A New Lignan from Isodon lophanthoides var. gerardianus (Labiatae)

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Abstract: A new lignan, together with a known one, was isolated from Isodon lophanthoides var. gerardianus [Bentham] H. Hara. The structure of the new lignan was elucidated as 1-acetyl-2-epi-piperonyl-6-6-[6-methoxy-piperonyl]-3,7-dioxabicyclo-[3,3,0]-octane mainly by 1D and 2D NMR techniques.

Key words: Isodon lophanthoides var. gerardianus; Labiatae; lignan: 1-acetyl-2-epi-piperonyl-6-6-[6-methoxy-piperonyl]-3,7-dioxabicyclo-[3,3,0]-octane

Isodon lophanthoides var. gerardianus [Bentham] H. Hara is widely distributed in South and Southeast Asia. It has been used as a folk medicine in China for treatment of enteritis, jaundice, hepatitis, laryngopharyngitis, lepromatous leprosy and ascariasis.[2-4]. As a continuation of our research on bioactive compounds from the Isodon genus, chemical investigation of 1. lophanthoides, collected from the northern part of Guangxi province, has led to the isolation of two lignans. One of them, 1-acetyl-2-epi-piperonyl-6-6-[6-methoxy-piperonyl]-3,7-dioxabicyclo-[3,3,0]-octane (2), was characterized as a new compound. Their structures were determined by spectroscopic analysis (including 1D and 2D NMR techniques).

1 Results and Discussion

Compound 1 was obtained as colorless cubic crystals and had a molecular formula of C₂₉H₃₉O₆ (HRFABS m/z [M+H]⁺: 413.1201, calcd. 413.1236 for C₂₉H₂₅O₈). According to the UV at 205, 238 and 287 nm, and IR at 1608 and 1503 cm⁻¹, it was evident that compound 1 was an aromatic compound. Inspection of EIMS and NMR spectra suggested that compound 1 possessed two phenyl groups, two dioxy-methylene, two methylenes, three methines, one quaternary carbon and one acetyl group. HMBC and 1H-1H COSY spectra revealed the presence of a fragment of –CH₂CHCH₂– (C-4 to C-6). Analysis of HMBC spectrum of compound 1 led to a conclusion that compound 1 was a lignan with a basic skeleton of 2,6-diaryl-3,7-dioxabicyclo-[3,3,0]-octane and had an...
acetoxy group at C-1. The dioxy-methylenes were located at C-3 and C-4 of the phenyl groups. All the evidences mentioned above and comparison of the spectral data of compound 1 with those of sesamin[5] and acetate of paulownin[6] concluded that compound 1 was 1-acetoxy-2e,6e-dipiperonyl-3,7-dioxabicyclo[3,3,0]-octane[6–8].

Compound 2 was yielded as an amorphous powder. Its molecular formula, C_{23}H_{32}O_9, was indicated by HRFABMS m/z [M + H]^+ 443.1284 (calcd. 443.1342) for C_{23}H_{32}O_9. A comprehensive analysis of IR, UV, MS, ^1H, ^13C and DEPT spectral data of compound 2 suggested that it was very similar to compound 1 except for one more methoxy group in compound 2. The ^1H and ^13C-NMR spectra of compound 2 exhibited that the methoxy group was at C-6” because the signal of the methine carbon at δ 120.2 (C-6”) in compound 1 was replaced by a quaternary carbon signal at δ 144.3. Meanwhile, the signal of C-5” shifted up-field and the signal of H-6” disappeared. This conclusion was further confirmed by the correlation between OMe and C-6” in the HMBC (Fig. 1).

![Fig. 1. The key HMBC correlations of compound 2.](image)

In view of the biogenetic aspects and the relative configurations of some similar compounds isolated from this plant, all three substituents of compound 2 were presumed in α-orientation and was further verified by a NOESY experiment. The correlations between H-2β and H-4β, H-2β and H-8β, H-4β and H-6β, H-6β and H-8β, and H-5α and H-4α were clearly observed (Fig. 2). Therefore, compound 2 was deduced to be 1-acetoxy-2e-piperonyl-6e-(6-methoxy-piperonyl)-3,7-dioxabicyclo[3,3,0]-octane.

2 Experimental

2.1 General experimental procedures

Mp was obtained on a Koffler apparatus (uncorrected). IR spectra were obtained on a Bio-Rad FTS-135 spectrometer with KBr pellets. NMR spectra were recorded on Bruker AM-400 and DRX-500 instruments with TMS as internal standard and pyride-d_5 as solvent. ^1H-NMR, ^1H–^1H COSY, NOESY spectra were measured at 400.13 and 500.13 MHz: ^13C-NMR and DEPT spectra were recorded at 100. 6 and 125. 8 MHz; HMOC and HMBC spectra were obtained at 500.13 MHz and 125.8 MHz, respectively. ^13C-NMR assignments were determined by ^1H–^1H COSY and HMOC spectra. FAB and EI MS were carried out on a VG Auto Spec-3000 spectrometer at 70 eV.

![Fig. 2. Principal NOESY correlations of compound 2.](image)

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### Table 1

Note: The data are based on the reported values.

