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POLYHALOGENATED MONOTERPENES FROM *PLOCAMIUM CARTILAGINEUM* FROM THE BRITISH COAST

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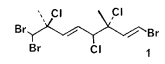
Abstract—*Plocamium cartilagineum* collected at several locations along the British coast contained polyhalogenated monocyclic monoterpenes, five of which have been fully characterised. The halogenated monoterpenes from the British samples are closely related to those previously found in *P. violaceum*. The linear polyhalogenated monoterpenes which are characteristic of *P. cartilagineum* collected in La Jolla were found in one sample of *P. cartilagineum* from Britain. The structures of the five new monocyclic monoterpenes were determined by comparison of the spectral data with those of known compounds and by chemical interconversion.

During investigations of the chemical constituents of the sea hare *Aplysia californica*, we found that the ether extracts of the digestive gland contained a complex mixture of polyhalogenated monoterpenes.[1] The major component of the monoterpene mixture, (3*R*,4*S*,7*S*) - 3,7 - dimethyl - 1,8,8 - tribromo - 3,4,7 - trichloro - 1(E),5(E) - octadiene (**1**),[2] was found to be a major constituent of the red alga *Plocamium cartilagineum*, which also contained eleven other linear polyhalogenated monoterpenes.[3] Other linear polyhalogenated monoterpenes have been reported from *Plocamium cartilagineum*,[4] *P. costatum*,[5] *Aplysia californica*[6] and *Chondrococcus hornemanni*.[7] Studies on *Plocamium violaceum* have resulted in the isolation of monocyclic monoterpenes belonging to two skeletal classes. Violacene-1 (**2**)[8,9] has an isoprenoid skeleton, while (1*R*,2*S*,4*S*,5*R*) - 1 - bromo - 2(E) - chlorovinyl - 4,5 - dimethylcyclohexane (violacene-2) (**3**)[10] and its dehydrobromination product, plocamene-B (**4**)[11] have a rearranged, non-isoprenoid skeleton. In this paper, we wish to describe the structural elucidations of five new monocyclic monoterpenes from *P. cartilagineum*, together with some chemical reactions of these compounds.

Plocamium cartilagineum collected at Bembridge, Isle of Wight, was oven-dried at 40°C, ground to a powder, and Soxhlet extracted successively with hexane, chloroform and methanol. A preliminary examination by vpc revealed that the same halogenated monoterpenes were found in all three extracts, which were combined and partitioned between ether and water. Chromatography of the ether extracts on florisil, followed by final separation on hplc, gave one major and four minor halogenated monoterpene constituents. Since the NMR spectra of three of the minor constituents were quite similar to those of compounds **2–4**, we have based the structural elucidation of each of these compounds on detailed comparisons of the spectral data.

The conjugated diene **5**, m.p. 104–5°, $[\alpha]_D^{20} = -13.2°$ ($c = 1.1$), had the molecular formula $C_{10}H_{13}BrCl_2$. The PMR spectrum of **5** was almost identical to that of **4**, except that the signal at δ 3.93 (dd, J = 10, 5.5 Hz) in **4** was at 4.22 ppm (dd, J = 10, 6 Hz) in **5**, suggesting the substitution of bromine for chlorine at C-4. Comparison of the CMR spectra supports this argument, since the greatest difference in the spectra is the replacement of the C-4 signal at 64.1 ppm (d) in **4** by a signal at 57.3 ppm (d) in **5**. In all new compounds, the coupling constants associated with the vinyl protons dictate an (E) chlorovinyl group. The relative configuration of **5** was found to be the same as **4** (see below). We have assigned arbitrary absolute configurations to all new compounds, most of which have been interconverted. We have chosen to assume that all new compounds have the absolute configuration of violacene-2 (**3**), which was determined by X-ray analysis.

A second minor product **6**, m.p. 86–87°, $[\alpha]_D^{20} = -36°$ ($c = 1.3$), had the molecular formula $C_{10}H_{14}Br_2Cl_2$ and appeared to be related to violacene-2 (**3**) by replacement of Br for one Cl atom. Again, the major difference in the PMR spectra was that the signal due to the axial proton at C-4 was at δ 3.81 in **3** and 4.05 ppm in **6**, indicating the change from Cl to Br. The CMR signals for C-4 (65.2 ppm in **3**, 58.0 ppm in **6**) show the expected chemical shift difference. Treatment of **6** with silver acetate in glacial acetic acid gave a quantitative yield of the diene **5**.



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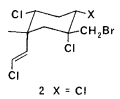
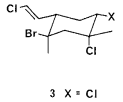


2 X = Cl
7 X = Br



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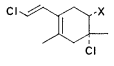
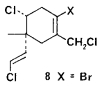
6 X = Br



4 X = Cl
5 X = Br



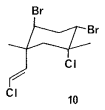
8 X = Br
9 X = Cl

The stereochemistry of **6** must be the same as for **3**, since any change in stereochemistry at either C-1 or C-5 would be expected to cause a considerable difference in the chemical shifts of signals due to the Me groups and to the axial ring protons. In a cyclohexane ring, a 1,3-diaxial interaction between a proton and a halogen causes the proton to shift downfield by about 0.5 ppm. Thus, the similarity in chemical shifts (δ 2.19 in **3** and 2.28 ppm in **6**) for the axial proton at C-3 indicated the presence of one axial halogen at C-1 or C-5 in each molecule. The signals due to the Me groups had such similar chemical shifts that it seemed most unlikely that the stereochemistry at C-1 and C-5 were not identical in **3** and **6**. In the PMR spectrum of **6**, as in that of **3**, the coupling constants between the axial proton at C-3 and those at C-2 (J = 13 Hz) and C-4 (J = 13 Hz) indicated an equatorial chlorovinyl group at C-2 and an equatorial bromine at C-4.

