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Acanthenes A To C: A Chloro, Isothiocyanate, Formamide Sesquiterpene Triad Isolated From The Northeastern Pacific Marine Sponge *Acanthella sp.* And The Dorid Nudibranch *Cadlina luteomarginata*

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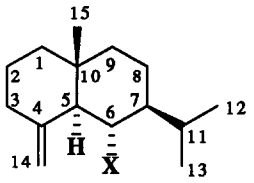
Abstract: *Acanthenes A (1) and B (2), two new eudesmane sesquiterpenoids, have been isolated from the marine sponge Acanthella. Acanthene C (3), the formamide analog of 1 and 2, has been isolated from the nudibranch Cadlina luteomarginata which feeds on Acanthella. The structures of 1 to 3 were solved by analysis of spectroscopic data. Acanthene A (1) appears to represent the first example of the co-occurrence a chloro sesquiterpenoid analog of sponge isothiocyanate, formamide or isonitrile sesquiterpenoids.*

Marine sponges in the family *Axinellidae* belonging to the genera *Axinella* and *Acanthella* have yielded a wide variety of interesting terpenoid metabolites containing isonitrile, isothiocyanate, formamide and isocyanate functionalities.[1-8] In many instances, a single sponge extract will contain a series of metabolites which are simply functional group analogs (i.e. isonitrile, formamide, isothiocyanate, etc.) of the same substituted terpene hydrocarbon prompting speculation that there may be biosynthetic interconversion of the various functional groups.[6] As part of an ongoing investigation of the chemistry of Northeastern Pacific marine invertebrates,[9] we have examined extracts of an undescribed species of sponge belonging to the genus *Acanthella* that was collected in the Queen Charlotte Island chain off the coast of British Columbia. The *Acanthella* sp. extracts were found to contain the two new sesquiterpenoids acanthene A (1) and B (2), six known sesquiterpenoids (4 - 10), and the known halogenated monoterpenoid violacene (11).[10] Skin extracts of specimens of the dorid nudibranch *Cadlina luteomarginata* collected at the same locale as the *Acanthella* sp. contained the new formamide acanthene C (3), the known sesquiterpenoids **4-6, 8** and **10**, as well as violacene (11). The discovery of acanthene A (1) is of particular interest because it apparently represents the first example of the co-occurrence of a chlorinated sesquiterpenoid[11] analog in an extract that is rich in isonitrile, isothiocyanate, and formamide containing sesquiterpenoids. Although no chloro sesquiterpenoid analogs appear to have been previously reported, chloro analogs of isonitrile diterpenoids have been reported from sponges in the *Axinellidae*.[7,12] For example, the diterpenoid isonitrile kalhinol F (12) and the corresponding chloroditerpenoid kalhinol B (13) co-occur in extracts of an *Acanthella sp.* collected in Guam.[7]

Specimens of the *Acanthella* sp.[13] and *C. luteomarginata* were collected off Conehead Point in Rennell Sound, Graham Island, British Columbia. Freshly collected sponge tissue was frozen on site and stored at -20°C until workup. Freshly collected nudibranchs were immediately immersed whole in methanol and stored at -20°C.



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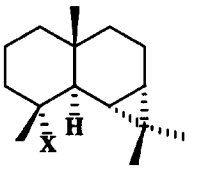
2 X= -NCS

3 X= -NHCHO



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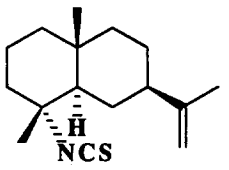
9 X= -NCS

10 X= -NC



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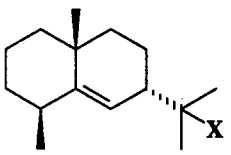

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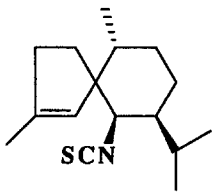
6 X= -NC



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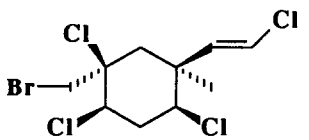

