Tetrahedron Letters,Vol.29,No.39,pp 4971-4972,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

EUDISTOMIN K: CRYSTAL STRUCTURE AND ABSOLUTE STEREOCHEMISTRY

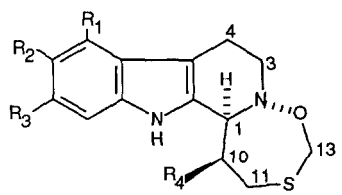
Robin J. Lake, John D. McCombs, John W. Blunt*, Murray H. G. Munro* & Ward T. Robinson

Department of Chemistry, University of Canterbury, Christchurch, NEW ZEALAND

ABSTRACT: The crystal structure of a derivative of the antiviral and antitumour compound eudistomin K **1a** has been determined, confirming the proposed structure and stereochemistry. The conformation found for the oxathiazepine ring in the solid state is similar to that proposed for the solution state from nmr spectroscopic measurements.

The oxathiazepine eudistomins, first reported from the Caribbean ascidian *Eudistoma olivaceum*[1] **1a-d**, and more recently from the New Zealand ascidian *Ritterella sigillinoides*[2] **1a-b,e**, are tryptophan derivatives of considerable synthetic and biological interest. These eudistomins are distinguished by the unusual structural combination of N, O, C and S, and as a group display potent antiviral and antitumour activity[1,2]. The original structure determination of this new class of alkaloid was based on nmr and mass spectrometric evidence[1], and supported by a subsequent, extensive nmr spectroscopic study[2]. We now report the crystal structure and confirm the absolute stereochemistry of the *p*-bromobenzoyl derivative of eudistomin K **1h** (Figure 1).

Eudistomin K **1a** was converted to the *p*-bromobenzoyl derivative **1h** by standard methods in good yield[3]. Recrystallisation from methanol/chloroform gave long, thin, tabular, transparent, needles suitable for single crystal X-ray structure analysis. The data were collected using a Nicolet XRD R3 single crystal four-circle diffractometer[4,5]. A Patterson calculation (SHELXS) revealed the position of the four bromine and two sulphur atoms in the asymmetric unit which contains two independent eudistomin K molecules and one methanol molecule. The remaining non-hydrogen atoms were located from difference Fourier syntheses (SHELXTL)[6]. All hydrogen atoms were inserted at calculated positions[7], except for the hydrogen on the methanol oxygen atom which is potentially able to hydrogen bond to several sites. Since it could not be located in difference Fourier syntheses it was omitted. With the exception of the indolic carbon atoms, all non-hydrogen atoms were assigned anisotropic thermal parameters, and the refinement of 451 least squares parameters converged with R = 0.049 and wR = 0.053. The final electron density maps showed no significant residual electron density and there were no abnormal discrepancies between observed and calculated structure factors[8]. The absolute configuration was determined unambiguously by eta refinement[9]. Fractional atomic coordinates for both eudistomin K molecules and the methanol solvate molecule are listed[10].



		R_1	R_2	R_3	R_4
1	**a**	H	H	Br	NH_2
	b	H	OH	Br	NH_2
	c	Br	OH	H	NH_2
	d	H	Br	H	NH_2
	e	H	H	H	NH_2
	f	H	H	Br	$^+NH_3$
	g	H	H	Br	$NHCOCH_3$
	h	H	H	Br	NH-*p*-Br-benzoyl

