Tetrahedron Vol. 49, No. 2, pp. 329-336, 1993
Printed in Great Britain

0040-4020/93 $5.00+.00

2-Aminoimidazoles and their Zinc Complexes from Indo-Pacific *Leucetta* Sponges and *Notodoris* Nudibranchs

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(*Received in USA* 1 *September* 1992; *accepted* 14 *October* 1992)

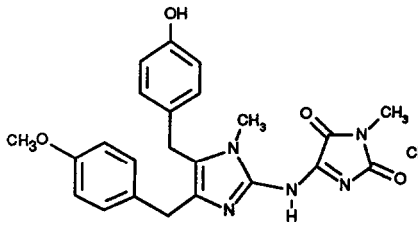
Abstract: This investigation explored aminoimidazoles from the nudibranch, *Notodoris gardineri*, and the sponge *Leucetta* sp. Five compounds were isolated and include known metabolites, clathridine (**7**) and its corresponding Zn complex (**8**), accompanied by new compounds, preclathridine A (**10**), clathridine B (**11**), and Zn-isonaamidine (**12**). Compounds **7**, **8**, **10**, and **11** were isolated from the nudibranch and **12** was obtained from the sponge. The organometallic complex **12** provides the second example of such a chemotype isolated from a sponge and this study reports the first instance of an organometallic compound isolated from a nudibranch.

INTRODUCTION

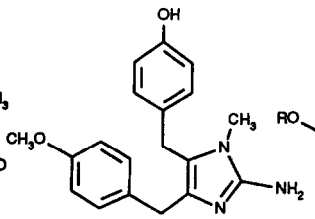
Some spongivorous nudibranchs are able to concentrate nitrogenous metabolites from their prey.[1] Nudibranchs associated with sponges of the class Demospongiae represent the most frequently studied case and were the source of the first examples of nitrogen containing products, the pupukainane sesquiterpene-isonitriles described by Scheuer, from the sponge *Ciocalypta* sp. and its nudibranch prey *Phyllidia varicosa*.[2] Karuso[2c] has published an extensive review of metabolites (including alkaloids) isolated from nudibranchs associated with Demospongiae sponges. A more recent milestone discovery is represented by Kashman's and Mebs' work on Red Sea nudibranchs and sponges containing polyketide-amino acids such as latrunculins A and B - *Latrunculia magnifica* (sponge)/*Glossodoris*[3] *quadricolor* (nudibranch)[4] - and by the University of California, Santa Cruz and University of Hawaii groups report of those same compounds from Indo-Pacific specimens - *Hyatella* sp.[3] (**3b**) (sponge)/*Chromodoris lochi* (nudibranch).[5]

Some years ago Wilkinson and Thompson separately suggested a fundamental rationale for studies involving hard sponges of the class Calcarea and their associated nudibranchs. Wilkinson[6] observed instances in which the yellow-black *Notodoris* nudibranchs were feeding on the yellow calcareous sponges of the genus *Leucetta* (Family Leucettidae, Order Clathrinida[7]) and Thompson[8] noted a similar circumstance for nudibranchs of the genus *Aegires* (synonym *Notodoris*) and the yellow calcareous sponges of the genus *Clathrina* (Family Clathrinidae, Order Clathrinida). The first indication that parallel alkaloids could be isolated from both organisms was provided by Kashman's report of substituted 2-aminoimidazole alkaloids including

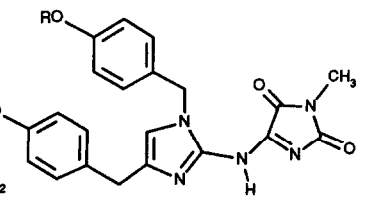
the naamidines (e.g., **1**), naamines (e.g., **2**), isonaamidines (e.g., **3**), and isonaamine (e.g. **4**) from both a sponge, *L. chagosensis*, and its associated nudibranch, *Notodoris citrina*.[9] In 1991 we reported dorimidazole A (**5**) and isonaamine A (**4**), from the Philippine nudibranch *Notodoris gardineri*, and suggested that these arise by biosynthetic union of a modified tyrosine plus guanidine.[10] Additional related metabolites have been published from sponges of the Order Clathrinida including pyronaamidine (**6**) from *Leucetta*,[11] but the most unique are the pair clathridine (**7**) and its organometallic congener Zn-clathridine (**8**) from *Clathrina clathrus*.[12] Faulkner's very recent discovery of **8** accompanied by (9*E*)-clathridine-9*N*-(2-sulfoethyl)imine (**9**) from the sponge *L. microrhaphis*[13] prompts this report which further extends the pattern of aminoimidazoles from *Leucetta* and *Notodoris*.



