

N,N-DIMETHYLAMINO-3-GUAIAZULENYLMETHANE  
FROM A DEEP SEA GORGONIAN

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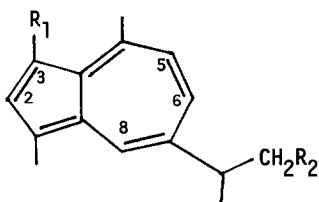
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**Abstract:** A naturally occurring nitrogenous azulene derivative (4) has been isolated from a deep sea gorgonian collected by minisubmersible at -350 m.

Azulenes bearing nitrogenous substituents have been known through the early synthetic efforts of Treibs<sup>1</sup> and Hafner<sup>2</sup>. Kurokawa<sup>3</sup> more recently has revived interest in these compounds because of their obvious structural relationship to biogenic amines. As far as we know, our isolation of a member of this class of compounds is the first report from a natural source.

We have previously described<sup>4</sup> the isolation of halogen derivatives of guaiazulene 1-3 from a blue gorgonian, Family Paramuriceidae, which we collected aboard the minisubmersible Makali'i off Makapuu, O'ahu at -350 m. The same animal has also furnished guaiazulene itself and an aquamarine-colored bis(3,3'-guaiazulenyl)methane, which is probably an artefact.<sup>5</sup>

The gorgonian coral (100 g) was frozen as soon as it was brought to the surface and without thawing was soaked in hexane (700 mL) for 5 h. After drying ( $\text{Na}_2\text{SO}_4$ ) and solvent removal the residual oil (800 mg) was chromatographed over BioBeads SX-8 (BioRad Laboratories, Richmond, CA) and eluted with benzene/hexane (1:1). A blue band between the aquamarine-colored "dimer" and guaiazulene was rechromatographed on the same adsorbent and eluted with toluene. The resulting blue oil was further purified on an alumina (neutral aluminum oxide, Woelm) column and eluted with hexane/EtOAc (1:1), which yielded N,N-dimethylamino-3-guaiazulenylmethane (20 mg) (4) as a viscous blue oil.



- 1  $R_1 = \text{Cl}, R_2 = \text{H}$   
2  $R_1 = \text{Br}, R_2 = \text{H}$   
3  $R_1 = \text{H}, R_2 = \text{Br}$   
4  $R_1 = \text{CH}_2\text{NMe}_2, R_2 = \text{H}$   
5  $R_1 = \text{CH}_2\text{NHMe}_2^+, R_2 = \text{H}$

The molecular formula  $\text{C}_{18}\text{H}_{25}\text{N}$  was established by HRMS (Found: 255.1987; calcd 255.1987). The base peak at  $m/z$  211 (Found: 211.1487; calcd for  $\text{C}_{16}\text{H}_{19}$ : 211.1487) corresponds to a loss of  $\text{Me}_2\text{N}$ -. A strong (79%) peak at  $m/z$  210 denotes loss of dimethylamine. UV<sup>6</sup> and NMR<sup>7</sup> spectra and their comparison with data for guaiazulene and the previously characterized haloguaiazulenes<sup>4</sup> constituted unambiguous proof of a

guaiazulene substituted with dimethylaminomethylene at C-3. Compound 4 had been prepared by Hafner and Senf<sup>2b</sup> via a Mannich reaction from guaiazulene, but it was only characterized by an elemental nitrogen analysis. The earlier authors<sup>2</sup> noted that azulenes bearing a benzylic substituent at C-3 readily form the bis compound in 2N acid. In our hands, this reaction occurs uncatalyzed >28°C.

For a synthesis of 4 we first prepared the hydriodide (5) by adding guaiazulene (198 mg, 1 mmole, Aldrich) in 20 mL C<sub>6</sub>H<sub>6</sub> dropwise to a sln (555 mg, 3 mmole) of Eschenmoser's salt<sup>8</sup> (Aldrich) in 5 mL EtOH at 16°C. Removal of solvent and addn of  $\phi$ Me furnished 5, blue needles, 284 mg (74%).<sup>9</sup> UV<sup>10</sup> and NMR<sup>11</sup> data are consistent with the assigned structure. It is worth noting that in the <sup>1</sup>HNMR spectrum of the salt < 22°C (5) the benzylic methylene protons are split by 5.5 Hz, as are the N-methyls (5.2 Hz). Both sets of doublets collapse when the ammonium proton (9.7 ppm) is irradiated.

