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CONSTITUTIONS OF DIARYLPROPANOIDS FROM *VIROLA MULTINERVIA**

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Key Word Index—*Virola multinervia*; Myristicaceae; diarylpropanoids; 1-(2-hydroxy-4-methoxyphenyl)-3-(3,4-methylenedioxyphenyl)-propane; 2-hydroxy-1-(2-hydroxy-4-methoxyphenyl)-3-(3,4-methylenedioxy phenyl)-propane; virolane, virolanol.

Abstract—The wood of *Virola multinervia* Ducke (Myristicaceae) contains sitosterol, stigmasterol and two novel diarylpropanoids virolane [1-(2-hydroxy-4-methoxyphenyl)-3-(3,4-methylenedioxyphenyl)-propane] and virolanol [2-hydroxy-1-(2-hydroxy-4-methoxyphenyl)-3-(3,4-methylenedioxyphenyl)-propane].

Virola species (Myristicaceae) have been noted for the high trimyristin content of their seed fats which are produced industrially;[1,2] and the presence of tryptamine and 1,2,3,4-tetrahydro-β-carboline derivatives[3,4] in their barks which are used in the preparation of hallucinogenic snuffs and pills by the Amazonian Indians.[5] *Virola cuspidata* (Benth.) Warb. contains hydroxyotobain and 3,5,4′-trimethoxy-*trans*-stilbene in the bark,[6] and 1,2,3,4-tetrahydroharman derivatives in the leaves and stems.[7]

Virola multinervia Ducke occurs in the western part of Amazonas State, from the Rio Negro to Peru, and is designated popularly 'ucuúba grande'. *N,N*-Dimethyltryptamine, which occurs in minute amounts in the bark of the tree, is accompanied by 5-methoxy-*N,N*-dimethyltryptamine in the root.[3] The wood contains, besides sitosterol and stigmasterol, two novel crystalline constituents, designated virolane and virolanol.

Functional analysis of virolane, $C_{17}H_{18}O_4$, disclosed the presence of one phenolic hydroxyl (UV shift in presence of NaOH, formation of a monoacetate), one aromatic methoxyl (PMR singlet at τ 6·22) and one aromatic methylenedioxy group (PMR singlet at τ 4·13). The PMR spectrum contained additionally signals due to 6 aromatic and 6 aliphatic protons. The chemical shifts, multiplicities and coupling constants of the signals at high field suggested the presence of a CH_2 group (τ 7·8–8·3, *m*, 2H), flanked by two benzylic methylenes (τ 7·48, approximate *t*, *J* 7·0 Hz, 4H). The total number of aromatic positions in virolane thus adding up to 12, two aromatic rings must be present, as indicated

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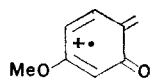
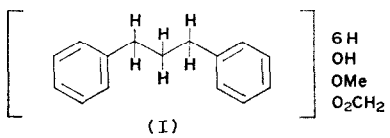
in the partial formula I. One of these rings sustains a 3,4-methylenedioxy group, since oxidation of the compound leads to piperonylic acid. The two remaining oxy-functions can only occupy the positions 2 and 4 of the other aromatic ring, *meta*-related to a relatively deprotected proton, whose PMR signal (τ 3·00, *d*, *J* 8·0 Hz) stands apart, at lower field, from other signals. The relative placement of the two oxy-groups was revealed by the MS, which included a strong peak at *m/e* 136 (Table 1) due to a fragmentation process commonly favoured in *ortho*-disubstituted benzenes; as well as by a strongly positive Gibbs test, which is consistent only with the presence of the hydroxyl at C-2′, *para*-related to an unsubstituted position. The constitution 1-(2-hydroxy-4-methoxyphenyl)-3-(3,4-methylenedioxyphenyl)-propane (IIa) was therefore proposed for virolane, and this was confirmed by synthesis.[8]

TABLE 1. INTERPRETED MS OF VIROLANE (IIa) AND VIROLANOL (IIc)

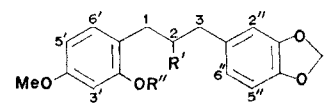
	m/e	IIa (%)	IIc (%)
$M^{+\cdot}$	302	—	51
$M^{+\cdot}$	286	62	—
$[M - 18]^{+\cdot}$	284	—	2
Ar–CH_2–CH=O$^+$H	167	—	38
Ar′–CH_2–CH=O$^+$H	165	—	9
Ar–CH_2–CH_2^+	151	20	—
Ar′–CH_2–CH_2^+	149	18	—
Ar–CH_2^+	137	100	100
Ar′–CH_2^+	135	33	44
	136	72	97

Ar—2-Hydroxy-4-methoxyphenyl; Ar′—3,4-methylenedioxyphenyl.

In comparison with virolane, virolanol, $C_{17}H_{18}O_5$, contains an additional oxygen. This belongs to a secondary alcohol, since the signal due to the carbinolic proton (τ 5·73–6·23, *m*) is displaced by more than 1 ppm to lower field upon acetylation (τ 4·83, *q*, *J* 6·5 Hz). The location of the CHOH group at the central position of the aliphatic chain is clearly defined by the MS peaks at *m/e* 167 and 165 (Table 1), as well as by the chemical shift of the 4 proton signal (τ 7·03–7·43, *m*) in the NMR spectrum of virolanol and of its acetate (τ 7·24, *d*, *J* 6·5 Hz). Two benzylic CH_2 groups must thus continue to exist in the new isolate. All other spectral data being closely comparable to the data described for virolane, the constitution 2-hydroxy-1-(2-hydroxy-4-methoxyphenyl)-3-(3,4-methylenedioxyphenyl)-propane (IIc) was proposed for virolanol, and this was confirmed by synthesis.[8]



(I)



(IIa) R′ = H ; R″ = H
(IIb) R′ = H ; R″ = Ac
(IIc) R′ = OH ; R″ = H
(IId) R′ = OAc; R″ = Ac

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The oxygenation of the aromatic rings of both 1,3-diarylpropanoids points to a mixed biosynthetic origin by one of two possible general routes: (1) cinnamoylation of a triacetate precursor to chalcone and flavanonol intermediates[9] whose reduction would lead respectively to virolane and virolanol; (2) cinnamylation of a triacetate precursor to a cinnamylphenol intermediate[10] whose reduction or hydration would lead respectively to virolane and virolanol. Whichever is the correct alternative, the two compounds are among the simplest flavanoids so far discovered.