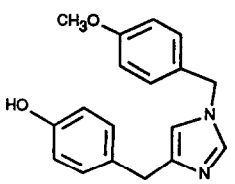
naamidine A (**1**)



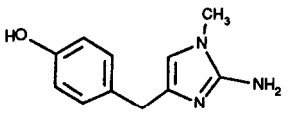
naamine A (**2**)



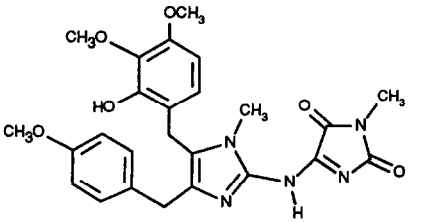
isonaamidine A (**3**) R = H
(**13**) R = CH_3



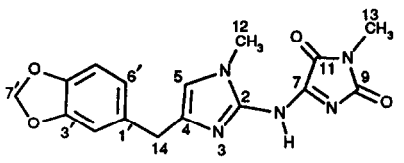
isonaamine A (**4**)



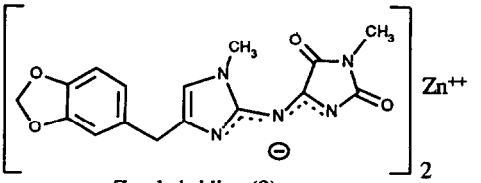
dorimidazole A (**5**)



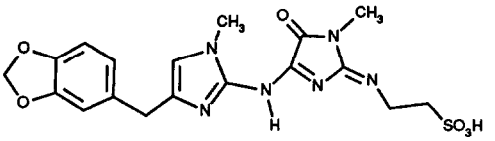
pyronaamidine (**6**)



clathridine (**7**)



Zn-clathridine (**8**)



(9*E*)-clathridine-9*N*-(2-sulfoethyl)imine (**9**)

RESULTS AND DISCUSSION

The MeOH extract of three bright yellow *Notodoris gardineri* nudibranchs, collected from Papua New Guinea, was partitioned in the usual fashion.[10] The *n*-BuOH soluble portion was fractionated by gel filtration (Sephadex LH 20) followed by reversed phase HPLC to give four compounds (**7**, **8**, **10**, **11**). As noted above, **7** and **8** have been previously isolated from the sponge *C. clathrus*.[12] The difference in the ^{1}H NMR signature of the benzylic protons in compounds **7** and **8** provides an important hint as to when the 2-aminoimidazole might be coordinated to a metal. The geminal benzylic protons present in the 2-aminoimidazoles **1** - **7** are all isochronous, reflective of their enantiotopic environment. By contrast, these benzylic protons in **8** appear as an AB pattern (see Figure 1) and are diastereotopic due to the presence of a tetrahedral Zn.[12,14]

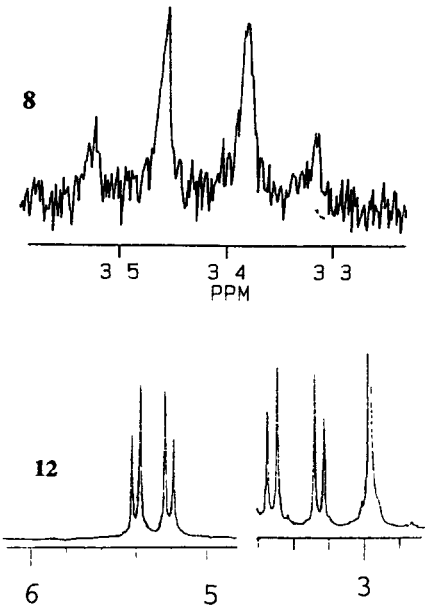
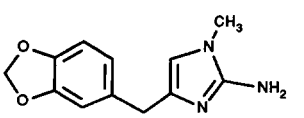
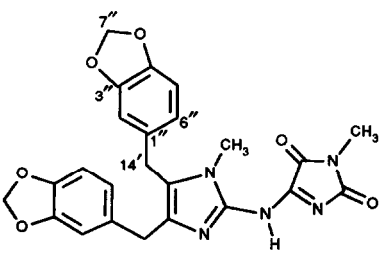


Figure 1. ^{1}H NMR spectra of the benzylic region.

