Tetrahedron Letters No. 44, pp 3905 - 3908, 1977. Pergamon Press. Printed in Great Britain.

THREE NEW POLYHALOGENATED MONOTERPENES FROM *PLOCAMIUM* SPECIES

R.S. Norton, R.G. Warren and R.J. Wells
Roche Research Institute of Marine Pharmacology, P.O. Box 255, Dee Why, N.S.W. 2099, Australia

(Received in UK 3 August 1977; accepted for publication 19 September 1977)

A non-destructive method, based on ^{13}C n.m.r., for assignment of the position of substitution of Br and Cl in a molecule containing both halogen atoms has been described[1]. Many marine metabolites are halogenated, and an increasing number of examples contain both Br and Cl[2]. Several species of the red algal genus *Plocamium* have yielded polyhalogenated monoterpenes containing both Br and Cl. Representatives of three monoterpene skeletons have been isolated: acyclic, monocyclic and rearranged monocyclic, exemplified by structures (1)[3], (2)[4] and (3)[5], respectively. We now describe one new monocyclic monoterpene of type (2) from *P.mertensii* (male) and two new rearranged monocyclic derivatives of type (3) from *P.cartilagineum.* The ^{13}C n.m.r. method described previously[1] was used to solve halogen substitution patterns.

Percolation of freeze-dried *P.mertensii*[6] with hexane gave an extract which deposited crystals of a new bromotrichloro terpene (4), analysing for $C_{10}H_{14}BrCl_3$, for which we propose the name mertensene. The ^1H n.m.r. spectrum of (4) in $CDCl_3$ indicated the presence of a *trans*-disubstituted double bond (δ6.08 and 5.82, each 1H, d, J 13.5Hz), two methyl singlets (δ1.78 and 1.28), two $CH(X)$-CH_2- signals (δ4.18 and 3.96, each 1H, dd, J 4.5, 12.5Hz) coupled to resonances centred at δ2.70 (1H, ddd, J 4.5, 4.5, 14Hz) and 2.36 (1H, ddd, J 12.5, 12.5, 14Hz). The remaining resonances were an AB system at δ2.22 and 2.48 (1H each, J 15Hz). These data were entirely consistent with general structure (5) for mertensene, in which the halogen substituents in the cyclohexane ring were equatorial. Reduction of (5) with chromous perchlorate in DMF gave the dichloro-derivative (6). The position of the Br and Cl atoms eliminated in this reaction therefore remained to be assigned. The ^{13}C-spin-lattice relaxation times and integrated intensities given in Table 1 for the carbons of (4) confirmed that the single Br atom was not attached to C-10, and also showed that it is not attached to C-1. This followed from the fact that resonances from C-1 and C-10 did not experience the reduction in integrated intensity expected for a quaternary brominated carbon and sp^2 hybridised brominated methine carbon, respectively[1]. In the case of C-1 the T_1 value also indicated that the carbon was not brominated, but for C-10 the T_1 value could not be utilised because the chlorovinyl group underwent internal rotation[7] about the C-5-C-9 bond[8] . It is preferable to utilise both intensities and T_1 values where possible[1]. Nevertheless, the combination of chemical evidence and ^{13}C relaxation data eliminated C-1, C-4 and C-10 as possible sites of bromination, and placed the Br on C-2. Note that the effect of Br on the spin-lattice relaxation of the C-2 resonance was less than experimental error (in contrast to the effect of Br on the relaxation of C-1 of bromocyclohexane[1]), and therefore could *not* be used for positive identification of C-2 as a brominated carbon. This is discussed below (also, see Ref. 1).

Because the *trans*-chlorovinyl group in (4) underwent considerable internal rotation it is probably equatorial. Such rotation would be more restricted in an axial orientation. Both methyl groups of (4) also underwent internal rotation (Table 1), which suggested that one was axial and the other equatorial. With the orientation of the secondary halogens proved by ^1H n.m.r., the total relative stereochemistry of mertensene is probably that shown in (4). This contrasts with the axial orientation of the halovinyl group found in other representatives of this system (e.g. 2).

Extraction of a freeze-dried Australian[9] collection of *P.cartilagineum* with CH_2Cl_2, followed by silica gel chromatography, gave (7), (0.2%) and (8) (0.06%) as the dominant compounds. (7) analysed for $C_{10}H_{14}BrCl_3$, whilst (8) analysed for $C_{10}H_{14}Br_2Cl_2$.