2.2 Plant material

Leaves of Isodon lophanthoides var. gerardianus (Bentham) H. Hara were collected from the Huaping Natural Reserve Area, Longsheng Prefecture of the Guangxi Zhuang Autonomous Region in the autumn of 1996. It was authenticated by Prof. Xi-Wen Li at Kunming Institute of Botany, The Chinese Academy of Sciences, where a voucher specimen (KIB 96-11-12 Lin) is deposited.

2.3 Extraction and isolation

Dried and powdered leaves (3.6 kg) were extracted with EtOH (7 000 mL × 3) under reflux for 2 h each time. The solution was treated with activated charcoal (100.0 g × 3) and then filtrated. After concentrating the
flltrate in vacuum, the residue was dissolved in EtOH and then diluted with water to a 20% alcoholic solution. The solution was partitioned with AcOEt (2 000 mL x 3) and the AcOEt extract was evaporated in vacuum to give a residue (164.0 g) which was then chromatographed on a silica gel column (200 - 300 mesh, 1.5 kg) and eluted with CHCl₃ containing increasing amounts of Me₂CO. The fractions were combined by TLC monitors. Fraction IV (obtained from CHCl₃-Me₂CO 9 : 1) was further decolorized by using MCI CC. The fractions were sublimed on a hot plate and eluted with solvent of increasing polarity (cyclohexane and iso-propyl alcohol) to obtain compounds 1 (148 mg) and 2 (118 mg).

2.4 Purification

1-Acetoxy-2-e. 6e-dipiperonyl-3. 7-dioxabicyclo-[3. 3. 0]octane (1) C₁₃H₂₁O₃ (positive HRFABMS m/z M + H) 413, 1201. calcd. 413, 1236. 6 for C₁₃H₂₁O₃), colorless crystals: mp 168.0 - 169.3 °C; [α]D20: +34.44° (c 0.47, CHCl₃); UV (CHCl₃) λmax (log ε nm: 205 (4.27), 238 (3.40), 287 (3.38); IR νKBr cm⁻¹: 3076 (m), 2992 (m), 2931 (m), 2877 (m), 2798 (w), 1855 (w), 1746 (s), 1608 (m), 1503 (s), 1446 (s), 1488 (s), 1364 (s), 1256 (s), 1241 (s), 1206 (s), 1039 (s), 1043 (s), 934 (s), 882 (m), 811 (s), 785 (s), 744 (m); 1H-NMR δ: 5.31 (1H, s, H-2β), 4.49 (1H, overlapped, H-4α), 3.88 (1H, dd; J = 9.3, 4.8 Hz, H-4β), 3.49 (1H, m, H-5α), 4.95 (1H, dd; J = 8.7, 4.6 Hz, H-6β), 4.69 (1H, d; J = 10.4 Hz, H-8α), 4.51 (1H, d; J = 10.4 Hz, H-8β), 7.20 (1H, s, H-2′), 7.22 (1H, s, H-2″), 6.94 (2H, overlapped, H2-5′, 5″), 7.05 (2H, overlapped, H2-6′, 6″), 5.99 (2H, s, H2-7), 5.93 (2H, d; J = 13.8 Hz, H2-7″), 1.66 (3H, s, OAc); EIMS m/z (%): 412 [M]+ (27), 219 (10), 202 (100), 172 (8), 161 (22), 149 (60), 131 (52), 121 (13), 103 (46).

1-Acetoxy-2-e-piperonyl-6e-[6-methoxy-piperonyl]-3. 7-dioxabicyclo-[3. 3. 0]octane (2) C₁₃H₂₂O₄ (positive HRFABMS m/z [M + H]+ 443.1284; calcd. 443.1342 for C₁₃H₂₂O₄), obtained as an amorphous powder: [α]D20: + 17.68° (c 0.70, CHCl₃); UV (CHCl₃) λmax (log ε nm): 205 (4.18), 240 (3.36), 288 (3.32); IR νKBr cm⁻¹: 3 092 (m), 2 990 (m), 2 920 (s), 2 850 (m), 1 848 (w), 1 740 (s), 1 608 (s), 1 507 (s), 1 480 (s), 1 378 (s), 1 244 (s), 1 210 (s), 1 040 (s), 1 010 (s), 903 (s), 850 (m), 780 (m); 1H-NMR δ: 5.31 (1H, s, H-2β), 4.50 (1H, d; J = 9.2 Hz, H-4α), 3.89 (1H, dd; J = 9.2, 5.0 Hz, H-4β), 3.54 (1H, m, H-5α), 4.96 (1H, d; J = 4.8 Hz, H-6β), 4.70 (1H, d; J = 10.6 Hz, H-8α), 4.53 (1H, d; J = 10.6 Hz, H-8β), 7.19 (1H, s, H-2′), 7.21 (1H, s, H-2″), 6.93 (2H, overlapped, H2-5′, 5″), 7.07 (1H, dd; J = 8.0, 1.6 Hz, H-6′), 6.01 (2H, s, H2-7″), 5.93 (2H, d; J = 10.9 Hz, H2-7′), 3.81 (3H, s, OMe), 1.66 (3H, s, OAc); EIMS m/z (%): 442 [M]+ (46), 249 (13), 233 (5), 217 (5), 203 (1), 191 (32), 180 (34), 161 (38), 149 (54), 135 (64), 118 (16), 103 (11).

References: