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Iridoid Glucosides from *Viburnum macrocephalum*

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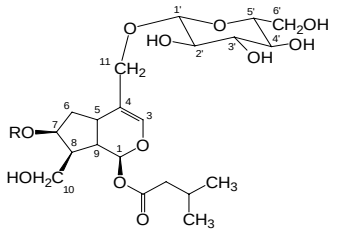
The phytochemical study of the aerial parts of *Viburnum macrocephalum* Fortune, an ornamental species of Chinese origin, led to the isolation, together with the phenolic glucoside triandrin, of three iridoid glucosides: the novel 7-cinnamoylpatrinoside (**1**), and the known 7-*p*-coumaroylpatrinoside (**2**) and patrinoside (**3**).

Keywords: *Viburnum macrocephalum*, Iridoids, 7-cinnamoylpatrinoside, 7-*p*-coumaroylpatrinoside, Patrinoside, Triandrin.

The genus *Viburnum* (Caprifoliaceae) includes more than 200 species, either shrubs or trees, most of which are widely distributed in Southern America and in Western Asia, where they are very abundant in the Chinese spontaneous flora [1a]. The phytochemical studies carried out in the past years on *Viburnum* species showed the frequent occurrence of *Valeriana*-type iridoid glycosides (characterised by a sugar moiety at C-11 and an isovaleroyl group at C-1) [1b]. In this article we report the phytochemical study of the aerial parts of *V. macrocephalum* Fortune, a deciduous or partly evergreen shrub of Asiatic origin, introduced into Europe from China in 1844. It is the largest of the "snowball Viburnums", widely cultivated for ornamental purposes because of its showy white inflorescences [1c].

The main constituents of the EtOAc and *n*-BuOH soluble fractions obtained from *V. macrocephalum* were separated by column chromatography. Together with the phenolic glucoside triandrin, first recovered from willow bark extracts [2a,2b], three iridoid glucosides were isolated: patrinoside (**3**) [2c], 7-*trans*-*p*-coumaroylpatrinoside (**2**) [2d] and the novel 7-*trans*-cinnamoylpatrinoside (**1**), in order of decreasing polarity. The structure of **1** was identified mainly by analysis of its NMR spectra. In particular, the ^{1}H NMR spectrum of **1** appeared almost identical to that of patrinoside [2c], except for the evident downfield shift of the H-7 signal, the value for which (δ 5.36) was in accordance with an acylation effect, and additional signals easily assigned to an acylating cinnamoyl group.



1. 7-*trans*-cinnamoyl-patrinoside

2. 7-*trans*-*p*-coumaroyl-patrinoside

3 R = H patrinoside

Further confirmation was obtained from ^{13}C NMR, ^{1}H-^{1}H COSY and ^{1}H-^{13}C COLOC experiments (which allowed the unambiguous assignments for the acylation sites). Finally, NOE-difference experiments allowed us to confirm the relative stereochemical assignments for the chiral centres at C-7 and C-8. Positive NOEs among the protons H-6b, H-5, H-9 and H_2-10 and, on the other side, among H-6a, H-7 and H-8 were observed. Assuming a β configuration for H-5, as in almost all the known iridoids, 7-β-OH and 8-β-CH_2OH configurations were assigned to **1**, also consistent with the stereochemistry of patrinoside.

Among the many papers published on taxonomic relationships between *Viburnum* species [3a-3d], Rehder's division of the genus into nine sections is still accepted today [3e]. The presence of *Valeriana*-type iridoids, so far recovered from the majority of

Rehder's sections, can be considered as a non-morphologic character to be successfully used for taxonomic purpose. These metabolites show, as main structural differences, the presence or absence of hydroxy groups at carbons 7 and 8. In particular, the substitution pattern of the iridoids reported in this paper [7–OH / 8–H] is typically found in species of Rehder's section Lantana, where *V. macrocephalum* belongs.

Experimental

General procedures and Plant material: Optical rotations were measured at room temperature in MeOH using a JASCO DIP-370 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz NMR spectrometer. FABMS spectra were run on a VG7070 EQ-HF mass spectrometer, equipped with its own FAB source, using *m*-nitrobenzyl alcohol (NBA) as matrix. TLC were performed on Si gel SiF_{254} (Merck) and plates were visualized using 2N H_2SO_4 as spray reagent. *Viburnum macrocephalum* was collected in the Botanical Garden of Rome and its identity was confirmed by the first author at the University "La Sapienza", Rome, Italy, where a voucher specimen is deposited (RO General Herbarium).

