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TETRAHYDROISOQUINOLINE ALKALOID *N*-METHYLNORSALSOLINOL FROM THE AUSTRALIAN MARINE SPONGE *Xestospongia* SP.

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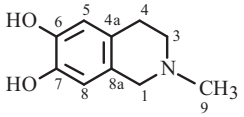
The EtOH extract from the Australian marine sponge *Xestospongia* sp. (Order Haplosclerida) collected during the 9th cruise of RV Akademik Oparin (Bougainville Reef, Australia) was studied during a search for antioxidants in marine organisms.

A lyophilized specimen of the marine sponge (100 g) was extracted exhaustively first with $CHCl_3$ and then EtOH (50%). The aqueous EtOH extract, which exhibited high activity for trapping DPPH radicals (2,2-diphenyl-1-picrylhydrazyl), was concentrated *in vacuo*. The aqueous residue was extracted with EtOAc and then *n*-BuOH. The aqueous and BuOH fractions showed antiradical activity. They were separated at low pressure over a column of C-18 silica gel (Fluka) using a H_2O:EtOH gradient. Antiradical activity was observed in the fraction eluted by H_2O during the separation of the *n*-BuOH fraction. It was concentrated *in vacuo* and crystallized from aqueous EtOH to afford **1** (132.4 mg), which was active for trapping DPPH radicals. An additional amount of **1** (8 mg) was isolated in the same manner from the aqueous fraction remaining after distribution between H_2O and *n*-BuOH.

Compound **1** (140.4 mg, 0.07% per dry sponge wt.), pale-yellow crystals (H_2O:EtOH), mp 270–273°C. UV spectrum (H_2O, λ_{max}, nm, log ε): 225, 283, 385 (3.56, 3.43, 2.54). The ^{13}C NMR spectrum of **1** contained resonances for 10 C atoms including one methyl, three methylene, two methine, and four quaternary C atoms. The PMR spectrum also showed resonances for one methyl, three methylenes, and two singlets of aromatic protons in addition to two exchangeable protons (δ 9.05 and 9.09) (Table 1). The high-resolution mass spectrum (HR-EI-MS) of **1** showed a base peak for $[M - H]^+$ at *m*/*z* 178.0867 ($C_{10}H_{12}NO_2$, 100%) that was characteristic of electron-impact decomposition of 1,2,3,4-tetrahydroisoquinolines [1]. 2D NMR spectroscopy experiments (HSQC, HMBC, COSY) enabled all resonances of **1** to be assigned. Thus, **1** was identified as 2-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (*N*-methylnorsalsolinol). A comparison of NMR spectra of **1** with those of 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (norsalsolinol) [2] confirmed that **1** was the *N*-methyl derivative of norsalsolinol. The PMR and ^{13}C NMR spectra of *N*-methylnorsalsolinol are given in Table 1 because these data have not been reported in the literature.



1

The antioxidant activity of **1** was checked using bleaching of DPPH radicals [3]. Compound **1** exhibited high activity for trapping DPPH radicals (IC_{50} 3.58 μg/mL) that was comparable with that of trolox (IC_{50} 4 μg/mL).

6,7-Dihydroxylated 1,2,3,4-tetrahydroisoquinolines such as salsolinol, norsalsolinol, and their *N*-methyl analogs are endogenous alkaloids of mammals that are found in human and rodent brain [4–6]. Links of these endogenous toxins with Parkinson's disease [7] and alcoholism [8] were found. *N*-Methylnorsalsolinol is an atypical metabolite of dopamine and probably can be formed in brain by a non-enzymatic pathway from dopamine and formaldehyde with subsequent endogenous *N*-methylation [9].

Recently Japanese researchers isolated the tetrahydroisoquinoline alkaloids salsolinol, norsalsolinol, *cis*-4-hydroxysalsolinol, and *trans*-4-hydroxysalsolinol from the marine sponge *Xestospongia* cf. *vansoesti* collected in Indonesia [2]. Our discovery was the first example of the observation of *N*-methylnorsalsolinol in a natural source and the second example of the observation of mammalian alkaloids in a marine sponge.

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TABLE 1. ^{13}C NMR (125 MHz), PMR (500 MHz, δ, ppm, J/Hz), and HMBC Spectra of **1**

C atom	DMSO-d_6			D_2O	
	δ_C	δ_H	HMBC	δ_C	δ_H[a]
1	53.2 (CH_2)	4.12 br.s	3, 4a, 8, 9	54.1 (CH_2)	4.03 (d, J = 15.1), 4.27 (d, J = 15.1)
3	50.4 (CH_2)	3.34 br.s	1, 4a, 9	51.2 (CH_2)	3.22 m, 3.58 m
4	24.4 (CH_2)	2.90 br.s	5, 8a	24.0 (CH_2)	2.96 m
4a	121.3 (C)			122.5 (C)	
5	115.2 (CH)	6.58 s	4, 7, 8a	115.3 (CH)	6.65 s
6	145.2 (C)			144.0 (C)	
7	144.4 (C)			142.8 (C)	
8	113.1 (CH)	6.53 s	1, 4a, 6	113.3 (CH)	6.56 s
8a	118.7 (C)			119.0 (C)	
9	41.9 (CH_3)	2.81 s	1, 3	41.9 (CH_3)	2.92 s
6-OH		9.05 s			
7-OH		9.09 s			

[a]δ_H of residual solvent resonance 4.75 ppm.

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