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A NOVEL BIPHENYL DERIVATIVE FROM *Cinnamomum insulari-montanum*

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*A novel biphenyl derivative, insularione (3,3′,4,4′,6-pentahydroxy-3,4-dihydro-[1,1′-biphenyl]-2,5-dione) (**1**), was isolated from the stems of* Cinnamomum insulari-montanum *Hayata (Lauraceae) along with six known compounds. The structure of the novel biphenyl derivative was characterized on the basis of spectral analysis.*

Keywords: *Cinnamomum insulari-montanum*, Lauraceae, biphenyl.

Cinnamomum insulari-montanum Hayata (Lauraceae) is an endemic tree that grows in Taiwan′s natural hardwood forest at elevations between 400 and 1500 m [1]. Previously, we isolated 16 compounds, including two butanolides, three lignans, two flavonoids, one coumarin, four steroids, and four benzenoids from this plant [2, 3]. In the course of screening for bioactive components from Formosan plants in the family Lauraceae [3–26], *C. insulari-montanum* was chosen for further phytochemical investigation. The chemical constituents in the stems of *C. insulari-montanum* Hayata were separated with column chromatography. A novel biphenyl derivative, insularione (3,3′,4,4′,6-pentahydroxy-3,4-dihydro-[1,1′-biphenyl]-2,5-dione) (**1**), along with eight known compounds, including a mixture of *β*-sitosterol (**2**) and stigmasterol (**3**) [27], coumarin (**4**) [28], cinnamyl alcohol (**5**) [28], cinnamic acid (**6**) [28], *p*-hydroxybenzoic acid (**7**) [28], kaempferol (**8**) [29], and kaempferitrin (**9**) [29], were isolated from *C. insulari-montanum* Hayata. In this paper, we report the isolation and structural elucidation of the novel compound.

Insularione (3,3′,4,4′,6-pentahydroxy-3,4-dihydro-[1,1′-biphenyl]-2,5-dione) (**1**) was obtained as a white amorphous powder from MeOH. Its molecular formula was deduced as $C_{12}H_{10}O_7$ by HR-ESI-MS *m/z* 289.0322 $[M + Na]^+$ (calcd 289.0324). The IR spectrum of **1** showed characteristic absorption bands due to the presence of the hydroxyl (3300 cm^{-1}) and carbonyl (1680 cm^{-1}) moieties. The ^1H NMR spectrum of **1** displayed the typical pattern of an ABX type at δ 7.41 (1H, d, J = 8.4 Hz, H-5′), 8.10 (1H, dd, J = 8.4, 2.0 Hz, H-6′), and 8.62 (1H, d, J = 2.0 Hz, H-2′) and two methines deshielded by two conjugated carbonyls appearing at δ 6.74/6.78 (each 1H, d, J = 2.0 Hz, H-4/3), indicating that **1** was probably a trisubstituted benzene. The ^{13}C NMR and DEPT experiments of **1** showed 12 resonance signals consisting of five methines and seven quaternary carbons. The structure **1** was also confirmed by 2D NMR experiments (Fig. 1). A COSY correlation was observed between the H-3 and H-4 and between the H-5′ and H-6′ (Fig. 1). The HETCOR experiment showed that the carbon signals at δ 94.2 for C-4, 99.2 for C-3, 116.6 for C-2′, 116.6 for C-5′, and 121.0 for C-6′ were correlated to the proton signals at δ 6.74 for H-4, δ 6.78 for H-3, δ 8.62 for H-2′, δ 7.41 for H-5′, and δ 8.10 for H-6′, respectively.

The relative configuration of **1** was assigned by analysis of the ^1H NMR coupling constants and NOESY experiment. The mutual gauche junction was deduced from the observation of the *quasi*-1,2-diequatorial interactions of H-3 and H-4, and the coupling constants were 2.0 Hz. Due to the small quantity of isolated material and instability of compound **1**, the absolute configuration of C-3 & 4 remains to be determined. Thus, **1** is a novel biphenyl derivative, which was further confirmed by COSY, HMBC, and NOESY experiments.

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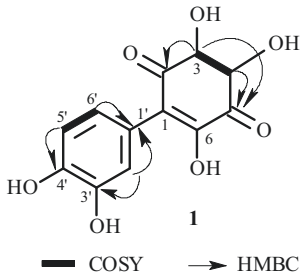

Fig. 1. Key COSY and HMBC correlations for **1**.

