

POLYHALOKETONES FROM THE RED SEAWEED

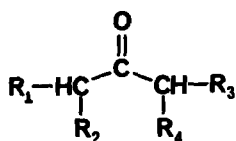
ASPARAGOPSIS TAXIFORMIS

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Two families of marine red algae, the Plocamiaceae and the Rhodomelaceae, are recognized for their genera which synthesize halogen-containing natural products. Halogenated monoterpenes<sup>1</sup> are characteristic of the Plocamiaceae (Plocamium), and halogenated phenols<sup>2</sup>, acetylenes<sup>3</sup> and terpenes<sup>4</sup> are found in various members of the Rhodomelaceae (Polysiphonia, Rhodomela, Odonthalia, Laurencia). While very little is known concerning halogen metabolism in these families, ultrastructure studies with the red seaweed Asparagopsis (Bonnemaisoniaceae) have shown that halogen metabolism probably occurs in specialized cells, "vesicular cells," near the surface of the plant<sup>5</sup>. In subsequent growth studies with Asparagopsis the vesicular cells failed to properly develop when bromide ion was excluded from the culture medium. It thus appears that bromine has been documented as an essential element for red algae in the family Bonnemaisoniaceae. Reported herein are the results of a study of the volatile halogenated metabolites of A. taxiformis, a widely distributed representative of this interesting family. The substances reported are potentially the products of bromine and chlorine metabolism within the vesicular cells.

Samples of A. taxiformis (Delile) Trev. were collected near Isla Angel de la Guarda in the Gulf of California. The partially air-dried alga was extracted with chloroform and the concentrated extract was chromatographed on silica gel. Fractions eluted with benzene (0.08% dry wt.) were combined and re-chromatographed on the same substrate to yield twelve fractions, each containing substances of a highly lacrymatory nature. The infrared spectra of each fraction showed the components to be carbonyl-containing compounds,  $\nu_{C=O} = 1670-1740 \text{ cm}^{-1}$ . The fractions were each analyzed by gas chromatography-mass spectrometry on a 3% OV-17 column operating isothermally at  $120^\circ$ . Eleven major components were readily observed, with moderate separation noted in the column chromatography fractions. Seven isomers of polyhaloacetone were the major components of these fractions (54%) and were

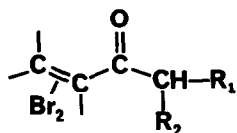


Compound	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	R <sub>4</sub>	Mixture %
1	Br	H	Br	H	9.7
2	Br	H	Br	Br	20.8
3	Br	Br	Br	Br	8.1
4	Br	H	Cl	H	1.0
5	Cl	H	Br	Br	2.7
6	Cl	Br	H	Br	8.8
7	Cl	Br	Br	Br	2.9

easily assigned to structures 1 - 7, based upon their mass spectral behavior (Table 1). The isotopic abundances of the molecular ions confirmed the halogen content of each isomer<sup>6</sup>. For compounds 1 - 7, prominent fragments are observed for an  $\alpha$ -cleavage reaction, yielding  $\text{CH}_2\text{X}$ ,  $\text{CHX}_2$  and the corresponding acylonium ions,  $\text{CH}_2\text{XCO}$ ,  $\text{CHX}_2\text{CO}$ , respectively. The simplicity of the mass spectra of these compounds is indicative of the limited modes of possible fragmentations. The isomeric monochlorodibromoacetones, 5 and 6, could be readily distinguished by a comparison of their respective base fragments, the mass and isotopic abundances of which established a monochloromethyl group in 5 and a monobromomethyl substituent in 6.

Confirmation of the structures of the haloacetones 1 - 7 was obtained by a synthesis previously described by Rappe<sup>7</sup>. Bromination of acetone at  $0^\circ$  gave compounds 1 - 3, with 3 being the major component. Bromination of monochloroacetone by the same method gave a mixture of the chlorobromoacetones 4 - 7. The nmr and mass spectra of the synthetic products and those from A. taxiformis were superimposable.

The remaining four constituents of the total benzene eluate, compounds 8 - 11, (40.5% mixture) were assigned as polyhalo-3-buten-2-one derivatives (methyl vinyl ketones) based upon intense carbonyl absorptions in the 1670-1680  $\text{cm}^{-1}$  region and by their easily understood mass spectral behavior. The major fragments (Table 1) for all four isomers consist of  $\text{C}_2\text{HBr}_2$ ,  $\text{C}_3\text{HOBr}_2$  and  $\text{CH}_2\text{X}$ ,  $\text{CHX}_2$ , which are obtained via a consistent  $\alpha$ -cleavage reaction and which strongly indicated a dibromovinyl



Compound	R <sub>1</sub>	R <sub>2</sub>	% Mixture
8	H	Br	25.2
9	H	Cl	8.9
10	Br	Cl	2.7
11	Br	Br	3.7

group. While no information could be obtained to determine the positions of the bromine substituents in this group, a consideration of the substituent effects on the chemical shift of the lone olefin proton (observed at  $\delta 7.40 - 7.65$  for 8 - 11) indicates vicinal rather than geminal substitution<sup>8</sup>.

