New Cinnamoyl Esters of Quinic Acid from Meum athamanticum

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Two new cinnamoyl quinic acid esters were isolated from the methanolic extract of Meum athamanticum rhizome. They were identified as 1-trans-O-caffeoyl quinic acid methyl ester and 1-trans-O-feruloyl quinic acid methyl ester by the spectral data of the natural products and those of the acetylated derivatives.

Introduction

Meum athamanticum Jacq. (Umbelliferae) is a wild plant common to siliceous soils and growing at an altitude of 400 to 1500 m [1]. Its occurrence is widespread in most of western and central European mountains [2]. Until the present time, Meum athamanticum is the only known species of the genus [3] and is valued for its stimulating, stomachic, diuretic and expectorant [5] properties in traditional medicine. Recently, in vitro tests have demonstrated inhibition of aggregation of human platelets by aqueous extracts of rhizome tissues [6].

Most of the constituents reported now, have been recovered from nonpolar extracts of the underground parts. Some of these are very ubiquitous in higher plants as 3-carene, 3-pinene, terpinolene [7] and 3-stigmasterol [8]. Others, such as falcarninolone [9] and ligustilide [7], are of common occurrence in the Umbelliferae. In addition to those components, a new hydrocarbon named viridene is presently specific to Meum [7].

This paper reports on the isolation and identification of two new cinnamoyl quinic esters from the methanolic extract of Meum athamanticum Jacq. rhizome.

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Results and Discussion

The plant material was successively lixivied with n-hexane, chloroform and methanol. The concentrated methanolic extract was redissolved in water and then partitioned with benzene, ethyl acetate and finally n-butanol. From the last layer, two compounds 1a and 2a were isolated and purified by column chromatography on Sephadex LH 20 and polyamide SC 6. The structures of both compounds were established on the basis of spectral data of the natural products and their acetylated derivatives.

1-trans-O-caffeoyl quinic acid methyl ester 1a

When compared with caffeic acid, this compound exhibited similar UV spectrum as well as the same white bluish fluorescence. However, its Rf values on cellulose and polyamide TLC were different from those of caffeic acid. Therefore, it was strongly suggested the presence of a caffeic acid unit in this compound, the o-diphenol group being free, as shown by the AlCl3 UV shift. Furthermore, the 1H NMR spectrum (CD3OD) of the natural product exhibited three aromatic protons of which an AB system (J = 8 Hz) at δ 6.94, 6.78 ppm, one singlet at δ 7.02 ppm and two trans-coupled ethylenic protons (J = 16 Hz) at δ 7.52 and 6.20 ppm. These observations were confirmed by the 1H NMR spectrum (CDCl3) of the acetylated derivative 1b which indicated two additional isochrone phenolic acetates at δ 2.30 ppm. Moreover, the fragmentation pattern recorded for this part of the molecule conformed with the presence of a caffeic acid moiety as indicated by the fragment ions at m/z 180, 163, 162 and 135 in the MS of 1a.

Examination of the 1H NMR spectrum of the acetylated derivative 1b, after irradiation experiments, gave evidence for three methane groups involved in the same chain –CH(a)–CH(b)–CH(c)–, with CH(a): δ 5.55 ppm – δδ – J 10, 10 and 4.5 Hz; CH(b): δ 5.10 ppm – δδ – J 10 and 3.5 Hz; CH(c): δ 5.59 ppm – δδ – J 3.5 and 3.5 Hz, those chemical shift values indicating their O-binding. In addition, the coupling constant Jab = 10 Hz corresponding to a trans-diaxial orientation permitted their incorporation in a cycle bearing two methylene groups observed as overlapped multiplets centered at δ 2.52 ppm. After irradiation of H(b), only two couplings (J = 10 and 4.5 Hz) for

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H(a) and one \((J = 3.5 \text{ Hz})\) for H(c) remained, specifying their positioning on the endocyclic methylene groups. Considering the molecular formula C\(_{17}\)H\(_{26}\)O\(_9\) deduced from measurement by mass spectrometry, in the high resolution mode, of 1a, those data do not account for three carbon atoms. Two of them were assigned to belong to a methyl ester characterized conjointly by a sharp singlet at \(\delta 3.68 \text{ ppm}\) on both \(^1\text{H NMR}\) spectra of 1a and 1b and IR absorptions at 1735 and 1430 cm\(^{-1}\) presented by 1a. The similarity in the chemical shift values of H-3, H-4 singlet at d3.68 ppm on both 'H NMR spectra of the comparative analysis of 'H NMR chemical shifts of H-3, H-4 and H-5 in the quinic acid derivative 1a. The results listed in Table I, for quinic acid 3 and the four isomeric forms of caffeoyl quinic acid 4–7, indicate that the methine group involved in acylation is largely deshielded in comparison with the two others, even in the case of CH-4 which is usually more shielded [10]. On the basis of the recorded chemical shift values for H-3, H-4 and H-5 of both the natural product 1a and its acetylated derivative 1b, one can certainly conclude that none of the methine groups is esterified with the phenolic acid. Consequently, the latter must be bound to position 1 of methyl quinate, resulting in 1-trans-O-caffeoyl quinic acid methyl ester 1a.

