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STRUCTURE AND CRYSTALLOGRAPHIC CHARACTERIZATION OF POLYOXYGENATED CYCLOHEXANE DERIVATIVE FROM *ACER CHIANGDAOENSE* SUNTISUK

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ABSTRACT

A polyoxygenated cyclohexane derivative, (-)-quebrachitol [(1*R*, 3*R*, 4*S*, 6*S*)-2-methoxy cyclohexane-1,3,4,5,6-pentol] **(1)** was isolated from the stems of *Acer chiangdaoense*. Additionally, this is the first report of phytochemical from this plant. The structure was recognised by spectral methods, principally 2D NMR spectroscopic techniques, which complicated pooled applications of COSY, HMQC and HMBC. The relative configurations of the molecular structure of **1** were similarly confirmed by single crystal X-ray diffraction.

Key words: *Acer chiangdaoense*, Sapindaceae, Crystallographic, Polyoxygenated cyclohexane.

INTRODUCTION

Acer, the genus which belongs to the Sapindaceae family, which consists of more than 200 species wildly distributed in the temperate zones of the northern hemisphere,

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including Asia, North America and Europe[1]. In Thailand, there are six species of Acer genus including *A. oblongum* Wall. ex DC., *A. calcaratum* Gagnep., *A. laurinum* Hassk., *A. chiangdaoense* Santisuk, *A. thomsonii* Miq. and *A. pseudowilsonii* Y. S. Chen[2,3].

A. chiangdaoense is confined to the open habitats along the edges of lower montane rain forests at an altitude of about 1300-2200 m. This includes the deep shade of lower montane rain forest in Doi Chiangdao in Chiangdao District, Chiang Mai, and Doi Tung in Mae Fa Luang District, Chiang Rai, Thailand[4].

Previous phytochemical investigations of the Acer genus have reported on the isolation of phenolic glycosides such as gallotannins from *A. rubrum*[5-7], acertannin from *A. saccharum*[8], salidroside from *A. tegmentosum*[9], and another phenolic compounds such as cathechins from *A. Rubrum* and *A. nikoense*[10,11], cyanidins from *A. platanoides* and *A. rubrum*[10,12], chalcone from *A. rubrum*[10], tyrosol from *A. tegmentosum*[9]. In addition, triterpenes have been also isolated from *A. mandshuricum*[13]. Here, we report the first isolation and identification of polyoxygenated cyclohexane derivative from *A. chiangdaoense*. The compound **1** was comprehensively elucidated by NMR and X-rays crystallographic techniques.

EXPERIMENTAL

General experiment procedure

The IR spectra in KBr disk were recorded on a Shimadzu 8900 FTIR spectrophotometer. ^{1}H and ^{13}C NMR, ^{1}H–^{1}H COSY, HMQC and HMBC spectra were recorded with a Unity *plus* 500 spectrometer (Varian Inc., USA) operating at 500 MHz for ^{1}H, and 125 MHz for ^{13}C-NMR, respectively. Melting points were recorded in degree Celsius (^{o}C) and were measured on a B-540 melting point apparatus (Büchi, Flawil, Switzerland). Low resolution mass spectra were recorded on a Thermo Finnegan Polaris Q mass spectrometer at 70 eV (probe) for EIMS. The X-ray data set was collected on a Bruker SMART APEX II diffractometer, using the Mo-Kα radiation, at 100 (2) K. Column chromatography was conducted on silica gel 60 (70-230 mesh, Merck KGaA, Darmstadt, Germany). TLC was performed on aluminium backed pre-coated silica gel 60 PF_{254} sheets and detection carried out with UV detector.

Plant material

The stems of *A. chiangdaoense* were collected at an altitude of about 1350 m in Doi Tung in Mae Fa Luang District, Chiang Rai, Thailand, and identified by Mr. Narong Nantasean. A voucher specimen (BKF 150554) has been deposited at The Forest Herbarium,

Department of National Park, Wildlife and Plant Conservation, Ministry of Natural Resources and Environment, Bangkok, Thailand.