A third minor compound **7**, m.p. 74–5°, $[\alpha]_D^{20} = 46°$ (c = 1.01), had the molecular formula $C_{10}H_{13}Br_2Cl_3$. The PMR spectrum of **7** closely resembled that of violacene-1 (**2**), with the signal due to the axial proton at C-4 appearing at δ 4.49, as opposed to 4.29 ppm in violacene-1. Since the signals due to the protons at C-2 and C-4 are both double doublets having the same coupling constants, we wanted to confirm the PMR assignments. Treatment of **7** and violacene-1 (**2**) with lithium chloride and lithium carbonate in refluxing dimethylformamide caused elimination of hydrogen bromide to obtain a vinyl bromide **8** and a vinyl chloride **9**, respectively.[12] Comparison of the PMR spectra showed that the signals due to the protons at C-3 were at lower field for the vinyl bromide **8**, while the chemical shifts of the axial α-chloro protons at C-2 (δ 3.99 in **8**; 3.96 in **9**) were almost the same for both molecules.

The major product **10**, $[\alpha]_D^{20} = +32.5$ (c = 1.75), obtained as an oil, had the molecular formula $C_{10}H_{14}Br_2Cl_2$, isomeric with **6**. The most striking feature of the PMR spectrum was a broad singlet at δ 4.42, assigned to an equatorial α-halogen proton. The equatorial proton was coupled to two methylene protons at δ 2.46 (equatorial) and 2.92 (axial), which were in turn coupled to an axial α-halogen proton. The PMR spectrum also contained signals assigned to a *trans* chlorovinyl group at δ 5.96 and 6.47 (J = 14 Hz), two methylene protons at δ 2.09 and 2.20 (J = 12 Hz) and Me groups at δ 1.20 and 1.70, implying that **10** contained a cyclohexane ring with substituents positioned on the same carbons as in violacene-1 (**2**). Comparison of the CMR spectrum of **10** with those of known compounds suggested that the Br atoms were at C-2 and C-4, with Cl atoms at C-5 and C-10. These assignments were confirmed by a series of chemical reactions.

Treatment of **10** with one equivalent of silver acetate in glacial acetic acid gave a quantitative yield of the conjugated diene **5**, identical in all respects with natural material. The rearrangement, which involved elimination of the axial Br atom with concommitant 1,2 migration of the axial chlorovinyl group, had been proposed to explain the biosynthesis of violacene-2 (**4**).[10] Reduction of **10** with zinc in acetic acid caused replacement of the axial Br atom by hydrogen to obtain **11** as the major product. In the PMR spectra of both **10** and **11**, the equatorial protons at C-2 and C-6 were coupled with a 1 Hz coupling constant in **10** and a 3 Hz coupling constant in **11**.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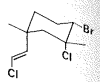
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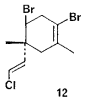
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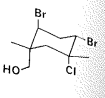
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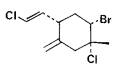
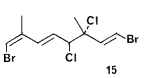

14

The reaction of **10** with lithium chloride and lithium carbonate in dimethylformamide caused elimination of hydrogen chloride to yield the vinyl bromide **12** as the major product. Ozonolysis of **10**, followed by reduction of the product with sodium borohydride, gave the alcohol **13**, which was used for a lanthanide-induced shift experiment (see below).

The remaining minor product **14**, $[\alpha]_D^{20} = -70.5°$ (c = 1), had the molecular formula $C_{10}H_{13}BrCl_2$ and was thus isomeric with the conjugated diene **5**. The PMR spectrum of **14** contained a single Me signal at δ 1.74, signals due to exocyclic methylene protons at 4.83 and 4.89, and an AB quartet at 2.43 and 2.83. An olefinic proton at δ 5.94 was coupled to a second olefinic proton at 6.05 and to an allylic proton at 2.79, which was in turn coupled to two methylene protons at 2.23, each of which was coupled to an axial α-halogen proton at 4.13 ppm. The PMR spectrum therefore indicated that **14** was a dehydrobromination product of **6**. When a solution of **6** in dimethylformamide was heated under reflux, a mixture of **5** and **14** was obtained in moderate yield.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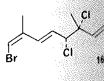
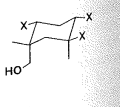

16


17 X = Br + 2 Cl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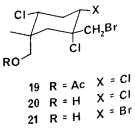
19 R = Ac X = Cl
20 R = H X = Cl
21 R = H X = Br

A second collection of *P. cartilagineum* was obtained from Overton, S. Wales. Because of the small quantity of algae collected, we were unable to identify all of the halogenated monoterpenes present. The major component was again compound **10**. We isolated four minor metabolites, three of which were linear monoterpenes **1**, **15** and **16**, identical in all respects to authentic samples isolated from Californian *P. cartilagineum*. The remaining minor metabolite **17** could not be fully characterised but is included, since it is the only example of a cyclic metabolite in which the methyl at C-5 was axial and the halogen equatorial. We were able to determine the stereochemistry of the molecule but could not distinguish between halogen atoms. The molecular formula of **17** was $C_{10}H_{14}BrCl_3$. The PMR spectrum of **17** contained signals due to two geminal methylene protons at δ 2.39 and 2.67 which were coupled to α-halogen protons at 3.84 and 4.15, two Me singlets at 1.25 and 1.65, an AB quartet at 2.20 and 2.58 due to an isolated methylene group, and a two-proton singlet at 6.17 ppm due to the chlorovinyl group. From this data we proposed the structure **17** (although we would expect chlorine at C-2, C-4 and C-10 and bromine at C-5 from chemical shift data), the stereochemistry of which was established by a lanthanide-induced shift study on the alcohol **18**.

