

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

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

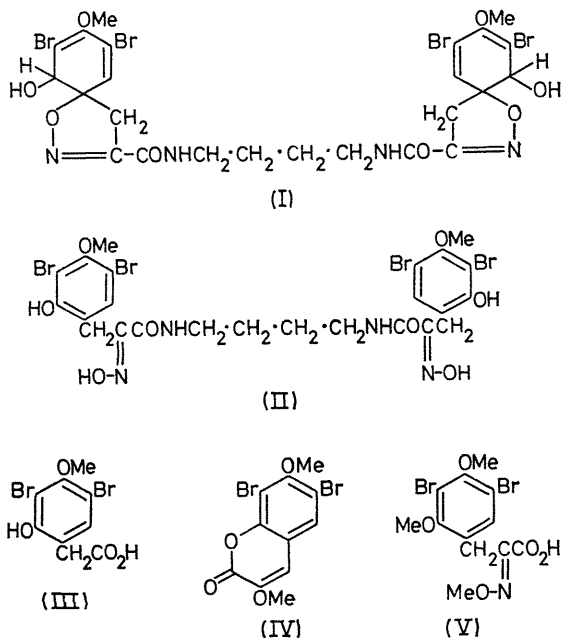
AEROTHERIONIN, $C_{24}H_{26}Br_4N_4O_8$ (elemental analysis and osmometric M.W.), m.p. 134–137° (dec.), $[\alpha]_D^{25} 252^\circ$ (acetone), the major bromo-compound in the sponges *Aplysina aerophoba* and *Verongia thiona*, is shown to be (I). It forms a diacetate and a bistetrahydropyranyl ether, and has the following spectral properties; λ_{max} (MeOH) 284 nm (ϵ 12,660) (cf. aeroplysinin-I¹), ν_{max} (Nujol) 3335, 3160, 1675, 1660, and 1550 cm^{-1} ; n.m.r. (100 MHz, CD_3COCD_3) δ 7.58 (2H, bt, $NHCH_2$), 6.50 (2H, s, $>C=CH$), 5.37 (2H, d, J 8 Hz, OH), 4.18 (2H, d, J 8 Hz, $>CHOH$), 3.72 (6H, s,

OCH_3), 3.84 and 3.14 (each 2H, d, J 18 Hz, CH_2), 3.34 (4H, m, $NHCH_2$), and 1.60 (4H, m, $NHCH_2CH_2$). These data show that aerotherionin 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.

Treatment of aerotherionin 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 \dagger), 7.99 (2H, b, $NHCH_2$), 7.59 (2H, s, ArH), 3.82 (10H, s, $ArCH_2$ and OCH_3), 3.40 and 1.62 (each 4H, m, $NHCH_2CH_2$). 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 ester¹), 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, ArH), 6.69 (1H, s, $>C=CH$), and 3.93 (6H, s, OCH_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 derived² from 3,5-dibromo-2,4-dimethoxybenzaldehyde and *N*-acetyl-glycine). Condensation of the acid chloride of (V) with 1,4-diaminobutane gave a product identical with the tetramethyl derivative of (II).

Like aeroplysinin-I¹ and two other brominated compounds isolated³ from *Verongia* spp., aerotherionin is probably biosynthesised from 3,5-dibromotyrosine which is



† 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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