

The Conformation of Heterocyclic Spiro Compounds.

VIII. 3,7-Dimethyl-3,7-diazabicyclo[3.3.1]nonane-9-spiro-5'-hydantoin

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Abstract

$C_{11}H_{18}N_4O_2$ is monoclinic, $P2_1/n$, with $a = 13.260$ (1), $b = 13.116$ (1), $c = 6.890$ (1) Å, $\beta = 97.47$ (1)°, $Z = 4$. Final $R = 0.054$ for 2850 observed reflexions. The bicyclo[3.3.1]nonane system adopts a chair-chair conformation. The structure is held together by hydrogen bonds.

Introduction

This structure determination is part of a study being carried out in this laboratory on heterocyclic spirohydantoin derivatives with pharmacological properties.

The present compound was obtained by Trigo, Galvez & Avendaño (1978). The results of proton NMR studies seemed consistent with an adamantane-like structure, in agreement with Douglass & Ratliff (1968), Fig. 1.

Support for this structure was derived from the position of the *N*-methyl resonance. However, the same authors admit that this fact does not constitute a definitive proof of this supposition. The present investigation was performed in order to verify the above statement and to elucidate the structure in the solid state.

Experimental

A single crystal $0.2 \times 0.2 \times 0.4$ mm was selected for X-ray investigation. The density was determined by

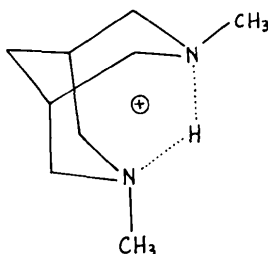


Fig. 1. Proposed molecular structure.

Table 1. Crystal data

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

Formula $C_{11}H_{18}N_4O_2$	$V = 1188.15$ (18) Å ³
$M_r = 238.29$	$Z = 4$
Space group $P2_1/n$	$D_x = 1.332$ Mg m ⁻³
$a = 13.260$ (1) Å	$D_c = 1.35$
$b = 13.116$ (1)	$F(000) = 512$
$c = 6.890$ (1)	$\lambda(\text{Mo } K\alpha) = 0.7107$ Å
$\beta = 97.47$ (1)°	$\mu = 0.08855$ mm ⁻¹

flotation. The lattice constants were obtained by least squares from 35 reflections measured on a four-circle diffractometer with Mo $K\alpha$ radiation. The cell dimensions and other pertinent crystal data are given in Table 1.

The intensities were collected on a Philips PW 1100 four-circle diffractometer. Intensities were recorded in the $\omega/2\theta$ scan mode with θ between 2 and 33°, using graphite-monochromated Mo $K\alpha$ radiation. 4483 reflections were measured of which 2850 had $I > 2\sigma(I)$, σ being the standard deviation calculated from the counting statistics. The intensities were corrected for Lorentz-polarization effects but not for absorption ($\mu = 0.08855$ mm⁻¹).

Solution and refinement of the structure

The structure was solved with *MULTAN 78* (Main, Woolson, Hull, Lessinger, Germain & Declercq, 1978) with the 150 largest E values. The highest combined figure of merit located a fragment of the molecule. The remaining atoms were found from a Fourier synthesis. Isotropic refinement of the non-hydrogen atoms gave $R = 0.20$. Further refinement with anisotropic temperature factors reduced R to 0.093.

The H atoms were located from a difference map and included in the refinement with fixed isotropic temperature factors equal to those of the C atoms to which they are bonded. The quantity minimized was $\sum w(\Delta F)^2$ where $w = K/\sigma_1^2 \sigma_2^2$, $\sigma_1 = a + b|F_o|$ with the coefficients given in Table 2. The final $R = 0.054$ and $R_w = 0.067$, where $R_w = (\sum w\Delta^2 / \sum w|F_o|^2)^{1/2}$.

Table 2. *Coefficients for the weighting scheme*

	<i>a</i>	<i>b</i>
$ F_o \leq 1.51$	0.429	0.120
$1.51 \leq F_o \leq 7.20$	0.569	0.058
$7.20 \leq F_o $	0.190	0.022

Table 3. *The positional parameters for non-hydrogen atoms and equivalent isotropic thermal parameters*

