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A REARRANGED DIBROMOTYROSINE METABOLITE FROM VERONGIA AUREA[1]

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Numerous marine natural products have been reported recently which can be regarded as metabolites of brominated tyrosines,[2] including 2,6-dibromophenol-4-acetamide[3] and 2,6-dibromo-4-hydroxy-2,5-cyclohexadienone-4-acetamide;[4] bromotyrosine,[5] dibromotyrosine,[6] and bromochlorotyrosine[7] themselves have also been reported. In the main these compounds have been isolated from sponges. We describe here the first skeletally rearranged dibromotyrosine metabolite, which is also the first hydroquinone in this family of marine natural products, and assign it structure 1.

During the course of our Baja California expedition on board the R. V. Alpha Helix[8] the extract of a small sample of an orange sponge (AHBE-3-III-74-3-2), subsequently identified as Verongia aurea (Hyatt, 1875),[9] was shown to give high lipid total halogen and high lipid bromine assays[8] and to inhibit the growth of B. subtilis, E. coli, and P. atrovenetum. A larger sample was ground under isopropyl alcohol in a blender and the extract was concentrated and partially redissolved in ether. On concentration of the ether solution crystals formed. Recrystallization from ether-methanol (19:1) gave 1, which had the bioactivities of the crude extract; $C_8H_7Br_2NO_3$ [Calcd: 324.8773 (middle peak, $^{79}Br^{81}Br$, of dibromo triplet). Found: 324.8771 (HRMS, Varian MAT 731)], mp 170-172° dec (corr), $uv_{max}^{0.1\ N\ NaOH}$ 250, 280, 368 nm (ε_{max} 4000, 2900, 7200). The infrared spectrum (KBr) shows primary amide I and II bands at 1658 and 1626 cm^{-1}, while the mass spectrum (direct probe, electron impact, high resolution) shows successive losses of ammonia and three moles of

carbon monoxide from the molecular ion (Figure 1).[10] Exhaustive trimsylation[12] of 1 introduces three trimsyl groups, yielding a pair of isomers ($M^{+\cdot}$ = 539, 541, 543) separated and identified on shipboard by combined gas chromatography-mass spectrometry (Varian MAT 111). These spectral results could be explained by the structure of a 2,6-dibromophenol with hydroxyl and acetamide substituents, a reasonable metabolite of dibromotyrosine[6] or 2,6-dibromophenol-4-acetamide.[3] The conclusive argument was provided, however, by an X-ray crystallographic determination, which established structure 1 for the compound.

