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Crystal and molecular structure of 2,6-dimethyl-3-acetyl-5-carbomethoxy-4-(4′-methoxyphenyl)-1,4-dihydropyridine

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2,6-Dimethyl-3-acetyl-5-carbomethoxy-4-(4′-methoxyphenyl)-1,4-dihydropyridine has been synthesized and characterized by X-ray diffraction analysis. The compound crystallizes in the monoclinic space group $P2_1/c$ with cell parameters $a = 16.085(2)$ Å, $b = 12.332(3)$ Å, $c = 8.479(4)$ Å, $\beta = 99.23(8)^\circ$, $Z = 4$. The structure exhibits both intra and intermolecular hydrogen bonds. The structure adopts a flat boat conformation in the dihydropyridine ring.

KEY WORDS: 1,4-Dihydropyridine derivatives; crystal structure.

Introduction

In recent years, some 1,4-dihydropyridine derivatives have been synthesized and developed as calcium antagonists which inhibit smooth and cardiac muscle contractions by blocking the influx of Ca^{2+} through calcium channels.[1–5] Some of these are currently being used as antihypertensive and antianginal drugs (e.g. Nifedipine, Nitrendipine).

The structure–activity relationship of 1,4-dihydropyridines(1,4-DHP) has been extensively studied, which revealed that the aryl group in the C4 position, an unsubstituted nitrogen, 2,6-dimethyl groups, and an electron-withdrawing group in the C3 and C5 positions of the dihydropyridine ring are necessary for activity.[6–8]

The conformation of the substituents at C3 and C5 and the resultant hydrogen bonding pattern play a major role and have been correlated with the calcium antagonist effect.[9–13] In view of the importance of the unsymmetrical nature at the C3 and C5 positions, the present compound was synthesized as per Scheme 1 and characterized by the X-ray diffraction method.

Other dihydropyridines were also investigated recently by our working group for multidrug resistance (MDR) of cancer cells and have often been correlated with the overexpression of *p*-glycoprotein(pgp). The XRD details were also studied earlier.[14–19]

Experimental

Preparation of 2,6-dimethyl-3-acetyl-5-carbomethoxy-4-(4′-methoxyphenyl)-1,4-dihydropyridine

A solution of 4-methoxybenzaldehyde (0.01 M), acetylacetone (0.01 M), methyl-3-

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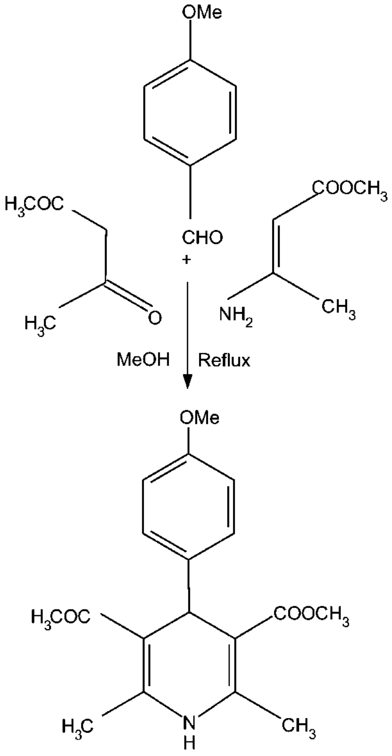

Scheme 1

aminocrotonate (0.01 M), and 2–3 drops of piperidine was formed in 20 ml of methanol and the mixture was refluxed for 18–20 h. The separated solid was collected by suction and purified by column chromatography (silica gel 60–120 mesh; ethyl acetate/hexane, 3:7). The product was recrystallized from ethyl acetate. The yield was 60%, with M.P. 188°C. [Calc.: C, 68.57; H, 6.66; N, 4.44; Found: C, 68.20; H, 6.13; N, 4.14]

Method of crystallisation

The compound (2 g) was dissolved in 25 ml of ethyl acetate. The charcoal (2 g) was added and heated on a water bath for 10 min. The solution was filtered while hot through Whatmann 42 filter paper. The solution was kept, slightly opened, in a stoppered conical flask for 72 h. The crystal was grown by thin film evaporation.

