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A Racemic Bicyclic Acylamidine from a Tripeptide Derivative

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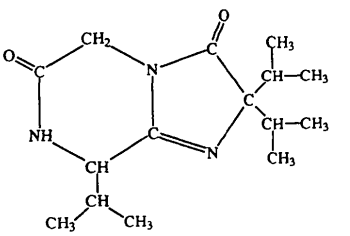
Abstract

The 2,2,8-triisopropyl-4,5,7,8-tetrahydroimidazo[1,2-*a*]-pyrazine-3,6-dione molecule, $C_{15}H_{25}N_3O_2$, has a double bond and two partial double bonds in the bicyclic skeleton, with some π-electron delocalization along C_1'—N_3—C_2'. The conformation parameters of the diisopropyl (Dip) residue reveal that it is in an unusually high-energy conformation. The peptide bond between the glycine and valine residues is *cis* [C_3^{α}—C_3'—N_1—C_1^{α} = −7.0 (3)°]. In the crystal, the molecules are held together in the *ac* plane of the *P2/n* space group by intermolecular hydrogen bonds formed around a twofold axis by molecules related by symmetry centres.

Comment

Peptides containing α,α-disubstituted glycines have received much attention, as amino acids have a high propensity to freeze specific conformations and dramatically slow enzymatic processes (Toniolo & Benedetti, 1988; Di Blasio, Pavone, Lombardi, Pedone & Benedetti, 1993). Recently, the synthesis of a very bulky amino acid, α,α-diisopropylglycine (Dip), and its peptide derivatives by the modified Ugi reaction at high pressure has been reported (Yamada, Yanagi, Omote, Miyazawa, Kuwata, Sugiura & Matsunoto, 1990, 1991). Further studies on the synthesis of various Dip-containing tripeptides have shown the unexpected formation of a bicyclic system (Yamada, Iwamoto, Yanagi, Miyazawa, Kuwata, Saviano & Pavone, 1993). This system was reported as an acylamidine by Rothe, Fahnle, Pudill & Schindler (1979). In this paper, we report the X-ray diffraction analysis of the title compound, (I), performed in order to determine the molecular conformation.



(I)

An *ORTEP* (Johnson, 1965) view of the acylamidine is shown in Fig. 1. The analysis of the geometric parameters reveals the presence of a double bond between N_2 and C_1' [1.276 (2) Å], and partial double bonds between C_1' and N_3 [1.387 (2) Å], and between C_2' and N_3 [1.383 (2) Å] with some π-electron delocalization along C_1'—N_3—C_2'. In addition, the angles N_2—C_1'—N_3 and C_1^{α}—C_1'—N_2 are narrower and wider, respectively, than the sp^2 angles as a result of the steric constraint of the five-membered ring. Two planes can be identified in the bicyclic backbone of the molecule: the first contains the atoms C_1^{α}, C_1', N_2, C_2^{α}, C_2', N_3 and C_3^{α}, while the other contains the atoms C_3^{α}, C_3', N_1 and C_1^{α}. These planes form a dihedral angle of 25.2 (1)°. The peptide bond between the glycine and valine residues is *cis* [C_3^{α}—C_3'—N_1—C_1^{α} = −7.0 (3)°]. This feature allows both O_3 and N_1—H to be involved in intermolecular hydrogen bonds.

The steric hindrance in the bicyclic structure forces the Dip residue to adopt an unusually high-energy conformation [φ = −0.4 (2)° and ψ = 0.5 (2)°]. Additional

