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Novel 2- and 5-Azido-*N*-(diphenylcarbamoyl)proline Methyl Esters. Examples of a Novel Proline Oxidation

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Abstract

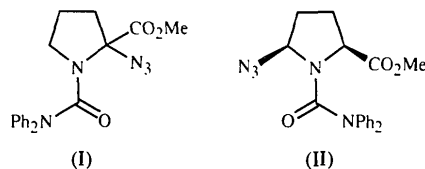
The crystal structures of two azido-substituted proline derivatives are reported. Racemic 2-azido-1-(diphenylcarbamoyl)proline methyl ester, (I), C₁₉H₁₉N₅O₃, is resolved upon crystallization from methylene chloride–diethyl ether. The azido moieties are nonlinear with N–N–N angles of 173 (1) and 170.3 (2)° for (I) and (II) [*cis*-5-azido-*N*-(diphenylcarbamoyl)proline methyl ester, C₁₉H₁₉N₅O₃], respectively. Close intramolecular contacts between the carbonyl O atom of the amide and the central N atom of the azido group are found. The contact distances between N7 and O14 are 2.780 (14) and 2.815 (2) Å for (I) and (II), respectively.

Comment

Proline is the only imino acid found to occur naturally in mammalian proteins. The phenomenon of *cis*–*trans* isomerism found in prolyl amides plays an important role in the secondary structure of proteins (Andres & MacDonald, 1993). In fact, the designs of several reverse-turn mimetics have been based on this important imino acid (Baldwin, Hulme, Schofield & Edwards, 1993).

Anodic amide oxidations of proline derivatives have been reported recently (Shono, 1984; Wong & Moeller, 1993), allowing the construction of bicyclic lactam rings with the potential of introducing conformational constraints in peptides.

We report here a novel oxidation of *N*-(diphenylcarbamoyl)proline methyl ester utilizing the (PhIO)_n/TMSN₃ reagent combination (Magnus, Hulme & Weber, 1994) at 233 K, giving crystalline compounds (I) and (II). The crystal structures of two pyrrolidine analogs of (I) and (II) have been reported recently (Lynch, Hulme, Magnus & Davis, 1994).



The azido group is slightly bent in both molecules. The direction of the bend is away from the carbonyl O atom, O14, so that the central N atom, N7, is closer to the O atom than to the two remaining N atoms, N6 or N8. The exocyclic bond angles around N1 are substantially different in (I) and (II).

The C13–N1–C angles, where C is azido substituted, are 119.1 (9) and 118.35 (14)° in (I) and (II), respectively; the remaining C13–N1–C(H₂) angles are 126.9 (9) and 127.35 (15)°. These facts are indicative of an electrostatic interaction between the carbonyl O atom, O14, and the azido group.

The five-membered pyrrolidinic ring is in an envelope conformation in (I) with C3 as the flap atom, displaced

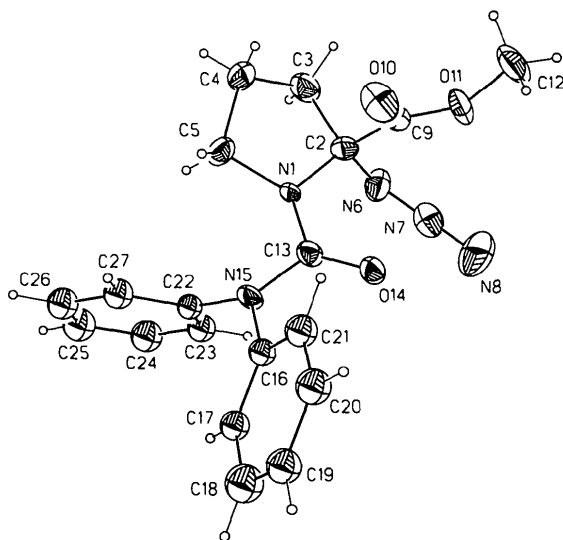


Fig. 1. View of (I) showing the atom-labelling scheme. Displacement ellipsoids are scaled to the 30% probability level. H atoms are drawn to an arbitrary scale.