Extraction and isolation

The air dried powdered stems of *A. chiangdaoense* (3.8 Kg) were successively percolated with hexane (10 L × 3 days × 4 times) and then extracted with ethyl acetate (10 L × 3 days × 4 times) and methanol (10 L × 3 days × 4 times) at room temperature, respectively and followed by filtration. The filtrates were combined and evaporated to dryness under reduced pressure to afford hexane, ethyl acetate and methanol extracts were 7.04, 21.56, and 229.5 g, respectively.

The methanol extract was separated by column chromatography, over of silica gel (Merck Art 7734, 700 g) with gradient systems of ethyl acetate-hexane, followed by the increasing amount of methanol in ethyl acetate and finally with methanol. Fractions (1000 mL each) were collected and combined on the basis of TLC behavior. The solvents were evaporated to dryness to give 7 fractions (F1-F7). Evaporation of F6 eluted with methanol : ethyl acetate (1:9 to 2:8) gave a colorless solid (450 mg) and it was repeatedly recrystallized from water (H_2O) to afford (-)-quebrachitol (**1**) (300 mg).

X-ray crystallographic analysis

Molecular formula $C_7H_{14}O_6$, Mr = 194.18, monoclinic, $P2_1$, a = 6.674 (2), b = 7.187 (2), c = 8.720 (3) Å, β = 90.226 (10)°, V = 418.3 (2) Å^3, Z = 2, Dc = 1.542 Mg/m^3, μ = 0.136 mm^{-1}, T = 100 (2) K. One thousand eight hundred and thirty one reflections (1819 independent, R_{int} = 0.0174) were collected in θ range from 2.34 to 25.14°. Largest electron density residue: 0.146 e.Å^{-3}, R_1 (for $I > 2\sigma(I)$) = 0.0320 and wR_2 = 0.0895 (all data) with $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$ and $wR_2 = \sum w(F_o^2 - F_c^2)^2/\sum w(F_o^2)^2)^{0.5}$. All the data for this structure were collected at 100 (2) K on a Bruker SMART APEX II diffractometer equipped with a graphite-monochromator Mo $K\alpha$ radiation (λ = 0.71073 Å). The structure was solved by direct methods using *SHELXS-97*[14] and all non-hydrogen atoms were refined anisotropically using the least-squares method on F^2 using *SHELXL-2013*[15]. All the H atoms in this compound was calculated geometrically with isotropic displacement parameters set to 1.2 (1.5 for hydroxyl and methyl groups) times the equivalent isotropic U values of the parent carbon atoms. Crystal data and refinement were listed in Table 1. The molecular graph was developed using *ORTEP*[16]. The CIF format crystallographic data of compound **1** (CCDC No. 1036774) is available free of charge *via* www. ccdc. cam. ac. uk/services/structure deposit/(or from Cambridge crystallographic data centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: + 44 1223 336033).

RESULTS AND DISCUSSION

Phytochemical investigation of the methanol extracted from the stems of *A. chiangdaoense* led to the isolation of the compound, (-)-quebrachitol **(1)**, which was obtained as colorless crystals, exhibited a molecular formular of $C_7H_{14}O_6$, m.p. 191.0-191.2°C and specific rotation $[a]_{589}^{25}$ – 33.38° (*c* 0.5, H_2O). The EIMS showed an ion peak $[M]^+$ at *m/z* 194. The IR spectrum showed the bands corresponding to hydroxyl groups at 3377 cm^{-1} and C-O stretching and O-H deformation of methoxyl and hydroxyl groups at 1138, 1101, 1051, 1013 cm^{-1}, respectively. The ^{1}H-NMR spectrum showed (Table 2) six oxymethine protons at δ_H 4.16 (*dd*, 3.6, 3.6; H-1), 3.95 (*dd*, 3.7, 3.7; H-6), 3.63 (*dd*, 9.6, 3.5; H-5), 3.51 (*m*; H-4), 3.48 (*m*; H-3), 3.29 (*dd*, 9.6, 3.5; H-2) and one methoxyl group at δ_H 3.34 (*s*; 2-OCH_3). The relationship between the dihedral angle and vicinal coupling constant (^3J) is given theoretically by the Karplus equation (1).

