

The Conformation of Heterocyclic Spiro Compounds. IX. The Structure of Tropane-3-spiro-5'-(2'-thiohydantoin)

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Abstract

$C_{10}H_{15}N_3OS$, orthorhombic, $P2_12_12_1$, $a = 11.081$ (1), $b = 10.156$ (1), $c = 9.236$ (1) Å, $Z = 4$. Final $R = 0.071$ for 920 observed reflexions. The piperidine ring has a distorted chair conformation. The CH_3 group is in an equatorial position. The molecules are held together by $N-H \cdots N$ and $N-H \cdots O$ hydrogen bonds.

Introduction

Following the conformational study of heterocyclic spiro derivatives carried out in our laboratory, the structure determination of the title compound was undertaken to compare molecular conformations of heterocyclic spiro hydantoins with that of a derivative in which the hydantoin ring has been changed to a thiohydantoin ring.

Experimental

Single crystals of the title compound were provided by Dr C. Avendaño of the Departamento de Química Orgánica y Farmacéutica de la Facultad de Farmacia, Madrid. Cell constants were obtained by least squares from 23 high-angle reflexions recorded on a diffractometer with $Mo K\alpha$ radiation. The crystal data are given in Table 1.

Intensities were collected on a Philips PW 1100 diffractometer by the $\omega-2\theta$ scan technique between 2 and 30° in θ with a crystal $0.3 \times 0.45 \times 0.35$ mm and graphite-monochromated $Mo K\alpha$ radiation. 1695 in-

dependent reflexions were measured, of which 775 were considered unobserved with $I < 2\sigma(I)$, where $I = C_p - C_{b1} - C_{b2}$ and $\sigma^2(I) = C_p + C_{b1} + C_{b2} + (0.041)^2$. I is the integrated intensity and $\sigma(I)$ its e.s.d.

The intensities were corrected for Lorentz and polarization effects but not for absorption.

Structure determination and refinement

Systematic absences, $h00$, $h = 2n + 1$, $0k0$, $k = 2n + 1$, $00l$, $l = 2n + 1$, indicated space group $P2_12_12_1$.

The structure was solved with *MULTAN* (Main, Lessinger, Woolfson, Germain & Declercq, 1977). The starting data were the 200 reflexions with $|E| > 1.4$. The set of phases with the highest figure of merit led to an E map in which 14 of the 15 non-hydrogen atoms were located. A Fourier synthesis gave the position of the remaining non-hydrogen atom. Scattering factors for S, O, N, C and H were taken from *International Tables for X-ray Crystallography* (1974). The structure was refined by full-matrix least squares. The function minimized was $\sum w(\Delta F)^2$ where $w = k/\sigma_1^2 \sigma_2^2$, $\sigma_1 = a + b|F_o|$ and $\sigma_2 = c + d \sin \theta/\lambda_T$ with

	<i>a</i>	<i>b</i>
$ F_o \leq 0.32$		
$0.32 \leq F_o \leq 13.50$	2.055	-0.103
$13.50 \leq F_o \leq 29.50$	0.718	0.004
$29.50 \leq F_o $		
	<i>c</i>	<i>d</i>
$\sin \theta/\lambda \leq 0.06$ (Å ⁻¹)		
$0.06 \leq \sin \theta/\lambda \leq 0.6$	0.739	0.307
$0.6 \leq \sin \theta/\lambda \leq 0.71$	-0.728	2.961.

Computations were carried out with *XRAY 70* (Stewart, Kundell & Baldwin, 1970) running on the Univac 1108 computer of the Centro de Proceso de Datos de la Junta de Energía Nuclear, Madrid. The final R and R_w are 0.071 and 0.056 for 920 observed reflexions.*

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35631 (14 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Crystal data*

E.s.d.'s in parentheses refer to the least significant digits.

