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# Mauritamide A and Accompanying Oroidin Alkaloids from the Sponge *Agelas mauritiana*[1]

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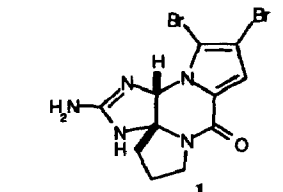
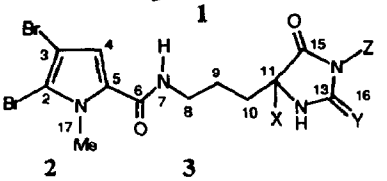
***Abstract:*** The alkaloid consitutents of a Fijian sponge, *Agelas mauritiana*, are described and consist of a new taurine containing compound, mauritamide A (**3**) accompanied by known oroidin alkaloids dibromophakellin (**1**) and midpacamide (**2**).

The orange to brownish, often massive sponges of the genus *Agelas* are prominent members of both Caribbean and Indo-Pacific Coral reefs.[2] These taxa are a reliable source of alkaloids since every *Agelas* species that has been reported on to date has yielded either oroidin type alkaloids, diterpenoids appended to a 9-methyladenine group, or acyclics and heterocyclics possessing guanidine functionality.[3]

We became interested in the constituents of *Agelas mauritiana*[4] (Carter, 1882) when the semipure fractions of material (coll. no. 89062) obtained from the Solomon Islands exhibited 100% inhibition of protein tyrosine kinase (PTK) at 100 μg/mL.[5] Unfortunately, the active consitituents appeared to be inseparable mixtures with $^1$H NMR properties similar to the bioactive bromopyrrole salts obtained by Rinehart from both *Agelas conifera* and *A. mauritiana*[3c]. Other collections of *A.* mauritiana were in hand, which differed considerably in morphology and included material from Fiji (coll. no. 88092) and Papua New Guinea (coll. nos. 990122, 90205, 91126), but none of their extracts were active in the primary PTK screen. In spite of these negative developments the Fijian sample was investigated further as unique $^1$H NMR resonances indicated that new compounds could be isolated from the polar semipure fractions. Important reference NMR data on constituents of *A. mauritiana* are contained in publications by Faulkner[6] (a purino-diterpene), Allen[7] (agelasimines A and B and two midpacamides), Rinehart[3c] (seven oroidin derivatives), and Natori[8] (four agelasphins). The isolation work eventually yielded two known oroidin derivatives, dibromophakellin (**1**)[9] and midpacamide (**2**),[10] plus a new, more biogenetically complex compound, mauritamide A (**3**).



**1**



**2**
X = H
Y = O
Z = Me

**3**
X = $NHCH_2CH_2SO_3Me$
Y = NH
Z = H

Standard sponge preservation and work-up procedures[5] were used to obtain a methanol extract from 0.62 Kg (wet weight) of sponge. A viscous oil (17.6 g) was acquired and it was subjected to solvent partitioning. The $CH_2Cl_2$ solvent partition fraction was purified by flash

chromatography (regular silica gel) and then reversed-phase HPLC ($H_2O$/MeOH, 2:1) to afford midpacamide (**2**)[10] (20 mg). The *n*-BuOH solvent partition fraction was chromatographed on Sephadex LH-20 ($CH_2Cl_2$/MeOH, 1:1) and reversed-phase HPLC ($H_2O$/MeOH 55:45) to give mauritamide (**3**) (9 mg) and dibromophakellin (**1**)[9] (100 mg).