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

	<i>x</i>	<i>y</i>	<i>z</i>	U_{eq}^* (\AA^2)
C(1)	0.9352 (1)	0.1488 (1)	0.9740 (2)	0.030
C(2)	0.8332 (1)	0.0981 (1)	0.9957 (3)	0.034
N(3)	0.7649 (1)	0.1676 (1)	1.0800 (2)	0.031
C(4)	0.8103 (1)	0.2137 (2)	1.2629 (2)	0.039
C(5)	0.9125 (1)	0.2646 (1)	1.2433 (2)	0.034
C(6)	0.9030 (1)	0.3552 (1)	1.1030 (3)	0.040
N(7)	0.8697 (1)	0.3258 (1)	0.8985 (2)	0.034
C(8)	0.9241 (1)	0.2381 (1)	0.8313 (2)	0.035
C(9,5')	0.9850 (1)	0.1840 (1)	1.1768 (2)	0.029
C(10)	0.6690 (1)	0.1183 (2)	1.1036 (3)	0.052
C(11)	0.8784 (2)	0.4134 (2)	0.7695 (4)	0.059
N(1')	1.0031 (1)	0.0999 (1)	1.3158 (2)	0.040
C(2')	1.1007 (1)	0.0953 (1)	1.4013 (3)	0.041
N(3')	1.1549 (1)	0.1692 (1)	1.3164 (2)	0.039
C(4')	1.0946 (1)	0.2248 (1)	1.1808 (2)	0.033
O(1)	1.1365 (1)	0.0367 (1)	1.5296 (3)	0.066
O(2)	1.1231 (1)	0.2939 (1)	1.0850 (2)	0.051

* Defined according to Hamilton (1959).

Table 4. *The positional and thermal parameters for H atoms*

	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> (\AA^2)
H(11)	0.983 (2)	0.098 (2)	0.926 (3)	1.66
H(21)	0.844 (2)	0.034 (2)	1.089 (4)	2.00
H(22)	0.795 (2)	0.074 (2)	0.865 (3)	2.00
H(41)	0.762 (2)	0.263 (2)	1.300 (4)	2.31
H(42)	0.813 (2)	0.162 (2)	1.367 (3)	2.31
H(51)	0.946 (2)	0.287 (2)	1.383 (4)	2.14
H(61)	0.972 (2)	0.390 (2)	1.120 (3)	2.08
H(62)	0.848 (2)	0.401 (2)	1.145 (4)	2.08
H(81)	0.885 (2)	0.212 (2)	0.700 (4)	1.97
H(82)	0.994 (2)	0.264 (2)	0.804 (3)	1.97
H(101)	0.621 (3)	0.174 (3)	1.148 (5)	2.18
H(102)	0.683 (2)	0.055 (2)	1.195 (4)	2.18
H(103)	0.635 (2)	0.102 (2)	0.979 (4)	2.18
H(111)	0.837 (2)	0.469 (2)	0.818 (5)	2.39
H(112)	0.838 (2)	0.398 (3)	0.626 (5)	2.39
H(113)	0.962 (2)	0.432 (3)	0.763 (5)	2.39
H(1')	0.961 (2)	0.068 (2)	1.360 (4)	2.33
H(3')	1.224 (2)	0.182 (2)	1.351 (4)	2.15

Scattering factors were taken from *International Tables for X-ray Crystallography* (1974). Computations were made with XRAY 70 (Stewart, Kundell & Baldwin, 1970) and weighting schemes were computed with PESOS (Martinez-Ripoll & Cano, 1975).

Tables 3 and 4 show parameters for the non-hydrogen and the H atoms.*

A final difference map showed no peak $> \pm 0.3 \text{ e \AA}^{-3}$.

Discussion

The atomic numbering is shown in Fig. 2. Bond lengths and angles are given in Table 5. Data for the least-squares planes through various groups of atoms appear in Table 6. Torsion angles are listed in Table 7.

* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35536 (32 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

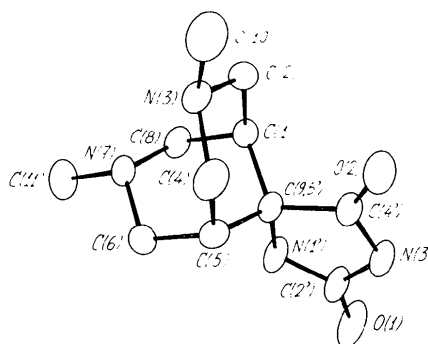


Fig. 2. Perspective view and numbering of the molecule.