$C_{10}H_{15}N_3OS$	$V = 1039.4$ (2) Å ³
$M_r = 225.31$	$Z = 4$
Space group $P2_12_12_1$	$D_m = 1.42$ Mg m ⁻³
$a = 11.081$ (1) Å	$D_c = 1.440$
$b = 10.156$ (1)	$F(000) = 480$
$c = 9.236$ (1)	$\mu = 0.275$ mm ⁻¹

Table 2. Positional parameters for heavy atoms and isotropic temperature factors equivalent to the refined anisotropic values

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> _{eq} (Å ²)
C(1)	0.2474 (6)	0.2266 (7)	0.1267 (8)	0.027
C(2)	0.1100 (6)	0.2294 (7)	0.1046 (8)	0.028
C(3,5')	0.0387 (5)	0.3172 (7)	0.2106 (8)	0.026
C(4)	0.1043 (6)	0.3344 (8)	0.3613 (7)	0.033
C(5)	0.2404 (6)	0.3273 (8)	0.3534 (8)	0.031
N(6)	0.2696 (4)	0.1953 (5)	0.2837 (7)	0.029
C(7)	0.3067 (7)	0.3616 (8)	0.1079 (8)	0.044
C(8)	0.3046 (7)	0.4271 (7)	0.2583 (8)	0.040
C(9)	0.3977 (6)	0.1557 (9)	0.3150 (10)	0.054
N(1')	-0.0809 (5)	0.2618 (5)	0.2421 (7)	0.033
C(2')	-0.1661 (6)	0.3570 (7)	0.2315 (8)	0.034
N(3')	-0.1206 (5)	0.4691 (6)	0.1704 (6)	0.028
C(4')	-0.0016 (7)	0.4516 (7)	0.1477 (8)	0.031
O(1)	0.0673 (5)	0.5291 (5)	0.0885 (6)	0.037
S(1)	-0.3074 (2)	0.3338 (2)	0.2896 (3)	0.044

Table 3. Positional and isotropic thermal parameters for H atoms

	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> (Å ²)
H(11)	0.272 (7)	0.160 (9)	0.065 (9)	2.5
H(21)	0.075 (8)	0.133 (9)	0.109 (10)	3.0
H(22)	0.086 (8)	0.244 (10)	0.007 (10)	3.0
H(41)	0.080 (10)	0.269 (9)	0.436 (9)	3.2
H(42)	0.083 (9)	0.427 (9)	0.409 (10)	3.2
H(51)	0.272 (8)	0.325 (9)	0.452 (9)	2.9
H(71)	0.281 (9)	0.411 (9)	0.034 (11)	4.0
H(72)	0.390 (8)	0.345 (9)	0.081 (10)	4.0
H(81)	0.376 (8)	0.435 (9)	0.289 (12)	4.0
H(82)	0.252 (8)	0.517 (10)	0.251 (11)	4.0
H(91)	0.450 (10)	0.215 (10)	0.293 (12)	5.0
H(92)	0.407 (10)	0.085 (11)	0.270 (14)	5.0
H(93)	0.395 (9)	0.129 (11)	0.409 (13)	5.0
H(1')	-0.088 (8)	0.188 (9)	0.288 (10)	3.3
H(3')	-0.180 (8)	0.566 (8)	0.170 (9)	2.8

The final positional parameters of the non-hydrogen atoms are given in Table 2, those of the H atoms in Table 3.

Discussion

The atomic numbering and bond lengths and angles are given in Fig. 1 and Table 4; torsion angles are in Table 5. The molecule consists of a piperidine ring with a methyl group attached to the N atom, and a five-membered ring joined to the former by a common C—N—C bridge and a 2'-thiohydantoin ring substituted at the spiranic C(3,5'). The piperidine ring adopts a distorted chair conformation in agreement with the results of Vooren, Schenk & MacGillavry (1970) and Smith-Verdier, Florencio & Garcia-Blanco (1977).

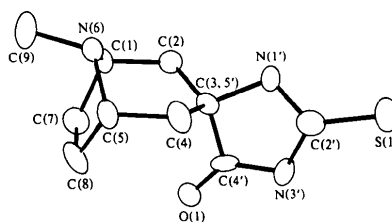


Fig. 1. Perspective view and numbering of the molecule.

