X-RAY STRUCTURE DETERMINATION OF 4-AMINO-3-HYDROXY-6-METHYLHEPTANOIC ACID, AN AMINE COMPONENT OF PEPSTATIN

Sir:

The chemical synthesis of 4-amino-3-hydroxy-6-methylheptanoic acid (AHMHA) starting from L-leucine and diethyl malonate has been reported.[1] However, the absolute configuration of AHMHA obtained by hydrolysis of pepstatin was not elucidated. In this paper we report the X-ray diffraction study of the N-*p*-bromobenzoyl derivative and the absolute configuration of AHMHA.

The crystals grown from propanol solution were transparent prisms elongated along the c axis. Oscillation and WEISSENBERG photographs indicated the space group $P2_12_12_1$. The lattice constants and the three-dimensional intensity data were derived from the measurements made on a Rigaku four-circle X-ray diffractometer. The crystal data are shown in Table 1. Intensities of 1250 reflections were obtained above 3σ level out of 1626 theoretically possible reflections within the 2θ value of 130°. These intensities were measured by the 2θ—ω scanning method using Ni filtered Cu$K\alpha$ radiation.

Table 1. Crystal data.

N-*p*-Bromobenzoyl derivative of 4-amino-3-hydroxy-6-methylheptanoic acid of pepstatin $C_{15}H_{20}O_4NBr$
M.W.358
Orthorhombic
$a=8.107\pm0.008$, $b=36.52\pm0.04$, $c=5.384\pm0.005$Å
$U=1594.1$Å^3
$Dx=1.492\,g\cdot cm^{-3}$
$Z=4$
Absent reflections: $h00$ when $h\neq2n$, $0k0$ when $k\neq2n$, $00l$ when $l\neq2n$
Space group: $P2_12_12_1$

The structure was solved by the heavy atom method. The first FOURIER synthesis phased by the bromine atom revealed all the atoms except for the three carbon atoms at the terminal isopropyl group. The complete structure was found and refined by the successive use of least-squares and difference FOURIER calculations. The R value was reduced to 0.062 allowing for the anisotropic thermal parameters for each

Table 2. Final atomic parameters and their estimated standard deviations in parentheses. The temperature factors are of the form, $T=\exp\{-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{23}kl+2\beta_{13}hl)\}$

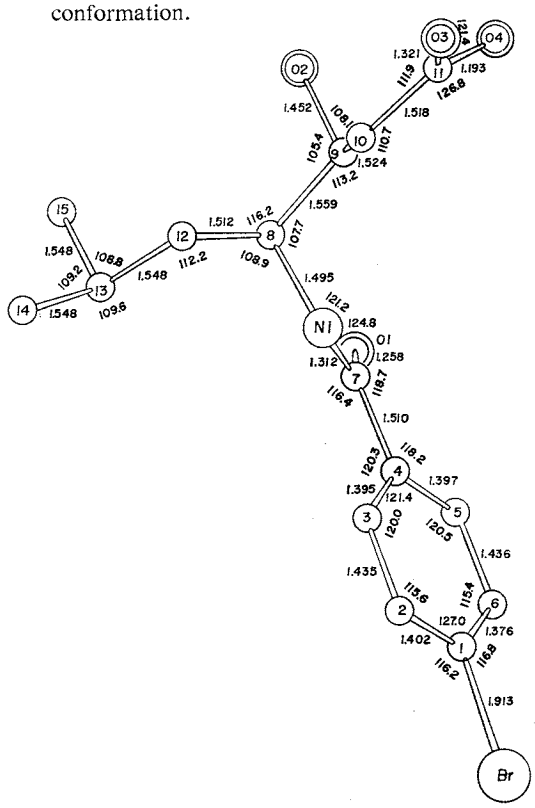
	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Br	0.5635(2)	0.5514(0)	0.2963(4)	0.0212(2)	0.0005(0)	0.1013(10)	−0.0008(0)	0.0111(6)	0.0003(1)
O1	0.3089(10)	0.3853(2)	0.7243(16)	0.0248(17)	0.0005(0)	0.0323(34)	−0.0002(2)	−0.0065(25)	0.0001(4)
O2	0.2168(9)	0.2760(2)	0.3949(14)	0.0136(12)	0.0005(0)	0.0302(32)	−0.0009(2)	−0.0033(19)	0.0009(3)
O3	0.4672(8)	0.2651(2)	−0.2509(14)	0.0137(12)	0.0007(1)	0.0243(28)	0.0010(2)	−0.0032(20)	−0.0001(4)
O4	0.5601(12)	0.2663(2)	0.1314(16)	0.0252(19)	0.0014(1)	0.0348(37)	0.0036(4)	−0.0133(27)	−0.0024(5)
N1	0.2516(10)	0.3762(2)	0.3147(17)	0.0129(14)	0.0003(0)	0.0276(37)	−0.0005(2)	−0.0007(22)	−0.0006(4)
C1	0.4915(14)	0.5022(2)	0.3530(29)	0.0160(20)	0.0004(1)	0.0680(75)	−0.0002(3)	0.0014(38)	0.0001(6)
C2	0.3838(15)	0.4875(3)	0.1757(28)	0.0228(25)	0.0005(1)	0.0539(67)	−0.0004(4)	0.0061(40)	−0.0005(7)
C3	0.3266(14)	0.4510(3)	0.2249(24)	0.0208(22)	0.0005(1)	0.0405(55)	−0.0005(4)	−0.0041(36)	−0.0005(7)
C4	0.3785(13)	0.4327(2)	0.4383(21)	0.0136(19)	0.0004(1)	0.0295(47)	0.0001(3)	−0.0001(27)	−0.0004(5)
C5	0.4862(13)	0.4491(3)	0.6078(22)	0.0142(19)	0.0006(1)	0.0392(52)	0.0000(4)	−0.0062(28)	−0.0008(6)
C6	0.5492(16)	0.4852(3)	0.5639(25)	0.0190(23)	0.0005(1)	0.0497(62)	−0.0007(4)	−0.0016(39)	−0.0007(6)
C7	0.3091(12)	0.3955(2)	0.5011(22)	0.0102(16)	0.0004(1)	0.0316(46)	0.0006(3)	−0.0035(27)	0.0001(5)
C8	0.1661(12)	0.3404(2)	0.3566(23)	0.0113(16)	0.0003(1)	0.0379(51)	−0.0004(3)	0.0006(30)	−0.0005(5)
C9	0.2922(12)	0.3093(2)	0.2999(22)	0.0118(16)	0.0003(1)	0.0312(47)	0.0001(3)	0.0021(29)	0.0002(5)
C10	0.3242(13)	0.3040(2)	0.0234(20)	0.0125(18)	0.0005(1)	0.0180(40)	0.0008(3)	0.0044(27)	0.0003(5)
C11	0.4621(13)	0.2766(3)	−0.0183(18)	0.0145(19)	0.0006(1)	0.0142(37)	0.0001(3)	−0.0010(26)	−0.0002(4)
C12	0.0081(12)	0.3399(2)	0.2074(23)	0.0084(14)	0.0006(1)	0.0386(53)	0.0001(3)	−0.0010(28)	−0.0005(6)
C13	−0.1369(15)	0.3581(3)	0.3478(31)	0.0131(20)	0.0011(1)	0.0699(82)	−0.0004(4)	0.0037(40)	−0.0038(9)
C14	−0.2755(15)	0.3680(4)	0.1617(40)	0.0137(21)	0.0011(1)	0.1059(17)	0.0011(4)	−0.0037(51)	0.0002(12)
C15	−0.2051(24)	0.3307(7)	0.5417(33)	0.0309(43)	0.0038(4)	0.0365(77)	−0.0022(11)	0.0067(57)	0.0017(15)