0.51 (1) Å from the plane defined by the remaining atoms of the ring. The pyrrolidine ring assumes a half-chair conformation in (II). The N—C13 bond lengths are asymmetric in (I) [N1—C13 1.346 (14), N15—C13 1.421 (14) Å] but are equivalent in (II) [N1—C13 1.377 (2), N15—C13 1.379 (2) Å].

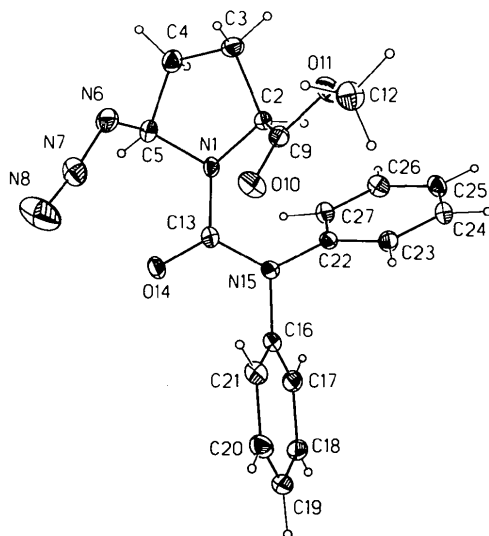


Fig. 2. View of (II) showing the atom-labelling scheme. Displacement ellipsoids are scaled to the 30% probability level. H atoms are drawn to an arbitrary scale.

Experimental

Full details of the synthetic procedures will be published elsewhere (Magnus, Hulme & Weber, 1994). Synthesis of (I) proceeded *via* an *N*-acyl iminium ion with C2 assuming a trigonal geometry resulting in a racemic product. However, the enantiomers were resolved upon crystallization from methylene chloride–diethyl ether. The absolute configuration could not be determined from the X-ray results and was assigned on the basis of comparison with that of the proline starting material.

Compound (I)

Crystal data

C₁₉H₁₉N₅O₃

M_r = 365.39

Orthorhombic

*P*2₁2₁2₁

a = 9.253 (2) Å

b = 12.558 (2) Å

c = 15.862 (8) Å

V = 1843.2 (10) Å³

Z = 4

D_r = 1.32 Mg m⁻³

Mo *K*α radiation

λ = 0.71073 Å

Cell parameters from 31 reflections

θ = 7.8–10.6°

μ = 0.0864 mm⁻¹

T = 298 (1) K

Needle

0.47 × 0.17 × 0.15 mm

Colorless

Data collection

Nicolet R3 diffractometer

ω scans

Absorption correction:

none

θ_{max} = 25.0°

h = -11 → 11

k = 0 → 14

l = 0 → 18

3532 measured reflections
1863 independent reflections
844 observed reflections
[*F* > 4σ(*F*)]
*R*_{int} = 0.026

2 standard reflections
monitored every 98
reflections
intensity decay: 1.5%

Refinement

Refinement on *F*

R = 0.0737

wR = 0.0632

S = 1.508

884 reflections

160 parameters

H-atom parameters not

refined

w = 1/[σ²(*F*) + 0.0004*F*²]

(Δ/σ)_{max} = 0.007

Δρ_{max} = 0.46 e Å⁻³

Δρ_{min} = -0.28 e Å⁻³

Extinction correction: none

Atomic scattering factors

from *International Tables*
for *X-ray Crystallography*
(1974, Vol. IV)

Table 1. Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å²) for (I)

*U*_{iso} for C16–C27 (phenyls); *U*_{eq} = (1/3)Σ_{*i*}Σ_{*j*}*U*_{*ij*}*a*_{*i*}²*a*_{*j*}² for others.

