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A New Benzylisoquinoline of Annona Cherimola

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ABSTRACT

(-)-Zishenine (1), a new benzylisoquinoline, has been isolated from the roots of Annona cherimola Mill. (Annonanceae). The structure was characterized and identified by spectral analysis.

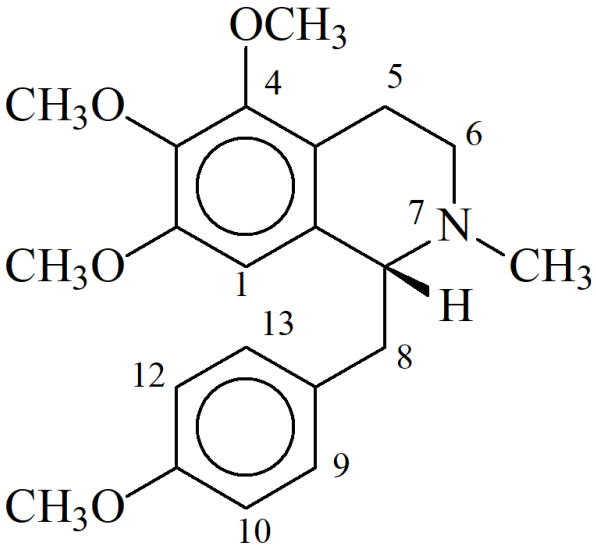
Keywords
Annona cherimola, Annonanceae, (-)-zishenine, Benzylisoquinoline.

Introduction

Annona cherimola Mill. (Annonanceae) is a subtropic fruit tree cultivated in the southern part of Taiwan. It grows indigenously in Ecuador and Peru and has been used for the treatment of skin disease, especially for boil in folk medicine [1]. Although Annonaceous acetogenins constitute the majority of natural products from Annonaceae of Taiwan, a large but significant number of alkaloids have been described [2]. These include oxoaporphines, aporphines, benzylisoquinolines, proaporphines, isoquinolones, and some amides. As part of our continuing investigation on the alkaloids of Formosan Annonaceous plants, we have isolated several alkaloids from the methanol stem extract of A. purpurea [3]. The chemical and the biological activity of the roots of A. cherimola have not yet been reported. In the course of screening for biologically and chemically novel agents from Formosan Annonaceous plants [3-26], A. cherimola was chosen for further phytochemical investigation. These observations provide useful information for potential chemopreventive drug design. The MeOH extract of its roots was subjected to solvent partitioning and chromatographic separation to afford a new benzylisoquinoline alkaloid. In this paper, we report the isolation and structural elucidation of this new alkaloid.

(-)-Zishenine (**1**) was obtained as a brown oil from $CHCl_3$, positive to Dragendorff's test. Its molecular formula was deduced as $C_{21}H_{27}NO_4$ by HR-ESI-MS (*m/z* 380.1837 ([M + Na]$^+$; calc. 380.1838)). The UV spectrum of (-)-zishenine (**1**) contained absorption bands typical of the benzylisoquinoline derivatives [27]. The ^{1}H NMR spectrum of (-)-zishenine (**1**) contained an AA'XX' pattern at δ 7.01 (2H, d, J = 8.0) and 6.80 (2H, d, J = 8.0) for H-10 & 12 and H-9 & 13, a singlet at δ 2.53 for N-CH3, and a singlet at δ 5.80 for H-1 in the aromatic region, in addition to four singlet methoxyl groups at δ 3.52, 3.78, 3.83 and 3.85 and seven aliphatic protons at δ 2.78 (4H, m), 3.21 (2H, m) and 3.73 (1H, t, J = 6.0), accounting for 27 protons. H-1 unusual high field position indicating that this proton lies below the plane of the benzene ring. The significant downfield signal at δ 3.73 (1H, t, J = 6.0) for H-7a indicated an electron-withdrawing group bonded to the nitrogen atom. The structure (-)-zishenine (**1**) was also confirmed by 2D NMR experiments. A COSY correlation was observed between the H-9 & 13 and H-10 & 12, between H-5 and H-6 and between H-7a and H-8. To confirm the structure of 1, the NOESY spectrum was examined. The typical high field aromatic proton resonance at δ 5.80 (s, H-1) showed correlation to methoxy group at δ 3.52 (OMe-2). Significant correlations between H-5 and H-6, between OMe-2, OMe-3 and OMe-4 as

