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POLYHALOGENATED 1-OCTENE-3-ONES, ANTIBACTERIAL METABOLITES FROM THE RED SEAWEED BONNEMAISONIA ASPARAGOIDES

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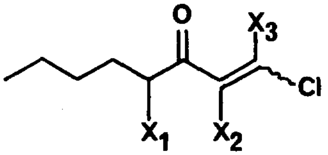
During our investigations of the halogenated constituents of red seaweeds of the family Bonnemaisoniaceae, we were prompted by a report of significant antibacterial activity from extracts of *Bonnemaisonia asparagoides* (Woodw.) C. Ag.[1] to direct our efforts toward elucidating the nature of these bioactive substances. Based on the existing knowledge of the secondary metabolism of this family of seaweeds, we initially presumed that the biologically-active components would be related to the polyhalogenated 2-heptanones isolated from *B. hamifera* collected in the Gulf of California[2]. We wish to report here that *B. asparagoides* does not contain polyhalogenated 2-heptanones but contains, instead, five closely related bromine- and chlorine-containing 1-octene-3-ones, **1** - **5**, each of which shows significant antibacterial activity toward *Staphylococcus aureus*. Interestingly, bromine- and iodine-containing 1-octene-3-ones have just recently been isolated from two Australian relatives of this alga, *Delisea fimbriata*[3] and *Ptilonia australasica*[4].



Compound	X_1	X_2	X_3	Halogen Compounds %	E/Z
1	H	Cl	Br	7.8	1.0
2	Cl	Cl	Br	66.5	20.0
3	Br	Br	Cl	5.7	--
4	Cl	Br	Br	17.1	E
5	Br	Br	Br	1.0	E

Only several small plants of *B. asparagoides* could be found during a collecting trip along the Spanish Mediterranean coast near La Escala, and they were immediately stored in 95% ethanol. Subsequently, the ethanol decant was repeatedly extracted with purified pentane. The combined pentane phases were carefully reduced by distillation, yielding a 10-mg residue which was examined by GC-MS. Five major halogen-containing compounds were eluted in the order 1 - 5, as the most volatile components of the extract. The structures of these compounds were tentatively assigned after interpretation of their mass spectral fragmentation patterns and subsequently the total structures and stereochemistry confirmed by synthesis.

The low resolution mass spectral data provided substantial structural information. Three intense ions, a McLafferty rearrangement (A) and both α-cleavage products (B,C), defined the α,β-unsaturated ketone and placed the number and kind of halogens at C-1, C-2, and C-4[5] (see Table 1). Parent ions could not be observed, even at 10 ev., but fragment ions from loss of X• were readily detected (D). Also, non-halogenated fragments at m/e = 43, 57, 71, and 99 for 1 and m/e = 41, 55, and 69 for 2 - 5 strongly suggested a total of eight carbon atoms. E and Z isomers of both 1 and 2 were recognized, since two partially resolved peaks giving identical spectra were observed for each[5].

Table 1. Mass Spectra of Polyhalogenated Octenones

	MW frag. ion/rel. intensity - % (halogen composition)			
Compound (MW)	A	B	C	D
1: E,Z-1-bromo-1,2-dichloro-1-octene-3-one (272)	216/32.0 ($BrCl_2$)	201/20.8 ($BrCl_2$)	173/14.0 ($BrCl_2$)	237/4.0 ($BrCl$) 193/12.8 (Cl_2)
2: E,Z-1-bromo-1,2,2-trichloro-1-octene-3-one (306)	250/9.8 ($BrCl_3$)	201/100.0 ($BrCl_2$)	173/13.7 ($BrCl_2$)	271/1.0 ($BrCl_2$)
3: 2,4-dibromo-1,1-dichloro-1-octene-3-one (350)	294/13.8 (Br_2Cl_2)	201/41.0 ($BrCl_2$)	173/9.6 ($BrCl_2$)	315/2.8 (Br_2Cl)
4: E-1,2-dibromo-1,4-dichloro-1-octene-3-one (350)	294/3.1 (Br_2Cl_2)	245/47.9 (Br_2Cl)	217/9.0 (Br_2Cl)	271/2.0 ($BrCl_2$)
5: E-1-chloro-1,2,4-tribromo-1-octene-3-one (394)	338/4.0 (Br_3Cl)	245/33.8 (Br_2Cl)	217/5.1 (Br_2Cl)	315/2.5 (Br_2Cl)

