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A NOVEL TYPE OF BIS-QUINOLIZIDINE ALKALOID FROM THE SPONGE *PETROSIA SERIATA* (1).

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SUMMARY : The structure of petrosin, the major alkaloid isolated from the sponge *Petrosia seriata*, has been determined by X-ray diffraction analysis. Petrosin is the first member of a new class of bis-quinolizidine alkaloids containing a C-16 macrocycle.

The methanol extract of sun-dried specimens of the sponge *Petrosia seriata* (Adociidae, Haplosclerida) collected around Laing Island, Papua-New Guinea, is toxic to the fish *Lebistes reticulatus* (LD≃50 mg/l). This toxicity is associated with a basic fraction from which, after several column chromatographies on silica gel and alumina, the ichthyotoxic alkaloid 1, named petrosin, was isolated (2.2% w/w of the methanolic extract, LD=10 mg/l).

Petrosin (1 : m.p. 215-216° ; $C_{30}H_{50}N_2O_2$ by HRMS, calculated 470.3872, measured 470.3860) is devoid of optical activity. Furthermore, although petrosin is a C_{30}-molecule, only 15 peaks (3) can be observed in its proton noise-decoupled ^{13}C NMR spectrum. These results imply that 1 contains a plane (S_1), a centre (S_2) or a two-fold rotation axis (C_2), or even that it is a case of stochastic achirality as with cis-1,2-dimethylcyclohexane (4).

The other spectral properties of 1 indicate that each half of the molecule possesses a ketone function ($\nu_{C=O}$ at 1712 cm^{-1} ; ^{13}C δ 213.83 (s)) and a secondary methyl group (^1H δ 0.94, J=6.4Hz). The tertiary nature of the nitrogen atoms follows from the lack of absorption at about 3500 cm^{-1} in the IR spectrum, while the nature of their adjacent carbon atoms (two methylenes and one methine for each nitrogen atom) follows from the presence of signals at δ 70.45 (CH), 64.83 (CH_2) and 56.01 (CH_2) in the ^{13}C NMR spectrum, and of a 10 H multiplet centered at δ 2.98 in the ^{1}H NMR spectrum. Together with the appearance of characteristic bands at 2770 and 2810 cm^{-1} (Bohlmann bands) in the IR spectrum of 1, these ^{13}C NMR values accord with the presence of quinolizidine ring systems in the molecule (5). Moreover, since the ^{13}C NMR spectrum demonstrates the absence of vinylic carbon atoms, petrosin must be pentacyclic.

From all these data, it can be deduced that the framework of petrosin (1) is most probably made up of two quinolizidine rings linked together through two polymethylene chains. Since compound 1 easily crystallizes from hexane/acetone, an X-ray study was undertaken. The title compound (M=470.75) crystallizes in the monoclinic space group $P2_1/c$ with a unit cell of dimensions a=9.980 (3), b=15.805 (3), c=17.801 (5) Å, β=90.43 (2)°, V=2807.7 (13) $Å^3$ (MoKα radiation, λ=0.71069 Å ; 2Θ max = 47°). Assigning four molecules to the unit cell gives a calculated density of 1.11 g cm^{-3}.

The structure was solved using the *MULTAN 80* system of programmes (6). The *SHELX 76* programme (7) was used to refine the structure to a final R value of 0.053 by a least-squares method. In the crystal the molecules adopt chiral conformations. The asymmetric unit consists of a single chiral molecule which is depicted in Figure 1 (8). It possesses a two-fold pseudo-axis passing through the middle of the 16-membered ring and perpendicular to the mean plane of the same ring. Since the space group is centrosymmetric, the two enantiomers obviously coexist in the crystal.

In solution, petrosin most probably exists as a mixture of two or more conformational isomers, at least at room temperature. Unfortunately, no definitive conclusion can be drawn concerning their interconversion from the symmetry revealed by the ^{13}C NMR spectrum. In fact, this does not imply an averaging process in view of the C_2 symmetry of the stable conformations of the molecule in the crystal.

Petrosin is the first representative of a novel type of bis-quinolizidine alkaloids. In the methanolic extract of *P. seriata*, it is accompanied at least by three minor stereoisomers, the structures of which are currently under investigation in our laboratory.

Although the quinolizidine nucleus is frequently encountered in alkaloids of plant origin (e.g. broom, nuphar, lupin, lycopodium...) up to now it has rarely been found in nitrogen-containing secondary metabolites of animal origin. Together with 1, the Coccinellidae alkaloids (9) are notable exceptions.

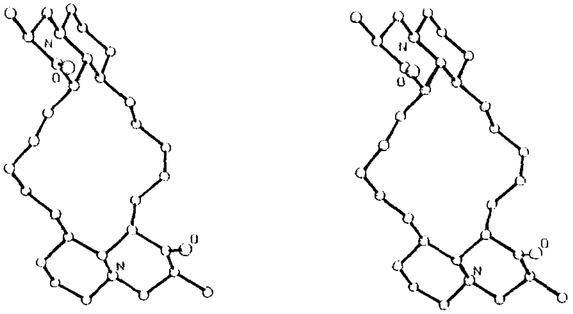
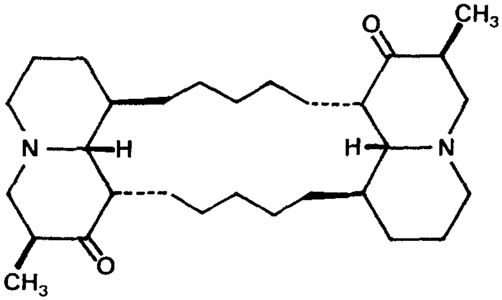


Figure 1 : A computer-generated stereoscopic view of petrosin (1).



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3- ^{13}C NMR ($CDCl_3$, TMS, 20.13 MHz) : 213.83 (C=O), 70.45 (CH), 64.83 (CH_2), 56.01 (CH_2), 51.92 (CH), 40.52 (CH), 37.04 (CH), 29.54 (CH_2), 28.76 (CH_2), 27.44 (CH_2), 25.14 (CH_2), 24.37 (CH_2), 24.12 (CH_2), 23.92 (CH_2),11.26 (CH_3). The signal multiplicities were determined through the INEPT sequence adapted by Dr. D. ZIMMERMANN to a WP 80 Brucker instrument.

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