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VIOLASTYRENE AND ISOVIOLASTYRENE, CINNAMYLPHENOLS FROM *DALBERGIA MISCOLOBIUM**

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Key Word Index—*Dalbergia miscolobium*; *D. violacea*; Leguminosae–Lotoideae; cinnamylphenols; neoflavonoids; isoflavones; benzophenone.

Abstract—The heartwood of *Dalbergia miscolobium* contains, in addition to the neoflavonoids (*S*)-4-methoxydalbergione, (*S*)-4′-hydroxy-4-methoxydalbergione and dalbergin, the isoflavone di-*O*-methyldaidzein, the benzophenone cearoin and two cinnamylphenols, violastyrene [*E*-1-(3-hydroxy-2,4-dimethoxybenzyl)-2-phenylethylene] and isoviolastyrene [*E*-1-(4-hydroxy-2,3-dimethyoxybenzyl)-2-phenylethylene]. The structural determination of the cinnamylphenols relied on spectra, degradations and synthesis.

INTRODUCTION

Our preliminary accounts on the natural occurrence of cinnamylphenols [2] and a styryl-*para*-quinonemethide [3] inspired a notable series of papers on their biogenesis [4], synthesis [5, 6] and astoundingly varied potential uses. Indeed, while obtusastyrene [2] and a series of synthetic cinnamylated phenols are sterilization agents of female flies [7], growth inhibitors of malaria mosquito larvae [8], algicides [9] and microbicides [10–13], obtusaquinone [3] and synthetic styryl-*para*-quinonemethides are highly ichthyotoxic [14] and effective in controlling marine borer attack [15].

The natural co-occurrence of analogously substituted cinnamylphenols, dalbergiquinols and 2-aryl-3-methyl-2,3-dihydrobenzofurans provided the basis for their incorporation into a unified biogenetic scheme [16]. From the biosynthetic point of view these and derived classes of constituents of *Dalbergia* and *Machaerium* species (Leguminosae–Lotoideae) are thus considered closely related, and are described, irrespective of skeleta, in the present series of papers on 'the neoflavonoid group of natural compounds' [1, 17, 18]. The genera contain additionally isoflavones [19], pterocarpans [20] and isoflavans [21], to be described in a series of papers on the 'isoflavonoid constituents of *Dalbergia* and *Machaerium* species'.

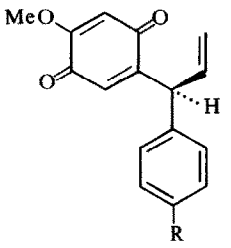
RESULTS AND DISCUSSION

The isolation of (*S*)-4-methoxydalbergione (**1a**) and (*S*)-4′-hydroxy-4-methoxydalbergione (**1b**) from the heartwood of *Dalbergia miscolobium* Benth. [syn. *D. violacea* (Vog.) Malme] was reported [17]. A re-examinatjon of the benzene extract gave, additionally, 6-hydroxy-7-methoxy-4-phenylcoumarin (dalbergin) [18], 7,4′-dimethoxyisoflavone (di-*O*-methyldaidzen), 2,5-dihydroxy-4-methoxybenzophenone (cearoin) [22] and two cinnamylphenols violastyrene and isoviolastyrene [2].

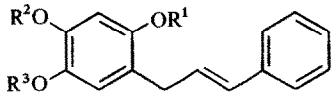
Violastyrene and isoviolastyrene are isomers, $C_{14}H_{11}(OMe)_2OH$, and have similar UV, IR and PMR characteristics. Since both give the same monomethyl ether, they differ only with respect to the relative positions of one hydroxy and one methoxy substituent. Their PMR spectra show the multiplets characteristic of the ABX_2 system associated with a *E*-CH=CH—CH_2-grouping [1], a five-proton multiplet (*ca* τ 2.7) and two one-proton singlets (*ca* τ 3.3 and 3.5). These data are compatible with structures **2a**, **2b** and **2c**. The alternative position of the double bond in the formulae was thought to be less likely on biogenetic grounds (cf. **1a** and ref. [16]). Indeed, oxidation of the methyl ether **2d** with OsO_4, and further oxidation of the resulting glycol with periodate, gave 2,4,5-trimethoxyphenylacetaldehyde and benzoic acid.

