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A NOVEL ANTIBIOTIC FROM A SPONGE OF THE GENUS VERONGIA

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Sponges of the genus Verongia have provided a series of antibiotics and other closely related compounds which may be considered as metabolites of dibromotyrosine 1. In 1967 Sharma and Burkholder[1] isolated an antibiotic, 2,6-dibromo-4-acetamido-4-hydroxycyclohexadienone 2, from Verongia cauliformis. When the same authors[2] isolated the dimethoxy ketal 3 from V. fistularis, they assumed that since the dimethoxy ketal 3 could not be formed by addition of methanol to the dienone 2, the ketal 3 was a naturally occurring compound. We wish to report that a mixed ketal 4 has been obtained from an undescribed species of Verongia, suggesting that the dienone 2, the dimethoxy ketal 3, and the mixed ketal 4 might all be formed from a common precursor by the addition of solvent during the extraction process.

During a recent cruise to the Gulf of California we found two species of Verongia, both of which showed antibiotic activity.[3] One species was identified as V. thiona while the second has not been identified and is probably an undescribed species. From both sponges we have isolated the dienone 2 and aerothionin 5.[4] From the unidentified sponge we also isolated the optically active lactone 6, which was subsequently reported by Minale et al.[5] Ethanol extracts of the unidentified sponge also contained a new antibiotic, which was purified by florisil chromatography.

Elemental analysis showed the antibiotic to have the molecular formula $C_{11}H_{15}NO_4Br_2$.[6] The mass spectrum[7] showed no parent ion but contained peaks corresponding to the loss of both methoxy (M-31) and ethoxy (M-45) groups. The ir spectrum[8] indicated the presence of hydroxyl, amide, olefin, and ketal functions while the nmr spectrum[9] showed signals for both ethoxy and methoxy groups, together

with two-proton singlets in the olefinic and methylene regions. We therefore postulated that the antibiotic was a mixed ketal 4. Hydrolysis of the ketal 4 in aqueous acetic acid gave the dienone 2, providing confirmation of the ketal structure. Careful examination of the 220 MHz nmr spectrum of the ketal 4 revealed two methoxy signals indicating that the ketal 4 existed as a mixture of diastereoisomers.

The presence of diastereoisomers suggested that the ketal 4 was not a natural product but had been formed during extraction and/or purification. The mixed ketal 4 would not be expected to be formed from the dienone 2 without simultaneous formation of the corresponding dimethoxy ketal 3 or diethoxy ketal 7, neither of which could be detected. Furthermore, reaction of the dienone 2 with ethyl orthoformate and para-toluenesulfonic acid in refluxing ethanol failed to yield the diethoxy ketal 7. We therefore propose that the dienone 2, the dimethoxy ketal 3, and the mixed ketal 4 may all be derived from a single intermediate by the addition of water, methanol or ethanol during the extraction process.

Kasperek et al[10] have recently shown that acid-catalyzed addition of methanol to 1,4-dimethylbenzene oxide gave 4-methoxy-1,4-dimethyl-2,5-cyclohexadienol. An analogous 1,4 addition of solvent to an arene oxide 8 could result in the formation of dienone 2 or the corresponding ketal 4. Although arene oxides have been proposed as intermediates in the biosynthetic oxidation of aromatic compounds[11] there is no evidence of their existence as natural products. The coexistence of the lactone 6 with dienone 2 and ketal 4 suggested that the imino-ether 9 should also be considered as a possible precursor of these compounds.

Acknowledgement

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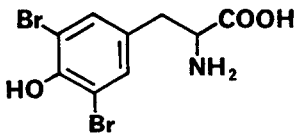
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HO
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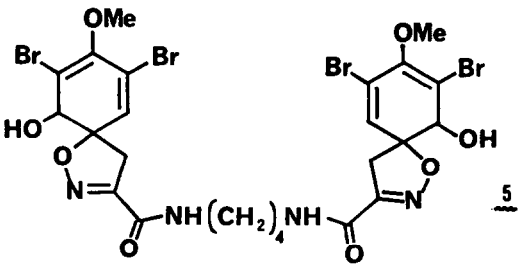
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OMe
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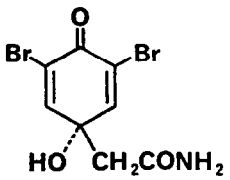
OH
O
N

5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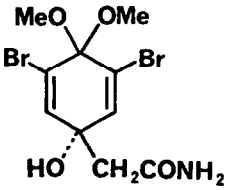
2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HO
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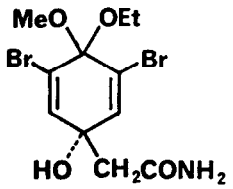
3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Br
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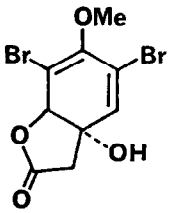
4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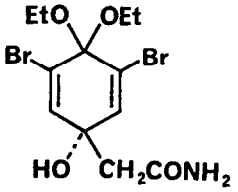
O
OH
O

6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Br
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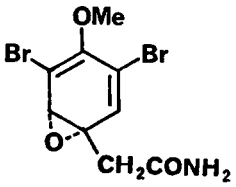
7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O
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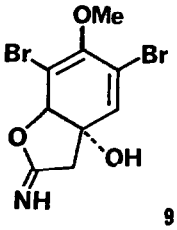
8


OMe
Br
Br
O
OH
NH

9

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6. Found: C, 34.21; H, 3.94; N, 3.51; Br, 41.35. $C_{11}H_{15}NO_5Br_2$ requires C, 34.30 H, 3.90; N, 3.64; Br, 41.53.

7. The mass spectrum was measured on an LKB 9000 mass spectrometer purchased by the Department of Chemistry, UCSD, with funds provided by the National Science Foundation (GP 18245). M/e 352, 354, 356, (M-31); 338, 340, 342 (M-45); 279, 281, 283 (M-104); 265, 267, 269 (M-118); base peak 53.

8. Ir spectrum (CH_2Cl_2) 3525, 3400, 3220, 1680, 1600, and 1100 cm^{-1}.

9. Nmr spectrum ($CDCl_3$) δ 1.25 (t, 3H, J=7Hz), 2.57 (s, 2H), 3.15 (s, 3H), 3.38 (q, 2H, J=7Hz), 5.33 (bs, 1H), 6.38 (bs, 1H), 6.77 (s, 2H).

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