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DALBERGIA SPECIES—V*.

ISOLATION OF R-5-*O*-METHYLLATIFOLIN FROM *DALBERGIA COCHINCHINENSIS*, PIERRE.

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Abstract—Extraction of the heartwood of *Dalbergia cochinchinensis*, Pierre. gave R-5-*O*-methyllatifolin and the known R-latifolin, R-4-methoxydalbergione, benzoic and salicylic acids.

AN INVESTIGATION of the heartwood of *Dalbergia cochinchinensis*, Pierre. has yielded the known compounds, R-latifolin (Ia)[1,2] (0·5 per cent dry wood basis), R-4-methoxydalbergione (II),[3] benzoic[4] and salicylic acids and, in addition, a colourless compound, $C_{15}H_{11}O(OMe)_3$ (0·03 per cent dry wood basis).

The spectral data of R-latifolin and R-4-methoxydalbergione permitted their identification and confirmation of these structures was obtained by comparison with authentic specimens. The benzoic and salicylic acids were identified by GLC analysis of their methyl esters.

The optically active compound, $C_{15}H_{11}O(OMe)_3$, although insoluble in sodium hydroxide, showed a strong absorption in the hydroxyl region of both its i.r. (KBr) and NMR ($CDCl_3$) spectra (ν_{max} 3472 cm^{-1}; 4·05 τ singlet). The hydroxyl group was characterised by the formation of a monoacetate (ν_{max} 1754 cm^{-1}). The u.v. [λ_{max} 213 nm ($\log\epsilon$ 4·39), 286 nm ($\log\epsilon$ 3·92)] and NMR spectra of the natural product closely resembled those of latifolin[2] (Ia). The 3,6 aromatic protons were represented as singlets at 3·46 τ and 3·32 τ and the singlets at 6·25 τ, 6·18 τ and 6·15 τ were assigned to the three methoxyl groups. A first order analysis indicated the major coupling constants and τ values of the four protons in the $>CH\cdot CH{=}CH_2$ grouping. Hydrogenation gave the dihydro derivative, and its NMR spectrum established the presence of a $>CHCH_2CH_3$ residue. Methylation of the natural product with methyl sulphate in base gave R-*O*-dimethyllatifolin (Ib). Thus the compound $C_{15}H_{11}O(OMe)_3$ was a monomethyl ether of R-latifolin, having structure (Ic) or (Id). Assignment of structure (Ic) resulted from the isolation of salicylic acid from the alkaline hydrogen peroxide degradation of the natural product.

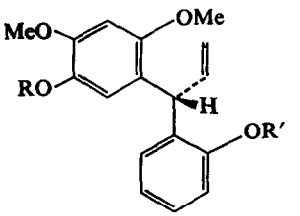
Isomerisation of the natural product occurred with base[5] to give optically inactive 5-*O*-methylisolatifolin (IIIa). The ethyl ether of IIIa was identical with a synthetic sample

* For part IV, see B. J. DONNELLY, D. M. X. DONNELLY and A. M. O'SULLIVAN, *Chem. & Ind.* 1498 (1966).

[1] S. BALAKRISHNA, M. M. RAO and T. R. SESHADRI, *Tetrahedron* **18**, 1503 (1962).
[2] C. B. DEMPSEY, D. M. X. DONNELLY and R. A. LAIDLAW, *Chem. & Ind.* 491 (1963).
[3] W. B. EYTON, W. D. OLLIS, I. O. SUTHERLAND, L. M. JACKMAN, O. R. GOTTLIEB and M. T. MAGALHAES, *Proc. Chem. Soc.* 301 (1962).
[4] W. D. OLLIS, *Experientia* **22**, 777 (1966).
[5] D. M. X. DONNELLY, M. R. GEOGHEGAN, B. J. NANGLE and R. A. LAIDLAW, *Tetrahedron Letters*, 4451 (1965).

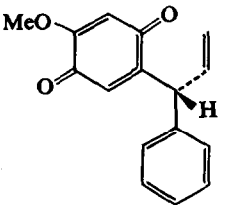
of 1-(2-ethoxyphenyl)-1-(2,4,5-trimethoxyphenyl)prop-1-ene (IIIb). The latter compound was prepared by Friedel-Crafts acylation of 1,2,4-trimethoxybenzene with *o*-ethoxybenzoyl chloride to yield 2'-ethoxy-2,4,5-trimethoxybenzophenone followed by treatment with ethyl magnesium iodide and subsequent dehydration with ethanolic sulphuric acid. The products of hydrogenation with Adam's catalyst of the synthetic propene and the natural *iso* derivative were also identical.

