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A new key intermediate in the synthesis of 6-oxopiperidine-2-carboxylate derivatives

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Key indicators

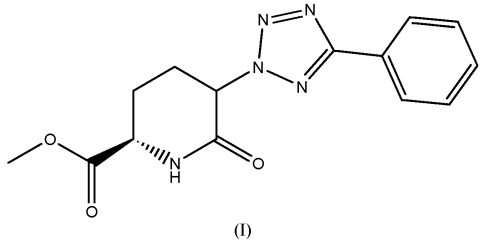
Single-crystal X-ray study
T = 296 K
Mean σ(C–C) = 0.003 Å
R factor = 0.044
wR factor = 0.108
Data-to-parameter ratio = 12.6

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

The relative stereochemistry of methyl 6-oxo-5-(5-phenyltetrazol-2-yl)piperidine-2-carboxylate, $C_{14}H_{15}N_5O_3$, has been determined. It confirms the *cis* configuration of the piperidine ring as well as the position of the substituent on the tetrazole ring. The packing of the molecules is influenced by N—H···O and C—H···N hydrogen bonds.

Comment

Pipecolic acid derivatives are an important class of compounds, which can be used as starting materials for several synthetic drugs, such as enzyme inhibitors (Perumattam *et al.*, 1991), immunosuppressors (Jones *et al.*, 1989), antibiotics (Sehgal *et al.*, 1983) and mycotoxic agents (Martens & Scheunemann, 1991). With the aim of developing new tetrazolic alpha-iminoacids derived from pipecolic acid, an analogue of *cis*-4-(tetrazolylalkyl)piperidine-2-carboxylic acid, giving selective and potential antagonistic activity at the *N*-methyl-D-aspartic acid receptor (NMDA; Orstein *et al.*, 1991), we have prepared a key intermediate, (I), starting from *meso*-dimethyldibromoadipate (Guha & Sankaran, 1955).



(I)

The double substitution of the dibromo derivative successively by 5-phenyl-1*H*-tetrazole and the azide group followed by catalytic hydrogenation led, *via* an intramolecular aminolysis, to the formation of a racemic mixture of two diastereoisomers (*SS*, *RR* and *SR*, *RS*) with a diastereoisomeric ratio of 5/1. The presence and the ratio of the two diastereoisomers were determined by ^{1}H NMR (300 MHz) analysis of the mixture, but determination of the relative stereochemistry of the piperidine core by this method was not possible. The major diastereoisomer was crystallized in a diethyl ether/ethyl acetate mixture, analysed by X-ray diffraction and shown to contain the *SS* and *RR* isomers. Consequently, the relative position of the substituents on the heterocyclic core is *cis* (Fig. 1). The formation of this isomer can be explained by successive S_N2 reactions of the Br atoms of the *meso*-dimethyldibromoadipate, which, after cyclization, would orient the two substituents in a *cis* position (diastereoisomer *SS*, *RR*). Nevertheless, this control is not total since some *trans* isomer

(diastereoisomer *SR*, *RS*) was obtained. Furthermore, the X-ray analysis shows that the first substitution, which corresponds to the alkylation by the 5-phenyl-1*H*-1-tetrazole, occurred only at the N2 position of the tetrazole ring. The angles between the C1—C13 and N2—C3 bonds are 148.6 (2) and 145.9 (2)°. The angle between the phenyl ring and the tetrazole ring is 13.2 (1)°. The crystal cohesion is assured by van der Waals interactions and hydrogen bonding (Fig. 2). Thus, atom N1 forms a hydrogen bond with atom O3($1-x$, $-y$, $-z$), and atom C3 forms a bond with atom N4(x, $\frac{1}{2}-y$, $-\frac{1}{2}+z$) (Table 1).

Experimental

The title compound was synthesized by successive alkylation of 5-phenyltetrazole in the presence of triethylamine and the action of sodium azide on *meso*-dimethyldibromoadipate, followed by catalytic hydrogenation over Pd/C. The crystallization was carried out at ambient temperature with a mixture of diethyl ether and ethyl acetate.