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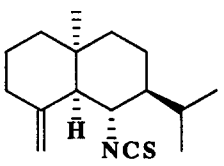
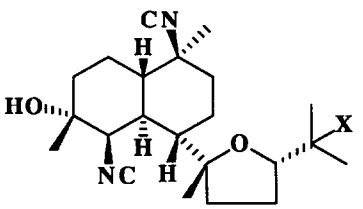


14



12 X= -NC

13 X= -Cl

Thawed sponge was homogenized with methanol and extracted repeatedly with fresh aliquots of methanol. The combined methanol extracts were concentrated in vacuo to yield an aqueous suspension that was successively extracted with hexanes, chloroform and ethyl acetate. Fractionation of the hexane soluble materials by combined silica-gel flash chromatography and normal phase HPLC gave pure samples of acanthenes A (1) (3mg from 500g wet weight of sponge) and B (2) (10 mg from 500 g wet weight of sponge), the known sesquiterpenoids 4-10 and the known monoterpenoid violacene (11). The methanol was decanted from the nudibranchs and they

were extracted twice more in a similar fashion with fresh methanol. The combined methanol extracts were fractionated as described above for the methanol extracts of *Acanthella* sp to give the new sesquiterpenoid formamide acanthene C (**3**) (3 mg/individual), the known sesquiterpenoids **4-6**, **8**, and **10** as well as violacene (**11**). The known compounds **4**,[8] **5**,[5] **6**,[5] axisonitrile-3 (**7**),[1] **8**,[14] **9**,[14] **10**[14] and violacene (**11**)[10] were all identified by comparison of their spectroscopic data with literature values.

Acanthene A (**1**) was obtained as a colorless oil that gave a parent ion cluster in the HREIMS at m/z 240.1652 and 242.1616 Da corresponding to molecular formulae of $C_{15}H_{25}{}^{35}Cl$ (ΔM 0.8mmu) and $C_{15}H_{25}{}^{37}Cl$ (ΔM 0.1mmu). The ^{13}C nmr spectrum of acanthene A (Table 1) contained thirteen intense resonances and two very weak resonances (C10: δ 38.9 and C4: δ 145.9), accounting for all fifteen carbon atoms required by the molecular formula. A pair of olefinic carbon resonances at δ 145.9 and 109.0 provided the only spectroscopic evidence for unsaturated functionality in **1** requiring that two of the three sites of unsaturation demanded by the molecular formula be present as rings. Two broad mutually coupled one proton resonances at δ 5.07 and 4.85 in the ^1H nmr spectrum (Table 1) of **1**, that were shown by an HMQC experiment to be coupled to the same olefinic carbon at δ 109.0 (C14), were assigned to an olefinic methylene. A deshielded methine resonance at δ 3.97 (dd, J=10.9,10.9 Hz: H6) in the ^1H nmr spectrum was assigned to a secondary chloride functionality and a partial ^1H nmr spin system consisting of a complex methine resonance at δ 2.64 (H11) that was coupled to two methyl doublet resonances at δ 0.77 (d, J=7Hz: Me12) and 0.87 (d, J=7Hz: Me13) was assigned to an isopropyl residue. A singlet resonance at δ 0.63 (Me15) that integrated for three protons was assigned to a tertiary methyl.

A detailed analysis of the COSY, HMQC and HMBC data collected on acanthene A (**1**) (Table 1) identified a partial ^1H spin system consisting of three contiguous aliphatic methylene groups (C_6D_6: δ1.20 (H1), 1.08 (H1'), 1.43 (H2), 1.52 (H2'), 2.24 (H3) and 1.87 (H3'). A COSY correlation between the methylene proton resonance at δ 1.87 (H3') and the olefinic proton resonance at δ 5.07 (H14'), attributed to allylic coupling, linked the three carbon fragment to the olefinic methylene functionality. Both of the olefinic methylene proton resonances at δ 4.85 (H14) and 5.07 (H14') showed COSY correlations, indicating allylic coupling, to a methine proton resonance at δ 2.11 (H5). Additional COSY correlations showed that the methine proton resonance at δ 2.11 (H5) was coupled to the secondary chloride methine proton resonance at δ 3.97 (H6) which was in turn coupled to a methine proton resonance at δ 1.59 (H7). COSY correlations also showed that the methine carbon (C7) bearing the proton at δ 1.59 was attached to a methylene carbon (C8) (δ 1.59 correlated to 1.10 (H8) and 1.29 (H8')) and to the isopropyl residue (δ 1.59 correlated to 2.64 (H11)).