EXPERIMENTAL

General. UV spectra were obtained in MeCN, and IR spectra were measured on a Hitachi 260-30 spectrophotometer. ^{1}H NMR (400 MHz, CD_3OD) and NOESY spectra were obtained on a Varian (Unity Plus) NMR spectrometer. Low-resolution ESI-MS spectra were obtained on an API 3000 (Applied Biosystems), and high-resolution ESI-MS spectra were recorded on a Bruker Daltonics APEX II 30e spectrometer. Silica gel 60 (Merck, 70–230 mesh, 230–400 mesh) was used for column chromatography. Precoated silica gel plates (Merck, Kieselgel 60 F-254), 0.20 and 0.50 mm, were used for analytical TLC and preparative TLC, respectively, visualized with 50% H_2SO_4.

Plant Material. The specimen of *C. insulari-montanum* Hayata was collected from Pingtung County, Taiwan, March 2003. A voucher specimen (Cinnamo. 3) was identified by Dr. Fu-Yuan Lu (Department of Forestry and Natural Resources College of Agriculture, National Chiayi University) and was deposited in the School of Medical and Health Science, the Fooyin University, Kaohsiung, Taiwan.

Extraction and Isolation. The stems (7.0 kg) of *C. insulari-montanum* Hayata were extracted repeatedly with MeOH at room temperature for 24–48 h. The MeOH extract was dried and evaporated to leave a viscous residue (82.4 g). The residue was placed on a silica gel column and eluted with $CHCl_3$ gradually enriched with MeOH to afford 17 fractions (Frs. 1–17). Part of Fr. 3 (12.5 g) was rechromatographed on silica gel (*n*-hexane–EtOAc, 18:1) and recrystallized from EtOAc to give coumarin (**4**) and a mixture of *β*-sitosterol (**2**) and stigmasterol (**3**) (201 mg). Part of Fr. 6 (26.3 g), eluted from *n*-hexane–EtOAc (1:2), was further chromatographed on silica gel elution with EtOAc–MeOH (15:1) and recrystallized from acetone to give cinnamic acid (**6**) (49 mg) and cinnamyl alcohol (**5**) (51 mg), respectively. Part of Fr. 11 (7.6 g) was purified by silica gel chromatography (EtOAc–MeOH, 10:1) to give colorless needles of kaempferol (**8**) (25 mg). Part of Fr. 14 (5.2 g) was purified by silica gel chromatography (EtOAc–MeOH, 8:1) to give colorless needles of *p*-hydroxybenzoic acid (**7**) (52 mg). Part of Fr. 16 (4.2 g) was subjected to silica gel chromatography by eluting with EtOAc–MeOH (4:1) and enriched with MeOH to furnish four further fractions (16-1–16-4). Fractions 16-3 (1.2 g) eluted with EtOAc–MeOH (4:1) was further purified using silica gel column chromatography and the same solvent system to give insularione (3,3′,4,4′,6-pentahydroxy-3,4-dihydro-[1,1′-biphenyl]-2,5-dione) (**1**) (9 mg). Part of Fr. 17 (13.6 g) was rechromatographed on silica gel (EtOAc–MeOH, 5:1) and recrystallized from MeOH to give kaempferitrin (**9**) (781 mg).

Insularione (1), white amorphous powder. UV (MeCN, λ_{max}, nm) (log ε): 397 (3.11). IR (ν_{max}, cm^{-1}): 3300 (br, OH), 1680 (C=O). ESI-MS *m/z* 289 $[M + Na]^+$; HR-ESI-MS *m/z* 289.0322 $[M + Na]^+$ (calcd for $C_{12}H_{10}O_7Na$, 289.0324). ^{1}H NMR (400 MHz, C_5D_5N, δ, ppm, J/Hz): 6.74 (1H, d, J = 2.0, H-4), 6.78 (1H, d, J = 2.0, H-3), 7.41 (1H, d, J = 8.4, H-5′), 8.10 (1H, dd, J = 8.4, 2.0, H-6′), 8.62 (1H, d, J = 2.0, H-2′). ^{13}C NMR (100 MHz, C_5D_5N, δ, ppm): 94.2 (C-4, CH), 99.2 (C-3, CH), 116.6 (C-2′, CH), 116.6 (C-5′, CH), 121.0 (C-6′, CH), 137.9 (C-1′, C), 147.1 (C-3′, C), 147.7 (C-4′, C), 157.4 (C-1, C), 162.4 (C-6, C), 165.5 (C-5, C=O), 177.2 (C-2, C=O).

