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The Structure of an Antisickling Agent, *N*-Phenylacetyl-L-phenylalanine Monohydrate

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Abstract. $C_{17}H_{17}NO_3.H_2O$, $M_r = 301{\cdot}3$, orthorhombic, $P2_12_12_1$, $a = 7{\cdot}357\ (1)$, $b = 30{\cdot}938\ (3)$, $c = 6{\cdot}959\ (1)$ Å, $V = 1583{\cdot}9\ (1)$ Å^3, $Z = 4$, $D_x = 1{\cdot}264$ g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, $\mu = 6{\cdot}56$ cm^{-1}, $F(000) = 640$, $T = 293$ K, $R = 0{\cdot}052$ for 1021 unique observed reflections. The molecule has adopted a compact and amphipathic conformation and is very similar to the structure of *N*-phenylacetyl-L-phenylalanine. Peptide torsion angles: L-Phe: $\varphi = -100{\cdot}0\ (8)$, $\chi^1 = -55{\cdot}3\ (8)$, $\chi^{2,1} = -66{\cdot}7\ (9)$, $\psi_T^1 = 2{\cdot}3\ (8)$; phenylacetyl: $\omega = -170{\cdot}4\ (8)$, O(acetyl)–C2(acetyl)–C1(acetyl)–C1(phenyl) = 69·8 (8), C2(acetyl)–C1(acetyl)–C1(phenyl)–C2(phenyl) = 58·4 (8)°. Intramolecular edge-to-face interaction between phenyl rings: phenyl(L-Phe)–phenyl(phenyl) centroid separation = 4·92 (1) Å and interplanar angle = 79·7 (5)°. Intermolecular edge-to-face interaction between phenyl rings: phenyl(L-Phe)–phenyl(phenyl′) centroid separation = 6·21 (1) Å and interplanar angle = 79·7 (5)°. Hydrogen bonds: N(L-Phe)–H···O(*W*) = 2·884 (7), O(acetyl)···H–OH(L-Phe′) = 2·638 (6), O(acetyl)···H–O(*W*′) = 2·881 (7), and O(L-Phe)···H–O(*W*′) = 3·035 (6) Å.

Introduction. The structure of the antisickling agent *N*-phenylacetyl-L-phenylalanine has been reported (Burley & Wang, 1987). I now report the solution of the structure of the monohydrate of *N*-phenylacetyl-L-phenylalanine, and provide a detailed comparison of these two unusual peptide analog structures.

Experimental. Rectangular crystal, 0·10 × 0·30 × 0·05 mm, Rigaku AFC6R diffractometer, Ni-filtered radiation, ω-scan method, $(\sin\theta)/\lambda < 0{\cdot}58$ Å^{-1}, lattice parameters from the 2θ values of 21 reflections with $40{\cdot}8 < 2\theta < 56{\cdot}3°$, no absorption corrections, $h = 0$ to 9, $k = 0$ to 38, $l = 0$ to 8, reflections 180, 03$\bar{2}$ and 190 as intensity standards, intensity variation <2%. 1385 unique reflections measured, 364 excluded during refinement [$F < 3\sigma(F)$]. Structure solved by the direct method (*MULTAN*78, Main, Hull, Lessinger, Germain, Declercq & Woolfson, 1978), first *E* map revealed the positions of ten non-H atoms and two successive Fourier cycles revealed all non-H atoms; least-squares refinement using *SHELX*76 (Sheldrick, 1976), *F* magnitudes; isotropic and then anisotropic temperature factors with weights = $0{\cdot}338/[\sigma^2(F) + 0{\cdot}0015F^2]$ gave $R = 0{\cdot}052$, $wR = 0{\cdot}052$ and $S = 1{\cdot}402$ with H atoms at positions calculated or located by difference synthesis. 206 parameters varied: x,y,z, U_{ij} for all non-H atoms, and a U for each group of H atoms of the two phenyl rings and the backbone atoms connecting the two phenyl rings. A U was varied for each H atom located by difference synthesis. In final cycle $(\Delta/\sigma)_{max} = 0{\cdot}176$, $(\Delta/\sigma)_{mean} = 0{\cdot}011$. Final difference synthesis $(\Delta\rho)_{max} = 0{\cdot}20$ and $(\Delta\rho)_{min} = -0{\cdot}23$ e Å^{-3}. Scattering factors from *International Tables for X-ray Crystallography* (1974).

Discussion. Table 1* gives the atom parameters and Fig. 1 shows the molecular structure and the numbering scheme drawn by *ORTEP*II (Johnson, 1976). The bond lengths and bond angles agree with those of *N*-phenylacetyl-L-phenylalanine within experimental error and are typical of peptide structures (Ramachandran, Colaskar, Ramakrishnan & Saisekharan, 1974).