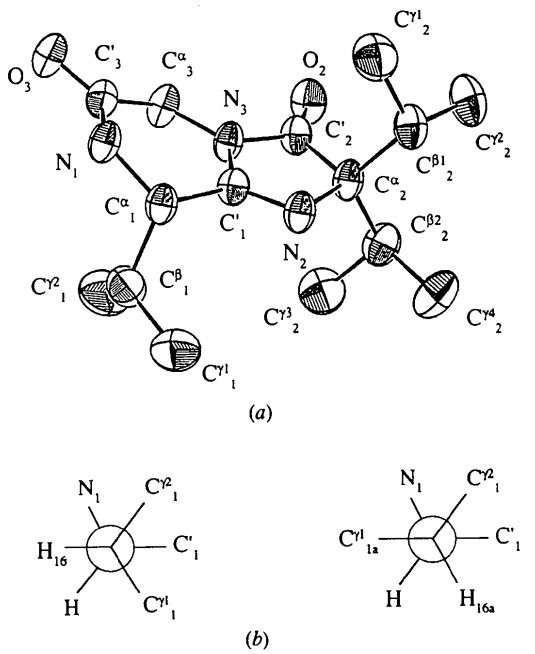


Fig. 1. (*a*) A view of the title compound showing the atom-numbering scheme. Displacement ellipsoids are shown at the 50% probability level. (*b*) Newman projections showing the isopropyl disorder.

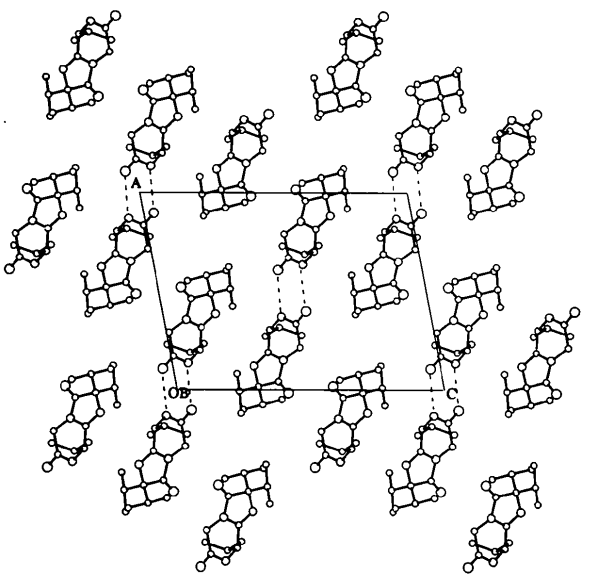


Fig. 2. The mode of packing of the acylamidine molecules viewed down **b**. The intermolecular hydrogen bonds are shown as dashed lines.

evidence for the presence of this strain is provided by the value of the N_2—C^{α}_2—C'_2 (τ) bond angle, 104.7 (3)°, which is compressed with respect to the tetrahedral value (Benedetti, 1982). In addition, the bond angle relating the two side chains of this residue, $C^{\beta 1}_2$—C^{α}_2—$C^{\beta 2}_2$, has a value of 113.4 (3)° and is larger than the corresponding average angle observed in peptide structures (Benedetti, 1982). The glycine and valine residues also display similar behaviour but the steric hindrance is lower [φ = −158.1 (3), ψ = −16.0 (3)° for Gly and φ = 27.2 (3), ψ = 155.3 (4)° for Val].

The valine side chain shows disorder (the C^{γ}_1 and C^{γ}_1a sites have occupancy factors of 0.6 and 0.4, respectively) with χ_1 angles *trans*, *gauche*$^+$ and *gauche*$^-$, *gauche*$^+$, respectively. The Dip side chains have $\chi_{1,1}$ and $\chi_{1,2}$ values of *gauche*$^-$, *gauche*$^+$ and *trans*, *gauche*$^-$, respectively.

In the crystal, the molecules are held together in the *ac* plane by intermolecular hydrogen bonds formed around a twofold axis by molecules related by symmetry centres [$N_1 \cdots O_3$ 2.940 (2) Å, $N_1 \cdots O_3$—C'_3 122.4 (1)°]. This results in dimers, which form layers parallel to the *ac* plane. The layers are stabilized in the *b* direction by van der Waals interactions. The packing along the *b* axis is shown in Fig. 2.