well as H-7a, H-8, H-9/H-13, H-10/H-12 and OMe-11, were observed in the NOESY spectrum. These observations confirmed the structure of 1 as the new benzylisoquinoline alkaloid, which we name (-)-zishenine.



Experimental

General

UV spectra were obtained in CH_3CN, IR spectra were measured on a Hitachi 260-30 spectrophotometer. ^1H NMR (500 MHz), HETCOR, HMBC, COSY, NOESY, and DEPT 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 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 mm and 0.50 mm, were used for analytical TLC and preparative TLC, respectively, visualized with 50% H_2SO_4 and Dragendorff's reagent.

Plant Material

The specimen of A. cherimola Mill. was collected from Chia-Yi County, Taiwan in January, 2015. A voucher specimen was identified by Professor 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 Sciences, Fooyin University, Kaohsiung, Taiwan.

Extraction and Isolation

The roots (3.1 kg) of *A. cherimola* were air dried and extracted repeatedly with MeOH (4 L × 3) at room temperature. The combined MeOH extracts (244.5 g) were then evaporated and further separated into 6 fractions by column chromatography on silica gel (9.8 kg, 70-230 mesh) with gradients of n-hexane/CH_2Cl_2/MeOH. Part of fraction 6 (22.1 g) was subjected to silica gel chromatography by eluting with CH_2Cl_2-MeOH, enriched with MeOH to furnish three further fractions (6-1-6-6). Fraction 6-2 (4.7 g) was further purified on a silica gel column using CH_2Cl_2/MeOH (15:1) mixtures to obtain (-)-zishenine (1) (7 mg).

(-)-Zishenine (**1**). Brown oil (CH_2Cl_2); $[\alpha]D^{25}$ -24.5° (*c* 0.15, CH_2Cl_2). UV (MeCN, λ_{max}, nm) (log ε): 280 (3.52). IR (neat, ν_{max}, cm^{-1}): 2900, 1210, 920. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm, J/Hz): 2.53 (3H, s, N-C*H*$_3$), 2.78 (4H, m, H-5, 6), 3.21 (2H, m, H-8), 3.52 (3H, s, C2-OC*H*$_3$), 3.73 (1H, t, J = 6.0, H-7a), 3.78 (3H, s, C11-OC*H*$_3$), 3.83 (3H, s, C3-OC*H*$_3$), 3.85 (3H, s, C4-OC*H*$_3$), 5.80 (1H, s, H-1), 6.80 (2H, d, J = 8.0, H-9,13), 7.01 (2H, d, J = 8.0, H-10,12). HR-ESI-MS *m/z* 380.1837 $[M + Na]^+$ (calcd for $C_{21}H_{27}NO_4Na$, 380.1838).

