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EURYCOMANONE AND EURYCOMANOL, QUASSINOIDS FROM THE ROOTS OF *EURYCOMA LONGIFOLIA*

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Key Word Index—*Eurycoma longifolia*; Simaroubaceae; quassinoids; eurycomanone; eurycomanol.

Abstract—From the roots of *Eurycoma longifolia*, used as an Indonesian folk medicine, two highly oxygenated quassinoids, named eurycomanone and eurycomanol were isolated. The structures of both new bitter principles were elucidated by NMR, MS, UV and IR.

INTRODUCTION

Eurycoma longifolia (Indonesian name: Bidara Pahit) is a slender small tree which is common in Thailand, Malaysia, Burma, Vietnam and Indonesia, especially around Kalimantan and Sumatra. In Indonesia, roots of this tree are a well-known folk medicine for treatment of dysentery and are used also as a remedy for glandular swelling. With regard to chemical constituents, 2, 6-dimethoxybenzoquinone and a bitter quassinoid named eurycomalactone were previously isolated from the bark [1]. The present paper deals with the isolation and structure determination of two new quassinoids from the roots.

RESULTS AND DISCUSSION

A suspension of the methanol extract of the roots was extracted with ether and then with *n*-butanol saturated with water. The butanol fraction was chromatographed on Si gel, affording two crystalline bitter principles named eurycomanone (**1**) and eurycomanol (**2**).

Eurycomanone (**1**), $C_{20}H_{24}O_9 \cdot H_2O$ was presumed to be a kind of quassinoid. These compounds are characteristic of plants of the Simaroubaceae and the structure was elucidated by means of a variety of spectroscopic procedures and comparison with the data of ailanthone (**3**) which was previously isolated from *Ailanthus altissima* [2–4]. An extensive study on the mass spectra of quassinoids was reported by Fourrey *et al.*[5]. Strong fragmentation ions at *m/z* 151 and 248 in the spectrum of **1** indicated the presence of partial structure **4**. A ketal ring system (C-11–C-30) of **1** was substantiated by its ^{13}C NMR spectral signals at δ 66.2 (*t*, C-30) and 107.8 (*s*, C-11) and ^1H NMR proton resonances as a pair of AB type doublets at δ 4.02 and 4.50 (1H each, $J = 8$ Hz, H-30). The presence of the same A-ring structure in **1** as that found in **3**, including the configuration of the C-1 hydroxyl group, was revealed by the spectral data. IR ν_{max}^{KBr} cm^{-1}: 1680 (C=O); UV λ_{max}^{EtOH} nm (log ϵ): 239 (4.01); ^1H NMR: δ 4.49 (1H, *s*, H-1), 6.16 (1H, *s*, H-3), 1.62 (3H, *s*, H-19), 1.81 (3H, *s*, H-17) and comparison of its ^{13}C NMR carbon signals due to C-1–C-6, C-10, C-17, C-19 with those of **3** (see Table 1). The CD value of **1**, $\Delta\epsilon_{316} + 1.21$ (MeOH; *c*0.021) indicated the same absolute configuration as that of **3** (CD: $\Delta\epsilon_{320} +$ 1.98) [2]. A six-membered lactone ring of **1** was demonstrated by IR (ν_{max}^{KBr} cm^{-1}: 1725) and a ^{13}C NMR carbon signal at δ 172.4 (*s*). A ^1H NMR triplet-like proton signal of **1** at δ 5.23 indicated that H-7 of **1** must be β-equatorial. The presence of a vinyl group in **1** was revealed by proton resonances at δ 5.63 and 6.07 (1H each, *br s*) and carbon signals at δ 146.0 (*s*) and 118.9 (*t*). This evidence as well as the biogenetic considerations, disclosed that **1** must have the quassinoid-skeleton of the same type as that of **3**.

