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Smenoqualone, a Novel Sesquiterpenoid from the Marine Sponge *Smenospongia sp.*

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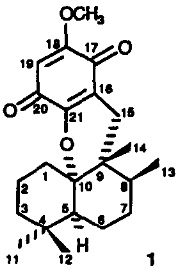
Abstract: *Smenoqualone, a novel quinonic terpenoid with a rearranged drimane skeleton was isolated from a marine sponge Smenospongia sp. The stereostructure was determined by detailed analyses of ^1H and ^{13}C NMR spectra, ^1H-^1H COSY, ^1H-^{13}C correlations via HMQC, HMBC and NOE difference NMR experiments.*

Cytotoxic sesquiterpene quinones and hydroquinones, previously reported from a marine sponge *Smenospongia sp.*[1], were shown to possess a common rearranged drimane skeleton. Recently, an investigation[2] of an unpurified fraction of the same sponge afforded the minor compound: smenoqualone **1**, with a rearranged drimane skeleton different from the earlier described in quinones **2**[1]. The structure of **1** was elucidated by extensive spectroscopic NMR analysis using COSY, HMQC, HMBC and NOE difference experiments.



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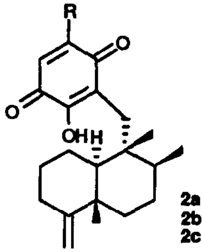

2a: R= OCH_3
2b: R= OH
2c: R= NH_2

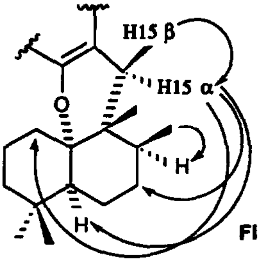

Fig. 1

Smenoqualone, a pale yellow oil, $[\alpha]_D$= +70° (c= 1.25 10^{-3}, $CHCl_3$), was assigned the molecular formula $C_{22}H_{30}O_4$ (*m/z* calcd. 358.21441, found 358. 2152) by HRMS, requiring 8 sites of unsaturation. The IR spectrum ($CHCl_3$) indicated the presence of conjugated carbonyls (1663 cm^{-1} and 1648 cm^{-1}) a double bond (1605 cm^{-1}) and an ether group (1221 cm^{-1}). UV absorptions at 204 nm (ε 5550) and 291 nm (ε 5900) suggested the presence of a quinone chromophore.

The ^1H NMR spectrum exhibited signals for one olefinic proton (δ: 5.70 ppm), one methoxy group (δ: 3.79 ppm), one methylene (δ: 2.83ppm, *J*= -18.7 Hz and 1.93 ppm, *J*= -18.7 Hz), one methyl doublet (δ: 1.07 ppm, *J*= 7.6 Hz) and three methyl singlets (δ: 0.98, 0.83 and 0.80 ppm), but no exocyclic methylene. These data suggest a tetramethyl decaline skeleton (*m/z* 191 in EIMS) not yet encountered in this sponge[1].

^1H-^1H COSY long range experiments showed strong correlation between CH_3 (δ: 0.83 ppm) and the methylenic proton H-15 (δ: 2.83 ppm), which established their trans-diaxial orientation and assigned to CH_3-14 and H-15 α the signals at δ: 0.83 ppm and δ: 2.83 ppm, respectively.

Complete proton-carbon connectivities were determined *via* HMBC and HMQC experiments. ^1H-^{13}C correlations *via* HMQC experiments assigned to CH_3-11 at δ: 29.73, CH_3-12 at δ: 31.91, CH_3-13 at δ: 17.13 and CH_3-14 at δ: 20.10 ppm (fig. 2).

The methyl singlets at δ: 0.98 (H-11) and 0.80 ppm (H-12) showed coupling to carbons at δ: 31.91, 33.43, 45.11 and δ: 29.73, 33.43 and 45.11 ppm respectively, fixing methyl groups CH_3-11 and CH_3-12 at C-4, and allowing respective assigments of C-3 and C-5 at δ: 33.43 and 45.11 ppm (fig. 2).