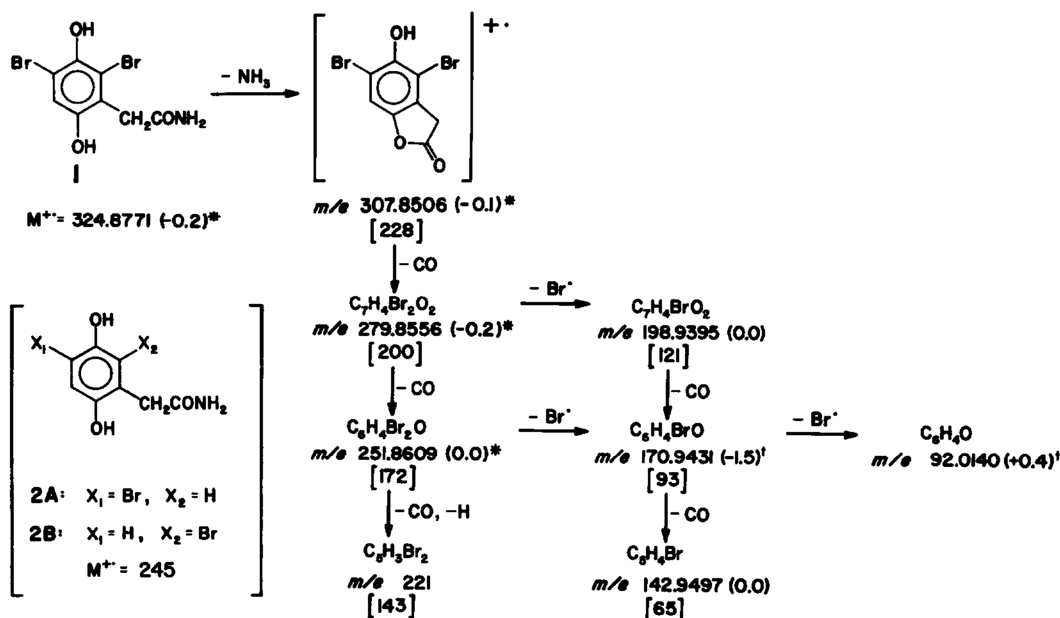

Figure 1. Mass spectral fragmentations of 1. Values marked* refer to center peak ($^{79}Br^{81}Br$) of Br_2 triplet; all others refer to ^{79}Br or $^{79}Br_2$ peaks. Precise masses determined by peak matching except for those values marked †, which were determined by computer evaluation of silver halide photoplates read by a Gaertner comparator-densitometer. Numbers in parentheses indicate mmu deviation from calculated values. Corresponding fragments from the monobromo analog (2A or 2B) are shown in brackets.

A small colorless crystal approximately 0.3 x 0.15 x 0.1 mm, obtained from an ether-methanol (19:1) solution, was used to collect intensity data on a Picker FACS-1 diffractometer with CuK_α radiation. The space group is $P2_1/c$ with four molecules of $C_8H_7Br_2NO_3$ per unit cell and cell dimensions: a = 6.823(4), b = 4.962(4), c = 28.721(26)Å, and β = 93.24(5)°.

The structure was solved by heavy atom methods. The positions of all atoms were refined by full-matrix least squares methods (with all non-hydrogen atoms being allowed to

vibrate anisotropically) to an R-factor of 0.097 on 1057 non-zero reflections. A stereo drawing of the molecule is shown in Figure 2. The bond lengths and bond angles agree with accepted values.

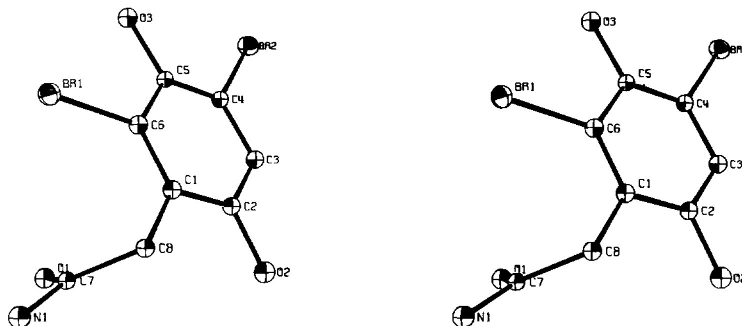

Figure 2. Stereoscopic view of a single molecule of 1.

The monobromo analog of 1 (2A or 2B) was also detected by gas chromatography-mass spectrometry in the ether extract of Verongia aurea (AHBE-3-III-74-3-2), where a major component shows precisely the same fragmentation pattern as 1 but at 78 amu lower mass,[13] as shown in Figure 1.

Structure 1 represents a major departure from the previously reported dibromotyrosine metabolites,[2] in which the aliphatic side chain remains in the para position relative to the hydroxyl group flanked by bromine atoms. An analogy for rearrangement of the tyrosine skeleton to a hydroquinoneacetamide is available, however, in the conversion of tyrosine (via the intermediate 4-hydroxyphenylpyruvic acid) to 2,5-dihydroxyphenylacetic acid (homogentisic acid).[14] The monobromo analog of 1 (2A or 2B) is presumably formed similarly, from monobromotyrosine.[4]

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9. The identification was provided by Dr. Gerald J. Bakus, Allan Hancock Foundation, University of Southern California, Los Angeles, from a sample preserved in 50% ethyl alcohol.

10. A field desorption (FD) spectrum[11] shows only the molecular ion (*m/e* 323, 325, 327) and a gas chromatographic mass spectrum lacks a molecular ion, showing only the ion M - NH_3 (*m/e* 306, 308, 310) and the fragments arising from it shown in Figure 1.

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13. The molecular ion at *m/e* 245 is missing in the GC-MS spectrum but present in the field desorption (FD) spectrum[11] of the crude sponge ether extract.

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