Experimental

Z-Val-(*N*-Bzl)Dip-Gly-OMe (Yamada, Yanagi, Omote, Miyazawa, Kuwata, Sugiura & Matsunoto, 1990) (751 mg, 1.36 mmol) underwent hydrogenolysis in the presence of 5% Pd–C (965 mg) in 1-butanol (15 ml) at 358 K for 4 h in the usual manner, as reported previously (Yamada, Iwamoto, Yanagi, Miyazawa, Kuwata, Saviano & Pavone, 1993). After removal of the catalyst, the reaction mixture was concentrated under reduced pressure, affording crystals. The racemization of the chiral centre occurs simultaneously with the hydrogenolysis. The crude product was purified by recrystallization from ethanol. Yield 227 mg (60%), m.p. 446–448 K, $[\alpha]_D^{25}$ 0° (*c* 1, MeOH). Found: C 64.51, H 9.17, N 15.06%. Calculated for $C_{15}H_{25}N_3O_2$: C 64.49, H 9.02, N 15.04%. IR (KBr): ν = 1728 (C=O), 1682 (C=O), 1651 cm^{-1} (C=N). ^1H NMR (500 MHz, $CDCl_3$): δ = 0.84 [*d*, 3H, *J* = 7.0 Hz, CH_3 (2-^{i}Pr$_A$)], 0.88 [*d*, 3H, *J* = 7.0, CH_3 (2-^{i}Pr$_B$)], 0.93 [*d*, 3H, *J* = 7.0, CH_3 (2-^{i}Pr$_A$)], 0.95 [*d*, 3H, *J* = 7.0, CH_3 (2-^{i}Pr$_B$)], 1.03 [*d*, 3H, *J* = 7.0, CH_3 (8-^{i}Pr)], 1.12 [*d*, 3H, *J* = 7.0, CH_3 (8-^{i}Pr)], 2.25 [*sep*, 1H, *J* = 7.0, CH (2-^{i}Pr$_A$)], 2.32 [*sep*, 1H, *J* = 7.0, CH (2-^{i}Pr$_B$)], 2.39 [*sep-d*, 1H, *J* = 7.0, 3.5, CH (8-^{i}Pr)], 4.01 (*d*, 1H, *J* = 18.0, 5-CH), 4.20 (*d*, 1H, *J* = 18.0, 5-CH), 4.32 (*t*, 1H, *J* = 1.8, 8-CH), 6.71 (*br*, 1H, NH).

Crystal data

$C_{15}H_{25}N_3O_2$
M_r = 279.40
Monoclinic
P2/*n* (unconventional setting of No. 13, *P*2/*c*)
a = 12.533 (2) Å
b = 7.6536 (9) Å
c = 16.804 (2) Å
β = 101.03 (1)°
V = 1582.1 (9) Å^3
Z = 4
D_x = 1.173 Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
λ = 1.5418 Å
Cell parameters from 25 reflections
θ = 20–24°
μ = 0.597 mm^{-1}
T = 293 K
Needle
0.5 × 0.4 × 0.2 mm
Colourless

Data collection

Enraf–Nonius CAD-4*F* diffractometer	$\theta_{max} = 70°$
$\omega/2\theta$ scans	$h = -15 \rightarrow 15$
Absorption correction: none	$k = 0 \rightarrow 9$
3360 measured reflections	$l = 0 \rightarrow 20$
3342 independent reflections	2 standard reflections
2700 observed reflections [$I \geq 3.0\sigma(I)$]	frequency: 60 min
	intensity decay: 2%

Refinement

Refinement on *F*	$(\Delta/\sigma)_{max} = 0.09$
$R = 0.045$	$\Delta\rho_{max} = 0.17$ e Å^{-3}
$wR = 0.042$	$\Delta\rho_{min} = -0.20$ e Å^{-3}
$S = 0.802$	Extinction correction: none
2700 reflections	Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)
191 parameters	
H-atom parameters not refined	
$w = 1/\sigma^2(F_o)$	

