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TWO MORE BASTADINS, 16 AND 17, FROM AN INDONESIAN SPONGE *IANTHELLA BASTA*

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ABSTRACT.—New bastadins 16 [1] and 17 [2] and the previously reported bastadins 3 [3], 5 [4], 6 [5], 8 [6], 9 [7], and 12 [8] were isolated from the sponge *Iantbella basta* collected in Indonesia.

The bastadins are a series of predominantly macrocyclic sponge metabolites, which are biogenetically derivable from four tyrosines by oxidative phenolic coupling of two tyramine-tyrosine units (1–8). A recent collection of marine invertebrates in Indonesia provided a specimen of *Iantbella basta* Pallas from which were isolated several known and two new bastadins.

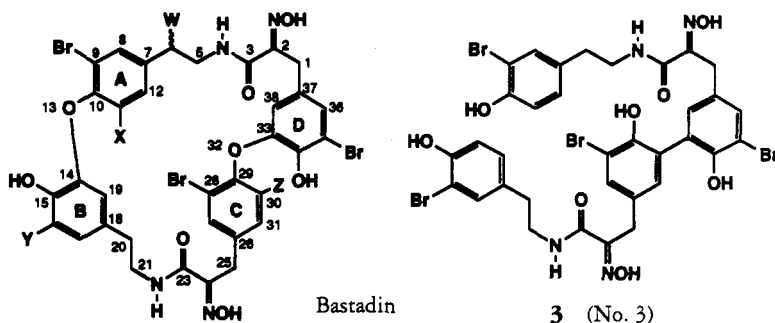
The *I. basta* extract was partitioned between hexanes-MeOH-H₂O (10:9:1) and the lower layer residue was subjected to reversed-phase followed by normal-phase flash chromatography to yield a fraction whose ¹H-nmr spectrum revealed structural features of bastadins. Purification of this fraction by reversed-phase hplc furnished the new bastadins 16 [1] and 17 [2] and known bastadins 3 [3] (2), 5 [4] (2), 6 [5] (2), 8 [6] (3,4), 9 [7] (3), and 12 (4). [Bastadin 9 of Miao *et al.* (4) and bastadin 12 of Butler *et al.* (5) have been renamed bastadin 12 and bastadin 13, respectively. See Carney *et al.* (6)].

A molecular formula of C₃₄H₂₇Br₅N₄O₈ for **1** was established by hrfabms, indicating that **1** was isomeric with bastadins 5 [4] and 15 [9] (7), but a preliminary inspection of its ¹H-nmr spectrum suggested that **1** was composed of a trisubstituted and three tetrasubstituted aromatic rings, two symmetric and one asymmetric. H-C and C-C connectivities were established by HMQC and HMBC nmr experiments (Table 1). The protons (δ 7.59) of symmetrically tetrasubstituted ring A showed H-C correlations to carbon signals at δ 146.6 (C-10), 117.7 (C-9 and C-11), and 33.9 (C-6). Correlations

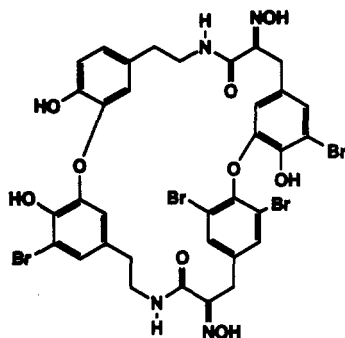
of the protons attached to C-6 (δ 2.71) to carbon signals at δ 139.8 (C-7) and 40.4 (C-5) established the dibromotyramine structure of N-4 to O-13.

Two benzylic protons (δ 3.55, H₂-1) were coupled in the HMBC experiment to α-oximino amide carbons (C-2, δ 151.4 and C-3, 163.0) and to ring D aromatic carbon signals at δ 128.2 (C-37), 127.0 (C-36), and 112.8 (C-38). A doublet at δ 7.07 (*J*=1.6 Hz, H-36), meta-coupled to a doublet at δ 6.15 (H-38), showed an H-C correlation to C-38, as well as to carbon signals at δ 109.8 (C-35) and 142.0 (C-34). H-38 showed a correlation to C-33 (δ 144.8), C-34, C-36, and C-37, thus establishing the structure of the segment C-3 to C-33. HMBC correlations of H₂-5 to C-3 and of an exchangeable triplet at δ 8.06 to C-3 and C-5 linked the preceding two moieties.

