NOELAQUINONE, A NEW HEXACYCLIC TRIAZINE QUINONE FROM AN INDONESIAN *XESTOSPONGIA* SP.

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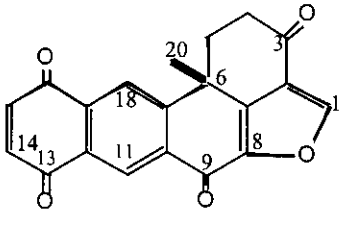
Abstract- Two derivatives of halenaquinone (**1**) have been isolated from a sponge, *Xestospongia* sp., from Derawan Island, Indonesia. In addition, a new quinone, which possesses an added triazine ring has been isolated. The regiochemistry of this compound was confirmed by spectroscopic methods.

In 1983 we[1] reported the structure of halenaquinone (**1**), which is a new pentacyclic quinone isolated from the Palauan sponge *Xestospongia exigua*. It represented a new ring system and exhibited *in vitro* antimicrobial activity against *Staphylococcus aureus* and *Bacillus subtilis*. Subsequently, two groups announced isolation of related structures from an Okinawan *Xestospongia sapra*. Kitagawa and coworkers[2] published the structures of the corresponding hydroquinone halenaquinol (**2**) and its monosulfate ester (**3**), while Nakamura *et al.*[3] reported a halenaquinone derivative, which lacked one of the two carbonyl groups *alpha* to the furan. They named it xestoquinone (**4**). During our examination of a sample of an undescribed species of *Xestospongia* from Derawan Island, Indonesia, we reisolated halenaquinone (**1**), Kitagawa's quinol (**2**) and monosulfate (**3**), and discovered a methoxyhalenaquinone (**5**), a hydroxyhalenaquinone (**6**), and an unprecedented hexacyclic compound, noelaquinone (**7**),[4] where the additional ring is a 1,2,4-triazine.

The freeze-dried sponge (67.2 g) had been collected in March, 1996, at Derawan Island, Indonesia, and identified as an undescribed species of *Xestospongia*.[5] Extraction with MeOH/CH_2Cl_2 followed by solvent partitioning and chromatography yielded halenaquinone (**1**), which was identify by comparison of NMR spectral data (Table 1) with literature values.[1,2] Similarly, identity of halenaquinol (**2**) and its sulfate (**3**) was established by matching NMR spectral data (Table 1) and optical rotation with literature values.



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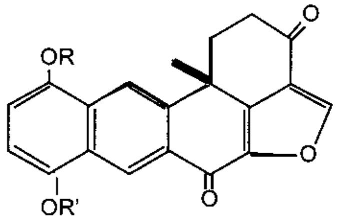
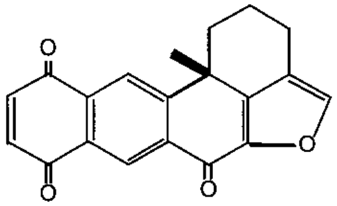


2 R, R'=H
3 R'=H; R=SO_3Na



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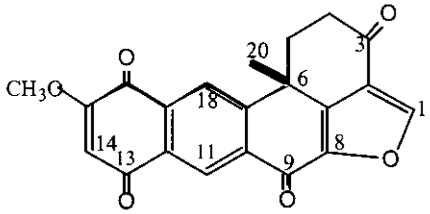

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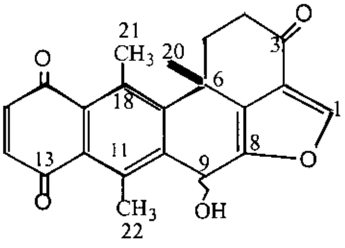

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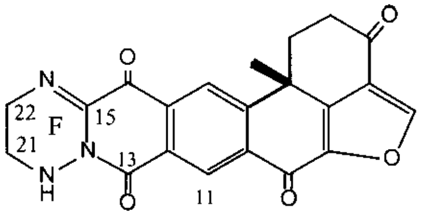

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15-Methoxyhalenaquinone (**5**) was isolated as a yellow solid. Its molecular formula, $C_{21}H_{14}O_6$, differed from that of halenaquinone (**1**)[1] by the elements of CH_2O, and comparison of ^1H NMR data (Table 2), replacement of a 2H singlet at 7.16ppm (H14, 15) by a 1H singlet at 6.30 ppm and a 3H singlet at 3.89 ppm, suggesting a methoxy derivative. In the ^{13}C-^1H long range couplings spectrum of (**5**), a proton signal at 6.30ppm is coupled to carbon signals at 180.1ppm (C13) and 126.7ppm (C12), thus placing the methoxy group at C15.