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{iso} / <i>U</i> _{eq}
N1	0.3676 (9)	0.1755 (7)	0.1906 (5)	0.037 (3)
C2	0.4819 (11)	0.1584 (9)	0.2517 (7)	0.041 (4)
C3	0.5663 (13)	0.0646 (9)	0.2184 (7)	0.062 (5)
C4	0.5524 (11)	0.0737 (10)	0.1237 (7)	0.063 (5)
C5	0.4009 (11)	0.1195 (9)	0.1092 (6)	0.051 (4)
N6	0.4230 (11)	0.1264 (8)	0.3352 (6)	0.060 (4)
N7	0.3918 (11)	0.1936 (9)	0.3876 (7)	0.061 (5)
N8	0.358 (2)	0.2478 (12)	0.4426 (7)	0.109 (6)
C9	0.5828 (12)	0.2580 (11)	0.2541 (8)	0.050 (5)
O10	0.6082 (9)	0.3076 (7)	0.1944 (5)	0.076 (4)
O11	0.6441 (8)	0.2651 (6)	0.3306 (5)	0.064 (3)
C12	0.7598 (10)	0.3426 (10)	0.3337 (8)	0.086 (6)
C13	0.2759 (11)	0.2575 (10)	0.2016 (8)	0.042 (5)
O14	0.2895 (7)	0.3216 (6)	0.2577 (5)	0.052 (3)
N15	0.1646 (8)	0.2646 (7)	0.1402 (5)	0.038 (3)
C16	0.0955 (7)	0.3647 (4)	0.1276 (4)	0.039 (3)
C17	-0.0546 (7)	0.3727 (4)	0.1219 (4)	0.045 (3)
C18	-0.1188 (7)	0.4711 (4)	0.1056 (4)	0.072 (4)
C19	-0.0330 (7)	0.5614 (4)	0.0948 (4)	0.057 (3)
C20	0.1170 (7)	0.5534 (4)	0.1004 (4)	0.059 (3)
C21	0.1813 (7)	0.4550 (4)	0.1168 (4)	0.052 (3)
C22	0.0903 (6)	0.1718 (4)	0.1135 (4)	0.036 (3)
C23	0.0298 (6)	0.1032 (4)	0.1730 (4)	0.049 (3)
C24	-0.0433 (6)	0.0119 (4)	0.1467 (4)	0.064 (4)
C25	-0.0558 (6)	-0.0108 (4)	0.0609 (4)	0.070 (4)
C26	0.0048 (6)	0.0578 (4)	0.0015 (4)	0.058 (3)
C27	0.0779 (6)	0.1491 (4)	0.0277 (4)	0.051 (3)

Table 2. Selected geometric parameters (Å, °) for (I)

C2—N1	1.451 (13)	N8—N7	1.15 (2)
C5—N1	1.502 (13)	O10—C9	1.16 (2)
C13—N1	1.346 (14)	O11—C9	1.342 (15)
C3—C2	1.51 (2)	C12—O11	1.448 (13)
N6—C2	1.487 (15)	O14—C13	1.205 (14)
C9—C2	1.56 (2)	N15—C13	1.421 (14)
C4—C3	1.51 (2)	C16—N15	1.425 (10)
C5—C4	1.532 (15)	C22—N15	1.417 (10)
N7—N6	1.22 (2)		
C2—N1—C5	110.8 (8)	O10—C9—C2	122.2 (11)
C2—N1—C13	119.1 (9)	O11—C9—C2	109.1 (10)
C5—N1—C13	126.9 (9)	C12—O11—C9	112.8 (9)
C3—C2—N6	106.9 (9)	O14—C13—N15	122.7 (10)
C3—C2—C9	108.9 (9)	O14—C13—N1	122.7 (10)
C3—C2—N1	105.1 (9)	N15—C13—N1	114.5 (10)
N6—C2—C9	114.4 (9)	C16—N15—C22	117.8 (6)
N6—C2—N1	111.6 (8)	C16—N15—C13	118.5 (8)
C9—C2—N1	109.4 (9)	C22—N15—C13	120.3 (8)
C4—C3—C2	104.1 (9)	C17—C16—C21	120.0 (5)
C5—C4—C3	104.8 (9)	C17—C16—N15	121.3 (5)