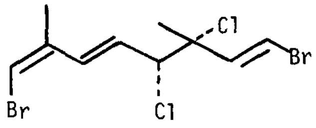
The ^1H n.m.r. spectrum of (7) in benzene-d_6 was as follows:- δ5.88 (1H, dd, J 13 , 9Hz; C9-H); 5.65 (1H, d, J 13Hz; C10-H); 3.27 (1H, dd, J 13, 4Hz; C4-H); 2.29 (1H, d, J 16Hz; C6-H); 1.05 (1H, d, J 16Hz; C6-H); 2.54 (1H, ddd, J 14, 13, 12Hz; C3-H); 1.56 (1H, ddd, J 14, 3.5, 4Hz; C3-H); 1.36 (3H, s); 1.2 (1H, ddd) and 0.98 (3H, s). This spectrum was consistent with general structure (9) in which both the halogen atom Y and the halovinyl group were equatorial[cf5]. The ^1H n.m.r. of the minor metabolite (8) in benzene-d_6 was qualitatively similar to that of (7) [δ5.82 (2H, m; C9-H + C10-H); 3.20 (1H, dd, J 12, 4Hz); 2.55 (1H, d, J 16Hz); 2.2 (1H, ddd); 2.06 (1H, d, J 16Hz); 1.9 (1H, ddd); 1.65 (3H, s); 1.6 (1H, ddd); 1.4 (1H, m); 1.22 (3H, s)]. Therefore (7) and (8) could be ascribed the same general formula (9). WXYZ = $BrCl_3$ in (7) and Br_2Cl_2 in (8).

The placement of the halogen atoms in (7) and (8) followed from an examination of ^{13}C T_1's and integrated intensities (Table 1). In (7) neither the quaternary carbon resonances C-1 and C-5, nor the sp^2 hybridised methine carbon C-10, experienced a reduction in T_1 or NOE (relative to the values calculated by assuming that relaxation is dominated by ^{13}C-^1H dipolar interactions[1,10]), indicating that they were not brominated (Table 1). The Br must therefore be placed on C-4. As in the case of C-2 of (4), the effect of Br on the relaxation of C-4 was within experimental error (Table 1), and could *not* be used for *positive* identification of C-4 as a brominated carbon. Support for the structure of (7) came from chemical evidence: treatment with DBU at 100°C for 1 hr. gave (10)[11] in good yield, and treatment with chromous sulphate gave (11) as the major product.

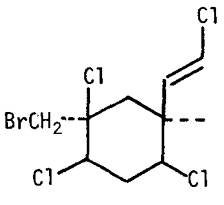
In (8) one Cl has been replaced by Br. The relaxation data in Table 1 indicated that this Br was attached to a quaternary carbon; the assignment to C-1 followed from a comparison of the chemical shifts (^1H and ^{13}C) of (7) and (8)[12]. C(1)-Br scalar relaxation is less efficient than for the allylic and aromatic brominated quaternary carbons examined previously[1]. This effect, coupled with the presence of six hydrogens two bonds removed from C-1, is responsible for the intermediate NOE (Table 1)[1,10].

The ^{13}C relaxation data for (7) and (8) indicated that there is some internal rotation about the C-2-C-9 bond in each case, which suggested that the chlorovinyl groups were equatorial. Pyrolysis of (7) at 200° for 30 minutes gave a mixture in which (10) and (12) were dominant. The coupling constants of $C3H_A,H_B$ in the pmr spectrum supported the suggestion that the chlorovinyl group of (7) was equatorial. The stereochemistry shown in (7) is probable. The occurrence of (7) and (8) in Australian *P. cartilagineum* contrasts with the report of acyclic monoterpenes, e.g. (1), in a Californian collection of the same species[3].

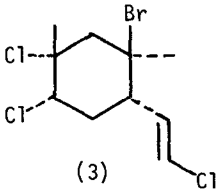
The results presented herein show that ^{13}C relaxation measurements can be used to detect Br atoms bound to quaternary carbons, provided that all contributions to ^{13}C relaxation other than those from ^{13}C-^1H dipolar and ^{13}C-halogen scalar interactions can be eliminated[1]. In the case of halogenated sp^3 hybridised methine carbons bromine substitution *may* cause a significant reduction in T_1 and NOE[1], but the *absence* of these effects does *not necessarily* eliminate the possibility that the carbon is brominated.



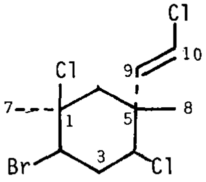
(1)



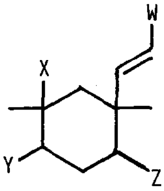
(2)



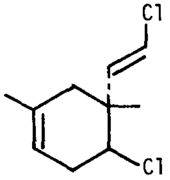
(3)



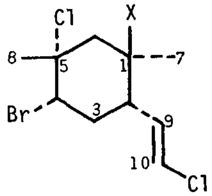
(4)



(5) WXYZ = 3Cl + Br

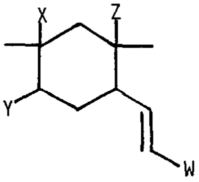


(6)

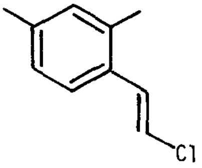


(7) X = Cl

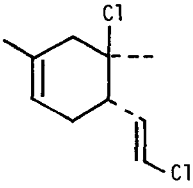
(8) X = Br



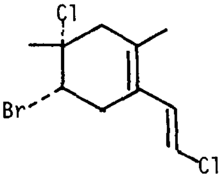
(9) WXYZ = 3Cl + Br
or 2Cl + 2Br



(10)



(11)



(12)

ACKNOWLEDGEMENT

We thank Mr. K. Harada of RRIMP for taxonomic identification. R.S.N. thanks the Queen's Fellowships Committee for the award of a Fellowship in Marine Science.