The ORD curve for 5-*O*-methyllatifolin showed it to have the R- configuration.[6]

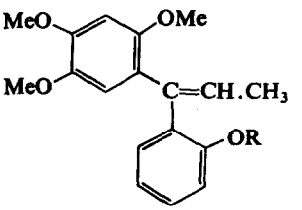


I

a R=R'=H
b R=R'=Me
c R=Me, R'=H
d R=H, R'=Me



II



III

a R=H
b R=Et

EXPERIMENTAL

Nuclear magnetic resonance spectra were determined on $CDCl_3$ solutions, using a Varian HR-60A spectrometer; tetramethylsilane was used as the internal standard. Infrared spectra were determined on a Grubb Parsons Spectromaster and u.v. spectra were determined on the Bausch and Lomb Spectronic 505 instrument. Rotations were determined on a Perkin Elmer Model 141 Polarimeter. M.p's are uncorrected.

Extraction of Dalbergia Cochinchinensis Heartwood

Shavings of the heartwood (2 kg) were successively extracted with *n*-hexane and methanol and the methanol fraction further extracted with benzene. The oils (0·45 kg, 32 g) obtained on removal of the *n*-hexane and benzene were studied separately.

Examination of the benzene extract. Isolation of benzoic and salicylic acids, R-latifolin (Ia) and R-5-O-methyllatifolin (Ic). The brown oil was separated into its acidic (0·2 g), phenolic (18 g) and neutral (8 g), components. The acidic fraction was sublimed, using an i.r. lamp as heat source, when benzoic acid separated in long needles (4 mg), m.p. and mixed m.p. 121°. Further sublimation of the residue at 120–140°/1 mm, esterification and subsequent GLC analysis (Apiezon L) defined the presence of the methyl esters of benzoic and salicyclic acids.

Column chromatography (silica gel) of the phenolic fraction (6 g) provided a crystalline substance (eluted with $CHCl_3$/benzene, 80:20) which was recrystallized from benzene to give R-latifolin (Ia) (3·45 g), m.p. 123–123·5° (lit.[1,2] m.p. 123–123·5°) $[\alpha]_D^{22°}$ −26·7° (methanol); the *acetate* crystallized from methanol in prisms, m.p. 124–125° (lit.[1,2] m.p. 124–125°).

Elution with $CHCl_3$ of an aliquot (5 g) of the neutral fraction from a silica gel column provided a crystalline substance which was recrystallized from benzene/di-*iso*propyl ether (50/50) to give R-5-*O*-methyllatifolin (Ic) (0·65 g), m.p. 106–107°, $[\alpha]_D^{20°}$ −40·2° (Methanol), ν_{max}^{KBr} 3472 cm^{-1} (—OH), 2845 cm^{-1} (—OMe), 1852 cm^{-1}, 1639 cm^{-1}, 1429 cm^{-1}, 995 cm^{-1}, 918 cm^{-1} (—CH=CH_2), (Found: C, 71·9; H, 6·7; OMe, 30·6 $C_{18}H_{20}O_4$ requires: C, 72·0; H, 6·6; 3 OMe, 31·0 per cent).

The *acetate*, prepared with anhydrous pyridine and acetic anhydride, crystallized from methanol (95 per cent) in prisms, m.p. 91–92°, $[\alpha]_D^{18°}$ 7·0° (methanol), NMR spectrum: 7·78 τ (s, OAc). (Found: C, 70·5; H, 6·6. $C_{20}H_{22}O_5$ requires C, 70·2; H, 6·4 per cent).

The *dihydro derivative* was prepared from the natural product by hydrogenation at atmospheric pressure in the presence of Adam's catalyst; it crystallized from di-*iso*propyl ether in prisms, m.p. 111–112°, $[\alpha]_D^{30°}$ −28·8° (methanol); ν_{max}^{KBr} 3420 cm^{-1} (—OH); NMR spectrum: 9·11 τ, 7·96 τ, 5·72 τ (m, J=7·2 c.p.s., >CH—CH_2—CH_3). (Found: C, 71·6; H, 7·4. $C_{18}H_{22}O_4$ requires: C, 71·5; H, 7·2 per cent).

[6] P. B. HULBERT, D. KLYNE, R. J. SWAN, D. M. X. DONNELLY and B. J. NANGLE, *J. Chem. Soc.*, in press.

R-Latifolin dimethyl ether (Ib). A mixture of R-5-*O*-methyllatifolin (Ic) (0·5 g.), methyl sulphate (1·0 ml), NaOH (1·0 ml, 40 per cent) and absolute ethanol (10 ml) was heated under reflux for 5 hr. Addition of ice-water gave R-latifolin dimethyl ether (Ib) which crystallized from methanol in prisms (0·38 g), m.p. 88–89°, undepressed on admixture with an authentic sample.[2]

Alkaline hydrogen peroxide oxidation of R-5-O-methyllatifolin. To a boiling solution of R-5-*O*-methyllatifolin (Ic) (0·3 g) in tetramethylammonium hydroxide (20 ml, 3 per cent) was added a solution of H_2O_2 (15 ml, 30 per cent), and the mixture heated under reflux for 2 hr. Acidification and ether extraction yielded an oil which was esterified (ethereal solution of diazomethane) and found by GLC analysis (Apiezon L) to contain methyl salicylate.