N1—C5—C4	103.6 (8)	C21—C16—N15	118.6 (6)	C16	0.6618 (2)	0.5301 (2)	0.38584 (10)	0.0249 (5)
N7—N6—C2	120.5 (10)	C23—C22—N15	120.0 (6)	C17	0.8271 (2)	0.5286 (2)	0.39175 (12)	0.0299 (6)
N8—N7—N6	172.6 (14)	C27—C22—N15	120.0 (6)	C18	0.9083 (3)	0.6166 (2)	0.41094 (13)	0.0345 (6)
O10—C9—O11	128.2 (12)			C19	0.8262 (3)	0.7058 (2)	0.42482 (12)	0.0354 (6)
				C20	0.6617 (3)	0.7072 (2)	0.41891 (13)	0.0364 (7)
				C21	0.5789 (3)	0.6195 (2)	0.39949 (12)	0.0319 (6)
				C22	0.6356 (2)	0.38888 (14)	0.28964 (11)	0.0229 (5)
				C23	0.6247 (3)	0.4381 (2)	0.21487 (11)	0.0278 (5)
				C24	0.6801 (3)	0.3906 (2)	0.14422 (12)	0.0320 (6)
				C25	0.7450 (3)	0.2948 (2)	0.14863 (12)	0.0322 (6)
				C26	0.7548 (3)	0.2453 (2)	0.22367 (13)	0.0323 (6)
				C27	0.7019 (3)	0.2924 (2)	0.29472 (11)	0.0285 (5)

Compound (II)*Crystal data*C₁₉H₁₉N₅O₃ $M_r = 365.39$

Orthorhombic

P2₁2₁2₁ $a = 8.379 (3) \text{ \AA}$ $b = 13.183 (8) \text{ \AA}$ $c = 16.294 (7) \text{ \AA}$ $V = 1799.8 (15) \text{ \AA}^3$ $Z = 4$ $D_x = 1.35 \text{ Mg m}^{-3}$ Mo K α radiation $\lambda = 0.71073 \text{ \AA}$

Cell parameters from 23 reflections

 $\theta = 10.3\text{--}11.15^\circ$ $\mu = 0.0884 \text{ mm}^{-1}$ $T = 173 (1) \text{ K}$

Needle

 $0.87 \times 0.31 \times 0.26 \text{ mm}$

Colorless

Data collection

Nicolet R3 diffractometer

 ω scans

Absorption correction:

none

6619 measured reflections

2965 independent reflections

2505 observed reflections

 $[F > 4\sigma(F)]$ $R_{\text{int}} = 0.011$ $\theta_{\text{max}} = 30.0^\circ$ $h = -11 \rightarrow 1$ $k = 0 \rightarrow 18$ $l = -22 \rightarrow 22$

4 standard reflections

monitored every 96

reflections

intensity decay: 2.0%

*Refinement*Refinement on F^2 $R = 0.0385$ $wR = 0.0411$ $S = 1.285$

2505 reflections

460 parameters

All H-atom parameters

refined

 $w = 1/[\sigma^2(F) + 0.0004F^2]$ $(\Delta/\sigma)_{\text{max}} = 0.02$ $\Delta\rho_{\text{max}} = 0.22 \text{ e \AA}^{-3}$ $\Delta\rho_{\text{min}} = -0.25 \text{ e \AA}^{-3}$

Extinction correction:

modified Larson (1970)

as in *SHELXTL-Plus*

(Sheldrick, 1991)

Extinction coefficient:

 $2.0 (6) \times 10^{-6}$

Atomic scattering factors

from *International Tables*for *X-ray Crystallography*

(1974, Vol. IV)

Table 3. Fractional atomic coordinates and equivalent isotropic displacement parameters (\AA^2) for (II)
$$U_{\text{eq}} = (1/3)\sum_i\sum_j U_{ij}a_i^*a_j^*$$

