We wish to thank the Computer Center of the University of Oklahoma for providing the computer facilities. We are grateful to the Contraceptive Development Branch, Center for Population Research, National Institute of Child Health and Human Development (Contract No. N01-HD-2846 to Oklahoma State University) for partial support of this work. We also thank Drs Kurt L. Loening and O. C. Dermer for advice on nomenclature.

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Model Compounds for Protein Nucleic Acid Interactions. IV. Crystal Structure of a Nucleoside Peptide with Anti-Viral Properties: 5-[*N*-(L-Leucyl)amino]uridine

BY POOJAPPAN NARAYANAN AND HELEN M. BERMAN

The Institute for Cancer Research, The Fox Chase Cancer Center, Philadelphia, Pennsylvania 19111, *USA*

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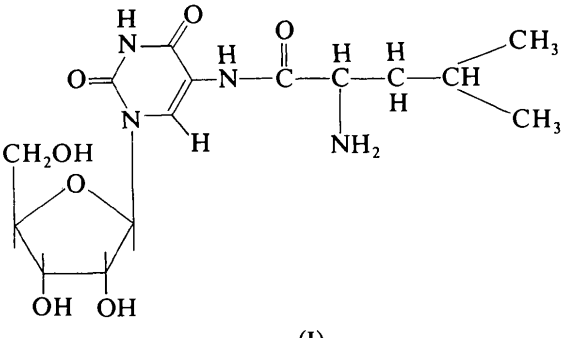
The crystal structure of an anti-viral agent, 5-[*N*-(L-leucyl)amino]uridine, has been determined. The compound crystallizes in the orthorhombic system, space group *I*222, with $a = 10{\cdot}883\,(3)$, $b = 23{\cdot}774\,(5)$, $c = 17{\cdot}038\,(7)$ Å, $V = 4408{\cdot}3$ Å^3, $Z = 8$, $d_m = 1{\cdot}34$ g cm^{-3}. The intensities of 1699 independent reflections were collected on an automatic diffractometer with θ–2θ scans and graphite-monochromatized Cu $K\alpha$ radiation. The structure was solved by direct phase determination and refined by full-matrix least squares to an R value of 0·080. The weighted R_w value and goodness of fit are 0·113 and 0·85 respectively. The crystal structure has three distinct regions: a layer of hydrogen-bonded uracil rings, a hydrophobic methyl columnar region and a hydrophilic water channel. There are no hydrogen bonds between the peptide and uracil ring.

Introduction

Nucleoside peptides have been found in nucleic acids (Robins *et al.*, 1971) and often have medicinal properties (Ivanovics, Rousseau & Robins, 1971). One of these, 5-[*N*-(L-phenylalanyl)amino]uridine (PAU), an anti-viral agent, has been studied crystallographically (Berman, Hamilton & Rousseau, 1973) and has demonstrated two kinds of amino acid–nucleic acid base interactions; there were uracil–phenyl group stacking and hydrogen-bonding between the base and the peptide backbone. Another aminoacyl derivative of 5-aminouridine, 5-[*N*-(L-leucyl)amino]uridine (I), also has anti-viral properties.

As part of a program of study (Berman, Hamilton & Rousseau, 1973; Berman, Zacharias, Carrell & Varghese, 1976; Narayanan, Berman & Rousseau, 1976) to elucidate new amino acid–nucleic acid base interactions, we have determined its crystal structure.



(I)

