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EVIDENCE FOR THE BIOGENESIS OF HALOGENATED MYRCENES FROM THE RED ALGA CHONDROCOCCUS HORNEMANNI

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Several new halogenated monoterpenes (3-6,10-15) have been isolated from Hawaiian Chondrococcus hornemanni which suggest that the halogenated myrcenes are formed by the enzymatic addition of BrCl followed by dehydrohalogenation.

Recently we[1] reported the isolation of some mono- and dihalogenated myrcenes and two novel dihalogenated dimethylhexahydrobenzofurans, chondrocoles A (1) and B (2), from Hawaiian Chondrococcus hornemanni (Mertens) Schmitz. During this work a striking difference was noted in the distribution of these compounds in two specimens of algae collected from Black Point and the Halona Blowhole, which are about 6 mi. apart on the island of Oahu. In this communication we describe several new polyhalogenated monoterpenes from these two seaweeds that indicate the halogenated myrcenes are formed by the enzymatic addition of BrCl (Markovnikov or anti-Markovnikov) to the Δ^1,Δ^6 and/or the C-3 methylene double bonds of 7-methyl-3-methylene-1,6-octadiene (myrcene) followed by the elimination of HCl and/or HBr, e.g. myrcene $\xrightarrow{BrCl}$ $\xrightarrow{-HBr}$ 2-chloro-7-methyl-3-methylene-1,6-octadiene $\xrightarrow{BrCl}$ 5 $\xrightarrow{-HCl}$ Z-3-bromomethylene-2-chloro-7-methyl-1,6-octadiene.

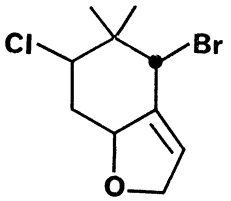
Dried seaweed (680 g) from Black Point was extracted with ether and the extract (6.8 g) chromatographed on silica gel with hexane at 5° to give four acyclic compounds, 3-6. Elemental analysis of the major component (3, 1 g) established its formula as $C_{10}H_{15}Cl_3Br_2$; the mass spectrum, however, exhibited no molecular ion, only a cluster of ions at m/e 319, 321, 323, 325 for loss of Br and a stronger one at m/e 283, 285, 287, 289 for loss of Br and HCl. The pmr spectrum of 3 in $CDCl_3$ had methyl singlets at δ1.78 and δ1.92, a pair of sharp doublets (J 2 Hz) at δ5.60 and δ5.82 for a terminal methylene, a halomethyl singlet at δ3.82 (doublets at δ3.38 and δ3.51, J 11 Hz, in benzene-d_6), a doublet for a methine-bearing halogen at δ4.01 (J 10 Hz), and a multiplet at δ2.64 (C-4 methylene) coupled to a multiplet at δ2.0 (C-5 methylene). The structure of 3 was secured by comparison of the pmr and cmr spectra with model compounds such as 6,7-dibromo-2-chloro-7-methyl-3-methylene-1-octene (7) and 6,7-dichloro-7-methyl-3-methylene-1-octene (8), prepared from the reaction of

equimolar amounts of bromine with 2-chloromyrcene and sulfuryl chloride with myrcene, respectively, and by dehalogenation of 3 with excess chromous sulfate in DMF to 7-bromo-2,6-dichloro-7-methyl-3-methylene-1-octene (9). Compound 9 showed pmr signals at δ5.28, 5.45, 5.52 and 5.66, very similar to those of 7 (δ5.24, 5.42, 5.50 and 5.63) and other 2-chloro-3-methylene-1,6-octadienes.[1,2]

Compounds 4-6, obtained in about 40 mg amounts from the extract, have pmr spectra which differ only slightly from that of 3. The pmr spectrum of 4 exhibited the identical olefinic and halomethyl signals; no signal, however, was present at δ4 for a proton on C-6 and the methyl signals were now at δ1.80 and δ1.84, similar to compounds with a Δ^6 double bond and a halogen on C-6.[1,2] Compound 4 also showed no molecular ion in its mass spectrum, but had prominent ion clusters at m/e 247, 249 and 251 (loss of HCl and Cl) and at 239, 241 and 243 (loss of Br). Compound 5 had no chlorine atom at C-6 as its pmr spectrum displayed a broad multiplet at δ5.1 for a proton on C-6 and methyl signals at 1.72 and 1.68 ppm. Compound 6 had a pmr spectrum which was identical to that of 3 except for the presence of a typical AMX vinyl pattern between δ5 and 6 instead of the terminal methylene signals and a shift of the halomethyl singlet to 3.69 ppm. The mass spectrum of 6 also did not have a molecular ion, but exhibited prominent ion clusters at m/e 249, 251, 253 ($C_{10}H_{15}ClBr$) and 205, 207, 209 ($C_{10}H_{15}Cl_2$).