EXPERIMENTAL

M.ps were taken on the Kofler block and are uncorrected. Column chromatography employed Merck's Kieselgel 0·05–0·20 mm. PMR spectra were taken on a Varian HA-60-IL instrument. TMS was used as internal standard. *s*—singlet; *d*—doublet; *t*—triplet; *dd*—double doublet; *q*—quintuplet; *m*—multiplet. MS were recorded with a Varian Atlas CH-7 instrument.

Isolation of the constituents of Virola multinervia. The ground wood (5·3 kg) was extracted with benzene. The solvent was evaporated and the residue (24 g) was chromatographed on silica (350 g), giving the following fractions with the indicated eluants: F_1 and F_2 (benzene), F_3 ($CHCl_3$). F_1 was recrystallized from benzene–light petrol. giving virolane (905 mg). F_2 was recrystallized from benzene–light petrol. giving a mixture of sitosterol and stigmasterol (250 mg). F_3 was recrystallized from benzene–light petrol. giving virolanol (254 mg).

Virolane (IIa). Rectangular rods, m.p. 99–100°. M found: 286·1210. $C_{17}H_{18}O_4$ requires: 286·1205. λ_{max}^{EtOH} (nm): 234, 285 (ε 13 600, 9000), $\lambda_{max}^{EtOH+NaOH}$ (nm): 241, 291 (ε 15 750, 10 650). Gibbs test,[11] λ_{max} (nm 620, 650 (absorbance 3·0, 2·6). ν_{max}^{KBr} (cm^{-1}): 3380, 1615, 1598, 1501, 1483, 1247, 1197, 1167, 1045. PMR 231, 284, 287 (ε 10 700, 6600, 6800, $\lambda_{max}^{EtOH+NaOH}$ (nm): 236, 292 (ε 11 000, 8700). Gibbs test, $^{11}\lambda_{max}$ (nm): ($CDCl_3$, τ): 3·00 (*d*, *J* 8·0 Hz, H-6′), 3·51 (*dd*, *J* 8·0 and 2·0 Hz, H-5′), 3·61 (*d*, *J* 2·0 Hz, H-3′), 3·28 (broad *s*, H-2″,5″,6″), 4·13 (*s*, O_2CH_2), 4·96 (broad *s*, OH), 6·20 (*s*, OCH_3), 7·40 (*t*, *J* 7·0 Hz, 2 $ArCH_2$), 7·8–8·3 (*m*, $CH_2CH_2CH_2$). Oxidation ($KMnO_4$, acetone, room temp.) led to piperonylic acid, m.p. and m.m.p. 229–231° MS: Table 1. *Acetate* (IIb). Oil. PMR ($CDCl_3$, τ): 2·86 (*d*, *J* 8·0, H-6′), 3·15–3·45 (*m*, H-3′,5′,2″,5″,6″), 4·08 (*s*, O_2CH_2), 6·18 (*s*, OCH_3), 7·36 (*t*, *J* 6·5 Hz, $ArCH_2$), 7·48 (*t*, *J* 6·5 Hz, $ArCH_2$), 8·13 (*m*, $CH_2CH_2CH_2$), 7·73 (*s*, $ArOCOCH_3$).

Virolanol (IIc). Leaflets, m.p. 114–115°. M found: 302·1155. $C_{17}H_{18}O_4$ requires: 302·1154. λ_{max}^{EtOH} (nm): 231, 284, 287 (ε 10 700, 6600, 6800), $\lambda_{max}^{EtOH+NaOH}$ (nm): 236, 292 (ε 11 000, 8700). Gibbs test,[11] λ_{max} (nm): 620, 660 (Absorbance 3·0, 2·0). ν_{max}^{KBr} (cm^{-1}): 3410, 3190, 1620, 1592, 1492, 1258, 1100, 1070, 1035. PMR ($CDCl_3$, τ): 3·09 (*d*, *J* 8·0 Hz, H-6′), 3·58 (*dd*, *J* 8·0 and 2·0 Hz, H-5′), 3·51 (*d*, *J* 2·0, H-3′), 3·33 (*m*, H-2″, 5″,6″), 4·09 (*s*, O_2CH_2), 6·23 (*s*, OCH_3), 5·73–6·23 (*m*, CHOH), 7·03–7·43 (*m*, 2 $ArCH_2$). MS: Table 1 *Acetate* (IId). Oil. PMR ($CDCl_3$, τ): 2·86 (*d*, *J* 8·0 Hz, H-6′), 3·25 (*dd*, *J* indet. and 2·5 Hz, H-5′), 3·15–3·45 (*m*, H-3′,2″,5″,6″), 4·05 (*s*, O_2CH_2), 6·19 (*s*, OCH_3), 4·83 (*q*, *J* 6·5 Hz, CHOAc), 7·24 (*d*, *J* 6·5, 2 $ArCH_2$), 7·77 (*s*, $ArOCOCH_3$), 8·03 (*s*, $CHCOCH_3$).

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