

Crystal Structure of Minoxidil

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The title compound, C₉H₁₅N₅O, is an antialopecia agent. The crystal belongs to space group *P*2₁ with cell dimensions *a* = 9.3799(5), *b* = 8.3319(4), *c* = 12.9984(7) Å and β = 90.191(3)°. The final *R* value is 0.092. There are two crystallographically independent molecules in an asymmetric unit. They adopt significantly different conformations. The hybridization states of the nitrogen atoms in piperidine rings are markedly different in these molecules.

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Minoxidil (6-(1-piperidiny)-2,4-pyrimidinediamine 3-oxide) has proven to be efficacious in patients with the most severe and drug-resistant forms of hypertension.¹ Minoxidil increases blood flow to the skin, skeletal muscle, gastrointestinal tract, and heart more than the central nervous system. Minoxidil was found to be associated with hypertrichosis, and this side effect is exploited in treating androgenetic alopecia.¹ Minoxidil enhances follicular size, resulting in thicker hair shafts, and stimulates and prolongs the anagen phase of the hair cycle, resulting in a longer and increased number of hairs. The exact mechanism of action of minoxidil is still not known. An X-ray analysis of minoxidil was undertaken to disclose its inherent three-dimensional structure so as to understand the molecular mechanism of the drug action. The chemical structure of minoxidil is shown in Fig. 1.

Single crystals were grown from an ethanol solution. It was extremely difficult to grow crystals of sufficient size, and most of the obtained crystals were twinned. A colorless crystal with a size of 0.15 × 0.05 × 0.05 mm was mounted on a glass fiber and used for data collection.

The structure was solved by direct methods and non-H atoms were refined by a full-matrix least squares method with anisotropic temperature factors. All H-atoms were found from difference Fourier maps and were refined with isotropic temperature factors. The crystal and experimental data are listed in Table 1. Atomic parameters of non-H atoms are listed in Table 2.

The molecular structure drawn by ORTEP-III⁴ is shown in Fig. 2. Selected bond lengths, bond angles and torsion angles are listed in Table 3. The bond lengths and bond angles are all

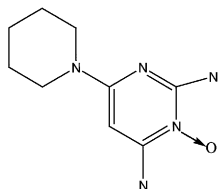


Fig. 1 Chemical structure of minoxidil.

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within the expected ranges.

There are two crystallographically independent molecules in an asymmetric unit. The two molecules adopt significantly different conformations, as described below. Two piperidine rings adopt chair conformations. It is noteworthy that the nitrogen atoms in both chair conformations are markedly different in the hybridization state. The bond lengths and angles around the nitrogen atoms indicate that the nitrogen atoms in molecules I and II take sp³ and sp² hybridization states, respectively. Both nitrogen atoms are not involved in hydrogen bonds. The chair conformation of molecule I is significantly flattened compared with that of molecule II, as suggested by the torsion angles in the rings. The pyrimidine rings in both molecules are essentially planar. The torsion angles of N101-C104-N105-C105 and N201-C204-N205-C205 being 34.6(9) and 0(1)°, respectively, indicate that the orientations of the piperidine and pyrimidine rings with respect to the C104-N105 and C204-N205 bonds are markedly different. The bond lengths and angles in the molecules are within the expected ranges. The exocyclic bond angles around the C101-N103 and C102-N104 bonds are highly asymmetric. The corresponding angles in molecule II are also asymmetrical. The exocyclic

Table 1 Crystal and experimental data

Formula: C ₉ H ₁₅ N ₅ O
Formula Weight = 209.25
Crystal system: monoclinic
Space group: <i>P</i> 2 ₁ <i>Z</i> = 4
<i>a</i> = 9.3799(5) Å
<i>b</i> = 8.3319(4) β = 90.191(3)°
<i>c</i> = 12.9984(7)
<i>V</i> = 1015.07(9) Å ³
<i>D</i> _x = 1.369 g/cm ³
No. of observations (<i>I</i> > 2.00σ(<i>I</i>)) = 1685
θ_{\max} = 68.22° with Cu K α
Residuals: <i>R</i> (<i>I</i> > 2.00σ(<i>I</i>)) = 0.092
(Δ σ) _{max} = 0.003
($\Delta\rho$) _{max} = 0.45 e/Å ³
($\Delta\rho$) _{min} = -0.53 e/Å ³
Measurement: Rigaku RAXIS-RAPID
Program system: CrystalStructure ¹
Structure determination: SIR92 ²
Refinement: full-matrix