Table 4. Bond lengths (Å) and angles (°) for non-hydrogen atoms with e.s.d.'s in parentheses

C(1)—C(2)	1.537 (9)	C(5)—C(8)	1.518 (11)
C(1)—N(6)	1.504 (10)	C(7)—C(8)	1.541 (11)
C(1)—C(7)	1.530 (11)	N(1')—C(2')	1.355 (8)
C(2)—C(3,5')	1.542 (10)	C(2')—N(3')	1.367 (9)
C(3,5')—C(4)	1.580 (10)	C(2')—S(1)	1.672 (7)
C(3,5')—N(1')	1.469 (8)	N(3')—C(4')	1.346 (9)
C(3,5')—C(4')	1.549 (10)	C(4')—O(1)	1.226 (9)
C(4)—C(5)	1.511 (9)	N(6)—C(9)	1.503 (9)
C(5)—N(6)	1.522 (10)		
C(2)—C(1)—N(6)	107.1 (6)	C(1)—N(6)—C(5)	100.8 (5)
C(2)—C(1)—C(7)	113.2 (6)	C(1)—N(6)—C(9)	113.3 (6)
N(6)—C(1)—C(7)	103.2 (6)	C(5)—N(6)—C(9)	110.8 (5)
C(1)—C(2)—C(3,5')	115.7 (6)	C(1)—C(7)—C(8)	106.1 (6)
C(2)—C(3,5')—C(4)	112.8 (6)	C(7)—C(8)—C(5)	104.0 (6)
C(2)—C(3,5')—N(1')	111.5 (5)	C(3,5')—N(1')—C(2')	109.9 (5)
C(2)—C(3,5')—C(4')	114.8 (6)	N(1')—C(2')—S(1)	121.9 (5)
C(4)—C(3,5')—C(4')	111.4 (5)	N(1')—C(2')—N(3')	111.6 (6)
N(1')—C(3,5')—C(4)	106.4 (5)	N(3')—C(2')—S(1)	126.6 (5)
N(1')—C(3,5')—C(4')	98.7 (5)	C(2')—N(3')—C(4')	108.4 (6)
C(3,5')—C(4)—C(5)	114.3 (6)	C(3,5')—C(4')—N(3')	109.9 (6)
C(4)—C(5)—N(6)	105.9 (6)	N(3')—C(4')—O(1)	126.5 (7)
C(4)—C(5)—C(8)	117.6 (6)	C(3,5')—C(4')—O(1)	123.6 (6)
N(6)—C(5)—C(8)	104.1 (6)		

Table 5. Torsion angles (°)

N(6)—C(1)—C(7)—C(8)	-26.3 (7)
C(7)—C(1)—N(6)—C(5)	43.6 (6)
C(8)—C(5)—N(6)—C(1)	-45.5 (6)
N(6)—C(5)—C(8)—C(7)	29.0 (7)
C(1)—C(7)—C(8)—C(5)	-1.8 (8)
C(2)—C(1)—N(6)—C(5)	-76.1 (6)
N(6)—C(1)—C(2)—C(3,5')	51.7 (7)
C(1)—C(2)—C(3,5')—C(4)	-27.1 (8)
C(2)—C(3,5')—C(4)—C(5)	29.9 (8)
C(3,5')—C(4)—C(5)—N(6)	-56.4 (7)
C(4)—C(5)—N(6)—C(1)	79.1 (6)

Bond lengths and angles are similar to those in other compounds of this series (Florencio, Smith-Verdier & Garcia-Blanco, 1979).

According to Schenk, MacGillavry, Skolnik & Laand (1967) in pseudotropine and Vooren, Schenk & MacGillavry (1970) in α -chlorotropine monohydrate, the position of the CH₃ group is equatorial, and this position is probably influenced by the formation of hydrogen bonds between adjacent molecules. However, tropine-3-spiro-5'-hydantoin (Smith-Verdier, Florencio & Garcia-Blanco, 1977) has the CH₃ in an axial position in spite of hydrogen bonds between

neighbouring molecules. In the present compound the CH_3 is equatorial. Consequently, the problem about the position of the CH_3 group on the piperidine is still unresolved. Perhaps the situation of the CH_3 group is only governed by steric interactions.

