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STRUCTURES OF XESTOSPONGIN A,B,C AND D, NOVEL VASODILATIVE COMPOUNDS FROM MARINE SPONGE, XESTOSPONGIA EXIGUA

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Summary: Xestospongin A,B,C and D represent a new class of macrocyclic 1-oxa-quinolizidines, have been isolated from Australian sponge Xestospongia exigua. The structure of xestospongin C has been determined by X-ray analysis.

Xestospongin A,B,C and D isolated from the Australian marine sponge, Xestospongia exigua, which are vasodilative compounds induce relaxation of blood vessel in vivo.[1] In the following we report the structures of these compounds.

Xestospongin C[1: $C_{28}H_{50}N_2O_2$,[2] mp 149-150°C(from ether); [α] -2.4°(c 0.54, $CHCl_3$); EI-MS, m/z 446(M^+)] shows IR(KBr) absorption at 2769 cm^{-1} assignable to Bohlmann bands[3] but no OH, NH and NH_2 groups were observed. The ^1H NMR[4] spectrum(360 MHz) of 1 showed the presence of two CH groups attached to N and O atoms(10-H, 10'-H), two gruops attached to O atoms(2-H, 2'-H), one high field proton(3α-H) and four low field CH_2 signals. The ^{13}C NMR spectrum (INEPT) exhibited the presence of 22 CH_2 and 6 CH gruops. Single crystals of 1 were submitted to X-ray analysis: orthorhombic, space groups P222, a=16.771(2), b=16.386(2), c=9.799(1) Å, Z=4, Dm=1.103(by flotation method), Dc=1.101 cm^{-1}.

The three dimensional intensity data from a colorlss and well shaped crystal(0.4 X 0.3 X 0.2 mm) were collected on the Rigaku AFC diffractometer equipped with the rotation anode generator(40kv-200mA), using Ni-filtered Cu-Kα radiation. The ω-2θ scanning mode was applied with 2θ=120°, the number of the measured reflections being 2438. The direct method MULTAN[5], revealed the positions of 27 atoms fragments of 32 non-hydrogen atoms by the starting refinement set. After least-squares refinement and Fourier synthesis yielded the positions of another 5 non-hydrogen atoms. The complete model refinement was carried out by the block-diagonal-matrix least-square method[6] with anisotropic temperature factors and given a final R value of 0.06. The position of N and O atoms were definitely found from their numbers of bonds, because all hydrogen atoms were located without any ambiguity. All bond lengths and angles were

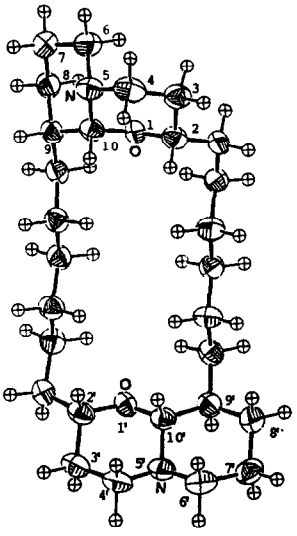
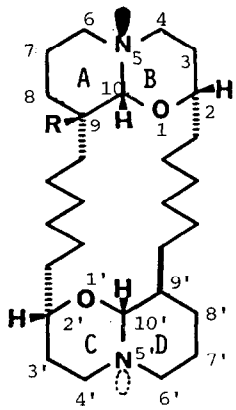


Figure 1. Perspective view of xestospongin C (1)

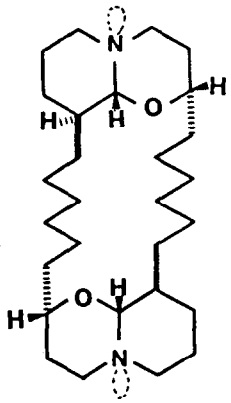
Table I. ^{13}C NMR of xestospongins (90 MHz, in $CDCl_3$)

	1	2	3	4
C-2	76.18(d)	76.54(d)	75.35(d)	76.28(d)
C-3	26.41(t)	26.67(t)		26.29(t)
C-4	53.26(t)	53.00(t)	53.35(t)	52.74(t)
C-6	46.03(t)	44.86(t)	54.55(t)	44.66(t)
C-7		21.74(t)		21.38(t)
C-8		23.69(t)		23.43(t)
C-9	40.84(d)	70.90(s)	40.95(d)	70.64(s)
C-10	88.18(d)	91.33(d)	96.32(d)	91.08(d)
C-2'	75.50(d)	75.50(d)		82.22(d)
C-3'				28.69(d)
C-4'	54.85(t)	54.71(t)		61.10(t)
C-6'	54.85(t)	54.71(t)		46.56(t)
C-9'	41.43(d)	41.07(d)		40.83(d)
C-10'	96.22(d)	96.09(d)		87.72(d)
C3'-Me				14.62(q)



1 R=H

2 R=OH



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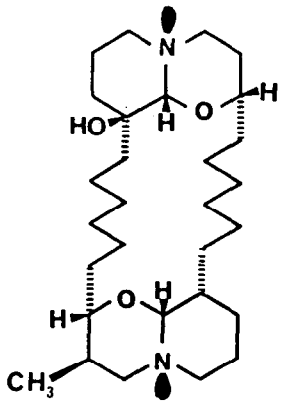

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close to the expected values. The mean bond lengths are 1.530 Å(1.508-1.530 Å) for C-C,1.465 Å for C-O. The interesting feature of the molecule is that the central twenty-membered monocyclic ring adopts the energetically favorable and stable rectangular[4646] conformation with a size of 4.5 X 6.8 Å; its peripheral heterocyclic C,D-rings constitute a trans-decalin system whereas the A,B-rings adopt a cis-fused non-steroidal conformation.[7]

Xestospongin D[2: $C_{28}H_{50}N_2O_3$, mp 156-157°C(from ether); [α] +18.43°(c 1.08, $CHCl_3$); EI-MS, m/z 462(M^+); IR(KBr) 3533(OH), 2762 cm^{-1}(Bohlmann bands)] showed similar ^1H NMR[8] and ^{13}C NMR spectral data with 1, the only conspicuous difference being caused by the hydroxy group at C-9, i.e., 10-H changes from a doublet(δ4.40) to a singlet(δ4.77) and the C-9 is shifted from δ40.84 to δ70.90 (s).