$$^3Jab = J^0\cos^2 f - 0.28\ (0° < f < 90°) \text{ and } ^3Jab = J^{180}\cos^2 f - 0.28\ (90° < f < 180°) \quad \ldots(1)$$

So, the relative configuration at H-1 and H-2, H-1 and H-6, H-5 and H-6 could be determined by the ^3J, H-C-C-H (3.5-3.7 Hz) coupling constant which indicated the two protons were located on the same side with dihedral angle 60°. In addition, proton H-2 and H-3, H-3 and H-4, H-4 and H-5 could be purposed coupling constant by the ^3J, H-C-C-H (9.6 Hz), which exhibited the two protons were located on the opposite side with dihedral angle 180°[17]. The ^{13}C-NMR and DEPT spectrums displayed seven carbon signals, which six carbon signals were assigned to oxygenated CH groups at δ_C 80.20 (C-2), 72.88 (C-3), 71.96 (C-4), 71.40 (C-6), 70.40 (C-5), 67.20 (C-1) and one OCH_3 group at δ_C 56.94 (2-OCH_3). The ^{1}H-^{1}H COSY spectrum suggested connectivities of proton H-1 to H-2 and H-6; H-2 to H-1 and H-3; H-3 to H-2 and H-4; H-4 to H-3 and H-5; H-5 to H-4 and H-6; H-6 to H-1 and H-5. In addition, the assignments of protons were supported by the HMBC correlations from H-1 to C-2, C-4, C-5, C-6; H-2 to C-1, C-3, C-4, 2-OCH_3; H-3 to C-2, C-4, C-5; H-4 to C-2, C-3, C-5; H-5 to C-3, C-4; H-6 to C-1, C-2, C-3, C-5 and proton of methoxyl group by correlation with C-2. The ^{1}H, ^{13}C and 2D-NMR spectra were compared to the previously reported for (-)-quebrachitol[18]. However, the structure was confirmed by the present evidence of the single crystal X-ray (Fig. 1).

Compound 1 presented one crystallographically independent molecule in the asymmetric unit as shown in Fig. 1. The cyclohexane ring adopted in the chair conformation has an average torsion angle of 56.48 (4)° and has ring puckering parameters (Ω, θ, φ) of 0.5799 Å, 2.60° and 123.38°, respectively[19]. The O atoms at C-1 and C-6 were in the expected axial position with an average torsion angle of 62.32 (3)° and the other four O

atoms were in equatorial positions with an average torsion angle of closed to 180° on the ring, due to the strength and directions of intermolecular hydrogen bond interactions.

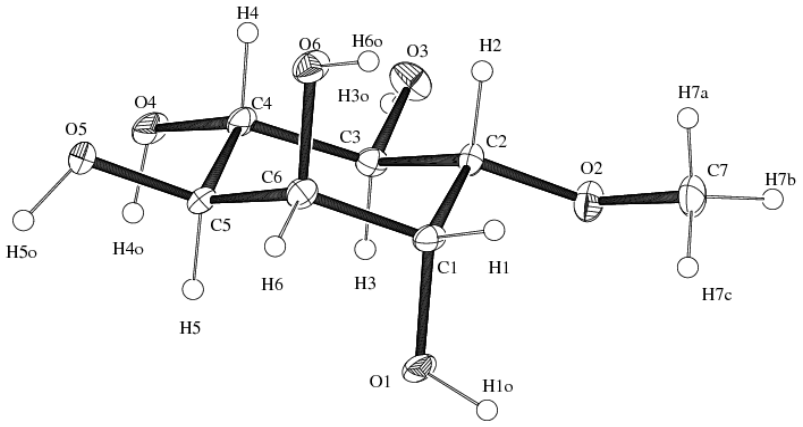

Fig. 1: ORTEP view of the asymmetric unit of 1 with the atom-labelling scheme, showing 25% probability displacement ellipsoids

