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THE STRUCTURE OF DIBROMOISOPHAKELLIN FROM THE MARINE SPONGE ACANTHELLA CARTERI

S.A.Fedoreyev, N.K. Utkina, S.G.Ilyin, M.V. Reshetnyak, and O.B. Maximov*

Pacific Institute of Bioorganic Chemistry, USSR Academy of Sciences, Far East Science Centre, Vladivostok-22, USSR

Abstract : A novel bromine-containing alkaloid, dibromoisophakellin hydrochloride, has been isolated from marine sponge Acanthella carteri. The structure of this compound has been determined on the basis of the spectroscopic data and X-ray analysis.

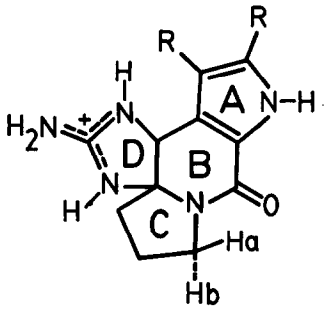
Three known nitrogen-containing metabolites[1,2] were identified by us among the constituents of an alcoholic extract of marine sponge Acanthella carteri (Devidy, 1889) collected off the Madagascar coast from the scientific research ship "Professor Bogorov"[3]. A fraction giving a bright orange coloration with diazotized benzidine was obtained from this extract by column chromatography on silica gel ($CHCl_3$-MeOH, 4:1). After purification on Sephadex LH-20, a novel compound of composition $C_{11}H_{11}Br_2N_5O.HCl$ was isolated : 0.09% relative to the animal weight; m.p. 275-277°C (MeOH), and $[\alpha]_D^{20}$-101° (c 0.56, MeOH).

On the basis of the spectroscopic data (vide infra) a structure 1 has been assigned to this compound.

Maxima at 274 nm ($\Delta\varepsilon$ 1.8), 242 nm ($\Delta\varepsilon$ 2.8) and a strong negative Cotton effect at 200 nm ($\Delta\varepsilon$ -40.9) are observed in the circular dichroism (CD) spectrum of 1. A maximum at 284.5 nm in the UV spectrum is indicative of the presence of pyrrole ring conjugated with a carbonyl group. The IR spectrum of 1 (KBr) exhibits bands assigned to the absorption of amino and methylene groups (3500 - 2900 cm^{-1}), amide function (1658 cm^{-1}), and C=N bond of the protonated guanidine group (1692, 1560).

The occurrence of two bromine atoms and of a guanidine moiety is confirmed by observation of fragments with m/z 391, 389, 387 (M^+), 374, 372, 370 ($M-NH_3$) and 349, 347, 345 ($M-NH_2CN$) in the mass-spectrum of 1.

Signals at δ 1.90 - 2.30 ppm (4H) and 3.35 - 3.70 ppm (2H) observed in the ^{1}H-NMR spectrum of 1 ($DMSO-d_6$) are assigned to methylene groups of



1: R = Br

2: R = H

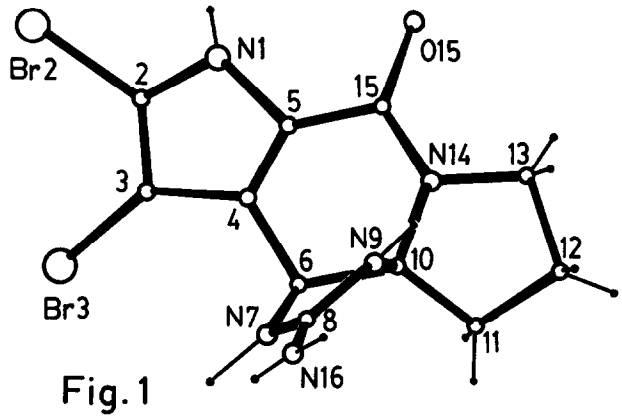


Fig. 1

the pyrrolidine ring and that at δ 5.19 ppm to methine proton. The chemical shift due to this proton is indicative of occurrence of a nitrogen atom at C-6 which makes the isolated compound distinct from the structurally related phakellin[4,5].