Experimental

5-[*N*-(L-Leucyl)amino]uridine, $C_{15}H_{24}N_4O_7.2{\cdot}5H_2O$ (LAU), was crystallized from water. The crystals were very small; one of them, 0·06 × 0·06 × 0·15 mm, was used to collect the intensity data at room temperature on a *P*1 diffractometer. The lattice constants were obtained from a least-squares fit of 15 reflections centered on the diffractometer with graphite-monochromatized Cu $K\alpha$ radiation. The cell dimensions are $a = 10{\cdot}883$ (3), $b = 23{\cdot}774$ (5), $c = 17{\cdot}038$ (7) Å, $V = 4408{\cdot}3$ Å^3, $Z = 8$, $d_m = 1{\cdot}34$ g cm^{-3}. Intensities for 1699 independent reflections below $2\theta < 120°$ were collected with Cu $K\alpha$ radiation by the θ–2θ method. The scan range was 2° and the scan speed varied between 2 and 24° min^{-1}. After every 60 reflections four standard reflections were monitored; no significant change in their intensities was observed. Of the 1699 reflections, 1448 reflections had their intensities $I \geq 2\sigma(I)$ [$\sigma(I)$ from counting statistics] and these were included in the refinement. Lorentz and polarization corrections were applied. Absorption and extinction corrections were not applied.

Structure determination and refinement

Systematic absences were consistent with space groups $I222$, $I2_12_12_1$ and $Imm2$. The structure was solved with the space group $I222$ assumed. A partial structure was derived with the program *MULTAN* (Germain, Main & Woolfson, 1971). The rest of the structure, including three water molecules, was derived with Fourier methods. Two disordered positions were found for O(5′). There were two additional peaks in the difference synthesis each with an electron density of about 1 e Å^{-3}. Since they were consistent with possible additional water positions, and since the measured density indicates that there are 3·5 water molecules per LAU, they were at first included in the refinement. Their temperature factors, however, were so high that they were later removed. No H atoms could be located in difference Fourier syntheses. The positions of the H atoms which could be fixed were calculated and assigned the isotropic temperature factors of the atoms to which they are bonded. The thermal parameters of the C, N and O atoms in the molecule and O($W1$), which is in a special position, were refined anisotropically by full-matrix least squares. The temperature factors of O($W2$) and O($W3$) were refined isotropically; their occupancies were also refined to final values of 0·78 and 0·50 respectively. The quantity minimized in refinement was $\Sigma w_{hkl}|F_o^{hkl} - F_c^{hkl}|^2$. The final values of $R = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ and $wR = [\Sigma w(F_o - F_c)^2/\Sigma wF_o^2]^{1/2}$ were 0·080 and 0·113 respectively. The goodness of fit was 0·85 for 256 variables. The weights [$w = 1/\sigma(F)^2$] were determined from an analysis of variance. For $F_o \leq 10{\cdot}0$, $\sigma = 5{\cdot}5$; $75{\cdot}0 \geq F_o > 10{\cdot}0$, $\sigma = 2{\cdot}0 + 0{\cdot}138(F_o - 10{\cdot}0)$; $F_o > 75$, $\sigma = 11{\cdot}0$. The final difference Fourier map still contained two diffuse peaks ($\simeq 1$ e Å^{-3}) which were in the empty regions that could logically be occupied by water molecules and probably do represent highly disordered water molecules. The scattering factors for O, N and C atoms were from *International Tables for X-ray Crystallography* (1968) and for H atoms from Stewart, Davidson & Simpson (1965). The coordinates of the atoms are given in Table 1.*

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32383 (9 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 1. *Fractional coordinates and isotropic thermal parameters of the atoms in 5-[N-(L-leucyl)amino]uridine*

The positional parameters of anisotropically refined atoms are multiplied by 10^4 and the other atoms by 10^3. Numbers in parentheses are standard deviations.