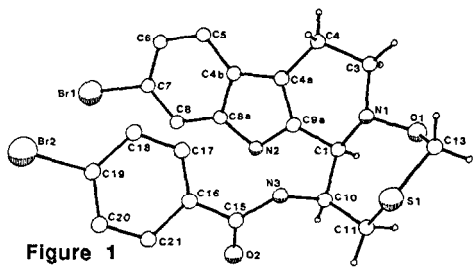


Figure 1

In the earlier nmr study of the structure and stereochemistry of eudistomin K[2], **1a**, use was made of the modified Karplus equation[11] to estimate vicinal dihedral angles in the oxathiazepine and β-carboline rings. These data, along with the observation of key nOe derived H/H relationships (1α/3α, 3β/13β, 13α/11α, but not 3α/13α, 3β/13α or 11β/13α), were critical in the confirmation of the structure of eudistomin K as **1a**, and in proposing the relative stereochemistry and a conformation for eudistomin K **1a** in solution (Figure 2b)[2]. Similar coupling constants and the same nOe relationships were observed for the salt **1f** and the acetyl and *p*-bromobenzoyl derivatives (**1g** and **1h**), indicating the same dominant conformation in solution for the oxathiazepine ring regardless of the polarity and steric bulk of the 10β N function. Although there are two independent molecules of **1h** in the asymmetric unit, they are conformationally equivalent, their slight differences being a

consequence of different packing environments. The conformation of the *p*-bromobenzoyl derivative **1h** in the crystalline state (Figure 2a) is remarkably similar to that proposed for eudistomin K **1a** in solution (Figure 2b) and strongly suggests that the factors determining the conformation of eudistomin K and its derivatives are essentially the same in both the liquid and crystalline state. The most noticeable difference between the conformations is the opening of the **N1C1C10N3** dihedral angle as indicated by the estimated dihedral angles for the oxathiazepine ring from the atomic coordinates (**1h**) and coupling constants (**1a**) (Table 1).

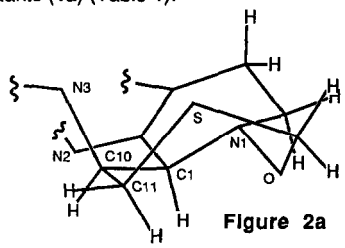


Figure 2a

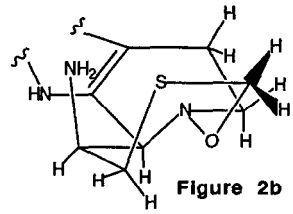


Figure 2b

Table 1 Estimated Dihedral Angles

	1a	(*J* in Hz)	**1 h**
3α/4β	180°	(11.8)	170°
3α/4α	50-60°	(4.0)	50°
3β/4β	50-60°	(4.6)	50°
3β/4α	60-70°	(2.2)	71°
1α/10α	80-90°	(<1)	43°
10α/11α	80-90°	(0)	65°
10α/11β	40°	(6.2)	54°

ACKNOWLEDGEMENTS: Support from The Harbor Branch Oceanographic Institution and the NZ UGC is gratefully acknowledged.