5-*O-Methylisolatifolin.* (IIIa) R-5-*O*-Methyllatifolin (Ic) (0·5 g) was added to KOH (1·5 g) in water (0·75 ml) at 120°, and was heated slowly to 160° for 0·5 hr and briefly to 180°. Acidification and ether extraction afforded an oil which, on elution with chloroform from a silica gel column, gave a solid which crystallized from di-*iso*propyl ether/light petroleum to give 5-*O*-methylisolatifolin (IIIa) (131 mg) as needles, m.p. 100–102°, $[\alpha]_D^{25°} \pm 0{\cdot}00°$ (ethanol). (Found: C, 72·2; H, 6·7. $C_{18}H_{20}O_4$ requires: C, 72·0; H, 6·6 per cent).

2′-*O-Ethyl-5-O-methylisolatifolin.* (IIIb) A mixture of 5-*O*-methylisolatifolin (IIIa) (0·15 g.), C_2H_5I (1·0 ml), NaOH (1·0 ml, 40 per cent) and absolute ethanol (10 ml.) was heated under reflux for 5 hr. Dilution with water, followed by ether extraction provided 2′-*O*-ethyl-5-*O*-methylisolatifolin (IIIb) which crystallized from di-*iso*propyl ether in prisms, m.p. 89·5–90°. (Found: C, 73·4; H, 7·5. $C_{20}H_{24}O_4$ requires: C, 73·2; H, 7·3 per cent).

The *dihydro derivative*, prepared by hydrogenation at atmospheric pressure in the presence of Adam's catalyst, crystallized from di-*iso*propyl ether in prisms, m.p. 80–81·5°. (Found: C, 73·2; H, 7·7. $C_{20}H_{26}O_4$ requires: C, 72·7; H, 7·8 per cent).

2′-*Ethoxy*-2,4,5-*trimethoxybenzophenone.* *o*-Ethoxybenzoyl chloride (6 g) was added to a mixture of $AlCl_3$ (12 g), 1,2,4-trimethoxybenzene (5 g) and ether (100 ml) at 0°. After 10 min crushed ice and HCl were added, the ethereal layer removed, washed with NaOH (10 per cent) and evaporated to yield 2′-ethoxy-2,4,5-trimethoxybenzophenone which crystallized from methanol in prisms (5·9 g), m.p. 92–93°, ν_{max}^{KBr} 1637 cm^{-1} (>C=O). (Found: C, 68·5; H, 6·4, OMe+OEt as OMe, 39·35. $C_{18}H_{20}O_5$ requires: C, 68·4; H, 6·3; 4 OMe, 39·25 per cent).

1-(2-*Ethoxyphenyl*)-1-(2,4,5-*trimethoxyphenyl*)*prop*-1-*ene.* (IIIb) A solution of 2′-ethoxy-2,4,5-trimethoxybenzophenone (1·3 g) in tetrahydrofuran (12 ml) was added to the Grignard reagent formed from C_2H_5I (6·2 g) and Mg (2 g) in tetrahydrofuran (90 ml). The mixture was heated under reflux for 3 hr and the solvent removed after a further 12 hr. The Grignard complex was decomposed with NH_4Cl (200 ml, 20 per cent) and the residue extracted with ether. Dehydration of the crude product by heating in ethanol (95 per cent) in the presence of a few drops of H_2SO_4 afforded 1-(2-ethoxyphenyl)-1-(2,4,5-trimethoxyphenyl)prop-1-ene (0·3 g) which crystallized from di-*iso*propyl ether in prisms, m.p. 89·5–90°, undepressed on admixture with 2′-*O-ethyl-5-O-methylisolatifolin.* (IIIb).

The *dihydro derivative*, prepared by hydrogenation at atmospheric pressure in the presence of Adam's catalyst, melted at 80–81·5° and was undepressed on admixture with *dihydro-2′-O-ethyl-5-O-methyllatifolin.*

Examination of the n-hexane extract. Isolation of R-4-methoxydalbergione (II), R-latifolin (Ia) and R-5-O-methyllatifolin (Ic). A portion (3 g) of the brown oil, on elution from a silica gel column with benzene/$CHCl_3$ (80:20), afforded a red oil. This oil solidified on the addition of di-*iso*propyl ether to give a solid (20 mg) which crystallized from ligroin in yellow needles, m.p. 116°. Comparison with an authentic sample previously isolated in this department allowed identification of the solid as R-4-methoxydalbergione (II). Further elution with benzene/$CHCl_3$ (30:60) gave, on evaporation of the solvent, a brown oil which was shown by TLC (silica gel) studies to contain latifolin and 5-*O*-methyllatifolin. An ethereal solution of the oil was extracted with NaOH (10 per cent) and evaporated to give R-5-*O*-methyllatifolin (Ic) (7 mg), which crystallized from benzene/di-*iso*propyl ether in needles, m.p. 106–107°. Ether extraction of the neutralized NaOH extract afforded R-latifolin (Ia) (100 mg), which crystallized from benzene in yellow needles, m.p. 122–123°.

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[7] B. J. Donnelly, D. M. X. Donnelly and C. B. Sharkey, *Phytochem.* 4, 337 (1965).