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7-CHLORO-3,7-DIMETHYL-1,4,6-TRIBROMO-1-OCTEN-3-OL, A NOVEL MONOTERPENE ALCOHOL FROM APLYSIA CALIFORNICA

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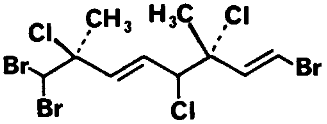
As part of an investigation[1] of the catabolism of brominated terpenes in the digestive gland of the sea hare, Aplysia californica, we have encountered a series of brominated and chlorinated monoterpenes, which are characterized by the presence of a terminal vinyl bromide group. The structure of the only crystalline member of this series, a tribromo-trichloro-monoterpene **1** was recently determined[2] by X-ray crystallography. We wish to report the structural elucidation of a second halogenated monoterpene, the alcohol **2**.



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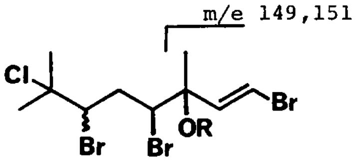
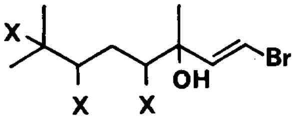


2 R = H

3 R = Ac

Silica gel chromatography of an ethanolic extract of the homogenized digestive glands gave the alcohol **2**, ir 3500 cm^{-1}, $[\alpha]_D^{20}$ -64° (c=2.25 in $CHCl_3$) as a colorless oil, which decomposed on attempted distillation and prolonged standing at room temperature. The molecular formula, $C_{10}H_{16}OBr_3Cl$, was established by combustion analysis of the corresponding acetate **3**, which was prepared by treatment of the alcohol 2 with acetic anhydride in pyridine at 50°. The mass spectra of both alcohol and acetate showed no molecular ion but gave base peaks at 149 and 151 indicating that the hydroxyl function was attached at carbon 3, adjacent to the terminal vinyl bromide group. The nmr spectrum of the alcohol 2 contained an AB quartet (δ 6.25 and 6.51 ppm, J=13.5 cps) which was assigned to the trans disubstituted vinyl bromide group. In the nmr spectrum of the acetate 3, the two protons of the vinyl bromide group appeared as a singlet at 6.47 ppm, again indicating the proximity of the alcohol and vinyl bromide groups. In addition to the vinyl signals, the nmr spectrum of the alcohol 2 contained three methyl singlets (δ 1.48, 1.67, and 1.78 ppm) and an ABXY pattern which was assigned to the remaining four protons (δ 2.30, 2.67, 4.31, and 4.40 ppm).

The spectral data were most easily accommodated by structure 4, but the positions of the chlorine and two remaining bromines could not be assigned on the basis of either nmr or mass spectral data. The first of the halogens was located when it was shown that treatment of the alcohol 2 with base gave an epoxide 5 with loss of a bromide ion from carbon 4. As expected, one of the signals in the ABXY system was now located at 3.11 ppm. Irradiation of this proton resulted in the observation of a 15% NOE for the methyl signal at 1.79 ppm indicating a cis relationship between the proton and the methyl group.



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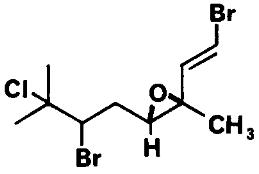

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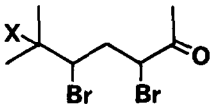
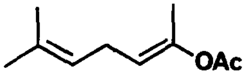
Oxidation of the alcohol 2 with Jones reagent gave a single ketone 6 in 39% yield. The structure of the ketone 6 was confirmed by synthesis. 6-Methyl-5-hepten-2-one was converted into an enol acetate 7 by treatment with isopropenyl acetate containing a catalytic quantity of concentrated sulfuric acid.[3] Bromination of the enol acetate 7 with N-bromoacetamide in tetrahydrofuran containing lithium chloride and a trace of hydrochloric acid at 0°[4] gave the ketone 6, which was identical in all respects to the sample obtained from the alcohol 2. In order to assign the structure of the ketone 6, we assumed that the chloride ion underwent addition to an intermediate bromonium ion at the most highly substituted carbon atom.[5] Comparison of the nmr spectra of the ketone 6 and the corresponding tribromoketone 8 supported this assignment.



6 X = Cl

8 X = Br



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The nmr spectra of all compounds in this series indicate that the bulk of the halogen atoms hold the molecules in a rigid conformation. Despite the rigidity of the molecules, it is not possible to determine the relative stereochemistry of the bromine atoms at carbons 4 and 6 by spectroscopic means.

The halogenated monoterpenes 1 and 2 could not be derived from any of the compounds previously isolated from algae. We therefore extracted samples of red algae on which the sea hare was known to graze. Both compounds were found as components of a hexane extract of the algae, Plocamium coccineum, which contains several more halogenated monoterpenes.

Acknowledgement

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2. D.J. Faulkner, M.O. Stallard, J. Fayos, and J.C. Clardy, submitted for publication.

3. D.S. Tarbell, R.M. Carman, D.D. Chapman, S.E. Cremer, A.D. Cross, K.R. Huffman, M. Kunstmann, N.J. McCorindale, J.G. McNall, Jr., A. Rosowsky, F.H.L. Varino, and R.L. West, J. Amer. Chem. Soc., 83, 3096 (1961).

4. These reaction conditions proved superior to those of M.J. Hageman and E. Havinga, Rec. Trav., 85, 1141 (1966), which gave a complex mixture of products with the tribromide **8** as the major product.

5. For a discussion of the stereochmistry of bromohydrin formation see D.R. Dalton, V.P. Dutton, and D.C. Jones, J. Amer. Chem. Soc., 90, 5498 (1968).