Crystal data

$C_{14}H_{15}N_5O_3$	$Z = 4$
$M_r = 301.31$	$D_x = 1.356$ Mg m^{-3}
Monoclinic, $P2_1/c$	Mo $K\alpha$ radiation
$a = 12.7980$ (6) Å	$\theta = 1$–25
$b = 10.8334$ (3) Å	$\mu = 0.10$ mm^{-1}
$c = 10.9142$ (3) Å	$T = 296$ (2) K
$\beta = 102.796$ (1)°	Block, colourless
$V = 1475.63$ (9) Å^3	0.10 × 0.08 × 0.05 mm

Data collection

Nonius KappaCCD diffractometer	$R_{int} = 0.020$
ω scans	$\theta_{max} = 25.0°$
Absorption correction: none	$h = -15 \rightarrow 14$
5170 measured reflections	$k = -12 \rightarrow 12$
2563 independent reflections	$l = -12 \rightarrow 12$
1777 reflections with $I > 2\sigma(I)$	

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0438P)^2 + 0.1856P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R[F^2 > 2\sigma(F^2)] = 0.044$	$(\Delta/\sigma)_{max} = 0.001$
$wR(F^2) = 0.108$	$\Delta\rho_{max} = 0.16$ e Å^{-3}
$S = 1.04$	$\Delta\rho_{min} = -0.15$ e Å^{-3}
2563 reflections	Extinction correction: *SHELXL*97
204 parameters	Extinction coefficient: 0.026 (4)
H atoms treated by a mixture of independent and constrained refinement	

Table 1
Hydrogen-bonding geometry (Å, °).

D—H···A	D—H	H···A	D···A	D—H···A
N1—H1N···O3^{i}	0.90 (2)	1.99 (2)	2.880 (2)	175
C3—H3···N4^{ii}	0.98	2.57	3.528 (2)	167

Symmetry codes: (i) $1-x, -y, -z$; (ii) $x, \frac{1}{2}-y, z-\frac{1}{2}$.

All H atoms were located in difference maps, but H atoms attached to C atoms were thereafter treated as riding atoms, with C—H distances of 0.98 (CH_3), 0.97 (CH_2) and 0.93 (C—H aromatic) Å and U_{iso}(H) = 1.2U_{eq}(C) or 1.5U_{eq}(C_{methyl}) [N—H1 = 0.89 (2) Å]. The N—H bond length was restrained to 0.89 (2) Å.

Data collection: *KappaCCD Server Software* (Nonius, 1998); cell refinement: *SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO* (Otwinowski & Minor, 1997); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997) and *CAMERON* (Watkin *et al.*, 1993); software used to prepare material for publication: *WinGX* (Farrugia, 1999).

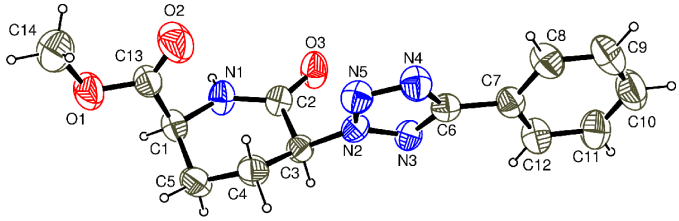


Figure 1
A view of (I), with the atom-labelling scheme. Displacement ellipsoids are drawn at the 50% probability level.

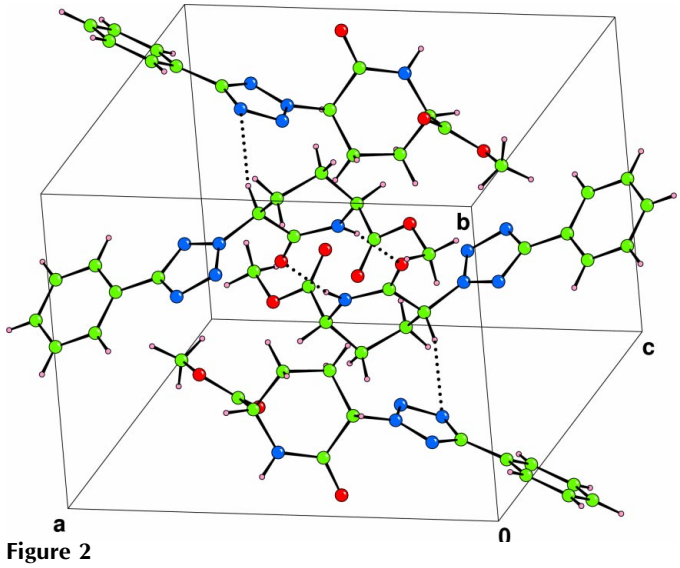


Figure 2
A view of the crystal packing, showing N—H···O and C—H···N intermolecular hydrogen interactions as dashed lines.

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