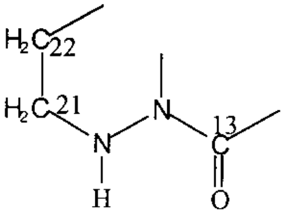
Another yellow solid, *9-hydroxy-11,18-dimethylhalenaquinone* (**6**) had *composition* $C_{22}H_{18}O_5$. *Difference* from halenaquinone by C_2H_6 provided few structural clues. However, NMR data (Table 2) revealed two methyls (6 Hs) at 2.74 ppm replacing 1H singlets at 8.88 ppm (H11) and at 8.37 ppm (H18). The carbonyl signal at 170.1 ppm in the ^{13}C NMR spectrum (Table 1) of **1** (C9) was missing. A new signal at 71.5 ppm plus an additional 2 protons in the molecular formula of **6** indicated that the C9 carbonyl in **1** *had been reduced to a hydroxyl, whose stereochemical orientation remains undetermined.*

Table 1. NMR Data for Compounds (1-3)

	1[a]		2[b]		3[c]	
No.	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	8.60S	150.7d	8.89s	150.6d	8.88s	150.6d
2		123.6s		123.7s		123.6s
3		191.6s		191.5s		191.6s
4	2.76dd(2.0,2.0)[d] 3.15ddd(6.0,5.5,5.5)	37.1t	2.73dd(2.5,2.5)[d] 3.20ddd(6.5,6.5,7.0)	37.1t	2.75dd(2.5,2.5)[d] 3.19ddd(6.5,6.5,6.5)	37.1t
5	2.76ddd(4.5,5.0,4.5) 3.05dd(2.0,2.0)	33.7t	2.40ddd(6.0,5.5,5.0) 3.08dd(2.5,2.0)	33.8t	2.37ddd(6.5,6.0,5.5) 3.07dd(2.5,2.5)	33.8t
6		37.8s		37.8s		37.7s
7		149.1s		149.0s		149.1s
8		145.6s		144.7s		145.7s
9		170.1s		171.0s		170.9s
10		138.0s		129.7s		131.0s
11	8.88s	126.5d	8.59s	126.6d	8.60s	126.6d
12		131.7s		123.7s		123.6s
13		184.6s		145.7s		141.1s
14	7.16s	139.9d	6.88s	112.1d	6.97s	109.7d
15	7.16s	140.0d	6.92s	110.2d	7.06s	110.0d
16		185.1s		147.0s		155.6s
17		134.8s		125.6s		125.7s
18	8.37s	124.7d	8.37s	120.3d	8.37s	121.0d
19		155.6s		153.1s		153.1s
20	1.78s(3H)	30.5q	1.79s(3H)	30.6q	1.79s(3H)	30.5q

[a]acetone-d_6, 500 MHz. [b] DMSO-d_6, 500 MHz. [c] DMSO-d_6, 500 MHz. [d] coupling constants in Hertz

The molecular formula of the final yellow solid (**7**) $C_{21}H_{15}N_3O_5$, differing from halenaquinone (**1**) by an additional CH_3N_3 and named noelaquinone[4] proved to have an unprecedented structure and represents a biogenetic puzzle. Comparison of NMR data of halena- (**1**) and noelaquinone (**7**) (Table 2) revealed significant differences in the carbon resonances of C13 and C15, to point to a changed naphthoquinone system. In noelaquinone (**7**) these two chemical shifts changed from 184.6 to 173.6ppm for C-13 and from 140.0 to 147.2ppm for C-15. Two new carbon resonances at 39.0 (C-21) and 48.2 ppm (C-22) in addition to a spin system, in which an exchangeable NH proton at 9.26 ppm was coupled to a 2H multiplet at 3.87 ppm, which in turn was coupled to a 2H triplet at 3.36 ppm, represented a new structural entity (A). Addition of a new 1,2,4-triazine ring in noelaquinone (**7**) was confirmed when the ^{13}C NMR spectrum was recorded in DMF-d_7 with added MeOH-d_4 to exchange the NH proton, resulting in upfield shifts of C13 and of C21.



A

Coexistence of noela- and the halenaquinones in the same animal is surprising, since halenaquinone and its congeners are constructed of a single aliphatic C_{20} chain with an additional methyl group, while noelaquinone is made up of C_{11} and C_7 carbon chains, plus the additional methyl. The new ring which destroys the thermodynamically stable naphthoquinone system is a 1,2,4-triazine.

Table 2. NMR Data for Compounds (5-7)

	5[a]		6[b]		7[c]	
No.	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C
1	8.56S	150.6d	8.52s	155.6d	8.89s	150.9d
2		122.6s		123.7s		122.4s
3		191.6s		191.1s		191.5s
4	2.78dd(1.5,2.0)[d] 3.15ddd(6.0,5.5,5.5)	37.1t	2.65dd(2.5,2.5)[d] 3.10ddd(14,6.5,7.0)	37.2t	2.66dd(3.5,2.0)[d] 3.08ddd(5.0,5.0,5.0)	36.2t
5	2.30ddd(4.5,5.0,4.5) 3.03dd(2.0,2.0)	33.7t	2.33ddd(6.0,5.5,5.0) 3.06dd(2.0,2.0)	33.8t	2.19ddd(4.0,4.0,4.5) 2.92dd(4.5,5.0)	32.3t
6		37.8s		37.9s		36.5s
7		145.6s		145.7s		148.5s
8		142.8s		149.1s		144.1s
9		170.0s	3.89s	71.5d		170.0s
10		137.6s		132.5s		137.3s
11	8.88s	125.1d		133.6s	8.74s	124.9s
12		126.7s		125.5s		131.1s
13		180.1s		184.6s		173.6s
14	6.30s	111.1d	7.06s	139.9d		
15	7.16s	162.2s	7.06s	140.0d		147.2s
16		182.3s		185.0s		178.2s
17		135.1s		134.0s		132.3s
18	8.37s	124.6d		134.1s	8.34s	124.1d
19		155.9s		154.5s		153.3s
20	1.76s(3H)	30.5q	1.20s	29.3q	1.64s	29.7q
21			2.74s	21.4q	3.87m	39.0t
22			2.74s	22.0q	3.36t(6.0)	48.2t
OCH_3	3.89s	50.9q				
NH					9.26bs	

