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CHEMISTRY OF SPONGES, VIII.[1] ANOMOIAN A, A BROMOTYROSINE DERIVATIVE FROM *ANOMOIANTHELLA POPEAE*

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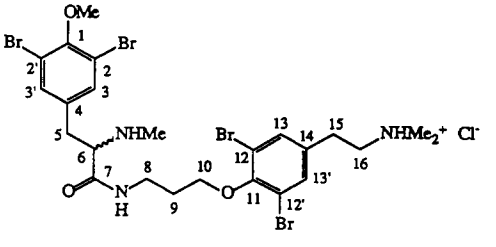
ABSTRACT.—Anomoian A [**1**], a new bromotyrosine-derived metabolite, has been isolated from the Verongid sponge *Anomoianthella popeae*, belonging to a new genus of the family Ianthellidae.

Metabolites derived from brominated or chlorinated tyrosine are distinct markers for marine sponges belonging to the order Verongida (1). Examples of these unusual secondary metabolites are aerothionin (2–4), fistularin 3 (5), psammaplysin A (6,7), and bastadin 1 (8). We have recently isolated aerothionin, homoaerothionin, and the new metabolites ceratinin A and ceratinin B from the verongid sponge *Pseudoceratina durisimma* (9). In a continuation of our investigation of sponges of the order Verongida, we now report the isolation of a new metabolite from *Anomoianthella popeae* Bergquist, which belongs to a new genus established within the family Ianthellidae (10).

Interest in *A. popeae* was stimulated by the potent in vitro antimicrobial and antifungal activity shown by the MeOH extract. The crude extract was separated from inactive material on Sephadex LH-20 followed by Si gel to give the new compound anomoian A [**1**] as a colorless, amorphous solid, $[\alpha]_D$ +5.1°, that exhibited strong antimicrobial activity.

Although anomoian A [**1**] showed a molecular ion cluster centered at $m/z = 730$, the peaks were too small (<2%) to obtain a high resolution ms. The molecular formula $C_{24}H_{31}N_3Br_4O_3 \cdot HCl$ for **1** was therefore obtained from the low resolution ms and the ^{13}C-nmr spectrum (24 carbons). The ir spectrum of **1** had bands characteristic of amine (3350 cm^{-1}) and amide (1645 cm^{-1}) groups, while the uv spectrum showed absorptions characteristic of a substituted aryl ring [λ max 245 (ε 12,300), 276 (9400), and 285 (7800) nm]. The ^1H-nmr spectrum of **1** contained signals at δ 7.46 (br s, 2H) and 7.41 (br s, 2H) that were assigned to two 1,2,4,6-tetrasubstituted aryl rings. A COSY spectrum showed coupling of the δ 7.41 signal to signals at δ 3.07 (br dd, 1H, $J = 13$, 6 Hz) and 2.95 (br dd, 1H, $J = 13$, 9 Hz). Mutual coupling between the signals at δ 3.07 and 2.95 and coupling to an additional signal at δ 3.70 (dd, 1H, $J = 9$, 6 Hz) indicated the presence of an Ar-CH_2-CHXR system. The ^1H-nmr spectrum also contained



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[1]For Part VII, see Kernan *et al.* (9).

signals assigned to an Ar-CH_2CH_2-X system. Thus, the signal due to the benzylic protons [δ 3.01 (m, 2H)] was correlated with a signal at δ 3.20 (m, 2H), and it exhibited a long range correlation to the signal assigned to the aromatic protons of the other 1,2,4,6-tetrasubstituted aryl ring [δ 7.46 (br s, 2H)]. A D_2O exchangeable proton [δ 7.52 (t, 1H, $J=6$ Hz)], assigned to an amide NH proton, had a correlation in the COSY spectrum to a signal at δ 3.53 (m, 2H). The latter signal was also coupled to signals at δ 1.90 (m, 1H) and 1.85 (m, 1H) which in turn showed further coupling to a signal at δ 3.99 (m, 2H). These data required the presence of an RNH-CH_2-CH_2-CH_2-O-system.