In our previous study,[8] we used the acetate **19** rather than the alcohol **20** for a lanthanide-induced shift (LIS) study to determine the stereochemistry of violacene-1 (**2**). We have therefore repeated the stereochemical determination using the alcohol **20** and have also determined the stereochemistry of compounds **7**, **10** and **17** by the LIS method. In each case the chlorovinyl group was ozonolyzed to obtain the ozonide, which was reduced directly to the corresponding primary alcohol with sodium borohydride in ethanol. The induced shifts in the PMR spectra of the alcohols **13**, **18**, **20** and **21** were measured by stepwise addition of Eu(fod)$_3$ to the deuterochloroform solution. A graph of chemical shift vs added Eu(fod)$_3$ was used to extrapolate the shifts induced by one equivalent of Eu(fod)$_3$. As expected, the induced shifts for the alcohol **20** were much greater than for the corresponding acetate **19**. In order to find the best location for the europium atom, we used a graphical method, plotting log $\Delta\delta$ vs log r ($\Delta\delta$ = induced shift for a proton; r = distance between europium and the proton) for each of the ring protons. Using a Dreiding molecular model to measure europium-proton distances, a "best location" for europium was found such that the points fell closest to a straight line of slope −3. The results are recorded in Table 1, where r_{obs} is the measured distance and r_{calc} is the distance calculated from the graph. In each case, the europium was found to be in a position such that the europium-oxygen distance was 3.4–3.6 Å only when the hydroxymethylene group was axial to the cyclohexane ring. In **19** and **20**, the induced shifts of the bromomethylene protons indicated that the bromomethylene group was equatorial. This stereochemical assignment was subsequently confirmed by X-ray analysis.[9] In **13**, the Me group at C-5 must be equatorial, while in **18** an axial Me group gave the best fit.

The PMR data for all compounds are listed in Table 2. We have found that some simple empirical correlations were very useful in determining the structure and stereochemistry of the halogenated cyclohexanes. The replacement of bromine for chlorine caused the expected downfield shift (mean $\Delta\delta$ = 0.21, n = 5) for the α-halogen proton. The 1,3-diaxial interactions between a halogen atom and a proton are quite noticeable. For example, replacement of the axial bromine in **10** by hydrogen caused a 0.65 ppm upfield shift in the chemical shift of the axial proton at C-4 and a 0.45 ppm upfield shift in the chemical shift of the axial proton at C-6. The axial halogen at C-5 in 2, 7 and 10 caused the vinyl protons at C-9 to shift downfield by 0.3–0.4 ppm from their positions in the corresponding dehydrohalogenation products **9**, **8** and **12**. The chemical shifts of the C-3 axial proton at δ 2.45 (vs 2.78 in **7** or 2.92 in **10**) and the C-9 proton at δ 6.17 (vs 6.53 in **7** or 6.47 in **10**) gave us the first clues that **17** had an axial methyl and equatorial halogen at C-5.

Table 1. Lanthanide-induced shifts ($\Delta\delta$, ppm); calculated and measured Europium-proton distances (Å)

	13			18			20			21		
H on C-#	$\Delta\delta$	r_{calc}	r_{meas}	$\Delta\delta$	r_{calc}	r_{meas}	$\Delta\delta$	r_{calc}	r_{meas}	$\Delta\delta$	r_{calc}	r_{meas}
2	4.2	6.7	6.9	2.97	6.8	7.1	2.18	7.1	7.5	1.95	7.3	7.4
3 (ax)	4.25	6.6	6.6	3.05	6.8	6.8	2.84	7.0	6.9	2.45	6.7	6.7
3 (eq)	2.33	8.2	8.0	2.25	7.5	7.6	1.75	8.2	8.2	1.44	8.1	8.1
4	2.65	7.9	8.0	1.65	8.2	8.2	1.80	8.1	8.3	1.35	8.3	8.3
6 (ax)	5.00	6.0	6.3	2.60	7.1	7.1	2.93	6.9	6.8	2.42	6.8	6.7
6 (eq)	9.60	5.1	4.7	4.00	6.1	5.8	5.70	5.5	5.4	4.93	5.4	5.3
7	3.10	7.4	7.1	2.65	7.0	6.6	1.37 and 1.13	8.9 and 9.5	6.5 to 8.6	1.20 and 0.90	6.6 and 9.5	6.5 to 8.6
7 (alternate configuration)			5.0			8.6			4.4 to 5.9			4.4 to 5.9
8	7.30	5.6	5.6	6.60	5.3	5.0	4.35	6.1	5.7	3.38	6.1	5.5

Table 2. ^{1}H NMR data (δ in ppm from TMS)

Compound #	H-2	H-3ax	H-3eq	H-4	H-6ax	H-6eq	H-7	H-8	H-9	H-10
2	3.64	2.64	2.44	4.29	2.16	2.32	3.48 3.95	1.29	6.44	6.02
3	2.83	2.19	1.99	3.81	2.63	2.91	1.64	1.91	6.00	6.10
4	--	2.59-2.73		3.93	2.51	∿2.65	1.67	1.76	6.72	6.11
5	--	2.73-2.88		4.21	2.59	2.71	1.73	1.76	6.80	6.14
6	2.87	2.28	2.13	4.05	2.71	3.01	1.68	1.95	6.02	6.17
7	3.70	2.78	2.57	4.49	2.27	2.40	3.57 3.95	1.26	6.53	6.08
8	3.99	3.05	2.84	--	2.25	2.61	4.16 4.23	1.23	6.13*	6.02*
9	3.96	2.87	2.67	--	2.24	2.60	4.17 4.21	1.24	6.13*	6.02*
10	4.42	2.92	2.46	4.60	2.18	2.12	1.70	1.20	6.47	5.96
11	1.37 1.89	2.40	2.06	3.93	1.69	2.30	1.65	1.02	6.20	5.87
12	4.06	2.92	3.14	--	2.25	2.20	1.82	1.18	6.06	5.90
13	4.25	2.84	2.52	4.61	1.89	2.32	1.74	1.11	3.59 4.04	
14	2.79	2.23	2.23	4.13	2.44	2.84	1.74	4.83 4.89	5.95	6.05
17	3.84	2.39	2.67	4.15	2.20	2.58	1.65	1.25	6.17	6.17
18	3.95	2.45	2.66	4.18	1.86	2.83	1.76	1.13	3.67 3.71	
20	3.85	2.63	2.51	4.36	1.98	2.49	3.60 3.97	1.18	3.67 4.18	
21	3.84	2.77	2.57	4.50	2.00	2.57	3.61 3.92	1.18	3.66 4.17	

* Assignment may be reversed.