Dried plants (77 g) collected at the Halona Blowhole were extracted to give 2 g of an oil which contained, in addition to 1 (480 mg), a 1:3 mixture of 6 and 10 (250 mg). Compounds 6 and 10 could not be separated on silica gel and alumina. Combustion analysis of the mixture confirmed the molecular formulae for 6 and 10 and the mass spectrum showed a strong ion cluster at m/e 293, 295, 297 ($C_{10}H_{15}Br_2$) for loss of HCl and Cl from the molecular ion of 10. In the pmr spectrum the chemical shift of the bromomethyl group of 10 is identical to that of 6 (δ3.69) whereas the methyl groups of 10 resonate at higher field (δ1.68 and 1.79) compared with those of 6. Compound 10 must therefore have a chlorine on C-3, a bromine on C-6 and a chlorine on C-7. Examination of the pmr spectrum of 6 from the Black Point alga showed that a small amount of 10 was present in the sample; furthermore, a close inspection of the cmr spectrum of 3 from the Black Point seaweed revealed that the isomeric 13 was present as a minor constituent in that sample.

6-Bromo-7-methyl-3-methylene-1,6-octadienes have already been found in the essential oil of C. hornemanni from Amami Island coasts of Japan.[2] In the extract of the Black Point alga we have found 100 mg of 6-bromo-2-chloromyrcene (11)[2] and 450 mg of a new related compound 12 (chondrocole C). Chondrocole C had a pmr spectrum similar to that of 2; the mass spectrum, however, showed a molecular ion cluster at m/e 308, 310, 312 ($C_{10}H_{14}Br_2O$) and the cmr spectrum exhibited peaks at 54.9 and 55.7 ppm for two methines bearing bromines.



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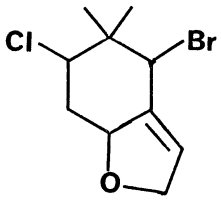

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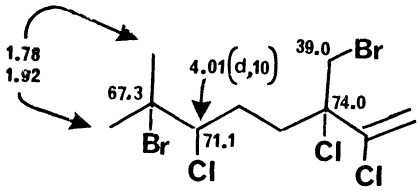

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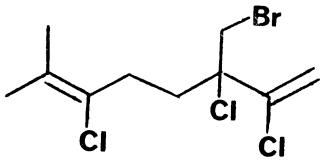

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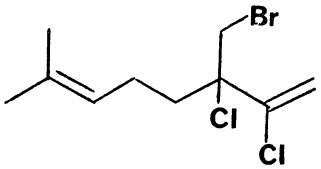

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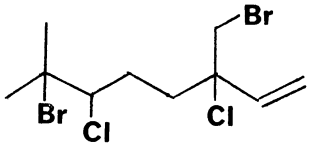

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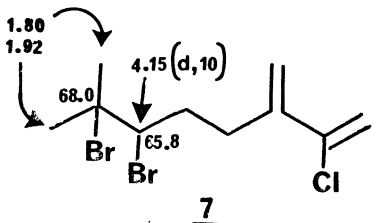

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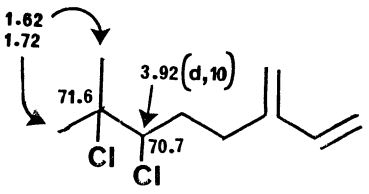

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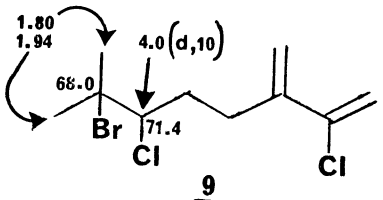

