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NMR elucidation and crystal structure analysis of 1-hydroxy-3,6-dimethoxy-8-methyl-9*h*-xanthen-9-one (lichexanthone) isolated from *Vismia baccifera* (Guttiferae)

[Elucidación por RMN y análisis de la estructura cristalina de 1-hidroxi-3,6-dimetoxi-8-metil-9*h*-xanten-9-ona (lichexanthone)]

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Abstract

In the present investigation the structural analysis of 1-hydroxy-3,6-dimethoxy-8-methyl-9*h*-xanthen-9-one (lichexanthone) isolated from *Vismia baccifera* var. *dealbata* collected in Mérida-Venezuela, was established by NMR (¹H and ¹³C), mass spectrometry and single crystal X-ray diffraction. Lichexanthone crystallizes in the monoclinic system, space group P2₁/c (N° 14) with unit cell parameters *a* = 11.6405(5) Å; *b* = 7.5444(3) Å; *c* = 15.2341(6) Å; β = 102.280(1)°; *V* = 1307.26(9) Å³; *Z* = 4. The structure refinement converged to *R* = 0.0397, *wR*² = 0.1076, *S* = 1.04. Lichexanthone had been isolated before from *Parmotrema* sp and *Ruprechtia tangarana* (Polygonaceae). However, to the best of our knowledge, this is the first report of this compound obtained from *V. baccifera* var. *dealbata* (Guttiferae).

Keywords: Lichexanthone, *Vismia baccifera*, Guttiferae, crystal structure analysis

Resumen

En la presente investigación el análisis estructural de 1-hidroxi-3,6-dimetoxi-8-metil-9*h*-xanten-9-ona (lichexanthone) aislada de *Vismia baccifera* var. *dealbata* colectada en Mérida-Venezuela, fue determinado por RMN (¹H y ¹³C), espectrometría de masas y difracción de rayos X. La lichexanthona cristaliza en un sistema monoclinico con un grupo espacial P2₁/c (N° 14) y parámetros de celda de *a* = 11.6405 (5) Å; *b* = 7.5444 (3) Å; *c* = 15.2341 (6) Å; β = 102.280(1)°; *V* = 1307.26(9) Å³; *Z* = 4. El refinamiento de la estructura convergió a los valores de *R* = 0.0397, *wR*² = 0.1076, *S* = 1.04. La lichexanthona ha sido aislada de *Parmotrema* sp y *Ruprechtia tangarana* (Polygonaceae). Sin embargo, para nuestro conocimiento, esta es la primera vez que se reporta el aislamiento de este compuesto en la especie *V. baccifera* var. *dealbata* (Guttiferae).

Palabras Clave: Lichexanthone, *Vismia baccifera*, Guttiferae, análisis de la estructura cristalina

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INTRODUCTION

The genus *Vismia*, family Guttiferae (Aristiguieta, 1973), is distributed mainly in tropical and subtropical areas of Central and South America, and about 50 species are known. In Venezuela, there are approximately 15 species, which are distributed all around the country (Ewan, 1962). *Vismia* species have been used in folk medicine to treat many skin diseases, such as herpes, dermatitis, leprosy, syphilis, scabies, and eczema (Bilia, *et.al.*, 2000).

Phytochemical studies carried out on several *Vismia* species have reported a variety of compounds, such as terpenes, lignans, sterols, flavonoids, anthrones and xanthenes (Tanaka and Takaishi, 2006; Dos Santos, *et. al.*, 2000). Particularly, xanthenes or 9*H*-xanthen-9-ones are a kind of oxygenated heterocyclic compounds that have been attributed several pharmacological properties such as antibacterial (Sukpondma, *et.al.*, 2005), antimalarial (Ignatushchenko, *et.al.*, 2007) and antitumor activity (Carvalho, *et.al.*, 2009).