We have found the CMR spectra (Table 3) less helpful than expected in structure determination. Our principal use for the CMR spectra has been in determining the location of different halogens in closely related molecules. Replacement of the chlorine at C-4 in violacene-1 (**2**) or violacene-2 (**3**) by bromine, giving **7** and **6**, respectively, caused an upfield shift of the C-4 signal by about 7 ppm, while all other signals were hardly altered. The C-7 chemical shifts in **2** and **7** were clearly more appropriate for a bromomethylene carbon than for the chloromethylene carbon originally assigned for **2** on the basis of mass spectral data.

Having found only linear halogenated monoterpenes in California *Plocamium cartilagineum*, we were surprised to find that the major constituents of English *P. cartilagineum* were cyclic halogenated monoterepenes, closely related to the constituents of Californian *P. violaceum*. The chemosystematic implications of this result are rather disturbing. We had previously proposed that the violacene-2 (**3**) skeleton was biosynthesized from the violacene-1 (**2**) skeleton through a 1,2 migration of the chlorovinyl group. The facile conversion of **10** to the conjugated diene **5** supports this contention. In fact, intrafacial migration of the chlorovinyl group of **10** with concommitant intrafacial migration of the C-2 bromine explains the biosynthesis of **6**.

Table 3. ^{13}C NMR spectra (δ in ppm from TMS)

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
2	41.6	63.9	37.9*	58.9	71.0	48.3	38.7*	27.0	135.1	118.7
3	67.4	52.7	35.3	65.2	71.2	57.4	32.1	28.0	131.4	120.8
4[11]	123.8	129.8	34.5	64.1	69.3	48.5	30.3	18.4	130.3	117.7
5	124.5	130.0	35.8	57.4	69.2	48.2	32.1	18.6	130.2	117.7
6	67.5	53.7	36.4	58.0	71.2	57.2	33.7	28.1	131.3	121.1
7	42.0	64.6	39.1*	51.1	70.8	48.5	40.3*	27.4	135.3	119.1
10	41.4	56.1	39.3	60.5	70.1	47.9	33.4	30.4	138.2	116.9
14	142.6	45.2	40.1	58.5	71.9	49.6	32.5	112.7	132.8	119.2

* Assignment may be reversed.

EXPERIMENTAL

UV spectra were recorded on a Hitachi Perkin-Elmer 124 spectrophotometer and IR spectra on a Perkin-Elmer 136 spectrophotometer. Optical rotations were determined using a Perkin-Elmer 141 polarimeter with a one decimeter microcell, thermostated at 20°. NMR spectra were recorded on Varian EM-360, HR-220 and CFT-20 instruments. Low resolution mass spectra were recorded on a Hewlett–Packard 5930A mass spectrometer system. High resolution mass measurements were obtained from the Cal Tech Analytical Service. M.ps were determined on a Fisher–Johns apparatus and are reported uncorrected.

Collection and extraction. Plocamium cartilagineum was collected at Bembridge Bay, Isle of Wight, U.K. The algae were oven dried at 40°C and ground to a fine powder (680 g) which was Soxhlet extracted with hexane, chloroform and methanol successively. The combined extracts (58.4 g) were partitioned between ether and water. The ether extracts were combined, dried over anhydrous sodium sulfate, and the solvent evaporated to yield a dark brown gum (15.8 g).

Chromatographic separations. The crude extract was applied to a 4 × 50 cm column of florisil (100/120 mesh) and the non-polar oil eluted with a hexane and benzene mixture (1:1). Fraction 1 contained only non-halogenated hydrocarbons (0.173 g). Fractions 2 and 3 contained polyhalogenated terpenes (1.83 g). The combined fractions 2 and 3 were separated into six fractions by hplc on a μ-Porisil column (2 ft × 1/4 in.) using hexane as eluant. Fraction 3 consisted of a mixture of **10** and **5**, while fractions 4, 5 and 6 consisted of pure samples of **6** (230 mg), **14** (70 mg) and **7** (110 mg), respectively. Fraction 3 was separated into two fractions using reverse phase hplc on a μ-Bondapak C_{18} (2 ft × 1/4 in.) with acetonitrile/water (3:1) as eluant. Each fraction was thoroughly extracted with hexane, the extracts were dried over $MgSO_4$, and the solvent was evaporated to yield pure samples of **10** (840 mg) and **5** (80 mg).

(4R*,5S*) - 5 - *Bromo* - 4 - *chloro* - 2,4 - *dimethyl* - (*E*)*chlorovinylcyclohexene* (**5**). M.p. 104–104.5°; λ_{max}^{EtOH} = 240 nm (ϵ = 15,400); ν_{max} 1567, 790, 757, 706 cm^{-1}; $[\alpha]_D^{20} = -13.2°$ (c = 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.73 (s, 3H), 1.76 (br s, 3H), 2.59 (d, 1H, J = 19 Hz), 2.71 (d, 1H, J = 19 Hz), 2.73–2.88 (m, 2H), 4.21 (dd, 1H, J = 6.2, 9.7 Hz), 6.14 (d, 1H, J = 13.5 Hz) and 6.80 (d, 1H, J = 13.5 Hz); ^{13}C NMR ($CDCl_3$) δ 18.6 (q), 32.1 (q), 35.8 (t), 48.2 (t), 57.4 (d), 69.2 (s), 117.7 (d), 124.5 (s), 130.0 (s), 130.2 (d); mass spectrum *m/e* 282, 284, 286, 288 (M$^+$); 223, 225, 227 ($C_{10}H_{13}Cl_2$)$^+$; 167, 189 (base peak); high resolution mass measurement, obs: 281.958 ± 0.010, $C_{10}H_{13}{}^{79}Br^{35}Cl_2$ requires: 281.958.