The distinction between structures **2a**, **2b** and **2c** for violastyrene and isoviolastyrene was achieved by comparison with synthetic compounds. Initially, the reduction of chalcones with $LiAlH_4/AlCl_3$ [23] appeared to be a potentially useful method. The required chalcones **3a**, **3b** and **3c** were prepared by the condensation of benzaldehyde with the appropriate benzyloxydimethoxy acetophenone. Reduction of **3c** gave a complex mixture from which the benzyl ethers of violastyrene or isoviolastyrene could not be isolated. On basis of this negative evidence, the two natural cinnamylphenols are represented by the structures **2a** and **2b**. Indeed, reduction of **3a**, followed by debenzylation of the reaction product, gave the cinnamylphenol **2a**, which proved to be identical with violastyrene; and **3b**, submitted to identical treatment, gave isoviolastyrene (**2b**). These syntheses established the location of the OH/OMe-substituents in violastyrene and isoviolastyrene, but did not provide additional, decisive proof for the position of the double bond in the C_3-unit, since double bond migration may occur during the reduction of chalcones to 1,3-diarylpropenes [23]. Any doubts concerning this point were removed by the Claisen rearrangement of

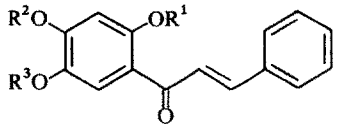
* Part 4 in the series 'The Neoflavonoid Group of Natural Products'. For Part 3 see ref. [1].



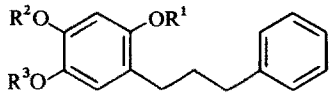
1a R = H
1b R = OH



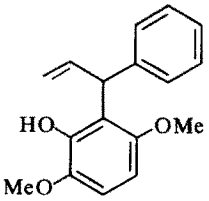
2a $R^1 = R^3 = Me$, $R^2 = H$
2b $R^1 = R^2 = Me$, $R^3 = H$
2c $R^1 = H$, $R^2 = R^3 = Me$
2d $R^1 = R^2 = R^3 = Me$
2e $R^1 = R^3 = Me$, $R^2 = CH_2Ph$



3a $R^1 = R^3 = Me$, $R^2 = CH_2Ph$
3b $R^1 = R^2 = Me$, $R^3 = CH_2Ph$
3c $R^1 = CH_2Ph$, $R^2 = R^3 = Me$



4a $R^1 = R^3 = Me$, $R^2 = H$
4b $R^1 = R^2 = R^3 = Me$



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2-cinnamyloxy-1,4-dimethoxybenzene. This gave violastyrene (**2a**), and the *ortho*-rearrangement product **5** in a 6:1 proportion.

EXPERIMENTAL

Unless otherwise stated spectra were measured in EtOH (UV), $CHCl_3$ (IR) and $CDCl_3$ (60 MHz PMR). All evapns of volatile material were performed under diminished pressure.

Isolation of the constituents. A specimen of *D. miscolobium* was collected in the 'cerrado' region, near Brasília, DF, Brasil, and identified by Ezequias Heringer. The C_6H_6 extract (53 g) of ground heartwood (8 kg) was chromatographed on Si gel (1.5 kg), eluting successively in 2 l. fractions with C_6H_6 (40 fractions), C_6H_6–$CHCl_3$ (1:1) (20 fractions), $CHCl_3$ (10 fractions), MeOH (3 fractions). Fractions 1–5 contained fatty esters. Fractions 6–8 were purified by chromatography on Si gel and crystallization from petrol to give **2a** (80 mg). Fractions 9–14 were separated by TLC [Si gel, petrol–EtOAc, 7:1] into the faster-running **2a** and a slower-running compound which crystallized from isopentane to give **2b** (30 mg). Fractions 15–17 were aliphatic in nature. Fractions 18–19 were separated by TLC into aliphatic material and a product which crystallized from MeOH to give cearoin (25 mg). Fractions 20–40 deposited crystals, and recrystallization from cyclohexane afforded **1a**. Fractions 41–47 deposited crystals, and recrystallization from EtOH gave **1b**. The residual material from these fractions was chromatographed on Al_2O_3. The C_6H_6–$CHCl_3$ (1:1) eluate gave gummy crystals which, by washing with petrol and recrystallization from EtOH, gave di-*O*-methyldaidzein (40 mg). The $CHCl_3$ eluate gave a product which, by TLC and crystallization from MeOH, gave dalbergin (50 mg). The $CHCl_3$–EtOAc (1:1) eluate gave a product which was separated by TLC to give dalbergin and **1b**. Fractions 48–73 contained resinous material.

