Synthesis and Crystal Structure of 3,5-Dicyano-2,6-dimethyl-4-phenyl-1,4-dihydropyridine

Madegowda MAHENDRA,* Beeranahally H. DORESWAMY,* Priti ADLAKHA,** Kena RAVAL,** Bharat VARU,** Anamik SHAH,** Mandayam A. SRIDHAR,* and Javaregowda. S. PRASAD*†

*Department of Studies in Physics, University of Mysore, Manasagangotri, Mysore 570 006, India

**Department of Studies in Chemistry, Saurashtra University, Rajkot, India

The title compound was synthesized by the Hantzsch method and characterized by the X-ray diffraction method. It crystallizes in monoclinic space group $P2_1/c$ with cell parameters $a = 8.722(7)\text{\AA}$, $b = 11.420(1)\text{\AA}$, $c = 13.307(1)\text{\AA}$ and $Z = 4$. The structure has N-H...N type intermolecular hydrogen bonds and exhibits a flattened boat conformation.

(Received July 7, 2003; Accepted August 25, 2003; Published on Web November 11, 2003)

In the last decade, synthetic studies on 1,4-dihydropyridine derivatives of Hantzsch-type¹ have been carried out in many research institutes all over the world because of their attractive biological activities. Dihydropyridine drug molecules, such as nifedipine, nicardipine, amlodipine and others, are clinically effective cardiovascular agents for the treatment of hypertension and have been intensively studied to elucidate the molecular requirements for their attractive calcium antagonists.^{2,3} In our earlier work, we have demonstrated that the Dihydropyridines (DHPs) are well known Ca^{2+} channel blockers and Multi Drug Resistant (MDR) reversal agents in tumor cells.⁴ They also possess other chemotherapeutic activity. The dicyano DHPs having cyanogroups at 3 and 5 position are reported in literature and various symmetric and unsymmetric moieties have been reported.⁵

The present work, reports synthesis and crystal structure of 3,5-dicyano-2,6-dimethyl-4-phenyl-1,4-dihydropyridine (AKPKX-1). The title compound is synthesized as per Scheme

Fig. 1 Scheme.

(Fig. 1) by the Hantzsch method.¹ A mixture of benzaldehyde (0.01 mol) and 3-aminocrotonitrile (0.02 mol) in acetic acid was refluxed on an oil bath for 12 – 15 h. The reaction was monitored by TLC. The reaction mixture was allowed to cool and the solid product that separated was filtered and recrystallized from methanol. Yield 70%, M.P 202°C.

The pure, single spot (on TLC) compound was taken in methanol (minimum quantity required) and heated with stirring, till it dissolved. A pinch of charcoal was added for decolorizing. The solution was then heated to boiling and immediately filtered while hot in a corkable 50 ml conical flask using Whatman filter paper. The flask was corked and kept for 2 days. The crystals grew due to thin layer evaporation. They were collected and washed with chilled methanol. The single crystals obtained were transparent with rectangular-shaped morphology. The constitution of 3,5-dicyano-2,6-dimethyl-4-phenyl-1,4-dihydropyridine was supported by IR, NMR and mass spectral studies.

Table 1 Crystal and experimental data

Formula	$\text{C}_{15}\text{H}_{13}\text{N}_3$
Formula weight	235.28
Crystal system	monoclinic
Space group	$P2_1/c$, $Z = 4$
a	8.722(7) Å
b	11.420(1) Å
c	13.307(1) Å
β	104.101(5)°
V	1285.5(2) Å ³
D_x	1.210 Mg/m ³
$2\theta_{\text{max}}$	64.8° with Mo $\text{K}\alpha$
R	0.0625
$(\Delta\rho)_{\text{max}}$	0.000
$(\Delta\rho)_{\text{max}}$	0.373 e Å ⁻³
$(\Delta\rho)_{\text{min}}$	-0.330 e Å ⁻³
Measurement	DipLabo Kappa
Program system	Denzo
Structure determination	SHELXS-97
Refinement	fullmatrix: SHELXL-97

† To whom correspondence should be addressed.
E-mail: jsp@uomphys.net

Table 2 Atomic coordinates and equivalent temperature factors ($\text{\AA}^2$)

Atom	x	y	z	U_{eq}
N13	0.8655(2)	0.78752(14)	0.02215(12)	0.0679(4)
C7	0.8071(2)	0.97909(15)	-0.12403(14)	0.0598(4)
C8	0.7615(2)	0.97578(15)	-0.02075(14)	0.0604(4)
C14	0.9281(2)	0.78180(16)	-0.06265(14)	0.0621(5)
C6	0.6639(2)	0.98761(14)	-0.21567(13)	0.0561(4)
C11	0.7856(2)	0.88537(16)	0.04464(14)	0.0617(5)
C1	0.6409(3)	1.08230(16)	-0.28316(16)	0.0689(5)
C16	0.9061(2)	0.87090(16)	-0.13110(15)	0.0612(4)
C5	0.5531(2)	0.89846(16)	-0.23507(15)	0.0658(5)
C9	0.6853(2)	1.07891(18)	0.00436(15)	0.0691(5)
C17	0.9700(2)	0.86490(18)	-0.21969(16)	0.0699(5)
C12	0.7358(3)	0.8798(2)	0.14394(16)	0.0783(6)
C2	0.5119(3)	1.08631(19)	-0.36767(16)	0.0794(6)
C15	1.0193(3)	0.67317(19)	-0.07043(17)	0.0774(6)
C4	0.4248(2)	0.90351(19)	-0.31988(17)	0.0766(6)
C3	0.4045(3)	0.9969(2)	-0.38603(17)	0.0790(6)
N18	1.0157(2)	0.8649(2)	-0.29337(16)	0.0930(6)
N10	0.6271(3)	1.16323(18)	0.02184(17)	0.0923(6)

$$U_{eq} = (1/3)\sum_i \sum_j U_{ij}(a_i^* a_j^*)(a_i \cdot a_j)$$

Table 3 Selected bond lengths ($\text{\AA}$) and angles ($^\circ$)