**1-trans-O-feruloyl quinic acid methyl ester 2a**

As for 1-trans-O-caffeoyl quinic acid methyl ester 1a, two parts were found again for compound 2a, a trans-cinnamoyl acid esterifying the same quinic acid methyl ester. On the \(^1\text{H NMR}\) spectrum, all the protons assigned to the skeleton of the trans-O-cinnamoyl quinic acid methyl ester were similar to those of the caffeoyl derivative 1a, except for a supplementary methyl group. This one was indicated by a sharp singlet at \(\delta 3.88 \text{ ppm}\). Effectively, the molecular ion of 2a was found at \(m/z\) 382 corresponding to molecular formula C\(_{18}\)H\(_{22}\)O\(_9\) (obtained by high resolution mass spectrometry) and the shift of 14 m.u. due to the additional methyl was reflected on the fragmentation pattern of the cinnamoyl part, leading to ions at \(m/z\) 194, 177 and 150. Those results, which agreed with the presence of a trans-feruloyl part in this molecule, were confirmed both by the characteristic blue fluorescence and the UV spectral data exhibited by 2a, in comparison with trans-ferulic acid.

Even weak, the whole ions resulting from the fragmentation of the acetylated quinic acid methyl ester were present in the MS of the acetylated derivative 2b. Situated at \(m/z\) 315, 273, 255, 213, 195 and 153, they arose, the one from the other by loss of a ketene or a molecule of water probably induced by the vicinality of the three acetyl functions on C-3, C-4 and C-5 of the quinic ring, as observed for the caffeoyl derivative 1b. The similarity in the chemical shift values of H-3, H-4

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**Table 1. Chemical shift values in \(^1\text{H NMR}\) (\(\delta \text{ ppm/TMS}\)) of H-3, H-4 and H-5 for quinic acid (3) and cinnamoyl derivatives (spectra were recorded in MeOH–D\(_2\) for 1a and 2a, CDC\(_3\) for 1b and in C\(_6\)D\(_6\)N for 3–7).**

<table>
<thead>
<tr>
<th></th>
<th>H-3</th>
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<tr>
<td>1a</td>
<td>5.20</td>
<td>4.10</td>
<td>5.25</td>
</tr>
<tr>
<td>1b</td>
<td>5.55</td>
<td>5.10</td>
<td>5.59</td>
</tr>
<tr>
<td>2a</td>
<td>5.19</td>
<td>4.12</td>
<td>5.24</td>
</tr>
<tr>
<td>3a</td>
<td>4.69</td>
<td>3.91</td>
<td>4.55</td>
</tr>
<tr>
<td>4a</td>
<td>4.78</td>
<td>4.04</td>
<td>4.63</td>
</tr>
<tr>
<td>5a</td>
<td>6.05</td>
<td>4.14</td>
<td>4.61</td>
</tr>
<tr>
<td>6a</td>
<td>5.01</td>
<td>5.48</td>
<td>4.80</td>
</tr>
<tr>
<td>7a</td>
<td>4.86</td>
<td>4.29</td>
<td>6.02</td>
</tr>
</tbody>
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*From reference 10.*
and H-5 on the 1H NMR spectra of the natural products 2a and 1a (Table I), associated with preceeding results, strongly suggest the same phenolic acid esterification pattern in both compounds. Compound 2a is consequently considered 1-trans-O-feruloyl quinic acid methyl ester, also showing the IR band at 1735 cm⁻¹.

Chlorogenic acid methyl ester was described once in Sambucus sieboldiana Blume. (Caprifoliaceae) [11]. On the other hand, the occurrence of 1-caffeoyl and 1-feruloyl quinic acid methyl ester, in the plant kingdom, is reported here for the first time.

**Experimental**

**Vegetal material**

Meum athamanticum Jacq. (Umbelliferae) was collected from Col du Lautaret, Hautes Alpes, France, at the beginning of its fruiting stage. The material was dried during a week at about 40 °C before use. A sample of the rhizome has been deposited at Laboratoire de Pharmacognosie, UER de Pharmacie de Grenoble, Domaine de La Merci, F-38700 La Tronche.

**Extraction and separation method**

The rhizome tissue (1180 g) was powdered and successively extracted with 12 l n-hexane, 13 l CHCl₃ and 12 l MeOH. The methanolic extract was allowed to stand for 15 days when 60 g sugar crystallized. After removal of the latter, the extract was evaporated under vacuum to residue (153 g) which was dissolved in 100 ml MeOH and precipitated by addition of an equal volume of benzene. The supernatant was dried by evaporation in vacuo, allowed to stand for 15 days when 60 g sugar deposited at Laboratoire de Pharmacognosie, UER de Pharmacie de Grenoble, Domaine de La Merci, F-38700 La Tronche.