The two new natural products that were isolated consisted of preclathridine A (**10**) of formula $C_{12}H_{13}N_3O_2$ (HREIMS *m/z* 231.1005 [M]$^+$, Δ 0.8 mmu calcd) and clathridine B (**11**) of composition $C_{24}H_{21}N_5O_6$, (HREIMS *m/z* 475.1454 [M]$^+$, Δ 3.8 mmu calcd). The EI mass spectrum of **10** showed fragmentations at *m/z* 216 (M^+-Me) and *m/z* 135 (M^+-$C_4H_6N_3$) indicative of an aminoimidazole group while its ^{1}H NMR spectrum exhibited one set of ortho coupled benzenoid ring protons (δ 6.75, 6.69, J = 8.0 Hz), accompanied by five singlets at δ 6.72 (1H), 6.50 (1H), 5.89 (2H), 3.71 (2H) and 3.41 (3H). These data, plus that from the ^{13}C NMR spectrum (see experimental) along with a comparison to properties of **10** published by Fattorusso,[12a] who obtained this compound by hydrolysis of **7**, justified our proposed structure which featured a single piperonyl residue. The second new metabolite clathridine B (**11**), was recognized as being a higher piperonyl homolog of clathridine (**7**) based on comparison of the NMR data of this pair. The major features apparent for **11** were two *N*Me's at δ 3.51 and 3.18; two benzylic methylenes as singlets at δ 3.87 (2H)



preclathridine A (**10**)

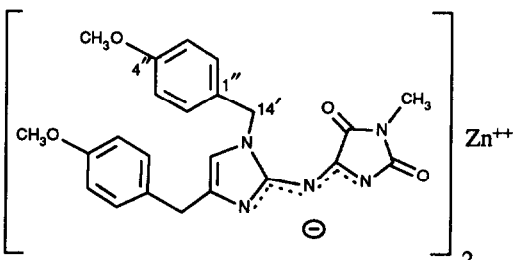


clathridine B (**11**)

and 3.85 (2H); and two piperonyl subunits identified from resonances including a singlet at δ 5.92 (2H), two sets of AB doublets at δ 6.46 (d, 1H, J = 7.5 Hz), 6.45 (d, 1H, J = 7.9 Hz) δ 6.71 (d, 1H, J = 7.5 Hz) and 6.68 (d, 1H, J = 7.7 Hz) and a singlet at δ 6.42 (2H). In addition, the mass spectrum of **11** showed the loss of two piperonyl units from the molecular ion peak.

Alongside the work described above was a parallel effort which sought 2-aminoimidazoles from specimens of *Leucetta* sp. collected from Fiji. One unique example containing this moiety was isolated but the elucidation of its correct structure as the Zn-complex **12** was protracted. Initially, we could not rationalize the significance of the APT formula of $C_{23}H_{22}$ in conjunction with the two sets of AB doublets shown for **12** in Figure 1. Eventually, we recognized that an organometallic dimer could explain the diastereotopic environment apparent for the benzylic hydrogens of **12**, but only after **7** and **8** had been isolated and characterized from the ongoing work with *Notodoris* as described above. The idea of an organometallic complex was substantiated by a HREIMS spectrum which was obtained for **12** revealing the proper molecular formula as $C_{46}H_{44}N_{10}O_8Zn$. Comparison of the MS formula to the APT formula indicated that the organic residue must form a dimeric sandwich with the Zn. Parallel features were evident in the NMR spectra of **12** versus those published by Kashman for isonaamidine A (**3**). The only difference was that **12** displayed extra signals for two OMe groups. It is important to point out that the unknown compound **13**, a close relative of **3**, represents the obvious precursor to the Zn-complex **12**.

