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Peptides in Higher Plants. II.[1] The Crystal Structure of Tri-N-methylfrangulanine Methiodide

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The crystal structure of tri-N-methylfrangulanine methiodide, $C_{32}H_{54}O_4N_4I$ has been determined in order to clarify the conformation and absolute configuration of frangulanine, $C_{28}H_{44}O_4N_4$, a peptide alkaloid isolated from Hovenia dulcis. The crystals are orthorhombic with space group $P2_12_12_1$ and unit cell dimensions are $a=8.826$ (8), $b=49.95$ (2), $c=8.296$ (8) Å, $Z=4$. The crystal structure was solved by the heavy-atom method and refined by the block-diagonal least-squares method including anisotropic thermal parameters. The final R value for 1383 observed structure factors was 0.10. The absolute configuration was determined by the use of the anomalous dispersion of iodine atom for Cu $K\alpha$ radiation. Frangulanine is composed of all L-amino acids and the conformation of the peptide units is of the β-pleated sheets structure.

Frangulanine is a peptide alkaloid with a 14 membered ring, whose structure has been established chemically.[3] However little has been known about its stereochemistry. Concerning to the absolute configuration, only β-hydroxyleucine moiety has been deduced to be L-*erythro* configuration by chemical and enzymic studies[4] and other amino acids have been assumed to possess L-configuration. In order to clarify the conformation and the absolute configuration, X-ray analysis was carried out for a heavy atom derivative. A preliminary report of this work has already been published.[5]

Experimental

The treatment of frangulanine with sodium hydride and methyl iodide in dimethyl sulfoxide gave tri-N-methylfrangulanine methiodide. The crystals were grown from methanol and ether as colourless prisms. The lattice constants and the intensity data were measured on a Philips four-circle diffractometer using graphite monochromated Cu $K\alpha$ radiation.

Crystal Data——Tri-N-methylfrangulanine methiodide, mp 242—244°, $C_{32}H_{54}O_4N_4I$, mol. wt=684.70. Orthorhombic, $P2_12_12_1$, $a=8.826$ (8), $b=49.95$ (2), $c=8.296$ (8) Å. $U=3657$ Å^3, $Z=4$, $Dx=1.243$ g cm^{-1}.

A total of 1383 independent three dimensional intensity data were collected within $2\theta=100°$. During the data collection, the intensities of the standard reflexions were decreased about 20% by a radiation damage. The intensity data were therefore normalized using the intensities of three standard reflexions and then corrected for Lorentz and polarization factors. A Wilson plot gave an approximate overall temperature factor of 4.6 Å^2.

Determination and Refinement of the Structure——The position of the iodine atom was determined from a Patterson function. The first Fourier map showed 20 atoms and the whole structure was established by the subsequent two sets of Fourier and difference Fourier syntheses. Refinement was made by the block-diagonal least-squares method using the *HLSB* program of Okaya and Ashida.[6] Twelve cycles of calculations gave an R value of 0.10 for 1383 observed reflexions. The weighting scheme was: $\sqrt{w}=65/Fo$, when

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5) M. Takai, Y. Ogihara, K. Kawai, Y. Iitaka, and S. Shibata, *J. C. S. Chem. Commun.*, **1974**, 653.
6) Y. Okaya and T. Ashida, "The Universal Crystallographic Computing System," Vol. I, The Crystallographic Society of Japan, Tokyo, 1967, p. 65.

Table I. Atomic Parameters

Temperature Factors are of the form $T=\exp[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)]$ ($\times 10^4$)

