PERGAMON

Phytochemistry 59 (2002) 191–195

PHYTOCHEMISTRY

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A macrocyclic ellagitannin trimer, oenotherin T_1, from *Oenothera* species

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Received 25 July 2001; received in revised form 12 September 2001

Abstract

Oenotherin T_1 was isolated from leaves of *Oenothera tetraptera* as a major ellagitannin. Its structure, that of a macrocyclic trimer with a new acyl group, an isodehydrovaloneoyl group, was established. This compound was also produced by callus tissues induced from *O. laciniata* leaves. © 2002 Published by Elsevier Science Ltd.

Keywords: *Oenothera tetraptera*; *Oenothera laciniata*; Onagraceae; Tannin; Ellagitannin trimer; Oenothein A; Oenotherin T_1; Isodehydrovaloneoyl group; Callus tissue culture

1. Introduction

Plants of the *Oenothera* species (Onagraceae) are indigenous to North and South America, and have been used for medicinal purposes (Hocking, 1997).

Two oligomeric ellagitannins with unique macrocyclic structures, oenotheins A (**1**) (Yoshida et al., 1991) and B (Hatano et al., 1990), were first isolated from *O. erythrosepala* and *O. biennis*, and later found in many species of the families Onagraceae, Lythraceae and Myrtaceae (Lee et al., 1997; Yoshida, et al., 1992b, 2000, Chen et al., 1999). Both of these tannins showed potent anti-tumor activity (Miyamoto et al., 1993a,b) and oenothein B also had an inhibitory effect on infection by the herpes simplex virus (Fukuchi et al., 1989).

Our investigation of the constituents of *Oenothera* species led to the isolation of a new trimeric tannin, named oenotherin T_1 (**2**), from the leaves of *O. tetraptera* as the main constituent. This tannin was also isolated from products of callus tissues of *O. laciniata* in the studies on tannin production in plant cell cultures. This paper describes the isolation and structure of this new tannin.

2. Results and discussion

2.1. Characterization of oenotherin T_1 (2)

Tannins, including a new tannin **2** in the leaves of *O. tetraptera*, were isolated from the highly polar fraction of an aqueous acetone homogenate of dried leaves by chromatography over Toyopearl HW-40 and the known tannins were identified as gemin D (Yoshida et al., 1985), oenothein B and oenothein A (**1**).

Oenotherin T_1 (**2**) was obtained as a pale yellow amorphous powder. The trimeric structure was suggested by its retention behavior in the normal-phase HPLC analysis (Okuda et al., 1989), which was longer than that for a dimer, oenothein B. ESI-MS showed an $[M+NH_4]^+$ ion peak at m/z 2386, corresponding to the molecular formula $C_{102}H_{72}O_{67}$. This molecular mass is 16 mass unit larger than that for a trimeric ellagitannin, oenothein A (**1**) ($C_{102}H_{72}O_{66}$).

The ^{1}H NMR spectrum of oenotherin T_1 (**2**) was complicated by the broadening and/or multiplication of signals. This spectral feature is characteristic of a macro-ring structure with poor flexibility, as observed for oenothein A (**1**) (Yoshida et al., 1991), and anomerization of the glucose cores.

Although the ^{13}C NMR spectrum of oenotherin T_1 (**2**) was also complicated, signals assignable to a conjugated carbonyl system [δ 194 (major), 195 (minor), 137

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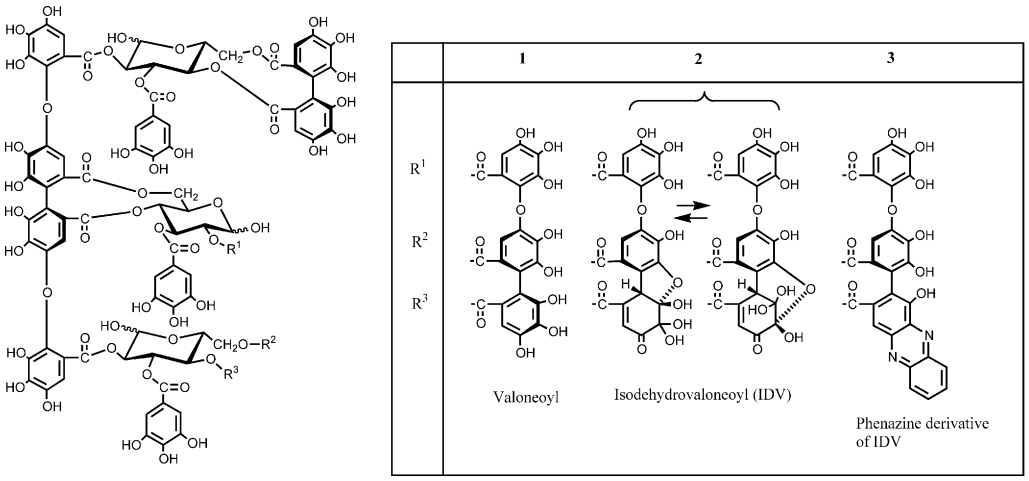
0031-9422/02/$ - see front matter © 2002 Published by Elsevier Science Ltd.
PII: S0031-9422(01)00435-6