***β*-Sitosterol (2)** and **stigmasterol (3)** as in [27], white needles (CH_2Cl_2), mp 138–140°C. IR (ν_{max}, cm^{-1}): 3400, 2910, 1620, 1450.

Coumarin (4) as in [28], colorless oil. UV (MeCN, λ_{max}, nm): 260, 330. IR (ν_{max}, cm^{-1}): 1730, 1630. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 6.43 (1H, d, J = 9.5, H-3), 7.29 (1H, td, J = 8.0, 1.2, H-6), 7.34 (1H, dd, J = 8.0, 1.2, H-5), 7.50 (1H, dd, J = 8.0, 1.2, H-8), 7.54 (1H, td, J = 8.0, 1.2, H-7), 7.72 (1H, d, J = 9.5, H-4).

Cinnamyl alcohol (5) as in [28], yellowish needles (CH_2Cl_2), mp 208–210°C. UV (MeCN, λ_{max}, nm): 260, 315. IR (ν_{max}, cm^{-1}): 1700, 1680, 1650, 980, 770. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 4.28 (2H, d, J = 5.6, H-1), 6.15 (1H, dt, J = 16.0, 5.6, H-2), 6.47 (1H, d, J = 16.0, H-3), 7.38 (3H, m, H-6, 7, 8), 7.58 (2H, m, H-5, 9).

Cinnamic acid (6) as in [28], yellowish needles (CH_2Cl_2), mp 208–210°C. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 6.63 (1H, d, J = 16.0, H-2), 7.38 (3H, m, H-6, 7, 8), 7.56 (1H, d, J = 16.0, H-3), 7.58 (2H, m, H-5, 9).

***p*-Hydroxybenzoic acid (7)** as in [28], brown powder (CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 6.85 (2H, d, J = 8.6, H-3, 5), 7.97 (2H, d, J = 8.6, H-2, 6).

Kaempferol (8) as in [29], yellow needles (MeOH), mp 275–277°C. ^{1}H NMR (400 MHz, CD_3OD, δ, ppm, J/Hz): 6.25 (1H, d, J = 2.0, H-6), 6.57 (1H, d, J = 2.0, H-8), 6.74 (2H, d, J = 8.8, H-3′, 5′), 7.38 (2H, d, J = 8.8, H-2′, 6′).

Kaempferitrin (9) as in [29], yellow amorphous powder. UV (MeCN, λ_{max}, nm): 220, 265, 360. IR (ν_{max}, cm^{-1}): 3400, 1680, 1620, 1560. ^{1}H NMR (400 MHz, CD_3OD, δ, ppm, J/Hz): 0.81 (3H, d, J = 5.6, 3-*O*-Rha-CH_3), 1.11 (3H, d, J = 6.4, 7-*O*-Rha-CH_3), 5.30 (1H, d, J = 1.6, 3-*O*-Rha-1″), 5.56 (1H, d, J = 1.6, 7-*O*-Rha-1″), 6.42 (1H, d, J = 2.4, H-6), 6.75 (1H, d, J = 2.4, H-8), 6.90 (2H, d, J = 8.8, H-3′, 5′), 7.75 (2H, d, J = 8.8, H-2′, 6′).