TABLE 1.

CHEMICAL SHIFTS, SPIN-LATTICE RELAXATION TIMES AND INTEGRATED INTENSITIES FOR CARBONS OF (4), (7) AND (8)[a]

CARBON[b]	MULT.[c]	(4)		(7)		(8)	
		δ[d]	T_1(int.)[e]	δ[d]	T_1(int.)[e]	δ[d]	T_1(int.)[e]
C-1	s	70.6	31 (2.8)	68.5[f]	21 (2.9)	67.5	16 (2.2)
C-2	d	67.1	3.2(2.9)	52.1	2.4(3.0)	53.7	3.5(3.0)
C-3	t	52.7	2.0(2.9)	36.4	1.2(2.9)	36.4	1.9(2.9)
C-4	d	55.2	3.1(2.8)	58.6	2.2(2.8)	58.0	3.1(3.0)
C-5	s	43.5	$\sim$36 (2.9)	67.8[f]	21 (3.0)	71.2	22 (2.9)
C-6	t	40.6	1.9(3.1)	53.1	1.3(3.0)	57.2	1.7(3.2)
C-7	q	26.1	2.0(2.9)	32.7	1.0(3.1)	28.1	1.1(2.8)
C-8	q	20.1	1.8(3.0)	34.0	1.1(3.0)	33.7	1.4(3.2)
C-9	d	140.6	$\sim$8 (3.0)	131.8	3.2(2.8)	131.3	5.2(3.0)
C-10	d	119.1	$\sim$6 (2.9)	120.4	3.2(3.0)	121.1	5.1(3.0)

[a] In $CDCl_3$ (degassed) at about 32°C. [b] Numbering system shown in structure diagram. [c] Multiplicity in single-frequency off-resonance proton-decoupled ^{13}C spectrum. [d] Chemical shift in ppm downfield from TMS (estimated accuracy is ± 0.1 ppm). [e] Spin-lattice relaxation times in sec., and integrated intensities (in parentheses). T_1 values were determined by the inversion-recovery method[13], with full proton decoupling, on a JEOL FX-60 spectrometer (15.04MHz for ^{13}C). Integrated intensities were obtained digitally from fully-relaxed, fully-decoupled spectra, and normalised by setting the arithmetic average of the intensities of resonances of C-3, C-6, C-7 and C-8 equal to 3.0. Estimated accuracy of T_1 values and intensities is ± 10%. [f] Assignments may be reversed.

REFERENCES

1. R.S. Norton. *Tetrahedron*, in press.
2. J.T. Baker and V. Murphy. "Compounds from Marine Organisms", CRC Press, 1976.
3. J.S. Mynderse and D.J. Faulkner. *Tetrahedron*, 31, 1963 (1975).
4. J.S. Mynderse and D.J. Faulkner. *J. Amer. Chem. Soc.*, 96, 6771 (1974). Structure recently amended by P. Crews and J. Clardy (D.J. Faulkner, personal communication).
5. J.S. Mynderse, D.J. Faulkner, J. Finer & J. Clardy. *Tetrahedron Lett.*, 2175 (1975).
6. Collected at Cape Jervis, South Australia; RRIMP Museum No. FN 1492.
7. D.E. Woessner. *J. Chem. Phys.*, 36, 1 (1962); D. Wallach, *ibid*, 47, 5258 (1967).
8. In addition, the cyclohexane ring of (4) does not behave as an isotropic rigid rotor (T_1 [C3, C6] > ½ x T_1 [C2, C4]).
9. Collected at Cronulla, near Sydney, N.S.W.; RRIMP Museum No. FN 1539.
10. R.S. Norton and A. Allerhand. *J. Amer. Chem. Soc.*, 98, 1007 (1976).
11. P. Crews and E. Kho. *J. Org. Chem.*, 40, 2568 (1975).
12. (8) has also been isolated by D.J. Faulkner and co-workers (personal communication), who determined the halogen substitution pattern by conventional chemical procedures.
13. R.L. Vold, J.S. Waugh, M.P. Klein and D.E. Phelps. *J. Chem. Phys.*, 48, 3831 (1968); R. Freeman and H.D.W. Hill, *ibid*, 51, 3140 (1969).