Table 5. *Bond lengths (\AA) and angles ($^\circ$), with e.s.d.'s in parentheses, for the non-hydrogen atoms*

C(1)–C(2)	1.532 (2)	N(7)–C(8)	1.464 (2)
C(1)–C(8)	1.524 (2)	N(7)–C(11)	1.466 (3)
C(1)–C(9,5')	1.537 (2)	N(1')–C(2')	1.351 (2)
C(2)–N(3)	1.458 (2)	N(1')–C(9,5')	1.460 (2)
N(3)–C(4)	1.456 (2)	C(2')–N(3')	1.381 (3)
N(3)–C(10)	1.453 (2)	C(2')–O(1)	1.220 (2)
C(4)–C(5)	1.532 (2)	N(3')–C(4')	1.361 (2)
C(5)–C(6)	1.527 (2)	C(4')–C(9,5')	1.545 (2)
C(5)–C(9,5')	1.538 (2)	C(4')–O(2)	1.211 (2)
C(6)–N(7)	1.472 (2)		
C(2)–C(1)–C(8)	112.6 (2)	C(1)–C(8)–N(7)	114.2 (1)
C(2)–C(1)–C(9,5')	108.8 (1)	C(1)–C(9,5')–C(5)	105.4 (1)
C(8)–C(1)–C(9,5')	110.5 (1)	C(1)–C(9,5')–N(1')	112.6 (1)
C(1)–C(2)–N(3)	111.7 (1)	C(1)–C(9,5')–C(4')	114.4 (1)
C(2)–N(3)–C(4)	113.4 (1)	C(5)–C(9,5')–N(1')	112.3 (1)
C(2)–N(3)–C(10)	111.4 (1)	C(5)–C(9,5')–C(4')	112.3 (1)
C(4)–N(3)–C(10)	110.9 (1)	N(1')–C(9,5')–C(4')	100.2 (1)
N(3)–C(4)–C(5)	112.1 (1)	C(2')–N(1')–C(9,5')	112.7 (1)
C(4)–C(5)–C(6)	113.2 (1)	N(1')–C(2')–N(3')	107.8 (1)
C(4)–C(5)–C(9,5')	108.8 (1)	N(1')–C(2')–O(1)	127.2 (2)
C(6)–C(5)–C(9,5')	110.5 (1)	N(3')–C(2')–O(1)	125.0 (2)
C(5)–C(6)–N(7)	113.1 (1)	C(2')–N(3')–C(4')	112.0 (1)
C(7)–N(7)–C(11)	109.7 (2)	N(3')–C(4')–O(2)	125.3 (1)
C(8)–N(7)–C(6)	114.2 (1)	N(3')–C(4')–C(9,5')	107.1 (1)
C(8)–N(7)–C(11)	110.0 (2)	C(9,5')–C(4')–O(2)	127.6 (1)

Table 6. *Some least-squares planes and distances (Å) of atoms from those planes*

Atoms used in fitting the least-squares planes are denoted by asterisks. The mean e.s.d. is 0.002 Å.

$$\text{Plane I: } 0.976X + 0.142Y + 0.164Z = 12.614$$

C(1)*	0.006	C(8)*	-0.006
C(5)*	-0.006	N(7)	-0.530
C(6)*	0.006	C(9,5')	0.766

$$\text{Plane II: } -0.384X + 0.652Y - 0.654Z = -7.501$$

C(1)*	0.002	C(5)*	-0.002
C(2)*	-0.002	N(3)	0.592
C(4)*	0.002	C(9,5')	-0.786

$$\text{Plane III: } -0.276X + 0.637Y + 0.719Z = 3.985$$

N(1')*	-0.028	O(1)	0.060
C(2')*	0.019	O(2)	-0.036
N(3')*	-0.000	N(3)	0.193
C(4')*	-0.015	N(7)	0.196
C(9,5')	0.024	C(10)	0.254
		C(11)	0.230

$$\text{Plane of pseudosymmetry: } -0.221X + 0.619Y + 0.754Z = 4.897$$

N(3)*	-0.004	C(6)	1.237
N(7)*	0.003	C(8)	-1.228
C(9,5')*	0.000	N(1')	0.008
C(10)*	0.002	C(2')	0.141
C(11)*	-0.001	N(3')	0.129
C(1)	-1.223	C(4')	0.032
C(2)	-1.220	O(1)	0.246
C(4)	1.215	O(2)	-0.002
C(5)	1.223		

$$\text{Plane IV: } 0.550X + 0.716Y - 0.429Z = 4.890$$

C(1)*	0.000	C(6)	1.262
C(5)*	0.000	N(7)	1.443
C(9,5')*	0.000	C(8)	1.246
C(2)	-1.295	C(10)	-2.673
N(3)	-1.430	C(11)	2.771
C(4)	-1.291		