[a] acetone-d_6, 500 MHz. [b] acetone-d_6, 500 MHz. [c] DMSO-d_6, 500 MHz. [d] coupling constants in Hertz

ACKNOWLEDGMENTS

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EXPERIMENTAL PART

NMR spectra were obtained on General Electric QE-300 and GN Omega 500 instruments. MS spectra were obtained with VG 70/SE mass spectrometers. IR spectra were measured on a Perkin-Elmer 1600 spectrophotometer. UV spectra were determined on a Hewlett Packard 8452A diode array spectrophotometer. Optical rotations were taken on a Jasco DIP370 digital polarimeter. Melting points were determined on a Fisher-Johns apparatus and are uncorrected. All solvents were distilled prior to use. *Xestospongia* sp. was collected in March, 1996, and was found at about –20 m at Derawan Island. It is elongate, 5 cm wide and thick, 10 cm high, and is blackish purple in life, with 1 cm flush oscules scattered randomly over the surface. The frozen sample (67.2 g) was extracted at room temperature with 3x 500 ml MeOH-CH_2Cl_2 (1:1) for 72 hours and the combined extracts were concentrated and successively partitioned with hexane, CH_2Cl_2 and n-BuOH. The CH_2Cl_2 phase was concentrated *in vacuo* to yield 2.5 g of dark yellow solid. The solid was subjected to silica flash chromatography with 50% EtOAc-hexane and 100% EtOAc, and further purified by silica HPLC.

15- Methoxyhalenaquinone (**5**)- yellow solid, 5 mg; mp: slowly decomposes >250 °C. UV (methanol) λ_{max} 207 (ε 45000), 213 (45000), 294 (45000); $[\alpha]_D^{23}$+33.2° (*c* 0.64, MeOH) ; IR ($CHCl_3$): 3019, 1737, 1640, 1422, 1215 cm^{-1}; ^1H and ^{13}CNMR data see Table 2. EIMS, *m/z* (relative intensity)362 (M^+, 70), 331(M^+- OCH_3, 30), 317 (M^+- OCH_3- CH_3, 100), 289 (13), 248 (30), 207 (3.4)

11,18-Dimethyl-9-hydroxyhalenaquinone(**6**)- yellow solid, 2.8 mg; mp:slowly decomposes>300 °C. UV (methanol) λ_{max} 207 (ε 45000), 211 (45000), 277 (45000); $[\alpha]_D^{23}$ +103° (*c* 0.02, MeOH); IR ($CHCl_3$): 3416, 3018, 1658, 1599, 1478, 1215 cm^{-1}; ^1H and ^{13}CNMR data see Table 2. EIMS, *m/z* (relative intensity) 362 (M^+, 27), 347 (M^+- CH_3, 59), 332 (M^+- 2xCH_3, 47), 317 (M^+- 3xCH_3, 100), 303 (34.1), 291 (20.0), 263 (23.8), 248 (30.3), 205 (10.5).

Noelaquinone (**7**)- yellow solid, 6 mg; mp: slowly decomposes >300 °C. UV(methanol) λ_{max} 206 (ε 45000) 215 (16661), 254 (10624); $[\alpha]_D^{23}$ +53.6° (*c* 0.25, MeOH); IR (MeOH): 3365, 2942, 2826, 1715, 1641, 1450, 1027 cm^{-1}; ^1H and ^{13}CNMR data see Table 2. EIMS, *m/z (* relative intensity)389 (M^+, 21), 374 (M^+- CH_3, 100), 346 (40), 331 (17), 303(36), 248 (21), 207 (8).

REFERENCES AND NOTES

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2. M. Koybayashi, N. Shimizu, Y. Kyogoku, and I. Kitagawa, *Chem. Pharm. Bull., 1985,* **33**, 1305.
3. H. Nakamura, J. Kobayashi, M. Kobayashi, Y. Ohizumi, and Y. Hirata, *Chem. Lett., 1985*, 713.

4. Noela is the name of the first author's daughter, who was born while this work was in progress.
5. A voucher specimen(BMNH 1997:9:20:1) is deposited at the British Natural History Museum, London, UK..

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