(1R*,2S*,4S*,5R*) - 5 - *Chloro* - 2 - (*E*)*chlorovinyl* - 1,4 - *dibromo* - 1,5 - *dimethylcyclohexane* (**6**). M.p. 86–87°; ν_{max} 1613, 763, 744 cm^{-1}; $[\alpha]_D^{20} = -35.7°$ (c = 1.13, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.68 (s, 3H), 1.95 (s, 3H), 2.13 (dt, 1H, 3.8, 4.2, 13 Hz), 2.28 (q, 1H, J = 12, 13, 13 Hz), 2.71 (d, 1H, J = 15 Hz), 2.87 (ddd, 1H, 3.8, 7.3, 13 Hz), 3.01 (d, 1H, J = 15 Hz), 4.05 (dd, 1H, J = 4.2, 12 Hz), 6.02 (dd, 1H, J = 7.3, 14.5 Hz), 6.17 (d, 1H, J = 14.5 Hz); ^{13}C NMR δ 28.1 (q), 33.7 (q), 36.4 (t), 53.7 (d), 57.2 (t), 58.0 (d), 67.5 (s), 71.2 (s), 121.1 (d), 131.3 (d); mass spectrum 362, 364, 366, 368 (M$^+$); 167, 169 (base peak); high resolution mass measurement, obs: 361.886 ± 0.010, $C_{10}H_{14}{}^{79}Br_2{}^{35}Cl_2$ requires: 361.884.

(1R*,2S*,4S*,5S*) - 4 - *Bromo* - 5 - *bromomethyl* - 1 - (*E*)*chlorovinyl* - 2,5 - *dichloro* - *methylcyclohexane* (**7**). M.p. 74–74.5°; ν_{max} 1616, 806, 746, 709 cm^{-1}; $[\alpha]_D^{20} = -43.8°$ (c = 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 3H), 2.27 (d, 1H, J = 14 Hz), 2.40 (d, 1H, J = 14 Hz), 2.57 (dt, 1H, J = 5, 5, 14 Hz), 2.78 (q, 1H, J = 11.5, 11.5, 14 Hz), 3.57 (d, 1H, J = 11 Hz), 3.95 (d, 1H, J = 11 Hz), 3.70 (dd, 1H, J = 5, 11.5 Hz), 4.49 (dd, 1H, J = 5, 11.5 Hz), 6.08 (d, 1H, J = 13 Hz), 6.53 (d, 1H, J = 13 Hz); ^{13}C NMR ($CDCl_3$) δ 27.4 (q), 39.1 (t), 40.3 (t), 42.0 (s), 48.5 (t), 51.1 (d), 64.6 (d), 70.8 (s), 119.1 (d), 135.3 (d); mass spectrum 396, 398, 400, 402 (M$^+$); 361, 363, 365, 367, 167, 169, 131 (base peak); high resolution mass measurement, obs: 395.845 ± 0.010, $C_{10}H_{13}{}^{79}Br_2{}^{35}Cl_3$ requires: 395.845.

(1R*,2R*,4S*,5R*) - 5 - *Chloro* - 1 - (*E*)*chlorovinyl* - 2,4 - *dibromo* - 1,5 - *dimethylcyclohexane* (**10**). ν_{max} 1611, 750, 736, 680 cm^{-1}; $[\alpha]_D^{20} = +32.3°$ (c = 1.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 3H), 1.70 (s, 3H), 2.12 (d, 1H, J = 20 Hz), 2.18 (d, 1H, J = 20 Hz), 2.46 (dt, 1H, J = 2.5, 3.6, 14.7 Hz), 2.92 (td, 1H, J = 3.6, 12.0, 14.7 Hz), 4.42 (br s, 1H, J = 2.5, 3.6, 1 Hz), 4.60 (dd, 1H, J = 3.6, 12 Hz), 5.96 (d, 1H, J = 14 Hz), 6.47 (d, 1H, J = 14 Hz); ^{13}C NMR ($CDCl_3$) δ 30.4 (q), 33.4 (t), 41.4 (s), 47.9 (t), 56.1 (d), 60.5 (d), 70.1 (s), 116.9 (d), 138.2 (d); mass spectrum *m/e* 362, 364, 366, 368 (M$^+$); 167, 169 ($C_{10}H_{12}Cl$)$^+$; 91 (base peak); high resolution mass measurement, obs: 361.884 ± 0.010, $C_{10}H_{14}{}^{79}Br_2{}^{35}Cl_2$ requires: 361.884.

(2S*,4S*,5R*) - 4 - *Bromo* - 5 - *chloro* - 2 - (*E*)*chlorovinyl* - 5 - *methyl* - *methylenecyclohexane* (**14**). ν_{max} 1650, 1604, 763, 743 cm^{-1}; $[\alpha]_D^{20} = -70.5°$ (c = 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.74 (s, 3H), 2.23 (m, 2H), 2.44 (br d, 1H, J = 14.5 Hz), 2.79 (ddd, 1H, J = 4, 8, 13 Hz), 2.84 (d, 1H, J = 14.5 Hz), 4.13 (dd, 1H, J = 5.6, 10.0 Hz), 4.83 (br s, 1H), 4.89 (br s, 1H), 5.95 (dd, J = 8, 13 Hz), 6.05 (d, 1H, J = 13 Hz); ^{13}C NMR ($CDCl_3$) δ 32.5 (q), 40.1 (t), 45.2 (d), 49.6 (t), 58.5 (d), 71.9 (s), 112.7 (t), 119.2 (d), 132.8 (d), 142.6 (s); mass spectrum, *m/e* 282, 284, 286, 288 (M$^+$); 167, 169 ($C_{10}H_{12}Cl$)$^+$; 131 (base peak); high resolution mass measurement, obs: 281.960 ± 0.010, $C_{10}H_{13}{}^{79}Br^{35}Cl_2$ requires: 281.958.