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REFERENCES

1. T. W. Hu, Y. T. Lin, and C. K. Ho, *Bull. Taiwan For. Res. Inst. Eng*., **78**, 18 (1985).
2. T. J. Hsieh, S. F. Hsieh, and C. Y. Chen, *Chem. Nat. Compd*., **46**, 99 (2010).
3. C. Y. Chen, C. L. Lin, C. L. Kao, C. T. Chen, and H. T. Li, *Chem. Nat. Compd*., **55**, 922 (2019).
4. J. Li, C. Y. Chen, J. Y. Huang, L. Wang, Z. Xu, W. Kang, M. H. Lin, and H. M. Wang, *Oxid. Med. Cell. Longev.*, **2020**, 1 (2020).
5. R. J. Lin, C. L. Kao, S. L. Liu, H. C. Yeh, P. L. Song, H. T. Li, H. M. Wang, and H. W. Chang, *Chem. Nat. Compd*., **56**, 604 (2020).
6. C. Y. Chen, C. M. Liu, H. M. Wu, H. C. Yeh, W. J. Li, H. T. Li, and H. W. Chang, *Chem. Nat. Compd*., **56**, 621 (2020).
7. C. T. Chen, C. L. Kao, W. J. Li, H. C. Yeh, H. T. Li, and C. Y. Chen, *Chem. Nat. Compd*., **55**, 1185 (2019).
8. C. Y. Chen, C. L. Kao, W. J. Li, H. C. Yeh, S. C. Huang, and H. T. Li, *Chem. Nat. Compd*., **54**, 562 (2018).
9. C. L. Lin, M. H. Perng, W. J. Li, H. T. Li, and C. Y. Chen, *Chem. Nat. Compd*., **54**, 628 (2018).
10. Z. L. Hong, J. C. Huang, S. Y. Kuo, and C. Y. Chen, *Nat. Prod. Commun.*, **6**, 1297 (2011).
11. C. Y. Chen, Z. L. Hong, W. L. Yang, M. H. Wu, and J. C. Huang, *Nat. Prod. Res*., **26**, 1218 (2012).
12. C. Y. Chen and Y. D. Wang, *Chem. Nat. Compd*., **47**, 215 (2011).
13. C. Y. Chen, *Chem. Nat. Compd*., **47**, 306 (2011).
14. Y. C. Chia, H. C. Yeh, Y. T. Yeh, and C. Y. Chen, *Chem. Nat. Compd*., **47**, 220 (2011).
15. I. J. Lin, H. C. Yeh, T. M. Cham, and C. Y. Chen, *Chem. Nat. Compd*., **47**, 43 (2011).
16. T. J. Hsieh, S. F. Hsieh, and C. Y. Chen, *Chem. Nat. Compd*., **46**, 99 (2010).
17. C. Y. Chen, H. M. Wang, S. H. Chung, W. L. Lo, W. L. Yang, and S. C. Yang, *Chem. Nat. Compd*., **46**, 474 (2010).
18. C. Y. Chen, W. L. Yang, and Y. R. Hsui, *Nat. Prod. Res*., **24**, 423 (2010).
19. M. J. Cheng, W. L. Lo, W. S. Tseng, H. C. Yeh, and C. Y. Chen, *Nat. Prod. Res*., **24**, 732 (2010).
20. I. J. Lin, W. L. Lo, Y. C. Chia, L. Y. Huang, T. M. Cham, W. S. Tseng, Y. T. Yeh, H. C. Yeh, Y. D. Wang, and C. Y. Chen, *Nat. Prod. Res*., **24**, 775 (2010).
21. R. J. Lin, M. J. Cheng, J. C. Huang, W. L. Lo, Y. T. Yeh, C. M. Teh, C. M. Lu, and C. Y. Chen, *J. Nat. Prod.*, **72**, 1816 (2009).
22. C. Y. Chen, C. H. Chen, Y. C. Lo, B. N. Wu, H. M. Wang, W. L. Lo, C. M. Yen, and R. J. Lin, *J. Nat. Prod.*, **71**, 933 (2008).
23. S. Y. Kuo, T. J. Hsieh, Y. D. Wang, W. L. Lo, Y. R. Hsui, and C. Y. Chen, *Chem. Pharm. Bull*., **56**, 97 (2008).
24. C. Y. Chen, C. H. Chen, C. H. Wong, Y. W. Liu, Y. S. Lin, Y. D. Wang, and Y. R. Hsui, *J. Nat. Prod.*, **70**, 103 (2007).
25. C. H. Chen, W. L. Lo, Y. C. Liu, and C. Y. Chen, *J. Nat. Prod.*, **69**, 927 (2006).
26. T. J. Hsieh, C. H. Chen, W. L. Lo, and C. Y. Chen, *Nat. Prod. Commun*., **1**, 21 (2006).
27. T. J. Hsieh, Y. C. Wu, S. C. Chen, C. S. Huang, and C. Y. Chen, *J. Chin. Chem. Soc.*, **51**, 869 (2004).
28. T. J. Hsieh, C. C. Su, C. Y. Chen, C. H. Liou, and L. H. Lu, *J. Mol. Struct.*, **741**, 193 (2005).
29. C. Y. Chen, S. L. Hsieh, M. M. Hsieh, S. F. Hsieh, and T. J. Hsieh, *Chin. Pharm. J*., **56**, 141 (2004).