	x	y	z	B
O(1′)	3787 (6)	7349 (2)	6958 (3)	
C(1′)	4367 (7)	6958 (4)	7477 (5)	
C(2′)	4455 (7)	6422 (3)	7014 (5)	
C(3′)	4717 (7)	6638 (4)	6186 (5)	
C(4′)	3884 (8)	7155 (4)	6148 (5)	
C(5′)	2617 (11)	7067 (6)	5822 (7)	
O(2′)	5283 (6)	6022 (3)	7308 (4)	
O(3′)	5970 (6)	6818 (4)	6145 (5)	
O(5′*A*)	2102 (15)	6649 (10)	6022 (9)	
O(5′*B*)	2595 (13)	6942 (8)	5051 (9)	
N(1)	3616 (6)	6910 (3)	8187 (4)	
C(2)	4170 (7)	6908 (3)	8908 (4)	
N(3)	3374 (6)	6820 (3)	9515 (4)	
C(4)	2138 (8)	6712 (4)	9480 (5)	
C(5)	1635 (7)	6710 (3)	8694 (4)	
C(6)	2360 (8)	6806 (4)	8087 (5)	
O(2)	5277 (5)	6966 (3)	9003 (3)	
O(4)	1519 (5)	6639 (3)	10088 (4)	
N(7)	378 (6)	6566 (3)	8652 (4)	
C^1	−246 (7)	6445 (4)	7993 (5)	
O^1	212 (6)	6496 (4)	7328 (3)	
C$^\alpha$	−1556 (8)	6237 (4)	8103 (5)	
N$^\alpha$	−2314 (7)	6376 (4)	7417 (5)	
C$^\beta$	−1467 (9)	5607 (4)	8236 (7)	
C$^\gamma$	−2706 (9)	5306 (4)	8361 (7)	
C$^{\delta_1}$	−3389 (13)	5549 (6)	9101 (10)	
C$^{\delta_2}$	−2450 (14)	4649 (6)	8441 (13)	
O($W1$)	5000 (0)	5000 (0)	6547 (10)	
O($W2$)	−50 (3)	664 (1)	579 (2)	16·5 (9)
O($W3$)	258 (3)	590 (1)	454 (2)	12·0 (8)
H(1′)	522	709	762	3·0
H(2′)	361	624	701	3·0
H(3′)	448	635	576	3·0
H(4′)	431	745	582	3·0
H(N3)	377	684	1005	3·0
H(6)	196	679	755	3·0
H(N7)	−14	653	913	4·5
H$^\alpha$	−191	642	859	3·0
H(1$^\beta$)	−96	550	873	5·5
H(2$^\beta$)	−104	539	781	5·5
H$^\gamma$	−321	537	789	5·5

Description of the structure

The molecular structure

L-Leucine is covalently bonded to the 5-amino group of 5-aminouracil. The numbering of the atoms as well as the distances and angles are given in Fig. 1. Each part of the molecule is now discussed.

The ribose ring is in the C(2′)-*endo* C(3′)-*exo* conformation (Table 2). The C(2′) atom is displaced 0·6 Å from the plane defined by atoms O(1′), C(1′), C(3′), and C(4′) and on the same side of the plane as C(5′). The pseudorotation phase angle P and maximum τ_N (Altona & Sundaralingam, 1972) are 170·6 and −39·9°. The bond distances and angles are consistent with those found in other $^2T_3$ structures (Sundaralingam, 1973). The ribose ring in phenylalanylaminouridine is also $^2T_3$. O(5′) is statistically disordered so that the conformation of C(4′)–C(5′) is either *g*–*g* or *t*–*g*. There is a distance of 3·05 Å between O(5′) and O^1. This may, in fact, represent a weak intramolecular hydrogen bond.

The uracil ring is *anti* ($\chi = 50·5°$) with respect to the ribose (Donohue & Trueblood, 1960). It does not display any unusual features and has a geometry similar to other uracil structures (Voet & Rich, 1970).

The values of the bond distances and angles of the leucine are comparable to those found in other leucyl structures (Rao, 1969; DiBlasio, Pedone & Sirigu, 1975; Subramanian, 1967; Chaney, Seely & Steinrauf, 1971). The conformation is almost mirror related (as one would expect) to D-leucyl-glycine (Rao, 1969).

The conformation angles around the bonds from N(3) to C$^\alpha$ are similar to but not the same as those in PAU (Fig. 2); the uracil and the peptide chain up to C$^\alpha$ are in one plane. The relation between N(7) and N$^\alpha$, as defined by the ψ angle, is 152·6° as compared with 134·8° in PAU. The smaller value allowed the O and N$^\alpha$ in PAU to be in such a position as to form complementary hydrogen bonds with O(4) and N(3) of a translationally related uracil ring. The high value for this conformation angle in LAU precludes this type of hydrogen bond.

