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ORIGINAL PAPER

Synthesis, Characterization, Crystal and Molecular Structure Analysis of 2,6-Dimethyl-3-Acetyl-5-Carbomethoxy-4-Phenyl-1, 4-Dihydropyridine

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Abstract The synthesis of a novel unsymmetrical dihydropyridine, bearing carboxy methyl and carbomethoxy groups at C(3) and C(5), respectively, has been achieved by applying the modified Hantzsch-type condensation, which involves the Michael addition of Knoevenagel adduct with an enamine. The product obtained was characterized by spectroscopic techniques and finally confirmed by X-ray diffraction studies. The title compound $C_{17}H_{19}NO_3$ crystallizes in Monoclinic crystal class in space group $P2_1/c$ with cell parameters $a = 9.9130(12)$ Å, $b = 7.3320(5)$ Å, $c = 22.018(3)$ Å, $\beta = 109.637(3)°$, $V = 1507.2(3)$ Å^3 and $Z = 4$. The final residual factor $R_1 = 0.0642$. The structure exhibits both intra and inter-molecular hydrogen bonding of the type C–H···O and N–H···O. The pyridine ring gives boat conformation.

Keywords 1,4-Dihydropyridine · Hantzsch synthesis · Crystal structure · Hydrogen bonding

Introduction

1,4-Dihydropyridine derivatives (1,4-DHPs) form a class of heterocyclic compounds with interesting pharmacological and biological properties [1–9]. It is well known that the 1,4-DHP nucleus serves as the scaffold of important cardiovascular drugs and it has been well established that the calcium modulator activity of this family of compounds is determined by structural requirements [10–14]. The systematic structural modification of the 1,4-DHP ring yields different compounds used in the treatment of hypertension and angina pectoris [15–23]. The most prominent of these compounds is nifedipine, which was the first generation calcium channel blocker, marketed by Bayer [24]. Since then, a wide variety of novel compounds belonging to the second and third generations of new biologically active substances from the 1,4-DHP class have been developed in order to obtain larger bioavailabilities or greater tissue selectivity [25, 26]. Felodipine, lercanidipine, and clinidipine are examples of newer DHP-calcium antagonists, which are effective antihypertensive compounds.

Up to now, 1,4-Dihydropyridine derivatives (1,4-DHPs) are still the most potent group of calcium channel modulators and, therefore, the design of DHP-calcium channel modulators has prompted the studies to investigate the functional and geometrical requirements at the DHP binding site [27]. Structure–activity relationships (SAR) show that the combination of the substituents at the C(3), C(4) and C(5) positions of nifedipine modulates the activity [28] and tissue selectivity [29], while the nature and position of C(4)-aryl ring substituents were determinant of voltage-dependent calcium channel (VDCC) antagonist activity. In general, the presence of an aryl group at C4, and esters, acyl, sulphonyl or nitrile groups at C(3) and C(5) of the 1,4-DHP ring has proved to be a fundamental requirement for the pharmacological activity [30–32]. The majority of 1,4-dihydropyridines synthesized possess similar groups (acetyl or ester) at C(3) and C(5). However, very few unsymmetrical 1,4-dihydropyridines having an acetyl group as one of the substituents on C(3) and C(5) positions, have been reported.

Earlier Tumor specific-cytotoxicity and MDR reversal activity of fifteen unsymmetric 1,4-dihydropyridines were

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studied [33]. These fifteen compounds containing substituted Carbamoyl group at C(5) while C(3) position was alternatively occupied by various functional groups like cyano, acetyl, methyl ester and ethyl ester. The C-3 position of phenyl ring of 1,4-dihydropyridine was fixed by NO_2 group [34]. The majority of the tested compounds were found to be the most effective MDR modulators and these derivatives caused a dose-dependent inhibition of the MDR p-glycoprotein [13, 35].

Previous studies indicated that the substituted aryl ring could influence the degree of puckering of the 1,4-dihydropyridine ring, which in turn may be related to the activity [36]. It was very pertinent to reinvestigate the functionality of various groups of 4-phenyl ring especially in unsymmetric dihydropyridines. So in the current work, earlier substitutions [37] were removed and unsubstituted phenyl ring attached to 1,4-dihydropyridine structure was synthesized. It was necessary to establish the divergence of calcium channel antagonism and cardiovascular activity [38] to achieve better mutidrug resistance (MDR) related reverting aptitude due to p-glycoprotein [39, 40] and therefore the cardiovascular functionality essentially inherited in 2-nitro/3-nitro group of phenyl ring of many DHP drug molecules and one of the esteric linkage is removed to introduce acetyl group in 1,4-dihydropyridine ring in the investigated molecule.

Owing to the potency of 1,4-Dihydropyridine derivatives (1,4-DHPs) and as a continuation of our previous work [41, 42], the title compound was synthesized by using modified Hantzsch-type condensation which involved Michael addition of a Knoevenagel adduct, benzylideneacetylacetone with an enamine, methyl-3-aminocrotonate. The structure of the product obtained was confirmed by X-ray crystallography.