Very few organometallic complexes are known as natural products from marine sponges. Likewise, just a small number of metal complexes have been synthesized starting from a marine sponge metabolite. At this writing, compounds **8** and **12** represent the only examples of the former. Alternatively, the isolation of a solid Li^+ complex of jasplakinolide,[15a] a ketide-amino acid, and the study of the association in solution between Co^{++} or Cu^{++} and kuanoniamine D, a pyridoacridine,[15b] are the only illustrations of the latter. Prior to our study, there were two instances where the Zn complex of clathridine (**8**) had been isolated from sponges (*Clathrina*[12] and *Leucetta*[13]). The new comparative biochemical information contributed here consists of an additional example of a Zn-complex, **12**, from a sponge (*Leucetta*). Also, this work provides the first example of a nudibranch (*Notodoris*) containing an organometallic compound in the form of Zn-clathridine (**8**) which is presumably concentrated from its sponge diet. The organometallic structures above have incorporated the reasonable assumption that the bonding to Zn[16] occurs to both atoms N-3 and N-8 of the 2-aminoimidazole backbone of **12** by analogy to what has been shown by X-ray crystal study of **8**.[12b]



Zn-isonaamidine C (**12**)

EXPERIMENTAL SECTION[17]

The NMR spectra were recorded at 300 or 250 MHz for ^1H, and 75.0 or 62.5 MHz for ^{13}C. Multiplicities of ^{13}C NMR resonances were determined from APT data or ^{13}C-^1H COSY NMR experiments. Both ^1H-^1H and ^{13}C-^1H COSY NMR data were used to assign resonances of clathridine (**8**) and Zn-isonaamidine C (**12**). Mass spectrometry data were obtained in various low and high resolution modes. High performance liquid chromatography (HPLC) used columns that included 10 μ ODS or 10 μ silica. All solvents were distilled and dried for HPLC use and were spectral grade for spectroscopy.

Identification. The sponge (coll. #89129) specimens of *Leucetta* sp. (Family Leucettidae, Order Clathrinida, Class Calcarea)[7] were collected from Fiji just off shore of Thang-galai Island, to the west of Moturiki Island. Our voucher specimen was carefully examined by M. C. Diaz (U. C. Santa Cruz, Institute of Marine Sciences) and exhibits the following characteristics. The sponge was always spherical or globular in shape. The specimens were bright yellow with occasional brown tinges. The consistency was firm and densely spiculated, typical of calcareous sponges. Two size categories of triactinial spicules were observed: type I clads, 300-400x15-20 μm, rhabds 500-700x20-25 μm; and type II, all rays: 60x100x5-10 μm. The type II triactines were heavily packed throughout the choanosome, and the type I tractines were mostly oriented sideways and close to the surface. The nudibranchs (coll. #91139) were collected in Milne Bay, Papua New Guinea at the Little China station. These were identified by comparison to characteristics we previously described in Ref. 9 for this species.

Extraction. The sponges were preserved by a unique procedure which is just as effective as freezing but avoids this cumbersome procedure in areas where cold storage is not available. The full details will be published elsewhere and consisted of soaking the freshly collected sponges for up to 24 h in a 1:1 EtOH/H_2O (seawater) solution which was then discarded. The damp sponges were then transported, at an ambient temperature to UCSC for work-up. The nudibranchs were placed in 100% ethanol and also returned to U.C. Santa Cruz for further workup. The sponge (1.2 kg wet wt) was soaked in CH_3OH (3000 mL x 3) for 48 h. The solvent was decanted and the oil concentrated to yield 14.1 g of a crude viscous oil. The crude oil was then successively partitioned between equal volumes (125 Ml of aqueous CH_3OH, percent adjusted to produce a biphasic solution) and a solvent series of hexanes (6.5 g) CCl_4 (4.6 g), CH_2Cl_2 (2.1 g). The CH_2Cl_2 fraction was subjected to gel filtration. The fourth fraction was chromatographed on silica gel (EtOAc/Hexanes 1:4) followed by normal phase HPLC (EtOAc) yielding pure **12** (31.7 mg). The nudibranchs were macerated and extracted with CH_3OH (100 mL x 3) for 48 h. The solvent was decanted and the oil concentrated to yield 0.90 g of a crude viscous oil. The crude oil was then successively partitioned as described above for the sponge. The most polar material remaining in the methanol was pulled out in *n*-BuOH. Further purification by gel filtration (Sephadex LH-20) with MeOH followed by reversed phase HPLC (add solvent) yielded compounds **7**, **8**, **10**, **11**.