Further, resonances due to five D_2O-exchangeable protons forming four broadened singlets at δ 13.35 ppm (pyrrolic NH), 9.65 (N7-H), 8.70 (C=NH) and 7.85 (2H, C-NH_2) are observed in the ^{1}H-NMR spectrum.

Under the conditions of catalytic hydrogenation (10% Pd-C), the compound 1 undergoes a ready debromination which results in formation of a compound 2 characterized by the following parameters : m.p. 300°C (dec.), M^+ 231, λ_{max}^{MeOH} 215 nm (ε 6240) and 275 nm (ε 8170), $[\alpha]_D^{20}$ -27° (c 0.34, MeOH), CD spectrum : 298 nm ($\Delta\varepsilon$ -0.11), 268 nm ($\Delta\varepsilon$ 1.34), 234 nm ($\Delta\varepsilon$ 1.38) and a negative Cotton effect at 198 nm ($\Delta\varepsilon$ -18.87). Signals due to two coupled aromatic protons of the pyrrole ring at 7.03 and 6.26 ppm (J=2.8 Hz) are observed in the ^{1}H-NMR spectrum of 2[6]. This is suggestive of the two bromine atoms located at positions C-2 and C-3 of the pyrrole ring of the compound 1.

The ^{13}C-NMR spectrum of 1 exhibits, due to eleven carbon atoms, signals, seven of which are assigned to quaternary carbons. The signals at δ 19.4, 39.0 and 44.2 ppm are related to C-11, C-12 and C-13 carbons of the pyrrolidine ring; the signal at δ 84.1 ppm (C-10) is shifted to low field due to the influence exerted by N-9 and N-14. Resonances at δ 157.2 and 154.8 ppm in the low field of the spectrum of 1 belong to carbons of the carbonyl group C-15 and of the guanidine moiety C-8, respectively. Signals at δ 122.8, 122.6, 108.6 and 96.5 ppm are assigned to pyrrole ring carbons by way of comparison of the ^{1}H- and ^{13}C-NMR spectra of 1 and 2[7,8].

The proposed structure of the compound 1 has been confirmed by X-ray analysis data obtained for a single crystal $C_{11}H_{11}Br_2N_5O \cdot HCl \cdot C_2H_5OH$ (90% C_2H_5OH). Configurations of two asymmetric centres C-6 and C-10 in 1 have been found to be S and R, respectively[12].

Crystal data : $C_{11}H_{11}Br_2N_5O \cdot HCl \cdot C_2H_5OH$, orthorhombic, space group $P2_12_12_1$, Z=4; a=32.19(2), b=9.594(6), c=5.806(5) Å; V=1793.1 Å^3, D_c = 1.74 g.cm^{-3}; μ=45.66 cm^{-1}, MoKα radiation, graphite monochromator, λ =0.71069 Å.

The intensities of 667 symmetry-independent reflexions with $I \geq 3\sigma$ (I) were measured on DARM-2.0 diffractometer at room temperature, using a crystal of approximately rectangular shape having dimensions 0.63 x 0.32 x 0.09 mm. The Lorentz, polarization and absorption corrections were applied. The structure was solved by direct methods and refined by full matrix least-squares procedure of the SHELX[9] system. Br, Cl, O, N atoms were included with anisotropic and C atoms with isotropic temperature factors. The scattering factors were corrected for anomalous dispersion. H atoms were included in the structure-factor calculations with fixed positional and thermal parameters. The least-squares calculations were carried out for both enantiomorphs and yielded R values of 0.081 and 0.086, respectively. The correct absolute configuration[10] has been determined from comparison of the R values for two the enantiomorphs. The spatial model of the molecule is given in Fig. 1. The bond lengths and the torsion angles in the rings are given in the references[11].

