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A NEW BUTANOLIDE FROM THE LEAVES OF *Cinnamomum reticulatum*

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*A new butanolide, isoreticulide ((4*R*,3*E*)-4-hydroxy-5-methylene-3-octadecylidenedihydrofuran-2-one) (**1**), along with nine compounds including one sesquiterpenoid, (3-methoxy-5*H*-9,11-dioxabenzo[3,4]cyclohepta[1,2-*f*])inden-7-yl)-methanol (**2**); six benzenoids,* p-*hydroxybenzoic acid (**3**),* p-*hydroxybenzaldehyde (**4**), protocatechuic acid (**5**), ferulic acid (**6**),* trans-*methyl* p-*coumarate (**7**), and* p-*dihydrocoumaric acid (**8**), and two amides,* N-trans-*feruloyltyramine (**9**) and dihydroferuloyltyramine (**10**), were isolated from the leaves of* Cinnamomum reticulatum *Hayata (Lauraceae). These compounds were characterized and identified by physical and spectral evidence.*

Keywords: *Cinnamomum reticulatum* Hayata, Lauraceae, butanolide, isoreticulide, sesquiterpenoid.

The *Cinnamomum* species (Lauraceae) have been used in folk medicine for its sweating, antipyretic, and analgesic effects [1]. There are only two papers describing the constituents of leaves of *Cinnamomum reticulatum* Hayata [1, 2]. In the course of screening for biologically and chemically novel agents from Formosan Lauraceous plants [2–17], *C. reticulatum* was chosen for further phytochemical investigation. The H_2O extract of its leaves was subjected to solvent partitioning and chromatographic separation to afford seven pure substances. The chemical constituents in the leaves of *C. reticulatum* were separated with column chromatography.

Investigation of the MeOH extract of the leaves has led to the isolation of ten compounds, one new butanolide: isoreticulide ((4*R*,3*E*)-4-hydroxy-5-methylene-3-octadecylidenedihydrofuran-2-one) (**1**); one sesquiterpenoid: (3-methoxy-5*H*-9,11-dioxabenzo[3,4]cyclohepta[1,2-*f*])inden-7-yl)-methanol (**2**); six benzenoids: *p*-hydroxybenzoic acid (**3**) [18], *p*-hydroxybenzaldehyde (**4**) [18], protocatechuic acid (**5**) [19], ferulic acid (**6**) [18], *trans*-methyl *p*-coumarate (**7**) [18], and *p*-dihydrocoumaric acid (**8**) [18]; and two amides: *N-trans*-feruloyltyramine (**9**) [20] and dihydroferuloyltyramine (**10**) [21]. These compounds were obtained and characterized by comparison of their physical and spectral data (UV, IR, NMR, and MS) with values obtained in the literature. In addition to **3** and **4**, all of these compounds were found for the first time from this plant. In this paper, we report the isolation and structural elucidation of butanolide **1** and sesquiterpenoid **2**.

Isoreticulide (**1**) was isolated as a pale yellowish liquid. Its molecular formula, $C_{23}H_{40}O_3$, was established by HR-ESI-MS. The UV absorption at 225 nm was similar to that of isoobtusilactone A [22], suggesting the presence of a β-hydroxy-γ-methylene-α,β-unsaturated-γ-lactone unit [23]. The IR spectrum showed absorption bands of a hydroxyl group at 3440 cm^{-1}, and an α,β-unsaturated γ-lactone moiety at 1770 and 1670 cm^{-1}. The ^1H NMR spectrum of **1** was similar to that of isoobtusilactone A [22], indicating that **1** has the same β-hydroxy-γ-methylene-α,β-unsaturated-γ-lactone skeleton and the same *E* geometry of the trisubstituted double bond. The presence of a broad singlet at δ 1.26 was attributed to protons in an aliphatic chain in **1**. The exocyclic olefinic protons appeared at δ 4.73, 4.96 and one hydroxymethine proton was located at δ 5.27. Compound **1** is dextrorotatory, that indicates an *R* configuration at C-4 [24]. Thus, the structure of isoreticulide is (4*R*,3*E*)-4-hydroxy-5-methylene-3-octadecylidenedihydrofuran-2-one, as represented in **1**.