Minor collection. Plocamium cartilagineum was collected at Overton (Gower Peninsula) on the Bristol Channel in July 1975. The algae were air dried and ground to a powder (150 g) which was Soxhlet extracted with chloroform. The extract was concentrated and the resulting oil partitioned between ether and water. The ether extracts were dried over sodium sulfate and the solvent evaporated to yield a gum (3.49 g). The crude material was chromatographed on florisil. Selected fractions were further purified by hplc chromatography on μ-Porasil or C-18 Bondapak to obtain **1** (190 mg), **6** (86 mg), **10** (235 mg), **15** (30 mg), **16** (20 mg) and **17** (25 mg). Compound **17**: oil; ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 3H), 1.65 (s, 3H), 2.20 (d, 1H, J = 15 Hz), 2.39 (q, 1H, J = 12, 12, 13 Hz), 2.58 (d, 1H, J = 15 Hz), 2.67 (dt, 1H, J = 5, 5, 13 Hz), 3.84 (dd, 1H, J = 12, 5 Hz), 4.15 (dd, 1H, J = 12, 5 Hz), 6.17 (s, 2H); mass spectrum, *m/e* 318, 320, 322, 324 (M$^+$).

(4S*,5R*) - 3 - *Bromo* - 4 - *chloro* - 1 - *chloromethyl* - 5 - (*E*)*chlorovinyl* - 5 - *methylcyclohexene* (**8**). Lithium chloride (10 mg, 0.23 mmoles) and lithium carbonate (10 mg, 0.14 mmoles) were added to a soln of **7** (10 mg, 0.025 mmoles) in DMF (1 ml), and the resulting suspension was boiled under reflux under an argon atmosphere for 1 hr. Water (30 ml) was added to the cooled soln and the organic material extracted with hexane (6 × 10 ml). The combined extracts were dried over $MgSO_4$ and the solvent evaporated *in vacuo* to obtain a yellow oil. Purification on μ-Porasil using 2.5% ether in hexane as eluant gave **8** as a colourless oil (5 mg, 63% yield): ^{1}H NMR ($CDCl_3$) δ 1.23 (s, 3H), 2.25 (br d, 1H, J = 17.5 Hz), 2.61 (br d, 1H, J = 17.5 Hz), 2.84 (br dd, 1H, J = 8.5, 17.5 Hz), 3.05 (br dd, 1H, J = 5.2, 17.5 Hz), 3.99 (dd, 1H, J = 5.2, 8.5 Hz), 4.17 (d, 1H, J = 11.5 Hz), 4.23 (d, 1H, J = 11.5 Hz), 6.02 (d, 1H, J = 13.5 Hz), 6.13 (d, 1H, J = 13.5 Hz); mass spectrum *m/e* 316, 318, 320, 322 (M$^+$); 135, 137 (base peak); high resolution mass measurement, obs: 315.919 ± 0.010, $C_{10}H_{12}BrCl_3$ requires: 315.919.

(4S*,4R*) - 1 - *Chloromethyl* - 5 - (*E*)*chlorovinyl* - 2,4 - *dichloro* - 5 - *methylcyclohexene* (**9**). A suspension of lithium chloride (70 mg, 1.61 mmoles), lithium carbonate (70 mg, 0.98 mmoles) and violacene-1 (**2**) (70 mg, 0.2 mmoles) in DMF (2 ml) was treated according to the procedure above to obtain **9** as a colourless oil (30 mg, 56% yield): ^{1}H NMR ($CDCl_3$) δ 1.24 (s, 3H), 2.24 (br d, 1H, J = 17.6 Hz), 2.60 (br d, 1H, J = 17.6 Hz), 2.67 (br dd, 1H, J = 8.2, 17.2 Hz), 2.87 (br dd, 1H, J = 5.2, 17.2 Hz), 3.96 (dd, 1H, J = 5.2, 8.2 Hz), 4.17 (d, 1H, J = 11.3 Hz), 4.21 (d, 1H, J = 11.3 Hz), 6.02 (d, 1H, J = 14 Hz), 6.13 (d, 1H, J = 14 Hz); mass spectrum *m/e* 272, 274, 276, 278 (M$^+$); 135, 137 (base peak); high resolution mass measurement, obs: 271.970 ± 0.010, $C_{10}H_{12}Cl_4$ requires 271.969.

(4R*,5R*) - 5 - (*E*)*Chlorovinyl* - 2,4 - *dibromo* - 1,5 - *dimethyl* - *cyclohexene* (**12**). A suspension of lithium chloride (20 mg, 0.47 mmoles), lithium carbonate (20 mg, 0.27 mmoles) and **10** (20 mg, 0.055 mmoles) in dimethylformamide was treated as in the penultimate procedure to obtain **12** as a colourless oil (9 mg, 50%

yield): ^{1}H NMR ($CDCl_3$) δ 1.18 (s, 3H), 1.82 (br s, 3H), 2.20 (d, 1H, J = 19 Hz), 2.25 (d, 1H, J = 19 Hz), 2.92 (dd, 1H, J = 7, 17 Hz), 3.14 (dd, 1H, J = 5.5, 17 Hz), 4.06 (d, 1H, J = 7 Hz), 5.90 (d, 1H, J = 13.5 Hz), 6.06 (d, 1H, J = 13.5 Hz); Mass spectrum *m/e* 326, 328, 330, 332 (M^+); 291, 293, 295 ($C_{10}H_{13}Br_2Cl)^+$; 180, 182, 184 (base peak); high resolution mass measurement obs: 325.907 ± 0.010, $C_{10}H_{13}{}^{79}Br_2{}^{35}Cl$ requires: 325.907.

Treatment of **10** *with silver acetate.* A soln of **10** (13 mg, 0.036 mmol) and AgOAc (6 mg, 0.036 mmol) in glacial AcOH (2 ml) was stirred at 100°C for 1 hr. The cooled product was adjusted to pH 9 with Na_2CO_3 aq, and the organic material was extracted with ether (5 × 15 ml). The combined extracts were dried over $MgSO_4$ and the solvent evaporated to obtain **5** as a white solid (10 mg, 95% yield), m.p. 103–4°, $[\alpha]_D^{20}$ – 12.7° (*c* = 0.97, $CHCl_3$), identical in all respects to an authentic sample.