The molecule has the four chiral centers at C(1,*R*), C(3,*R*), C(4,*S*), C(6,*S*) with an absolute structure parameter of –0.3 (17). The bond distances and angles are in normal range. The crystal structure is stabilized by the intermolecular hydrogen bond interactions. The molecule and adjacent molecules are held together to form one dimensional chains *via* strong O(1)–H(1o)···O(4)^{I} interaction; symmetric code (i) x, y+1, z along the *b* axis as illustrated in Fig. 2 and listed in Table 1.

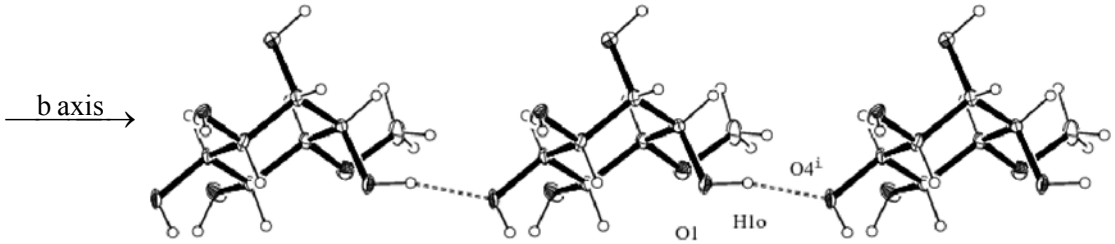

Fig. 2: ORTEP drawing of a chain *via* strong intermolecular O(1)–H(1o)···O(4)^{i} interactions along to [010]

The chains are linked together to generate two dimensional supramolecular layers *via* strong O (3, 4, 6)-H (3o, 4o, 6o)···O((5)^{ii}, (1)^{iv}, (2)^{v}) interactions of other hydroxyl groups and weak C(1)–H (1)···O (6)^{ii} interaction and the layered suparmolecular interactions

are held to produce the three dimensional supramolecular network *via* strong O(5)–H(5o)···O(3)^{iii} interactions as illustrated in Fig. 3 and listed in Table 1.