HMBC correlations (Table 1) were observed between the tertiary methyl protons (δ 0.63, Me15) and a quaternary carbon at δ 38.9 (C10), a pair of methylene carbons at δ 42.2 (C1) and 40.2 (C9), and a methine carbon at δ 58.9 (C5). The Me15 to C1, C5 and C10 correlations established one six-membered ring in acanthene A (**1**) and the Me15 to C9 (δ 40.2) correlation demonstrated that C10 was attached to an additional methylene carbon that could not be connected to any other portion of the molecule by the COSY data due to congestion in the upfield region of the ^1H nmr spectrum. Simply joining the only two remaining unsatisified valences in the identified fragments of **1**, namely a bond to the C9 methylene carbon and a bond to the C8 methylene carbon, created another six membered ring revealing that acanthene A (**1**) had a eudesmane skeleton.

The relative stereochemistry of acanthene A (**1**) was deduced from nOe and coupling constant data. The

Table 1. NMR data for Acanthenes A (1) (C_6D_6), B (2) ($CDCl_3$), and C (3) ($CDCl_3$).

	Acanthene A (1)					Acanthene B (2)				Acanthene C (3)	
Carbon No.	δ ^{1}H	COSY Correlations[a]	nOes[b]	δ ^{13}C	HMBC[c] Correlations	δ^1H	COSY Correlations[a]	nOes[b]	δ^{13}C	δ^1H	δ^{13}C
1	1.20,m	H2',H3		42.2	H15	1.42,m	H2,H2',H3		42.0	1.50,m	42.2
	1.08,m	H2,H15				1.30,m	H2,H2',H15			1.2,m	
2	1.43,m	H1',H2',H3'		24.3		1.54,m	H1,H1',H3,H3'		23.9	1.6,m	24.2
	1.52,m	H1,H2,H3,H3'				1.60,m	H1,H1',H3,H3'			1.6,m	
3	2.24,m	H1,H2',H3'		38.2	H14,H14'	2.36,m	H1,H2,H2',H3'	H3',H14'	37.5	2.31,m	38.3
	1.87,dt,J=6.1,12.8	H2,H2',H3,H14'				1.99,dt,J=5.8,13.0	H2,H2',H3,H14'	H3		1.89,m	
4				145.9					146.0		145.7
5	2.11,d,J=10.9	H6,H14,H14'		58.9	H14',H15	2.06,d,J=10.8	H6,H14,H14'		56.3	1.75,d,J=10.6	57.0
6	3.97,dd,J=10.9	H5,H7	H12,H14,H15	62.0		3.57,dd,J=10.8	H5,H7	H12,H14,H15	56.5	4.05,ddd,J=10.6	46.1
7	1.59,m	H6,H8,H8'		51.6	H12,H13	1.55,m	H6		49.8	1.12,m	50.5
8	1.10,m	H7,H8'		19.7		1.54,m			18.5	1.52,m	18.4
	1.29,m	H7,H8				1.25,m				1.37,m	
9				40.2	H15	1.50,m			39.8	1.55,m	40.4
						1.23,m	H15			1.25,m	
10				38.9	H15				37.6		
11	2.64,m	H12,H13		27.5	H12,H13	2.17,m	H12,H13		27.7	1.90,m	26.5
12	0.77,d,J=7.0	H11		21.3	H13	0.87,d,J=7.0	H11	H6,H11	16.0	0.91,d,J=6	16.1
13	0.87,d,J=7.0	H11		15.3	H12	0.98,d,J=7.0	H11	H11	21.0	0.91,d,J=6	21.6
14	4.85,bs	H5,H14'		109.0		4.61,bs	H5,H14'	H6,H14'	108.0	4.64,bs	108.0
	5.07,bs	H3',H5,H14				5.02,bs	H3',H5,H14	H3,H14		4.84,bs	
15	0.63,s	H1'	H6	17.1		0.71,s	$H1'_{ax}$,$H9'_{ax}$	H6	17.0	0.77,s	17.3
NH										4.5,bs	
CHO										8.13,s	160.8