In the present investigation the structural analysis of 1-hydroxy-3,6-dimethoxy-8-methyl-9*h*-xanthen-9-one (lichexanthone) isolated from *Vismia baccifera* var. *dealbata* collected from Mérida-Venezuela was established by NMR (^1H and ^{13}C), mass spectrometry and X-ray single crystal structure determination.

MATERIALS AND METHODS

Plant material: fresh leaves of *Vismia baccifera* (Guttiferae) Trina & Planch were collected from Santa Rosa, La Hechicera, Mérida state, 1800 m above sea level. The leaves were separated from the stems, air-dried and powdered. A voucher sample (JR 25) is lodged in the Dr Luis E Ruiz Terán Herbarium, Facultad de Farmacia y Bioanálisis, Universidad de los Andes, Venezuela.

Extraction and Column chromatographic separation: Powdered *V. baccifera* leaves (2500 g), were submitted to continuous extraction in a soxhlet in isopropyl alcohol (5 L) for 2 days. After filtration, the extract was concentrated to dryness (312 g). The concentrated extract was fractionated on a column (50 x 8 cm) containing silica gel (mesh 230-400). Elution was initially with *n*-hexane (2 L), followed by mixtures of *n*-hexane/dichloromethane (CH_2Cl_2), (9:1,

500 mL; 8:2, 500 mL; 7:3, 500 mL; 6:4, 500 mL; 5:5, 500 mL; 4:6, 500 mL; 3:7, 500 mL; 2:8, 500 mL; 1:9, 500 mL); CH_2Cl_2 100 % 1000 mL, CH_2Cl_2 /Methanol (MeOH), (9:1, 500 mL; 8:2, 500 mL; 7:3, 500 mL; 6:4, 500 mL; 5:5, 500 mL; 4:6, 500 mL; 3:7, 500 mL; 2:8, 500 mL; 1:9, 500 mL) and MeOH 100 % (500 mL). Samples (600), each of 20 mL, were collected and examined by TLC.

Thin layer chromatography (TLC): All the fractions eluted from the various columns were examined by TLC. Silica gel F254 (Merck, UK) layers were utilized and different mixtures of *n*-hexane, CH_2Cl_2 , EtOAc and MeOH were used, depending on the polarity of the compounds to be analyzed. The separated compounds were located by spraying the plates with sulfuric acid 10% reagent and heating in an oven at 80 °C for 10 min.

Chemical characterization: melting point (uncorrected) was determined using a hot stage microscope Fisher-Johns. Infrared spectrum (KBr) was measured using a Perkin Elmer FT-IR spectrometer. ^1H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in CDCl_3 using a Bruker-Avance DRX 400 instrument. Chemical shifts were measured in ppm against a solution of tetramethylsilane as internal standard. MS spectrum was recorded using a Hewlett Packard HP, GC/MS, System 5988 A, 70 eV.

X-ray data collection: Single crystal X-ray data collection was carried out on a Bruker APEX Duo CCD Diffractometer with Mo- $\text{K}\alpha$ radiation ($\lambda=0.71073$) and a graphite monochromator (Bruker, 2009). The data were integrated, reduced, and corrected for absorption using SAINT and SADABS (Bruker, 2009). The structure was solved by direct methods and refined by least-squares techniques with SHELXS and SHELXL, respectively (Sheldrick, 2008).

Hydrogen atoms were placed in calculated positions and refined using a *riding model* with their displacement parameters equal to $1.2U_{\text{iso}}$ of the non-hydrogen atom to which they are attached ($\text{C}-\text{H} = 0.93\text{--}0.98 \text{ \AA}$ and $\text{O}-\text{H} = 0.82 \text{ \AA}$). CCDC 787210 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