A ^1H-^{13}C correlation was observed between the methyl protons at δ: 1.07 ppm and carbons at δ: 27.74, 39.01 and 37.91 ppm, assigned to C-7, C-8 and C9 respectively. A ^1H-^{13}C correlation observed between the methyl singlet at δ: 0.83 ppm and carbons at δ: 39.01, 37.91; 30.69 and 87.77 located the methyl on C-9 and fixed chemical shifts of C-8, C-9, C-15 and C-10 respectively. ^1H-^{13}C correlations via HMQC experiments confirmed these observations and allowed confident assignments of C-6, C-7 and C-1 as methylene at δ: 22.45, 27.74 and 28.92 ppm respectively, supported by ^1H-^1H COSY correlations.

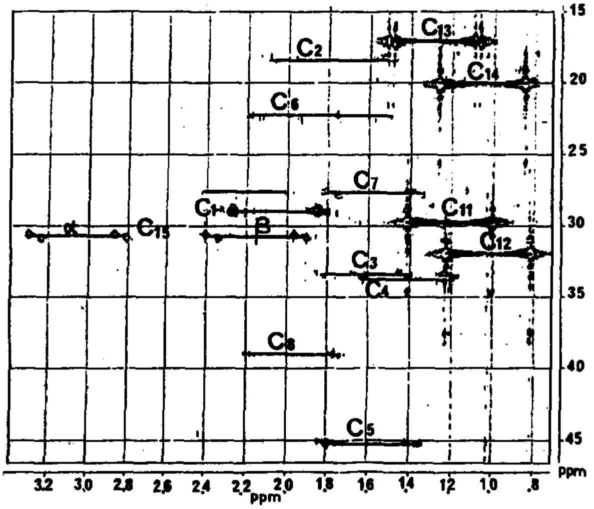

Fig.2: ^1H-^{13}C correlations observed from the HMQC spectrum

Therefore, the resonance observed at δ: 18.27 ppm was assigned to C-2. The resonance for C-10 at δ: 87.77 ppm was in accordance with an ether linkage between C-6' and C-10.

An intense NOE enhancement between the olefinic proton at δ: 5.70 ppm and the methoxyl determined their vicinal position. ^1H-^{13}C long-range correlations between on the one hand the olefinic proton at δ: 5.70 ppm and carbons at δ: 181.51 and 151.09 ppm and on the other hand, between CH_2-15 protons and the same carbons secured the paraquinonic structure of the molecule. Thus, taking in account that the intensity of the ^{13}C signal at δ: 181.51 ppm was ascribed to the two carbonyls, unambiguous assignments of the quinone ring were determined.

Hence, according to these spectral data, especially LR experiments, the same rearranged drimane skeleton was found in smenoqualone as previously in strongylin A, isolated from the marine sponge *Strongylophora hartmani*[4]. Moreover, selected NOE enhancements (fig.1) indicated the same relative stereochemistry.

It appears rather surprising to find this rearranged drimane skeleton while all the other compounds isolated from the same sponge exhibit a different one. Furthermore, this new compound proved inactive in antimicrobial, antifungal and cytotoxic assays. This would indicate that a free hydroxyl group on the quinone ring is important for the biological activity.

REFERENCES AND NOTES

1. Kondracki,M.L.; Guyot, M. *Tetrahedron*, **1989**, 45, 7, 1995-2004.
2. *Smenospongia sp.*, collected by SCUBA in the Gulf of Aden, near Djibouti. Fresh specimens (2kg) were extracted twice with 500 ml of a 1/1 methanol-chloroform mixture. The combined extracts were concentrated under reduced pressure and extracted with dichloromethane. The CH_2Cl_2 extract (8g) was repeatedly chromatographed on silicagel ($CHCl_3$/ increasing amounts of MeOH and 30% AcOEt in hexane) to yield 2 mg of smenoqualone 1 (10^{-4} % wet weight).
3. ^{13}C NMR spectrum (75.47 MHz, $CDCl_3$): 28.92 (C-1), 18.27 (C-2), 33.43 (C-3), 33.71 (C-4), 45.11 (C-5), 22.45 (C-6), 27.74 (C-7), 39.01 (C-8), 37.91 (C-9), 87.77 (C-10), 29.73 (C-11), 31.91 (C-12), 17.13 (C-13), 20.10 (C-14), 30.69 (C-15), 115.25 (C-1'), 181.51 (C-2'), 159.47 (C-3'), 104.65 (C-4'), 181.51 (C-5'), 151.09 (C-6'), 56.32 (C-3'-OMe).
4. Wright, A.E.; Rueth, S.A.; Cross, S.S. *J. Nat. Prod.*, **1991**, 54, 1108-1111.

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