Tetrahedron Letters No. 26, pp 2155 - 2158, 1975. Pergamon Press. Printed in Great Britain.

CHONDROCOLE A AND B, TWO HALOGENATED DIMETHYLHEXAHYDROBENZOFURANS FROM THE RED ALGA CHONDROCOCCUS HORNEMANNI (MERTENS) SCHMITZ

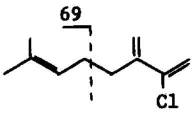
B. J. Burreson, Frank X. Woolard, and Richard E. Moore*

Department of Chemistry, University of Hawaii
Honolulu, Hawaii 96822

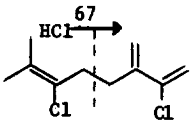
(Received in USA 13 March 1975; received in UK for publication 13 May 1975)

Recently a number of halogenated monoterpenes[1] have been identified[2] in the essential oil of Chondrococcus hornemanni (Mertens) Schmitz from the Amami Island coasts of Japan. We have isolated several new odoriferous compounds from Hawaiian C. hornemanni in addition to the reported chlorine and bromine containing myrcenes and present in this communication the structure determination of three of these new compounds. Interestingly, we have also found that the essential oils of algae collected from two different locations show remarkable diversity in composition.

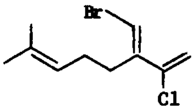
Fresh seaweed was collected at Black Point and at the Halona Blowhole, Oahu, and frozen. Essential oil was obtained by drying the thawed seaweed in vacuo in a large desiccator and collecting the volatiles in a trap cooled with Dry Ice. The oil in the resulting aqueous emulsion was transferred into methylene chloride and the dried extract was evaporated to give the essential oil (0.3-0.5% yield based on dry weight of seaweed). Fractionation of 1 g oil was achieved by chromatography on a 5' X 1" column of silica gel at 5°C. The major component (60%) of the Black Point oil, 2-chloro-7-methyl-3-methylene-1,6-octadiene[3] (1) was eluted with n-pentane and had ms and pmr spectra that were identical with those reported.[2] Continued elution with n-pentane removed the previously unreported 2,6-dichloro-7-methyl-3-methylene-1,6-octadiene (2,20%)[ms M^+ m/e 204, 206, 208 ($C_{10}H_{14}Cl_2$)] which possessed a pmr spectrum that was very similar to that of 1, with singlets at δ1.69 and 1.79 for the methyl groups, a singlet at 2.53 for the two allylic methylenes, and broad singlets at 5.12, 5.38, 5.41, and 5.55 ppm for the methylene protons. Consistent with the structure of 3 was the off-resonance decoupled cmr spectrum which exhibited four singlets at δ126.8, 128.1, 140.0 and 142.5, four triplets at 31.5, 34.7, 112.8 and 117.6 and two quartets at 20.2 and 21.8 ppm.[4] Only traces of compounds 1 and 2 were found in the Halona Blowhole oil by gc-ms analysis.



1



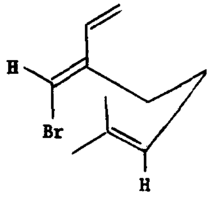
2



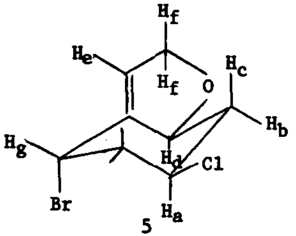
3

The major halo-substituted myrcenes in the Halona Blowhole oil were *Z*-3-bromomethylene-2-chloro-7-methyl-1,6-octadiene (3,50%) and *Z*-3-bromomethylene-7-methyl-1,6-octadiene (4,20%) with ms and pmr spectral data identical to those in the literature.[2] The third major constituent in the oil (15%), chondrocole A, $(\alpha)_D$ -16°(c 6.2, $CDCl_3$), to which we have assigned structure 5, was eluted after the halogenated myrcenes with 1:1 pentane-methylene chloride. A molecular composition of $C_{10}H_{14}BrClO$ was determined by high resolution mass spectrometry [M^+ m/e (rel. intensity) 264 (12), 266 (14), 268 (5)]. Shown also in the mass spectrum was a prominent loss of bromine from the molecular ion to give the base peak at m/e 185 (100), 187 (33) followed by elimination of HCl from this ion to give an ion at m/e 149 (28). The oxygen was concluded to be an ether from the strong band at 1080 cm^{-1} and the absence of hydroxyl and carbonyl bands in the ir spectrum (CH_2Cl_2). The presence of a geminal dimethyl group was shown by strong bands at 1360 and 1380 cm^{-1} in the ir spectrum and the 3H singlets at δ1.15 and 1.33 in the pmr spectrum. Immediately evident from the pmr spectrum of 5 was a $-CH_aX-CH_bH_c-CH_dX-$ group in a cyclic system in which the methine protons H_a and H_d had to be axially disposed and bearing strongly electronegative substituents; a 1H doublet of doublets at δ4.45 (H_a) was coupled to a 1H multiplet at δ2.65 (H_b) by 4 Hz and to another 1H multiplet at δ2.05 (H_c) by 13 Hz, H_b and H_c being the protons of a nonequivalent methylene group (J_{gem} -12 Hz) that were also coupled to H_d by 6 and 10 Hz respectively. A complex 1H multiplet at δ5.0 assigned to H_d was shown by nmdr experiments to be further coupled *allylically* to a 1H multiplet at δ5.78 (H_e) by 2 Hz and *homoallylically* to a 2H doublet of doublets at δ4.72 (magnetically equivalent H_f protons) by 5 Hz,[5] the H_e and H_f protons interacting with a coupling of 2 Hz.[6] The low chemical shift of the H_f protons indicated that a strongly electronegative substituent was attached to the allylic methylene group. Finally there was a sharp 1H singlet at δ4.64 (H_g) in the pmr spectrum. The off-resonance cmr spectrum of 5 supported the pmr assignments by exhibiting two singlets at δ41.7 and 137.6, four doublets at 54.4, 63.8, 80.7, and 122.3, two triplets at 41.7 and 75.4, and two quartets at 21.0 and 27.6 ppm.

