Pergamon

Tetrahedron Letters 43 (2002) 2941–2943

TETRAHEDRON LETTERS

Lotthanongine, an unprecedented flavonoidal indole alkaloid from the roots of Thai medicinal plant, *Trigonostemon reidioides*

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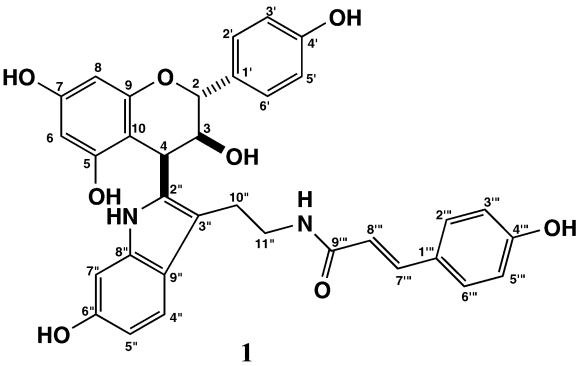
Received 11 January 2002; revised 27 February 2002; accepted 1 March 2002

Abstract—Lotthanongine, a novel flavonoidal indole alkaloid, was isolated from the roots of *Trigonostemon reidioides* (Euphorbiaceae) together with afzelechin-(4α→8)-afzelechin. The structural elucidations were based on analysis of the spectroscopic data.

Trigonostemon reidioides Craib (Euphorbiaceae, Thai name: Lot-Tha-Nong) is a shrub up to 1.5 m high, distributed in South-East Asia. The aqueous extract of the roots causes vomiting, and is used in Thai traditional medicine as an antidote for detoxification of poisonous mushrooms, as well as external use for antiseptic purposes. In the previous investigations, a phenanthrenone (trigonostemonone) and a daphnane diterpenoid (rediocide A) have been reported.[1,2]

Roots of *T. reidioides* (2 kg) were collected in Phitsanulok Province, northern Thailand, in August 2001. The methanolic extract (61 g) was suspended in H_2O and partitioned with CH_2Cl_2 and *n*-BuOH, successively. The *n*-BuOH part (21 g) was chromatographed on a column of silica gel, then followed by a combination of octadecylsilyl silica gel and prep. HPLC-ODS to afford compounds **1** (13 mg) and **2** (55 mg). Compound **1** was found to be a novel flavonoidal indole alkaloid, to which we have given the trivial name lotthanongine (Table 1). Compound **2** was identified as afzelechin-(4α→8)-afzelechin based on our spectroscopic and physical data.[3] This compound has previously been reported by Hsu and co-workers,[4] without NMR spectral data.



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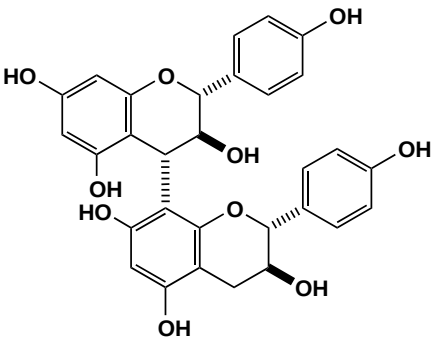

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Lotthanongine (**1**) was obtained as an amorphous powder, $[\alpha]_D^{15}$ +106.0° (*c* 0.80, MeOH). The molecular for-

Keywords: *Trigonostemon reidioides*; Euphorbiaceae; lotthanongine; flavonoidal alkaloid; afzelechin-(4α→8)-afzelechin.

