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Y. Venkateswarlu, M. Venkata Rami Reddy, and J. Venkateswara Rao

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BIS-1-OXAQUINOLIZIDINES FROM THE SPONGE *HALICLONA EXIGUA*¹

Y. VENKATESWARLU,* M. VENKATA RAMI REDDY,

Organic Chemistry Division-1,

and J. VENKATESWARA RAO

Toxicology Unit, Indian Institute of Chemical Technology, Hyderabad 500 007, India

ABSTRACT.—A new bis-1-oxaquinolizidine alkaloid, 3 α -methylaraguspongine C [**1**], and four known bis-1-oxaquinolizidines, araguspongines C [**2**], D [**3**], and E [**4**], and xestospongine D [**5**], have been isolated and characterized by spectroscopic methods from the sponge *Haliclona exigua*.

In continuation of our studies on marine organisms for biologically active secondary metabolites, we have examined the sponge *Haliclona exigua* (Kirkpatrick), collected at Chidiatapu, Andaman Islands, during March 1992. A literature survey revealed that the genus *Haliclona* produces complex macrocyclic alkaloids, including the β -carboline-derived oncolytic alkaloids manzamines A, B, and C (1,2), and the pentacyclic alkaloids papuamine (3) and haliclonadamine (4), which have antifungal and antimicrobial properties. The ¹H- and ¹³C-nmr spectra of a defatted crude extract revealed that *Haliclona exigua* contained bis-1-oxaquinolizidine alkaloids. The presence of these vasodilatory alkaloids in *Xestospongia* sp. has been reported in previous publications (5–8).

Freeze-dried specimens (400 g) were extracted successively with *n*-hexane, EtOAc, and MeOH at room temperature. The crude EtOAc extract showed moderate antibacterial activity at 200 μ g/disk on *Bacillus subtilis* (2 mm zone of inhibition), *Pseudomonas fluorescens* (5 mm), *Escherichia coli* (7 mm), and *Klebsiella pneumoniae* (7 mm). This extract was subjected to cc on Sephadex LH-20 (CH₂Cl₂-MeOH, 1:1) and Si gel to afford four known bis-1-oxaquinolizidine alkaloids, araguspongine C [**2**] (7),

araguspongine D [**3**], xestospongine A (5), araguspongine E [**4**] (7), xestospongine D [**5**] (5), and a new bis-1-oxaquinolizidine, 3 α -methylaraguspongine C [**1**]. Compounds **2–5** were characterized by comparing physico-spectral data with reported values (5,7).

Compound **1** (5 mg) was obtained as an amorphous solid [α]_D +1.2° (*c*=0.15, CHCl₃) and analyzed for C₂₉H₅₂N₂O₄. Its ir spectrum showed a peak at 3498 cm⁻¹ indicating the presence of a hydroxyl group and no Bohlmann bands, suggesting the absence of a *trans*-quinolizidine system (9). The ¹H- and ¹³C-nmr spectra of compound **1** showed close similarities with those of araguspongine C [**2**]. Particularly diagnostic were the H-10 and H-10' signals at δ 4.03 (1H, s) and 4.06 (1H, s), due to effects of the lone-pair electrons of the tertiary nitrogens (10,11). Further, the ¹H-nmr spectrum of **1** showed the presence of a secondary CH₃ group at δ 0.68 (3H, d, *J*=6.5 Hz in CDCl₃) (δ 0.51, d, *J*=6.5 Hz in C₆D₆). The position of this secondary CH₃ group was deduced by direct comparison with xestospongine B [**6**] in which the Me-3 group resonated at δ 0.51 in C₆D₆ (5). The ¹³C-nmr chemical shifts of the bottom half of the molecule of compound **1** were almost identical to those of araguspongine C [**2**] and Me-3, C-2, and C-4 resonated at δ 14.62, 82.6, and 60.34, respectively, comparable with analogous data for xestospongine B [**6**] (Table 1) (5).

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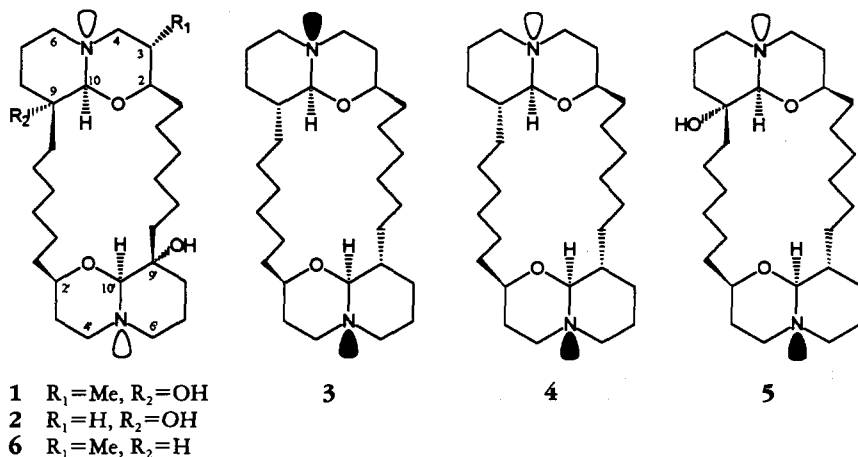