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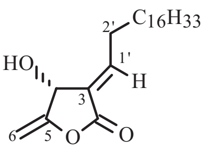
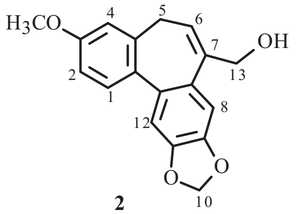


1



2

Compound **2** was isolated as a white, amorphous powder with the molecular formula $C_{18}H_{16}O_4$, as determined by HR-EI-MS (obsd. $[M]^+$ at *m/z* 296.1048; calcd $[M]^+$ 296.1049). This formula agrees with deductions from the ^{1}H and ^{13}C NMR data and corresponds to 11 degrees of unsaturation. The UV spectrum contained absorption bands typical of 5*H*-dibenzo[*a,c*]cycloheptene derivatives [3]. IR absorption peaks at 920, 1070, and 3300 cm^{-1} indicated the presence of methylenedioxy and hydroxy functionalities, respectively. The ^{1}H NMR resonances of **2** were well dispersed in $CDCl_3$ and displayed an ABX pattern (H-4 at δ 6.69, H-2 at 6.75, and H-1 at 7.32) and singlets at δ 7.06, 7.12 for H-12 and H-8, respectively, in addition to the methylenedioxy protons at δ 6.02, accounting for seven protons. A three-proton singlet at δ 3.88 indicated the presence of the methoxy group. The C-6 olefinic proton (δ 6.15, t, J = 7.5 Hz) was coupled to the C-5 and C-13 methylene protons, the latter four hydrogens resonating at δ 2.74 (dd, J = 13.0, 6.5 Hz, H-5a), 3.04 (dd, J = 13.0, 8.5 Hz, H-5b), 4.33 (d, J = 13.0 Hz, H-13a), and 4.49 (d, J = 13.0 Hz, H-13b), respectively. The ^{13}C NMR and DEPT spectra of **2** showed 18 resonances comprising one methyl, three methylene, six methine, and eight quaternary carbons. Structure **2** was also confirmed by 2D NMR experiments. A COSY correlation was observed between H-1 and H-2, and between H-5 and H-6. A triplet of quartets at δ 6.15 was assigned to H-6 and showed coupling to the nearby C-5 and C-13 methylene protons, which appeared at δ 2.74 and 3.04, and at δ 4.49, respectively. Thus, the structure of **2** was elucidated as (3-methoxy-5*H*-9,11-dioxabenzo[3,4] cyclohepta[1,2-*f*])inden-7-yl)-methanol.

EXPERIMENTAL

The leaves of *C. reticulatum* were collected from Pingtung County, Taiwan, May 2005. Plant material was identified by Professor Fu-Yuan Lu (Department of Forestry and Natural Resources College of Agriculture, National Chiayi University). A voucher specimen (Cinnamo. 6) was deposited in the School of Medical and Health Sciences, Fooyin University, Kaohsiung County, Taiwan. The air-dried leaves of *C. reticulatum* (3.4 kg) were extracted with *n*-hexane (30 L × 5), $CHCl_3$ (30 L × 5), and H_2O (30 L × 5) at room temperature, and an *n*-hexane extract (43.5 g), $CHCl_3$ extract (151.5 g), and H_2O extract (105.2 g) were obtained upon concentration under reduced pressure. The *n*-hexane extract (43.5 g) was chromatographed over silica gel (980 g, 70–230 mesh) using *n*-hexane–EtOAc–acetone mixtures as eluents to produce five fractions. A part of fraction 1 (5.42 g) was subjected to silica gel chromatography by eluting with *n*-hexane–EtOAc (75:1) and enriched gradually with EtOAc to furnish four fractions (1-1 – 1-4). Fraction 1-2 (2.23 g) was further purified on a silica gel column using *n*-hexane–EtOAc mixtures to obtain isoreticulide (**1**) (24 mg). The H_2O extract was chromatographed over silica gel (3500 g, 70–230 mesh) using $CHCl_3$–MeOH as eluent to produce six fractions. Fraction 1 (3.12 g) was subjected to Si gel chromatography by eluting with *n*-hexane–EtOAc (20:1) to obtain (3-methoxy-5*H*-9,11-dioxabenzo[3,4]cyclohepta[1,2-*f*])inden-7-yl)-methanol (**2**) (6 mg). Part of fraction 2 (8.71 g) was subjected to Si gel chromatography by eluting with *n*-hexane–EtOAc (10:1), then enriched with EtOAc to furnish nine fractions (2-1 – 2-3). Fraction 2-1 (1.54 g) was resubjected to Si gel chromatography, eluting with *n*-hexane–acetone (50:1) and enriched gradually with acetone to obtain *N*-*trans*-feruloyltyramine (**9**) (20 mg) and dihydroferuloyltyramine (**10**) (16 mg). Fraction 2-2 (2.13 g) was resubjected to Si gel chromatography, eluting with *n*-hexane – acetone (50:1) and enriched gradually with acetone to obtain ferulic acid (**6**) (14 mg), *trans*-methyl *p*-coumarate (**7**) (7 mg), and *p*-dihydrocoumaric acid (**8**) (16 mg). Fraction 2-3 (2.87 g) was resubjected to Si gel chromatography, eluting with *n*-hexane–acetone (40:1) and enriched gradually with acetone to obtain *p*-hydroxybenzoic acid (**3**) (4 mg), *p*-hydroxybenzaldehyde (**4**) (5 mg), and protocatechuic acid (**5**) (12 mg).