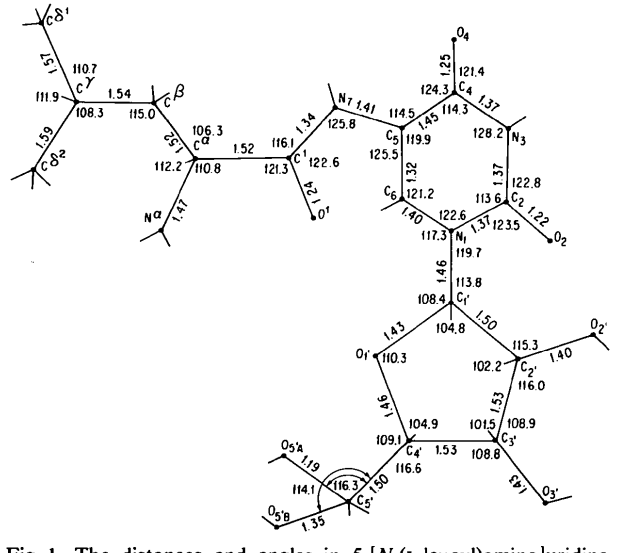


Fig. 1. The distances and angles in 5-[*N*-(L-leucyl)amino]uridine. The standard deviations in Å are 0·010 for C–N and C–O bonds, 0·012 for C–C bonds, 0·018 for the C–C$^{\delta1}$ and C$^{\delta2}$ bonds, and 0·023 for the C(5′)–O(5′) bonds. The average error in the angles is 0·7°.

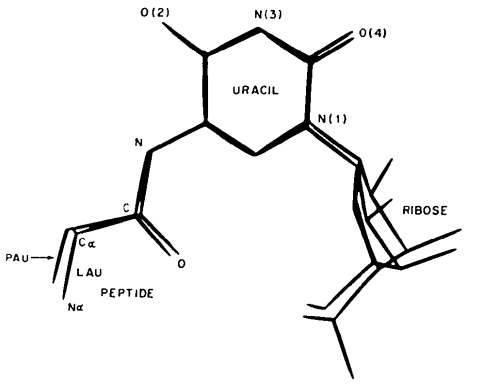


Fig. 2. A comparison between the conformations of phenylalanyluridine and leucyluridine.

The crystal structure

In the structure of PAU, we found two amino acid–uracil interactions. As mentioned, the amino and carboxyl groups of the peptide chain formed weak complementary hydrogen bonds with N(3) and O(4) of the uracil ring. In addition, the phenyl rings were

Table 2. *Torsion angles in* 5-[*N*-(L-*leucyl*)*amino*]*uridine*

Ribose sugar		
ψOO	O(1′)–C(4′)–C(5′)–O(5′*A*)	−77·3°
	O(1′)–C(4′)–C(5′)–O(5′*B*)	+173·5
ψOC	C(3′)–C(4′)–C(5′)–O(5′*A*)	+41·3
	C(3′)–C(4′)–C(5′)–O(5′*B*)	−67·9
χ	O(1′)–C(1′)–N(1)–C(6)	+50·5
τ_0	C(4′)–O(1′)–C(1′)–C(2′)	−18·8
τ_1	O(1′)–C(1′)–C(2′)–C(3′)	+36·4
τ_2	C(1′)–C(2′)–C(3′)–C(4′)	−39·4
τ_3	C(2′)–C(3′)–C(4′)–O(1′)	+28·6
τ_4	C(3′)–C(4′)–O(1′)–C(1′)	−6·6
Peptide*		
ψ_1	N$^\alpha$–C$^\alpha$–C^1–N(7)	+152·6
ω_1	C$^\alpha$–C^1–N(7)–C(5)	+173·2
ϕ_2	C^1–N(7)–C(5)–C(4)	−168·6
ψ_2	N(7)–C(5)–C(4)–N(3)	+176·4
ω_2	C(5)–C(4)–N(3)–C(2)	−1·8
$\chi_1^{1,1}$	N$^\alpha$–C$^\alpha$–C$^\beta$–C$^\gamma$	−58·7
$\chi_2^{2,1}$	C$^\alpha$–C$^\beta$–C$^\gamma$–C$^{\delta1}$	−60·2
$\chi_2^{2,2}$	C$^\alpha$–C$^\beta$–C$^\gamma$–C$^{\delta2}$	+176·8

* Nomenclature conforms to IUPAC–IUB (1970) rules.