N13-C14	1.370(3)	N13-C11	1.387(2)
C11-C12	1.490(3)	C7-C6	1.521(3)
C7-C8	1.522(2)	C16-C17	1.423(3)
C7-C16	1.523(2)	C5-C4	1.383(3)
C8-C11	1.333(3)	C9-N10	1.139(3)
C8-C9	1.431(3)	C17-N18	1.145(3)
C14-C16	1.348(2)	C14-C15	1.491(3)
C14-N13-C11	122.5(2)	C8-C11-N13	119.4(2)
C6-C7-C8	112.4(1)	C8-C11-C12	125.3(2)
C6-C7-C16	111.7(2)	N13-C11-C12	115.3(2)
C8-C7-C16	108.2(1)	C2-C1-C6	120.8(2)
C11-C8-C9	119.6(2)	C14-C16-C17	120.2(2)
C11-C8-C7	125.1(2)	C14-C16-C7	124.1(2)
C9-C8-C7	115.4(2)	C17-C16-C7	115.6(2)
C16-C14-N13	120.1(2)	C6-C5-C4	120.7(2)
C16-C14-C15	124.7(2)	N10-C9-C8	177.5(2)
N13-C14-C15	115.1(2)	N18-C17-C16	176.2(2)

A single crystal of AKPKX-1 of dimensions $0.2 \times 0.3 \times 0.2$ mm was chosen for X-ray diffraction studies. The measurements were made on a DIPLabo Kappa Imaging Plate system with graphite monochromated radiation ($\text{Mo K}\alpha$). Thirty six frames of data were collected by using the oscillation method. Successive frames were scanned in steps of $5^\circ/\text{min}$ with an oscillation range of 5° for an exposure of 400 s/frame. Image processing and data reduction were done by using Denzo.⁶ All the frames could be indexed with monoclinic primitive lattice. The structure was solved by direct methods and refined by full-matrix least squares methods with anisotropic temperature factors for the non-H atoms. All H atoms were placed at chemically acceptable positions and were refined with isotropic temperature factors. The final coordinates and equivalent thermal parameters of non-H atoms are listed in Table 2. Table 3 gives selected bond distances and bond angles; they agree with their standard values. Figure 2 represents the ORTEP diagram of the molecule with thermal ellipsoids at 50% probability.

Both the phenyl ring and the DHP ring are independently planar with a maximum deviation of $0.055 \text{ \AA}$ for C7, and are almost perpendicular to each other. The dihedral angle found between them is $87.64(1)^\circ$. The structure of AKPKX-1 has intermolecular hydrogen bonds of the type N-H...N. The

Fig. 2 ORTEP of the molecule at 50% probability.

intermolecular distance between atoms is as follows: N13-H13...N18 has length $3.034(3) \text{ \AA}$ and an angle of 147° , with symmetry code $(x, 3/2 - y, 1/2 + z)$. The molecular packing exhibits a linear chain structure (when viewed down b axis).

The value of the torsion angle C5-C6-C7-C16 *i.e.*, $59.1(2)^\circ$ determines the conformation around the inter-ring bond. The closer this angle is to 60.0° , the closer the aryl group comes to bisecting the DHP ring. The other structure aspect characteristic of AKPKX-1 is the conformation of cyano groups. Each cyano group can be oriented in synperiplanar (*cis*) or in antiperiplanar (*trans*) conformation with respect to the adjacent C=C of the 1,4-DHP ring. The DHP ring adopts a flattened boat conformation. The crystal structure shown that the substitutions of 2,6-dimethyl and electron-withdrawing 3,5-dicyano groups in dihydropyridine ring may have an opposite effect on calcium channels, such as agonist and antagonist activity.^[2,3] The activity studies on this compound are underway.

Acknowledgements

The authors would like to express their thanks to DST, Government of India, for financial assistance under the project SP/I2/FOO/93.

References

1. F. Bosser, H. Beyer, and E. Wehinger, *Angew. Chem. Int. Edn. Engl.*, **1981**, 20, 762.
2. F. R. Buhler and W. Kiowski, *J. Hypertens.*, **1987**, S3, 5.
3. J. L. Reid, P. A. Meredith, and F. Pasanisi, *J. Cardiovasc. Pharmacol.*, **1985**, S18, 7.
4. A. Shah, M. Kawase, H. Grevaria, N. Motohashi, H. Sakagami, A. Varga, and J. Molnair, *J. Biorg. Med. Chem.*, **2002**, 10, 1051.
5. P. Cozzi, G. Briatico, D. Giudici, A. Rossi, and E. D. Salle, *Med. Chem. Res.*, **1996**, 6:9, 611.
6. Z. Otwinowski and W. Minor, "Processing of X-ray Diffraction Data Collected in Oscillation Mode", *Methods Enzymol.*, 276: Macromolecular Crystallography, part A, **1997**, 307-326, ed. C. W. Carter, Jr. and R. M. Sweet, Academic Press.