(major), 136 (minor) and 152 (major)], a *gem*-diol (δ 94) and a hemiacetal carbon (δ 97) suggested the presence of an oxidized polyphenolic acyl group such as a dehydrohexahydroxydiphenoyl (DHHDP) group (Okuda et al., 1982). Since the DHHDP group is easily converted into an HHDP group on treatment with $Na_2S_2O_4$, as observed for the reduction of isoterchebin to tellimagrandin II (Okuda et al., 1982), oenotherin T_1 (**2**) was treated in an analogous way, to give oenothein A (**1**).

Oenotherin T_1 (**2**) was treated with *o*-phenylenediamine, to yield a phenazine derivative, $C_{108}H_{74}N_2O_{64}$ (**3**). Methylation of **3** with diazomethane and subsequent methanolysis for the quantitative analysis (Hatano et al., 1989) of the constituent phenolic acyl groups in **3** gave methyl tri-*O*-methylgallate (**4**), dimethyl hexamethoxydiphenate (**5**) (Okuda et al., 1983), and tetramethyl deca-*O*-methylwoodfordinate (**6**) (Yoshida et al., 1991) in a molar ratio of 3:1:1 along with products derived from an acyl group with the phenazine moiety, while the analogous treatment of oenothein A (**1**) yielded **4**, **5**, **6** and trimethyl octa-*O*-methylvaloneate (**7**) in a molar ratio of 3:1:1:1. Although **7** was absent among the products from **3**, the result of the reduction of oenotherin T_1 (**2**) which gave oenothein A (**1**) indicated that the acyl group attributed to the phenazine formation in oenotherin T_1 (**2**) is closely related to the valoneoyl group.

Further separation of the products other than **4**, **5** and **6** from **3** gave phenazine derivatives **8** and **9**. Although an oxidized valoneoyl group was found in eugeniflorin D_2 (Lee et al., 1997), **8** and **9** were not identical with the phenazine derivative (**10**) obtained from the eugeniflorin D_2.

The ESI–MS of **8** showed an $[M+H]^+$ ion peak at *m*/*z* 703 and the high-resolution ESI–MS indicated the molecular formula $C_{36}H_{35}N_2O_{13}$. Its ^1H NMR spectrum (acetone-d_6) showed four aromatic protons forming an ABXY system at δ 8.00, 8.04 (H-6, H-7), 8.28 and 8.30 (H-5, H-8), three aromatic singlets at δ 7.21 (H-3′), 7.37 (H-6″) and 8.52 (H-3), and nine 3H singlets arising from methoxyl groups at δ 3.37-4.19, suggesting the structure **8**. Rotating frame Overhauser enhancement correlation spectroscopy (ROESY) displayed only a cross peak due to ROE between an aromatic singlet (δ 7.37, H-6″) and a methoxyl signal (δ 3.93, OMe at C-5″), confirming the structure. The ^{13}C NMR spectrum of **8** showing 36 resonances due to 24 sp^2, three ester carbonyl and nine methoxyl carbons also satisfied the assigned structure.

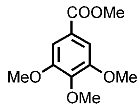
The phenazine derivative **9** was identified as (*S*)-methyl 4-methoxy-3-(4,5,6-trimethoxy-2-methoxycarbonyl phenyl)phenazine-2-carboxylate, based on a comparison of its spectral and physical data (see Experimental section) (Okuda et al., 1977, 1981). The production of **9** is attributed to the cleavage of the ether linkage in a parent polyphenolic acyl group which gave **8** (Yoshida et al., 1992a).

The structure **8** including the stereostructure was therefore assigned, and the structure of the new parent acid moiety named the isodehydrovaloneoyl (IDV) group, was consequently assigned as shown in the formula. Oenotherin T_1 was thus represented by formula **2**.

Although many *Oenothera* species produce mainly oenotheins B and A (Yoshida et al., 1995), the main constituent of *O. tetraptera* was oenotherin T_1 (**2**).

