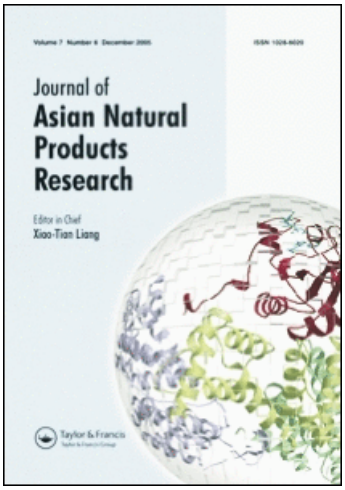

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Acretoside, a new sucrose ester from *Aristolochia cretica**

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A new sucrose ester, acretoside, has been isolated from the roots of the Greek endemic species *Aristolochia cretica* and identified as 6-*O*-*p*-coumaroyl-β-D-fructofuranosyl-(2 → 1)-α-D-glucopyranoside (**1**). In addition, a known sucrose ester, identified as arillatose B, two phenylpropanoid glucose esters, and five derivatives of aristolochic acids have been isolated. Their structures have been elucidated on the basis of MS and NMR data.

Keywords: *Aristolochia cretica*; acretoside; phenylpropanoid glycosides

1. Introduction

Aristolochia is regarded as a genus of the family Aristolochiaceae, which consists of perennial herbs and climbers distributed in the tropical and temperate zones [1]. There are about 400 species of this genus worldwide and more than 50 have been studied. These plants, and especially their roots, have been known for their medicinal properties since antiquity. They have played important roles in folk medicine and are used as analgesics, expectorants, emmenagogues and in the treatment of arthritis, snakebite, pruritus and fever [2–4].

The broad pharmacological activity of *Aristolochia* roots stimulated our interest in the investigation of the roots of Greek species *Aristolochia cretica*, which is endemic in the islands of Crete and Carpathos. It is a perennial pubescent herb (up to 60 cm) with dull purple flowers [1]. Its constituents have not been reported previously.

Phytochemical analysis of the extracts of the roots led to the isolation and structural elucidation of 6-*O*-*p*-coumaroyl-β-D-fructofuranosyl-(2 → 1)-α-D-glucopyranoside (**1**), a new sucrose ester. Moreover, its known analogues arillatose B (**2**), two phenylpropanoid glucose esters identified as 6-*O*-*p*-coumaroyl-α-D-glucopyranose (**3**) and 6-*O*-*p*-coumaroyl-β-D-glucopyranose (**4**), and five derivatives of aristolochic acids identified as aristolochic

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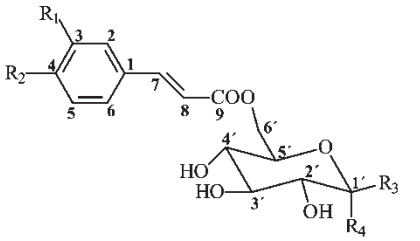
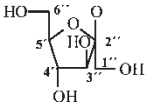
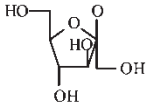


1: $R_1 = R_3 = H$, $R_2 = OH$, $R_4 =$ 

2: $R_1 = R_2 = OH$, $R_3 = H$, $R_4 =$ 

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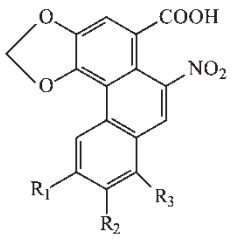
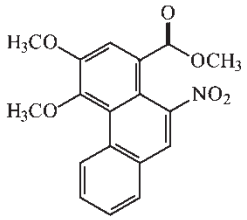
4: $R_1 = R_4 = H$, $R_2 = R_3 = OH$





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5: $R_1 = R_2 = H$, $R_3 = OCH_3$

6: $R_1 = H$, $R_2 = OH$, $R_3 = OCH_3$

7: $R_1 = OH$, $R_2 = R_3 = H$

8: $R_1 = R_2 = R_3 = H$

Figure 1. Structures of 6-*O*-*p*-coumaroyl-β-D-fructofuranosyl-(2 → 1)-α-D-glucopyranoside (**1**), arillatose B (**2**), 6-*O*-*p*-coumaroyl-α-D-glucopyranose (**3**), 6-*O*-*p*-coumaroyl-β-D-glucopyranose (**4**), aristolochic acid I (**5**), 7-hydroxyaristolochic acid I (**6**), aristolochic acid IIIa (**7**), aristolochic acid II (**8**) and ariskanin A (**9**).

acid I (**5**), 7-hydroxyaristolochic acid I (**6**), aristolochic acid IIIa (**7**), aristolochic acid II (**8**) and ariskanin A (**9**) have been isolated (figure 1).