The pyrrole ring A of the molecule has a planar conformation. The conformation of the six-membered ring B is a flattened 10-sofa (the atom N-9 is an axial substituent of the ring). The amide group and the pyrrole ring constitute a flattened system of atoms. The pyrrolidine ring C has an 11-envelope conformation. The conformation of the ring D is a distorted 10-envelope. The rings B and C have a quasi-trans junction. The rings B and D have a cis junction.

The protonated base 1 and the alcohol contain six hydrogen atoms which are covalently bonded to nitrogen or oxygen and all this atoms are involved in the formation of hydrogen bonds. The crystal structure contains six independent hydrogen bonds i.e. N1...O15', 2.76 Å; N7...O(EtOH), 2.75 Å; N9...Cl$^-$, 3.06 Å; N16...Cl$^-$, 3.37 Å; N16...Cl$^-$', 3.31 Å; O(EtOH)...Cl$^-$, 3.10 Å in which the first atoms are donors.

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6. 2: ^{1}H-NMR (250 MHz) $\delta^{CD_3OD}_{TMS}$ 2.07-2.43 (m, 4H, 2H-11 and 2H-12), 3.59 (t-d, 1H, H_b-13, J = 8.3; -10.6 Hz), 3.74 (d-d-d, 1H, H_a-13, J = 4.5; 6.2; -10.6 Hz), 5.19 (s, 1H, H-6), 6.26 (d, 1H, H-3, J = 2.8 Hz), 7.03 (d, 1H, H-2, J = 2.8 Hz).
7. 1: ^{13}C-NMR (OFR, 63.9 MHz) $\delta^{DMSO\text{-}d_6}_{TMS}$ 19.4 (t, C-12), 39.0 (t, C-11), 44.2 (t, C-13), 54.2 (d, C-6), 84.1 (s, C-10), 96.5 (s, C-5), 108,6(s, C-3), 122.6 (s, C-4), 122.8 (s, C-2), 154.8 (s, C-8), 157.2 (s, C-15).
8. 2: ^{13}C-NMR (OFR, 63.9 MHz) $\delta^{CD_3OD}_{TMS}$ 20.9 (t, C-12), 40.1 (t, C-11), 45.3 (t, C-13), 58.0 (d, C-6), 86.0 (s, C-10), 107.8 (d, C-3), 122.0 (s, C-5), 125.2 (s, C-4), 126.4 (d, C-2), 158.9 (s, C-8), 159.2 (s, C-15).
9. G.M. Sheldrick, SHELX 76: Program for crystal structure determination. Univ. of Cambridge, Cambridge, England.
10. The atomic coordinates for this work are available on request from the Director of the Cambridge Crystallographie Data Center, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.
11. Bond lengths (Å): N1-C2, 1.34(3); C2-C3,1.42(4); C2-Br2, 1.91(3); C3-C4, 1.47(3); C3-Br3, 1.75(3); C4-C5, 1.32(4); C4-C6, 1.45(4); C6-N7, 1.46(4); C6-C10, 1.51(3); N7-C8, 1.30(3); C8-N9, 1.24(4); C8-N16, 1.37(4); N9-C10, 1.46(4); C10-C11, 1.57(3); C10-N14, 1.48(4); C-11-C12, 1.49(4); C12-C13, 1.56(4); C13-N14, 1.41(3); N14-C15, 1.32(4); C15-O15,1.26(4).
Endocyclic torsion angles: ring A N1-C2, 10°; C2-C3, -5°; C3-C4, -3°; C4-C5, 9°; C5-N1, -12°; ring B C4-C6, 26°; C6-C10, -37°; C10-N14, 36°; N14-C15, -18°; C15-C5, 4°; C5-C4, -9°; ring C C10-C11, 37°; C11-C12, -38°; C12-C13, 23°; C13-N14, 0°; N14-C10, -23°; ring D C6-N7, 21°; N7-C8, -4°; C8-N9, -17°; N9-C10, 29°; C10-C6, -30°.
12. After the given paper had been sent to the Journal the publication by D. De Nanteuil et al., Tetrahedron, vol.41, N°24, 6019 (1985) in which the isolation of dibromocantharelline, enantiomer of dibromoisophakellin, was reported, appeared.

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