Treatment of **6** *with silver acetate.* A soln of **6** (3.5 mg, 0.01 mmol) and AgOAc (1.7 mg, 0.01 mmol) in glacial AcOH was treated according to the procedure above to obtain **5** (2.5 mg, 89% yield), $[\alpha]_D^{20}$ – 12.6°, identical in all respects to an authentic sample.

Dehydrobromination of **6**. A soln of **6** (10 mg, 0.028 mmol) in DMF (1 ml) was heated at 150° with stirring under an atmosphere of argon for 1 hr. Water (10 ml) was added to the cooled soln and the organic material extracted with hexane (5 × 15 ml). The combined organic layers were dried over $MgSO_4$ and the solvent evaporated to yield a yellow oil (7 mg). The oil was chromatographed on μ-Porasil to obtain **5** (1.5 mg, 19% yield), $[\alpha]_D^{20}$ – 12.4° (*c* = 0.04, $CHCl_3$), identical to an authentic sample, and **14** (20 mg, 26% yield), $[\alpha]_D^{20}$ – 70.6° (*c* = 0.05, $CHCl_3$), identical to the natural material.

(1*R**,4*S**,5*R**) - 4 - *Bromo* - 5 - *chloro* - 1 - (*E*)*chlorovinyl* - 1,5 - *dimethylcyclohexane* (**11**). Powdered Zn (6 mg, 0.09 mmol) was added to a soln of **10** (12 mg, 0.033 mmol) in glacial AcOH (2 ml) and the resulting suspension stirred at 100° for 1 hr. The product was adjusted to pH 9 with Na_2CO_3 aq and the organic material extracted with ether (5 × 15 ml). The combined ether extracts were dried over $MgSO_4$ and the solvent removed to yield a yellow oil (10 mg). Chromatography on μ-Porasil using hexane as eluant gave **10** (2 mg, 16% recovery), **5** (1 mg, 11% yield) and **11** (6 mg, 64% yield); compound **11**: ^{1}H NMR ($CDCl_3$) δ 1.02 (s, 3H), 1.65 (s, 3H), 1.37 (td, 1H, J = 3.5, 13.3, 14 Hz), 1.69 (d, 1H, J = 14.4 Hz), 1.89 (dq, 1H, J = 3.2, 3.5, 3.5, 14 Hz), 2.06 (dq, 1H, J = 3.1, 3.5, 3.5, 13.3 Hz), 2.30 (dd, 1H, J = 3.2, 14.4 Hz), 2.40 (dq, 1H, J = 3.5, 12.2, 13.3, 13.3 Hz), 3.93 (dd, 1H, J = 4.2, 12.2 Hz), 4.87 (d, 1H, J = 13 Hz), 6.20 (d, 1H, J = 13.5 Hz); mass spectrum *m/e* 284, 286, 288 (M^+); 249, 251, 253; 167, 171 and 133 (base peak); high resolution mass measurement obs: 283.974 ± 0.010, $C_{10}H_{15}{}^{79}Br^{35}Cl_2$ requires: 283.973.

Ozonolysis of **10**. A mixture of O_3 in oxygen was bubbled through a soln of **10** (20 mg, 0.055 mmol) in dichloromethane (1 ml) at −78° until a persistent blue colour was obtained. Excess O_3 was removed by bubbling a stream of argon through the soln at −78°. A soln of $NaBH_4$ (5 mg, 0.1 mmol) in EtOH (1 ml) was added, and the soln was stirred for 30 min at 0°. 1% NaOH aq (10 ml) was added, and the organic material was extracted with ether (5 × 15 ml). The ether extracts were dried over $MgSO_4$ and the solvent removed to yield a crystalline **13** (18 mg, 98% yield), m.p. 89–90°: ^{1}H NMR ($CDCl_3$) δ 1.11 (s, 3H), 1.74 (s, 3H), 1.89 (d, 1H, J = 14 Hz), 2.32 (d, 1H, J = 14 Hz), 2.52 (dt, 1H, J = 2.8, 3.4, 4, 14 Hz), 2.84 (td, 1H, J = 3.4, 14, 14 Hz), 3.58 (d, 1H, J = 10 Hz), 4.04 (d, 1H, J = 10 Hz), 4.25 (br s, 1H), 4.61 (dd, 1H, J = 2.8, 14 Hz); mass spectrum, *m/e* 314, 316, 318 ($M-H_2O)^+$; 266, 268, 270 ($M-CH_3OCl)^+$; 107 (base peak).

Since we could not detect a molecular ion in the mass spectrum of **13**, we have measured the mass of the molecular ion of the corresponding aldehyde, obtained by dimethyl sulfide workup of the ozonolysis reaction. The aldehyde: ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 3H), 1.75 (s, 3H), 2.21 (d, 1H, J = 15 Hz), 2.52 (dt, 1H, J = 13.4, 3.5 Hz), 2.59 (dd, 1H, J = 15, 2 Hz), 2.81 (td, 1H, J = 13, 13, 3.5 Hz), 4.50 (dd, 1H, J = 13, 4 Hz), 4.78 (dd, 1H, J = 4, 3.5 Hz), 9.41 (s, 1H); mass spectrum, *m/e* 330, 332, 334, 336 (M^+); 187, 189; 91 (base peak); high resolution mass measurement obs: 329.900 ± 0.010, $C_9H_{11}{}^{79}Br_2{}^{35}ClO$ requires 329.902. The aldehyde was reduced to **13** in quantitative yield by treatment with $NaBH_4$ in MeOH at 0°.