Table 1. Mass Spectra of Polyhaloketones

Compound	molecular ion	base peak (100%)	major fragments (% base)		
1,3-dibromoacetone (1)	$\text{C}_3\text{H}_4\text{OBr}_2$	$\text{C}_2\text{H}_2\text{OBr}$	$\text{CH}_2\text{Br}$ (88)	$^{79}\text{Br}, ^{81}\text{Br}$ (50)	
1,1,3-tribromoacetone (2)	$\text{C}_3\text{H}_3\text{OBr}_3$	$\text{C}_2\text{H}_2\text{OBr}$	$\text{CHBr}_2$ (24)	$\text{CH}_2\text{Br}$ (22)	$\text{C}_2\text{HOBr}_2$ (10)
1,1,3,3-tetrabromoacetone (3)	$\text{C}_3\text{H}_2\text{OBr}_4$	$\text{C}_2\text{HOBr}$	$\text{C}_2\text{HOBr}_2$ (92)	$\text{CHBr}_2$ (86)	
1-bromo-3-chloroacetone (4)	$\text{C}_3\text{H}_4\text{OBrCl}$	$\text{C}_2\text{H}_2\text{OBr}$	$\text{CH}_2\text{Br}$ (52)	$\text{C}_2\text{H}_2\text{OCl}$ (46)	$\text{C}_2\text{HBr}_3$ (39)
1-chloro-3,3-dibromoacetone (5)	$\text{C}_3\text{H}_3\text{OBr}_2\text{Cl}$	$\text{C}_2\text{H}_2\text{OCl}$	$\text{CHBr}_2$ (21)	$\text{C}_2\text{HOBr}_2$ (10)	
1-chloro-1,3-dibromoacetone (6)	$\text{C}_3\text{H}_3\text{OBr}_2\text{Cl}$	$\text{C}_2\text{H}_2\text{OBr}$	$\text{CH}_2\text{Br}$ (34)	$^{79}\text{Br}, ^{81}\text{Br}$ (26)	$\text{C}_3\text{H}_3\text{OBr}_2$ (8)
1-chloro-1,3,3-tribromoacetone (7)	$\text{C}_3\text{H}_2\text{OBr}_3\text{Cl}$	$\text{C}_2\text{HOBr}_2$	$\text{CHBr}$ (80)	$\text{C}_2\text{HOBrCl}$ (66)	$\text{CHClBr}$ (56)
tribromo-3-buten-2-one (8)	$\text{C}_4\text{H}_3\text{OBr}_3$	$\text{C}_3\text{HOBr}_2$	$\text{C}_2\text{HBr}_2$ (24)	$\text{C}_2\text{H}_2\text{OBr}$ (16)	$\text{CH}_2\text{Br}$ (18)
chlorodibromo-3-buten-2-one (9)	$\text{C}_4\text{H}_3\text{OBr}_2\text{Cl}$	$\text{C}_3\text{HOBr}_2$	$\text{C}_2\text{HBr}_2$ (38)	$\text{C}_2\text{H}_2\text{OCl}$ (12)	$\text{CH}_2\text{Cl}$ (3)
chlorotribromo-3-buten-2-one (10)	$\text{C}_4\text{H}_2\text{OBr}_3\text{Cl}$	$\text{C}_3\text{HOBr}_2$	$\text{C}_2\text{HBr}_2$ (14)	$\text{C}_2\text{HOBrCl}$ (14)	$\text{CHClBr}$ (12)
tetrabromo-3-buten-2-one (11)	$\text{C}_4\text{H}_2\text{OBr}_4$	$\text{C}_3\text{HOBr}_2$	$\text{CHBr}_2$ (18)	$\text{C}_2\text{HBr}_2$ (16)	$\text{C}_4\text{H}_2\text{OBr}_3$ (4)

Substances of this nature, 1 - 11, are uncommon natural products and cannot be rationalized as occurring by known biosynthetic pathways<sup>9</sup>. There is a strong possibility that molecules of this type are catabolic products from larger molecules. An oxidative olefin cleavage of a polyhalogenated isoprenoid precursor would give haloacetones and halo-C<sub>4</sub> ketones, depending on the positions of the double bonds.

The halo ketones reported here show strong antimicrobial activity against a variety of microorganisms (Staphylococcus, Fusarium, Vibrio). Molecules analogous to 1 - 11 are also widely accepted as human toxins. Indeed, repeated exposure to vapor phase quantities of these ketones during chromatography procedures caused great discomfort. In this regard, it is interesting to note that the Hawaiians savor A taxiformis as a seaweed addition to their diet<sup>10</sup>.

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