On the basis of these data we rationalized that chondrocole A is 5. Its carbon skeleton is compatible with the isoprene rule and the bromine and chlorine substituents are located at positions similar to those in the halogenated myrcenes. Furthermore the bromine is in an allylic environment to explain the facile loss of bromine rather than chlorine from the molecular ion in the mass spectrum and also H_g is equatorial and therefore should not show long-range coupling[7] with H_e and the two H_f protons. Chondrocole A is a minor constituent of the Black Point oil (1%) as are 3 (4%) and 4 (1%).



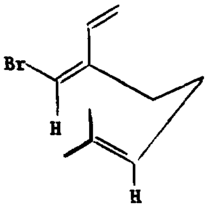
4



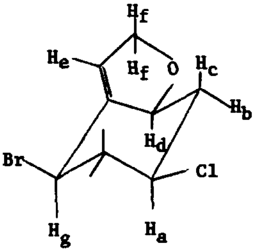
5

Eluted just prior to 5 on silica gel chromatography of the Black Point oil is the epimer 7 (chondrocole B) which exhibits a mass spectrum identical with that of 5. In the pmr spectrum of 7, however, the axial H_g proton (δ4.34) is diamagnetically displaced from that of 5 and now shows both allylic coupling to H_e (δ5.88) and homoallylic coupling to the two H_f protons (δ4.72). In addition H_a (δ3.96) and H_d (δ4.8) are diamagnetically shifted whereas the axial methyl group (δ1.36) and H_e show small paramagnetic shifts with respect to those of 5. The remaining pmr signals of 7 have chemical shifts that are identical to those of 5.

Biogenetically chondrocoles A and B are probably formed from 4 and its E isomer 6, respectively. If 4 and 6 are first oxidized to the C-4 alcohols, subsequent attack of a chloronium ion on the Δ^6 double bond and concomitant cyclization between C-7 and the bromomethylene carbon and between C-1 and a hydroxyl on C-4 leads to 5 and 7, respectively. Highly suggestive that the pathways 4 → 5 and 6 → 7 are operative in the alga is the fact that the pool sizes of 4 and 5 or 6 and 7 are always comparable. In the Halona Blowhole oil 4 and 5



6



7

are major constituents whereas 6 and 7 are present in trace amounts (<1%). In the Black Point oil the concentrations of 4, 5, 6, and 7 are all about the same.

Acknowledgment. This research was supported by a grant from the National Science Foundation (GP 43763X). We thank Dr. Peter Roller (NCI) for determining some of the mass spectra and Mitchell D. Hoyle (Department of Botany) for identifying the seaweed.

REFERENCES

1. Polyhalogenated acyclic and monocyclic monoterpenes have been found previously in red algae belonging to the genus Plocamium: J. S. Mynderse and D. J. Faulkner, J. Amer. Chem. Soc., 96, 6771 (1974); P. Crews and E. Kho, J. Org. Chem., 39, 3303 (1974).

2. N. Ichikawa, Y. Naya, and S. Enomoto, Chemistry Letters, 1333 (1974).

3. In Ref. 2 compounds 1, 2, 3 are unconventionally named 7-chloromyrcene, Z-10-bromomyrcene, and Z-10-bromo-7-chloromyrcene, respectively.

4. Nmr spectra were determined in chloroform-d and chemical shifts are reported in δ units (parts per million) using $(CH_3)_4Si$ as an internal reference (δ0).

5. The homoallylic coupling in 2,5-dihydrofurans and similar systems show rather large coupling constants: see L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Oxford, 1969, p. 328.

6. It is not unusual to observe larger homoallylic than vicinal coupling in 2,5-dihydrofurans and related systems: L. F. Johnson, A. V. Robertson, W. R. J. Simpson, and B. Witkop, Aust. J. Chem., 19, 115 (1966).

7. See Ref. 5, p. 316 and p. 325.