ISOLATION OF 1-METHYL-4,5-DIBROMOPYRROLE-2-CARBOXYLIC ACID AND ITS 3'-(HYDANTOYL)PROPYLAMIDE (MIDPACAMIDE) FROM A MARINE SPONGE

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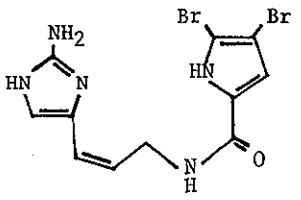
From an unidentified marine sponge collected in the Marshall islands we have isolated 1-methyl-4,5-dibromopyrrole-2-carboxylic acid (III) and its 3'-(hydantoyl)propylamide, midpacamide (II). The acid was synthesized and the structure of the amide was determined by spectral analysis and by hydrolysis in alkaline and acid media.

Marine sponges have become recognized as prolific producers of novel organic structures, yet relatively few contain nitrogen.[3] An intriguing nitrogenous metabolite is oroidin (I), which embraces a 4,5-dibromo-2-carboxamide moiety

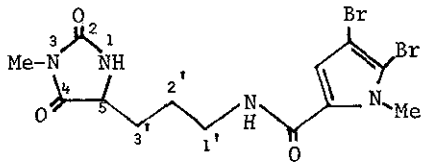


(I)

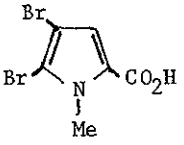
linked by a three carbon bridge to 2-aminoimidazole. It was first isolated from the sponge Agelas oroides, which also elaborates the bromopyrrolecarboxylic acid portion of the molecule.[4] Oroidin was subsequently isolated from two other Mediterranean sponges of the genus Axinella.[5]

We encountered a similar biogenetic pattern, a 4,5-dibromo-1-methylpyrrole-

2-carboxamide, linked by a three carbon bridge to a 3-methylhydantoyl moiety in a metabolite from an unidentified orange sponge collected on the ocean side of Elmer, Enewetak atoll, Marshall islands. We have named the compound midpacamide[6] and have assigned structure II to it. The corresponding pyrrole acid (III) is a major constituent of the sponge.



(II)



(III)

The frozen animals (200 g dry weight) were first soaked in ethanol, then acetone, finally extracted (Soxhlet) with methylene chloride. The residue of this extract (1.5 g) after BioSil A chromatography yielded by chloroform elution 228 mg of III, mp 142-144°, after recrystallization from hexane. Ethyl acetate elution furnished midpacamide (II), mp 93-95°, 128 mg, after recrystallization from acetonitrile.

Composition of III was shown to be $C_6H_5Br_2NO_2$ by high resolution mass spectrometry. Three pmr (acetone-d_6) signals at δ 7.04 (1H,s), 3.99 (3H,s), and 3.94 (1H,s) were assigned to an aromatic, three N-methyl, and a carboxylic acid proton respectively. Five cmr (dioxane + D_2O) signals at 163.8, 127.2, 121.17, 116.10, 100.21, and 37.52 ppm, uv (MeOH) maxima at 207 (3.8), 240 (3.9), and 272 (4.0) nm, and ir (KBr) bands at 3140, 2840, 1670, 1420, 1360 and 1254 cm^{-1}, in conjunction with the previous isolation of the demethyl analog from a sponge[4] strongly suggested 1-methyl-4,5-dibromopyrrole-2-carboxylic acid (III) as the correct structure. Since this appeared to be a previously unreported compound, we synthesized it by brominating (Br_2, I_2, CCl_4) N-methylpyrrole-2-carboxylic acid (Aldrich) and recrystallized the resulting III from chloroform, mp 153°. Spectral comparison (uv, ir, pmr) of the two acids and of the derived methyl esters

(Diazald, ether), mp 87°, proved their identity. The methyl ester is known as a synthetic product,[7] mp 87-90°, λ_{max} 240 (3.81), 279 (4.11) nm, compatible with our uv data, λ_{max} 206 (3.7), 239 (3.9), 276 (4.05) nm.

Mass spectrometry of midpacamide (II) revealed a composition of $C_{13}H_{16}Br_2N_4O_3$ and suggested a relationship to III by showing only one major fragment of composition $C_6H_4Br_2NO$. This was confirmed by base hydrolysis (4N KOH, 4 hr, 100°), which after acidification and EtOAc extraction yielded III, identical with the natural product.

The pmr data (acetone-d_6) of II accounted for the sole pyrrole proton (δ 6.95, 1H,s) and for the pyrrole N-methyl (δ 3.93, 3H,s). A second N-methyl (δ 2.85, 3H,s), an NH (δ 7.72 or 7.41, each a broad singlet), and a one proton multiplet at δ 4.16 suggested a 3-methyl hydantoin moiety. By comparison, 1-methylhydantoin[8] has pmr signals at δ 10.7 (NH), 3.9 ($-CH_2-$), and 2.8 (NMe). The one proton multiplet at δ 4.16 (H-5) becomes a singlet upon irradiation of a four proton multiplet at δ 1.68 (H-2',3'). The same experiment also collapses a two proton multiplet at δ 3.38 (H-1') to a doublet. These data define the three carbon chain which links the carboxamide (δ 7.41 or 7.72 for a second NH) to the hydantoyl portion of the molecule. Thirteen cmr (pyridine-d_5) signals are fully compatible with II: 174.896, 160.982, 158.164, 128.927, 114.308, 111.049, 98.016, 57.418, 39.188, 35.754, 29.853, 26.066, 24.481 ppm. Supporting evidence of the assigned structure II for midpacamide came from automated amino acid analysis of II under acidic conditions, which furnished ornithine.

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