Table 7. *Torsion angles (°)*

N(3)-C(2)-C(1)-C(9,5')	59.0 (2)
C(4)-N(3)-C(2)-C(1)	-53.0 (2)
C(5)-C(4)-N(3)-C(2)	52.8 (2)
C(9,5)-C(5)-C(4)-N(3)	-58.4 (2)
C(1)-C(9,5')-C(5)-C(4)	62.9 (1)
C(2)-C(1)-C(9,5')-C(5)	-63.3 (1)
N(7)-C(8)-C(1)-C(9,5')	-54.5 (2)
C(1)-C(8)-N(7)-C(6)	46.2 (2)
C(5)-C(6)-N(7)-C(8)	-46.8 (2)
C(9,5')-C(5)-C(6)-N(7)	56.1 (2)
C(1)-C(9,5')-C(5)-C(6)	-61.9 (1)
C(8)-C(1)-C(9,5')-C(5)	60.8 (1)
N(3')-C(4')-C(9,5')-N(1)	-3.4 (2)
C(4')-C(9,5')-N(1')-C(2')	4.8 (2)
C(9,5')-N(1')-C(2')-N(3')	-4.5 (2)
N(1')-C(2')-N(3')-C(4')	2.0 (2)
C(2')-N(3')-C(4')-C(9,5')	1.1 (2)

Table 8. *Asymmetry parameters*

Ring I: $\Delta C_{3,5'}^{9,5'} = 1.17$; $\Delta C_{2,9,5'}^{9,5'} = 6.38$; $\Delta C_{2,5'}^{9,5'} = 14.85$
 Ring II: $\Delta C_{3,5'}^{9,5'} = 0.37$; $\Delta C_{2,9,5'}^{9,5'} = 4.71$; $\Delta C_{2,4'}^{9,5'} = 10.2$

The molecule consists of two piperidine rings with a methyl group attached to each N. The two rings are joined by a common C-C-C bridge whose central atom is the spiranic C at which the hydantoin ring is substituted.

The bicyclononane ring shows a symmetry that approximates to *m* [a mirror plane defined by C(10), N(3), C(9,5'), N(7) and C(11)]. The atomic distances from this plane are almost the same for each pseudo-symmetric pair.

The conformation of the bicyclononane system can be explained in terms of steric interactions similar to those discussed in previous compounds of this series (Florescio, Smith-Verdier & García-Blanco, 1978, 1979, and references therein).

The asymmetry parameters (Duax & Norton, 1975) are given in Table 8 which shows that the two piperidine rings have distorted chair conformations. The deviations of N(7) and C(9,5') from the mean plane through C(1), C(5), C(6) and C(8) are 0.529 and -0.765 Å, and the displacements of N(3) and C(9,5') from the mean plane through C(1), C(2), C(4) and C(5) are 0.593 and -0.786 Å, respectively (Table 6). Consequently, the C(1), C(2), N(3), C(4), C(5) and C(1), C(5), C(6), N(7), C(8) parts of the rings are more flattened than the opposite parts in both rings. The flattening of the piperidine rings is also shown in the displacements of the atoms from the plane through C(1), C(9,5'), C(5). In the ideal twin-chair conformation, the displacements of N(3) and N(7) would not differ from the displacements of C(2), C(4), C(6) and C(8), whereas in fact the displacements of N(3) and N(7), -1.430 and 1.443 Å, are larger than the displacements of C(2), C(4), C(6) and C(8), -1.295, -1.291, 1.262 and 1.246 Å.

This deformation is due to the interaction between N(3) and N(7) shown in the non-bonded distance N(3)⋯N(7) of 2.873 Å and in the C(2)-C(1)-C(8) and C(4)-C(5)-C(6) angles of 112.6 and 113.2° respectively. These values are different from those expected in a bicyclic system with an ideal chair-chair

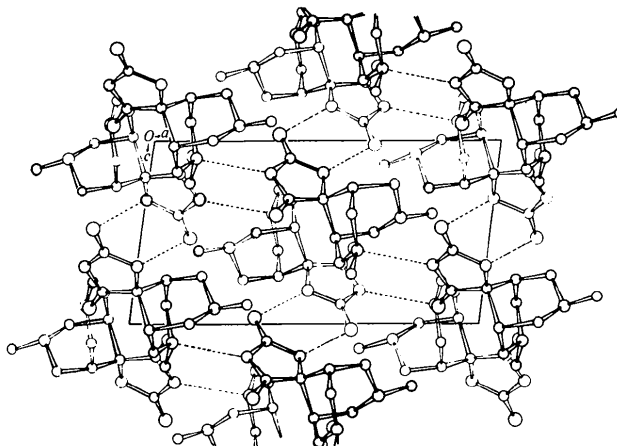
Fig. 3. Projection of the structure down *b*.