A two-dimensional ^{13}C-^1H-nmr chemical shift correlation experiment (11) enabled the complete assignment of all protonated carbons (Table 1). Furthermore, the results of a long-range ^{13}C-, ^1H-nmr correlation experiment (COLOC) (12) established the structure **1** which was confirmed by comparison of the ^{13}C-nmr spectrum of **1** with that of psammaplysin A [**2**] (Table 2). Psammaplysin A [**2**] and **1** have identical partial structures between C-8 and C-16, and the ^{13}C-nmr spectra of these carbons show excellent correlation. Anomoian A was obtained both as a hydrochloride salt of a tertiary amine and as the corresponding free base. As with aplysamine 2 [**3**] (13), treatment of **1** in CD_3OD with

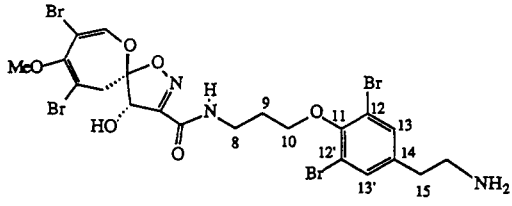

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TABLE 1. ^{13}C-^1H-nmr Chemical Shift Assignments and Long Range Correlations for Anomoian A [**1**] ($CDCl_3$).

Atom	δ ^{13}C	δ ^1H (mult., J)	Long range ^{13}C-^1H correlation
1	152.6 (C)	—	7.41 (H-3, H-3′)
2,2′	118.6 (2C)	—	7.41 (H-3, H-3′)
3,3′	134.2 (2CH)	7.41 (br s)	—
4	135.7 (C)	—	3.07 (H-5)
5	37.2 (CH_2)	3.07 (dd, J = 13, 6 Hz)	—
		2.95 (dd, J = 13, 9 Hz)	—
6	63.9 (CH)	3.70 (dd, J = 9, 6 Hz)	2.51 (NMe)
7	169.4 (C)	—	—
8	36.7 (CH_2)	3.53 (ddd, J = 14, 8, 6 Hz)	—
		3.40 (dt, J = 14, 7 Hz)	—
9	30.0 (CH_2)	1.90 (m)	3.53, 3.40 (H-8)
10	71.1 CH_2	3.91 (m)	—
		3.89 (m)	—
11	153.9 (C)	—	7.46 (H-13), 3.91, 3.89 (H-10)
12,12′	118.9 (2C)	—	7.46 (H-13, 13′)
13,13′	133.6 (2CH)	7.46 (br s)	—
14	134.7 (C)	—	—
15	30.2 (CH_2)	3.01 (m)	7.46 (H-13, 13′)
16	58.9 (CH_2)	3.20 (m)	—
-NMe	33.1 (Me)	2.52 (s, 3H)	—
-NMe_2	43.4 (2Me)	2.82 (s, 6H)	—
-OMe	60.9 (Me)	3.77 (s, 3H)	—

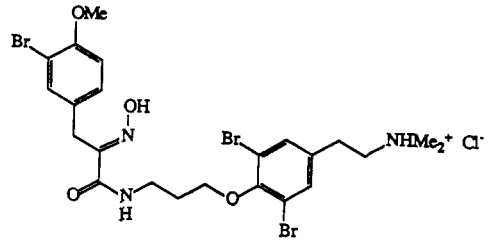

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TABLE 2. Comparison of ^{13}C-nmr Chemical Shifts of Anomoian A [1] and Psammaplysin A [2] ($CDCl_3$).

Carbon	Compound	
	1	2[a]
C-8	36.7	36.7
C-9	30.0	28.8
C-10	71.1	70.5
C-11	153.9	151.5
C-12, -12′	118.9	119.4
C-13, -13′	133.6	132.6
C-14	134.7	139.5
C-15	30.2	31.5
C-16	58.9	40.1

[a]Psammaplysin A has been renumbered for nmr comparisons.

NaOH (aqueous) resulted in the formation of the free base. The *N,N*-dimethyl resonance in the free base was shifted upfield (δ −0.58) as was the signal of the α-methylene protons (δ −0.80); the *N*-methyl resonance shifted only slightly (δ −0.15). Treatment of the free base with HCl (aqueous) reversed the chemical shift differences and regenerated the natural product. Thus anomoian A is the hydrochloride salt of a tertiary amine and was assigned the structure **1**.

Anomoian A [1] inhibited the growth of *Staphylococcus aureus* at 10 μg/disk, *Bacillus subtilis* at 5 μg/disk, and *Candida albicans* at 25 μg/disk in in vitro antimicrobial assays.