The benzylic protons (δ 3.68, H₂-25) adjacent to the other oxime showed H-C correlations to two α-oximino amide carbon signals (δ 150.7, C-24; 163.3, C-23), as well as to carbon signals at δ 137.8 (C-26) and 133.7 (C-27 and C-31) of symmetrically tetrasubstituted ring C. H-C correlations of a two-proton singlet at δ 7.63 (H-27, H-31) to C-31 and C-27 as well as carbon signals at δ 117.2 (C-28 and C-30), and 146.1 (C-29) confirmed part structure C-23 to O-32. H-C correlations of an exchangeable triplet at δ 7.94 (H-22) to C-23 and to a carbon signal at δ 38.8 (C-21) connected C-23 to N-22. A two-proton triplet at δ 2.67 (H₂-20) also showed a correlation to C-21 and to aromatic carbon signals at δ 129.5 (C-18), 122.9 (C-17), and 112.5 (C-19).



- | | | |
|----|-----------------------|----|
| 1 | W=H, X=Br, Y=H, Z=Br | 16 |
| 2 | W=OH, X=H, Y=H, Z=Br | 17 |
| 4 | W=H, X=H, Y=Br, Z=Br | 5 |
| 5 | W=H, X=Br, Y=Br, Z=Br | 6 |
| 6 | W=OH, X=H, Y=Br, Z=Br | 8 |
| 7 | W=H, X=H, Y=H, Z=Br | 9 |
| 8 | W=OH, X=Br, Y=Br, Z=H | 12 |
| 9 | W=H, X=Br, Y=Br, Z=H | 15 |
| 10 | W=OH, X=H, Y=Br, Z=H | 10 |



A one-proton doublet at δ 6.81 ($J=8.2$ Hz, H-16), ortho-coupled to a proton at δ 6.67 ($J=8.2$ and 1.8 Hz, H-17), which was in turn meta-coupled to a proton at δ 6.17 ($J=1.8$ Hz, H-19), showed correlations to C-14 (δ 144.1), C-15 (144.3), and C-18. HMBC cross-peaks from H-19 to C-17 and C-14 secured the structure of the final segment N-22 to C-14.

Many of the known bastadins (2–5) share a common eastern moiety, N-4 to C-23. It gives rise to a characteristic ion fragment cluster in their *ei* mass spectra centered at m/z 500 and corresponding to a molecular formula of $C_{16}H_9Br_3N_2O_2$. An identical fragment ion was observed in the hreims spectrum of **1**, thus confirming the sequence N-4 to C-23.

In our previous work with bastadin

14 (6), we were unable to detect couplings of the phenolic protons to aromatic ring carbons in the HMBC experiment. Consequently, the compound was transformed to its tetramethyl ether, which allowed assignment of all proton and carbon nmr signals and hence unambiguous placement of the phenyl ether linkages between rings A/B and C/D. Fortunately, both phenolic protons in **1** showed 3-bond HMBC correlations to the appropriate aromatic carbon signals: OH-15 to C-14 and C-16, and OH-34 to C-33 and C-35. Because the assignments of the carbon signals of rings B and D were unambiguously established, the ether linkages between rings A/B and rings C/D must be from C-10 to C-14 and C-29 to C-33. The carbon chemical shifts

TABLE 1. Nmr Data for **1** (DMSO- d_6) and **2** (DMSO- d_6).

