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XESTOQUINONE. A NOVEL CARDIOTONIC MARINE NATURAL PRODUCT ISOLATED FROM THE OKINAWAN SEA SPONGE XESTOSPONGIA SAPRA[1)]

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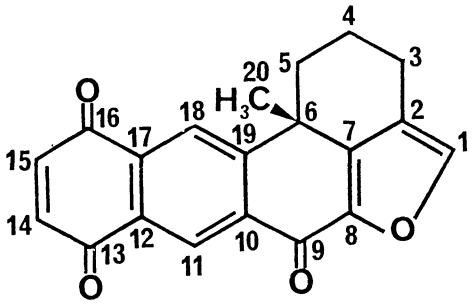
A new pentacyclic quinone, xestoquinone was isolated from the Okinawan sea sponge Xestospongia sapra as a cardiotonic constituent and the structure was identified from its spectral data.

Recently much attention has been given to bioactive sponge metabolites which have rare functionalities and structural variety.[2)] In the course of our program on physiologically active substances of marine organisms,[3,4)] we examined pharmacological actions of extracts of about 500 species of marine organisms by using isolated muscle preparations. As a result, the extract of the Okinawan sea sponge Xestospongia sapra showed a powerful cardiotonic activity. We followed the activity and obtained the active principle, named xestoquinone (1).



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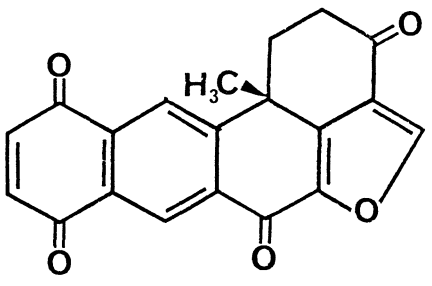

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Table 1. Comparison of xestoquinone (**1**) with halenaquinone (**2**) in ^{1}H NMR

H at	**1**[a)]	**2**[b)]
C-1	7.62 (t, 1H, J=2 Hz)	8.76 (s, 1H)
C-3	2.68 (dddd, 1H, J=17,10,9,2 Hz)	
	2.92 (dddd, 1H, J=17,8,3,2 Hz)	
C-4	2.1-2.4 (m, 2H)	2.22 (dd, 1H),
		2.94 (dd, 1H)
C-5	1.78 (ddd, J=13,13,5 Hz)	2.74 (dd, 1H)
	2.59 (ddd, J=13,4,4 Hz)	3.11 (ddd, 1H)
C-11	9.14 (s, 1H)	8.66 (s, 1H)
C-14,15	7.12 (s, 2H)	7.13 (s, 2H)
C-18	8.32 (s, 1H)	8.28 (s, 1H)
C-20	1.52 (s, 3H)	1.68 (s, 3H)

a) Recorded in $CDCl_3$ at 270 MHz.

b) Recorded in $(CD_3)_2SO$ (Ref. 6).

Table 2. Comparison of xestoquinone (**1**) with halenaquinone (**2**) in ^{13}C NMR

Atom	**1**[a)]	**2**[b)]		**1**[a)]	**2**[b)]
C-1	146.0 (d)[c)]	150.4 (d)	C-11	124.8 (d)	125.2 (d)
C-2	121.6 (s)	122.1 (s)	C-12	129.9 (s)	129.9(s)
C-3	17.8 (t)	190.9 (s)	C-13	183.8 (s)	183.3 (s)
C-4	16.2 (t)	32.3 (t)	C-14	139.0 (d)	138.7 (d)
C-5	30.3 (t)	36.1 (t)	C-15	139.0 (d)	138.8 (d)
C-6	37.0 (s)	36.4 (s)	C-16	184.2 (s)	183.8 (s)
C-7	142.9 (s)	143.9 (s)	C-17	133.1 (s)	133.3 (s)
C-8	147.8 (s)	147.9 (s)	C-18	122.9 (d)	123.5 (d)
C-9	169.2 (s)	169.5 (s)	C-19	136.8 (s)	136.3 (s)
C-10	155.8 (s)	154.1 (s)	C-20	31.7 (q)	29.7 (q)

a) Recorded in $(CD_3)_2SO$ at 22.5 MHz.

b) Recorded in $(CD_3)_2SO$ at 75.6 MHz (Ref. 6).

c) Multiplicities were determined by off-resonance decoupling techniques.

Collections were made in Kerama Rettō, Okinawa, using SCUBA (-10 ∿ -20 m). The benzene soluble portion of methanolic extracts of the fresh sea sponge (3 kg) was chromatographed on a silica gel column with chloroform as eluant by monitoring the cardiotonic activity using the guinea pig left atria stimulated electrically. The resulted active fraction was further separated by a silica gel column using a 2:3 mixture of ethyl acetate and hexane to afford 20mg of xestoquinone (1) as a yellow powder, mp 212-214 °C (decomposed).[5]

The molecular formula of $C_{20}H_{14}O_4$ was determined by high resolution mass measurements of the molecular ion at m/z 318.0870. The optical rotation value ($[\alpha]_D^{25}$ +17.2°, c 1.16, CH_2Cl_2) indicated an unsymmetrically fused ring structure. The fused aromatic structure of **1** was identified by interpretation of the spectral data. Comparison of the ^1H NMR data (Table 1) and ^{13}C NMR data (Table 2) of **1** with those of the known natural compound halenaquinone (**2**).[6] indicated that these molecules were identical in the C-6 to C-20 region. In the ^1H NMR spectrum ($CDCl_3$) the proton signals of the furan ring in **1** was observed at δ 7.62 (t, 1H, J = 2 Hz), which is in a higher field region than that of **2** (δ 8.76). The furan proton signals couples with the methylene proton signals at δ 2.68 (dddd, 1H, J = 17, 10, 9, 2 Hz) and 2.92 (dddd, 1H, J = 17, 8, 3, 2 Hz), and this suggests that the C-3 position of **1** is a methylen group instead of the carbonyl group in **2**. The structure of C-3 to C-5 region was revealed by homonuclear spin decoupling experiments. The absolute configuration of C-6 position is not yet determined.

Xestoquinone (1) showed a marked inotropic action and also caused a concentration-dependent inhibitory effect on the Na,K-ATPase isolated from pig cerebral cortex. Xestoquinone is the first example of marine natural products having parallelism between the inotropic action and Na,K-ATPase inhibition as well as cardiotonic glycosides.[7-9] The pharmacological actions of xestoquinone will be reported elsewhere in detail.

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5) **1**: IR($CHCl_3$) νmax 2950, 1680, 1610, 1450, 1320 cm^{-1}; UV(CH_3CN) λmax 217 (ε 14400), 252 (14400), 259 (sh, 13600), 296 (8020), 340 nm (4280).

6) **2** has been isolated from the sea sponge Xestospongia exigua as an antimicrobial constituent and the structure has been determined by X-ray analysis [D. M. Roll, P. J. Scheuer, G. K. Matsumoto, and J. Clardy, J. Am. Chem. Soc., 105, 6177 (1983)].

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