

The Conformation of Heterocyclic Spiro Compounds.

I. The Crystal and Molecular Structure of *N*-Methyltropane-3-spiro-5'-hydantoin

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Crystals of *N*-methyltropane-3-spiro-5'-hydantoin, $C_{10}N_3O_2H_{15}$, are monoclinic: space group $P2_1/c$, $a = 6.183$ (1), $b = 21.519$ (1), $c = 8.040$ (1) Å, $\beta = 111.97$ (1)°, and there are four molecules in the unit cell. The structure was determined by direct methods and refined by Fourier and least-squares calculations. The piperidine ring has a deformed chair form. The CH_3 group is in an axial position. The molecules are bound by $N-H\cdots N$ and $N-H\cdots O$ bridges.

Introduction

The chemical study of the heterocyclic spiro derivatives of nortropane and granatanine has been carried out by Gonzalez Trigo, Avendaño & Martínez Moreno (1974) in order to obtain information about their biological properties. The piperidine ring is included in both nortropane and granatanine systems and it seemed to be of interest to determine the conformation of the piperidine ring and to establish the situation of the methyl group at the ternary N atom. Therefore, an accurate structure analysis of these compounds has been undertaken.

In the present paper the structure of *N*-methyltropane-3-spiro-5'-hydantoin is studied and in a future publication the structure of *N*-methylgranatanine-3-spirohydantoin will be presented.

Experimental

Single crystals of the title compound were kindly provided by Dr C. Avendaño and Dr M. Martínez Moreno of the Departamento de Química Orgánica y Farmaceutica de la Facultad de Farmacia, Madrid. A preliminary survey of film data collected indicated that the compound crystallizes with monoclinic symmetry.

Table 1. *Crystal data*

Standard deviations, given in parentheses, refer to the least significant digits.

Formula $C_{10}N_3O_2H_{15}$	
Molecular weight 209.25	
Space group $P2_1/c$	
$a = 6.183$ (1) Å	$Z = 4$
$b = 21.519$ (1)	$D_x = 1.40$ g cm ⁻³
$c = 8.040$ (1)	$D_c = 1.432$
$\beta = 111.97$ (1)°	$F(000) = 448$
$V = 992.00$ (8) Å ³	$\lambda(\text{Mo } K\alpha) = 0.7107$ Å

Accurate cell constants were obtained by least-squares treatment of 15 high-angle reflexions recorded on a four-circle 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 ω - 2θ scan technique between 2 and 30° in θ with a crystal of dimensions 0.20 × 0.10 × 0.12 mm and graphite-monochromated Mo $K\alpha$ radiation. 2862 independent reflexions were measured of which 535 were considered unobserved by the criterion I is unobserved if $I < 2\sigma(I)$, where $I = C_p - C_{b1} - C_{b2}$ and $\sigma^2(I) = C_p + C_{b1} + C_{b2} + (0.04I)^2$. I is the integrated intensity and $\sigma(I)$ its estimated standard deviation.

The intensities were corrected for Lorentz and polarization effects. No absorption correction was applied ($\mu = 1.1034$ cm⁻¹).

Structure determination and refinement

The direct-method programs *MULTAN* 74 (Main, Woolfson, Lessinger, Germain & Declercq, 1974) were used to solve the structure. The set of signs with the highest combined figure of merit produced an E map with all the heavy atoms immediately recognizable. Refinement of the positional and isotropic thermal parameters reduced R to 0.149. A cycle of full-matrix least squares with anisotropic thermal parameters led to an R of 0.094, at which point a difference synthesis enabled all the H atoms to be located. Two cycles of full-matrix least-squares refinement including the heavy atoms with anisotropic temperature factors and the H atoms with isotropic thermal parameters (the value of the adjacent heavy atom) were carried out. The quantity minimized was $\sum w(\Delta F)^2$. The final unweighted and weighted agreement indices for the observed reflexions were $R = 0.052$ and $R_w = 0.062$ where $R_w = (\sum w\Delta^2 / \sum w|F_o|^2)^{1/2}$. As a check of the