The presence of one tertiary and two additional secondary hydroxyl groups in **1** was demonstrated by its ^{13}C NMR carbon signals at δ 78.0 (*s*), 79.2 (*d*) and 74.8 (*d*) and its ^1H NMR proton signals at δ 4.75 (1H, *s*) and 5.60 (1H, *s*), the location of which should be restricted to C-14, C-12 and C-15, respectively. The formation of the lactone ring between the 7α-hydroxyl and the 16-carboxyl group required the β-configuration of the C-14 *tert*-hydroxyl group. The upfield shifts of the carbon signals due to C-30 and C-7 of **1** compared with those of **3** (see Table 1) can be reasonably explained in terms of the γ-substituent effect [6, 7] by the β-hydroxy substitution at C-14. The ^{13}C NMR signals of C-9 and C-12 of **1** were observed at almost the same positions as those of **3** which appeared at lower field than those of 12α-hydroxy quassinoids [4]. This indicated a β-equatorial configuration of the C-12 hydroxyl group of **1**. With reference to the reported data for the ^1H NMR spectrum of quassinoids [2, 3, 8], proton signals of **1** at δ 3.76 (1H, *s*) and 5.60 (1H, *s*) were reasonably assigned to H-9 and H-15, respectively. The observation of the strong NOE (24%) between these two proton signals revealed a β-equatorial configuration of the C-15 hydroxyl group of **1** (see stereostructure **1a**). It follows that **1** should be represented by 14β, 15β-dihydroxyailanthone. The displacement of ^{13}C NMR carbon signals due to C-8, C-14, C-15 and

C-16 on going from **3** [4] to **1** is also consistent with this formulation (Table 1).

Eurycomanol (**2**), $C_{20}H_{26}O_9 \cdot \frac{1}{2}H_2O$ showed no UV absorption maximum and no IR band due to a carbonyl group near 1680 cm^{-1}. This indicated the absence of the α, β-unsaturated ketone system such as the A-ring of **1**. In comparison to the ^{13}C NMR spectrum of **2** with those of glaucarubin (**5**) [4] and **1** (Table 1), signals due to the A-ring; C-1–C-5, C-17 and C-19 were observed at very similar positions to those of **5**, while all of the other carbon resonances of **2**; C-6–C-9, C-11–C-16, C-18 and C-30 appeared at almost the same positions as those of **1**. The presence of a 1, 2-*trans*-glycol system in the A-ring of **2** was further confirmed by its ^1H NMR proton signals at δ 4.05 (1H, *d*, $J = 7$ Hz, H-1) and 4.60 (1H, *m*, H-2) with reference to the reported data for quassinoids of this type [9]. These results led to the structure formulation shown for **2**. It was found that both **1** and **2** exhibited no inhibitory activity against the NIH lymphocytic leukemia P388.

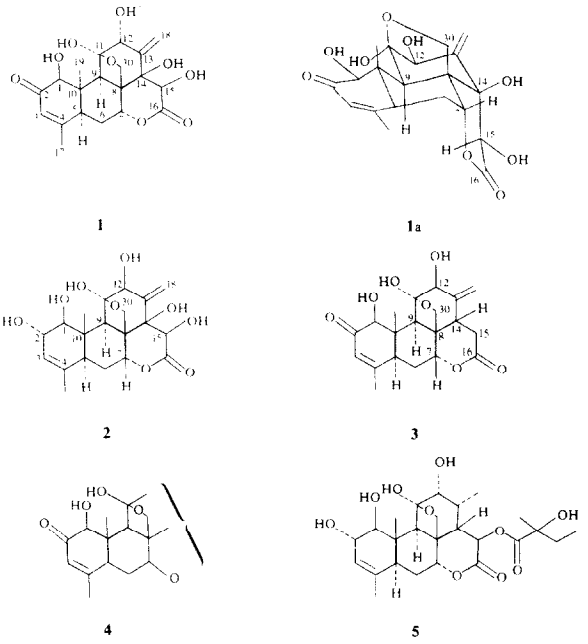

Table 1. ^{13}C NMR chemical shifts of compounds **1–3** and **5** (25.15 MHz, in DMSO-d_6)