[a] Correlations to proton resonance in δ^1H column. [b] Proton resonance in δ^1H column was irradiated. [c] Correlations to carbon resonance in δ^{13}C column.

H6 resonance (δ3.97) appeared as an apparent triplet with a coupling constant of 10.9 Hz indicating that H5, H6 and H7 were all axial. Irradiation of H6 (δ3.97) induced a nOe in the Me15 resonance (δ 0.63) demonstrating that Me15 was also axial and, therefore, that acanthene A (1) contained a trans decalin ring system as shown.

Acanthene B (2) was obtained as an optically active ($[\alpha]_D$ -34°) amorphous white solid that gave a parent ion in the EIHRMS at m/z 263.1714 Da corresponding to a molecular formula of $C_{16}H_{25}NS$ (ΔM 0.1mmu). A fragment ion observed at m/z 204 Da ($C_{15}H_{24}$) was attributed to the loss of HNCS suggesting the presence of either an isothiocyanate or a thiocyanate functionality. The ^1H and ^{13}C nmr data for acanthene B (2) (Table 1), with the exception of the chemical shifts for H6 and C6, was very similar to the nmr data for acanthene A (1) (see Experimental for ^1H nmr data in $CDCl_3$), suggesting that the two molecules only differed in the nature of the functionality at C6. A detailed analysis of the COSY, HMBC and HMQC data collected on 2 confirmed the relationship between the two molecules.

Several recent reports of the co-occurrence of thiocyanate and isothiocyanate containing terpenoids in the same sponge extract[15,16] points out that care must be taken to distinguish between the two types of functionalities. The ^{13}C nmr chemical shifts of the thiocyanate or isothiocyanate carbons are diagnostic,[15] however, the limited sample of acanthene B (2) that was available gave only a weak ^{13}C nmr spectrum that did not show a resonance for the functional group carbon atom. Addition of sulfur to the corresponding isonitrile analog can also provide proof of an isothiocyanate, however, the isonitrile analogue of 2 was not available. An intense broad band at 2080-2180 cm^{-1} in the IR spectrum of 2 was suggestive of an isothiocyanate rather than a thiocyanate functionality.[15] Thiocyanates typically show sharp IR stretching bands of medium intensity at 2150 cm^{-1}. The chemical shifts of the H6 (δ 3.57) and C6 (δ 56.5) resonances in the nmr spectra of 2 were also consistent with the presence of an isothiocyanate functionality. Acanthene B (2) is a stereoisomer of the previously reported isothiocyanate 14. The presence of the isothiocyanate functionality in 14 was unambiguously verified by adding elemental sulfur to the corresponding isonitrile.[17] The relative stereochemistry of the two molecules is identical at C5, C6 and C7 and the H6 coupling constants in the two molecules are nearly identical (2: J= 10.8, 14: J=11.2) indicating that H5, H6 and H7 are all axial in both 2 and 14. The chemical shifts of δ 3.57 and 56.5 ($CDCl_3$) observed for H6 and C6 in acanthene B (2) are very similar to the chemical shifts of δ 3.69 and 58.2 (or 59.0) ($CDCl_3$) reported for H6 and C6 in 14 supporting the presence of an isothiocyanate funtionality in 2. The question of which chiral centers in the molecules 2 and 14 (i.e. the group C5, C6 and C7, or the single center C10) are antipodal remains to be answered.