Extraction and isolation: Fresh leaves and branches of *Viburnum macrocephalum* (600 g) were extracted at room temperature with MeOH, filtered and concentrated to dryness. The residue (52 g) was suspended in H_2O (500 mL) and extracted first with EtOAc (3 x 300 mL) and then *n*-BuOH (3 x 200 mL). Evaporation of the EtOAc fraction gave a residue (12 g) which was chromatographed on silica gel using $CHCl_3$:MeOH (9:1), affording the new iridoid glucoside, 7-*trans*-cinnamoylpatrinoside (**1**) (24 mg), together with the known iridoid glucoside 7-*trans*-*p*-coumaroylpatrinoside (28 mg). Column chromatography of the *n*-BuOH fraction (15 g) on silica gel using $CHCl_3$:MeOH (4:1) led to the isolation of the known iridoid glucoside, patrinoside (79 mg), and the phenolic glucoside triandrin (43 mg). The identifications of all known compounds were performed by comparison with authentic samples.

7-Cinnamoylpatrinoside (**1**)
Amorphous powder.
$[\alpha]_D$: -34.6 (*c* 0.4, MeOH).
Rf : 0.7 ($CHCl_3$-MeOH, 4:1).
UV λ_{max} (MeOH) nm (log ε): 226 (2.88), 288 (sh. 3.80), 300 (4.10).
^{1}H NMR (400 MHz, CD_3OD): 0.87 (6H, d, *J* = 6.6 Hz, $(CH_3)_2$CHCH$_2$COO-), 2.00-1.95 (2H, m, H-6a and H-6b), 2.03 (2H, m, Me$_2$C*H*CH$_2$COO- and H-8), 2.10 (2H, d, *J* = 6.9 Hz, Me$_2$CHCH_2COO-), 2.14 (1H, m, H-9), 2.94 (1H, m, H-5), 3.10 (1H, d, *J* = 8.1 and 9.7 Hz, H-2'), 3.20 (3H, partially masked by the solvent signal, H-3', H-4' and H-5'), 3.58 (2H, m, H-6'b and H-10b), 3.68 (1H, d, *J* = 7.9 and 11.3 Hz, H-10a), 3.80 (1H, dd, *J* = 2.5 and 12.0 Hz, H-6a), 4.03 (1H, d, *J* = 12.0 Hz, H-11b), 4.20 (1H, dd, *J* = 12.0 Hz, H-11a), 4.22 (1H, d, *J* = 8.1 Hz, H-1'), 5.36 (1H, bs, H-7), 5.95 (1H, d, *J* = 4.9 Hz, H-1), 6.33 (1H, br s, H-3), 7.38 (1H, d, *J* = 16.3 Hz, H-α), 7.32 (3H, m, H-3", H-4", H-5"), 7.53 (2H, dd, *J* = 4.5 and 7.8 Hz, H-2", H-6"), 7.61 (1H, d, *J* = 16.3 Hz, H-β).
^{13}C NMR (100 MHz, CD_3OD): 21.3 (2CH_3, $(CH_3)_2$CHCH$_2$COO-), 25.5 (CH, Me$_2$*C*HCH$_2$COO-), 32.6 (CH, C-5), 36.8 (CH$_2$, C-6), 42.3 (CH, C-9), 42.7 (CH$_2$, Me$_2$CH*C*H$_2$COO-), 44.4 (CH, C-8), 60.3 (CH$_2$, C-6'), 61.5 (CH$_2$, C-10), 68.3 (CH$_2$, C-11), 70.4 (CH, C-4'), 73.8 (CH, C-2'), 75.2 (CH, C-7), 76.8 (2CH, C-5' and C-3'), 91.6 (CH, C-1), 101.9 (CH, C-1'), 114.3 (C, C-4), 117.7 (CH, C-α), 127.9 (2CH, C-3" and C-5"), 128.7 (2CH, C-2" and C-6"), 130.2 (CH, C-4"), 134.0 (C, C-1"), 139.2 (CH, C-3), 145.0 (CH, C-β), 167.2 (C, Cinn-*C*OO-), 171.9 (C, Me$_2$CHCH$_2$*C*OO-).
FABMS *m/z*: $[M + Na]^+$ 615 [592 + 23].

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