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters (Å^2)*

$B_{eq} = (8\pi^2/3)\sum_i\sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$

	x	*y*	*z*	B_{eq}
N_1	0.1329 (1)	0.4127 (2)	0.0592 (1)	3.16 (3)
C_1^α	0.1981 (1)	0.2827 (2)	0.1117 (1)	2.86 (4)
C_1^β	0.1860 (1)	0.0986 (3)	0.0741 (1)	3.99 (5)
$C_1^{\gamma 1}$†	0.2305 (3)	−0.0345 (5)	0.1324 (2)	3.90 (10)
$C_1^{\gamma 1}a$‡	0.0800 (5)	0.0288 (9)	0.0634 (4)	7.18 (17)
$C_1^{\gamma 2}$	0.2266 (2)	0.0870 (4)	−0.0052 (1)	5.97 (7)
C_1'	0.3135 (1)	0.3436 (2)	0.1333 (1)	2.65 (4)
N_2	0.3816 (1)	0.2972 (2)	0.1962 (1)	2.99 (3)
C_2^α	0.4843 (1)	0.3903 (3)	0.1933 (1)	2.99 (4)
$C_2^{\beta 1}$	0.5761 (1)	0.2576 (3)	0.1901 (1)	3.85 (5)
$C_2^{\gamma 1}$	0.5493 (2)	0.1412 (3)	0.1152 (1)	5.37 (6)
$C_2^{\gamma 2}$	0.6013 (2)	0.1469 (4)	0.2672 (1)	5.48 (6)
$C_2^{\beta 2}$	0.5083 (1)	0.5135 (3)	0.2686 (1)	3.64 (5)
$C_2^{\gamma 3}$	0.4204 (2)	0.6510 (3)	0.2655 (1)	5.15 (6)
$C_2^{\gamma 4}$	0.6197 (1)	0.6020 (4)	0.2788 (1)	5.10 (6)
C_2'	0.4597 (1)	0.4976 (3)	0.1152 (1)	3.02 (4)
O_2	0.5167 (1)	0.5981 (2)	0.0861 (1)	4.09 (3)
N_3	0.3521 (1)	0.4608 (2)	0.0825 (1)	2.95 (3)
C_3^α	0.2881 (1)	0.5391 (3)	0.0104 (1)	3.46 (4)
C_3'	0.1673 (1)	0.5251 (2)	0.0091 (1)	3.03 (4)
O_3	0.1047 (1)	0.6185 (2)	−0.0382 (1)	3.97 (3)

† Site occupancy 0.6. ‡ Site occupancy 0.4.