Table 2. Positional parameters ($\times 10^5$) for the heavy atoms

	x	y	z
C(1)	23087 (24)	90544 (7)	22951 (20)
C(2)	36740 (26)	89563 (7)	43078 (20)
C(3,5')	62571 (25)	87924 (6)	47355 (18)
C(4)	64717 (26)	83353 (7)	33308 (20)
C(5)	48498 (25)	84955 (7)	14053 (19)
N(6)	23726 (21)	85036 (6)	12087 (16)
C(7)	34276 (28)	93444 (7)	14877 (21)
C(8)	51119 (26)	91653 (8)	8577 (20)
C(9)	14322 (35)	79199 (9)	15841 (26)
N(1')	77760 (23)	93362 (6)	49963 (16)
C(2')	95652 (26)	93332 (7)	65998 (18)
N(3')	92720 (25)	88275 (6)	75771 (17)
C(4')	73203 (28)	84950 (7)	66042 (20)
O(10)	11719 (22)	97047 (6)	71330 (15)
O(11)	65761 (29)	80442 (7)	71086 (19)

Table 3. Positional ($\times 10^3$) and isotropic thermal ($\times 10^5$) parameters for the hydrogen atoms

	x	y	z	U
H(1)	63 (4)	915 (1)	210 (3)	16 (5)
H(21)	356 (4)	933 (1)	496 (3)	13 (5)
H(22)	301 (4)	860 (1)	482 (3)	20 (6)
H(41)	814 (4)	835 (1)	341 (3)	16 (5)
H(42)	613 (3)	791 (1)	363 (3)	10 (4)
H(5)	509 (3)	816 (1)	58 (2)	8 (4)
H(71)	425 (4)	988 (1)	241 (3)	17 (5)
H(72)	218 (4)	975 (1)	47 (3)	18 (5)
H(81)	676 (4)	932 (1)	142 (3)	26 (6)
H(82)	457 (4)	917 (1)	-51 (3)	26 (6)
H(91)	200 (5)	778 (1)	280 (4)	36 (7)
H(92)	-28 (5)	796 (1)	129 (4)	32 (7)
H(93)	169 (5)	756 (1)	89 (4)	41 (8)
H(1')	788 (4)	960 (1)	414 (3)	17 (5)
H(3')	1030 (4)	871 (1)	876 (3)	26 (6)

correctness of the structure a difference map was computed; this had no peaks $>0.23 \text{ e } \text{\AA}^{-3}$. The atomic scattering factors were taken from *International Tables for X-ray Crystallography* (1974). The computations were made with programs of the XRAY 70 system (Stewart, Kundell & Baldwin, 1970). Final atomic coordinates and isotropic temperature factors for non-hydrogen and H atoms are given in Tables 2 and 3.*

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 32692 (14 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Discussion

The atomic numbering and the bond lengths and bond angles in the molecule are given in Fig. 1. The displacements of the atoms from various planes in the molecule are pertinent to a detailed description of the molecular conformation and are shown in Table 4.

The conformation of tropine derivatives was studied many years ago by several authors using various techniques; Visser, Manassen & De Vries (1954) have shown that the piperidine ring has a chair conformation with the CH_3 group on the N atom in an equatorial position with respect to this ring; Closs (1959) is also in accordance with this result. MacGillivray & Fodor