Table 3. *Hydrogen-bond lengths*

Donor	Acceptor	Distance	Symmetry operations for the atoms which accept hydrogen bonds
N(3)	O(2)	2·94 Å	$1-x, y, 2-z$
N(7)	O(4)	2·98	$-x, y, 2-x$
O(2′)	N^{α}	2·75	$1+x, y, z$
O(3′)	N^{α}	3·05	$1+x, y, z$
O(3′)	O(5′*B*)	2·58	$1-x, y, 1-z$
O(3′)	O(*W*3)	2·93	$1-x, y, 1-z$
O(5′*A*)	O^{1}	3·08	x, y, z
O(5′*A*)	O(*W*2)	2·86	x, y, z
O(5′*A*)	O(*W*3)	3·13	x, y, z
O(5′*B*)	O(*W*2)	2·79	$-x, y, 1-z$
O(5′*B*)	O(*W*3)	2·62	x, y, z
O(*W*1)	O(2′)	2·77	$x, y, z; 1-x, 1-y, z$
O(*W*2)	O(*W*2)	2·90	$-x, y, 1-z$
O(*W*2)	O^{1}	2·76	x, y, z
O(*W*2)	O(*W*3)	2·91	$-x, y, 1+z$

intercalated between the uracil rings. In the structure of LAU (Table 3, Fig. 3), however, there are no peptide–uracil hydrogen bonds. The only interaction that exists between the amino acid and nucleic acid base is weakly hydrophobic; one methyl of the leucyl side chain is 3·4 Å from the uracil ring.

The crystal structure itself has three distinct regions. The uracil rings are held together by layers of hydrogen-bonding ribbons; N(3) is the donor of a hydrogen bond to O(2) and N(7) is the donor of a hydrogen bond to O(4). A large water channel separates the layers; the water molecules form hydrogen bonds with sugar and peptide O atoms as well as with one another. The presence of the water channel can probably be correlated with the lack of peptide–uracil hydrogen bonding in this structure. Since it is a weak interaction, water can easily disrupt it. Thus, complementary peptide–base hydrogen bonds probably occur only in areas where a nucleic acid is in contact with a highly hydrophobic cleft of a protein.

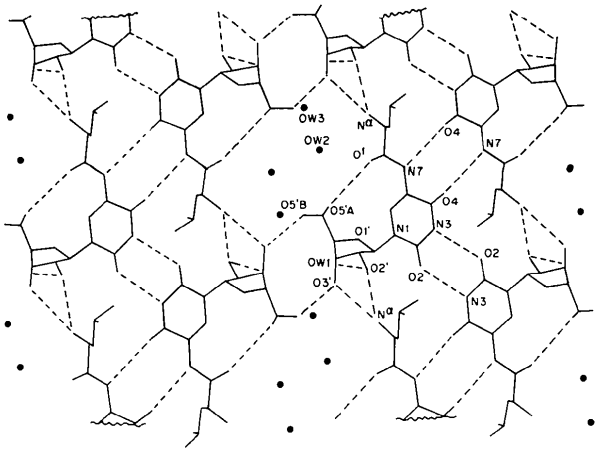


Fig. 3. A view of one layer of the crystal structure.

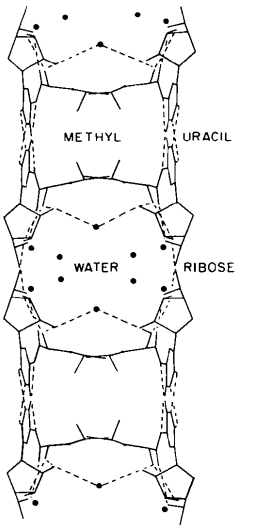


Fig. 4. A view of the alternating hydrophilic and hydrophobic regions of the crystal structure.

