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HALOGENATED SESQUITERPENOIDS FROM THE HAWAIIAN MARINE ALGA LAURENCIA NIDIFICA. II. NIDIFIDIENOL

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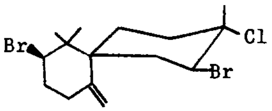
In Part I of this series two halogenated sesquiterpenoids from Laurencia nidifica, nidificene (1) and nidifidiene (2), were described.[1] Closely related compounds of the same structural class have recently been discovered in Laurencia glandulifera,[2] a Pacific species, and Laurencia intricata,[3] an Atlantic species. We report herein the structure of nidifidienol (3), a major constituent of the organic extract from the Hawaiian species L. nidifica.



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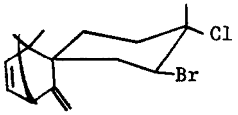

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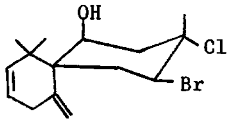

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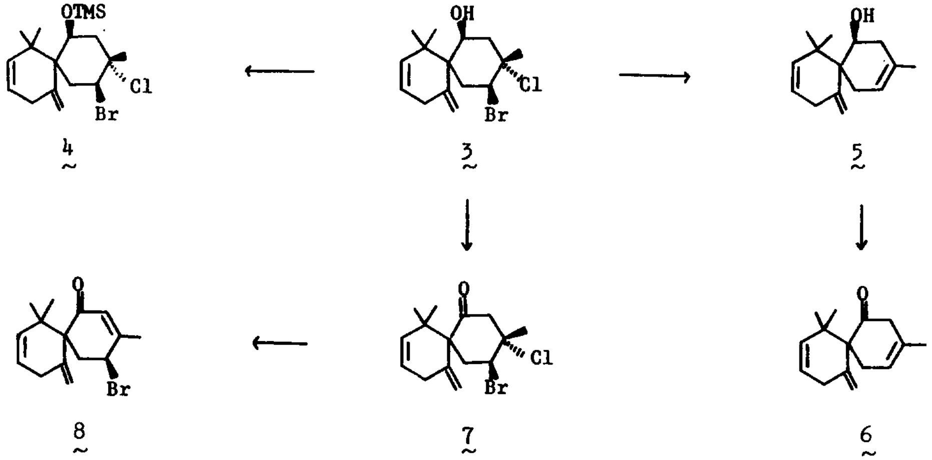
The alga was collected off the Kahala Reef on the island of Oahu, Hawaii during the summer of 1973 and January 1974. The more recent collections were separated into two types, a clumpy variety and a nonclumpy variety. Although both of these have been identified as a single species, Laurencia nidifica, we have now found their sesquiterpenoid content to be remarkably different. Thus, the clumpy variety produces laurinterol as the major organic-soluble component together with smaller amounts of aplysin and pacifenol.[1] Nidificene (1) and nidifidiene (2), both previously reported to accompany laurinterol, aplysin, and pacifenol in L. nidifica,[1] and nidifidienol (3) are not detectable in the clumpy variety but instead are produced by the nonclumpy type. These differences in chemical constitution strongly suggest that the clumpy and nonclumpy forms represent two distinct species of Laurencia, and this possibility is currently under investigation.[4]

Silica gel chromatography of the nonclumpy L. nidifica extract with benzene afforded nidifidienol (3) mixed with small amounts of laurinterol. Since complete separation of the clumpy alga from the nonclumpy is difficult, this laurinterol could be a contaminant from the clumpy form. Separation of the two sesquiterpenoids was achieved by preparative tlc on silica gel developing the plates four times with CCl_4. Nidifidienol (3) was obtained in 0.8% yield (dry weight of alga).