Clathridine (**7**). A yellow oil (8.5 mg). HREIMS (positive ion) *m/z* (%): 341.1115 [M^+, $C_{16}H_{15}N_5O_4$, Δ

0.6 of calcd]. LREIMS (positive ion) *m/z* (%): 341 (M^+, 100), 326 (15), 256 (21), 228 (32), 175 (18) and 135 (20). UV (MeOH): λ_{max}: 373, 284 nm; ^{1}H NMR (CD_3OD): δ 3.18 (s, *N*Me-13), 3.71 (s, *N*Me-12), 3.81 (s, H_2-14), 5.94 (s, H_2-7′), 6.45 (s, H-5), 6.72 (s, H-2′), 6.66 (d, *J* = 8.0 Hz, H-6′) and 6.72 (d, *J* = 8.0 Hz, H-5′); ^{13}C NMR (CD_3OD) δ 24.7 (*N*Me-13), 32.2 (C-14), 34.4 (*N*Me-12), 101.0 (C-7′), 108.3 (C-5′), 109.2 (C-2′), 117.6 (C-5), 121.7 (C-6′), 131.0 (C-1′), 132.7 (C-4), 139.6 (C-2), 144.3 (C-7), 146.2 (C-4′), 147.8(C-3′), 155.0 (C-9) and 162.0 (C-11).

Zn-clathridine (8). A yellow oil (3.2 mg). UV (MeOH): λ_{max}: 399, 374, 361 and 284. ^{1}H NMR (CD_3OD): δ 3.02 (s, *N*Me-13), 3.35 and 3.49 (AB, *J* = 16.3 Hz, H_2-14), 3.79 (s, *N*Me-12), 5.87, 5.90 (AB, *J* = 1.3 Hz, H_2-7′), 6.23 (s, H-5), 6.25 (d, *J* = 8.5 Hz, H-6′), 6.49 (d, *J* = 8.5 Hz, H-5′) and 6.63 (s, H-2′). ^{13}C NMR: δ 24.6 (*N*Me-13), 32.6 (*N*Me-12), 33.2 (C-14), 101.2 (C-7′), 107.8 (C-2′), 108.5 (C-5′), 117.5 (C-5), 121.2 (C-6′), 131.1 (C-1′), 136.3 (C-4), and due to the small sample the most of quaternary carbon resonances could not be observed.

Preclathridine A (10). A yellow oil (6 mg). HREIMS (positive ion) *m/z* (%): 231.1005 [M^+, $C_{12}H_{13}N_3O_2$, Δ 0.8 of calcd]. LREIMS (positive ion) *m/z* (%): 231 (100), 216 (36), 175 (19) and 135 (11). UV (MeOH): λ_{max} 285, 208 nm. ^{1}H NMR (CD_3OD) δ: 3.41 (s, *N*Me-12), 3.71 (s, H_2-14), 5.89 (s, H_2-7′), 6.50 (s, H-2′), 6.69 (d, *J* = 8.0 Hz, H-5′), 6.72 (s, H-5) and 6.75 (d, *J* = 8.0 Hz, H-6′). ^{13}C NMR (CD_3OD): δ 29.9 (*N*Me), 31.0 (C-14), 101.1 (C-7′), 107.9 (C-2′), 108.6 (C-5′), 113.8 (C-5), 121.4 (C-6′), 126.4 (C-4), 130.5 (C-1′), 146.8 (C-3′), 146.9 (C-4′), and 148.1 (C-2).

Clathridine B (11). A yellow oil (3 mg). HREIMS (positive ion) *m/z* (%): 475.1454 [M^+, $C_{24}H_{21}N_5O_6$, Δ 3.8 of calcd]. LREIMS (positive ion) *m/z* (%): 475 (M^+, 100), 341 (30), 280 (15), 135 (25). UV (MeOH): λ_{max} 377, 285 nm. ^{1}H NMR (250 MHz, CD_3OD): δ 3.18 (s, *N*Me-13), 3.51 (s, *N*Me-12), 3.85 (s, H_2-14), 3.87 (s, H_2-14′), 5.91 (s, H-7′), 5.92 (s, H-7″), 6.42 (s, H-2′, H-2″), 6.45 (d, *J* = 7.9 Hz, H-5′), 6.46 (d, *J* = 7.5 Hz, H-5″), 6.68 (d, *J* = 7.7 Hz, H-6′), 6.71 (d, *J* = 7.5 Hz, H-6″). ^{13}C NMR (62.5 MHz, CD_3OD): δ 24.7 (*N*Me-13), 29.2 (C-14), 30.0 (C-14′), 33.0 (*N*Me-12), 100.9 (C-7″), 101.1 (C-7′), 108.3 (C-5″), 108.4 (C-5′), 108.9 (C-2′,2″), 120.8 (C-6″), 121.2 (C-6′), and due to the small sample the quaternary carbon resonances could not be observed.