Identifications. Dalbergin [18] and cearoin [22] were identified by direct comparison with authentic samples.

Di-O-methyldaidzein. Mp 159–160° (EtOH). [Found: M 282.0899. $C_{17}H_{14}O_4$ requires: M 282.0899]. λ_{max} (nm): 237 inf., 262, 303 *sh* (ε 19000, 27000, 8500). ν_{max} (cm^{-1}): 1625, 1610, 1575. PMR (τ): 2.10 (H-2), 3.05, 3.11, 1.77 (ABX system, $J_{AX} = 8$ Hz, $J_{AB} = 2$ Hz, H-6, H-8, H-5), 2.51, 3.04 (AA'XX' system, $J_{AX} = J_{A'X'} = 8$ Hz, H-2', H-6', H-3', H-5'), 6.08, 6.17 (2 *s*, 2 OMe). This compound was shown to be identical with 7,4'-dimethoxyisoflavone obtained from formononetin (10 mg), MeI (0.25 ml), K_2CO_3 (5 g) in Me_2CO (10 ml).

Violastyrene (**2a**). Mp 85–86°. [Found: C, 75.89; H, 6.92; M 270.1250. $C_{17}H_{18}O_3$ requires: C, 75.53; H, 6.71%; M 270.1256]. λ_{max} (nm): 251, 286, 294 (ε 19900, 7400, 7600). ν_{max} (cm^{-1}): 3550, 1610, 1040, 970. PMR (τ): 2.70 (*m*, Ph), 3.27, 3.40 (2 *s*, H-3, H-6 of benzyl), *ca* 3.60 (*m*, AB part), 6.55 (*dd*, X_2 part of ABX_2 system, $J_{BX} = 5$ Hz, $J_{AX} = 2.5$ Hz), 6.18, 6.22 (2 *s*, 2 OMe), 4.40 (*s*, OH). *Methyl ether* (**2d**) (**2a**, Me_2SO_4, K_2CO_3, Me_2CO, refl., 2 hr) oil. *Dihydroviolastyrene* (**4a**) (**2a**, H_2, 10% Pd/C, EtOH, room temp. and pressure) mp 53–54°. *Methyl ether of dihydroviolastyrene* (**4b**) (**4a**, Me_2SO_4 etc., as above), mp 41–42° (isopentane). [Found: C, 75.48; H, 7.53. $C_{18}H_{22}O_3$ requires: C, 75.50; H, 7.74%].

Isoviolastyrene (**2b**). Mp 86–88°. [Found: M 270.1250. $C_{17}H_{18}O_3$ requires: M 270.1256]. λ_{max} (nm): 251, 291, 296 (ε 20000, 7500, 7600). ν_{max} (cm^{-1}): 3550, 1635, 1030, 967. PMR (τ): 2.77 (*m*, Ph), 3.27, 3.53 (2 *s*, H-3, H-6 of benzyl), *ca* 3.65 (*m*, AB part), 6.58 (*dd*, X_2 part of ABX_2 system), 6.15, 6.23 (2 *s*, 2OMe), 4.88 (*s*, OH). *Methyl ether* (**2d**) (**2b**), Me_2SO_4 etc., as above) oil, identical (IR, PMR, MS) with the methyl ether of violastyrene.