Table 2 Atomic coordinates and equivalent isotropic thermal parameters (B_{eq})

atom	x	y	z	B_{eq}
molecule I of minoxidil				
O(101)	0.9597(5)	0.8849(9)	0.8686(3)	4.2(1)
N(101)	0.8254(6)	0.4892(8)	0.9172(4)	4.1(1)
N(102)	0.8757(6)	0.7525(7)	0.8606(4)	3.5(1)
N(103)	1.0077(7)	0.6384(9)	0.9896(5)	4.7(1)
N(104)	0.7365(7)	0.8877(9)	0.7450(5)	4.6(1)
N(105)	0.6468(7)	0.3394(8)	0.8414(5)	4.8(1)
C(101)	0.9012(7)	0.6214(8)	0.9229(5)	3.7(1)
C(102)	0.7624(7)	0.7517(9)	0.7954(4)	3.9(1)
C(103)	0.6823(8)	0.6126(8)	0.7861(5)	3.9(1)
C(104)	0.7160(7)	0.4811(8)	0.8483(5)	3.8(1)
C(105)	0.6283(9)	0.2412(9)	0.9352(7)	5.2(2)
C(106)	0.502(1)	0.294(1)	0.9940(6)	5.2(2)
C(107)	0.3700(9)	0.289(1)	0.9295(7)	6.1(2)
C(108)	0.3874(9)	0.378(1)	0.8272(8)	6.2(2)
C(109)	0.5186(9)	0.322(1)	0.7734(6)	5.7(2)
molecule II of minoxidil				
O(201)	0.4686(5)	0.927(1)	0.6438(4)	4.5(1)
N(201)	0.3043(7)	0.5606(8)	0.5539(4)	4.5(1)
N(202)	0.3754(6)	0.8022(7)	0.6369(4)	3.8(1)
N(203)	0.5012(8)	0.700(1)	0.5023(6)	5.2(1)
N(204)	0.2600(8)	0.9023(9)	0.7786(5)	5.3(1)
N(205)	0.0985(8)	0.4305(9)	0.6023(6)	5.6(2)
C(201)	0.3917(8)	0.6848(9)	0.5636(5)	4.0(1)
C(202)	0.2655(7)	0.7894(9)	0.7045(5)	3.9(1)
C(203)	0.1678(7)	0.6680(9)	0.6932(5)	4.1(1)
C(204)	0.1885(8)	0.5527(9)	0.6173(5)	4.1(1)
C(205)	0.1166(8)	0.3087(9)	0.5230(5)	4.5(1)
C(206)	0.138(1)	0.145(1)	0.5731(6)	5.2(2)
C(207)	0.0072(9)	0.107(1)	0.6406(6)	5.2(2)
C(208)	-0.0086(9)	0.238(1)	0.7207(6)	5.4(2)
C(209)	-0.027(1)	0.398(1)	0.6675(8)	6.4(2)

$$B_{eq} = 8/3 \pi^2 (U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\gamma + 2U_{13}(aa^*cc^*)\cos\beta + 2U_{23}(bb^*cc^*)\cos\alpha)$$

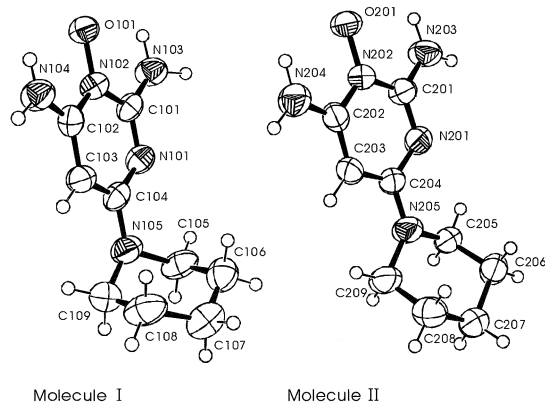


Fig. 2 Molecular structures of minoxidil along with the labeling atoms. Thermal ellipsoids of non-H atoms are drawn at the 50% probability level.

