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STRUCTURES OF (19*R*)-KOUMINOL AND (19*S*)-KOUMINOL FROM *GELSEMIUM ELEGANS*

F. SUN, Q.Y. XING,

Department of Chemistry, Peking University, Beijing, 100871, China

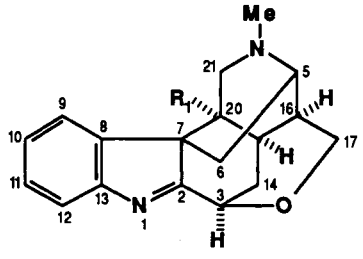
and X.T. LIANG*

Institute of Materia Medica, Chinese Academy of Medical Sciences, Beijing, 100050, China

ABSTRACT.—Two new indole alkaloids were isolated from *Gelsemium elegans*, and their structures were determined as (19*R*)-kouminol [**1**] and (19*S*)-kouminol [**2**] on the basis of ir, uv, ms, and ^{1}H-nmr and ^{13}C-nmr spectra, as well as chemical transformations.

Gelsemium elegans Benth. (Loganiaceae) grows in the southwestern part of China and is used as a folk medicine for relief of migraine and other pain (1). The present investigation uncovered two new indole alkaloids with structures elucidated as (19*R*)-kouminol [**1**] and (19*S*)-kouminol [**2**], along with two known compounds, koumine [**3**] (1) and gelsemine (2).

(19*R*)-Kouminol [**1**], has $[\alpha]^{18}D$ $-153.8°$ [$c=1.3$, MeOH-$CHCl_3$ (1:1)], $C_{20}H_{24}N_2O_2$ (324.1836, calcd 324.1838). Its uv spectrum showed the pseudoindole chromophore [λ max (EtOH) 225, 265 nm, λ min 243 nm] similar to that of koumine [**3**]. The ^{13}C-nmr spectrum of **1** gave 20 peaks, most of which closely resembled those given by koumine [**3**] (Table 1), indicative of an identical skeleton. The signals at δ_H 7.74 (1H, d), 7.68 (1H, d), 7.41 (1H, t), and 7.30 (1H, t) precluded any extra substituents on the benzene ring. The ir of **1** exhibited the absorption of hydroxyl (3400 cm^{-1}), which was best accommodated at the C-19 position to account for the δ_c 67.2 (d) and δ_H 3.0 (1H, m) as well as 0.93 (3H, d) signals.



1 $R_1 = -\overset{19}{C}HOH\overset{18}{C}H_3$ (*R*)
2 $R_1 = -CHOHCH_3$ (*S*)
3 $R_1 = -CH=CH_2$
4 $R_1 = -Ac$

(19*S*)-Kouminol [**2**], $[\alpha]^{18}D$ $-209.9°$ ($c=1.0$, EtOH), has a molecular formula $C_{20}H_{24}N_2O_2$ (324.1846, calcd 324.1838), identical with that of **1**. Its spectral data are as follows: ir 3400 cm^{-1} (OH); uv λ max (EtOH) 225, 260, λ min 235 nm; ^{1}H nmr (400 MHz) δ_H 0.77 (3H, d),

TABLE 1. ^{13}C-nmr Spectral Data of (19*R*)-Kouminol [**1**], (19*S*)-Kouminol [**2**], and Koumine [**3**].[a]

Carbon (DEPT)	Compound		
	1	**3**	**2**
C-2	187.0	185.7	187.3
C-3	70.8	71.0	70.7
C-5	56.8	56.9	56.9
C-6	28.0	28.6	30.3
C-7	58.0	58.0	57.1
C-8	143.5	143.7	143.6
C-9	123.6	123.1	123.5
C-10	126.3	126.0	125.8
C-11	129.1	128.2	128.3
C-12	122.1	121.1	121.6
C-13	155.0	154.9	154.6
C-14	24.5	25.3	24.2
C-15	39.6	38.9	39.7
C-16	28.9	33.1	27.3
C-17	61.1	61.4	61.3
C-18	16.2	115.9	19.1
C-19	67.2	137.2	68.1
C-20	47.8	45.3	47.5
C-21	56.8	57.8	54.7
N-Me	42.5	42.7	42.4

[a]Chemical shifts in ppm downfield from TMS.