Position	Compound					
	1			2		
	^{13}C	^1H (J , Hz)	HMBC	^{13}C	^1H (J , Hz)	HMBC
1	27.4	3.55, 2H, s	36, 38	27.4	3.52, 2H, s	36, 38
2	151.4	11.65, 1H, s	1	151.0	11.77, 1H, s	1, NOH-2
3	163.0		1, 4, 5	162.9		1, 4, 5
4		8.06, 1H, t (6.0)			7.77, 1H, t (6.3)	
5	40.4	3.28, 2H, m	4, 6	47.7	2.92, 1H, m	OH-6
6					3.38, 1H, m	
OH-6	33.9	2.71, 2H, t (6.6)	8, 12	70.5	4.58, 1H, m	OH-6, 8, 12
7					5.53, 1H, d (4.4)	
7	139.8		6	139.3		OH-6, 11
8	133.2	7.59, 1H, s	6, 12	129.8	7.62, 1H, d (1.9)	12
9	117.7		8	111.4		8, 11
10	146.6		8, 12	153.1		8, 11, 12
11	117.7		12	117.4	6.73, 1H, d (8.5)	
12	133.2	7.59, 1H, s	6, 8	126.2	7.13, 1H, dd (8.5, 1.9)	8
14	144.1		OH-15,16,19	142.5		OH-15,16,19
15	144.3		17, 19	146.9		17, 19
OH-15		9.25, 1H, s			9.36, 1H, s	
16	116.6	6.81, 1H, d (8.2)	OH-15, 17	116.5	6.83, 1H, d (8.2)	OH-15
17	122.9	6.67, 1H, dd (8.2, 1.8)	16, 19, 20	126.1	6.81, 1H, dd (8.2, 1.9)	19, 20
18	129.5		16, 20	130.6		16, 19, 20
19	112.5	6.17, 1H, d (1.8)	17, 20	121.1	6.76, 1H, d (1.9)	17, 20
20	33.3	2.67, 2H, t (6.6)	17, 19	34.1	2.65, 2H, t (6.3)	17, 19
21	38.8	3.29, 2H, m	20, 22	39.2	3.40, 2H, m	22
22		7.94, 1H, t (6.0)			7.95, 1H, t (6.3)	
23	163.3		22, 25	163.0		22, 25
24	150.7	11.86, 1H, s	25	150.4	11.91, 1H, s	NOH-24, 25
25	28.7	3.68, 2H, s	27, 31	28.7	3.51, 1H, d (12.9)	27, 31
					3.56, 1H, d (12.9)	
26	137.8		25	137.6		25
27	133.7	7.63, 1H, s	31	133.6	7.58, 1H, s	25, 31
28	117.2		27	117.2		27
29	146.1		27, 31	146.0		27, 31
30	117.2		31	117.2		31
31	133.7	7.63, 1H, s	25, 27	133.6	7.58, 1H, s	25, 27
33	144.8		OH-34, 38	144.6		38
34	142.0		36, 38	141.8		36, 38
OH-34		9.99, 1H, s			9.98, 1H, s	
35	109.8		OH-34, 36	109.7		36
36	127.0	7.07, 1H, d (1.6)	1, 38	126.8	7.03, 1H, d (1.9)	1, 38
37	128.2		1, 38	128.0		1, 38
38	112.8	6.15, 1H, d (1.6)	1, 36	113.1	6.24, 1H, d (1.9)	1, 36

of C-1 (27.4) and C-25 (28.7) indicated that both oximes had *E* geometry (9), and therefore the structure of bastadin 16 is **1**.

The presence of a one-proton multiplet at δ 4.58 (H-6) in the ^1H -nmr spectrum of **2** suggested that, by analogy with bastadins **8** [6], **10** [10], and **12** [8], it contained a benzylic alcohol. A molecular formula of $\text{C}_{34}\text{H}_{28}\text{Br}_4\text{N}_4\text{O}_9$, determined by hrfabms, supported this and indicated that **2** was isomeric with bastadin **10** [10]. The ^1H -nmr spectrum indicated the presence of two trisubstituted and two tetrasubstituted aromatic rings, one symmetric and one asymmet-

ric. Extensive HMQC and HMBC data (Table 1) revealed that **2** shared the entire sequence O-13 to C-23 with bastadin **8** [6], leaving trisubstituted ring B to be elucidated. A one-proton doublet at δ 6.83 ($J=8.2$ Hz, H-16), ortho-coupled to a proton at δ 6.81 ($J=8.2$ and 1.9 Hz, H-17), which was in turn meta-coupled to a proton at δ 6.76 ($J=1.9$ Hz, H-19), showed H-C correlations to C-14 (δ 142.5), C-15 (δ 146.9), and C-18 (δ 130.6). Correlations of H-19 (δ 6.76) to carbon signals at δ 126.1 (C-17), 142.5 (C-14), 130.6 (C-18), 146.9 (C-15) and 34.1 (C-20) established the structure of

the remaining portion, and HMBC cross-peaks from NH-22 to C-21 and C-23 completed the macrocycle.