Fig. 4 shows a view of the crystal structure which emphasizes the three aspects of the structure – the uracil layers, the hydrophobic methyl channel bounded by the uracil layers and the hydrophilic water channel. In this respect, the packing is not unlike that found in the L-phenylalanyl-5-aminouridine which also has alternating hydrophobic and hydrophilic regions.

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The Crystal Structures, Molecular Structures, and Absolute Configurations of the Hydrobromides of the Aporphine Alkaloids Leucoxine and Isoboldine*

By George M. Brown and Lowell H. Hall†

Chemistry Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee 37830, *USA*

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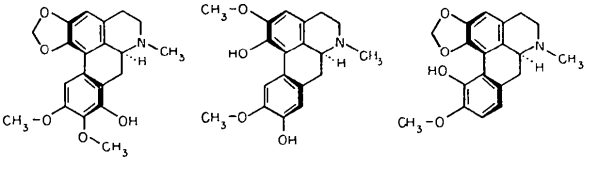
The X-ray crystal-structure analysis of leucoxine (I) hydrobromide ($C_{20}H_{21}O_5N.HBr$) completes the elucidation of the molecular structure of this alkaloid and establishes its absolute configuration as that of the *S* series of aporphines. The structure analysis of isoboldine (II) hydrobromide ($C_{19}H_{21}O_4N.HBr$) furnishes details of its molecular structure and confirms the absolute configuration (also *S* series) implied from the configurational assignment made previously for its isomer isoboldine from an optical rotatory dispersion study. The twist from coplanarity about the central bond of the biphenyl moiety is ~14° in (I).HBr and ~21° in (II).HBr (*cf.* ~30° in the *N*-methylbulbocapninium ion). The different twists result from the different substituents on the basic aporphine ring system. Both hydrobromides are orthorhombic ($P2_12_12_1$) with $Z = 4$. Cell parameters [23 ± 1·5 °C, λ(Cu $K\alpha_1$) = 1·54051 Å] are: [(I).HBr] a = 7·1929 (8), b = 18·3715 (24), c = 13·8490 (9) Å, D_c = 1·583 g cm^{-3}; [(II).HBr] a = 7·543 (1), b = 21·402 (2), c = 11·503 (1) Å, D_c = 1·486 g cm^{-3}. $R(F)$ is 0·030 for (I).HBr and 0·056 for (II).HBr. E.s.d.'s of bond lengths not involving H atoms are 0·003 to 0·005 Å for (I).HBr and 0·005 to 0·011 Å for (II).HBr.

Introduction and structure analysis

Leucoxine hydrobromide

Leucoxine ($C_{20}H_{21}O_5N$, formula I) is an alkaloid extracted from the leaves and stems of *Ocotea leucoxylon* (family Lauraceae). The preliminary characterization (Goodwin, Smith & Horning, 1960; Goodwin, 1965) by chemical, ultraviolet spectroscopic, and NMR methods indicated that it is a member of the aporphine series with a methylenedioxy group, two methoxyl groups, and a hydroxyl group. A structure such as (I) was postulated (Goodwin, 1965), but with ambiguity as to which of the three substituted positions on the lower benzenoid ring bears the hydroxyl group and without any conclusion as to absolute configuration.



(I) (II) (III)

Two crystals, one about 0·2 × 0·1 × 0·1 mm and the other about 0·4 × 0·4 × 0·4 mm, were cut from prismatic specimens of leucoxine hydrobromide furnished by Dr S. Goodwin and used in the data collection with the Oak Ridge computer-controlled X-ray diffractometer (Busing, Ellison, Levy, King & Roseberry, 1968). The larger crystal was used in the determination

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† Present address: Department of Chemistry, Eastern Nazarene College, Quincy, Massachusetts 02170. Participation in this research supported by Oak Ridge Associated Universities.