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Cyclosmenospongine, a new sesquiterpenoid aminoquinone from an Australian marine sponge *Spongia* sp.

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Abstract—A new sesquiterpenoid aminoquinone, cyclosmenospongine (**1**), containing a dihydropyran ring, was isolated from an Australian marine sponge *Spongia* sp., along with the known metabolites, smenospongiarine, ilimaquinone and smenospongine. The structure of **1** was determined from spectroscopic data. © 2002 Published by Elsevier Science Ltd.

A variety of compounds having a quinone or hydroquinone moiety attached to a sesquiterpenoid skeleton have been isolated from marine sponges.[1] The sesquiterpenoid moiety of these compounds frequently has a rearranged drimane skeleton. Sesquiterpenoid quinones and hydroquinones have attached much interest in recent years due to their biological properties such as antitumor,[2] antimicrobial,[3] and anti-HIV activities.[4]

In the course of our search for biologically active metabolites from marine sponges we have investigated the EtOH extract of an Australian marine sponge *Spongia* sp. (order Dictyoceratida, family Spongiidae),[†] which exhibited marked antimicrobial and cytotoxic activities. We have isolated a new sesquiterpenoid quinone, named cyclosmenospongine (**1**), from the EtOH extract of the sponge together with the known compounds, smenospongiarine,[5] ilimaquinone,[6] and smenospongine.[7] The known compounds were identified by comparison of their spectral data with published values. In this report we describe the isolation and structural elucidation of the new compound **1**.

The EtOH extract of the freeze-dried sponge was chromatographed on a LH-20 Sephadex column in $CHCl_3$ to give, in order of elution, smenospongiarine[5] (0.027% of the dry weight of the sponge), ilimaquinone[6] (2.36%), and smenospongine[7] (0.057%), and after this in EtOH to yield **1** (0.016%). Cyclosmenospongine (**1**) was isolated as a wine-colored oil, $[\alpha]_D^{25}$ −18 (*c* 0.12, $CHCl_3$); UV (EtOH) λ_{max} (log ε) 211 (3.01), 313 (2.84) nm; IR (CCl_4) 3479, 3416 (NH_2), 1669, 1638 (C=O), 1599 (C=C), 1244 (C-O-C) cm^{-1}; EI MS (70 eV) *m*/*z* (%) 343 (33) [M^+], 191 (100), 153 (36); anal. calcd for $C_{21}H_{29}NO_3$: C, 73.47; H, 8.45; N, 4.08; found: C, 73.32; H, 8.54; N, 4.00.

Compound **1** has the molecular formula $C_{21}H_{29}NO_3$ as determined by microanalysis, EI MS, and ^{13}C NMR data (Table 1). The ^{13}C NMR and DEPT spectra revealed 21 carbons and indicated the presence of 4 methyls, 6 methylenes, 3 methines, and 8 quaternary carbons. The ^1H and ^{13}C NMR spectra (Table 1) and the fragment ion at *m*/*z* 191 in the mass spectrum of **1** showed the presence of a rearranged drimane skeleton in **1**. The UV and IR (1669, 1638, 1599 cm^{-1}) spectra indicated the presence of a 1,4-benzoquinone moiety in **1**. Moreover, the IR spectrum contained the bands of an amino group. The bathochromic shift of the absorption maximum of the quinoid chromophore in the UV spectrum of **1** indicated the location of the amino group on the quinoid moiety. The upfield shifts of the quinoid proton (δ 5.54 ppm) in the ^1H NMR spectrum and the sp^2 methine carbon (δ 98.1 ppm) in the ^{13}C NMR spectrum of **1** were due to an *ortho*-situated amino group as in the case of smenospongine.[7] The ^1H and ^{13}C NMR spectra and the unsaturation requirements of the molecular formula indicated **1** to be tetracyclic. Since the molecular formula of **1** required the three

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† Collected at Cockburn Reef, northern part of the Australian Great Barrier Reef, at a depth of 10 m by hand using scuba.