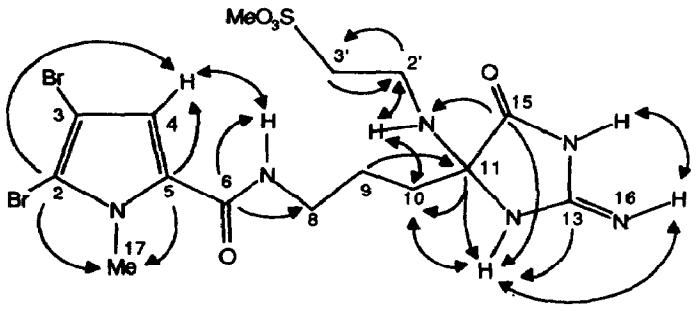
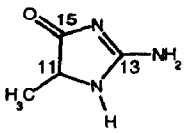



**Figure 1.** 2D NMR correlations for **3**:
↔ $^1$H-$^1$H ROESY; ⤳ $^{13}$C-$^1$H HMBC

Characterization of mauritamide (**3**)[11] commenced once several FAB mass spectra were in hand. The presence of two bromines was indicated by an intense [M-H]$^-$ ion cluster in the negative ion FAB mass spectrum at *m/z* 555/557/559 and by the [M+H]$^+$ ion cluster in the positive ion FAB mass spectrum at *m/z* 557/559/561. The complete formula of $C_{15}H_{22}N_6O_5SBr_2$ was established from the positive ion HRFABMS *m/z* peak at 556.9817 ($\Delta$ = 0.0 mmu of calcd.) and 558.9798 ($\Delta$ = 0.1 mmu of calcd.). The IR spectrum showed absorptions at 3650-2750, 1708 and 1643 cm$^{-1}$ eventually attributed respectively to NH groups, a γ-lactam and an amide carbonyl group. An atom count of $C_{15}H_{17}$ (2 $CH_3$'s, 5$CH_2$'s, 1$CH_1$ and 7$CH_0$'s) was identified from both an APT and HMQC NMR spectrum and this data implied that the five additional protons (see MF) present in **3** must be attached to hetero atoms. The 2D NMR correlations summarized in Figure 1 allowed two substructures to be initially identified; one encompassed atoms 1-10 and 17 while the other consisted of carbons 2'-3'. Although the EIMS trace did not show a molecular ion it displayed a prominent cluster at *m/z* 281/283/285 expected for fragmentation between the N7—C8 bond. Also, the $^1$H and $^{13}$C resonances for the atoms of the former substructure were nearly identical to those analagous atoms (CH1-10 and CH17) in midpacamide (**2**) as shown in Table 1. The two carbon containing subunit was expanded to a substituted taurine methyl ester by comparison of the NMR shifts at C2'/3' of **3** versus those for the $NHCH_2CH_2SO_3H$ residue of melemeleones A and B (δ 38 and 48).[5b]

What proved to be difficult was generating a substructure for the remaining unassigned atoms of **3**, $C_3H_3N_3O$, which also represented three unsaturation equivalents. The three quaternary carbons were all observed at relatively lowfield shifts of δ 96.2, 167.1 and 176.7 and the three hydrogens had to be attached to either *N* or *O*. An aminoimidazolone group with a quaternary sp$^3$ ring carbon was eventually envisioned.



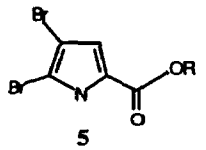

alacreatinine (**4**)

Comparison of the $^{13}$C NMR shifts of alacreatinine (**4**), including δ 160 (C13) and δ 177.3 (C15)[12] to the three lowfield carbons noted above provided support for assigning the δ 176.7 signal as a carbonyl. Additional support for an aminoimidazolone group was obtained from the $^1$H NMR spectrum in DMSO-$d_6$ where each of the *N*H protons was observed as a separate resonance. Important correlations could be observed in the $^1$H-$^1$H ROESY NMR spectra from the -NH- proton chemical shift at δ 8.62 [N(16)-H] to both

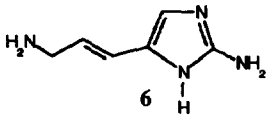
Table 1. NMR data for compounds 2 and 3.

