X-RAY STRUCTURE DETERMINATION OF (2S, 3R)-3-AMINO-2-HYDROXY-4-PHENYLBUTANOIC ACID, A NEW AMINO ACID COMPONENT OF BESTATIN

Sir:

As reported in the preceding paper,[1] 3-amino-2-hydroxy-4-phenylbutanoic acid is a component in bestatin, an inhibitor of aminopeptidase B and leucine aminopeptidase. The absolute determination of its stereochemistry is possible by X-ray crystallographic analysis of a suitable derivative. Therefore, the hydrobromide of its methyl ester was crystallized and subjected to X-ray analysis. The results indicate a (2S, 3R)-configuration and confirmed that an experimental rule for the determination of configuration of α-amino-β-hydroxy acids developed by SHIBA *et al.*[2] can be applied to this β-amino-α-hydroxy acid.

A methanol solution (11.5 mg of 3-amino-2-hydroxy-4-phenylbutanoic acid in 5 ml) of material isolated from the acid hydrolysate of bestatin, and 0.2 ml of hydrobromic acid (d=1.48) was kept at room temperature for a week. After evaporation of the solvent, the methyl ester hydrobromide was crystallized from methanol-benzene, m.p. 172~173°C, $\nu_{C=O}^{KBr}$ 1740 cm^{-1}. The crystals are thin, colorless, transparent plates. A crystal with approximate dimensions 0.55×0.4×0.03 mm was used for the X-ray diffraction study. The diffraction data were collected with a Philips PW 1100 diffractometer equipped with a graphite monochromator (Cukα radiation). The crystal data are given in Table 1.

Table 1. Crystal data

Methyl 3-amino-2-hydroxy-4-phenylbutanoate hydrobromide
M. W.=290.16.
Monoclinic, space group $P2_1$, Z=2.
a=13.051(6), b=8.736(5), c=5.486(3)Å, β=94.4(1)°.
U=623.6Å^3, Dx=1.546 gcm^{-3}.

Intensities were measured using the $\theta-2\theta$ scan method with a scan speed of 4° θ min^{-1}. Of the 1334 reflections with θ angle less than 78°, 1323 reflections were measured with $I>2\sigma$ (I). For the 847 hkl reflections with θ angle less than 60°, $h\bar{k}l$'s were also measured in order to determine the absolute configuration. No absorption correction was applied to the intensity data. The phase angles were evaluated by the anomalous dispersion method[3] coupled with the usual heavy atom method. The locations of 15 light atoms were found on the electron density map. The structural parameters were refined by the block-matrix least-squares method to an R value of 0.086. The final parameters are listed in Table 2. The absolute configuration was confirmed by calculating the ratios Fc(hkl)/Fc($h\bar{k}l$) and by comparing with the corresponding observed ratios. The dispersion corrections to the scattering factors for bromine (Cukα radiation) were taken to be $\Delta f'=-0.767$ and $\Delta f''-1.283$. 132 of the 147 hkl and $h\bar{k}l$ pairs for which the calculated ratios differed from the unity by more than 5%, showed agreement with those of the observed ones. The absolute configuration (2S, 3R) was then established as shown in Fig. 1. The bond lengths and angles are also shown in Fig. 1. The values are consistent with those expected for the chemical structure. The e.s.d.'s of these

Fig. 1. Bond lengths and angles.

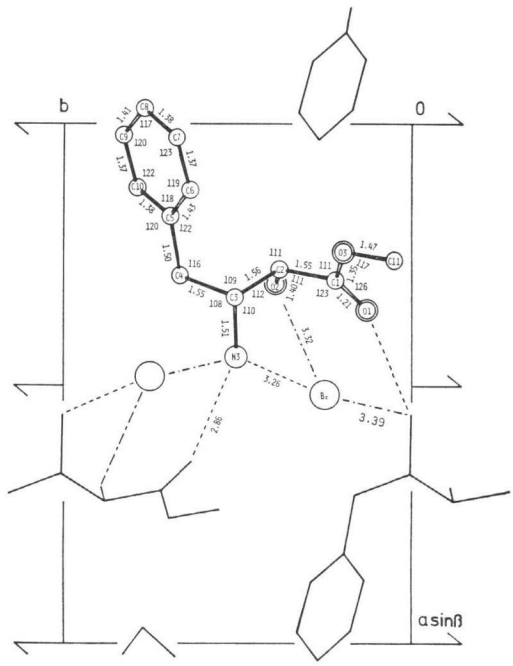

Table 2. Final atomic parameters ($\times 10^4$)

The temperature factors are of the form: $T=\exp[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)]$. Absolute configuration is represented by the right-hand coordinate system.

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
BR	5180(1)	2500(0)	361(3)	42(1)	116(2)	272(6)	8(2)	6(2)	−52(5)
C1	2960(11)	2189(18)	4063(26)	28(7)	78(28)	163(47)	1(11)	−9(15)	− 3(27)
C2	2753(12)	3805(19)	5063(27)	42(9)	54(20)	127(48)	3(12)	11(17)	0(26)
C3	3289(12)	5051(20)	3586(28)	27(9)	57(18)	184(55)	− 6(10)	12(18)	1(29)
C4	2882(13)	6647(20)	4253(31)	38(10)	67(23)	242(61)	1(12)	7(19)	−12(31)
C5	1762(12)	6939(19)	3578(29)	33(9)	68(20)	201(52)	− 5(11)	11(17)	18(29)
C6	1255(14)	6384(25)	1359(35)	43(11)	129(30)	256(67)	2(16)	−21(22)	−29(39)
C7	244(16)	6755(28)	785(37)	53(13)	155(35)	302(76)	5(18)	− 8(24)	−10(45)
C8	−302(14)	7704(37)	2227(36)	51(11)	147(43)	379(73)	12(22)	9(23)	28(56)
C9	214(16)	8282(30)	4378(42)	47(13)	199(43)	403(93)	14(20)	21(27)	−80(53)
C10	1214(14)	7886(24)	5009(35)	43(10)	128(39)	329(69)	2(15)	23(22)	−60(39)
C11	2597(17)	499(22)	649(37)	85(16)	69(25)	290(73)	−18(17)	24(27)	−48(36)
O1	3545(10)	1282(16)	5110(24)	64(9)	96(19)	276(49)	23(12)	−15(17)	− 7(26)
O2	3031(10)	3900(16)	7573(22)	67(9)	87(18)	185(42)	10(11)	13(15)	10(24)
O3	2430(9)	1962(14)	1875(21)	53(8)	67(16)	220(40)	− 3(09)	−16(14)	8(22)
N3	4431(10)	5021(19)	4233(25)	26(8)	87(19)	228(52)	− 3(10)	15(16)	−19(29)

Table 3. Torsion angles

O1-C1-C2-O2	− 20°	nearly *cis*
C1-C2-C3-C4	168°	*trans*
O2-C2-C3-N3	52°	*gauche*
C2-C3-C4-C5	− 64°	*gauche*
N3-C3-C4-C5	176°	*trans*
C3-C4-C5-C6	− 38°	twisted

values were calculated to be 0.02Å and 1°. Some important torsion angles are tabulated in Table 3, which shows the conformation of the molecule.

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