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## 2,8-Dimethyl-5,11-dipropyl-1,4,5,6,7,10,11,12-octahydroimidazo[4,5-*h*]-imidazo[4,5-*c*][1,6]diazecine Hexahydrate

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### Abstract

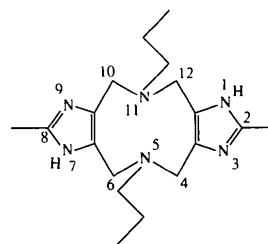
Crystals of the title compound, C<sub>18</sub>H<sub>30</sub>N<sub>6</sub>·6H<sub>2</sub>O, are composed of molecules of pronmeim (the condensation product of 2-methylimidazole, *n*-propylamine and formaldehyde) and water linked together by hydrogen bonds to form a two-dimensional network. The diazecine ring is in a chair conformation. Bond lengths and angles are within the normal ranges.

### Comment

The chemistry of imidazole is of special interest because of its wide occurrence in biological compounds, notably as part of the amino acid histidine and metabolites like histamine. Synthetic imidazole derivatives are also used as antihistamine drugs. New imidazole-containing compounds are being developed by our group in order to study their properties in relation to the role played by the imidazole group in different enzymes (Bouwman, Driessen & Reedijk, 1990). The development of simple processes for the synthesis of new imidazole derivatives is, therefore, a matter of constant research.

The Mannich reaction, which is one such powerful and simple process, is a one-step method for attaching aminomethylene groups to the imidazole ring (Stocker, Kurtz, Byron & Forsyth, 1970). The reaction of aldehydes, in particular formaldehyde, with different substrates and conditions has been used widely in organic synthesis. Some of these reactions involve coordinated amino acids (Teo, Ng & Tiekink, 1993;

Berndt, 1970), coordinated amines (Geue, Höhn, Ralph, Sargeson & Willis, 1994), aromatic rings and secondary amines (Karunakaran & Kandaswamy, 1994) and secondary amines and 2,4(5)-disubstituted imidazoles (Baumann, Summers, Hutchinson, Zubieta & Marzilli, 1984; Stocker *et al.*, 1970). We used this reaction under basic conditions to condense propylamine, formaldehyde and 2-methylimidazole. A double addition of formaldehyde on the 4 and 5 positions of imidazole and a further condensation with propylamine resulted in the title compound, pronmeim, a novel heterocyclic 10-membered hexahydrodiazecine ring with two imidazole rings fused through the bond between C4 and C5. The crystal and molecular structure of this compound (which crystallized as the hexahydrate) are described here. The results of this study were required for comparative studies with analogous compounds containing different amine moieties and their coordination complexes (Mendoza-Díaz, Driessen & Reedijk, 1994).



Pronmeim

The molecular structure of the title compound is shown in Fig. 1. The 2-methyl group and the methylene C atoms attached directly to the imidazole ring lie essentially in the plane of the imidazole ring, with deviations from the least-squares plane through the ring of 0.088 (11), 0.006 (10) and -0.033 (14) Å for C7, C8 and the 2-methyl group, respectively. The slight twist of C7 out of this plane possibly results from it being part of the diazecine ring. The angles made by the bonds C4—C7 and C5—C8 and the least-squares plane of the imidazole ring are 3.33 (14) and 0.26 (14)°, respectively, whereas the angle made by the bond between the 2-methyl group and the imidazole moiety (C2—C6) and this plane is 1.21 (14)°. The ten-membered diazecine ring has a chair-type conformation. The distance between the two centres of mass of the imidazole rings is 4.5897 Å. The angles at the nitrogen bridge in the diazecine ring sum to 334.1°, indicating a pyramidal conformation.

Crystals of the title compound consist of pronmeim and water molecules in the ratio 1:6. The water molecules form a two-dimensional network of hydrogen bonds along the crystallographic planes (100) and (010). Four of these water molecules (containing O50 and O51, but not O52) form a hydrogen-bond ring between two adjacent pronmeim molecules, shown in Fig. 2(a).

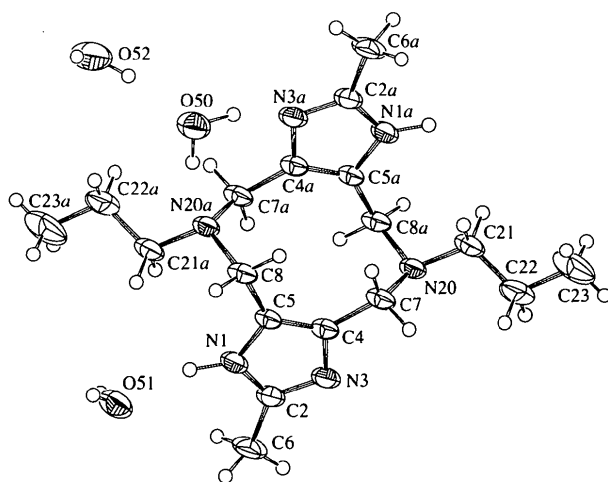


Fig. 1. *PLUTON92* (Spek, 1992) plot showing the molecular structure of the title compound with the atom labelling. Displacement ellipsoids are shown at the 50% probability level.