When 5 is dissolved in methylene chloride and extracted with 5% NaHCO<sub>3</sub>, the free amine (4), can be isolated, which is identical in all spectral data with the natural product.

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#### References and Notes

1. Treibs, W.; Mühlstädt, M.; Köhler, K.-D. Naturwissenschaften **1958**, 45, 336-337.
2. (a) Hafner, K. Angew. Chem. **1958**, 70, 419-430; (b) Hafner, K.; Senf, W. J. Liebigs Ann. Chem. **1962**, 656, 34-39.
3. Kurokawa, S. Chem. Lett. **1981**, 1569-1572 and references therein.
4. Li, M. K. W.; Scheuer, P. J. Tetrahedron Lett. **1984**, 25, 587-590.
5. Okuda, R. K.; Klein, D.; Kinneil, R. B.; Li, M.; Scheuer, P. J. Pure Appl. Chem. **1982**, 54, 1907-1914.
6. UV (CHCl<sub>3</sub>):  $\lambda_{max}$  247 (23600), 293 (36600), 307 sh (18500), 355 (5560), 372 (4870), 612 nm (460).
7. <sup>1</sup>HNMR (CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$  8.11 (1H d,  $\underline{J}$  = 2 Hz, H-8), 7.48 (1H s, H-2), 7.33 (1H dd,  $\underline{J}$  = 11, 2 Hz, H-6), 6.94 (1H d,  $\underline{J}$  = 11 Hz, H-5), 3.82 (2H s, -CH<sub>2</sub>N<), 3.14 (3H s C-4 Me), 3.05 (1H m, Me<sub>2</sub>>CH), 2.62 (3H s, C-1 Me), 2.27 (6H s, Me<sub>2</sub>N-), 1.36 (6H d,  $\underline{J}$  = 7 Hz, Me<sub>2</sub>CH-); <sup>13</sup>CNMR (CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$  146.8, 142.1, 139.5, 138.1, 135.1, 134.5, 133.7, 127.2, 124.8, 123.8, 60.0, 45.0(2), 38.1, 26.2, 25.0, 24.8, 12.9.
8. Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. Angew. Chem. Int. Ed. (Engl.) **1971**, 10, 330.
9. Even the salt dimerizes when one attempts to determine the mp.
10. UV (CHCl<sub>3</sub>):  $\lambda_{max}$  242 (28000), 293 (31400), 305 sh, 351 (4400), 368 (4400), 620 (420) nm.
11. <sup>1</sup>HNMR (CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$  9.7 (1H brs, >NH), 8.28 (1H d,  $\underline{J}$  = 1.8 Hz, H-8), 7.87 (1H s, H-2), 7.52 (1H dd,  $\underline{J}$  = 10.8, 1.8 Hz, H-6), 7.17 (1H d,  $\underline{J}$  = 10.8 Hz, H-5), 4.87 (2H d,  $\underline{J}$  = 5.5 Hz, -CH<sub>2</sub>N<), 3.12 (1H m, Me<sub>2</sub>CH), 3.09 (3H s, C-4 Me), 2.69 (6H d,  $\underline{J}$  = 5.2 Hz, -NMe<sub>2</sub>), 2.63 (3H s, C-1 Me), 1.37 (6H d,  $\underline{J}$  = 6.9 Hz, Me<sub>2</sub>CH-); <sup>13</sup>CNMR (CD<sub>2</sub>Cl<sub>2</sub>):  $\delta$  145.5, 144.8, 142.8, 139.7, 136.1, 135.3, 135.1, 130, 125.5, 112.3, 57.6, 42.4(2), 37.9, 28.9, 24.5(2), 12.8.

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