2.2. Production of oenotherin T_1 (2) by callus cultures of *O. laciniata*

Previously, we reported the production of the macrocyclic ellagitannin oligomers, oenotheins A (**1**) and B, along with monomeric tannins, tellimagrandin I and other galloylglucoses by *O. laciniata* callus culture (Taniguchi et al., 1998). Further investigation of the products of the callus culture revealed the presence of oenotherin T_1 (**2**) as a minor constituent. Oenotherin T_1 (**2**) is regarded as an oxidative metabolite of oenothein A (**1**).



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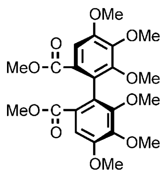

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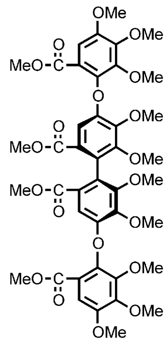

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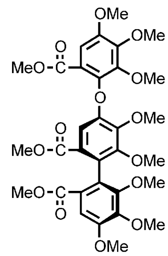

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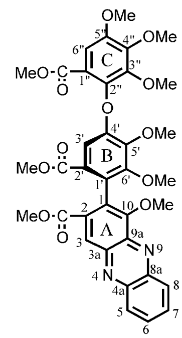

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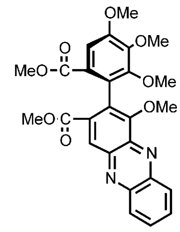

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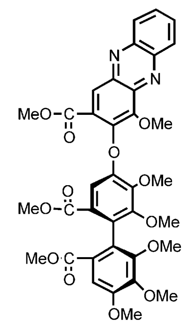

10

3. Experimental

3.1. General procedures

^{1}H and ^{13}C NMR spectra were measured in acetone-d_6 on a Varian VXR-500 instrument (500 MHz for ^{1}H NMR and 126 MHz for ^{13}C NMR). Chemical shifts are given in δ (ppm) values relative to that of the solvent signals of acetone-d_6 (δ_H 2.04; δ_C 29.8) on a tetramethylsilane scale. ESI–MS were recorded using a Micromass AutoSpec OA-Tof mass spectrometer with a solvent of 50% MeOH + 0.1% $AcONH_4$. The flow rate was set at 20 µl/min. Normal phase HPLC was conducted on a YMC-pack SIL-60 (250×4.6 mm i. d.) column with a solvent system (N1) which consists of *n*-hexane–MeOH–THF–HCO_2H (60:45:15:1) containing oxalic acid (500 mg/1.2 l), or a solvent system (N2) consisting of *n*-hexane–EtOAc (2:1), at a flow rate of 1.5 ml/min. Detection for HPLC analysis was at 280 nm.

3.2. Plant material

The plants of *O. tetraptera* were cultivated in the medicinal plant garden of the Faculty of Pharmaceutical Sciences, Okayama University.

3.3. Isolation of tannins from leaves of O. tetraptera

The dried aerial part (245 g) was homogenized in 70% acetone (3l×3). The concentrated filtrate (800 ml) from the homogenate was subjected to CC over Dia-ion HP-20 (Mitsubishi Chemical) (70×470 mm) eluted stepwise with H_2O→20% MeOH→40%→60%→100% MeOH (each 4 l). Part (1.8 g) of the 20% v/v MeOH eluate (6.5 g) was further applied to a Toyopearl HW-40 (Toso) (fine grade, 22×640 mm) column eluted with 70% EtOH→EtOH–H_2O–acetone (7:2:1) to yield gemin D (40.5 mg), oenothein B (36.7 mg) and **2** (171 mg) from the eluate with 70% EtOH, and **1** (93.9 mg) from the eluate with EtOH–H_2O–acetone (7:2:1).

3.4. Isolation of oenotherin T_1 from callus tissue of O. laciniata

A fraction of CC of the extract from callus tissues of *O. laciniata* (Taniguchi et al., 1998) on Toyopearl HW-40 was subjected to CC on MCI-gel CHP-20 (Mitsubishi Chemical) (11×170 mm) (H_2O→20% MeOH→30%→100% MeOH) to give **2** in a yield of 0.023%/(fr. wt).

