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2-HYDROXY, 3,5-DIBROMO, 4-METHOXYPHENYLACETAMIDE. A DIBROMOTYROSINE METABOLITE FROM PSAMMOPOSILLA PURPUREA

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In our continuing study of anticancer agents in marine organisms,[3] we examined the sponge, Psammoposilla purpurea, which was collected from Enewetak in 1973. The isopropanol-water (1/1, v/v) extract was worked up in the usual manner with preliminary fractionation using a trichloroethane (TCE)-methanol blend of the lypholyzed extract. Partitioning of the TCE-methanol triturate with water and subjecting the organic solubles to the Kupchan scheme,[4] resulted in a chloroform-soluble fraction which was active in the PS in vitro bioassay.

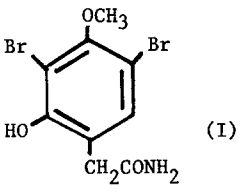
In this communication we wish to report the first isolation of another sponge metabolite in a family of compounds whose likely precursor is dibromotyrosine.

Silica gel column and thick-layer chromatography of the chloroform extract (via Kupchan procedure)[4] afforded the racemic aeroplysinin-2, mp 127-128°, and the (+)-enantiomer of aeroplysinin-1, mp 112-113°, $[\alpha]_D$ + 193° (c 0.63, acetone), whose infrared, ultraviolet, and nuclear magnetic resonance characterizations were identical with that reported in the literature[5,6].

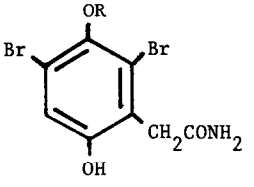
A crystalline non-optically active compound, $C_9H_9O_3NBr_2$ (Calcd., %: C, 31.86; H, 2.65; N, 4.13. Found, %: C, 31.89; H, 2.61; N, 4.15. M^+ 325 amu), whose molecular formula is the same as aeroplysinin-1 but having a different melting point, 174-176°, was isolated by silica gel preparative thick-layer chromatography. Its Rr_f valve relative to cholesterol is 0.21 while aeroplysinin-2 and aeroplysinin-1

showed higher valves of 0.40 and 0.30 respectively on silica gel $PF_{254-366}$ using a 3/1 (v/v) hexane-acetone solvent system.

From the molecular formula, nmr [$CDCl_3$-deuterioacetone, δ 3.80 (3H), 3.62 (2H), 7.22 (1H), and 7.70 (1H exchangeable with D_2O)], ir [KBr, ν_{max} 3410, 3090, 1688 cm^{-1}] and uv [methanol, λ_{max} 314sh (ε 450), 290 (2500), 250sh (1610)], two structures (I) and (II) were considered for this compound.



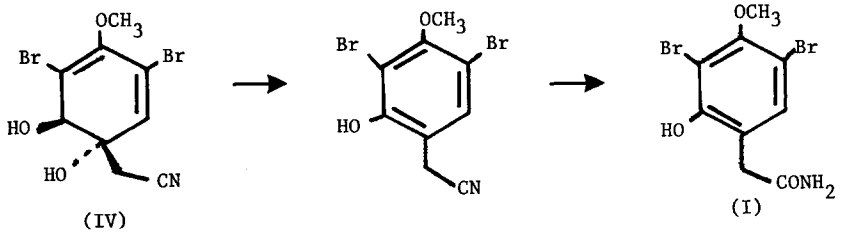
(I)



(II) R = CH_3
(III) R = H

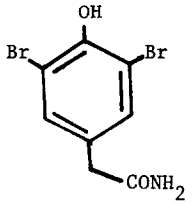
By virtue of the methoxy protons resonance at δ 3.80, which is compatible for a methoxy ortho to two bromine atoms, the compound may have structure (I), or alternatively, the rearranged monomethyl ether (II) of the hydroquinone (III), which was isolated previously by the Rinehardt group.[7] Calculation of the expected aromatic proton shift by the method of Ballantine and Pillinger,[8] however, favors structure (I) [Calcd., Ar-H: (I) δ 7.10; (II) δ 6.75.[9]]

Compound (I), the transformation product secured under drastic conditions from aeroplysinin-1 (IV), was obtained previously by Minale and coworkers.[5a] Since our observed data appeared consistent with that reported for 2-hydroxy, 3,5-dibromo, 4-methoxyphenylacetamide (I), aeroplysinin-1 was converted to (I) via Minale's procedure (scheme 1). Comparison of our compound isolated from P. purpurea with the transformation product proved to be identical.

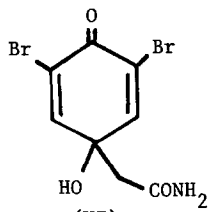


Scheme 1. Preparation of the amide (I) from aeroplysinin-1.

In our hands the workup procedure was not conducive for the auto-transformation of aeroplysinin-1 to the aromatic amide (I), which, therefore, is a natural metabolite of P. purpurea. Thus, (I) is yet another metabolite of the 3,5-dibromotyrosine precursor from which other amide compounds, 4-hydroxy, 3,5-dibromophenylacetamide (V),[11] 2,5-dihydroxy, 4,6-dibromophenylacetamide (III),[7] and 4-hydroxy, 4-acetamido, 2,6-dibromo, 2,5-cyclohexadienone (VI)[12] were reported.



(V)



(VI)

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References

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3. A. J. Weinheimer and T. K. B. Karns, "Proceedings of the Fourth Food-Drugs from the Sea Conference, 1974". Marine Technology Society, Washington, D.C., 1976, pp. 491-496.

4. S. M. Kupchan, R. W. Britton, M. F. Zeigler, and C. W. Sigel, J. Org. Chem., 38, 178 (1973).

5. a. E. Fattorusso, L. Minale, and G. Sodano, J. Chem. Soc. Perkin I, 16 (1971).
   b. E. Fattorusso, L. Minale, and G. Sodano, Chem. Commun., 751 (1970).
   c. W. Fulmor, G. E. Van Lear, G. O. Morton, and R. D. Mills, Tetrahedron Letters, 4551 (1970).

6. L. Minale, G. Sodano, W. R. Chan, and A. M. Chen, J. Chem. Soc. Chem. Commun., 674 (1972).

7. G. E. Krejcarek, R. H. White, L. P. Hager, W. O. McClure, R. D. Johnson, K. L. Rinehardt, Jr., P. D. Shaw, and R. C. Brusca, Tetrahedron Letters, 507 (1975).

8. J. A. Ballantine and C. T. Pillinger, Tetrahedron, 23, 1961 (1967).

9. The calculation of the chemical shift using the $-CH_2-Ar$ contribution of + 0.10 ppm should be adjusted to reflect the electronic effects of the amide carbonyl function. However, this does not seem to be significant in distinguishing (I) from (II).

10. No acids or bases were used in the work-up procedure. Neutral silica gel was used as the adsorbent. Evaporation of solvent in vacuo was done with a water bath temperature below 40 degrees C.

11. G. M. Sharma and P. R. Burkholder, Tetrahedron Letters, 4147 (1967).

12. M. R. Stempien, Jr., J. S. Chib, R. G. Nigrelli, and R. A. Mierzwa, "Proceedings of the Third Food-Drugs from the Sea Conference, 1972", Marine Technology Society, Washington, D.C., 1973, p. 105.