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NIDIFOCENE: A REASSIGNMENT OF STRUCTURE

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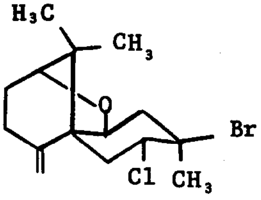
Nidifocene, a minor metabolite of the Hawaiian marine alga *Laurencia nidifica*, was described and assigned structure 1 in a previous communication.[1] The unusual halogen placement prompted us to reexamine the structure. The biogenesis of halogenated marine sesquiterpenes of the chamigrene type appears to involve introduction of bromine and chlorine by electrophilic attack of a bromonium ion on an olefin followed by nucleophilic attack of chloride ion. Based only on electronic considerations one would anticipate attachment of chlorine to the tertiary center as in 2. This halogenation pattern is the one commonly observed. Such naive arguments cannot be used definitively in structural analysis, however, because examples of the reversed placement of bromine and chlorine are known, e.g. isocaespitol (3).[2] Such reversal could result from a rearrangement of the diaxial dihalide to a diequatorial dihalide[3] or stereoelectronic requirements of the enzyme-substrate complex.[4] A hypothetical biogenetic scheme has been put forward by Gonzalez *et al.*[4] This scheme embraces all known stereostructures of halogenated chamigrenes from the red alga *Laurencia obtusa*. If the halogenation pattern of nidifocene were that shown



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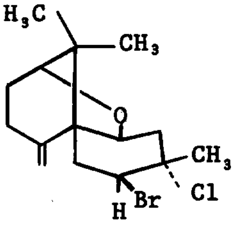

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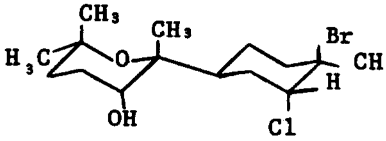

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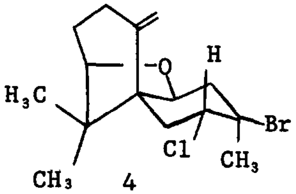
in 1 the stereochemistry of nidifocene should be revised to that shown in 4 in order to be in harmony with their proposed biogenesis.[5]



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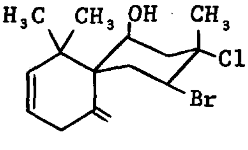

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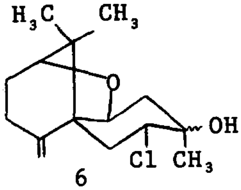

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Spectroscopic and chemical properties have been described elsewhere.[1] Subsequent recording of the cmr spectrum suggested that the bromine was attached to a secondary rather than a tertiary carbon. The chemical shift of the secondary carbon was 60.8 (ppm downfield from TMS, C_6D_6), comparable to that of the secondary carbon hearing the bromine in nidifidienol (5).[6] The situation was complex enough that an unambiguous answer was sought in an X-ray diffraction experiment. Nidifocene was obtained as a colorless oil from the ether eluants of silica gel chromatography of L. nidifica ether extracts (0.1% dry weight). Slow evaporation of a hexane solution afforded crystals, mp 79-81°.

Preliminary X-ray photographs indicated that nidifocene belonged to the monoclinic crystal class. The systematic extinction hkl (missing if h+k = 2n+1) and the known chirality required space group C_2. Accurate cell constants were a = 29.737(10), b = 6.955(5), c = 24.092(10)Å and β = 142.13(9)°. An approximate density of 1.44 g/cc required eight molecules of composition $C_{15}H_{22}BrClO$ in the unit cell or two per asymmetric unit. All unique data with $2\theta \leq 114°$ was collected using graphite monochromated CuKα (1.54178Å) radiation. After correction for Lorentz, polarization and background effects only 921 (49%) of the 1913 reflections surveyed were judged observed. The independent halogens were located with some difficulty by deconvoluting the Patterson synthesis and the remaining atoms were located on subsequent electron density syntheses.[7] No hydrogens, in view of the limited data, were included in the model. Full matrix least squares refinements with anisotropic temperature factors for all atoms and anomalous scattering corrections for Br and Cl have converged to conventional crystallographic residuals of 0.076 for the structure and 0.077 for the enantiomer.[8] While this difference is statistically significant[9] we are skeptical about relying on such small differences in a model of only moderate accuracy.