TABLE 1. Selected ¹³C-Nmr Chemical Shifts in δ (ppm) of Compounds 1, 2, and 6 (CDCl₃).

Carbon	Compound		
	1	2	6
C-2	82.60	76.27	82.22
C-2'	76.36	76.27	76.28
C-4	60.34	52.40	61.10
C-4'	52.53	52.40	52.74
C-6	45.17 ^a	44.12	46.56
C-6'	44.20 ^a	44.12	44.66
C-9	70.75	70.58	40.83
C-9'	70.75	70.58	70.64
C-10	90.75 ^b	90.14	87.27
C-10'	90.20 ^b	90.14	91.08
C ₃ -Me	14.62	—	14.62

^{a,b}Values may be interchanged.

From the foregoing spectral data, the relative stereochemistry of compound 1 was assigned as 3 α -methylaraguspongine C. To our knowledge this is the first instance of the isolation of bis-1-oxaquinolizidines from *Haliclona* sp.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Optical rotations were measured with a Jasco Dip-370 polarimeter. ¹H-Nmr (200 MHz) and ¹³C-nmr (50 MHz) spectra were recorded on a Varian Gemini 200 MHz spectrometer, using TMS as internal standard. Elemental analysis was carried out on a Perkin-Elmer 240C instrument. Chemical shifts were reported in δ (ppm) values and coupling constants (*J*) in Hz. Ir spectra were recorded on an Ft-ir Nicolet-740 spectrophotometer. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer.

COLLECTION, EXTRACTION, AND ISOLATION.

The sponge *Haliclona exigua* was collected at Chidiatapu, Andaman and Nicobar Islands, during March 1992. A voucher specimen (IIC-052) is on deposit at NIO, Goa, India. The freshly collected sponge (400 g dry wt) was soaked in MeOH until workup. After removal of the initial MeOH, the sponge was freeze-dried and extracted successively with hexane, EtOAc, and MeOH. The crude EtOAc extract was fractionated on Sephadex LH-20 using CH₂Cl₂-MeOH (1:1) as eluent. The fractions thus obtained were evaluated for antibacterial activity; the active fractions were subjected to Si gel chromatography eluting with hexane, hexane/C₆H₆, C₆H₆, and C₆H₆/Me₂CO gradients to afford the isolation of araguspongine C (2, 900 mg), araguspongine D (3, 11 mg), araguspongine E (4, 14 mg), xestospongine D (5, 95 mg), and 3 α -methylaraguspongine C (1, 5 mg). Compound 1 was obtained as an amorphous solid by repeated Si gel cc eluting with Me₂CO-C₆H₆ (2:3). *Anal.*, found C 70.61%, H 10.70%, N 5.72%; required for C₂₉H₂₂N₂O₄, C 70.69%, H 10.64%, N 5.69%. *Ir* ν max (KBr) 3498, 2925, 2847, 1466, and 1177 cm⁻¹; ¹H nmr (200 MHz, CDCl₃) δ 4.06 (1H, s), 4.03 (1H, s), 3.56 (1H, br t, *J*=10.6 Hz, H-2'), 2.95–3.20 (5H, m, H-6' α , H-6 α , H-2, H-4' α , H-4' β), 2.87 (1H, br dd, *J*=13.0 and 4.5 Hz, H-4 β), 2.64 (1H, br t, *J*=13 Hz, H-4 α), 2.36 (2H, br t, *J*=10 Hz, H-6 β , H-6' β), 0.68 (3H, d, *J*=6.5 Hz, Me-3 α); ¹³C nmr (50 MHz, CDCl₃) δ 90.32, 90.20, 82.66, 76.37, 70.75 (2C), 60.36 52.53, 45.17, 44.20, 38.69, 38.5, 36.25, 33.0, 32.29 (2C), 31.58, 29.83, 29.72, 29.58, 28.27, 28.16, 26.03, 25.83, 24.99 (2C), 22.68, 20.95, 14.62; *eims* *m/z* 492 (M⁺, 31), 474 (25), and 112 (100).

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