Acanthene C (3) was isolated as an amorphous white solid that gave a parent ion in the HREIMS at m/z 249.2098 Da appropriate for a molecular formula of $C_{16}H_{27}NO$ (ΔM +0.6mmu). Detailed analysis of the nmr data for acanthene C (3) (Table 1), including the results from COSY and HMQC experiments, showed that it was a C6 functional group analog of acanthenes A (1) and B (2). A carbonyl resonance at δ160.8 in the ^{13}C nmr spectrum and resonances at δ 4.5 (NH) and 8.31 (CHO) in the ^1H nmr spectrum of 3 were assigned to a formamide functionality. The formamide NH resonance at δ 4.5 showed a COSY correlation to the H6 resonance at δ 4.05 as expected.

The halogenated monoterpenoid violacene (11) was isolated from specimens of *Acanthella* sp. collected in two different years so its presence is not a chance event. Violacene (11) is a known metabolite of the red alga *Plocamium violaceum*[10] and it is almost certainly not a biosynthetic product of *Acanthella* sp. How it comes to be

in the sponge extracts is not clear. The most obvious explanation would simply be that the sponge tissue was physically contaminated with some quantity of a *Plocamium* species of alga. While it is difficult to completely rule out this possibility, careful scrutiny of the sponge surface and interior tissues showed them to be free of any trace of alga. It is also interesting to note that violacene (**11**) was isolated from the specimens of the nudibranch *C. luteomarginata* collected on or near *Acanthella* sp. in Rennell Sound. *C. luteomarginata* is not known to feed on red algae and we have never found algal metabolites in dozens of previous examinations of *C. luteomarginata* skin extracts from other B.C. locations. Therefore, it seems reasonable to assume that violacene (**11**) is actually present in the sponge tissues and not in some contaminating algal tissue, and that *C. luteomarginta* is sequestering it from the Rennell Sound *Acanthella.* sp. along with the sesquiterpenoids **3-6, 8,** and **10.** If this scenario is correct, it represents a rather unique example of metabolite transfer from a red alga to a sponge and then to a mollusc. A related observation was recently reported by Giodano *et al.* who isolated halogenated metabolites typical of *Laurencia* species of red algae from the Mediterannean sponge *Mycale rotilis.*[18]

Acanthene A (**1**), to the best of our knowledge, represents the first example of a chloro analog co-occurring with a series of sesquiterpenoids containing some combination of isonitirile, isothiocyanate, formamide, etc. functionalities. A number of isotope labelling studies have shown that the isonitrile functionalities found in sponge terpenoids come directly from cyanide[6,19,20] and there is evidence that the isonitrile functionality is a biosynthetic precursor to the formamides and isothiocyanates.[21] It has also been suggested that cyanide ion traps a terpenoid carbocation to give the isonitrile substituent.[6] Trapping a terpenoid carbocation precursor by chloride ion instead of cyanide represents a competing pathway that could lead to chloro analogs such as acanthene A (**1**). The discovery of the sesquiterpenoid acanthene A (**1**) in the Rennell Sound *Acanthella* sp. and the diterpenoid kalihinol B (**13**) in an *Acanthella* sp. from Guam[7] suggests that the chloro analogs may be more widespread than has thus far been recognized.