2.78 (3H, s), 7.23 (1H, d), 7.30 (1H, t), 7.41 (1H, t), 7.63 (1H, d). Because of the similarity of the ^{13}C-nmr spectrum of **2** with that of **1**, compound **2** can be deduced as an epimer of **1**. By comparison of ^{1}H-nmr data with **1**, the C-18 methyl group of **2** exhibited an upfield shift of 0.16 ppm (0.77 vs. 0.93) as a result of the positive shielding by the aromatic ring. Moreover, the H-9 of **1** had a downfield shift of 0.50 ppm (7.73 vs. 7.23) by its closer proximity to the hydroxyl group. Given the absolute configuration of the koumine skeleton (3), the configurations at C-19 for **1** and **2** can be readily deduced as *R* and *S*, respectively, by careful examination of molecular models. The *R* configuration for **1** was in complete agreement with the result of Horeau's method (4).

Oxidation of **1** with CrO_3/pyridine afforded the compound **4** with molecular ion at *m/z* 322. As expected, the ir of **4** exhibited an absorption of carbonyl group at 1700 cm^{-1}, and the methyl group appeared at δ_H 1.79 as a singlet.

EXPERIMENTAL

GENERAL METHODS.—Optical rotations were measured on a Perkin-Elmer model 241 polarimeter; the ir spectra on Nicolet 5-MX as a KBr pellet; mass spectra on ZAB-HS; ^{1}H- and ^{13}C-nmr spectra were recorded on Varian XL-400 spectrometer in $CDCl_3$ solution. A polyvinyl-sulfonic-ion-exchange resin, H^+-form (linking 1 × 1.1, from Chemical Factory of Nankai University), was used for the isolation of the total alkaloids. Si gel H for chromatography and Si gel G for tlc were from Qingdao Haiyang Chemical Factory. Al_2O_3 for chromatography (180–200 mesh) was obtained from Shanghai Chemical Reagents Factory.

PLANT MATERIAL.—The plant material was collected from Nanning, Guangxi Province, China, and the sample was identified by professor Z.Y. Zhu of Institute of Materia Medica, Chinese Academy of Medical Sciences, where a voucher specimen was deposited.

EXTRACTION OF TOTAL ALKALOIDS.—Powdered roots of *G. elegans* (3.9 kg) were percolated with about 90 liters of 0.05 N HCl, and the percolate was run through a column of 3.4 kg wet resin. After exchange, the resin was washed repeatedly on a suction filter with deionized H_2O. It was then spread out and air-dried overnight. The resin was moistened with 10% NH_3 until it contained 83% H_2O and continuously extracted with Et_2O in a specially designed extractor under reflux for 8 h. Crude alkaloids (55 g) from the Et_2O extracts were collected by evaporation.

ISOLATION AND IDENTIFICATION OF THE ALKALOIDS.—The crude mixture of alkaloids (6 g) was chromatographed on a column of Si gel (200 g) using a mixture of $CHCl_3$-MeOH (100:5) as the eluent and collecting 150-ml fractions. Fractions 8 and 9 were combined (1.65 g) and rechromatographed on a basic Si gel column (170 g, containing NaOH 0.5%) using CH_2Cl_2-MeOH (100:2) and collecting 100-ml fractions. Fractions 31 and 32 (800 mg) contained koumine [**3**]; fractions 34–36 (250 mg) contained gelsemine; fraction 52 (48 mg) gave (19*R*)-kouminol [**1**]. Fractions 81–89 (200 mg) were rechromatographed on preparative Si gel plates with CH_2Cl_2-MeOH (10:1.5) to give (19*S*)-kouminol [**2**] (60 mg).