Table 9. Bond lengths (Å) and angles (°), with e.s.d.'s in parentheses, involving H atoms

C(1)–H(11)	1.01 (3)	C(8)–H(82)	1.03 (2)
C(2)–H(21)	1.06 (3)	C(10)–H(101)	1.04 (4)
C(2)–H(22)	1.02 (1)	C(10)–H(102)	1.04 (3)
C(4)–H(41)	0.97 (3)	C(10)–H(103)	0.94 (3)
C(4)–H(42)	0.98 (2)	C(11)–H(111)	0.99 (3)
C(5)–H(51)	1.05 (1)	C(11)–H(112)	1.08 (3)
C(6)–H(61)	1.01 (2)	C(11)–H(113)	1.14 (3)
C(6)–H(62)	1.02 (3)	N(1')–H(1')	0.79 (3)
C(8)–H(81)	1.04 (2)	N(3')–H(3')	0.93 (3)
C(2)–C(1)–H(11)	111 (1)	C(1)–C(8)–H(81)	108 (1)
C(8)–C(1)–H(11)	108 (1)	C(1)–C(8)–H(82)	111 (1)
C(9,5')–C(1)–H(11)	106 (1)	H(81)–C(8)–H(82)	107 (2)
C(1)–C(2)–H(21)	111 (1)	N(7)–C(8)–H(81)	109 (1)
C(1)–C(2)–H(22)	113 (1)	N(7)–C(8)–H(82)	107 (1)
H(21)–C(2)–H(22)	108 (2)	N(3)–C(10)–H(101)	107 (2)
N(3)–C(2)–H(21)	107 (1)	N(3)–C(10)–H(102)	109 (2)
N(3)–C(2)–H(22)	106 (1)	N(3)–C(10)–H(103)	109 (2)
C(5)–C(4)–H(41)	111 (2)	H(101)–C(10)–H(102)	117 (2)
C(5)–C(4)–H(42)	115 (1)	H(101)–C(10)–H(103)	101 (3)
H(41)–C(4)–H(42)	103 (2)	H(102)–C(10)–H(103)	113 (2)
N(3)–C(4)–H(41)	107 (2)	N(7)–C(11)–H(111)	106 (2)
N(3)–C(4)–H(42)	108 (1)	N(7)–C(11)–H(112)	110 (2)
C(4)–C(5)–H(51)	108 (1)	N(7)–C(11)–H(113)	110 (2)
C(6)–C(5)–H(51)	111 (1)	H(111)–C(11)–H(112)	102 (3)
C(9,5')–C(5)–H(51)	105 (1)	H(111)–C(11)–H(113)	116 (3)
C(5)–C(6)–H(61)	106 (1)	H(112)–C(11)–H(113)	112 (2)
C(5)–C(6)–H(62)	106 (2)	C(9,5')–N(1')–H(1')	126 (2)
H(61)–C(6)–H(62)	112 (2)	C(2')–N(1')–H(1')	120 (2)
N(7)–C(6)–H(61)	113 (1)	C(2')–N(3')–H(3')	124 (2)
N(7)–C(6)–H(62)	107 (1)	C(4')–N(3')–H(3')	123 (2)

Table 10. Interatomic distances (Å) and angles (°) in the hydrogen bonds

a	b	c	ab	bc	ac	$\angle abc$
N(3')	H...N(7)	$(x + \frac{1}{2}, -y + \frac{1}{2}, z + \frac{1}{2})$	0.93 (3)	1.92 (3)	2.831 (2)	166 (2)
N(1')	H...O(1)	$(-x, -y, -z + 1)$	0.80 (3)	2.10 (3)	2.877 (2)	170 (2)

conformation [the distance N(3)···N(7) would be 2.38 Å]. The hydantoin ring is practically planar. Bond lengths and angles are in good agreement with those found in all compounds of this series. Bond lengths and angles involving H atoms are given in Table 9.

The packing of the molecules in the crystal is shown in Fig. 3. N(1') and N(3') from the hydantoin ring form two donor hydrogen bonds, one with O(1) of the hydantoin group and the other with N(7) of the piperidine ring. There is an interaction between N(3') and N(3) shown by the short contact 3.053 (2) Å, but this is not a hydrogen bond since the N(3')–H(3')···N(3) angle is 114.7°. Therefore, the adamantane-like structure proposed (Fig. 1) is not present in the crystalline state.

The geometry of the hydrogen bonds is given in Table 10. Other intermolecular distances correspond to van der Waals interactions.

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