Nidifidienol (3) analyzed for $C_{15}H_{22}BrClO$ by mass spectroscopy: m/e M^+ 336, 334, 332; high resolution m/e 332.05226 (calcd for $C_{15}H_{22}Br^{79}Cl^{35}O$, 332.05425). Its ir spectrum (CCl_4) displayed 3650, 3125, 3050, 3000, 2960, 2900, 1655, 1640, 1450, 1390, 1375, 1370, 1310, 1220, 1195, 1155, 1105, 1040, 1010, and 910 cm^{-1} indicating an exocyclic double bond, a second olefinic group, and a monomeric OH. The nmr spectrum ($CDCl_3$) showed three methyl singlets at 1.07, 1.27, and 2.00 δ, the OH proton as a broad signal at 1.37 δ, the oxygen methine and bromomethine protons as multiplets centered at 4.50 δ, the exocyclic vinyl hydrogens as two broad singlets at 4.80 and 5.33 δ, the two endocyclic olefinic hydrogens as multiplets at 5.17 and 5.64 δ, and the remaining protons as a series of multiplets between 2.10 and 2.96 δ. In benzene—d_6 the OH proton appeared as a broad doublet at 0.40 δ (J = 4 Hz), the oxygen methine as a broad multiplet at 3.87 δ, and the bromomethine as a doublet of doublets at 4.54 δ (J = 11, 5 Hz). The OH signal at 0.40 δ could be removed by shaking the sample with D_2O and regenerated by shaking with H_2O; upon irradiation of the multiplet at 3.87 δ, the OH signal collapsed to a broad singlet.

The equatorial nature of the bromine is indicated by the axial-equatorial and axial-axial coupling of the axial bromomethine proton to the adjacent methylene group. Similiarly, the axial nature of the OH group is indicated by the closely-spaced multiplet for the equatorial oxygen methine proton resulting from axial-equatorial and equatorial-equatorial coupling to the adjacent methylene group. One of the gem-dimethyl groups and the methyl group on the chlorine-bearing carbon are located 1,3-diaxial to the OH group. Both of these methyl groups are shifted downfield compared to their positions in nidifidiene (2) (1.27 vs. 0.97 δ and 2.00 vs. 1.75 δ). The hindered nature of the OH group is further evidenced by its position in both the ir and nmr, showing it to be essentially free of intermolecular association. All attempts at acetylation or dehydration of nidifidienol (3) failed. However, 3 was successfully converted to the trimethylsilyl ether (4) with bis-trimethylsilyltrifluoracetamide (80°, 3 days for 75% conversion). The TMS derivative displayed m/e 408, 406, 404 (M^+), 393, 391, 389, 365, 363, 361, 326, 324, 322, 318, 316, 314, 303, 301, 299, 289, 283, 281, 273, 265, 263, 235, 207, 199, 183, 157, 143, 119, 105, 91, 75, and 73; ir (CCl_4) 3090, 3035, 2980, 2890, 1655, 1635, 1450, 1385, 1370, 1360, 1305, 1265, 1255, 1210, 1195, 1155, 1100, 1060, 1035, 1015, 905, 890, and 850 cm^{-1}; nmr (CCl_4) δ 0.27 (s, 9H), 1.05 (s, 3H), 1.27 (s, 3H), 1.95 (s, 3H), 2.44 (m, 4H), 2.85 (m, 2H), 4.35 (d of d, J = 11, 5 Hz, 1H), 4.60 (br. m, 1H), 4.83 (br. s, 1H), 5.17 (m, 1H), 5.40 (br. s, 1H), and 5.64 (m, 1H).

Reduction of nidifidienol (3) with $LiAlH_4$[5] afforded the dehalogenated alcohol 5: m/e 218 (M^+) 203, 200, 185, 175, 174, 159, 157, 147, 145, 144, 143, 142, 135, 133, 132, 131, 129, 128, 121, 119, 117, 115, 109, 107, 105, 93, 91, 81, 79, and 77; ir (CCl_4) 3580, 3100, 3030, 2975, 2925, 2880, 2830, 1655, 1640, 1470, 1430, 1395, 1380, 1365, 1200, 1150, 1075, 1060, 1040, 1030, 1000, 895, and 870 cm^{-1}; nmr ($CDCl_3$) δ 0.87 (s, 3H), 1.23 (s, 3H), 1.63 (br. s, 3H), 1.90-2.47 (br. m, 4H), 2.77



(m, 2H), 4.33 (br. m, 1H), 4.65 (finely split s, 1H), 4.94 (finely split s, 1H), and 5.48 (m, 3H).