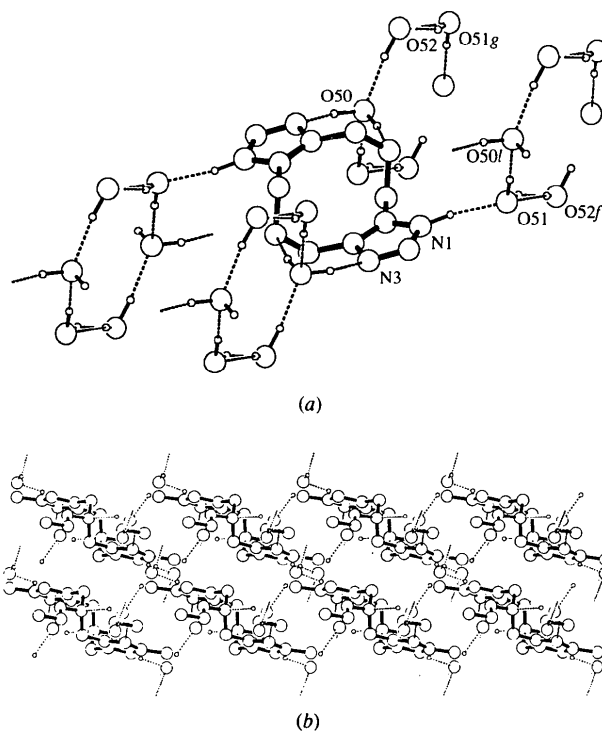


Fig. 2. *PLUTON92* (Spek, 1992) plot showing two views of the hydrogen-bond network. (a) Hydrogen-bond-ring formation between two adjacent pronmeim molecules. (b) View of the water-molecule network. Notice the formation of six-membered rings by the water molecules.

All three types of water molecules participate in the formation of the two-dimensional network, as shown in Fig. 2(b).

The enzyme ribonuclease A contains two imidazole rings (His12 and His119) which act as the acid and

base catalysts in the cleavage of ribonucleic acid. In the proposed mechanism, water must be activated by the concerted formation of a hydrogen bond with the phosphate diester (Breslow, 1991). The observed chain linkage in the present structure of pronmeim could help in the understanding of the imidazole-ring behaviour in acid–base catalysis.

## Experimental

4.10 g (0.05 mol) of 2-methylimidazole and 7.30 g (0.12 mol) of *n*-propylamine were added to 20 ml of distilled water. To this mixture, 8.6 g of a 35% formaldehyde solution (0.1 mol) was added slowly with stirring. The pH was adjusted to 11–12. The mixture was refluxed for 24 h and then stirred for another 3 days. A first microcrystalline white precipitate was filtered off and washed with cold water (yield 4.87 g, 22.2%). The remaining solution was allowed to evaporate slowly. After two weeks a second crop of a crystalline product was isolated, washed with cold water and dried in air, yielding another 4.5 g (total yield 43%). The product crystallized as colourless prisms with well developed faces.

### Crystal data

$C_{18}H_{30}N_6 \cdot 6H_2O$

$M_r = 438.57$

Triclinic

$P\bar{1}$

$a = 8.286(2) \text{ \AA}$

$b = 6.824(4) \text{ \AA}$

$c = 11.755(4) \text{ \AA}$

$\alpha = 110.90(4)^\circ$

$\beta = 92.05(2)^\circ$

$\gamma = 92.37(4)^\circ$

$V = 619.5(5) \text{ \AA}^3$

$Z = 1$

$D_x = 1.176 \text{ Mg m}^{-3}$

Mo  $K\alpha$  radiation

$\lambda = 0.71073 \text{ \AA}$

Cell parameters from 24 reflections

$\theta = 10\text{--}12^\circ$

$\mu = 0.08 \text{ mm}^{-1}$

$T = 293 \text{ K}$

Prism

$0.40 \times 0.35 \times 0.30 \text{ mm}$

Colourless

### Data collection

Enraf–Nonius CAD-4 diffractometer

$\omega/2\theta$  scans

Absorption correction: none

5404 measured reflections

5404 independent reflections

2357 observed reflections

$[I > 2\sigma(I)]$

$\theta_{\max} = 34.89^\circ$

$h = -13 \rightarrow 13$

$k = -10 \rightarrow 10$

$l = 0 \rightarrow 18$

3 standard reflections

frequency: 83.3 min

intensity decay: 13.2%

### Refinement

Refinement on  $F$

$R = 0.054$

$wR = 0.058$

$S = 2.469$

2357 reflections

199 parameters

Only coordinates of H atoms refined

Weighting scheme based on measured e.s.d.'s

$(\Delta/\sigma)_{\max} = 0.016$

$\Delta\rho_{\max} = 0.465 \text{ e \AA}^{-3}$

$\Delta\rho_{\min} = -0.566 \text{ e \AA}^{-3}$

Extinction correction: none

Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV, Tables 2.2B and 2.3.1)

Table 1. Fractional atomic coordinates and equivalent isotropic displacement parameters (Å<sup>2</sup>)
$$U_{eq} = (1/3) \sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j$$