3.5. Oenotherin T_1 (2)

A pale yellow powder. $[\alpha]_D$ +130° (MeOH; *c* 0.4). ESI–MS *m/z*: 2386 $[M+NH_4]^+$. (Found: C, 46.7; H, 4.1%. calc. for $C_{102}H_{72}O_{67}\cdot 14H_2O$ requires: C, 46.7; H, 3.8%). R_t of HPLC (N1): 13 min (oenothein B showed an R_t of 10 min under the same conditions). UVλ_{max}^{MeOH} nm (log ε): 218 (5.28), 267 (4.87). CD (MeOH): $[\theta]_{219}$ $+4.02\times10^5$, $[\theta]_{241}$ $+1.99\times10^5$, $[\theta]_{262}$ -1.66×10^4, $[\theta]_{283}$ $+1.19\times10^5$.

3.6. Reduction of oenotherin T_1 (2) to oenothein A (1)

To an aq. soln (2 ml) of **2** (20 mg) was added $Na_2S_2O_4$ (20 mg) and the reaction mixture was kept at 70°C for 20 min. The mixture was then acidified with 1% HCl and applied to a Sep-pak C-18 cartridge (Merk). After washing of the cartridge with water, adsorbed materials were eluted with H_2O→10% MeOH→20%→25% →30%→100% MeOH. The elutate obtained with 20 and 25% MeOH gave a product (11.6 mg), which was identified as **1** by HPLC, $[\alpha]_D$ (+112°, MeOH, lit. +113°) and ^{1}H NMR (500 MHz) (Yoshida et al., 1991).

3.7. Preparation of a phenazine derivative of oenotherin T_1 (2)

A mixture of **2** (20 mg) and *o*-phenylenediamine (5 mg) in 50% AcOH (1.2 ml)–MeOH (0.4 ml) was left standing overnight at room temp. The solvent was evaporated,

and the residue was purified by reprecipitation with MeOH–$CHCl_3$ to give a phenazine derivative (**3**) (23 mg) as a light brown powder, $[\alpha]_D$ +211° (MeOH; *c* 0.4), ESI–MS *m/z* : 2423 $[M+H]^+$.

3.8. Quantitative analysis of the constituent polyphenolic acids in the phenazine derivative (3) and oenothein A (1)

CH_2N_2–Et_2O (1 ml) was added to an EtOH soln (0.1 ml) of **3** (1 mg) and the mixture was left to stand for 2 h. After removal of the solvent under an N_2 stream, the residue was treated with 0.2% NaOMe in MeOH (1 ml) overnight at room temp. The reaction mixture was then acidified with 10% HCl and the solvent was removed by evaporation in vacuo. The residue was partitioned between EtOAc and H_2O, and HPLC analysis (N2) of the EtOAc soluble portion showed the presence of **4** (R_t 3.7 min), **5** (R_t 7.3 min), and **6** (R_t 29.1 min) in a molar ratio of 3:1:1. Oenothein A (**1**) was treated in an analogous way, and HPLC analysis of the methanolyzates showed the presence of **4**, **5**, **6** and **7** (R_t 14.1 min) in a molar ratio of 3:1:1:1.

3.9. Methylation of the phenazine derivative (3) followed by methanolysis

The phenazine derivative (**3**) (83 mg) in EtOH (20 ml) was treated (×3, for 2 h each) with CH_2N_2–Et_2O. After removal of the solvent, the residue was treated with 0.2% NaOMe in MeOH (0.5 ml) overnight at room temp. The reaction mixture was acidified with 10% HCl and the solvent was removed in vacuo. The residue was partitioned between EtOAc and H_2O, and the solvent of the EtOAc layer was also removed in vacuo. The residue was subjected to preparative TLC over Kieselgel PF_{254} (Merk) with *n*-hexane–$CHCl_3$–acetone (6:3: 1), to give **4** (14.4 mg), **5**{(4.5 mg), $[\alpha]_D$ −35.9° (MeOH; *c* 0.4)}, **6** {(5.6 mg), $[\alpha]_D$ +22.4° (MeOH; c 0.5)}, **8** (1.8 mg) and **9** (1.1 mg). The identification of compounds **5** and **6** was based on comparisons of their spectral data with those of authentic specimen (Okuda et al., 1983; Yoshida et al., 1991).