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0040-4039/02/$ - see front matter
PII: S0040-4039(02)00445-8

Table 1. NMR spectral data of lotthanongine (**1**)[a]

No.	Carbon[b]	Proton[c]
2	79.6	4.94 (1H, d, $J=9.5$ Hz)
3	71.7	4.14 (1H, dd, $J=9.5$, 5.6 Hz)
4	36.2	4.66 (1H, d, $J=5.6$ Hz)
5	157.4	
6	96.7	5.95 (1H, d, $J=2.4$ Hz)
7	153.5	
8	95.7	5.99 (1H, d, $J=2.4$ Hz)
9	159.0	
10	102.8	
1′	131.6	
2′, 6′	130.1	7.27 (2H, d, $J=8.8$ Hz)
3′, 5′	116.8	6.76 (2H, d, $J=8.8$ Hz)
4′	158.5	
2″	133.9	
3″	111.7	
4″	119.3	7.32 (1H, d, $J=8.6$ Hz)
5″	109.6	6.54 (1H, dd, $J=8.6$, 2.2 Hz)
6″	158.0	
7″	97.7	6.73 (1H, d, $J=2.2$ Hz)
8″	138.5	
9″	123.9	
10″	25.2	3.03 (2H, m)
11″	41.2	3.51 (1H, m); 3.72 (1H, m)
NH		9.23 (1H, br s)
NH–CO		7.24 (1H, br s)
1‴	127.8	
2‴, 6‴	130.6	7.23 (2H, d, $J=8.6$ Hz)
3‴, 5‴	116.1	6.77 (2H, d, $J=8.6$ Hz)
4‴	160.3	
7‴	141.4	7.35 (1H, d, $J=15.6$ Hz)
8‴	118.6	6.26 (1H, d, $J=15.6$ Hz)
9‴	169.3	

[a] Recorded on a JEOL JNM A-400 spectrometer.
[b] ^{13}C NMR 100 MHz, methanol-d_4.
[c] ^{1}H NMR 400 MHz, methanol-d_4.

mula was determined as $C_{34}H_{30}N_2O_8$ by HR-FAB mass spectrometry ($[M-H]^-$ m/z 593.1919, calculated 593.1924). The ^{1}H NMR spectral data revealed a portion of the flavanol skeleton, corresponding to afzelechin,[4] deduced from two *meta*-coupling protons of H-6 and H-8 (δ 5.95 and 5.99, each doublet, $J=2.4$ Hz), a set of AA′BB′ protons (δ 6.76 and 7.27, each doublet, $J=8.8$ Hz), as well as three proton signals of H-2 (δ 4.94, d, $J=9.5$ Hz), H-3 (δ 4.14, dd, $J=9.5$, 5.6 Hz), and H-4 (δ 4.66, d, $J=5.6$ Hz). The coupling constants between H-2 and H-3, and between H-3 and H-4 provided the stereochemistry of this flavanol skeleton as 2,3-*trans*-3,4-*cis*.[5,6] Inspection of the IR spectrum showed the characteristic band at 3479 cm^{-1} for N–H stretching in the indole moiety and the band at 3412 cm^{-1} for N–H stretching of the secondary amide, as well as the typical band at 1648 cm^{-1} for the N–C=O stretching of an amide.[7,8] The side chain attached to C-3″ of the indole moiety comprised two methelene carbons (C-10″ and C-11″) and a secondary amide. This part was further confirmed by the ^{1}H and ^{13}C NMR spectral data, which was identical to that of a tryptamine derivative.[7,9] In the ^{1}H NMR spectrum, the tryptamine derivative unit showed the presence of an ABX system at δ 7.32 (d, $J=8.6$ Hz), 6.54 (dd, $J=8.6$, 2.2 Hz) and 6.73 (d, $J=2.2$ Hz) in the aromatic region together with the absence of the H-2″ proton, indicating that H-2″ and one proton in the aromatic ring were replaced. The substituted group in the aromatic ring was pointed to a hydroxyl group due to the appearance of a downfield quaternary carbon signal at δ 158.0 in the ^{13}C NMR spectrum. The position of the hydroxyl group was decided at C-6″ since irradiation of the N–H signal (δ 9.23) caused NOE enhancement at H-7″ (δ 6.73, d, $J=2.2$ Hz). The residual part of this structure was identified as a *p-trans*-coumaroyl moiety from the remaining nine signals in the ^{13}C NMR spectrum and from the chemical shifts in the ^{1}H NMR spectrum of H-2‴,6‴ and H-3‴,5‴ (δ 7.23 and 6.77, each d, $J=8.6$ Hz) for the disubstituted aromatic ring, and two olefinic protons of H-7‴ and H-8‴ (δ 7.35 and 6.26, each d, $J=15.6$ Hz). This moiety formed an amide linkage to the N-terminal of the tryptamine derivative, established by the characteristic band of an amide in the IR spectrum. The complete assignments were concluded by 2D NMR analyses, including COSY, HSQC and HMBC, in which significant correlations were found between (1) H-4 and C-2,3,2″ and 3″; (2) H-10″ and C-2″,3″,9″, 11″ and (3) H-11″ and C-3″,10″ and 9‴ as shown in Fig. 1. On the basis of this evidence, the flavanol skeleton was connected to the tryptamine derivative unit through the 4β→2″ bond, and the tryptamine derivative unit was connected to the *p*-coumaroyl unit through an amide bond. The molecular mass for $C_{34}H_{30}N_2O_8$ is fully compatible with the derived structure. Accordingly, lotthanongine (**1**) was elucidated as afzelechin-(4β→2″)-*N*-(*p*-coumaroyl)-6″-hydroxytryptamine.