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References

1. Kan WS. Mannual of Medicinal Plants in Taiwan; National Research Institute of Chinese Medicine: Taiwan. 1971; 246.
2. Wu YC, Chang FR. The phytochemistry of Annonaceous acetogenins. J Chin Chem Soc. 1995; 53: 76-93.
3. Chang FR, Chen CY, Wu PH, et al. New alkaloids from Annona purpurea. J Nat Prod. 2000; 63: 746-748.
4. Chen CY, Chang FR, Wu YC. The constituents from the stems of Annona cherimola. J Chin Chem Soc. 1997; 44: 313-319.
5. Chen CY, Chang FR, Wu YC. Cherimoline, a novel alkaloid from the stems of Annona cherimola. Tetrahedron Lett. 1997; 38: 6247-6248.
6. Chen CY, Chang FR, Wu YC. Cherinonaine, a novel dimeric amide from the stems of Annona cherimola. Tetrahedron Lett. 1998; 39: 407-410.
7. Chen CY, Chang FR, Wu YC. Amides from the stems of Annona cherimola. Phytochemistry. 1998; 49: 1443-1447.
8. Chen CY, Wu TY, Chang FR, et al. Lignans and kauranes from the stems of Annona cherimola. J Chin Chem Soc. 1998; 45: 629-634.
9. Chen CY, Chang FR, Wu YC. Cheritamine, a new N-fatty acyl tryamine and other constituents from the stems of Annona cherimola. J Chin Chem Soc. 1999; 46: 77-86.
10. Chen CY, Chang FR, Chiu FF, et al. Aromin-A, a new Annonaceous acetogenin from Annona cherimola. Phytochemistry. 1999; 51: 429-433.
11. Hsieh TJ, Chen CY, Kuo RY, et al. Two new alkaloids from Artabotrys uncinatus. J Nat Prod. 1999; 62: 1192-1193.
12. Chang FR, Chen CY, Wu PH, et al. New alkaloids from Annona purpurea. J Nat Prod. 2000; 63: 746-748.
13. Chen CY, Chang FR, Cho CP, et al. ent-Kaurane diterpenoids from Annona glabra. J Nat Prod. 2000; 63: 1000-1003.
14. Chang FR, Chen CY, Hsieh TJ, et al. Chemical constituents from Annona glabra III. J Chin Chem Soc. 2000; 47: 913-920.
15. Chen CY, Chang FR, Shih YC, et al. Cytotoxic constituents of Polyalthia longifolia var. pendula. J Nat Prod. 2000; 63: 1475-1478.
16. Chen CY, Chang FR, Pan WB, et al. Four alkaloids from Annona cherimola. Phytochemistry. 2001; 56: 753-757.

17. Kuo RY, Chang FR, Chen CY, et al. Antiplatelet activity of N-methoxycarbony1 aporphines from Rollinia mucosa. Phytochemistry. 2001; 57: 421-425.
18. Hsieh TJ, Chang FR, Chia YC, et al. Cytotoxic constituents of the fruits of Cananga odoratas. J Nat Prod. 2001; 64: 616-619.
19. Hsieh TJ, Chang FR, Chia YC, et al. The alkaloids of Artabotrys uncinatus. J Nat Prod. 2001; 64: 1157-1161.
20. Chen CY, Wu YC. Annocherine C, A New C-α Hydroxy Benzylisoquinoline and Other Constituents from the Leaves of Annona Cherimola. J Chin Chem Soc. 2001; 48: 1203-206.
21. Chen CH, Hsieh TJ, Liu TZ, et al. Annoglabayin, a novel dimeric kaurane diterpenoid and apoptosis on Hep G2 cells of annomontacin from the fruits of Annona glabra. J Nat Prod. 2004; 67: 1942-1946.
22. Hsieh TJ, Wu YC, Chen SC, et al. Chemical constituents from Annona glabra. J Chin Chem Soc. 2004; 51: 869-876.
23. Kuo RY, Chen CY, Lin AS, et al. A new phenanthrene alkaloid, romucosine I, from Rollinia mucosa Baill. Z Naturforsch B. 2004; 59b: 334-336.
24. Wu YC, Chang FR, Chen CY. Tryptamine-derived amides and alkaloids from the seeds of Annona atemoya. J Nat Prod. 2005; 68: 406-408.
25. Chang CT, Kao CL, Yeh HC, et al. A new N-fattyl tryptamine from Annona atemoya. Chem Nat Compd. 2020; 56: 1100-1101.
26. Chen CY, Kao CL, Kuo CE, et al. Secondary metabolites of Annona cherimolia. Chem Nat Compd. 2021; 57: 141-144.
27. Bhaumik PK, Mukherjee B, Juneau JP, et al. Alkaloids from leaves of Annona squamosa. Phytochemistry. 1979; 18: 1584-1586.