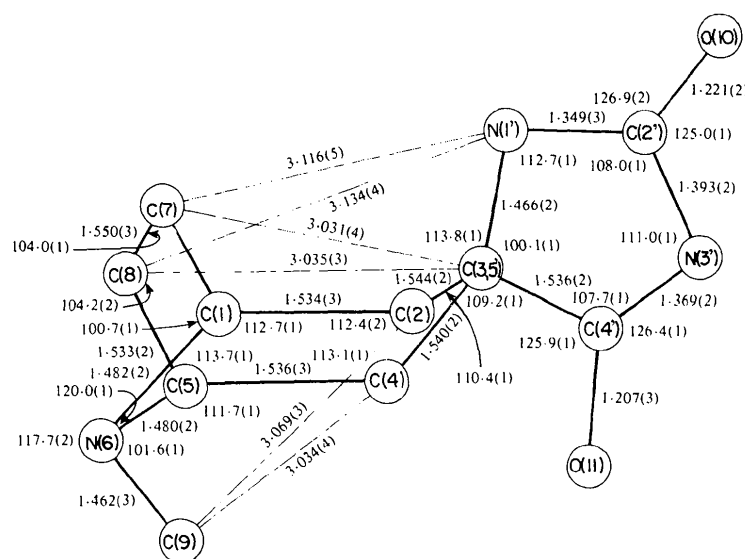


Fig. 1. Bond lengths (Å) and angles ($^\circ$) with their estimated standard deviations in parentheses. Angles not shown: $\text{C}(4)\text{--C}(3,5')\text{--N}(1') = 112.9 (1)$, $\text{C}(2)\text{--C}(3,5')\text{--C}(4') = 110.4 (1)^\circ$.

(1964) show that in *N*-ethylnortropine methobromide the last CH₃ group introduced is equatorially attached, in agreement with Fodor's prediction (Fodor, Toth & Vincze, 1955). Schenk, MacGillavry, Skolnik & Laand (1967) in pseudotropine, and Vooren, Schenk & MacGillavry (1970) in α -chlorotropane monohydrate found also that the CH₃ group is attached to the N atom in an equatorial position, and the piperidine ring has a deformed chair conformation.

In the present compound the CH₃ group is in an axial position and the piperidine ring adopts also a deformed chair conformation with C(3) and N(6) displaced by 0.538 and -0.808 Å respectively out of the plane defined by the remaining ring atoms. The deformation is probably due to the steric interaction between the ethylene bridge and the hydantoin ring attached to the piperidine ring through the spiranic C atom.

The asymmetric parameters (Duax & Norton, 1975) are $\Delta C_s^{(3,5')} = 0.61$, $\Delta C_2^{2-(3,5')} = 13.4$ and $\Delta C_2^{1-2} = 27.0^\circ$. Consequently, a mirror symmetry is dominant with an approximate C_s plane passing through C(3,5') and N(6).

It is interesting to compare some dihedral angles of the piperidine ring with those found in pseudotropine and α -chlorotropane monohydrate. Viewed along the

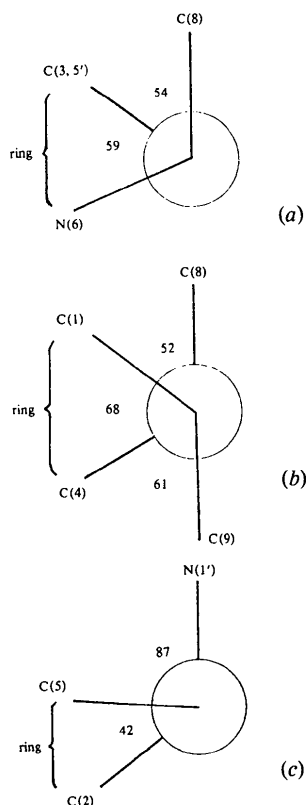


Fig. 2. Newman projections along bonds (a) C(5)-C(4), (b) N(6)-C(5), (c) C(4)-C(3,5').