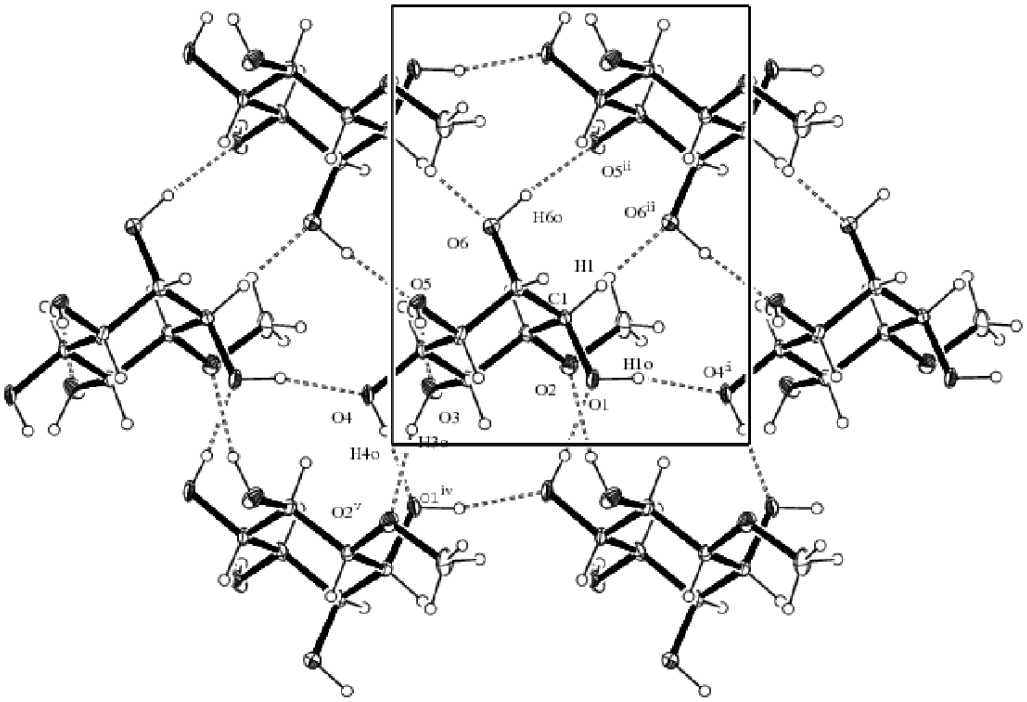

Fig. 3: ORTEP drawing of the three dimensional supramolecular network *via* strong intermolecular O–H···O and weak C–H···O interactions perpendicular to [100]

Table 1: The selected hydrogen bond interactions in 1

D–H···A	d[D–H] (Å)	d[H···A] (Å)	d[D···A] (Å)	∠[D–H···A] (°)
O(1) –H(1o)···O(4)^{i}	0.920(19)	1.80(2)	2.703(3)	166(4)
O(6) –H(6o) ···O(5)^{ii}	0.934(19)	1.83(2)	2.754(3)	168(4)
O(5) –H(5o) ···O(3)^{iii}	0.931(18)	1.85(2)	2.725(3)	155(4)
O(4) –H(4o) ···O(1)^{iv}	0.928(18)	1.83(2)	2.756(3)	172(4)
O(3) –H(3o) ···O(2)^{v}	0.92(2)	1.90(2)	2.791(4)	162(3)
C(1) –H(1) ···O(6)^{ii}	1.00	2.55	3.236(4)	125

Symmetry codes: (i) x,y+1,z; (ii) -x+2,y+1/2,-z+1; (iii) x+1,y,z; (iv) -x+2,y-1/2,-z; (v) -x+1,y-1/2,-z

Table 2: ^{1}H-NMR (500 MHz), ^{13}C-NMR (125 MHz), ^{1}H-^{1}Hand ^{1}H-^{13}C correlations in D_2O data for the isolated compound 1

Position	δ^{13}C, ppm (DEPT)	δ^{1}H, ppm(*mult*, J Hz)	COSY	HMBC
1	67.20 (CH)	4.16 (*dd*, 3.6, 3.6)	H-2, H-6	C-2, C-4, C-5, C-6
2	80.20 (CH)	3.29 (*dd*, 9.6, 3.5)	H-1, H-3	C-1, C-3, C-4, 2-OCH_3
3	72.88 (CH)	3.48 (*m*)	H-2, H-4	C-2, C-4, C-5
4	71.96 (CH)	3.51 (*m*)	H-3, H-5	C-2, C-3, C-5
5	70.40 (CH)	3.63 (*dd*, 9.6, 3.5)	H-4, H-6	C-3, C-4
6	71.40 (CH)	3.95 (*dd*, 3.7, 3.7)	H-1, H-5	C-1, C-2, C-3, C-5
2-OCH_3	56.94 (CH_3)	3.34 (*s*)	-	C-2, C-3

Note: δ in ppm from TMS [coupling constants (*J*) in Hz are given in parentheses]

(-)-quebrachitol (1)

MP: 191.0-191.2ºC.

$[\alpha]_D$: - 33.38^{o} (*c* 0.5, H_2O).

IR (KBr): 3377, 2941, 2928, 1138, 1101, 1051, 1013 cm^{-1}.

EIMS (EI, 70 eV): *m/z* (%) = 194 [M^+] (5), 180 (5), 179 (4), 164 (9), 162 (9), 126 (100), 109 (51), 92 (46), 75 (11).

Supplementary data

NMR spectra (^{1}H-NMR (500 MHz, D_2O), ^{13}C-NMR (125 MHz, D_2O), DEPT, COSY and HMBC) for compound **1** are also available.

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