**Analytical controls**

TLC controls of the natural products were performed on polyamide 6 F₂₅₄ Macherey Nagel with MeOH (system 1) or benzene-MEK-MeOH (75:10:15) (system 2). The Rₜ of 1a and 2a were 0.70 and 0.80 respectively in system 1 and 0.57 for 2a in system 2.

HPLC controls used a reversed phase column (μBondapack C₁₈ 30 cm × 3.9 mm I.D.) and H₂O-MeOH-AcOH (70:30:0.5) (flow rate 1 ml/min, UV detection at 320 nm). Retention times were observed 14.8 mn for 1a and 29.6 mn for 2a.

**Acetylated derivatives**

Acetylation was effected with acetic anhydrid and pyridine at room temperature. Purification of 1b was carried out on a silica column with an elution gradient from CHCl₃ up to CHCl₃-Et₂O (2:8). Isolation of 2b was achieved on silica gel F₂₅₄ TLC with benzene-Et₂O (7:3).

1-trans-O-caffeoyl quinic acid methyl ester (1a): MS (70 eV) m/z (%): 368 (M⁺; 8; 368.1108), C₁₇H₂₀O₄ = 368.1107), 336 (M-MeOH; 21), 180 (66), 163 (100), 162 (45), 135 (25), 134 (18), 134 (19), 129 (13), 110 (86), 94 (100), 89 (18), 83 (14), 81 (17), 77 (13). IR νₘₐₓ cm⁻¹: 3480, 2980, 2940, 1735, 1730, 1690, 1630, 1600, 1515, 1380, 1280, 1190, 1135, 1090, 1045, 980, 850, 810, 745, 690.

UV λₘₐₓ nm: 325, 297 sh, 243 sh, 232 sh, 220 sh; λₘₐₓ nm: 370, 302 sh, 260; λₘₐₓ nm: 355, 307 sh, 260, 255 sh; λₘₐₓ nm: 325, 297 sh, 243 sh, 232 sh, 215; λₘₐₓ nm: 385 sh, 336, 297 sh, 243; λₘₐₓ nm: 350, 297 sh, 253. ¹H NMR (CDCl₃: 250 MHz): δ 2.10 (4H, m, H-1', H-5'), 6.78, 7.02 (AB pattern, J = 16 Hz, H-7', H-8'). 6.78, 6.94 (AB pattern, J = 8 Hz, H-5', H-6'). 7.02 (1H, s, H-2').

Acetylated derivative (1b): MS (70 eV) m/z (%): 578 (M⁺; 4), 494 (100; 494.1409), C₂₃H₁₆O₁₂ = 494.1423), 452 (10; 452.1318), C₂₁H₂₅O₁₁ = 452.1318), 434 (20; 434.1222), C₂₁H₂₂O₁₀ = 434.1670), 392 (8), 315 (41; 315.1084), C₁₉H₁₆O₈ = 315.1079), 273 (6; 273.0977), C₁₇H₁₆O₇ = 273.0974), 255 (5), 247 (20), 213 (13; 213.0765), C₁₀H₁₇O₃ = 213.0762), 205 (19), 195 (5; 195.0659), C₁₀H₁₁O₃ = 195.0657), 180 (19; 180.0429), C₈H₆O₄ = 180.0422), 171 (6), 163 (47), 162 (90; 162.0322), C₉H₄O₃ = 162.0316)}.
153 (28; 153.0554; C₈H₆O₃ = 153.0651), 135 (6), 134 (20; 134.0367; C₈H₇O₂ = 134.0367), 111 (7; 111.0445; C₆H₁₂O₃ = 111.0446), 43 (67).

1IR νmax cm⁻¹: 3510, 3000, 2898, 1780, 1745, 1735, 1715, 1640, 1615, 1590, 1450, 1430, 1380, 1375, 1330, 1308, 1260, 1240, 1225, 1195, 1190, 1185, 1165, 1130, 1095, 1080, 1050, 1020, 970, 950, 925, 915, 885, 880, 845, 810, 780, 760, 640, 670, 650.

2UV λmax nm: 275, 215 sh. 1H NMR (CDCl₃; 250 MHz): δ 2.00 (3H, s, -CH₂OAc), 2.07 (3H, s, -CH₂OAc), 2.14 (3H, s, -CH₂OAc), 3.68 (3H, s, -COOCH₃), 4.12 (1H, m, H-4), ca. 5.19 (1H, m, H-3), 5.24 (1H, m, H-5), 6.32, 7.58 (AB pattern, J = 16 Hz, H-7', H-8'). 7.04 (1H, d, J = 8.5 and 1.5 Hz, H-5'), 7.18 (1H, d, J = 1.5 Hz, H-2').

Acetylated derivative (2b): MS (70 eV) m/z (%): 550 (M⁺; 5), 508 (100), 466 (5), 406 (2), 315 (6), 284 (7), 273 (3), 256 (13), 255 (4), 219 (12), 213 (5), 194 (35), 177 (57), 176 (62), 173 (40), 153 (29), 149 (76), 148 (12), 145 (10), 117 (7), 111 (29), 91 (14), 60 (60), 43 (100). UV λmax nm: 310 sh, 277, 235 sh.

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