Crystal structure determination

A single crystal with appropriate dimensions of $0.2 \times 0.3 \times 0.2$ mm^3 was chosen for X-ray diffraction studies. The measurements were made on a DIPLabo Imaging Plate system with graphite monochromated radiation (Mo K_α). The crystal to detector distance was fixed at 120 mm, with a detector area of 440×241 mm^2. Thirty-six frames of data were collected by the oscillation method. Successive frames were scanned in steps of 5°/min, with an oscillation range of 5°. Image processing and data reduction were done by using Denzo.[20] All the frames could be indexed with monoclinic primitive lattice. No absorption correction was applied. The structure was solved by direct methods using SHELXS-97.[21] All the non-hydrogen atoms were revealed in the first map itself. Least-squares refinement using SHELXL-97[22] with isotropic temperature factors for all the non-hydrogen atoms converged the residual $R1$ to 0.1531. Subsequent refinements were carried out with anisotropic thermal parameters for non-hydrogen atoms and isotropic temperature factors for the hydrogen atoms which were placed at chemically acceptable positions. After eight cycles of refinement the residuals finally converged to 0.0678. The highest peak and the deepest hole in the final difference map are 0.277 and −0.282 e./Å^3 respectively. The details of crystal data and refinement are given in Table 1.

Results and discussion

The bond lengths and angles of all the non-hydrogen atoms are tabulated in Table 2; they agree with their standard values. Selected torsion angles are listed in Table 3. Figure 1 represents the ORTEP[23] diagram of the molecule with thermal ellipsoids at 50% probability. Both the phenyl and 1,4-DHP rings are independently approximately planar. The dihedral angle between them is 88.7(2)° and indicates that the rings are nearly perpendicular to each other. The 1,4-DHP ring in the structure has a flat boat conformation,

Table 1. Experimental crystallographic data

Empirical formula	$C_{18}H_{21}N_1O_4$
Formula weight	315.36
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Cell dimensions	$a = 16.085(2)$ Å
	$b = 12.332(3)$ Å
	$c = 8.479(4)$ Å
	$\beta = 99.23(8)^\circ$
Volume	1660.1(8) $Å^3$
Z	4
Density(calculated)	1.262 mg/m^3
Absorption coefficient	0.089 mm^{-1}
F_{000}	672
Crystal size	$0.2 \times 0.3 \times 0.2$ mm^3
Index ranges	$-16 \leq h \leq 16$
	$-12 \leq k \leq 12$
	$-8 \leq l \leq 8$
Reflections collected	2539
Independent reflections	1637 [$R(\text{int}) = 0.0318$]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1637/0/209
Goodness-of-fit on F^2	1.143
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0678$
R indices (all data)	$R1 = 0.0783$
Largest diff. peak and hole	0.277 and −0.282 e/$Å^3$
Deposition number	CCDC 226571

Table 2. Bond lengths (Å) and bond angles (°)

Atoms	Length	Atoms	Length
N1—C6	1.375(6)	C5—C6	1.367(6)
N1—C2	1.386(5)	C5—C13	1.469(7)
O11—C9	1.340(6)	C3—C9	1.469(6)
O11—C12	1.455(6)	C6—C7	1.496(6)
C2—C3	1.341(6)	O20—C19	1.375(6)
C2—C8	1.518(6)	O20—C21	1.422(7)
C16—C23	1.377(6)	C17—C18	1.396(6)
C16—C17	1.380(6)	C13—C15	1.510(7)
C16—C4	1.527(6)	C9—O10	1.201(6)
C4—C5	1.525(6)	C18—C19	1.362(7)
C4—C3	1.533(6)	C19—C22	1.375(7)
O14—C13	1.212(6)	C23—C22	1.385(7)
	Angle		Angle
C6—N1—C2	123.5(4)	C5—C6—N1	120.1(4)
C9—O11—C12	116.8(4)	C5—C6—C7	127.1(4)
C3—C2—N1	119.8(4)	N1—C6—C7	112.8(4)
C3—C2—C8	129.1(4)	C19—O20—C21	117.1(4)
N1—C2—C8	111.2(4)	C16—C17—C18	122.4(4)
C23—C16—C17	117.2(4)	O14—C13—C5	123.8(4)
C23—C16—C4	121.8(4)	O14—C13—C15	119.0(4)
C17—C16—C4	121.0(4)	C5—C13—C15	117.2(4)
C5—C4—C16	111.8(3)	O10—C9—O11	121.0(4)
C5—C4—C3	111.7(3)	O10—C9—C3	123.6(5)
C16—C4—C3	109.4(3)	O11—C9—C3	115.4(5)
C6—C5—C13	121.2(4)	C19—C18—C17	118.8(5)
C6—C5—C4	119.7(4)	C18—C19—O20	124.2(5)
C13—C5—C4	119.1(4)	C18—C19—C22	120.1(4)
C2—C3—C9	125.8(4)	O20—C19—C22	115.6(4)
C2—C3—C4	120.8(4)	C16—C23—C22	121.1(5)
C9—C3—C4	113.4(4)	C19—C22—C23	120.3(5)