Carbon no.	3*	1	2	5*
1	82.5	82.5	82.2	82.6
2	197.2	197.1	71.2	71.3
3	125.0	124.9	125.6	125.7
4	162.5	162.7	133.9	133.8
5	43.3	40.7	39.9	40.1
6	25.1	24.7	24.6	24.9
7	77.7	70.6	70.3	77.9
8	44.5	51.3	51.2	46.7
9	46.1	46.2	46.4	40.9
10	44.5	44.8	41.2	44.1
11	108.9	107.8	107.8	109.1
12	79.1	79.2	79.3	78.5
13	146.6	146.0	146.0	31.4
14	41.1	78.0	77.7	44.6
15	34.3	74.8	75.1	69.5
16	169.1	172.4	172.4	167.1
17	22.2	22.4	21.0	20.9
18	119.7	118.9	119.0	14.8
19	9.5	9.7	9.8	10.1
30	71.2	66.2	66.3	70.1

*Cited from ref. [4].

EXPERIMENTAL

Mps are uncorr. ^1H NMR at 100 MHz in C_5D_5N and ^{13}C NMR at 25.15 MHz in DMSO-d_6; int. standard: TMS.

Extraction and isolation of compounds. The plant material was collected and identified by Mr. F. Tobo, Department of Pharmacognosy, University of Hasanuddin, Jalan Mesjid Raya, Ujung Pandang, Indonesia. A voucher specimen is deposited in the Herbarium of this University.

Roots of the plant (1.7 kg) collected in Indonesia were dried, ground and extracted with MeOH. The MeOH extract was concd to dryness *in vacuo*. A suspension of the residue (83 g) in H_2O was extracted with Et_2O and then with *n*-BuOH satd with H_2O. The BuOH layer was evaporated to dryness *in vacuo* and the residue (10 g) was chromatographed on a Si gel column. Elution with EtOAc–EtOH–H_2O (100:10:1) afforded two crystalline bitter principles, **1** (350 mg) and **2**(360 mg).

Eurycomanone (**1**) was obtained as colorless needles, mp 253–255° from MeOH–EtOAc, $[\alpha]_D^{10} + 32.0°$ (C_5H_5N; *c*0.69). (Found: C, 56.21; H, 5.99. $C_{20}H_{24}O_9 \cdot H_2O$ requires: C, 56.33; H, 6.15%.) MS *m/z*: 408 $[M]^+$, 390, 248, 151 and 135.

Eurycomanol (**2**) was isolated as colorless needles, mp 273–275° from MeOH–H_2O, $[\alpha]_D^{10} + 87.7°$ (C_5H_5N; *c*0.65), IR ν_{max}^{KBr} cm^{-1}: 3300, 1725. (Found: C, 57.10; H, 6.51. $C_{20}H_{26}O_9 \cdot \frac{1}{2}H_2O$ requires: C, 57.27; H, 6.49%.) ^1H NMR: δ 1.73 (3H, *s*, H-17), 1.63 (3H, *s*, H-19), 3.53 (1H, *s*, H-9), 4.05 (1H, *d*, $J = 7$ Hz, H-1 overlapping on one of the signals due to H-30), 4.05 and 4.55 (1H each, a pair of AB *doublets*, $J = 8$ Hz, H-30), 4.60 (1H, *m*, H-2), 4.78 (1H, *s*, H-12), 5.17 (1H, *triplet* like *br s*, H-7), 5.48 (1H, *s*, H-15), 5.62 and 6.10 (1H each, *d*, $J = 2$ Hz, H-18) and 5.80 (1H, *br s*, H-3). MS *m/z*: 410 $[M]^+$, 392, 377, 364 and 348.

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