Zn-isonaamidine C (12). A yellow solid. HREIMS: 928.2674 [M^+, $C_{46}H_{44}N_{10}O_8Zn$, Δ 3.9 mmu of calcd]. LREIMS (positive ion), *m/z* (%): 928 (M^+, 6), 929 ([M+1] $^+$, 3), 930 ([M+2]$^+$, 4), 807 (12), 433 (100), 323 (16), 312 (87), 227 (62), 121 (98), 106 (42). UV (MeOH) λ_{max}: 580, 367, 275, 263 nm; ^{1}H NMR ($CDCl_3$ 300 MHz): δ 2.96 (s, *N*Me-12), 3.26 and 3.52 (AB system, *J* = 17.0 Hz, H_2-14), 3.68 (s, C-4′ OMe), 3.80 (s, C-4″ OMe), 5.20 and 5.40 (AB, *J* = 14.6 Hz, H_2-14′), 6.62 (s, H-5), 6.53 (s, H-2′ and H-3′), 6.91 (d, *J* = 9.7 Hz, H-3″), 7.35 (d, *J* = 9.7 Hz, H-2″); ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 24.4 (*N*Me-12), 32.7 (C-14), 48.8 (C-14), 55.1 (C-4-OMe), 55.4 (C-4′ OMe), 113.6 (C-3′), 114.4 (C-3″), 116.1 (C-5), 128.2 (C-1′), 129.0 (C-2′), 129.3 (C-1″), 130.0 (C-2″), 136.5 (C-4), 148.5 (C-2), 154.8 (C-7), 158.1 (s, C-4′), 159.7 (C-4″), 161.3 (C-11), 164.6

(C-9).

Acknowledgment. Partial research from NOAA, National Sea Grant College Program, Department of Commerce, under grant number NA85AA-D-SG140 project number R/MP-45, through the California Sea Grant College Program. Additional support was from NIH grant CA47135. We are grateful to the Fiji government for their cooperation, to Dr. D. Niles of the Institute of Papua New Guinea Studies for his assistance, and to Mr. R. Vanderloos, skipper of the PNG vessel TANIA, for his enthusiastic cooperation.

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1. Recent examples of alkaloids from nudibranch-sponge associations include: (a) related ketide-amino acids - the halichondramides from the sponge *Halichondria* sp., the nudibranch *Hexabranchus sanguineus* and its egg masses [Kernan, M. R.; Molinski, T. F.; Faulkner, D. J. *J. Org. Chem.* **1988**, *53*, 5014-5020] while the ulapualides [Roesener, J. A.; Scheuer, P. J. *J. Am. Chem. Soc.* **1986**, *108*, 846-847] and kabiramides [Matsunaga, S.; Fusetani, N.; Hashimoto, K.; Koeseki, K.; Noma, M. *J. Am. Chem. Soc.* **1986**, *108*, 847-848] are each reported solely from the nudibranch egg masses. (b) Aromatic type alkaloids, the renierones have been isolated from the Indo-Pacific nudibranch *Jorunna funebris* and its sponge food source *Xestospongia* sp. [Ref. 2c].

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3. Important taxonomy issues include: (a) suggestion that the name *Glossodoris* be abandoned and *Chromodoris* be employed: Burn, R. *The Western Aust. Naturalist* **1968**, *10*, 173-178; (b) two names have been employed in the chemical literature for a sponge that Prof. P. R. Bergquist (U. of Auckland, N. Z.) indicates after examining both the U. C. Santa Cruz and U. of Hawaii vouchers (private communications) are the same: *Spongia mycofijiensis* (Ref. 5a, 5b) and *Hyattella* sp. (Ref. 5c).

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