Aerothionin, a Tetrabromo-compound from *Aplysina aerophoba* and *Verongia thiona*

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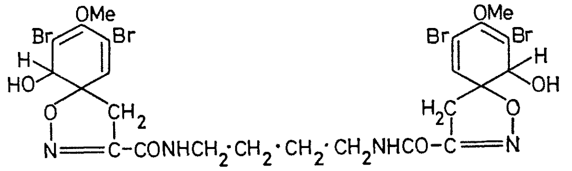
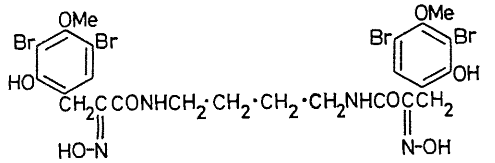
Summary Aerothionin, a tetrabromo-compound from the sponges *Aplysina aerophoba* and *Verongia thiona* is shown to be the spiro-cyclohexadienylisoxazole derivative (I).

AEROTHIONIN, $C_{24}H_{26}Br_4N_4O_8$ (elemental analysis and osmometric M.W.), m.p. 134—137° (dec.), $[\alpha]_D$ 252° (acetone), the major bromo-compound in the sponges *Aplysina aerophoba* and *Verongia thiona*, is shown to be (I). It forms a diacetate and a bistetrahydropyranyl ether, and has the following spectral properties; λ_{max} (MeOH) 284 nm (ϵ 12,660) (*cf.* aeroplysinin-I[1]), ν_{max} (Nujol) 3335, 3160, 1675, 1660, and 1550 cm.$^{-1}$; n.m.r. (100 MHz, CD_3COCD_3) δ 7·58 (2H, bt, N*H*CH$_2$), 6·50 (2H, s, >C=C*H*), 5·37 (2H, d, *J* 8 Hz, O*H*), 4·18 (2H, d, *J* 8 Hz, >C*H*OH), 3·72 (6H, s, OC*H*$_3$), 3·84 and 3·14 (each 2H, d, *J* 18 Hz, C*H*$_2$), 3·34 (4H, m, NHC*H*$_2$), and 1·60 (4H, m, NHCH$_2$C*H*$_2$). These data show that aerothionin is a symmetrical molecule, the two halves being the same (not mirror images). The >CHOH structure attached to two tertiary carbon atoms was confirmed by addition of D_2O when the signal at δ 5·37 disappeared and the doublet at δ 4·18 collapsed to a singlet, and by the downfield shift (to δ 5·83) of the methine proton signal on acetylation. Addition of DCl eliminated the NH signal at δ 7·58 and simplified the multiplet at δ 3·34, while coupling between the signals at δ 3·34 and 1·60 was confirmed by double irradiation. This spectral evidence is fully consistent with structure (I) and is supported by the following reactions.


(I)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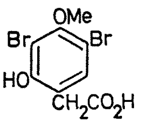
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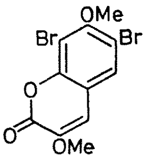
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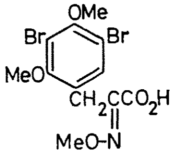
(V)

Treatment of aerothionin with dilute alkali gave the dihydric phenol (II), m.p. 189—191·5°, λ_{max} (MeOH) 292 nm (ϵ 5880); n.m.r., δ 10·93 (2H, s, exchangeable with D_2O, OH†), 7·99 (2H, b, N*H*CH$_2$), 7·59 (2H, s, Ar*H*), 3·82 (10H, s, ArC*H*$_2$ and OC*H*$_3$), 3·40 and 1·62 (each 4H, m, NHC*H*$_2$·C*H*$_2$). The relative positions of the aromatic substituents in (II) were established by cleavage in hot 6N-hydrochloric acid which gave (III) (identified as its methyl ester[1]), and a lactone, converted by methylation with diazomethane into (IV); λ_{max} (MeOH) 286, 298, and 318 nm (ϵ 11,730, 12,090, and 9950), ν_{max} (Nujol) 1740 cm.$^{-1}$; n.m.r. ($CDCl_3$) δ 7·56 (1H, s, Ar*H*), 6·69 (1H, s, >C=C*H*), and 3·93 (6H, s, OC*H*$_3$, split into two 3H singlets by addition of C_6D_6).

The phenol (II) formed a tetramethyl derivative, m.p. 130—131° (M^+ 871·9107 (quintet), $C_{28}H_{34}{}^{79}Br_3{}^{81}BrN_4O_8$ requires 871·9092), which on hydrolysis with 25% aqueous ethanolic potassium hydroxide gave (V) (synthesised from methoxyamine and the arylpyruvic acid derived[2] from 3,5-dibromo-2,4-dimethoxybenzaldehyde and *N*-acetylglycine). Condensation of the acid chloride of (V) with 1,4-diaminobutane gave a product identical with the tetramethyl derivative of (II).

Like aeroplysinin-I[1] and two other brominated compounds isolated[3] from *Verongia* spp., aerothionin is probably biosynthesised from 3,5-dibromotyrosine which is

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† One OH signal was not observed.

condensed with a C_4–N_2 unit possibly derived from ornithine. The spiro-structure could arise either by nucleophilic attack by an oxime function on an arene epoxide,[4] or conversion of the latter into a phenol followed by intramolecular phenol–oxime coupling.

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