(19*R*)-KOUMINOL [**1**].—Compound **1** (48 mg): amorphous; eims *m/z* $[M]^+$ 324 (100 %), 306 (11.5), 279 (69), 235 (16), 206 (34), 70 (97); ^{1}H-nmr (400 MHz) 0.93 (3H, d, J = 6.3 Hz), 1.59 (1H, d, J = 14.4 Hz), 3.01 (1H, m), 3.14 (1H, s), 3.61 (1H, d, J = 11.7 Hz), 4.22 (1H, q, J_1 = 4.8, J_2 = 11.7 Hz), 5.00 (1H, br s), 7.31 (1H, t, J = 7.7 Hz), 7.42 (1H, t, J = 7.7 Hz), 7.67 (1H, d, J = 7.7 Hz), 7.73 (1H, d, J = 7.7 Hz) ppm.

(19*S*)-KOUMINOL [**2**].—Compound **2** (60 mg): amorphous; eims *m/z* $[M]^+$ 324 (100%), 306 (6.5), 295 (10), 279 (69), 236 (21), 206 (25), 70 (90); ^{1}H-nmr (400 MHz) 0.77 (3H, d, J = 6.9 Hz), 2.26 (1H, d, J = 13.4 Hz), 2.78 (3H, s), 3.62 (1H, d, J = 11.2 Hz), 4.26 (1H, q, J_1 = 4.3, J_2 = 11.2 Hz), 5.05 (1H, br s), 7.23 (1H, d, J = 7.7 Hz), 7.30 (1H, t, J = 7.7 Hz), 7.41 (1H, t, J = 7.7 Hz), 7.67 (1H, d, J = 7.7 Hz) ppm.

KOUMINE [**3**].—Compound **3** (610 mg): colorless prisms from Me_2CO; mp 170°; $[\alpha]^{18}D$ −254° (c = 1.0, EtOH); ms *m/z* $[M]^+$ 306 (100%). The ir, ^{1}H-nmr and ^{13}C-nmr spectra were identical with those of an authentic sample.

GELSEMINE.—Gelsemine (160 mg): colorless needles from Me_2CO; mp 177–179°; $[\alpha]^{18}D$ +10° (c = 1.1, $CHCl_3$); $C_{20}H_{22}N_2O_2$ (322.1681, calcd 322.1686); eims *m/z* $[M]^+$ 322 (40), 279 (48), 251 (24), 108 (100). The ir, ^{1}H- and ^{13}C-nmr spectra were identical with those of an authentic sample (1,2).

DETERMINATION OF THE CONFIGURATION AT C-19.—(19*R*)-Kouminol [**1**] (20 mg) was

added to a solution of anhydrous pyridine (1 ml) containing 2-phenylbutyric anhydride (100 mg), and the resulting mixture was maintained at 0° for 24 h. A drop of H_2O was added, and the solution was allowed to stand for 0.5 h. The rotation was −0.6796°. Addition of triethylamine (0.1 ml) to the latter solution gave a value of −0.822°. The configuration of the C-19 is *R* because the increment in rotation readings is definitively negative (4). This solution was treated with 0.1 N HCl and extracted with C_6H_6 (three 10-ml portions). The residue after evaporating the solvent gave an optical rotation of $[\alpha]^{18}D$ +0.74° (c = 9.6, C_6H_6), which provided support for the *R* configuration of C-19.

OXIDATION OF (19*R*)-KOUMINOL [**1**].—(19*R*)-Kouminol [**1**] (6 mg) in anhydrous pyridine (0.5 ml) was treated with CrO_3/pyridine complex (30 mg), and the reaction mixture was kept at room temperature with stirring for 2 h. The mixture was filtered through an Al_2O_3 column (1 g) and evaporated in vacuo to give 3 mg of **4**: ir 1700, 1610, 1590, 1425, 1400, 1080, 780 cm^{-1}; ^1H nmr 1.59 (1H, d, J = 14.4 Hz), 1.79 (3H, s), 2.68 (3H, s), 3.60 (1H, d, J = 11.6 Hz), 4.23 (1H, q, J = 4.8, J = 11.6 Hz), 5.01 (1H, br s), 7.22 (1H, t, J = 7.7 Hz), 7.35 (1H, t, J = 7.7 Hz), 7.48 (1H, d, J = 7.7 Hz), 7.65 (1H, d, J = 7.7 Hz) ppm; ms *m/z* $[M]^+$ 322 (28), 279 (75), 249 (36), 206 (20), 84 (100).

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