The mixture was then left at room temp. under N_2 for further 45 min. The deep brown alkaline soln was subsequently acidified with HCl (without exposure to air), extracted with ether, washed with water, sodium meta-bisulphite, water respectively and finally dried over Na_2SO_4. After removal of the solvent, a deep brown pasty mass was left. It gave single spot on TLC plate and crystallised from a mixture of benzene and petrol in colourless crystals, m.p. 82° (dec) (yield, 70%). The substance turned dark brown when kept exposed to air (Found: C, 60.20; H, 5.9. $C_7H_8O_3$ requires: C, 60.00; H, 5.71%).

Preparation of ethyl benzoylacetate. To a vigorously stirred suspension of NaH (23.2 g) in dry ether (100 ml) in a 2-necked round bottomed flask, 30 ml of diethyl carbonate was added. Then a soln of freshly distilled acetophenone (14.2 g) in dry ether (100 ml) was added dropwise through a stoppered dropping funnel to the mixture. After addition the mixture was stirred and refluxed for 24 hr, cooled, poured in crushed ice and acidified. The ether layer was separated and worked up. After removal of solvent, the residual oil was heated under reduced pressure (10 mm) on a water bath to remove excess of diethyl carbonate. Then the oil was distilled under reduced pressure to obtain the desired ethyl benzoyl ester at 120°/0.9 mm, ν_{max} 1730, 1710, 1680 cm^{-1} (Found: C, 68.45; H, 5.98; O, 24.86. $C_{11}H_{12}O_3$ requires: C, 68.75; H, 6.25; O, 25.0%).

von Pechmann condensation of O-*methoxyhydroquinone* (**8**) *with ethyl benzoylacetate.* Dakin product **8** (3.5 g) was taken in a 2-necked flask fitted with a guard tube. It was cooled in ice-salt mixture followed by the addition of benzoyl acetic ester (4 g) with vigorous shaking. Treatment with cooled conc. H_2SO_4 (4 ml) effected cyclisation, the temp. being maintained at 0°. The mixture was then left at r.t. overnight. The product was poured over crushed ice. The reddish brown gummy solid separated. It was extracted with chloroform, made acid free and dried. Evaporation of the solvent gave a brown solid which on repeated crystallisation from benzene afforded pale yellow crystals of dalbergin, m.p. 209° (yield, 65%) λ_{max}^{EtOH} 238, 304 nm (log ϵ3.91, 3.49 respectively); $\lambda_{max}^{EtOH+NaOH}$ 260 and 318. nm; ν_{max} 3240, 1710, 1680 cm^{-1} (Found: C, 71.89; H, 4.52; O, 23.91. $C_{16}H_{12}O_4$ requires: C, 71.64; H, 4.48; O, 23.88%). NMR: δ4.00 (3H, s), 6.2 (1H, s), 6.96 (2H, d, J = 2 Hz), 7.21 (1H, s, D_2O-exchangeable), 7.53 (5H, s). Mass spectrum: *m/e* 268 (M^+, 100%), 240, 225, 197, 168, 155, 141, 127.

Nordalbergin from dalbergin. Dalbergin (500 mg) was dissolved in dry CH_2Cl_2 (100 ml, freshly distilled over P_2O_5) under N_2 in a 2-necked flask. The mixture was cooled in ice. BBr_3 (0.5 ml, 2 equiv.) in dry CH_2Cl_2 (25 ml) was then added dropwise with constant stirring (always maintaining the temp. at 0°). The mixture was then left overnight under N_2 at r.t. Usual work up and removal of the solvent gave a pale yellow solid. It crystallised from MeOH in prisms to furnish nordalbergin m.p. 265° (yield, 62%), λ_{max}^{EtOH} 262, 356 nm, $\lambda_{max}^{EtOH+NaOH}$ 270, 360 nm; ν_{max}: 3450, 3150, 1700, 1680 cm^{-1} (Found: C, 71.05; H, 4.01; O, 25.19. $C_{15}H_{10}O_4$ requires: C, 70.87; H, 3.94; O, 25.20%). NMR: δ6.1 (1H, s), 6.82 (2H, d, J = 2 Hz), 7.53 (5H, s), 9.42 (2H, br, D_2O-exchangeable). Mass spectrum: *m/e* 254, 226 (100%), 197, 181, 169, 152, 141, 127, 115, 102.

Demethylation experiment was repeated with 48% HBr and also anhydrous *aluminium chloride* ($AlCl_3$) and the observations were exactly the same.

Nordalbergin has also been prepared from protocatechuic aldehyde. It was subjected to Dakin reaction to afford 1,2,4-trihydroxy benzene which on subsequent condensation with ethyl benzoylacetate produced nordalbergin in good yield (75%).

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