with C4 and N1 being −0.264 and −0.106 Å, respectively, from the plane defined by C2, C3, C5, and C6. The maximum deviation of these latter four atoms from their mean plane is 0.091(4) Å for C5. The degree of ring distortions at N1 and C4 is directly reflected in the magnitude of torsion angles emanating from these two atoms. The torsion angle value of C3—C4—C5—C6 or C2—C3—C4—C5 is higher in the 1,4-DHP ring, which indicates that there is greater puckering at C4 than at N1. The 4-methoxyphenyl ring occupies an axial position on C4 and thereby lies above the 1,4-DHP boat. Another conformation of the planarity of the 1,4-DHP ring is the sum of magnitudes of the six intra-ring torsion angles, P, around the ring.[24] For the title compound, P is 76.3°. This value is relatively more than that reported nifedipine, i.e., 72°.[25] Such a mild flatenning might have significant implications for the calcium modulatories of the above compound, as it has been suggested[24,26] that the most active compounds in the nifedipine and nisoldipine series possess the shallowest boat conformations.

The conformation of the dihydropyridine ring is also described in terms of the torsion angles about the intra-ring bonds (see Table 3). The torsion angles C3—C4—C16—C17, C3—C4—C16—C23, C5—C4—C16—C17, and C5—C4—C16—C23 determine the conformation of the junction between the methoxyphenyl and 1,4-DHP rings. The other structural aspect characteristic of the molecule is the conformation of carbomethoxy and acetyl groups. Each group can be oriented in synperiplanar (cis) or antiperiplanar (trans) conformation with respect to the adjacent C=C of the

Table 3. Selected torsion angles (°)

Atoms	Atoms	Atoms	Atoms	Angles
C2	N1	C6	C5	10.6(6)
C2	N1	C6	C7	−169.5(4)
C6	N1	C2	C3	−10.9(6)
C6	N1	C2	C8	167.8(4)
C8	C2	C3	C4	175.4(4)
C8	C2	C3	C9	−4.8(7)
N1	C2	C3	C4	−6.2(6)
N1	C2	C3	C9	173.6(4)
C2	C3	C4	C5	20.9(5)
C2	C3	C4	C16	−103.4(5)
C9	C3	C4	C5	−159.0(4)
C2	C3	C9	O10	−165.7(5)
C2	C3	C9	O11	15.3(6)
C4	C3	C9	O10	14.1(6)
C9	C3	C4	C16	76.8(4)
C3	C4	C5	C13	161.3(4)
C5	C4	C16	C17	−53.4(5)
C5	C4	C16	C23	128.2(5)
C16	C4	C5	C6	102.1(4)
C16	C4	C5	C13	−75.7(5)
C3	C4	C16	C17	70.9(5)
C4	C5	C6	N1	6.8(6)
C4	C5	C6	C7	−173.1(4)
C13	C5	C6	N1	−175.5(4)
C4	C5	C13	C15	−8.0(6)
C6	C5	C13	O14	−6.0(7)
C6	C5	C13	C15	174.3(4)
C4	C5	C13	O14	171.7(4)
C13	C5	C6	C7	4.6(7)
C4	C3	C9	O11	−164.9(4)
C3	C4	C5	C6	−20.9(5)
C3	C4	C16	C23	−107.6(4)

1,4-DHP ring. Thus, torsion angles of the latter have been observed to be C2—C3—C9—O10 and C6—C5—C13—O14, which exhibits trans/cis conformation. The structure exhibits both intra and intermolecular hydrogen bonds of the type C—H···O and N—H···O, which helps in stabilizing the crystal structure. The packing diagram of the molecules down the *b* axis indicate that the molecules are linked by the hydrogen bonds forming an infinite chain (Fig. 2). In addition, these chains are interlinked by the hydrogen bonds. The presence of hydrogen bonding in the crystal structure shows the importance of the major role of calcium in antagonist effect.$^{9-13}$ All hydrogen bonds of acceptor atoms are at C3- and C5-substituent groups ie., at O10, O11, and O14. The four observed independent hydrogen bonds are listed below.