	X	Y	Z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
C (1)	0.8344(34)	0.0936(6)	0.4349(38)	120(46)	6(2)	187(69)	5(8)	−65(51)	11(9)
C (1A)	0.9221(33)	0.0659(5)	0.4610(47)	159(49)	2(1)	343(91)	8(6)	−14(66)	−2(10)
C (1B)	1.0463(41)	0.0685(7)	0.6093(40)	229(72)	7(2)	189(63)	1(10)	116(63)	3(9)
C (1C1)	1.2082(47)	0.0765(7)	0.5292(62)	331(83)	8(2)	450(125)	−13(11)	194(104)	−27(15)
C (1C2)	1.0048(53)	0.0908(8)	0.7298(42)	299(83)	10(3)	201(68)	−23(15)	−33(89)	−3(11)
C (1D)	1.2908(65)	0.0567(8)	0.4753(91)	538(132)	7(2)	883(214)	6(15)	36(191)	−23(22)
C (1E1)	0.8852(40)	0.0178(7)	0.4948(48)	240(64)	9(2)	236(76)	13(11)	21(81)	11(13)
C (1E2)	0.7253(45)	0.0457(7)	0.6565(38)	351(87)	7(2)	87(58)	−29(11)	109(63)	−2(9)
C (1E3)	9.7063(39)	0.0450(6)	0.3614(43)	192(66)	6(2)	222(77)	13(9)	−77(65)	1(10)
C (2)	0.9401(31)	0.1588(5)	0.3097(34)	154(52)	2(1)	298(55)	5(7)	185(48)	8(8)
C (2A)	0.8131(28)	0.1342(6)	0.2878(39)	25(38)	5(2)	223(68)	2(7)	−68(47)	9(9)
C (2B)	0.7389(33)	0.1376(5)	0.1124(38)	116(47)	4(1)	187(62)	−8(7)	52(52)	−7(8)
C (2C)	0.6397(37)	0.1129(7)	0.0667(43)	147(54)	7(2)	243(81)	8(9)	−88(59)	−13(10)
C (2D1)	0.4992(36)	0.1095(6)	0.1855(39)	105(46)	7(2)	250(67)	−24(9)	25(66)	−10(9)
C (2D2)	0.5811(41)	0.1148(7)	−0.1071(50)	191(63)	7(2)	296(89)	−4(10)	24(68)	−10(12)
C (2E)	1.0099(40)	0.0998(5)	0.1837(39)	181(57)	4(1)	259(67)	14(9)	59(75)	8(9)
C (3)	0.9959(32)	0.2199(5)	0.4257(34)	78(40)	6(2)	188(55)	−10(8)	−1(54)	−11(8)
C (3A)	1.0585(29)	0.1910(5)	0.4719(43)	111(43)	3(1)	273(74)	2(6)	8(59)	2(9)
C (3B)	1.1278(32)	0.1892(6)	0.6346(35)	107(47)	6(2)	114(59)	14(8)	−50(49)	3(8)
C (3C)	1.1972(37)	0.1628(6)	0.6639(50)	168(62)	4(2)	390(102)	−15(8)	−90(72)	26(11)
C (3D1)	1.3314(41)	0.1559(8)	0.5742(47)	188(64)	10(2)	259(87)	23(11)	78(67)	−8(12)
C (3D2)	1.2298(50)	0.1615(7)	0.8580(42)	360(92)	6(2)	156(71)	13(12)	28(75)	11(10)
C (3E)	0.8022(32)	0.1728(5)	0.5556(41)	152(51)	4(1)	146(84)	−7(7)	−137(59)	8(9)
C (4A)	1.0196(45)	0.2607(6)	0.2638(35)	254(71)	5(2)	142(55)	−1(11)	49(69)	16(8)
C (4B)	0.9010(40)	0.2616(6)	0.1795(35)	267(70)	4(2)	84(53)	13(9)	−48(55)	5(8)
C (4C)	0.8140(37)	0.2360(6)	0.1495(38)	180(58)	4(2)	169(66)	11(8)	−120(57)	2(9)
C (4D1)	0.8834(34)	0.2176(5)	0.0405(37)	175(52)	4(1)	168(68)	10(8)	59(56)	12(9)
C (4D2)	0.6799(39)	0.2303(5)	0.2212(38)	193(60)	4(2)	197(72)	4(8)	−73(58)	23(9)
C (4E1)	0.8197(39)	0.1912(6)	0.0129(46)	248(64)	6(2)	188(69)	−4(9)	−97(76)	9(11)
C (4E2)	0.6142(41)	0.2047(7)	0.2046(40)	229(70)	8(2)	159(68)	24(11)	7(62)	16(10)
C (4F)	0.6993(35)	0.1845(6)	0.1109(39)	140(54)	6(2)	159(63)	7(8)	11(54)	18(9)
C (4G)	1.2323(39)	0.2259(6)	0.2733(45)	201(65)	4(2)	316(90)	−3(9)	188(67)	20(10)
N (1)	0.8064(26)	0.0447(4)	0.4881(39)	171(41)	3(1)	309(64)	−2(5)	−26(61)	−2(9)
N (2)	0.8866(28)	0.1089(4)	0.3024(31)	158(43)	2(1)	200(53)	5(6)	−19(44)	−3(7)
N (3)	0.9270(23)	0.1730(4)	0.4400(27)	83(32)	4(1)	157(47)	4(5)	30(34)	−7(6)
N (4)	1.0868(32)	0.2348(5)	0.3266(32)	259(57)	4(1)	163(50)	−6(7)	13(49)	−1(7)
O (1)	0.7310(22)	0.1007(3)	0.5248(27)	177(33)	4(1)	188(43)	4(5)	21(41)	5(6)
O (2)	1.0477(20)	0.1576(3)	0.2099(22)	125(34)	4(1)	148(36)	8(5)	123(31)	−6(5)
O (3)	0.8872(23)	0.2285(4)	0.5979(28)	229(28)	5(1)	210(45)	−1(5)	99(47)	10(7)
O (4)	0.6337(23)	0.1598(4)	0.1204(29)	130(34)	5(1)	278(52)	0(5)	−19(40)	2(6)
I	0.0156(3)	0.0239(0)	0.0187(3)	293(4)	6(0)	240(4)	7(1)	−9(6)	2(1)