bond angles facing the O101 and O201 atoms are significantly smaller than their counterparts. There are six intramolecular and four intermolecular hydrogen bonds. They are listed in Table 4. It is notable that the intramolecular C-H...N hydrogen bond in each molecule seems to play a key role to determine the relative orientation of the piperidine ring with respect to the pyridine ring.

Acknowledgements

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Table 3 Selected bond lengths (Å), bond angles (°) and torsion angles (°)

molecule I of minoxidil			molecule II of minoxidil				
O(101)	N(102)	1.359(9)	O(201)	N(202)	1.363(9)		
N(101)	C(101)	1.313(9)	N(201)	C(201)	1.331(1)		
N(101)	C(104)	1.361(9)	N(201)	C(204)	1.366(9)		
N(102)	C(101)	1.380(9)	N(202)	C(201)	1.373(9)		
N(102)	C(102)	1.357(8)	N(202)	C(202)	1.361(8)		
N(103)	C(101)	1.328(9)	N(203)	C(201)	1.31(1)		
N(104)	C(102)	1.33(1)	N(204)	C(202)	1.35(1)		
N(105)	C(104)	1.35(1)	N(205)	C(204)	1.34(1)		
N(105)	C(105)	1.48(1)	N(205)	C(205)	1.46(1)		
N(105)	C(109)	1.50(1)	N(205)	C(209)	1.48(1)		
C(101)	N(101)	C(104)	119.0(6)	C(201)	N(201)	C(204)	118.2(6)
C(101)	N(102)	C(102)	119.7(6)	C(201)	N(202)	C(202)	118.6(6)
C(101)	N(102)	O(101)	119.5(5)	C(201)	N(202)	O(201)	121.1(5)
C(102)	N(102)	O(101)	120.3(6)	C(202)	N(202)	O(201)	120.3(6)
C(104)	N(105)	C(105)	119.2(6)	C(204)	N(205)	C(205)	124.0(7)
C(104)	N(105)	C(109)	120.7(7)	C(204)	N(205)	C(209)	124.0(7)
C(105)	N(105)	C(109)	109.6(6)	C(205)	N(205)	C(209)	112.0(7)
N(101)	C(101)	N(102)	122.6(6)	N(201)	C(201)	N(202)	123.5(6)
N(101)	C(101)	N(103)	122.2(6)	N(201)	C(201)	N(203)	120.3(7)
N(102)	C(101)	N(103)	115.2(6)	N(202)	C(201)	N(203)	116.2(7)
C(103)	C(102)	N(102)	118.8(6)	C(203)	C(202)	N(202)	119.7(6)
C(103)	C(102)	N(104)	124.8(6)	C(203)	C(202)	N(204)	124.4(6)
N(102)	C(102)	N(104)	116.4(7)	N(202)	C(202)	N(204)	115.9(7)
N(101)	C(104)	N(105)	116.6(6)	N(201)	C(204)	N(205)	116.8(6)
N(101)	C(104)	C(103)	120.7(6)	N(201)	C(204)	C(203)	120.5(6)
N(105)	C(104)	C(103)	122.7(6)	N(205)	C(204)	C(203)	122.7(7)
C(106)	C(105)	N(105)	110.9(7)	C(206)	C(205)	N(205)	109.7(6)
N(105)	C(109)	C(108)	110.7(7)	N(205)	C(209)	C(208)	109.2(8)
molecule I of minoxidil			molecule II of minoxidil				
C(104)N(101)C(101)N(103)	178.8(6)	C(204)N(201)C(201)N(203)	-177.7(7)				
C(101)N(101)C(104)N(105)	176.3(6)	C(201)N(201)C(204)N(205)	176.8(6)				
O(101)N(102)C(101)N(101)	-178.7(6)	O(201)N(202)C(201)N(201)	179(5)(8)				
O(101)N(102)C(101)N(103)	1.7(8)	O(201)N(202)C(201)N(203)	0.3(9)				
C(102)N(102)C(101)N(103)	-175.0(6)	C(202)N(202)C(201)N(203)	-178.2(6)				
O(101)N(102)C(102)N(104)	-2.8(9)	O(201)N(202)C(202)N(204)	-2.5(9)				
O(101)N(102)C(102)C(103)	177.5(6)	O(201)N(202)C(202)C(203)	176.4(6)				
C(101)N(102)C(102)N(104)	173.8(6)	C(201)N(202)C(202)N(204)	176.0(6)				
C(105)N(105)C(104)N(101)	34.6(9)	C(205)N(205)C(204)N(201)	0(1)				
C(105)N(105)C(104)C(103)	-147.6(7)	C(205)N(205)C(204)C(203)	179.5(7)				
C(109)N(105)C(104)N(101)	175.7(6)	C(209)N(205)C(204)N(201)	176.3(7)				
C(109)N(105)C(104)C(103)	-6(1)	C(209)N(205)C(204)C(203)	-3(1)				
C(104)N(105)C(105)C(106)	84.2(9)	C(204)N(205)C(205)C(206)	116.6(8)				
C(109)N(105)C(105)C(106)	-60.8(8)	C(209)N(205)C(205)C(206)	-60.6(8)				
C(104)N(105)C(109)C(108)	-83.7(9)	C(204)N(205)C(209)C(208)	-116.6(9)				
C(105)N(105)C(109)C(108)	60.7(9)	C(205)N(205)C(209)C(208)	60.6(9)				
N(104)C(102)C(103)C(104)	-176.1(6)	N(204)C(202)C(203)C(204)	-176.5(7)				
C(102)C(103)C(104)N(105)	-177.5(6)	C(202)C(203)C(204)N(205)	179.5(7)				
N(105)C(105)C(106)C(107)	56(1)	N(205)C(205)C(206)C(207)	58.7(8)				
C(105)C(106)C(107)C(108)	-51(1)	C(205)C(206)C(207)C(208)	-58.4(9)				
C(106)C(107)C(108)C(109)	50(1)	C(206)C(207)C(208)C(209)	59.1(9)				
C(107)C(108)C(109)N(105)	-55(1)	C(207)C(208)C(209)N(205)	-59.4(9)				