3.10. Phenazine derivative (8)

An orange powder. $[\alpha]_D$ −21.5° (MeOH; *c* 0.4). ESI–MS *m/z*: 703 $[M+H]^+$. HR–MS *m/z*: 703.2183 $[M+H]^+$ (Calc. for $C_{36}H_{35}N_2O_{13}$ 703.2139). UV λ_{max}^{MeOH} nm (log ϵ): 217 (4.78), 262 (4.68), 368 (3.97). CD (MeOH): $[\theta]_{200}$ -2.20×10^4, $[\theta]_{228}$ $+7.00\times10^4$, $[\theta]_{253}$ -5.84×10^4, $[\theta]_{309}$ $+8.67\times10^3$. ^{1}H NMR (acetone-d_6) δ: 3.37 (3H, *s*; COOMe at C-2′), 3.59 (6H, *s*) 3.64, 3.88, 4.04, 4.19 (3H each, *s*) [COOMe at C-1″ (δ 3.59), OMe at C-10, C-5′, C-6′, C-3″, C-4″)], 3.92 (3H, *s*; COOMe at C-2), 3.93 (3H, s; OMe at C-5″), 7.21 (1H, *s*; H-3′) 7.37 (1H, *s*; H-6″), 8.00, 8.04 (each 1H, *ddd*, *J* = 1.5, 6.5, 8.0 Hz; H-6, H- 7), 8.28, 8.30 (each 1H, *m*; H-5, H-8), 8.52 (1H, s; H-3). ^{13}C NMR (acetone-d_6) δ: 51.8 (COO<u>C</u>H_3 at C-2′), 51.9 (COO<u>C</u>H_3 at C-1″), 53.1 (COO<u>C</u>H_3 at C-2), 56.3 (OMe at C-5″), 60.7, 60.8, 60.9, 61.1, 62.8 (OMe at C-10, C-5′, C-6′, C-3″, C-4″), 109.8 (C-6″), 113.7 (C-3′), 128.6 (C-3), 129.2, 129.8, 130.4 (C-1, C-1′, C- 2′), 130.6, 130.7 (C-5, C-8), 131.5 (C-2), 132.2, 133.0 (C-6, C-7), 140.0, 144.3 (C-4a, C-8a), 141.4, 147.9 (C-3a, C-9a), 141.9, 145.3, 146.4, 146.6 (C-5′, C-2″, C-3″, C-4″), 152.1, 152.2, 152.7 (C-10, C-4′, C-6′), 153.3 (C-5″), 165.7 (<u>C</u>OOCH_3 at C-2), 166.7 (<u>C</u>OOCH_3 at C-2′), 167.2 (<u>C</u>OOCH_3 at C-1″).

3.11. (S)-Methyl 4-methoxy 3-(4,5,6-trimethoxy-2-methoxycarbonylphenyl)phenazine-2-carboxylate (9) (Okuda et al., 1977, 1981)

An orange powder. $[\alpha]_D$ −33.6° (MeOH; *c* 0.4). ESI–MS *m/z*: 493 $[M+H]^+$. UV λ_{max}^{MeOH} nm (log ϵ): 208 sh (4.66), 266 (4.74), 371 (3.93). CD (MeOH): $[\theta]_{200}$ $+6.54\times10^3$, $[\theta]_{208}$ -1.39×10^4, $[\theta]_{240}$ -3.91×10^4, $[\theta]_{265}$ $+6.55\times10^4$, $[\theta]_{299}$ -1.92×10^4. ^{1}H NMR (acetone-d_6) δ: 3.50 (3H, s; COOMe at C-2′), 3.60, 3.99, 4.04 (3H each, *s*; OMe at C-10, C-4′, C-6′), 3.73 (3H, *s*; COOMe at C-2), 3.92 (3H, *s*; OMe at C-5′), 7.48 (1H, *s*; H-3′), 7.98, 8.00 (each 1H, *m*; H-6, H-7), 8.26, 8.28 (each 1H, m; H-5, H-8), 8.58 (1H, *s*; H-3). ^{13}C NMR (acetone-d_6) δ: 51.9 (COO<u>C</u>H_3 at C-2′), 52.5 (COO<u>C</u>H_3 at C-2), 56.4, 60.9, 62.5 (OMe at C-10, 4′, 6′), 60.9 (C-12), 61.0 (C-9′), 110.0 (C-3′), 125.7 (C-2′), 126.9 (C-1′), 127.6 (C-3), 130.3 (C-1), 130.5, 130.8 (C-5, C-8), 132.0, 132.4 (C-6, C-7), 135.5 (C-2), 140.4 (C-9a), 143.8, 143.9 (C-4a, C-8a), 144.5 (C-3a), 146.6 (C-5′), 152.2, 153.7 (C-6′, C-10), 153.7 (C-4′), 166.9 (<u>C</u>OOCH_3 at C-2), 167.1 (<u>C</u>OOCH_3 at C-2′).

Acknowledgements

This study was supported in part by a Grant-in-Aid (No. 13771333) for Scientific Research from the Japan Society for the Promotion of Science. The NMR instrument used in this study is in the SC-NMR Laboratory of Okayama University.

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