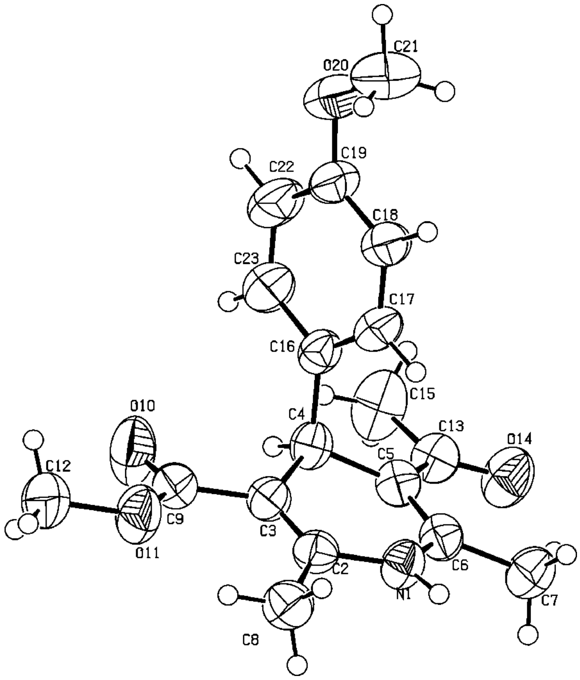

Fig. 1. ORTEP of the molecule at 50% probability.

D–H···*A*	*D*–H	H–*A*	*D*–*A*(Å)	*D*–H···*A*(°)	Symmetry codes
N1–H15···O14	0.96	2.04	2.995(5)	171	$1 - x, 1/2 + y, 3/2 - z$
C8–H14A···O11	0.96	2.08	2.809(6)	131	
C7–H17A···O14	0.96	2.02	2.776(6)	134	
C18–H23···O10	0.96	2.52	3.473(7)	174	$x, y, -1 + z$

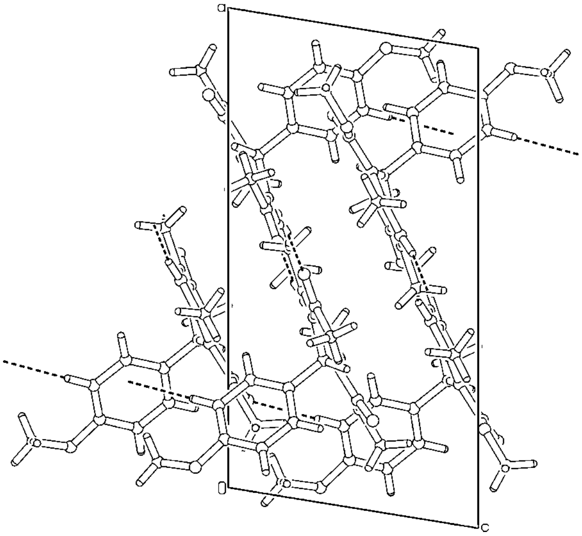

Fig. 2. Packing of the molecules down *b* axis. Dashed lines represent the hydrogen bonds.

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Supplementary material The crystallographic data have been deposited in the Cambridge Crystallographic Data Center, under reference CCDC 226571.