Seven flavonoidal alkaloids have been reported from the plant sources; ficine and isoficine from *Ficus pantoniana*,[10] phyllospadine from *Phyllosphadix iwatensis*,[11] vochysine from *Vochysia quianensis*,[12] lilaline from *Lilium candidum*,[13] and aquiledine and isoaquiledine from *Aquilegia ecalcarata*.[14] To the best of our knowledge, lotthanongine (**1**) is the first report of a flavonoidal indole alkaloid.

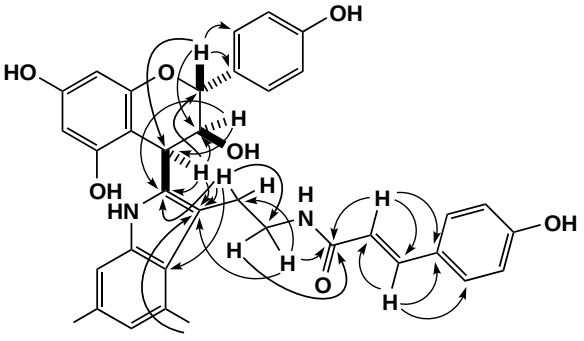

Figure 1. The significant HMBC correlations of lotthanongine (**1**).

Acknowledgements

We would like to thank the Research Center for Molecular Medicine, Hiroshima University for the use of its NMR facilities.

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3. Afzelechin-(4α→8)-afzelechin (**2**): amorphous powder, $[\alpha]_D^{15}$ −251.3° (*c* 3.55, MeOH); ^{1}H NMR (JEOL JNM A-400 spectrometer, methanol-d_4, 400 MHz): δ 4.32 (1H, d, J=9.8 Hz, H-2), 4.30 (1H, dd, J=9.8, 7.6 Hz, H-3), 4.39 (1H, d, J=7.6 Hz, H-4), 4.50 (1H, d, J=8.1 Hz, H-2″), 3.72 (1H, ddd, J=8.7, 8.1, 5.6 Hz, H-3″), 2.80 (1H, dd, J=16.1, 5.6 Hz, H-4″), 2.45 (1H, dd, J=16.1, 8.7 Hz, H-4″); ^{13}C NMR (JEOL JNM A-400 spectrometer, methanol-d_4, 100 MHz): δ 83.6 (C-2), 73.7 (C-3), 38.5 (C-4), 158.5 (C-5), 97.3 (C-6), 158.0 (C-7), 96.2 (C-8), 157.8 (C-9), 107.2 (C-10), 132.1 (C-1′), 130.0 (C-2′,6′), 115.7 (C-3′,5′), 157.2 (C-4′), 82.5 (C-2″), 69.1 (C-3″), 29.5 (C-4″), 154.9 (C-5″), 96.7 (C-6″), 155.6 (C-7″), 108.3 (C-8″), 155.8 (C-9″), 102.5 (C-10″), 131.1 (C-1‴), 129.5 (C-2‴,6‴), 115.7 (C-3‴,5‴), 157.2 (C-4‴); negative FAB MS m/z 545 $[M-H]^-$.
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