In the six-membered ring the asymmetry parameters (Duax & Norton, 1975) are: $\Delta C_3^{3,5'} = 3.6$, $\Delta C_2^{2-3,5'} = 20.8$, $\Delta C_2^{1-2} = 49.1^\circ$, so that the piperidine ring adopts a very deformed chair conformation with an approximate C_s mirror passing through $C(3,5')$ and $N(6)$. The deviations of these atoms from the mean plane through the remaining atoms of the ring are 0.371 and -0.904 \AA . Comparison of these displacements with those in tropane-3-spiro-5'-hydantoin (0.538 and -0.808 \AA respectively) shows that in the present compound the flattening of the $C(1), C(2), C(3,5'), C(4), C(5)$ part of the chair and the opposite puckering are noticeably greater. This increase of the deformation could be due to the different position of the thiohydantoin ring on $C(3,5')$, since in the present compound this group is rotated 180° about $C(3,5')$ with respect to its position in the former compound, and there is a greater interaction between the ethylene bridge and the O atom of the 2'-thiohydantoin group. This interaction is shown in the value of the non-bonded

Table 6. Deviations (\AA) of atoms from some least-squares planes

Plane A: C(1), C(2), C(4), C(5)	$0.0509X + 0.9055Y - 0.4214Z = 1.7487$
Plane B: C(1), C(5), C(7), C(8)	$-0.8844X + 0.4079Y - 0.2270Z = -1.7459$
Plane C: N(1'), C(2'), N(3'), C(4'), C(3,5')	$-0.1520X - 0.3515Y - 0.9238Z = -2.9210$

	Plane A	Plane B	Plane C
C(1)	-0.018 (7)	-0.006 (7)	0.614 (8)
C(2)	0.016 (7)		1.025 (7)
C(3,5')	0.371 (7)		-0.073 (7)
C(4)	0.021 (8)		-1.531 (7)
C(5)	0.022 (8)	0.005 (7)	-1.668 (7)
N(6)	-0.904 (6)	-0.682 (5)	-0.651 (6)
C(7)	1.329 (8)	0.012 (8)	0.194 (8)
C(8)	1.345 (7)	-0.011 (8)	-1.320 (8)
C(9)	-1.318 (9)		-0.992 (9)
N(1')			0.057 (6)
C(2')			-0.049 (7)
N(3')			-0.004 (6)
C(4')			0.052 (7)
O(1)			0.164 (5)
S(1)			-0.224 (2)

Table 7. Interatomic distances (\AA) and angles ($^\circ$) in the hydrogen bonds

a	b	c	ab	bc	ac	$\angle abc$
$N(1')\text{---}H\cdots O(1)(\bar{x}, -\frac{1}{2} + y, \frac{1}{2} - z)$			0.86 (9)	1.985 (5)	2.837 (7)	167.2 (4)
$N(3')\text{---}H\cdots N(6)(\bar{x}, \frac{1}{2} + y, \frac{1}{2} - z)$			1.18 (8)	1.702 (5)	2.861 (8)	164.6 (4)

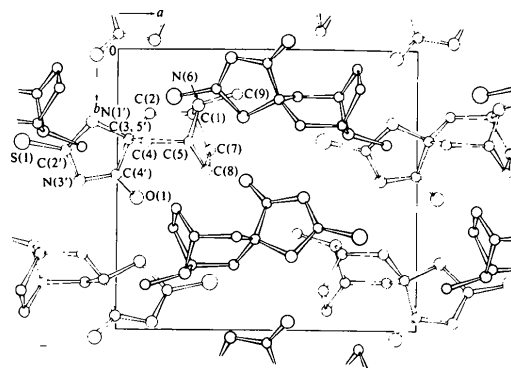


Fig. 2. Projection of the structure down c .

$O(1)\cdots C(8)$ and $O(1)\cdots C(7)$ distances of 3.232 and 3.157 \AA respectively.