Table 4 Hydrogen bonds. D and A denote hydrogen donor and acceptor, respectively

D-H...A	D-H(Å)	H...A(Å)	D...A(Å)	∠ D-H...A(°)
N(103)-H(2)...O(101) ⁱⁱ	1.1(1)	1.9(2)	2.818(9)	149(11)
N(103)-H(3)...O(101)	0.95(6)	2.16(5)	2.62(1)	109(4)
N(104)-H(4)...O(101)	0.82(8)	2.28(8)	2.634(8)	106(7)
N(104)-H(5)...O(201)	0.950(9)	1.934(8)	2.851(8)	161.6(7)
N(203)-H(17)...O(201) ⁱⁱⁱ	0.95(1)	2.05(1)	2.98(1)	166.5(9)
N(203)-H(18)...O(201)	0.95(1)	2.25(1)	2.66(1)	104.5(7)
N(204)-H(19)...O(201)	0.95(1)	2.279(9)	2.638(9)	101.5(7)
N(204)-H(20)...O(101) ⁱⁱⁱ	0.95(1)	2.188(9)	3.057(9)	151.6(7)
C(105)-H(6)...N(101)	0.95(1)	2.41(1)	2.78(1)	103.0(8)
C(205)-H(21)...N(201)	0.95(1)	2.34(1)	2.77(1)	106.6(7)

Symmetry code: (i) $(2-x, -1/2+y, 2-z)$; (ii) $(-x, -1/2+y, 1-z)$; (iii) $(-1+x, y, z)$

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