| Atom | 2 ($CDCl_3$)[7] | | 3 (DMSO-$d_6$) | |
|---|---|---|---|---|
| | δ H (m) | δ C (m) | δ H (m) | δ C (m) |
| 2 | | 111.9 | - | 110.45 (s) |
| 3 | | 98.0 | - | 96.90 (s) |
| 4 | 6.66 (s) | 113.7 | 6.99 (s) | 114.00 (d) |
| 5 | | 127.4 | - | 127.89 (s) |
| 6 | | 157.6 | - | 159.71 (s) |
| 7 | 6.2 (brt) | - | 8.20 (t) | - |
| 8 | 3.4 (m) | 38.8 | 3.12 (m) | 38.05 (t) |
| 9 | 1.6-2.02 (m) | 28.7 | 1.23 (m) | 22.69 (t) |
| 10 | - | 25.1 | 1.88 (m) | 33.13 (t) |
| 11 | 4.12 (m) | 56.7 (d) | - | 96.23 (s) |
| 12 | 7.41 (s)°,+ | - | 9.36 (s) | - |
| 13 | - | 160.7 | - | 167.18 (s) |
| 14 | - | - | 9.18 (s) | - |
| 15 | - | 174.1 | - | 176.73 (s) |
| 16 | 6.52 (s) | - | 8.62 (s) | - |
| 17 | 3.95 (s) | 35.8 | 3.85 (s) | 35.40 (q) |
| 1' | | | 9.8 (t) | - |
| 2' | | | 3.63 (m) | 38.94 (t) |
| 3' | | | 2.76 (t) | 49.06 (t) |
| OMe | | | 3.02 (s) | 50.55 (q) |

° acetone; + can be switched




5

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the δ 9.18 [N(14)-H] and the 9.36 [N(12)-H] resonances. HMBC correlations outlined in Figure 1 such as from the δ 9.36 N(12)-H proton to the C=N carbon at δ 167.18 (C13), to the quaternary carbon at δ 96.23 (C11), and to the amide carbonyl carbon at δ 176.73 provided the final justification for the aminoimidazolone and supported the tautomeric form shown.

The HMBC and $^1H$-$^1H$ ROESY NMR results guided assembly of the three substructures described above. The most important results included correlations from the δ 9.8 [N(1')-H] to the methylene group resonances at δ 3.63 (m)/38.94 (C2') and to the carbon at δ 176.73 (C15) and from the protons at δ 1.88 (H10) to the carbon at δ 96.23 (C11).

The oroidin type alkaloids are known from sponges of the genera *Agelas* (family Agelasidae, order Agelasida), *Phakellia* (family Axinellidae, order Axinellida), and *Hymeniacidon* (family Halichondridae, order Halichondrida). These are considered as condensation products of highly modified prolines, such as **5**, isolated from *A. mauritiana*[6] and *Lissodendoryx* sp.,[13] and **6**, isolated from two different Axinellidae sponges.[14] Mauritamide A (**3**) is the first member of the oroidin alkaloid class having a taurine biosynthetic moiety. In addition, the aminoimidazolone ring present in **3** is uncommon and finds analogy in just a few compounds such as sceptrin and oxysceptrin from *Agelas*[3b,c], stevensine derivatives from *Hymeniacidon*[15] and palau'amine from *Stylotella*.[16]

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4. This specimen was identified by Ms. M. C. Diaz and is described as follows: shape - thick (5-10 cm) fan; color - bright orange to brownish; ectosome - irregular surface, with amorphous protuberances and depressions, having round and key-hole shaped oscules; consistency - compressible with a skeleton formed by a fibroreticle, with primaries echinated by stout acanthostyles (150-240) x (8-10) μM, with less than 20 verticiles. This specimen fits the morphology of *Agelas mauritiana* described in ref. 2c.
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11. **3**: amorphous white solid $[\alpha]_D^{20} = +1.3$ (c 0.003, MeOH) u.v. (MeOH) λ (nm) 278 (ε 3914), 258 (ε 6108), and 254 (ε 6199). IR $\upsilon_{max}$: 3550-2750, 1708, 1643, 1607, 1557, 1220, 1107 cm-1. EIMS *m/z* (%): 335/337/339 (3), 323/325/327 (3) 309/311/313 (14), 281/283/285 (100). (+) FABMS, *m/z* %: 579/581/583 ($[M+Na]^+$, 10), 557/559/561 ($[M+H]^+$, 48), 525/527/529 ($[M-OMe]^+$, 20).
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