C(5)-C(4) bond (Fig. 2a) the dihedral ring angle is very similar to the corresponding angles found in pseudotropine (59.8°) and in α -chlorotropane (57°). The dihedral angle about the C(4)-C(3,5') bond (Fig. 2c) shows a similar value to the corresponding angle in pseudotropine (42.1°) and so deviates 8° from the corresponding value found in α -chlorotropane (34°). Finally, the dihedral angle about N(6)-C(5) (Fig. 2b) is 68°, which deviates by 6 and 9° respectively from the values given for pseudotropine (74.2°) and α -chlorotropane (77°). As a result of this, the C(1), C(2), C(4), C(5), N(6) part of the molecule is more planar than the corresponding part in pseudotropine and α -chlorotropane monohydrate. The dihedral angle N(6)-C(1,5)-C(2,4) (Fig. 3) is greater than the corresponding angle in pseudotropine and α -chlorotropane monohydrate and C(7,8)-C(1,5)-N(6) is smaller; consequently, the N(6) atom is near the C atoms of the ethylene bridge. Perhaps for this reason the CH₃ group is attached to the piperidine ring in the axial position instead of the equatorial, since in the latter case the non-bonded distances C(9)···C(7) and C(9)···C(8) would be much too short.

The molecular geometry approximates to *m* [mirror plane through C(9), N(6), C(3,5')] as can be seen in Fig. 1 and Table 4]. N(1'), C(4') and O(10) of the hydantoin ring are practically in this plane; only C(2'), N(3') and O(11) deviate slightly from it.

The hydantoin ring is practically planar (Table 4) and the deviations of O(10) and O(11) from the plane through the hydantoin ring atoms are -0.061 and 0.081 Å respectively.

Bond lengths and bond angles in the hydantoin ring are in good agreement with those found by Mootz (1965) in DL-allantoin and by Walker, Folting & Merritt (1969) in 2-thiohydantoin. The C-C bond length involving the tetrahedral C(3,5') atom, 1.536 Å, is closer to the value of 1.535 Å found in DL-allantoin than the value of 1.508 Å shown in 2-thiohydantoin. This lengthening in DL-allantoin and in the present compound could be due to the bulky substituent on the tetrahedral C atom.

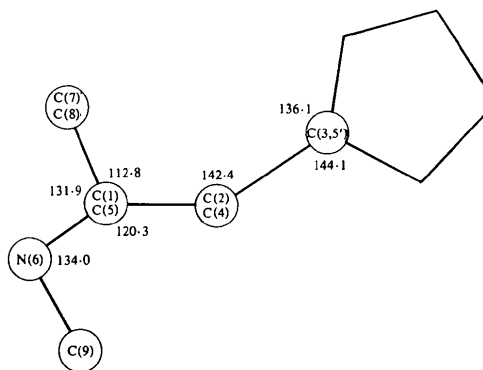
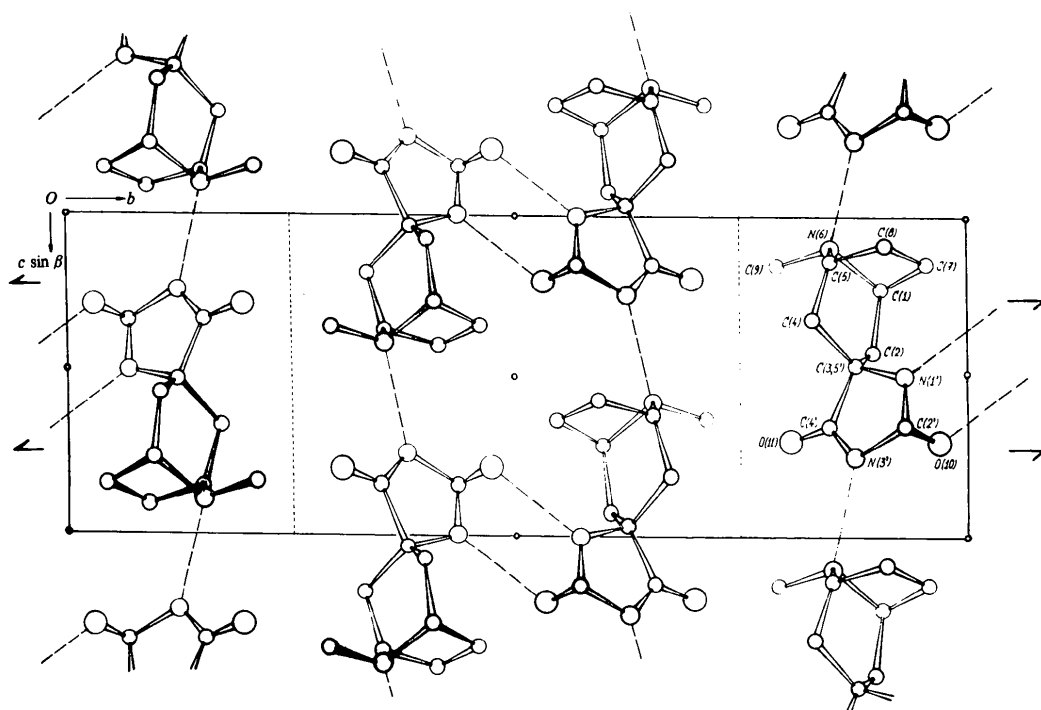