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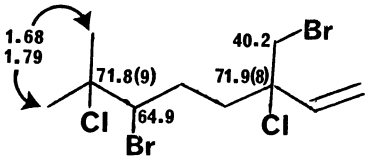

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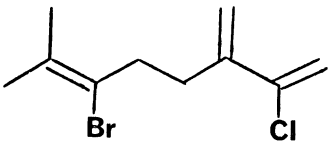

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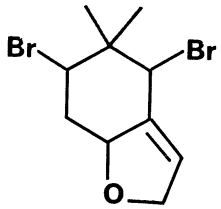

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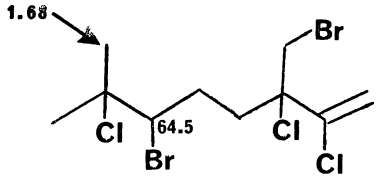

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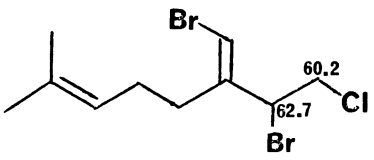

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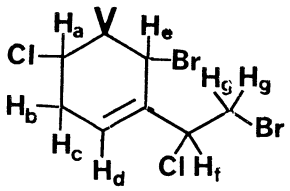

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Two compounds (14 and 15) with the elements of BrCl added to the Δ^1 double bond of myrcene have been isolated from Hawaiian C. hornemanni. From the Halona Blowhole extract was obtained 30 mg of 14 which showed in its mass spectrum a molecular ion and a strong ion cluster at m/e 249, 251, 253 for loss of the allylic bromine. The cmr spectrum confirmed that a chlorine was on the C-8 methylene and that bromine was attached to the C-7 methine. The pmr spectrum of 14 showed singlets at δ1.66 and 1.71 for the olefinic methyls, a 4H multiplet centered at 2.29, a typical ABX pattern for the $-CHBrCH_2Cl$ group (CH_2 at 3.2, J_{gem} -11 Hz, and CH at 4.61), a multiplet at 5.17 for the olefinic proton, and a singlet at 6.46 ppm for the bromomethylene. Finally, chromous sulfate dehalogenation of 14 gave Z-3-bromomethylene-7-methyl-1,6-octadiene, which was identical with the natural compound.[1]

Compound 15 (60 mg from the Black Point extract) was found to be cyclic and related to the chondrocoles. The mass spectrum again did not show a molecular ion, but had ion clusters at m/e 327, 329, 331 and 333 ($C_{10}H_{14}Br_2Cl$) and 283, 285, 287, 289 ($C_{10}H_{14}Cl_2Br$), indicating a molecular formula of $C_{10}H_{14}Br_2Cl_2$ and the presence of an allylic bromine and an allylic chlorine. The cmr spectrum was consistent with 15 having two methines bearing chlorine (61.2 and 60.0 ppm), a methine with a bromine on it (56.2 ppm), and a bromomethylene (40.0 ppm). The pmr spectrum of 15 had singlets at δ1.25 and 1.36 for a gem-dimethyl group, a 2H doublet at 3.78 (H_g) coupled to a 1H triplet at 5.10 (H_f) which in turn was allylically coupled by 1 Hz to an olefinic proton (H_d) resonating as a broad singlet at 5.92 ppm. Proton H_d was also coupled allylically by 1 Hz to H_e (δ4.86) and vicinally by 4 Hz to H_b and H_c (δ2.76). The H_b and H_c protons were coupled vicinally by 7 Hz to a 1H triplet at δ4.13 (H_a) and homoallylically to H_e by 2.5 Hz. The H_a proton must be axial, as in 1 and 2, to account for the large coupling with H_b and H_c. By analogy with 1, 2 and 14, the allylic bromine and chlorine are on the ring and side chain, respectively (tentative assignments).

2-Bromo-7-methyl-3-methylene-1,6-octadienes have been found in Japanese C. hornemanni. To date no compounds have been found with both bromine on C-3 and a chloromethyl group at C-3. Such compounds should be present as 3-chloromethylene-7-methyl-1,6-octadienes have been reported in the essential oil of Japanese C. hornemanni.[2]

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