Oxidation of violastyrene methyl ether (**2d**). **2d** (0.28 g) and OsO_4 (0.25 g) in dry dioxan (10 ml) were kept at room temp. for 48 hr. The mixture was satd with H_2S and the black ppt. removed by filtration. The filtrate was evapd and the oily residue

dissolved in MeOH (5 ml) and stirred with sodium metaperiodate (0.1 g) in EtOH (5 ml) *ca* 18 hr. The soln was diluted with H_2O and extracted with Et_2O. The Et_2O soln was dried and evapd and the residue purified by TLC (Si gel). The main band gave 2,4,5-trimethyoxyphenylacetaldehyde (15 mg). ν_{max} (cm^{-1}): 2800, 1720, 1610. PMR (τ): 0.33 (*t*, J = 2.5 Hz, CHO), 6.42 (*d*, J = 2.5 Hz, CH_2), 3.32 (*s*, H-6), 3.43 (*s*, H-3), 6.10, 6.17, 6.20 (3*s*, 3OMe). Extraction of the remaining silica from the TLC gave an oil which was purified by sublimation to give benzoic acid (5 mg), identified by direct comparison with an authentic sample.

Preparation of 2'-benzyloxy-4',5'-dimethoxychalcone (**3c**). 2,5-Dihydroxy-4-methoxyacetophenone [24] and Me_2SO_4 etc. as above gave 2-hydroxy-4,5-dimethoxyacetophenone (71%), mp 113–114°. This cmpd, $PhCH_2Cl$, K_2CO_3, Me_2CO, refl., 5 hr, gave by the usual work up 2-benzyloxy-4,5-dimethoxyacetophenone (68%), mp 120–121°. [Found: C, 71.28, H. 6.24. $C_{17}H_{18}O_4$ requires: C, 71.31; H, 6.34%]. PMR (τ): 2.50–2.62 (*m*, Ph, H-6), 3.43 (*s*, H-3), 4.83 (*s*, CH_2), 6.12 (*s*, 2OMe), 7.42 (*s*, OAc). This cmpd (1.43 g) and PhCHO (0.53 g) in MeOH (20 ml) were treated dropwise with an aq. KOH soln (25 g/35 ml) (15 min). Stirring was continued *ca* 18 hr. The mixture was acidified and extracted with Et_2O. The Et_2O soln was evapd. The residue, crystallised from EtOH, gave **3c** (64%), mp 102–104°. [Found: C, 76.90; H, 6.13. $C_{24}H_{22}O_4$ requires: C, 76.98; H, 5.92%]. λ_{max} 235, 308, 362 (ε 15400, 21000, 10700). PMR (τ): 2.30–2.75 (*m*, 2Ph, H-6, CH=CH), 3.40 (*s*, H-3'), 4.90 (*s*, CH_2), 6.10, 6.13 (2*s*, 2OMe).

Synthesis of violastyrene (**2a**) *by reduction of chalcone.* (a) *Preparation of 4'-benzyloxy-2',5'-dimethoxychalcone* (**3a**). 4-Benzyloxy-2,5-dihydroxyacetophenone [24] and Me_2SO_4 etc. as above gave 4-benzyloxy-2,5-dimethoxyacetophenone (76%), mp 102–103°. [Found: C, 70.97; H, 6.02. $C_{17}H_{18}O_4$ requires: C, 71.31, H, 6.34%]. This cmpd and PhCHO etc. as above gave **3a** (80%), mp 87–88° (EtOH). [Found: C, 76.77; H, 6.00. $C_{24}H_{22}O_4$ requires: C, 76.98; H, 5.92%]. λ_{max} 232, 306, 365 (ε 13200, 22800, 11500). (b) *Preparation of* E-1-(4-*benzyloxy*-2,5-*dimethoxybenzyl*)-2-*phenylethylene* (**2c**). **3a** (1.8 g), $LiAlH_4$ (0.33 g) and $AlCl_3$ (2.33 g) in Et_2O (20 ml) were heated under reflux (15 min) and cooled. Excess hydride was decomposed with EtOAc. Excess aq. 10N H_2SO_4 was added, the organic layer separated, dried and evapd. The residue, purified by chromatography on Si gel, gave **2e** (29%), mp 92–95° (isopentane). [Found: C, 79.92; H, 6.97. $C_{24}H_{24}O_3$ requires: C, 79.97; H, 6.71%]. PMR (τ): 2.3–3.1 (*m*, 2Ph), 3.25 (*s*, H-6), 3.47 (*s*, H-3), 3.4–3.8 (AB part), 6.55 (*m*, X_2 part of ABX_2 system), 6.20, 6.30 (2*s*, 2OMe), 4.87 (*s*, CH_2). (c) *Preparation of* E-1-(4-*hydroxy*-2,5-*dimethoxybenzyl*)-2-*phenylethylene* (**2a**). **2e** (0.25 g) in HCl/MeOH (10%) was heated under reflux (5 hr). The mixture was evapd and the residue purified by chromatography (Si gel, C_6H_6). The major product, crystallised from petrol, gave **2a** (32%), mp 84–85°, identical with natural violastyrene.