	<i>x</i>	<i>y</i>	<i>z</i>	<i>U</i> <sub>eq</sub>
N1	0.7783 (2)	0.2679 (2)	0.3461 (1)	0.0344 (7)
C2	0.8711 (2)	0.2374 (3)	0.4337 (2)	0.0361 (9)
N3	0.7862 (2)	0.2432 (2)	0.5279 (1)	0.0360 (7)
C4	0.6290 (2)	0.2804 (3)	0.4989 (2)	0.0313 (8)
C5	0.6226 (2)	0.2965 (3)	0.3865 (2)	0.0299 (8)
C6	1.0484 (3)	0.2059 (4)	0.4248 (3)	0.051 (1)
C7	0.4962 (2)	0.2837 (3)	0.5824 (2)	0.0342 (8)
C8	0.4838 (2)	0.3345 (3)	0.3120 (2)	0.0331 (8)
N20	0.5131 (2)	0.4581 (2)	0.7019 (1)	0.0314 (7)
C21	0.3855 (2)	0.4357 (3)	0.7812 (2)	0.0388 (9)
C22	0.4140 (3)	0.2696 (4)	0.8366 (2)	0.054 (1)
C23	0.2809 (5)	0.2510 (5)	0.9159 (3)	0.077 (2)
O50	0.8313 (2)	0.3740 (2)	0.7795 (1)	0.0498 (8)
O51	1.0318 (2)	0.7434 (3)	0.8535 (2)	0.0515 (8)
O52	0.8269 (3)	0.0874 (4)	0.9068 (2)	0.068 (1)

Table 2. Selected geometric parameters (Å, °)

N1—C2	1.343 (3)	O51—H511	0.79 (3)
N1—C5	1.388 (2)	O51—H512	0.96 (3)
N1—H11	1.02 (3)	O52—H521	1.00 (3)
C2—N3	1.323 (3)	O52—H522	0.57 (3)
C2—C6	1.495 (3)	O50...N3	2.774 (2)
N3—C4	1.391 (2)	O50...N20	2.905 (2)
C4—C5	1.363 (3)	O50...O51	2.803 (3)
C4—C7	1.496 (3)	O50...O52	2.856 (4)
C5—C8	1.507 (3)	O51...O50	2.803 (3)
C7—N20	1.480 (2)	O51...O52	2.854 (3)
C8—N20 <sup>i</sup>	1.481 (3)	O51...N1	2.851 (3)
N20—C21	1.473 (3)	O51...O52	2.824 (3)
C21—C22	1.517 (4)	O52...O50	2.856 (4)
C22—C23	1.499 (5)	O52...O51	2.854 (3)
O50—H501	1.04 (3)	O52...O51	2.824 (3)
O50—H502	0.93 (3)		
C2—N1—C5	107.6 (2)	N1—C5—C8	123.0 (2)
N1—C2—N3	111.3 (2)	C4—C5—C8	131.2 (2)
N1—C2—C6	123.4 (2)	C4—C7—N20	114.8 (2)
N3—C2—C6	125.2 (2)	C5—C8—N20 <sup>i</sup>	116.6 (1)
C2—N3—C4	106.0 (2)	C7—N20—C21	110.4 (1)
N3—C4—C5	109.2 (2)	C7—N20—C8 <sup>i</sup>	111.6 (2)
N3—C4—C7	120.7 (2)	C21—N20—C8 <sup>i</sup>	112.1 (2)
C5—C4—C7	129.9 (2)	N20—C21—C22	114.1 (2)
N1—C5—C4	105.9 (2)	C21—C22—C23	112.3 (2)

Symmetry code: (i) 1 - *x*, 1 - *y*, 1 - *z*.

All H atoms were located in difference Fourier maps and subsequently refined.

Data collection: *CAD-4 Software* (Enraf-Nonius, 1989). Cell refinement: *CAD-4 Software*. Data reduction: *Xtal AD-DREF SORTREF* (Hall, Flack & Stewart, 1992). Program(s) used to solve structure: *Xtal*. Program(s) used to refine structure: *Xtal CRYLSQ*. Molecular graphics: *PLATON93* (Spek, 1993), *PLUTON92* (Spek, 1992). Software used to prepare material for publication: *Xtal BONDLA CIFIO*.

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates, complete geometry and contact distances have been deposited with the IUCr (Reference: NS1004). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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## 3-(6-Methoxy-2-benzimidazolyl)benzothiazolin-2-imine

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## Abstract

The title compound, C<sub>15</sub>H<sub>12</sub>N<sub>4</sub>OS, was unexpectedly isolated from the reaction of *N*-[2-(6-methoxy-1*H*-benzimidazol-2-ylthio)phenyl]thiourea with dicyclohexylcarbodiimide. The compound showed considerable anti-cancer activity *in vitro*. The benzimidazole and iminobenzothiazoline rings are coplanar *via* hydrogen bonding between the N atom of the imino group of benzothiazole and the H—N bond of benzimidazole. The whole molecule has a planar structure.

## Comment

During our studies towards the synthesis of 1,3,5-thiadiazepine for potential biological applications (Vec-