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Table 1. ^{13}C (75.5 MHz) and ^{1}H (300 MHz) NMR data of **1** ($CDCl_3$, TMS standard)

No.	δ C	δ H (J)	HMBC
1	29.1 (CH_2)	1.84 m, 1.49 m	
2	17.8 (CH_2)	1.59 m, 1.51 m	
3	40.9 (CH_2)	1.51 m, 1.25 m	
4	33.2 (C)		
5	45.7 (CH)	1.51 m	
6	22.0 (CH_2)	1.66 m, 1.51 m	
7	30.1 (CH_2)	1.54 m, 1.29 m	
8	32.3 (CH)	0.98 m	
9	37.6 (C)		
10	88.6 (C)		
11	22.4 (CH_3)	1.02 s	3, 4, 5, 12
12	32.4 (CH_3)	0.98 s	3, 4, 5, 11
13	16.3 (CH_3)	0.78 d (6.4)	7, 8, 9
14	17.1 (CH_3)	0.97 s	8, 9, 10, 15
15	26.7 (CH_2)	H_a 2.57 d (18.8)	9, 10, 16, 17
		H_b 2.06 d (18.8)	8, 9, 14, 16, 17
16	113.3 (C)		
17	153.6 (C)		
18	180.5 (C)		
19	98.1 (CH)	5.54 s	18, 20
20	152.3 (C)		
21	177.6 (C)		
NH_2		5.65 br	

oxygens and the IR spectrum indicated the absence of an hydroxyl function, the third oxygen must be an ether linkage. The chemical shift of the quaternary carbon (δ 88.6 ppm) in the ^{13}C NMR spectrum and the band at 1244 cm^{-1} in the IR spectrum of **1** confirmed the presence of an ether linkage. 2D NMR studies (HMQC, ^{1}H–^{1}H-COSY, HMBC) allowed completion of the assignments and determined the planar structure of **1**.

The relative stereochemistry of **1** was elucidated through a series of difference NOE experiments (Fig. 1). Irradiation of the Me-14 protons resulted in a NOE to H-5, H-7 (δ 1.25) and H-1 (δ 1.47), suggesting the *trans* fusion of the decalin system, and to the Me-13 protons indicating the β-orientation of both methyl groups. Moreover, the following NOE correlations were observed: H-1 (δ 1.84)/H-15 (δ 2.06); Me-13/H-15 (δ 2.57), Me-14; Me-12/H-5, H-3 (δ 1.25), H-6 (δ 1.66). The structure of **1** was thus determined.

To our knowledge, a few compounds have a dihydropyran ring formed by an ether linkage between C-10 of the same rearranged drimane skeleton and a benzenoid moiety: aureol,[8] strongylin A,[9] and smenoqualone.[10] All these sponge metabolites have the *cis* fusing decalin system. Cyclosmenospongine (**1**) differs from these compounds stereochemically bearing the *trans* fusion of the decalin system. Moreover, compound **1** is the first example of an aminoquinone which is connected to a

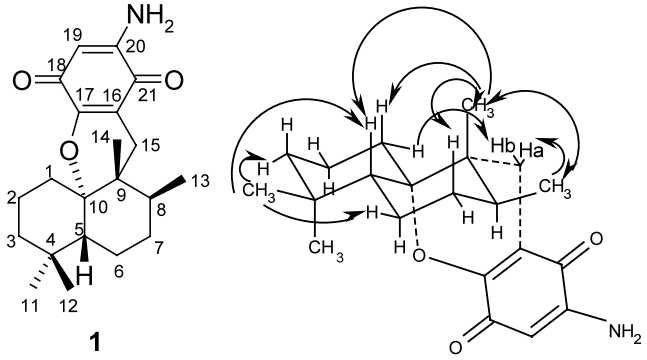

Figure 1. Selected NOE data for **1**.

rearranged drimane through a dihydropyran ring. Cyclosmenospongine (**1**) showed moderate cytotoxic activity against mouse Ehrlich carcinoma cells (IC_{100} 145 μM) and moderate hemolytic activity, inducing 50% hemolysis of mice blood erythrocytes at a concentration of 70 μM in 10 min.

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