2. Results and discussion

Compound **1** was obtained as an amorphous powder. Its molecular formula was determined by HRFABMS as $C_{21}H_{28}O_{13}$. The IR spectrum shows a conjugated ester group (1715 cm^{-1}) and an aromatic ring (1607 and 1517 cm^{-1}). The ^1H NMR spectrum of **1** contains the signals

of four aromatic protons at δ 7.47 (2H, d, $J = 8.5$ Hz), and 6.79 (2H, d, $J = 8.5$ Hz) corresponding to an AA′ BB′ system, which displays the presence of a *para* bisubstituted aromatic ring. In addition, the ^{1}H NMR spectrum also shows signals for two *trans* double bond protons at δ 7.65 (1H, d, $J = 15.0$ Hz) and 6.39 (1H, d, $J = 15.0$ Hz), suggesting a *trans*-coumaroyl moiety. This is supported by the ^{13}C NMR spectrum, which in the low field region has signals for a coumaroyl moiety at δ 168.8 (s), 160.8 (s), 146.2 (d), 130.4 (d), 126.4 (s), 116.0 (d), 114.1 (d). Furthermore, the ^{13}C NMR spectrum shows twelve carbon signals arising from a disaccharide moiety (table 1).

The two anomeric carbon signals at δ 104.4 (s) and 92.4 (d), and three methylene groups at δ 63.0 and 62.7 (two signals) suggest that this disaccharide is sucrose [5]. This was proven by the ^{1}H NMR spectrum, in which the characteristic doublet signal with a small coupling constant at δ 5.39 (1H, d, $J = 4.0$ Hz) is assignable to the anomeric proton in the α-D-glycopyranose unit. The point of linkage of the coumaroyl moiety with the sucrose moiety was solved by analysis of the HMBC experiment. In this spectrum, a long-range correlation (^3J) between the coumaroyl carbonyl carbon signal at δ 168.8 and the proton signals at δ 4.48 (1H dd, $J = 12.5, 2.0$ Hz) and 4.28 (1H, dd, $J = 12.5, 6.0$ Hz) due to H-6 of glucose suggests that the coumaroyl moiety is connected at C-6′. In addition, in the same spectrum the anomeric carbon of the fructose moiety (at δ 104.4) is correlated (^3J) with the anomeric proton of glucose at δ 5.39 (1H, d, $J = 4.0$ Hz). Compound **1** was therefore elucidated as 6-*O*-*p*-coumaroyl-β-D-fructofuranosyl-(2 → 1)-α-D-glycopyranoside. All proton and carbon signals in the NMR spectra (table 1) of compound **1** were assigned from its COSY, DEPT, HMQC and HMBC spectra.

Table 1. NMR data (^{1}H: 400 MHz, ^{13}C: 50 MHz) for compound **1** in CD_3OD solution.

Position	δ_C *(ppm)*	δ_H *(ppm)*[a]
Aglycon		
1	126.4	–
2/6	130.4	7.47 (d, $J = 8.5$)
3/5	116.0	6.79 (d, $J = 8.5$)
4	160.8	–
7	146.2	7.65 (d, $J = 15.0$)
8	114.1	6.39 (d, $J = 15.0$)
9	168.8	–
Glucose		
1′	92.4	5.39 (d, $J = 4.0$)
2′	72.7	3.46 (dd, $J = 10.0$,4.0)
3′	73.5	3.76[b]
4′	71.0	3.33 (t, $J = 9.5$)
5′	70.7	4.11 m
6′	63.0	4.28 (dd, $J = 12.5, 6.0$)
		4.48 (dd, $J = 12.5, 2.0$)
Fructose		
1″	62.7	3.60 (d, $J = 12.5$)
		3.58 (d, $J = 12.5$)
2″	104.4	
3″	78.2	4.09 (d, $J = 8.0$)
4″	75.0	4.06 (t, $J = 8.0$)
5″	82.9	3.85[b]
6″	62.7	3.79[b]
		3.82[b]

[a] Multiplicity and coupling constants (J in Hz) are in parentheses.
[b] Overlapping signals.