A drawing of nidifocene, now clearly established as 2, is presented in the Figure. The configuration and conformation of both independent molecules are the same and only one is shown. As can be seen the chlorine is attached to the tertiary center and the bromine to the secondary carbon. The ring containing the halogens is in a twist boat conformation. The absolute configuration marginally predicted by the X-ray experiment is that predicted by the Gonzalez biogenetic model.[4]

The original assignment of the halogens' positions was done on the basis of the formation of tertiary alcohol 6 when nidifocene was treated with $LiAlH_4$.[1] The incorporation of a hydroxyl group on $LiAlH_4$ reduction of a cyclohexyl halide has been noted previously by one of us,[10] but in this case a rearrangement of the chloride has also occurred. If the halogen-bearing ring of nidifocene is converted into the chair form in solution, the halides become diaxial and could rearrange.[2,3,4,11] A halonium-carbonium ion intermediate, if present,[11] could be intercepted by hydroxide at this point. Later incorporation of the hydroxide by replacement of the tertiary bromide is also possible. The source of the hydroxyl group is not known.

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Notes and References:

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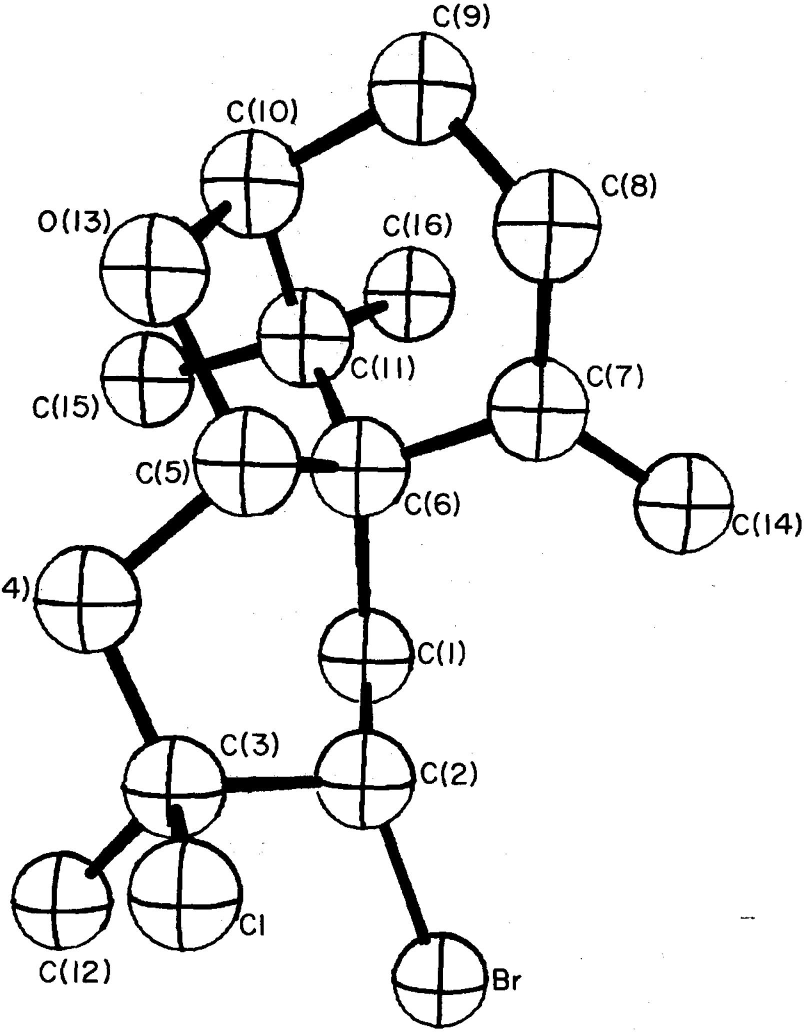
6. S. Waraszkiewicz and K.L. Erickson, Tetrahedron Letters, 281 (1975).
7. The following library of crystallographic programs was used: C.R. Hubbard, C.O. Quicksall, and R.A. Jacobson, "The Fast Fourier Algorithm and the Programs, ALFF, ALFFDP, ALFFT, and FRIEDEL", USAEC Report IS-2625, Iowa State University -- Institute for Atomic Research, Ames, Iowa, 1971; W.R. Busing, K.O. Martin, and H.A. Levy, "A Fortran Crystallographic Least Squares Program", USAEC Report ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1965; C. Johnson, "ORTEP, A Fortran Thermal-Ellipsoid Plot Program", U.S. Atomic Energy Commission Report ORNL-3794, Oak Ridge, Tenn., 1965.
8. Tables of fractional coordinates, bond distances, bond angles and observed and calculated structure factors are available as a Supplement



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