RESULTS AND DISCUSSION

From column chromatography separation on fractions eluted with *n*-hexane/CH₂Cl₂ 4:6, an amorphous yellow powder was observed that after crystallization from methanol turned to beige needles (42 mg, m.p. 165 °C). MS analysis gave a molecular ion (M⁺) at *m/z* 286 (calcd for C₁₆H₁₄O₅, 286) and significant fragments at *m/e* 258 (-CHO), 228 (-CH₂O), 200 (-CO). The ¹H NMR spectrum, recorded in CDCl₃, showed one methyl singlet at δ 2.84 (3H, -CH₃), two singlets at 3.86 (3H, -OCH₃) and 3.89 (3H, -OCH₃), four doublets δ 6.29 (1 H, *J* = 2.1 Hz), δ 6.32 (1 H, *J* = 2.1 Hz), δ 6.65 (1 H, *J* = 2.04 Hz) and δ 6.67 (1 H, *J* = 2.06 Hz), corresponding to two unsaturated rings and a singlet signal at δ 13.39 (1 H, OH) due to the presence of a hydroxyl group.

The ¹³C NMR spectrum showed a total of 16 carbon signals between δ 23.4–182.7, indicative of a xanthone type of structure. All signals were corroborated by the 2D-NMR spectra gHSQC (heteronuclear single quantum coherence) and gHMBC (heteronuclear multiple bond correlation). From the spectroscopic and spectrometric information obtained and by comparison with literature data (Carvalho, *et.al.*, 2009; Letcher, 1968), it was concluded that the compound isolated was 1-hydroxy-3,6-dimethoxy-8-methyl-9*h*-xanthen-9-one (lichexanthone).

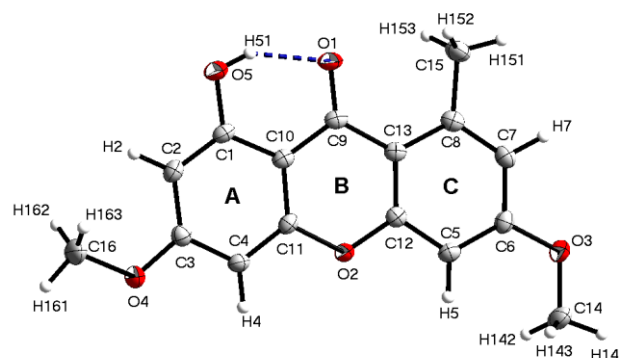
This compound was recently isolated from the lichen *Parmotrema* sp (Micheletti, *et.al.*, 2009). A search performed using the Cambridge Structural Database, Version 5.31 (Allen, 2002), indicated that the structure of lichexanthone, isolated from *Ruprechtia tangarana* (Polygonaceae), had already been reported by Pettit *et al.* (Pettit, *et.al.*, 2003) and is indexed in the CSD with REFCODE ILUCOH. However, to the best of our knowledge, this is the first report of this compound for *V. baccifera* var. *dealbata* (Guttiferae).

Analysis of the Crystal Structure

Lichexanthone crystallizes in the monoclinic system, space group P2₁/c (N^o 14) with unit cell parameters *a*=11.6405(5), *b*=7.5444(3), *c*=15.2341(6) Å, β=102.280(1)°, *V*=1307.26(9) Å³, *Z* = 4. The final refinement values were *R* = 0.0397, *wR*² = 0.1076, *S*=