The molecular structure of *N*-phenylacetyl-L-phenylalanine monohydrate (PAF-H_2O) is very similar to that

* Lists of structure-factor amplitudes, anisotropic thermal parameters, bond lengths and bond angles and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 43772 (11 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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of *N*-phenylacetyl-L-phenylalanine (PAF). The presence of the water of crystallization in PAF-H_2O gives rise to the small differences in the peptide torsion angles (see Table 2). Both compounds adopt compact, amphipathic conformations that are not stabilized by intramolecular hydrogen bonds. Instead, an enthalpically favorable intramolecular edge-to-face interaction between the $\delta(+)$ H atoms of the phenylacetyl group and the $\delta(-)$ π electrons of L-phenylalanine (L-Phe) maintains this unusual conformation. The small variations in torsion angles permit the *ortho*-C atom of the phenylacetyl group to approach even closer to the π electrons of L-Phe with an interplanar angle nearer to the perpendicular than in PAF (see Table 2).

Fig. 2 shows the packing in the unit cell. As with the molecular structures, the crystal structures of PAF-H_2O and PAF are similar. The presence of the water of crystallization does not alter the space group, and results only in small changes in the shortest two crystallographic axes. The packing of these compact, amphipathic molecules in the unit cell is unchanged and resembles a repeating lipid bilayer in which the bisphenyl cluster occupies the same position as the nonpolar carbon chains. All possible hydrogen bonds are satisfied [N(L-Phe)—H···O(*W*) = 2·884 (7), O(acetyl)···H—OH(L-Phe′) = 2·638 (6), O(acetyl)···H—O(*W*′) = 2·881 (7), and O(L-Phe)···H—O(*W*′) = 3·035 (6) Å], and the O(acetyl)···H—OH(L-Phe′) hydrogen bond is seen in the crystal structures of both PAF-H_2O and PAF. Finally, the intermolecular interaction between nearby phenyl rings is preserved in both crystal structures (see Table 2). The crystal and molecular structures of *N*-phenylacetyl-L-phenyl-

Table 1. *Atomic coordinates and equivalent isotropic thermal parameters with e.s.d.'s in parentheses*

$U_{eq} = \frac{1}{3}(U_{11} + U_{22} + U_{33})$.

	x	*y*	*z*	U_{eq}(Å^2)
C1(*A*1)	0·8304 (7)	0·07525 (15)	0·8528 (9)	0·036
C2(*A*1)	0·6285 (7)	0·06600 (14)	0·8556 (9)	0·032
OC2(*A*1)	0·5460 (6)	0·06353 (11)	1·0117 (5)	0·040
C1(*P*1)	0·8731 (8)	0·12170 (16)	0·9118 (7)	0·035
C2(*P*1)	0·7957 (9)	0·15576 (18)	0·8110 (9)	0·052
C3(*P*1)	0·8382 (9)	0·19803 (18)	0·8635 (12)	0·060
C4(*P*1)	0·9578 (10)	0·2059 (2)	1·0113 (11)	0·062
C5(*P*1)	1·0330 (12)	0·1722 (2)	1·1085 (11)	0·069
C6(*P*1)	0·9884 (10)	0·12979 (19)	1·0588 (9)	0·056
N(*F*2)	0·5479 (6)	0·06172 (14)	0·6873 (6)	0·034
C*A*(*F*2)	0·3528 (7)	0·05941 (15)	0·6618 (8)	0·034
C*B*(*F*2)	0·2943 (9)	0·08587 (15)	0·4850 (8)	0·041
C*G*(*F*2)	0·3557 (8)	0·13217 (16)	0·4929 (8)	0·037
C*D*1(*F*2)	0·2873 (8)	0·16026 (17)	0·6310 (10)	0·049
C*E*1(*F*2)	0·3422 (9)	0·20285 (17)	0·6353 (12)	0·059
C*Z*(*F*2)	0·4647 (10)	0·21840 (19)	0·5023 (12)	0·063
C*E*2(*F*2)	0·5346 (10)	0·1911 (2)	0·3681 (11)	0·066
C*D*2(*F*2)	0·4798 (9)	0·14795 (18)	0·3604 (9)	0·054
C(*F*2)	0·2930 (8)	0·01271 (16)	0·6368 (8)	0·035
O(*F*2)	0·3922 (6)	−0·01837 (12)	0·6432 (8)	0·059
OH(*F*2)	0·1175 (6)	0·00922 (11)	0·6079 (7)	0·051
O(*W*)	0·7627 (7)	0·04611 (16)	0·3477 (7)	0·070

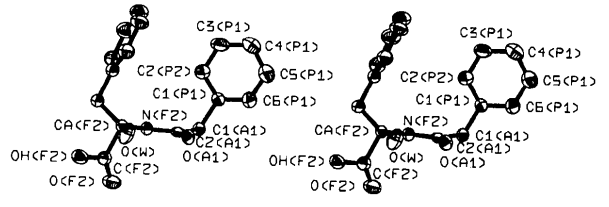

Fig. 1. Stereodrawing of the molecular structure showing the numbering scheme. The thermal ellipsoids are at the 50% level.