Synthesis of isoviolastyrene (**2b**) *by reduction of chalcone.* (a) *Preparation of 5'-benzyloxy-2',4'-dimethoxychalcone* (**3b**). 2,5-Dihydroxy-4-methoxyacetophenone [24] and $PhCH_2Cl$ etc. as above gave 5-benzyloxy-2-hydroxy-4-methoxyacetophenone (74%), mp 140–142° (EtOH). [Found: C, 70.90; H, 5.76. $C_{16}H_{16}O_4$ requires: C, 70.57; H, 5.88%]. PMR (τ): 2.58–2.70 (*m*, Ph), 2.93 (*s*, H-6), 3.58 (*s*, H-3), 4.92 (*s*, CH_2), 6.13 (*s*, OMe), 7.62 (*s*, OAc). This cmpd and Me_2SO_4 etc. as above gave 5-benzyloxy-2,4-dimethoxyacetophenone (87%), mp 61°. [Found: C, 71.60; H, 6.30. $C_{17}H_{18}O_4$ requires: C, 71.31; H, 6.34%] This cmpd and PhCHO etc. as above gave **3b** (66%), mp 97–98°. [Found: C, 77.30; H, 6.25. $C_{24}H_{22}O_4$ requires: C, 76.98; H, 5.92%]. λ_{max} (nm): 234, 306, 362 (ε 14800, 21500, 9900). PMR (τ): 2.32–2.75 (*m*, 2Ph, CH=CH, H-6'), 3.50 (*s*, H-3'), 4.91 (*s*, CH_2), 6.12, 6.15 (2*s*, 2OMe). (b) *Preparation of* E-1-(5-*hydroxy*-2,4-*dimethoxybenzyl*)-2-*phenylethylene* (**2b**). **3b** and $LiAlH_4/AlCl_3$ etc. as above followed by HCl/MeOH as above gave a product which was purified by TLC to **2b** (10%), mp 86–88°, identical with natural isoviolastyrene.

Synthesis of violastyrene (**2a**) *by Claisen rearrangement* 2,5-Dimethoxyphenol [25] (1.95 g), cinnamyl bromide (2.55 g), K_2CO_3 (3.5 g) in Me_2CO (25 ml) were stirred (room temp., 60 hr). The usual work up gave 1-cinnamyloxy-2,5-dimethoxybenzene (58%), mp 77–79° (cyclohexane). [Found: C, 75.19; H, 6.60. $C_{17}H_{18}O_3$ requires: C, 75.53; H, 6.71%]. This cmpd (1 g) in *N,N*-dimethylaniline (5 ml) was heated under reflux (N_2, 3 hr). The mixture was cooled, diluted with C_6H_6, washed with 2N HCl (100 ml) and extracted with aq. 3% NaOH (12 × 50 ml). The alkaline soln was acidified and extracted with Et_2O. The Et_2O soln was dried and evapd. The residue was separated by TLC (Si gel, C_6H_6) into two components. The faster moving component was 3-(2'-hydroxy-3',6'-dimethoxyphenyl)-3-phenylpropene (**5**) (0.05 g). PMR (τ): 2.78 (*s*, Ph), 3.30, 3.67 (AB system, J_{AB} = 10 Hz, H-4', H-5'), 4.25 (*s*, OH), 4.55–4.95 (*q*, 2 H-1, H-3), 6.20, 6.35 (2*s*, 2OMe). The slower moving component was **2a** (0.3 g), identical with natural violastyrene.

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