	x	y	z	U_{eq}
N1	0.3686 (2)	0.32449 (12)	0.38493 (8)	0.0227 (4)
C5	0.2704 (2)	0.2691 (2)	0.44258 (11)	0.0269 (5)
C4	0.2200 (3)	0.1779 (2)	0.39224 (12)	0.0320 (6)
C3	0.1845 (3)	0.2253 (2)	0.30817 (13)	0.0315 (6)
C2	0.3026 (2)	0.31539 (14)	0.30181 (10)	0.0228 (5)
N6	0.1186 (2)	0.3230 (2)	0.46451 (11)	0.0378 (5)
N7	0.1278 (2)	0.3938 (2)	0.51245 (12)	0.0406 (6)
N8	0.1137 (3)	0.4586 (2)	0.5560 (2)	0.0828 (11)
C9	0.2210 (2)	0.4127 (2)	0.27586 (11)	0.0251 (5)
O10	0.2134 (2)	0.48902 (11)	0.31577 (9)	0.0387 (5)
O11	0.1579 (2)	0.40167 (11)	0.20154 (8)	0.0358 (4)
C12	0.0705 (3)	0.4879 (2)	0.17024 (14)	0.0406 (7)
C13	0.4660 (2)	0.40020 (14)	0.41463 (10)	0.0232 (5)
O14	0.4553 (2)	0.42848 (11)	0.48599 (7)	0.0304 (4)
N15	0.5788 (2)	0.43949 (13)	0.36185 (9)	0.0252 (4)

Table 4. Selected geometric parameters (\AA , $^\circ$) for (II)

C5—N1	1.447 (2)	C16—N15	1.437 (3)
C2—N1	1.468 (2)	C22—N15	1.434 (2)
C13—N1	1.377 (2)	C17—C16	1.388 (3)
C4—C5	1.515 (3)	C21—C16	1.386 (3)
N6—C5	1.501 (3)	C18—C17	1.382 (3)
C3—C4	1.535 (3)	C19—C18	1.381 (3)
C2—C3	1.550 (3)	C20—C19	1.382 (4)
C9—C2	1.514 (3)	C21—C20	1.385 (3)
N7—N6	1.219 (3)	C23—C22	1.383 (3)
N8—N7	1.117 (4)	C27—C22	1.390 (3)
O10—C9	1.200 (2)	C24—C23	1.390 (3)
O11—C9	1.329 (2)	C25—C24	1.376 (3)
C12—O11	1.445 (3)	C26—C25	1.389 (3)
O14—C13	1.224 (2)	C27—C26	1.387 (3)
N15—C13	1.379 (2)		
C5—N1—C2	110.12 (15)	C16—N15—C22	116.71 (15)
C5—N1—C13	118.35 (14)	C16—N15—C13	118.34 (15)
C2—N1—C13	127.35 (15)	C22—N15—C13	124.4 (2)
C4—C5—N6	105.6 (2)	C17—C16—C21	120.1 (2)
C4—C5—N1	101.99 (15)	C17—C16—N15	119.3 (2)
N6—C5—N1	113.4 (2)	C21—C16—N15	120.5 (2)
C3—C4—C5	102.4 (2)	C18—C17—C16	119.7 (2)
C2—C3—C4	104.3 (2)	C19—C18—C17	120.5 (2)
C9—C2—N1	111.01 (15)	C20—C19—C18	119.8 (2)
C9—C2—C3	112.3 (2)	C21—C20—C19	120.3 (2)
N1—C2—C3	103.97 (14)	C16—C21—C20	119.7 (2)
N7—N6—C5	117.5 (2)	C23—C22—C27	120.5 (2)
N8—N7—N6	170.3 (2)	C23—C22—N15	118.9 (2)
O10—C9—O11	124.4 (2)	C27—C22—N15	120.6 (2)
O10—C9—C2	125.7 (2)	C24—C23—C22	119.7 (2)
O11—C9—C2	110.0 (2)	C25—C24—C23	120.1 (2)
C12—O11—C9	115.9 (2)	C26—C25—C24	120.1 (2)
O14—C13—N15	121.9 (2)	C27—C26—C25	120.3 (2)
O14—C13—N1	120.7 (2)	C22—C27—C26	119.2 (2)
N15—C13—N1	117.3 (2)		

The H atoms and the phenyl rings (C16—C21, C22—C27) were idealized during the refinement of (I), with bond lengths of 1.395 Å and bond angles of 120°. The C atoms of the phenyl rings in (I) were refined with isotropic displacement parameters.