The halogenated metabolites 1 - 5 (except 3) were synthesized, beginning with commercially available 1-octyn-3-ol (6), by methods partially described by Sims[3]. Treatment of 6 with either Br_2 or Cl_2 and excess NaOH in MeOH/H_2O[6] gave 1-bromo- and 1-chloro-1-octyne-3-ol, 7a and 7b (bp 7a: 86-88°/1.4 mm, 7b: 66-67°/ 0.6 mm). Jones oxidation of 7a and 7b gave the corresponding ketones 8a and 8b in *ca.* 40% yields. When the bromoketone 8a was treated with xs. Cl_2 in glacial HOAc (cat. H_2SO_4), a 50% conversion to 1-bromo-4-chloro-1-octyn-3-one resulted (9). This mixture was further chlorinated with Cl_2/LiCl/HOAc, yielding a 1:1 ratio of 1 and 2, each of which was obtained as an E/Z mixture in the identical ratio observed in *B. asparagoides*. E and Z isomers for 2 were assigned based on the following information. Addition of Cl_2/LiCl to 8a in $CHCl_3$ also gave 2, but the ratio of GC peaks was 0.181 instead of 20.0. Assuming that the Z isomer (the kinetic *trans* Cl_2 addition product) is produced first in $CHCl_3$ but is less stable than the E isomer due to the sterically repulsive interactions in the tri-halo olefin system, it can be concluded that isomerization to the thermodynamically more favored E isomer occurs during chlorination in HOAc. Supporting this contention, an attempt to brominate at C-4 in 2 with the E/Z = 0.181 mixture above, using Br_2 in HOAc/H_2SO_4, resulted exclusively in isomerization of the olefin, yielding the E/Z = 20.0 ratio found in naturally-occurring 2.

Compounds 4 and 5 were prepared sequentially by halogenation of the chloroketone 8b. Bromination (Br_2 in $CHCl_3$) gave 5 directly, with no indication of isomerism, as evidenced by GC and GC-MS analysis. Compound 5 was assigned as the E isomer, assuming a *trans* addition of Br_2 under the conditions of the reaction. The structure of 4 was confirmed by a simple conversion of the C-4 bromine in 5 to chlorine by treatment with KCl/acetone/40°C/15 hrs. Mass spectra and GC retention times of the synthetic ketones 1, 2, 4, and 5 were identical with those of the natural product.

A small amount of the extract consists of a dibromo-dichloro analog we assign as structure 3. Treatment of 2 with xs. NaBr in acetone (40°C) gave E-1,4-dibromo-1,2-dichloro-1-octene-3-one (10). Although this compound exhibits characteristic MS fragments which clearly relate it to 3, it is not identical. Since the differences (retention time and MS relative abundances) could not be accounted for by a C-1/C-2 geometrical isomer, **3** was assigned as the remaining alternative.

We believe that the polyhalo 1-octene-3-ones reported here and also found in *Delisea*[3] and *Ptilonia*[4] species, as well as the *Delisea* C_9 lactones[7], have a common origin in acetate-derived precursors. Specifically, we suggest that polyhalogenated nona-2,4-diones (with hydroxylation at C-6 for some of the lactones) undergo base-induced Favorsky reactions presumably analogous to the reactions of haloacetones found in *Asparagopsis* species[8]. Favorsky reactions involving the C-2 carbonyl could yield, after decarboxylation and concommitant halogenation, the halo 1-octene-3-ones. Reactions involving the C-4 carbonyl could yield a C-4 carboxylate substituted n-octane skeleton which, through enolization of the remaining carbonyl toward C-1, could cyclize to give the *Delisea* lactones.

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