Ozonolysis of **7**. A mixture of O_3 in oxygen was bubbled through a soln of **7** (2 mg, 0.005 mmol) in methylene chloride (1 ml) at −78°. The experiment was carried out according to the procedure above to obtain **21** (1.5 mg, 79% yield). ^{1}H NMR ($CDCl_3$) δ 1.18 (s, 3H), 2.00 (d, 1H, J = 15.6 Hz), 2.57 (dt, 1H, J = 13, 4.8, 4.8 Hz), 2.77 (q, 1H, J = 13, 12.5, 12.5 Hz), 3.61 (d, 1H, J = 10.6 Hz), 3.66 (d, 1H, J = 11.5 Hz), 3.84 (dd, 1H, J = 12.5, 4.8 Hz), 3.92 (d, 1H, J = 10.6 Hz), 4.17 (d, 1H, J = 11.5 Hz), 4.50 (dd, 1H, J = 12.5, 4.8 Hz); mass spectrum, *m/e* 366, 368, 370, 372, 374 (M^+); 300, 302, 304, 306 ($C_8H_{11}Br_2Cl)^+$; 185, 187 ($C_8H_{10}Br)^+$; 105 ($C_8H_9^+$, base peak); high resolution mass measurement, obs: 365.878 ± 0.010, $C_9H_{14}{}^{79}Br_2{}^{35}Cl_2O$ requires: 365.879.

Ozonolysis of **17**. A stream of O_3 in oxygen was bubbled through a soln of **17** (16 mg, 0.05 mmol) in methylene chloride at −78°. The experiment was carried out according to the procedure above to obtain **18** (12 mg, 83% yield): ^{1}H NMR ($CDCl_3$) δ 1.13 (s, 3H), 1.76 (s, 3H), 1.86 (d, 1H, J = 15 Hz), 2.45 (q, 1H, J = 13, 13, 13 Hz), 2.66 (dt, 1H, J = 3.4, 15 Hz), 2.83 (d, 1H, J = 15 Hz), 3.71 (br s, 2H), 3.95 (dd, 1H, J = 4.13 Hz), 4.18 (dd, 1H, J = 3, 13 Hz).

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THE RELATIVE BASICITY OF SULFUR CONTAINING ESTERS

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Abstract—The relative gas phase proton affinities for an amide, ester, and thiolester have been established as $CH_3CONHCH_3 > CH_3COSCH_3 > CH_3COOCH_3$ using ion cyclotron resonance techniques. A dithioester is more basic than the thiolester: $CH_3CSSCH_3 > CH_3COSCH_3$. *d*-Orbitals are unimportant in the electronic structure of thiolesters.

It is important to understand how the electronic structure may control the chemistry of thiolesters because of the crucial part these esters play in metabolism and biosynthesis.[1] Several authors have pointed out that esters are more stable than thiolesters because π-orbital overlap between sulfur $3p_z$ and carbon $2p_z$ atomic orbitals is smaller than the corresponding overlap between oxygen $2p_z$ and carbon $2p_z$ orbitals.[1–3]

The hydrolysis of thiolesters is catalyzed by hydronium ion[4–7] and the rate determining step is addition of water to the CO of the ester.[8] Acid catalysis is more effective for esters than thiolesters,[9] a fact which may be explained by assuming a lower solution basicity for thiolesters than esters. Thiolesters exert a smaller effect than esters on the stretching frequency of the acetylenic C–H bond of phenylacetylene.[10] In addition, the carbonyl stretching frequency for thiolesters is lower than ketones. IR spectroscopists have argued that since $3p_\pi$–$2p_\pi$ bonding is unimportant for the CO carbon sulfur bond of thiolesters then sulfur must withdraw electron density from the CO π-bond into nominally empty d-orbitals through $3d_\pi$–$2p_\pi$ bonding.[10–12] Thus, d_π–p_π bonding will decrease the carbonyl π-bond order thereby lowering the CO stretching frequency and will decrease the amount of electron density associated with oxygen rendering the thiolester less basic.

Since these arguments are based on isolated molecule electronic effects, they are more properly tested by measurements in the gas phase. The purpose of this research was to use a combination of CNDO/2 calculations and ion cyclotron resonance spectroscopy to evaluate the basicity of methyl thiolacetate relative to N-methylacetamide and methyl acetate and the basicity of methyl dithioacetate relative to methyl thiolacetate.

RESULTS AND DISCUSSION

Riveros *et al.* briefly reported that thiolesters have about the same basicity as the corresponding esters.[13] We found the relative gas phase basicities for an amide, ester and thiolester to be $CH_3CONHCH_3 > CH_3COSCH_3 > CH_3COOCH_3$. The basicity order of these CO compounds is analogous to the relative gas phase basicities of other nitrogen, sulfur, and oxygen compounds.[14] There is a reversal in relative basicity in the gas phase as compared to solution for the ester and thiolester. This reversal is similar to that observed for other noncarbonyl oxygen and sulfur compounds.

A comparison of the relative gas phase basicity for π-bonded sulfur and oxygen was done in order to determine if the above mentioned reversal in relative solution and gas phase basicity was unique to divalent σ-bonded oxygen and sulfur. Thiocarbonyl compounds are less basic than the corresponding CO compounds in solution, e.g. the pKa of protonated acetamide[15] is −0.9 while that of protonated thioacetamide[16] is −2.6. We found methyl dithioacetate to be more basic than methyl thiolacetate in the gas phase. This is the first example of the comparison of the gas phase basicities between a thiocarbonyl and the corresponding carbonyl compound.

Before explaining these results the site of protonation of CO compounds should be discussed. It is generally accepted that in solution protonation occurs at CO oxygen for amides, esters and thiolesters.[17] In addition, Olah has demonstrated oxygen protonation for thiolesters in magic acid.[18] However, a reversal of protonation site may occur in the gas phase. Using a semi-empirical SCFMO method, Yonezawa predicted electrophilic attack at the sulfur of methyl thiolacetate because the HOMO is of the π type localized largely on sulfur.[19] We have performed CNDO/2 calculations on carbonyl oxygen and sulfur protonated methyl thiolacetate and found carbonyl oxygen protonation is more stable regardless of d-orbital participation (Table 1).

Table 1. Stability of protonated methyl thiolacetate

	$-E_T(au)$
$CH_3C(HO^+)SCH_3$	55.3684
$CH_3C(HO^+)SCH_3$	55.6388†
$CH_3C(O^+H)SCH_3$	55.2377
$CH_3C(O^+H)SCH_3$	55.5430†

†With d-orbitals.