For both compounds, data collection: *P3/V Diffractometer Program* (Siemens, 1989); cell refinement: *P3/V Diffractometer Program*; data reduction: *SHELXTL-Plus* (Sheldrick, 1991); program(s) used to solve structures: *SHELXTL-Plus*; program(s) used to refine structures: *SHELXTL-Plus*; molecular graphics: *SHELXTL-Plus*; software used to prepare material for publication: *MPLN* (Cordes, 1983); *FUER* (Larson, 1982).

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: SZ1008). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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N^α-*tert*-Butoxycarbonyl-*N*^τ-benzylhistidine *p*-Nitrobenzyl Ester

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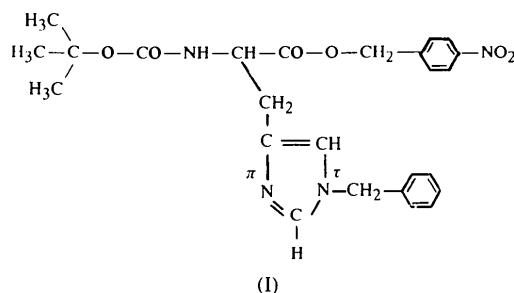
Abstract

The determination of the structure of the title compound, C₂₅H₂₈N₄O₆, shows that the benzyl group is attached to the N atom at the τ position of the imidazole ring of histidine. In the solid state, the molecule displays a conformation that is favourable for intramolecular α-C proton abstraction by the π-N atom of the imidazole ring, as has been suggested in the explanation of the racemization mechanism.

Comment

Activated histidine derivatives are more prone to racemization during peptide synthesis than other amino acids (Fields & Noble, 1990). The racemization mechanism has been proposed to be an intramolecular α-C proton abstraction by the π-N atom of the imidazole ring (Fletcher, Jones, Ramage & Stachulski, 1979).

It was interesting to verify whether there were conformational features of [Boc-His(*N*^τ-Bzl)-O-Bzl(NO₂)], (I), favourable for such an interaction in the crystalline state. To our knowledge, this is the first report of a crystal structure of an *N*^τ isomer of an *N*^{im}-modified histidine derivative. As seen in Fig. 1, the histidine derivative has been modified at the τ-N atom of the imidazole ring.



The molecule adopts a closed conformation, similar to that found in molecule A of L-*N*-acetylhistidine monohydrate (Kistenmacher, Hunt & Marsh, 1972), in which the imidazole ring is folded back on top of the carboxylate group. The torsion angles C(1')—C(1A)—C(1B)—C(1C) and C(1')—C(1A)—N(1)—C(1) in the molecule have values of 73.2 (6) and −72.4 (5)°, respectively. In the crystalline state, the molecule displays a conformation that is favourable for intramolecular α-C proton abstraction by the imidazole π-N atom, as suggested for the racemization mechanism for activated histidine derivatives (Brown, Jones & Wallis, 1982). The distance between the α-C H atom [H(C1A)] and the π-N atom of the imidazole ring [N1D1] is 2.71 (3) Å.

The atoms of the imidazole ring are coplanar. The dihedral angle between the plane of the imidazole and the plane of the adjacent phenyl ring is 113.8 (4)°.

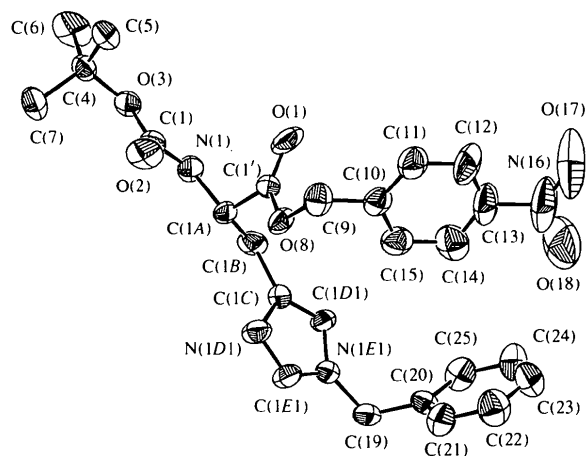


Fig. 1. View of the title compound showing the atomic numbering scheme. Displacement ellipsoids are shown at the 50% probability level.