Table 2. *Selected geometric parameters (Å, °)*

N_1—C_1^α	1.470 (3)	C_3'—O_3	1.233 (2)
N_1—C_3'	1.332 (2)	C_2^α—$C_2^{\beta 1}$	1.544 (3)
C_1^α—C_1^β	1.540 (3)	C_2^α—$C_2^{\beta 2}$	1.560 (3)
C_1^α—C_1'	1.496 (3)	C_2^α—C_2'	1.529 (3)
C_1^β—$C_1^{\gamma 1}$	1.449 (5)	$C_2^{\beta 1}$—$C_2^{\gamma 1}$	1.526 (3)
C_1^α—C_3'	1.514 (3)	$C_2^{\beta 1}$—$C_2^{\gamma 2}$	1.529 (3)
C_1^β—$C_1^{\gamma 2}$	1.516 (3)	$C_2^{\beta 2}$—$C_2^{\gamma 3}$	1.517 (4)
C_1^β—$C_1^{\gamma 1}a$	1.411 (7)	$C_2^{\beta 2}$—$C_2^{\gamma 4}$	1.532 (3)
C_1'—N_2	1.276 (2)	C_2'—O_2	1.215 (2)
C_1'—N_3	1.387 (2)	C_2'—N_3	1.383 (2)
N_2—C_2^α	1.480 (2)	N_3—C_3^α	1.449 (2)
C_1^α—N_1—C_3'	127.3 (3)	$C_2^{\beta 1}$—C_2^α—C_2'	110.6 (3)
N_1—C_1^α—C_1^β	111.9 (3)	$C_2^{\beta 2}$—C_2^α—C_2'	110.3 (3)
N_1—C_1^α—C_1'	109.6 (3)	C_2^α—$C_2^{\beta 1}$—$C_2^{\gamma 1}$	111.4 (3)
C_1^β—C_1^α—C_1'	113.6 (3)	C_2^α—$C_2^{\beta 1}$—$C_2^{\gamma 2}$	111.6 (3)
C_1^α—C_1^β—$C_1^{\gamma 1}$	111.8 (4)	$C_2^{\gamma 1}$—$C_2^{\beta 1}$—$C_2^{\gamma 2}$	110.6 (3)
C_1^α—C_1^β—$C_1^{\gamma 2}$	113.0 (3)	C_2^α—$C_2^{\beta 2}$—$C_2^{\gamma 3}$	111.5 (3)
C_1^α—C_1^β—$C_1^{\gamma 1}a$	114.6 (5)	C_2^α—$C_2^{\beta 2}$—$C_2^{\gamma 4}$	112.8 (3)
$C_1^{\gamma 1}$—C_1^β—$C_1^{\gamma 2}$	113.7 (4)	$C_2^{\gamma 3}$—$C_2^{\beta 2}$—$C_2^{\gamma 4}$	109.7 (3)
$C_1^{\gamma 1}$—C_1^β—$C_1^{\gamma 1}a$	92.9 (6)	C_2^α—C_2'—O_2	130.4 (3)
$C_1^{\gamma 2}$—C_1^β—$C_1^{\gamma 1}a$	109.4 (6)	C_2^α—C_2'—N_3	104.6 (3)
C_1^α—C_1'—N_2	125.2 (3)	O_2—C_2'—N_3	125.0 (3)
C_1^α—C_1'—N_3	119.2 (3)	C_2'—N_3—C_3'	108.4 (3)
N_2—C_1'—N_3	115.7 (3)	C_1'—N_3—C_3^α	125.4 (3)
C_1'—N_2—C_2^α	106.6 (3)	C_2'—N_3—C_3^α	126.1 (3)
N_2—C_2^α—$C_2^{\beta 1}$	110.1 (3)	N_3—C_3^α—C_3'	112.0 (3)
N_2—C_2^α—$C_2^{\beta 2}$	107.4 (3)	N_1—C_3'—C_3^α	118.8 (3)
N_2—C_2^α—C_2'	104.7 (3)	N_1—C_3'—O_3	122.6 (3)
$C_2^{\beta 1}$—C_2^α—$C_2^{\beta 2}$	113.4 (3)	C_3^α—C_3'—O_3	118.7 (3)

The structure was refined by full-matrix least squares with anisotropic displacement parameters for all non-H atoms. Subsequent difference Fourier analysis revealed a statistical disorder for the Leu side chain. The occupancy factors for the side-chain atoms $C^{\gamma 1}$ of Val were refined and their final values were 0.6 and 0.4. H atoms were included in their stereochemically expected positions with the isotropic displacement parameter of the carrying atom. Their parameters were kept fixed and they were included in the structure-factor calculations.

Program used to solve structure: *MULTAN*80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980). All calculations were performed using Enraf–Nonius *SDP* software (B. A. Frenz & Associates Inc., 1986) on a MicroVAX 3100 computer.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: NA1214). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Anti-Inflammatory Drugs. III. Salts of Diclofenac with *N*-(2-Hydroxyethyl)-piperidine, *N*-(2-Hydroxyethyl)morpholine and *N*-(2-Hydroxyethyl)piperazine

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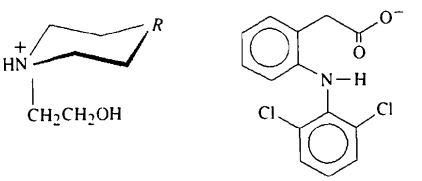
Abstract