Spectra for arillatose B (**2**) [6], 6-*O*-*p*-coumaroyl-α-D-glucopyranose (**3**) [7], 6-*O*-*p*-coumaroyl-β-D-glucopyranose (**4**) [7], aristolochic acid I (**5**) [3], 7-hydroxyaristolochic acid I (**6**) [7], aristolochic acid IIIa (**7**) [8] aristolochic acid II (**8**) [2], and ariskanin A (**9**) [4] were in complete agreement with published data.

Although aristolochic acids are the main components in the family Aristolochiaceae, this is the first time that a derivative of sucrose ester or other phenylpropanoid glycose ester has been isolated from the well-studied *Aristolochia* genus.

3. Experimental

3.1 General experimental procedures

Optical rotations were measured with a Perkin-Elmer 341 polarimeter. UV spectra were recorded on a Shimadzu-160A spectrophotometer; ε values are given in parentheses. IR spectra were taken on a Perkin-Elmer Paragon 500 instrument.

NMR spectra (400 MHz) were measured on a Bruker DRX-400 spectrometer and ^{13}C NMR spectra (50 MHz) on a Bruker AC-200 instrument. Chemical shifts (δ) are given in ppm with respect to TMS as an internal standard. Coupling constants (*J*) are given in Hz. The signals in the ^{1}H and ^{13}C spectra were assigned unambiguously using 2D NMR techniques: COSY, COSY LR, HMQC and HMBC. These 2D experiments were performed using standard Bruker microprograms. HR-FABMS spectra were obtained on an AEI MS-902 mass spectrometer. Column chromatography was conducted using flash silica gel 60 Merck (40–63 μm), with an overpressure of 300 mbar. Medium-pressure liquid chromatography (MPLC) was performed with a Buchi model 688 apparatus on columns containing RP-18 silica gel 60 Merck (20–40 μm).

3.2 Plant material

The roots of *A. cretica* were collected on the island of Crete in April, 2000. A voucher specimen (KL001) has been deposited in the herbarium of the Division of Pharmacognosy and Natural Products Chemistry, University of Athens.

3.3 Extraction and isolation

The air-dried roots of *A. cretica* (1200 g) were extracted with CH_2Cl_2 and then with MeOH (3 × 2 L). The methanol extract was then evaporated to dryness, yielding 62.1 g dry wt., and then fractionated by MPLC using a MeOH–H_2O gradient. The less polar fractions (1.1 g) were rechromatographed by MPLC to afford 6-*O*-*p*-coumaroyl-β-D-fructofuranosyl-(2 → 1)-α-D-glycopyranoside (**1**) (15 mg) and arillatose B (**2**) (22 mg) and two phenylpropanoid glucose esters **3** (18 mg) and **4** (20 mg). The more polar fractions were rechromatographed by MPLC using a MeOH–H_2O gradient to afford four aristolochic acid derivatives, **5** (12 mg), **6** (15 mg), **7** (10 mg) and **8** (14 mg). Part of the dichloromethane extract was evaporated to dryness, yielding 1.2 g dry wt., and then fractionated by column chromatography using a cyclohexane–CH_2Cl_2 gradient to afford ariskanin A (**9**) (18 mg).

Acretoside (**1**), $[\alpha]_D + 13.3°$ (*c* 0.3, MeOH); UV (MeOH) λ_{max} (nm): 312 (3.96), 290 (sh), 226 (3.95), 205 (4.04); IR (MeOH) ν_{max} (cm^{-1}): 1715, 1607, 1517; ^1H NMR and ^{13}C NMR, see table 1; HR-FABMS found: *m/z* 489.1534 $[M + H]^+$, calculated for $[C_{21}H_{29}O_{13}]^+$ 489.1530.

Acknowledgements

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