The characteristic ion fragment at m/z 500 for the eastern part of the molecule was not observed in the ei mass spectrum of **2**, but an ion cluster at m/z 418/420/422 (1:2:1) was prominent. The isotope pattern suggested that the fragment contained two bromines instead of the expected three, and hreims of the ion at m/z 418 corresponded to a formula of $C_{16}H_8Br_2N_2O_2$, indicating 13 double bond equivalents and a loss of HBr from the expected fragment. The ei mass spectrum of bastadin 13 [**11**], which has the eastern hemisphere in common with **2**, gave rise to the same fragment and composition as determined by hreims (5).

The chemical shifts of C-1 and C-25 indicated that both oximes in **2** also had *E* geometry. The expected three-bond correlations of OH-15 to C-14 and C-16 were observed in the HMBC experiment, thus demonstrating that **2** contains the common C-10 to C-14 bastadin ether linkage found in all bastadins except bastadin 13 (5). The 1H -nmr signal for OH-34 was too broad to observe the desired couplings; attempts at sharpening this signal by adding TFA to the nmr sample and by variable temperature nmr experiments were unsuccessful, but all available data are consistent with a C-29 to C-33 ether linkage found in all bastadins reported to date.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—

These have been reported previously (6).

SPONGE COLLECTION AND ISOLATION.—The sponge was collected in October 1992, in Manado Bay, Sulawesi, and identified by Dr. Peter Karuso, Macquarie University. A voucher specimen is preserved at the University of Hawaii, Manoa.

The freeze-dried sponge (40.2 g) was extracted for 2 days with 400 ml of CH_2Cl_2 -*i*PrOH (1:1), and the residue (3.02 g) was partitioned between 400 ml of hexanes-MeOH- H_2O (10:9:1). The lower layer residue (2.03 g of red solid) was subjected sequentially to C-18 MeOH- H_2O (7:3)

and Si gel CH_2Cl_2 -MeOH (95:5) flash chromatography, yielding a 120 mg of mixture of bastadins. The mixture was separated by reversed-phase hplc [ODS, 10×250 mm, MeCN-MeOH- H_2O (1:1:1), 2 ml/min] yielding **1** (5 mg), **2** (4 mg), **3** (17 mg), **4** (6 mg), **5** (13 mg), **6** (4 mg), **7** (18 mg), and **8** (16 mg).

Bastadin 16 [**1**].—Hrfabms m/z $[M+H]^+$ 1018.7792 (calcd for $C_{34}H_{28}N_4O_8^{79}Br_3^{81}Br_2$, 1018.7783); hreims m/z 499.8166 (calcd for $C_{16}H_8N_2O_2^{79}Br_2^{81}Br$, 499.8194); ir ν max (Nujol) 3500–3300, 1650, 1630, 1480, 1240, 1225 cm^{-1} ; uv λ max (MeOH) (log ϵ) 280 (3.6) nm; 1H and ^{13}C nmr see Table 1.

Bastadin 17 [**2**].—Hrfabms m/z $[M+H]^+$ 956.8606 (calcd for $C_{34}H_{28}N_4O_8^{79}Br_2^{81}Br_2$, 956.8627); hreims m/z 417.8925 (calcd for $C_{16}H_8N_2O_2^{79}Br_2$, 417.8953); ir ν max (Nujol) 3600–3100, 1660, 1640, 1490, 1470, 1285, 1220 cm^{-1} ; uv λ max (MeOH) (log ϵ) 278 (4.1) nm; 1H and ^{13}C nmr see Table 1.

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