Table II. Comparison of the Calculated and Observed Intensity Ratio used for the Establishment of the Absolute Configuration

$h\ k\ l$	$\lvert Fc\rvert^2(h,k,l)/\lvert Fc\rvert^2(\bar{h},\bar{k},\bar{l})$	$Io^2(h,k,l)/Io^2(\bar{h},\bar{k},\bar{l})$
1 1 1	1.8858	>1
1 5 1	0.7356	<1
1 9 1	1.4862	>1
2 1 1	0.5152	<1
2 2 1	1.0966	>1
2 5 1	1.2005	>1
3 6 1	0.8389	<1
3 8 1	1.2715	>1
4 2 1	0.8800	<1
4 3 1	0.8236	<1

$Fo>65$, $\sqrt{w}=1$, when $5<Fo<65$, $\sqrt{w}=0$, when $Fo<5$. The final atomic parameters are presented in Table I.[7]

The absolute configuration of the structure was determined by the anomalous-dispersion method. The dispersion terms of the iodine scattering factor for Cu $K\alpha$ radiation were taken to be $\Delta f'=-1.1$ and $\Delta f''=7.2$.[8] Table II lists the calculated and observed intensity ratio of the Friedel pair of reflexions used for the determination of the absolute configuration.

Discussion

Frangulanine is composed of all L-amino acids and the stereochemistry of the β-hydroxyleucine group was confirmed to be L-*erythro* form. The bond lengths and angles are shown in Fig. 1. These values are normal except for those involving the terminal atoms. The mean estimated standard deviation of the C–C bond distances is 0.04 Å and that of the C–C–C angles is 2.4°.

In Table III are listed the mean bond lengths arranged in groups of similar type, which agreed well with the normally accepted values. Some important torsion angles are listed in Table IV. When the ϕ, ψ values are plotted on the Ramachandran ϕ–ψ chart, they fall within the upper right part of the allowed region for the β-structure. The benzene ring and neighbouring double bond are twisted as much as 73°.