Table 2. *Comparison of molecular structural parameters of N-phenylacetyl-L-phenylalanine monohydrate* (PAF-H_2O) *and N-phenylacetyl-L-phenylalanine* (PAF)

The peptide torsion angles are standard for proteins (IUPAC–IUB Commission on Biochemical Nomenclature, 1970).

Torsion angles (°)	PAF-H_2O	PAF
L-Phenylalanine:		
φ	−100·0 (8)	−76·8 (4)
ψ_T^1	2·3 (8)	−19·6 (5)
χ^1	−55·3 (8)	−61·2 (5)
$\chi^{2.1}$	−66·7 (9)	−72·6 (5)
Phenylacetyl:		
ω	−170·4 (8)	−171·5 (4)
OC2(*A*1)–C2(*A*1)–C1(*A*1)–C1(*P*1)	69·8 (8)	80·4 (5)
C2(*A*1)–C1(*A*1)–C1(*P*1)–C2(*P*1)	58·4 (8)	72·6 (5)
Intramolecular phenyl–phenyl interactions		
Centroid separation (Å)	4·92 (1)	5·05 (1)
Interplanar angle (°)	79·7 (6)	70·1 (5)
Intermolecular phenyl–phenyl interactions		
Centroid separation (Å)	6·21 (1)	4·85 (1)
Interplanar angle (°)	79·7 (6)	70·1 (5)

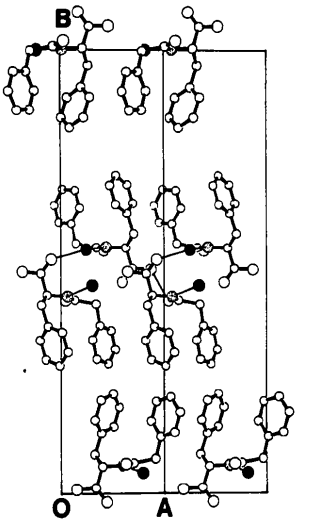

Fig. 2. Packing of the molecules in the unit cell. Atoms are identified by the following: N = large shaded circles, O = large open circles, H_2O = large black circles, C = small open circles. Hydrogen bonds are indicated by a narrow line connecting the donor and acceptor atoms.

alanine monohydrate are also very similar to those of three other model therapeutic agents for the treatment of sickle-cell disease (Wang & Burley, 1987*a*,*b*; Fujii, Burley & Wang, 1987). These structures are stabilized by a weakly polar interaction, which results from the characteristic segregation of partial charges in aromatic moieties (Burley & Petsko, 1986). A mechanism of antisickling action has been proposed by Burley, Wang, Votano & Rich (1987).

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Structure of an Intermediate Related to a Steroid

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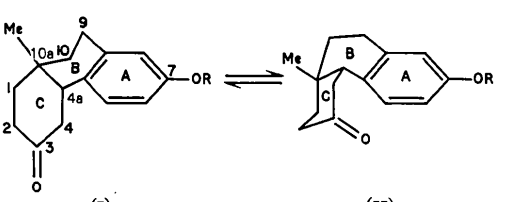
Abstract. 1,2,3,4,4a,9,10,10a-Octahydro-7-methoxy-10aβ-methyl-(4aβH)-3-oxophenanthrene, $C_{16}H_{20}O_2$, $M_r = 244{\cdot}33$, monoclinic, $P2_1/c$, $a = 9{\cdot}922\,(2)$, $b = 8{\cdot}642\,(2)$, $c = 16{\cdot}068\,(2)$ Å, $\beta = 100{\cdot}29\,(1)°$, $V = 1355{\cdot}6\,(5)$ Å^3, $Z = 4$, $D_x = 1{\cdot}20$ g cm^{-3}, λ(Cu $K\alpha$) = 1·5418 Å, μ(Cu $K\alpha$) = 6·18 cm^{-1}, $F(000) = 528$, room temperature, $R = 0{\cdot}043$ for 1705 reflections. The ring junction is *cis*-fused between two six-membered rings and the ring-fusion methyl carbon atom is axial to the *B* ring. The unsaturated six-membered ring of the molecule is substantially planar while the other two saturated six-membered rings are respectively in chair and half-chair conformations.

Introduction. The presence of partially aromatized hydrocarbons related to steroids has been noticed in geological samples and the first identification of one type has been reported (Schaefle, Ludwig, Albrect & Ourison, 1978). In connection with the total synthesis of this partially aromatized hydrocarbon and related compounds, a stereospecific *cis*-reduction of a hydrophenanthrene derivative yielded the title compound, a *B*/*C*-*cis* ketone, as an intermediate (Chatterjee, Chaudhury & Chatterjee, 1982). It is suggested that compounds having this type of *B*/*C*-*cis* configuration usually equilibrate between two conformers, where the ring-fusion methyl carbon and hydrogen atoms may be axial and equatorial respectively to the *B* ring (I) or *vice versa* (II), owing to the flexible nature of the rings. An X-ray diffraction study of this ketone has been undertaken to confirm the stereospecificity of this *cis* reduction as well as to determine its three-dimensional molecular structure.



(I) (II)

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