The molecular and crystal structures of three salts of the same anion, *N*-(2-hydroxyethyl)piperidinium 2-(2,6-dichlorophenylamino)phenylacetate, $C_7H_{16}NO^+.C_{14}H_{10}Cl_2NO_2^-$, *N*-(2-hydroxyethyl)morpholinium 2-(2,6-dichlorophenylamino)phenylacetate, $C_6H_{14}NO_2^+.C_{14}H_{10}Cl_2NO_2^-$, *N*-(2-hydroxyethyl)piperazinium 2-(2,6-dichlorophenylamino)phenylacetate, $C_6H_{15}N_2O^+.C_{14}H_{10}Cl_2NO_2^-$, have been determined by X-ray diffraction. Strong anion–cation interactions *via* hydrogen bonds are the prime driving force for crystal self-assembly. Packing is determined by weak hydrogen-bonding interactions (C—H···O and C—H···Cl). The three compounds are isomorphous and are characterized by the same network of hydrogen bonds. Structural results are related to the different solubilities of the three salts.

Comment

We are currently investigating the crystal and molecular structures of some salts of diclofenac [2-(2,6-dichlorophenylamino)phenylacetic acid, hereafter HD]. These studies have been prompted by the need to rationalize the factors affecting the salt solubility, which is important in controlling the availability, and therefore the activity, of these non-steroidal anti-inflammatory drugs (NSAIDs). Although the rather low solubility of HD may be generally increased by using its salts, the solubility of the latter do not seem to follow a simple pattern as a function of the counterion (Fini, Fazio & Rapaport, 1993). We hoped, therefore, that a systematic study of the structures of these salts would cast light on the subject. In recent papers, we have investigated the salts of HD with both 1-(2-hydroxyethyl)pyrrolidine (D.HEP) (Castellari & Sabatino, 1994) and diethanolamine (D.HNDEA) (Castellari & Ottani, 1995). While the diclofenac derivative most widely used in therapy is its sodium salt, the diethylammonium and hydroxyethylpyrrolidinium (D.HEP) salts are also employed for topical applications (Rosenthal & Bauhous, 1993). Solubility, seen as the control step in a complex series of events taking place in the human body, can be described with the aid of empirical scales based, for example, on the ratio of the number of hydrophilic to the number of hydrophobic groups present in the solute (Hansch & Leo, 1979) or on an empirical parameter such as the polarity of the solvent (Reichard, 1988). HD is hydrophobic and poorly soluble in water. Substitution of the carboxyl by a carboxylate group increases the dissolution rate of the drug as a consequence of the better solubility of the solid salt particles in the surrounding saturated microphase auto-buffered at a slightly higher pH (Zecchi, Rodriguez, Tartarini & Fini, 1984; Fini, Zecchi & Tartarini, 1985). Therefore, since the long-distance ordering in the crystal corresponds somewhat to local ordering in the liquid, it becomes important to determine the solid-state structure of the salts of HD, especially when the counterion is an organic base capable of strong hydrogen bonding, as in the case of the title compounds *N*-(2-hydroxyethyl)piperidinium 2-(2,6-dichlorophenylamino)phenylacetate, (1), *N*-(2-hydroxyethyl)morpholinium 2-(2,6-dichlorophenylamino)-phenylacetate, (2), and *N*-(2-hydroxyethyl)piperazinium 2-(2,6-dichlorophenylamino)phenylacetate, (3).



(1) $R = CH_2$
(2) $R = O$
(3) $R = NH$

The crystals of compounds (1), (2) and (3) are isomorphous and this means that the packing forces present are almost identical. The common anion, D^-, shows the same geometry in all three salts, similar to that shown by HD (Moser, Sallmann & Wiesenberg, 1990). The twist angle between the two phenyl rings of D^- is 66.8 (1)° for compounds (1) and (3), and 68.3 (1)° for compound (2). The interplanar angles between the carboxyl groups and the dichloro-substituted aromatic rings are 30.8 (1), 27.6 (1) and 31.0 (1)° for compounds (1), (2) and (3), respectively. The cations, though differing