Isoreticulide [(4*R*,3*E*)-4-hydroxy-5-methylene-3-octadecylidenedihydrofuran-2-one] (1): pale yellowish liquid; $[\alpha]_D^{25}$ +17.2° (*c* 0.05, $CHCl_3$). UV (MeCN, λ_{max}, nm, log ε): 225 (4.13). IR (neat, ν_{max}, cm^{-1}): 3440 (br, OH), 1770, 1670 (*α,β*-unsaturated *γ*-lactone), 1465, 1270, 1025. ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.88 (3H, t, J = 6.5, CH_3-18′), 1.26 (28H, br.s, H-4′ – H-17′), 1.53 (2H, m, H-3′), 2.45 (2H, m, H-2), 4.73 (1H, dd, J = 3.0, 1.5, H-6a), 4.96 (1H, dd, J = 3.0, 1.5, H-6b), 5.27 (1H, br.s, H-4), 7.10 (1H, td, J = 8.0, 2.0, H-1′). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 14.1 (C-18′), 22.7 (C-17′), 31.9 (C-16′), 28.3–29.7 (C-2′–C-15′), 66.5 (C-4), 91.4 (C-6), 127.3 (C-3), 150.2 (C-1′), 157.6 (C-5), 166.6 (C-2). HR-ESI-MS *m/z* 387.2872 $[M + Na]^+$ (calcd for $C_{23}H_{40}O_3Na$, 387.2875).

(3-Methoxy-5*H*-9,11-dioxabenzo[3,4]cyclohepta[1,2-*f*])inden-7-yl)-methanol (2): white amorphous powder. UV (MeCN, λ_{max}, nm, log ε): 235 (3.23), 255 (2.65), 290 (2.11). IR (neat, ν_{max}, cm^{-1}): 3300 (br, OH), 3000, 1700, 1250, 1070, 920 (methylenedioxy). ^{1}H NMR (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.74 (1H, dd, J = 13.0, 6.5, H-5a), 3.04 (1H, dd, J = 13.0, 8.5, H-5b), 3.88 (3H, s, 3-OMe), 4.33 (1H, d, J = 13.0, H-13a), 4.49 (1H, d, J = 13.0, H-13b), 6.02 (each 1H, d, J = 1.0, H-10), 6.15 (1H, t, J = 7.5, H-6), 6.69 (1H, d, J = 2.5, H-4), 6.75 (1H, dd, J = 8.5, 2.5, H-2), 7.06 (1H, s, H-12), 7.12 (1H, s, H-8), 7.32 (1H, d, J = 8.5, H-1). ^{13}C NMR (125 MHz, $CDCl_3$, δ, ppm): 33.1 (C-5), 55.3 (3-OMe), 66.2 (C-13), 101.2 (C-10), 106.0 (C-8), 109.6 (C-12), 111.5 (C-4), 111.8 (C-2), 127.7 (C-6), 129.7 (C-7a), 130.6 (C-1), 131.0 (C-12b), 134.7 (C-12a), 137.4 (C-7), 143.6 (C-4a), 146.5 (C-8a), 146.5 (C-11a), 159.2 (C-3). EI-MS *m/z* 296 $[M]^+$ (15), 285 (5), 279 (8), 265 (24), 255 (4), 239 (20), 236 (6), 222 (3), 192 (5), 185 (8), 167 (8), 154 (10), 149 (14), 137 (10), 134 (37), 129 (25), 116 (18), 111 (52), 109 (41), 97 (100), 83 (86), 69 (90). HR-EI-MS *m/z* 296.1048 $[M]^+$ (calcd for $C_{18}H_{16}O_4$, 296.1049).

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