References

1. Loev, B.; Goodman, M.M.; Snader, K.M.; Tedeschi, R.; Macko, E. *J. Med. Chem.* **1995**, *17,* 956.
2. Bossert, F.; Horstmann, H.; Meyer, H.; Vater, W. *Arzneim.-Forsch./Drug Res.* **1979**, *29*(I), 226.
3. Iwanami, M.; Shibanuma, T.; Fujimoto, M.; Kawai, R.; Tamazawa, K.; Takenaka, T.; K. Takahashi, Murakami, M. *Chem. Pharm. Bull.* **1979**, *27,* 1426.
4. Imai, H.; Matsui, K.; Ochi, S.; Nakazawa, M.; Nakagawa, Y.; Imai, S. *Arzneim.-Forsch./Drug Res.* **1987**, *37*(II), 12.
5. Derk, K.; Stoepel, K.; Leibowitz, D.; Taylor, R.; Vanov, S. In *Nitrendipine*; Scriabine, A.; Vanov, S.; Deck, K., Eds.; Urban and Schwarzenberg: Baltimore, 1984; 397 p.
6. Triggle, D.J. In *Cardiovascular Pharmacology*; Antonaccio, M., Ed.; Raven Press: NewYork 1990; pp. 107–160.
7. Wehingner, E.; Gross, R. *Ann. Rep. Med. Chem.* **1986**, *21,* 85.
8. Janis, R.A.; Triggle, D. J. *J. Med. Chem.* **1983**, *26,* 775.
9. Coburn, R.A.; Wierzba, M.; Suto, M.J.; Solo, A.J.; Triggle, A.M., Triggle, D. J. *J. Med. Chem.* **1988**, *31,* 2103.
10. Mahmoudian, M.; Richards, W. C. *J. Chem. Soc. Chem. Commun.* **1986**, 739.
11. Triggle, D.J.; Langs, D.A.; Janis, R.A. *Med. Res. Rev.* **1989**, *9,* 123.
12. Fossheim, R. *J. Med. Chem.* **1986**, *29,* 305.
13. Fossheim, R. *Acta Chem. Scand.* **1986**, *B41,* 581.
14. Shah, A.; Gaveriya, H.; Motohashi, N.; Kawase, M.; Saito, S.; Sakagami, H.; Satoh, K.; Solymosi, A.; Walfard, K.; Molnar, J. *Anticancer Res.* **2000**, *20,* 373.
15. Gunics, G.; Motohashi, N.; Molnar, J.; Farkas, S.; Kawase, M.; Saito, S.; Shah, A. *Anticancer Res.* **2001**, *21,* 269.
16. Gunics, G.; Farkas, S.; Motohashi, N.; Shah, A.; Harsukh, G.; Kawase, M.; Molnar, J. *Int. J. Antimicrobial Agents* **2002**, *20,* 227.
17. Kawase, M.; Shah, A.; Gaveriya, H.; Motohashi, N.; Sakagami, H.; Varga, A.; Molnar, J. *Biol. Med. Chem.* **2002**, *10,* 1051.
18. Lokanath, N.K.; Sridhar, M.A.; Prasad, J.S.; Joshi, M.; Thaker, D.A.; Shah, A. *Z. Kris.—New Cryst. Struct.* **1997**, *212,* 13.
19. Devarajegowda, H.C.; Prasad, J.S.; Sridhar, M.A.; Gaveriya, H.C.; Shah, A. *Mol. Cryst. Liq. Cryst.* **2000**, *348,* 301.
20. Otwinowski, Z.; Minor, W. In *Methods in Enzymology*, Vol. 276: Macromolecular Crystallography, Part A; Carter, C.W., Jr.; Sweet, R.M.; Eds.; Academic Press: University of Texas, Southwestern Medical Center, Dallas, 1997; pp. 307–326.
21. Sheldrick, G.M. *SHELXS–97*; University of Göttingen: Germany, 1997.
22. Sheldrick, G.M. *SHELXL–97*; University of Göttingen: Germany, 1997.
23. Johnson, C. K. *ORTEP-II, A Fortran Thermal-Ellipsoid Plot Program*, Report ORNL-5138; Oak Ridge National Laboratory: Oak Ridge, Tennessee, 1976.
24. Fossheim, R.; Joslyn, A.; Solo, A. J.; Luchowski, E.; Rutledge, A.; Triggle, D. J. *J. Med. Chem.* **1988**, *31,* 300.
25. Miyamae, A.; Koda, S.; Morimoto, Y. *Chem. Pharm. Bull.* **1986**, *34,* 3071.
26. Fossheim, R.; Svarteng, K.; Mostad, A.; Romming, C.; Shelter, E.; Triggle, D. J. *J. Med. Chem.* **1982**, *25,* 126.