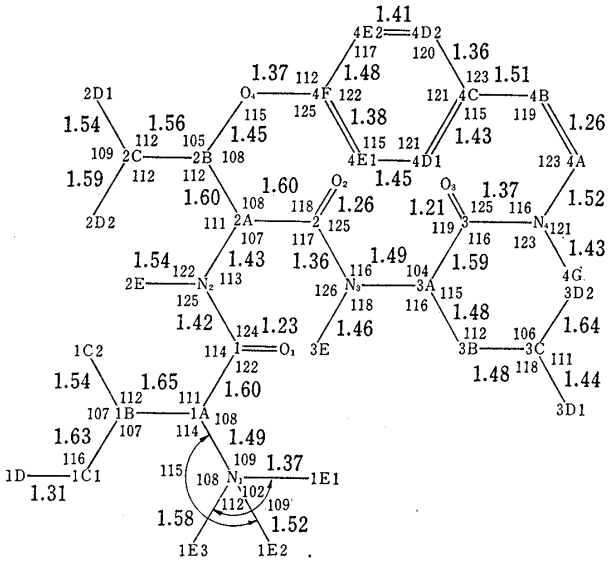

Fig. 1. Bond Lengths (Å) and Angles (°)

Table III. Mean Bond Lengths Arranged in Groups of Similar Bonds

Aromatic C–C	1.41 Å
C=C	1.26
C=O	1.23
Amide C–N	1.38
$C(Sp^3)$–$C(Sp^3)$	1.53
$C(Sp^3)$–N	1.47

Table IV. Some Important Torsion Angles

N(1)-C(1A)-C(1)-N(2)	$134=\phi_1$
C(1)-N(2)-C(2A)-C(2)	$-117=\phi_2$
N(2)-C(2A)-C(2)-N(3)	$115=\phi_2$
C(2)-N(3)-C(3A)-C(3)	$-108=\phi_3$
N(3)-C(3A)-C(3)-N(4)	$131=\phi_3$
C(4A)-C(4B)-C(4C)-C(4D1)	73
C(4E1)-C(4F)-O(4)-C(2B)	−38

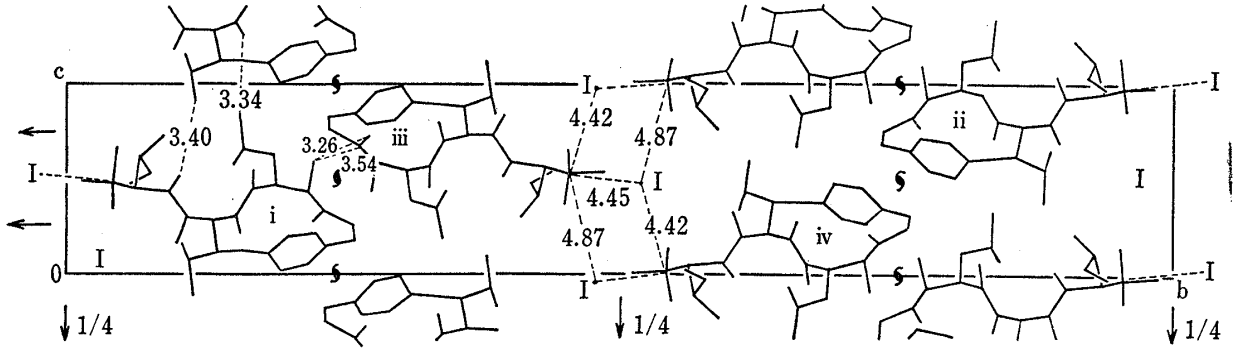

Fig. 2. Projection of the Crystal Structure along the *a* Axis

The positions of the molecules are: i at x, y, z; ii at $1\frac{1}{2}-x, 1-y, \frac{1}{2}+z$; iii at $-\frac{1}{2}+x, \frac{1}{2}-y, 1-z$; iv at $1-x, \frac{1}{2}+y, \frac{1}{2}-z$; where x, y, and z are the coordinates given in Table I.

7) Table for the observed and calculated structure factors may be obtained from the first author.
8) "International Tables for X-ray Crystallography," Vol. III, Kynoch Press, Birmingham, 1962, p. 215.

The crystal structure projected along the *a* axis is shown in Fig. 2. The short intermolecular distances less than 3.6 Å are shown in this figure. The distances between N(1) and iodine atoms are 4.42, 4.45 and 4.87 Å.

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