Xestospongin A[3: $C_{28}H_{50}N_2O_2$, mp 135-136°C(from ether); [α] +6.90°(c 0.84, $CHCl_3$); EI-MS, m/z 446(M^+); IR(KBr) 2812, 2758 cm^{-1}(Bohlmann bands)] is isomeric with 1. The ^{13}C NMR(INEPT) spectrum showed only 14 signals and the ^1H NMR[9] spectrum only showed peaks due to rings C/D besides CH_2 groups. The structure of 2 thus possesses a point of symmetry.

Xestospongin B[4: $C_{29}H_{54}N_2O_3$, mp 179-181°C(from ether); [α] +7.10°(c 0.91, $CHCl_3$); EI-MS, m/z 477(M^++1); IR(KBr) 3521 cm^{-1}(OH)] showed no Bohlmann bands in the IR spectrum thus suggesting that it lacks the trans quinolizidine system. The 10-H and 10'-H signals[10] appeared at the low field of δ4.17, 4.40 due to effects of the lone pair electrons of tertiary nitrogens.[11] These data support that both bicyclic rings in 4 adopt cis-fused non-steroidal conformation as in the A,B-rings of 1 and 2. The similarity in the ^1H NMR and ^{13}C NMR signals arising from A,B-rings in 4 and 2 suggests the ring structure to be same. The ^1H NMR showed the presence of secondary CH_3 at δ0.51; its position was deduced from the coupling patterns of the 4'α-H(δ2.83,dd,J=13.4, 4.5 Hz) and 4'β-H(δ2.72,dd,J=13.4, 11.0 Hz) signals. Studies on the absolute comformation and biogenesis of the xestospongins which represent a new class of macrocyclic 1-oxaquinolizidines are under investigation.

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References

(1) Details of biological activities will be reported elsewhere.

(2) Satisfactory elemental analysis and high resolution EI-MS were obtained for 1 and 2.

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(4) H NMR(360 MHz, C_6D_6) 4.40(brd,J=1.4 Hz,H_{10}), 3.48(brt,J=10.9 Hz,H_2), 3.30 (brt,J=10.8 Hz,$H_{2'}$), 3.13(d,J=8.6 Hz,$H_{10'}$), 3.12(m,$H_{6\alpha}$), 2.82(dd,J=13.5,3.0 Hz,$H_{4\alpha}$), 2.64(brd,J=11.2 Hz,$H_{6',\alpha}$), 2.36(brd,J=10.9 Hz,$H_{6\beta}$), 2.04(ddd,J= 12.0,12.0,2.8 Hz,$H_{4',\beta}$), 0.77(brd,J=13.0 Hz,$H_{3\alpha}$).

(5) P.Main, S.E.Hull, L.Lessinger, G.Germain, J.P.Declerq, M.M.Woolfson, "MULTAN 78". A system of computer programs for the automatic solution of crystal structures from X-ray diffraction data, Universities of York & Louvain, 1978.

(6) T.Asada, "NISCS Program System"; Crystallographic Research Center, Institute for Protein Research, Osaka University, Osaka, 1979;pp 53..

(7) The automatic co-ordinates will be deposited at the Cambridge Crystallographic Data Center, University Chemical Laboratory, Lensfield road, Cambridge CB2 IEW, England.

(8) H NMR(360 MHz, C_6D_6) 4.17(s,H_{10}), 3.43(brt,J=11.0 Hz,H_2), 3.28(brt,J=11.0, Hz,$H_{2'}$), 3.13(d,J=8.5 Hz,$H_{10'}$), 2.94(ddd,J=11.1,11.1,3.4 Hz,$H_{6\alpha}$), 2.88(ddd, J=12.6,11.1,3.4 Hz,H), 2.78(ddd,J=11.2,3.9,1.9 Hz,H), 2.68(dd,J=12.6, 4.5 Hz,H), 2.65(brd,J=11.3 Hz,H).

(9) H NMR(360 MHz, C_6D_6) 3.28(brt,J=11.5 Hz,H_2), 3.06(d,J=9.1 Hz,H_{10}), 2.75 (ddd,J=11.0,4.1,2.5 Hz,$H_{4\alpha}$), 2.60(brd,J=10.3 Hz,$H_{6\alpha}$), 2.00(ddd,J=11.0,11.0, 2.7 Hz,$H_{4\beta}$), 1.87(ddd,J=10.3,10.3,2.5 Hz,$H_{6\beta}$).

(10) H NMR(360 MHz, C_6D_6) 4.40(brd,$H_{10'}$), 4.17(s,H_{10}), 3.43(brt,J=11.3 Hz, H_2), 2.95(ddd,J=13.7,13.7,2.7 Hz,$H_{6\alpha}$), 2.90(ddd,J=13.7,13.7,3.3 Hz,$H_{4\beta}$), 2.68(brd,$H_{4\alpha}$), 2.45(brd,J=10.2 Hz,$H_{6',\beta}$), 2.09(brd,J=13.7 Hz,$H_{6\beta}$), 0.65 (brd,J=13.5, Hz,$H_{3\alpha}$), 0.51(d,J=6.5 Hz,$C_{3',\beta}$-Me).

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