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HALOGENATED SESQUITERPENOIDS FROM THE HAWAIIAN MARINE ALGA LAURENCIA NIDIFICA. IV. NIDIFOCENE

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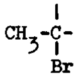
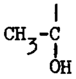
The Hawaiian marine alga Laurencia nidifica has been divided into several varieties characterized by their secondary metabolites: a clumpy pink variety containing laurinterol, aplysin, and pacifenol[1], a nonclumpy pink variety containing nidifidienol, nidifidiene, and nidificene[1,2], and a green variety containing nonhalogenated sesquiterpenoid alcohols together with halogenated nonterpenoid C_{15} compounds[3]. We have now isolated and characterized a fourth component of the nonclumpy pink algal extract, nidifocene.

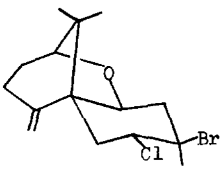
Nidifocene (0.1% yield, dry weight of alga) analyzed for $C_{15}H_{22}BrClO$ by mass spectroscopy: m/e M^+ 336, 334, 332; high resolution m/e 332.05522 (calcd for $C_{15}H_{22}Br^{79}Cl^{35}O$, 332.05424). Its ir spectrum exhibited absorption at 1640 and 900 cm^{-1} characteristic of an exocyclic terminal double bond. The pmr spectrum indicated the presence of three quaternary methyl groups: one on a halogen-bearing carbon at 1.82 δ, one at 1.20 δ, and a third at 0.90 δ. Also evident were an equatorial methine proton at 4.00 (t, J = 3 Hz) δ, two axial methine protons at 4.40 (dd, J = 15.3 and 6.6 Hz) and 4.50 (dd, J = 14.7 and 4.8 Hz) δ, exocyclic methylene protons at 4.82 (d, J = 2.4 Hz) and 5.00 (d, J = 2.4 Hz) δ, and eight methylene protons between 1.7 and 2.8 δ. The difference in chemical shift values between the two exocyclic vinyl protons was much less than that observed in nidifidienol, nidifidiene, and nidificene (0.18 vs 0.35-0.43 δ) indicating a change in the environment of these protons in nidifocene.

When nidifocene was treated with $LiAlH_4$ in an attempt to dehalogenate the molecule, only one halogen was lost and an OH group was introduced in its place[4]. The mass spectrum of this new compound indicated a molecular formula of $C_{15}H_{23}ClO_2$ (M^+ 272). The ir spectrum displayed OH absorption at 3575 cm-1 in addition to the exocyclic vinyl absorption at 1640 and 900 cm^{-1}, and the pmr spectrum showed that the quaternary methyl on the halogen-bearing carbon (1.82 δ) had been replaced by a quaternary methyl on a oxygen-bearing carbon (1.25 δ). All other protons in the pmr were essentially unchanged from those of nidifocene. The following structural change is therefore indicated:

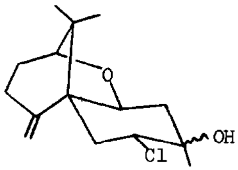

$CH_3\text{-}\overset{|}{\underset{\underset{Br}{|}}{C}}\text{-}$


$CH_3\text{-}\overset{|}{\underset{\underset{OH}{|}}{C}}$

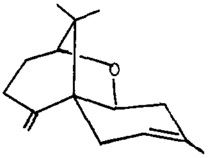
Treatment of nidifocene with chromous sulfate[5] resulted in a clean dehalogenation of the molecule to an olefin, thereby establishing that the halogens were on adjacent carbons. The pmr spectrum of this olefin showed that the methyl on the bromine-bearing carbon (1.82 δ) had been replaced by a vinyl methyl (1.72 δ). The olefin contained two methine protons, which must be oxygen methines, one axial at 4.30 (t, J = 7 Hz) δ, and one equatorial at 4.00 (t, J = 3Hz) δ. Since nidifocene itself displayed two axial and one equatorial methine, the axial methine that is lost in the dehalogenation must be that on the chlorine-bearing carbon. This data, together with a comparison of the spectral properties of nidifocene with its related compounds from L. nidifica, suggests structure **1** for nidifocene, **2** for the LiAlH$_4$ "reduction" product, and **3** for the dehalogenated material.



1



2



3

The stereochemistry of the chlorine is equatorial since the chlorine methine hydrogen is axial. The relative stereochemistry of the bromine and methyl cannot be assigned with the data available, but the chemical shift of the methyl group (1.82 δ) suggests that it is axial[6], which would place the bromine equatorial and trans to the chlorine as is found in all of the other compounds of this class. However, the positioning of the halogens in nidifocene is interchanged, a situation encountered only in isocaespitol[7] and isocespitol[8] where the halogens are both axial.

Acknowledgements

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References

1. S. M. Waraszkiewicz and K. L. Erickson, Tetrahedron Letters, 2003 (1974).
2. S. M. Waraszkiewicz and K. L. Erickson, Tetrahedron Letters, 281 (1975).
3. H. H. Sun, S. M. Waraszkiewicz, and K. L. Erickson, Tetrahedron Letters, In Press.
4. This reaction has been observed with a number of halogen compounds in our laboratory. "Oxygenation" during a lithium aluminum hydride reaction has also been observed previously: S. C. Pakrashi et al. Ind. J. Chem. **9**, 1220 (1971).
5. C. E. Castro and W. C. Kray, Jr., J. Amer. Chem. Soc. **85**, 2768 (1963); W. C. Kray, Jr., and C. E. Castro, ibid., **86**, 4603 (1964).
6. H. J. Hageman and E. Havinga, Rec. Trav. Chim. **85**, 1141 (1966).
7. A. G. Gonzalez, J. Darias, J. D. Martin, and C. Perez, Tetrahedron Letters, 1249 (1974).
8. A. G. Gonzalez, J. Darias, J. D. Martin, C. Perez, J. J. Sims, G. N. Y. Lin, and R. M. Wing, Tetrahedron, **31**, 2449 (1975).