REFERENCES & NOTES

1. (a) Rinehart, K. L. Jr., Kobayashi, J., Harbour, G. C., Hughes, R. G. Jr., Mizsak, S. A., and Scahill, T. A., *J. Am. Chem. Soc.*, 1984, **106**, 1524-6; (b) Rinehart, K. L. Jr., Kobayashi, J., Harbour, G. C., Gilmore, J., Mascal, M., Holt, T. G., Shield, L. S., and Lafargue, F., *J. Am. Chem. Soc.*, 1987, **109**, 3378-87.
2. (a) Blunt, J.W., Lake, R. J., Munro, M. H. G., and Toyokuni, T., *Tetrahedron Lett.*, 1987, **28**, 1825-26; (b) Lake, R. J., Blunt, J. W., Munro, M. H. G., *Aust. J. Chem.*, (submitted).
3. Eudistomin K **1a** (10mg) was reacted with *p*-bromobenzoyl chloride (16mg) in CH_2Cl_2 (5mL) with added triethylamine (22mg) for 16 hr. The product mixture was purified by normal phase HPLC (silica gel semi-preparative column, 2mL/min $CHCl_3$) to give the *p*-bromobenzoyl derivative of eudistomin K **1h** (11mg, 73%), which was recrystallised from methanol/chloroform to give needles, m.p. 192-193°; $[\alpha]_D$=-200°, (c 0.1 in $CHCl_3$); λ_{max} 279nm (ε 10700), 230nm (ε 57500); δ_H ($CDCl_3$ referenced to $CHCl_3$ at 7.25ppm) 8.72, bs, indole NH; 7.43, 2H, d, *J* = 8.6, H18 and H20; 7.37, 2H, d, *J* = 8.6, H17 and H21; 7.36, d, *J* = 1.7, H8; 7.30, brd, *J* = 9.5, benzoyl NH; 7.22, d, *J* = 8.4, H5; 7.11, dd, *J* = 8.4, 1.7, H6; 5.16, m, H10; 4.99, d, *J* = 9.1, H13α; 4.88, d, *J* = 9.1, H13β; 4.23, brs, H1; 3.63, ddd, *J* = 10.1, 5.1, 1.7, H3β; 3.43, d, *J* = 14.5, H11α; 3.17, ddd, *J* = 11.5, 10.2, 4.8, H3α; 2.90, dddd, *J* = 15.5, 11.5, 5.1, 2.1, H4; 2.88, dd, *J* = 14.5, 5.8, H11β; 2.79, m, *J* = 15.5, 4.8, 1.7 and small, H4; δ_C ($CDCl_3$ referenced to 77.01ppm) 166.7, C=O; 137.9, C8a; 132.6, C4b; 131.8, C17 and C21; 130.9, C16; 128.5, C18 and C20; 126.5, C9a; 125.0, C19; 122.7, C6; 119.1, C5; 115.5, C7; 114.3, C8; 109.4, C4a; 71.1, C13; 69.0, C10; 54.7, C3; 47.3, C1; 32.3, C11; 20.6, C4.
4. Mo Kα (λ 0.71069 Å) radiation from a crystal monochromator was used. The cell parameters were determined from a least squares refinement of 22 accurately centred high angle reflections (19°<2θ<33°). Data were corrected for Lorentz and polarisation effects. An empirical absorption correction, based on ψ-scan data, was applied. The space group was determined unambiguously as a result of the structure analysis reported below, but initially indicated by systematic absences of the appropriate reflections.
5. Crystal data. $C_{21}H_{19}N_3O_2SBr_2$, M 535, crystal dimensions 0.8 x 0.4 x 0.1 mm, monoclinic, $P2_1$, a 9.994(2), b 21.115(8), c 10.788(2) Å, β 104.82(2), U 2200(2) $Å^3$, D_C 1.61 cm^{-3}, Z 4, F(000) 1072, μ(Mo Kα) 3.72 mm^{-1}, absorption correction: max 0.755, min 0.414. ω-scan intensity measurements (4°<2θ<55°), at 133K, yielded 4374 unique reflections 3009 were judged observed ($I > 3\sigma(I)$). Crystal stability was monitored by measuring three check reflections every 500 and no significant variations were observed.
6. Sheldrick, G.M., "SHELXTL User Manual", Revision 4.1 (1981) Nicolet XRD Corporation, Madison, Wisconsin, U.S.A., and Sheldrick, G.M., "SHELXS. Program for Crystal Structure Solution". University of Gottingen, Federal Republic of Germany.
7. Using a riding model with thermal parameters equal to 1.2U of their carrier atoms.
8. Blocked cascade refinements, with reflection weights of $1/[\sigma^2(F)+0.00084(F^2)]$, and the function minimized was $\Sigma(|F_o| - |F_c|)^2$.
9. Rogers, D., *Acta Cryst.*, 1981, **A37**, 734. η +0.95(3).
10. Atom Coordinates (x 10^4) and Temperature Factors ($Å^2$ x 10^3)