Fig. 3. Angles (°) between planes in the molecule perpendicular to the mirror plane.

Fig. 4. Projection of the structure along *a*.Table 4. Deviations (\AA) of the atoms from some least-squares planes in the molecule

Plane *A* through atoms: C(9), N(6), C(3,5')
 $-0.8083X + 0.5117Y + 0.2912Z = 8.7347$

Plane *B* through atoms: C(1), C(2), C(4), C(5)
 $0.5570X + 0.8299Y + 0.0315Z = 16.6371$

Plane *C* through atoms: N(1'), C(2), N(3'), C(4'), C(3,5')
 $-0.7533X + 0.5558Y + 0.3517Z = 9.9520$

Atoms	Deviations		
	<i>A</i>	<i>B</i>	<i>C</i>
C(1)	1.139	-0.003	
C(2)	1.275	0.002	
C(3,5')	0.000	0.538	-0.036
C(4)	-1.257	-0.002	
C(5)	-1.156	0.003	
N(6)	0.000	-0.808	
C(7)	0.747		
C(8)	-0.802		
C(9)	-0.000		
N(1')	-0.040		0.035
C(2')	-0.200		-0.018
N(3')	-0.160		-0.009
C(4')	0.001		0.027
O(10)	0.007		-0.061
O(11)	0.109		0.081

The bond lengths and bond angles involving H atoms are given in Table 5.

The molecular packing as viewed along *a* is shown in Fig. 4. Hydrogen bonds of types N-H...O and N-H...N link the molecules together. Two

Table 5. Bond distances and valence angles involving hydrogen atoms

Distances are in \AA and angles in degrees, with e.s.d.'s from least squares in parentheses.