Anomoian A bears some relationship to aplysamine 2 [3], a cytotoxic metabolite of the Australian verongid sponge, *Aplysina* sp. (13).

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—These were as in Karuso *et al.* (14) except as follows. Ir spectra were obtained either on a Shimadzu IR-27G spectrometer or a Bio-Rad FTir spectrometer. All solvents were distilled prior to use. Hplc was carried out with a Shimadzu LC-6A solvent delivery system equipped with a Waters R401 r.i. detector, using a Merck LiChrosorb Si gel column (25 × 1 cm). 2D nmr experiments were performed on a Bruker 400 MHz nmr spectrometer following literature procedures (11,12).

ISOLATION OF ANOMOIAN A.—Freeze-dried *A. popeae* (AMSA-holotype, Reg. No. Z3869, Darwin, Australia) (236 g dry wt), collected from the Great Barrier Reef, Australia in 1988, was extracted with MeOH, and the purple extract was filtered and concentrated in vacuo to yield a purple solid (2.43 g). A portion (810 mg) of the extract was purified by cc on Sephadex LH-20 [CH_2Cl_2-MeOH (1:1)] and Si gel (10–25% MeOH in CH_2Cl_2) to obtain anomoian A [1] (80.5 mg, 0.10%) and its free base (15.0 mg, 0.02%).

ANOMOIAN A.—The compound was obtained as a white powder: mp 200° (dec); $[\alpha]_D$ +5.1° (MeOH, c = 0.013); uv (MeOH) λ max 283 (ε 7800), 276 (ε 9400), 245 (ε 12,300); ir ν ($CHCl_3$) 3350 (br, NH), 1645 (-NHCO-), 1535, 1515, 1470, 1450, 1240, 980 cm^{-1}; ^{1}H and ^{13}C nmr see Table 1; deims (rel. int.) *m/z* $[M+H]^+$ 726/728/730/732/734 (1.7%), 448/450/452 (25:50:25), 403/405/407 (10:15:10), 320/322/324 (50:100:50).

ANOMOIAN A FREE BASE.—The compound was obtained as an oil, and was prepared from a solution of anomoian A (1 mg) in CD_3OD (0.5 ml) by the addition of NaOH (aqueous, 3 M, 10 μl). Anomoian A, identical by ^{1}H nmr to the natural product, was regenerated from the free base after the addition of HCl (aqueous, 3 M, 20 μl). ^{1}H nmr (CD_3OD + aqueous NaOH) δ 7.48 (s, H-13, -13′), 7.44 (s, H-3, -3′), 3.92 (m, H-10), 3.73 (s, OMe), 3.48 (dd, J = 9, 5 Hz, H-6), 3.34

(m, H-8), 2.89 (dd, J = 13, 5 Hz, H-5), 2.80 (dd, J = 13, 9 Hz, H-5), 2.72 (t, J = 7 Hz, H-16), 2.50 (t, J = 7 Hz, H-15), 2.31 (s, NMe), 2.28 (s, NMe_2), 1.84 (m, H-9); ^{1}H nmr ($CDCl_3$) δ 7.51 (t, J = 7 Hz, 2 NH), 7.34 (s, H-3, -3′, -13, -13′), 3.97 (m, H-10), 3.83 (s, OMe), 3.58 (m, H-8), 3.16 (dd, J = 8, 4 Hz, H-6), 3.03 (dd, J = 13, 4 Hz, H-5), 2.72 (dd, J = 13, 8 Hz, H-5), 2.72 (t, J = 7 Hz, H-16), 2.57 (t, J = 7 Hz, H-15), 2.34 (s, NMe_2), 2.33 (s, NMe), 2.01 (m, H-9); ^{13}C nmr ($CDCl_3$) δ 172.7 (s, C-7), 152.9 (s, C-1 or C-11), 151.1 (s, C-11 or C-1), 138.7 (s, C-4 or C-14), 136.5 (s, C-14 or C-4), 133.2 (d, C-3, -3′ or C-13, -13′), 132.8 (d, C-13, -13′ or C-3, -3′), 118.2 (s, C-2, -2′ or C-12, -12′), 71.0 (t, C-10), 65.6 (d, C-6), 60.5 (q, OMe), 60.4 (t, C-16), 45.0 (q, NMe_2), 37.8 (t), 36.3 (t), 35.3 (q, NMe), 32.5 (t), 29.6 (t).

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