atom. The final atomic parameters are listed in Table 2. The absolute configuration was determined by the anomalous dispersion method. The dispersion corrections for the bromine scattering factor for Cu$K\alpha$ radiation were taken to be $\Delta f' = -0.9$ and $\Delta f'' = 1.5$. The structure factors for the FRIEDEL pairs of reflections of $hk1$ and $hk2$ were calculated and compared with the observed values. Comparison of 15 pairs of reflections indicated clearly that the absolute configuration should be represented by taking the right-handed coordinate system for the coodinates given in Table 2.

The structure of the molecule drawn with the correct absolute configuration is shown in Fig. 1. It should be noted that both C8 and C9 take the S configuration in accordance with the result obtained by the chemical study of KINOSHITA *et al.*[2] Fig. 1 also shows the bond lengths and valency angles. The estimated standard deviations of these values are ±0.015Å and ±1°. No abnormal lengths or angles are found in the present structure. The conformation angles along the backborn of the molecule are: O4—C11—C10—C9=−17°, C11—C10—C9—C8=173°, C10—C9—C8—N1=−74°, C10—C9—C8—C12=48°, C9—C8—C12—C13=153°, C8—C12—C13—C14=162°, C8—C12—C13—C15=−79°. Where, the angle denoted by A—B—C—D is defined as the angle formed by the projection of the A—B bond with that of C—D when the projection is taken along the B—C bond, and the angle is taken as positive if the rotation to bring the projection of A—B into that of C—D coincides with that of the right-handed screw advancing along the B—C bond. It is to be noted that the conformation about the C8—C9 bond is staggered but N1 is situated nearly at the *trans* position with respect to O2, the conformation angle O2—C9—C8—N1 being 168°. The plane formed by the amide group is twisted at an angle of about 20° from the plane of the benzene ring.

Within the crystal, the molecules are arranged about the two-fold screw axis parallel to the *a* axis lying their β-hydroxy carboxylic acid groups nearly parallel to the screw axis. Strong intermolecular hydrogen bonds are formed between O2 and O3 (2.64Å) of the molecules related by the screw axis, and also between O2 and O3 (2.81Å) of the molecules related by the translation G. No direct hydrogen bond is formed between the two carboxyl groups as is commonly found in carboxylic acids.

Fig. 1. Molecular structure showing the absolute configuration, bond lengths, bond angles and conformation.



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References

1) MORISHIMA, H.; T. TAKITA & H. UMEZAWA: Synthesis of 4-amino-3-hydroxy-6-methylheptanoic acid, an amine component of pepstatin. J. Antibiotics 26: 115~116, 1973.

2) KINOSHITA, M.; S. ABURAKI, A. HAGIWARA & J. IMAI: Absolute configuration of 4-amino-3-hydroxy-6-methylheptanoic acid present in pepstatin A and stereospecific synthesis of all four isomers. J. Antibiotics 26: 249~251, 1973.