	Molecule 1				Molecule 2					Molecule 1				Molecule 2			
Atom	x/a	y/b	z/c	U	x/a	y/b	z/c	U	Atom	x/a	y/b	z/c	U	x/a	y/b	z/c	U
BR1	7152(1)	0000(0)	5796(1)	32(1)	12191(1)	5959(1)	10808(2)	36(1)	C7	8418(12)	381(5)	4965(12)	25(3)	10513(12)	5514(5)	10109(12)	23(3)
BR2	8414(1)	2829(1)	8612(1)	32(1)	12497(1)	3181(1)	14416(1)	32(1)	C8	9802(12)	272(5)	5425(12)	25(3)	9452(12)	5554(5)	10710(13)	25(3)
S1	15923(3)	2551(2)	5297(3)	28(2)	2853(3)	3429(1)	10530(3)	25(2)	C8a	10697(12)	587(5)	4826(12)	24(3)	8206(12)	5254(5)	10121(12)	23(3)
O1	15212(7)	1806(4)	3196(8)	25(5)	2631(7)	4187(4)	8476(8)	26(5)	C9a	12492(12)	999(6)	4199(12)	27(3)	6073(12)	4855(5)	9551(13)	25(3)
O2	13953(8)	1079(4)	7936(8)	28(5)	6207(8)	4617(4)	13490(8)	29(5)	C11	16064(12)	1738(5)	5879(12)	22(7)	3218(11)	4227(5)	11166(12)	22(7)
N1	13867(10)	1760(4)	3449(9)	22(6)	4145(9)	4160(5)	8714(10)	28(6)	C13	15783(15)	2400(6)	3614(13)	39(8)	2122(13)	3608(6)	8832(13)	35(8)
N2	12135(9)	575(4)	5074(10)	22(6)	6968(10)	5221(4)	10462(9)	25(6)	C15	13358(12)	1525(5)	7270(12)	23(7)	6550(11)	4236(5)	12773(12)	24(7)
N3	13765(9)	1740(4)	6250(10)	23(6)	5763(10)	4106(5)	11581(10)	28(6)	C16	12119(11)	1848(5)	7506(12)	24(7)	7958(12)	3927(5)	13120(12)	22(7)
C1	13951(12)	1183(5)	4277(12)	23(7)	4611(12)	4698(5)	9618(11)	22(7)	C17	11025(12)	2045(5)	6574(13)	28(7)	8579(14)	3837(5)	14427(12)	30(8)
C3	12893(12)	1672(6)	2183(12)	28(7)	4384(11)	4307(5)	7427(12)	23(7)	C18	9869(13)	2320(5)	6850(13)	27(7)	9947(14)	3608(5)	14846(14)	34(8)
C4	11396(12)	1674(6)	2347(12)	26(7)	5925(12)	4275(5)	7504(12)	25(7)	C19	9388(12)	2408(5)	8140(12)	24(7)	10620(15	3469(6)	13912(16)	42(9)
C4a	11320(11)	1243(5)	3396(11)	20(3)	6703(12)	4650(5)	8639(12)	24(3)	C19	9888(12)	2408(5)	8140(12)	24(7)	10620(15)	3469(6)	13912(16)	42(9)
C4b	10164(11)	998(5)	3782(12)	21(3)	8046(12)	4901(5)	8972(12)	23(3)	C20	10988(11)	2195(5)	9113(12)	22(7)	10004(12)	3548(5)	12599(13)	28(7)
C5	8737(12)	1093(5)	3337(13)	28(3)	9172(12)	4859(5)	8420(13)	31(3)	C21	12102(12)	1914(5)	8802(13)	24(7)	8650(12)	3786(6)	12224(13)	32(8)
C6	7864(13)	795(5)	3933(13)	29(3)	10398(13)	5174(5)	8971(13)	28(3)									
Cm	5838(15)	2481(6)	71(15)	45(4)					Om	6042(8)	3124(4)	234(8)	32(2)				

Structure factor and molecular dimension tables have been deposited with the Cambridge Crystallographic Data Centre.

11. Haasnoot, C. A. G., de Leeuw, F. A. A. M., and Altona, C., *Tetrahedron*, 1980, **36** 2783-92.

(Received in UK 26 July 1988)