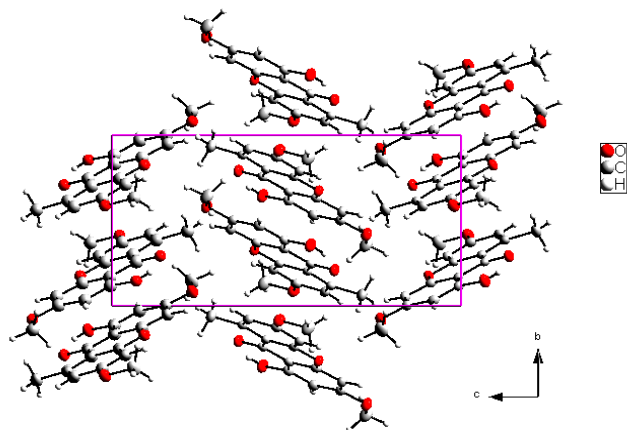
1.04. Figure 1 shows the molecular structure with the atom and ring labeling scheme. The three six-membered rings, A (C1-C2-C3-C4-C11-C10 atoms), B (C9-C10-C11-O2-C12-C13 atoms), and C (C5-C6-C7-C8-C13-C12 atoms), exhibit a planar conformation as given by the asymmetry parameters: ΔC₂(1-2)_{min} = 0.53(19), ΔC₂(2-3)_{max} = 2.47(19), ΔC_S(1)_{min} = 0.66(15), ΔC_S(3)_{max} = 2.07(15) for ring A, ΔC₂(9-10)_{min} = 0.86(17), ΔC₂(9-13)_{max} = 1.87(18), ΔC_S(10)_{min} = 0.08(14), ΔC_S(11)_{max} = 1.36(14) for ring B, and ΔC₂(6-7)_{min} = 0.38(19), ΔC₂(7-8)_{max} = 0.92(19), ΔC_S(7)_{min} = 0.08(15), ΔC_S(8)_{max} = 0.69(15) for ring C. Only one hydrogen bond (which is intramolecular) occurs for O5---H51...O1 (Table 1) and is represented by the graph set symbol S(6) (Etter, *et.al.*, 1990).

Figure 1: Molecular structure of lichexanthone showing the atom and ring labeling scheme and the intramolecular hydrogen bond (ellipsoids drawn at the 50% level of probability).



The lichexanthone molecules form chains along the *b* axis which interact with other neighboring chains along the *c* axis through van der Waals contacts between the methyl groups in a “hearing-bone” fashion (Figure 2).

In the present investigation, the refinement converged to lower values of the reliability factors, compared to the study of Pettit *et al.* (*R* = 0.0539). This may be the result of collecting data at low temperature, which improves significantly the quality of the study.

Figure 2: Packing arrangement of lichexanthone down the *a*-axis**1-hydroxy-3,6-dimethoxy-8-methyl-9*h*-xanthen-9-one (lichexanthone)**

Beige needles (42 mg, m.p. 165 °C), IR (KBr): 3300-3450 (OH), 2810-2930 (C-H), 1680 (C=O), 1450-1490 (C-H, C-C), 1150-1230 (C-H, C-C, C-O), 630-670 (C-O) cm^{-1} . ^1H NMR (400 MHz CDCl_3 , TMS): δ 2.84 (3H, $-\text{CH}_3$), δ 3.86 (3H, $-\text{OCH}_3$), δ 3.89 (3H, $-\text{OCH}_3$), δ 6.29 (1H, $=\text{CH}_2-$), δ 6.32 (1H, $=\text{CH}_4-$), δ 6.65 (1H, $=\text{CH}_5-$), δ 6.67 (1H, $=\text{CH}_7-$), δ 13.39 (1 H, $-\text{OH}$). ^{13}C NMR (100 MHz CDCl_3 , TMS): δ 23.4 (C_{15}), δ 55.6 (C_{16}), δ 55.7 (C_{14}), δ 92.1 (C_4), δ 96.8 (C_2), δ 98.5 (C_5), δ 104.3 (C_{10}), δ 113.0 (C_{13}), δ 115.4 (C_7), δ 143.8 (C_8), δ 157.0 (C_{11}), δ 159.5 (C_{12}), δ 163.7 (C_6), δ 163.8 (C_1), δ 165.9 (C_3), δ 182.7 (C_9). EI-MS m/z : 286 (calcd for $\text{C}_{16}\text{H}_{14}\text{O}_5$), m/e 258 ($-\text{CHO}$), 228 ($-\text{CH}_2\text{O}$), 200 ($-\text{CO}$).

Table 1: Geometry of the intramolecular S (6) hydrogen bond present in $\text{C}_{16}\text{H}_{14}\text{O}_5$.

Bond	D-H (Å)	H-A (Å)	D-A (Å)	D-H-A (°)
O5---H51...O1	0.8400	1.8000	2.5531(15)	148.00

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