In order to establish the position of the OH relative to the halogens, 5 was oxidized with CrO$_3$ to give the unconjugated ketone 6:[6] m/e 216 (M$^+$), 201, 188, 173, 145, 133, 131, 105, 91, 79, and 77; ir (CCl$_4$) 3080, 3025, 2975, 2925, 2875, 2820, 1715, 1655, 1635, 1455, 1440, 1420, 1395, 1390, 1375, 1370, 1360, 1195, 1150, and 895 cm^{-1}; nmr (CDCl$_3$) δ 0.87 (s, 3H), 1.25 (s, 3H), 1.67 (br. s, 3H), 2.75 (m, 6H), 5.10 (br. s, 1H), 5.27 (br. s, 1H), and 5.56 (m, 3H). The uv spectrum showed only end absorption.

Oxidation of nidifidienol (3) directly with CrO$_3$ led to bromochloroketone 7:[6] m/e 334,332, 330 (M$^+$),$\sim$319, 317, 315, 278, 276, 274, 253, 251, 215, 200, 199, 173, 171, 159, 147, 145, 143, 131, 129, 128, 121, 119, 117, 107, 105, 91, 79, 77, 67, 65, 53, 51, and 39; ir (CCl$_4$) 3090, 3030, 2980, 2940, 2880, 2825, 1725, 1655, 1640, 1465, 1430, 1385, 1360, 1315, 1290, 1275, 1185, 1140, 1085, 1045, 990, 905, and 830 cm^{-1}; nmr (CDCl$_3$) δ 0.92 (s, 3H), 1.18 (s, 3H), 1.67 (s, 3H), 2.25-3.50 (3m, 6H), 4.96 (d of d, J = 13, 5 Hz, 1H), 5.10 (br. s, 1H), and 5.41 (m, 3H). The two methyl groups originally shifted downfield in nidifidienol (3) because of their 1,3-diaxial relationship to the OH are found at their more normal positions in the ketone.

Dehydrohalogenation of 7 with triethylamine afforded triethylamine hydrochloride and the conjugated bromoketone 8 confirming the placement of the chloro and bromo groups. Compound 8 was unstable discoloring rather rapidly on standing. A freshly-purified sample displayed m/e 215 (M-Br), 199, 173, 171, 159, 145, 143, 141, 135, 133, 131, 129, 128, 121, 119, 107, 105, 91, 79, 77, 67, 65, 53, and 51; ir (CCl$_4$) 3080, 3030, 2980, 2930, 2880, 2820, 1680, 1650, 1635, 1470, 1440, 1390, 1380, 1315, 1235, 1200, 1150, 1135, 1050, 900, 880, and 850 cm^{-1}; nmr (CDCl$_3$) δ 1.05 (s, 3H), 1.30 (s, 3H), 2.13 (finely split s, 3H), 2.50-3.00 (2m, 4H), 4.73 (br. s, 1H), 5.00

(m, 1H), 5.19 (br. s, 1H), 5.50 (m, 2H), and 5.95 (m, 1H); uv λ_{max}^{EtOH} 230 nm, ϵ = 10,400.

We are continuing work on the halogenated components in the *L. nidifica* extracts.

Acknowledgements

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5. The course of the reduction of nidifidienol is markedly dependent upon the activity of the hydride reagent. With less active lithium aluminum hydride, a variety of oxygenated compounds are produced whose structures are under investigation.
6. Satisfactory elemental analyses were obtained on compounds **3**, **6**, and **7**.