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EXPERIMENTAL

***Collection and isolation data. Acanthella* sp.:** Specimens of *Acanthella* sp. (0.5 kg wet weight) were collected by hand using SCUBA (-5 m) in Rennel Sound, Queen Charlotte Islands, B. C. and transported frozen to Vancouver. Whole sponge was immersed in methanol (1.2L) for 72 hours at room temperature. Concentration of the methanolic extract *in vacuo* gave an aqueous suspension (100mL) which was sequentially extracted with hexanes (2 X 100mL), chloroform (2 X 100mL) and ethyl acetate (2 X 100mL). Evaporation of the hexanes extract gave a brown oil (200mg). Normal phase silica flash chromatography utilising a step gradient elution pattern from hexane to ethyl acetate in 25% increments yielded five fractions. The fraction which eluted off the column with 1:3 EtOAc:hexane contained acanthene A (**1**) which was further purified by normal phase HPLC (hexane). The fraction eluting off the flash column with 1:1 EtOAc:hexane was found to contain acanthene B (**2**) as well as compounds **4-7, 9-10** and violacene (**11**) which were purified by normal phase HPLC using either hexane or 1:19 EtOAc:hexane. The fraction eluting off the column with 3:1 EtOAc:hexane contained the formamide **8**, while the last fraction was found to consist of polyunsaturated fatty acids. ***Cadlina luteomarginata*:** specimens of *Cadlina luteomarginata* were collected by hand at the same location as *Acanthella* sp. and immediately immersed in methanol. The methanolic extract was reduced *in vacuo* to yield an aqueous suspension (50 mL) which was partitioned between water and dichloromethane (3 X 50 mL). Evaporation of the organic solvent yielded 155 mg of a yellow oil. Normal phase silica flash chromatography (1 X 20 cm) utilizing a slightly different step gradient (2:3 hexane:CH_2Cl_2; 1:4 hexane:CH_2Cl_2; CH_2Cl_2; 1:4 Et_2O:CH_2Cl_2) yielded fractions containing compounds **4-6, 10** and **11**; **3**; and **8** respectively. Further purification of acanthene C(**3**) was accomplished by normal phase HPLC (1:19 hexane:EtOAc).

***Acanthene A (1)*:** obtained as a colorless oil; **HREIMS:** m/z 242.1616 ($C_{15}H_{25}{}^{37}Cl$ ΔM 0.1 mmu) and 240.1652 ($C_{15}H_{25}{}^{35}Cl$ ΔM 0.8 mmu); **LREIMS** m/z (rel. int.): 242 (6), 240 (18), 227 (9), 225 (27), 205 (9), 204 (14), 197 (51), 191 (37), 189 (3), 169 (23), 161 (45), 149 (27), 135 (43), 133 (39), 121 (30), 119 (35), 105 (62), 91 (86), 81 (100), 67 (60), 55 (58), 41 (96). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.73 (s, 3H, Me15), 0.84 (d, J = 7.0 Hz, 3H, Me12), 0.95 (d, J = 7.0 Hz, 3H, Me13), 1.99 (m, H3'), 2.17 (d, J = 10.9 Hz, H5), 2.35 (m, H3), 2.48 (m, H11), 3.95 (t, J = 10.9 Hz, H6), 4.65 (s, H14), 5.01 (s, H14'). **^{13}C NMR** see Table 1.

Acanthene B (2): obtained as a white solid; $[\alpha]_D$ -34° (*c* 0.18 $CHCl_3$); **HREIMS** m/z 263.1714 ($C_{16}H_{25}NS$ ΔM 0.6 mmu); **LREIMS** m/z (rel. int.) 263 (27), 248 (19), 221 (73), 205 (22), 204 (5), 161 (16), 149 (50), 135 (34), 109 (100), 95 (83), 81 (56), 69 (42), 67 (33), 55 (44), 41 (50); **^{1}H NMR** (500 MHz, $CDCl_3$) see Table 1; **^{13}C NMR** (75 MHz, $CDCl_3$) see Table 1; **FTIR** (film) 2080-2180 (br) cm^{-1}.

Acanthene C (3): isolated as a white amorphous solid (3.0 mg; 1 animal); **HREIMS** m/z 249.2098 ($C_{16}H_{27}NO$ ΔM +0.6mmu); **LREIMS** m/z (rel. int.) 249 (7), 234 (9), 204 (84), 189 (17), 161 (100), 133 (33), 119 (30), 105 (47), 91 (47), 81 (39), 67 (29), 55 (33), 41 (26); **DCIMS** m/z (rel. int.) 250 (100); **^{1}H nmr** (500 MHz, $CDCl_3$) see Table 1; **^{13}C nmr** (125 MHz, $CDCl_3$) see Table 1; **FTIR** (film); 3271, 3058, 2955, 2932, 2846, 1659, 1548, 1382, 901, 765 cm^{-1}.

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