The five-membered ring of the bicyclic portion shows an N-envelope conformation [$\Delta = 40.87^\circ$ and $\phi = 46.53^\circ$, Altona, Geise & Romers (1968)]. The deviation of the N atom from the least-squares plane through $C(1), C(5), C(7), C(8)$ is $-0.682 (5) \text{ \AA}$.

Bond lengths and angles in the 2'-thiohydantoin ring show some differences from those found by Walker, Foltg & Merritt (1969) in 2-thiohydantoin itself. Moreover, S(1) and O(1) deviate significantly from the mean plane through the ring, Table 6. These differences could be due to the bulky substituents at $C(3,5')$.

Fig. 2 shows the packing of the molecules. There are two crystallographically independent hydrogen bonds: $N(1')\text{---}H\cdots O(1)(\bar{x}, -\frac{1}{2} + y, \frac{1}{2} - z) = 2.837 (7)$ and $N(3')\text{---}H\cdots N(6)(\bar{x}, \frac{1}{2} + y, \frac{1}{2} - z) = 2.861 (8) \text{ \AA}$. The geometries of these H bonds are given in Table 7. There are no other contacts $< 4 \text{ \AA}$.

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X-ray Structure Analysis and Molecular Conformation of *N*-Propionylproline

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Abstract

$C_8H_{13}NO_3$, $a = 14.310$ (7), $b = 12.520$ (6), $c = 5.079$ (3) Å, $V = 909.63$ Å³, $M_r = 171.18$, $D_m = 1.250$, $D_c = 1.249$ Mg m⁻³, orthorhombic, space group $P2_12_12_1$, $Z = 4$, $F(000) = 368$; final $R = 5.1\%$ for 963 observed reflections. The molecules are joined together in pairs by a hydrogen bond: $O' \cdots OH = 2.58$ (1) Å. C^α is in the *cis* configuration. The absolute configuration of the noncentrosymmetric structure and, therefore, of the molecular conformation was determined by anomalous dispersion. The $NC^\alpha C^\gamma C^\delta$ group in the pyrrolidine ring is fairly planar. C^β deviates by -0.592 (3) Å from the best plane of the five-membered ring; C^α , C^β and C^δ are on the same side whereas N and C^γ are on the opposite side of the plane in relation to the carboxyl C' . Therefore, *N*-propionylproline is C_s-C^γ -*exo* (C^β -*endo*). This derivative belongs to conformation *B*, since the dihedral angle $\chi_1 = 36.8$ (4)° at the ring takes a positive value.

Introduction

It is known that the presence of proline at the amino terminal of a polypeptide chain causes steric interactions for the preceding amino acids, especially when there is a C^β atom in its side chain. For this reason proline has been regarded as a helix breaker. In addition to steric interactions from neighbouring amino acids at the amino terminal, there are steric interactions of the carboxyl group of the proline and on a polypeptide chain of the amide of the carboxyl group

with the pyrrolidine of the proline, especially its C^β -CH₂ group (Schimmel & Flory, 1968).

To study the cause of these neighbouring-group effects along a polypeptide chain after and before the position of a proline residue, so as eventually to come to some conclusions concerning the protein conformation, it is essential to study peptides containing proline with different side residues at the amino and carboxyl terminal of the proline or to study model substances so as to generalize certain aspects, especially to obtain the conformation of cyclic pyrrolidine systems in proline. The model system used here is *N*-propionylproline.

Experimental and results

The crystals were grown from ethyl acetate. Approximate cell dimensions and space-group information were obtained from Weissenberg photographs. The θ - 2θ mode (3–68°) with the three-measurements technique was adopted (Dreissig, 1969; Allen, Rogers & Troughton, 1971). 1041 reflexions were collected of which 963 were regarded as observed with $I > 2\sigma(I)$. Ni-filtered Cu $K\alpha$ radiation was used ($\lambda = 1.5418$ Å). No absorption correction was applied (diameter of crystal < 0.8 mm).

Structure determination and refinement

The phase problem was solved with *MULTAN 77* (Main, Lessinger, Woolfson, Germain & Declercq,