C(1)-H(1)	1.01 (3)	C(3,5')-C(4)-H(41)	107 (1)
C(2)-H(21)	0.98 (3)	C(3,5')-C(4)-H(42)	109 (2)
C(2)-H(22)	1.06 (2)	H(41)-C(4)-H(42)	109 (2)
C(4)-H(41)	1.01 (3)	C(4)-C(5)-H(5)	107 (1)
C(4)-H(42)	0.99 (3)	N(6)-C(5)-H(5)	110 (1)
C(5)-H(5)	1.03 (2)	C(8)-C(5)-H(5)	114 (1)
C(7)-H(71)	1.03 (2)	C(1)-C(7)-H(71)	111 (2)
C(7)-H(72)	0.99 (2)	C(1)-C(7)-H(72)	109 (2)
C(8)-H(81)	1.01 (3)	C(8)-C(7)-H(71)	113 (2)
C(8)-H(82)	1.02 (3)	C(8)-C(7)-H(72)	112 (2)
C(9)-H(91)	0.96 (3)	H(71)-C(7)-H(72)	108 (2)
C(9)-H(92)	1.00 (3)	C(5)-C(8)-H(81)	113 (2)
C(9)-H(93)	1.00 (3)	C(5)-C(8)-H(82)	107 (2)
N(1')-H(1')	1.12 (2)	C(7)-C(8)-H(81)	111 (2)
N(3')-H(3')	0.96 (3)	C(7)-C(8)-H(82)	111 (2)
		H(81)-C(8)-H(82)	110 (3)
C(2)-C(1)-H(1)	108 (1)	N(6)-C(9)-H(91)	117 (2)
C(7)-C(1)-H(1)	113 (1)	N(6)-C(9)-H(92)	111 (2)
N(6)-C(1)-H(1)	109 (1)	N(6)-C(9)-H(93)	113 (2)
C(1)-C(2)-H(21)	109 (3)	H(91)-C(9)-H(92)	102 (3)
C(1)-C(2)-H(22)	112 (1)	H(91)-C(9)-H(93)	104 (3)
C(3,5')-C(2)-H(21)	110 (1)	H(92)-C(9)-H(93)	108 (3)
C(3,5')-C(2)-H(22)	106 (1)	C(3,5')-N(1')-H(1')	127 (1)
H(21)-C(2)-H(22)	106 (2)	C(2')-N(1')-H(1')	118 (1)
C(5)-C(4)-H(41)	109 (3)	C(2')-N(3')-H(3')	126 (2)
C(5)-C(4)-H(42)	109 (1)	C(4')-N(3')-H(3')	123 (2)

N(1')...O(10) bonds of length 2.906 (2) \AA and N(1')-H...O(10) angles of 163.0° are formed between pairs of molecules related by a centre of

symmetry, while the N(3')...N(6) bond of length 2.915 (4) Å, and N(3')—H...N(6) angle of 178.0 (3)°, links the molecules forming chains along *c*. The other distances for intermolecular contacts correspond to normal van der Waals interactions.

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Calcium Binding to α -Amino Acids: The Crystal Structure of Calcium L-Glutamate Chloride Monohydrate

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Crystals of calcium L-glutamate chloride monohydrate [CaCl(C₅H₈NO₄)·H₂O] are orthorhombic, space group *P*2₁2₁2₁, with *a* = 5.0731 (5), *b* = 8.2168 (5), *c* = 23.067 (2) Å and four formula weights per unit cell. A trial structure was obtained by Patterson and Fourier techniques and refined by full-matrix least-squares calculations. The final *R* index, at convergence, is 0.045 for 2463 absorption-corrected, Mo *K* α , diffractometer data. The Ca ion is coordinated by carboxyl O atoms from five different glutamate anions. The sixfold coordination polyhedron is completed by the water molecule and is a distorted octahedron. Ca...O distances range from 2.319 to 2.396 Å. The glutamate carboxyl groups do not chelate Ca ions but serve only as unidentate ligands in the Ca coordination shell.

Introduction

The biological functions of the Ca ion are numerous and varied. Processes in which Ca plays a role include biological mineralization, muscle contraction, and nerve transmission. In many of these processes, protein–calcium complexes have been implicated.

Crystal-structure studies of a number of proteins that have calcium-binding sites have been reported in recent years (Stroud, Kay & Dickerson, 1971; Matthews, Colman, Jansonius, Titani, Walsh & Neurath, 1972; Edelman, Cunningham, Reeke, Becker, Waxdal & Wang, 1972; Cotton, Bier, Day, Hazen & Larsen,

1972; Kretsinger & Nockolds, 1973; Bode & Schwager, 1975). In most of these structure determinations, resolution was sufficient to establish the identity and spatial distribution of the residues that form the binding sites, and the results confirm that aspartate and glutamate residues are the major components of these sites.

To obtain information about structural factors that are likely to influence Ca interactions with proteins, we are currently investigating the crystal structures of several calcium–glutamate and –aspartate complexes. In this paper we describe the crystal structure of calcium L-glutamate chloride monohydrate and com-