Synthesis

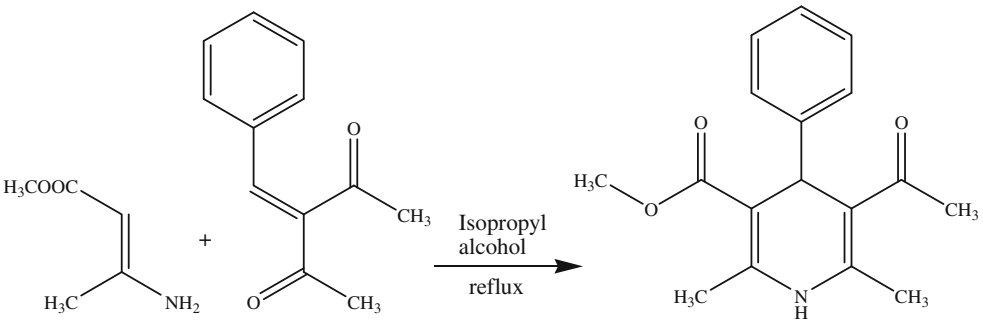
Synthesis of 2,6-Dimethyl-3-Acetyl-5-Carbomethoxy-4-Phenyl-1,4-Dihydropyridine

A mixture of substituted benzylideneacetylacetone (0.01 mol) and methyl-3-aminocrotonate (0.01 mol) was refluxed on an oil bath for 18 h using isopropyl alcohol as a solvent (25 mL). The reaction was monitored by TLC. After completion of the reaction, the reaction mass was cooled to room temperature. The excess of solvent was distilled out with the help of rotavapour and residual pale yellow-orange oil was crystallized from ether:ethanol (20:1) gave faint yellow crystals. (M.P. 170–172 °C; Yield, 69%).

Table 1 Crystal data and structure refinement

Empirical formula	$C_{17}H_{19}NO_3$
Formula weight	285.33
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Spacegroup	$P2_1/c$
Cell dimensions	$a = 9.9130(12)$ Å
	$b = 7.3320(5)$ Å
	$c = 22.018(3)$ Å
	$\beta = 109.637(3)°$
Volume	1507.2(3) Å^3
Z	4
Density (calculated)	1.257 Mg m^{-3}
Absorption coefficient	0.086 mm^{-1}
F_{000}	608
Crystal size	0.3 × 0.3 × 0.25 mm
Theta range for data collection	2.18°–25.02°
Index ranges	$-10 \le h \le 10$
	$-7 \le k \le 7$
	$-26 \le l \le 26$
Reflections collected	4013
Independent reflections	2257 [R(int) = 0.0209]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2257/0/195
Goodness-of-fit on F^2	1.083
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0642$, $wR_2 = 0.1798$
R indices (all data)	$R_1 = 0.0770$, $wR_2 = 0.1945$
Extinction coefficient	0.136(18)
Largest diff. peak and hole	0.676 and −0.294 e Å^{-3}

Fig. 1 Reaction scheme



Anal. Calc. (in %) C = 71.56, H = 6.71, N = 4.91; Found C = 71.49, H = 6.80, N = 4.95.
IR (KBr, cm^{-1}): 3396(N–H stretching), 3030(C–H stretching, Asymmetric), 2930(C–H stretching, Symmetric), 1703(C=O stretching, ester), 1670(C=O stretching, ketone), 1589(N–H deformation).
^{1}H NMR (300 MHz, δ ppm): 7.12–7.22 (m, 5H, Ar–H), 6.07 (s, 1H, NH), 5.01 (s, 1H, CH), 3.70 (s, 3H, $COOCH_3$), 2.34 (s, 3H, $COCH_3$), 2.30 (s, 3H, CH_3), 2.16 (s, 3H, CH_3).
MS (m/z): 285.

Method of Crystallization

The pure 2,6-Dimethyl-3-acetyl-5-carbomethoxy-4-phenyl-1,4-dihydropyridine (0.25 g) was taken in 25 mL of isopropyl alcohol. The resulting solution was warmed with charcol on a water bath and 8–10 drops of DMF was added to the solution. The solution was filtered while hot through whatmann 42 filter paper. The solution was kept in a stopper conical flask slightly opened. Crystals grew after 30 days due to thin layer evaporation. They were filtered and washed with chilled methanol. The method employed for synthesis is shown in Fig. 1.

Table 2 Bond length (Å)

Atoms	Length
N1–C6	1.374(3)
N1–C2	1.379(3)
C2–C3	1.357(3)
C2–C7	1.493(3)
C3–C9	1.462(3)
C3–C4	1.512(3)
C4–C16	1.528(3)
C4–C5	1.529(3)
C5–C6	1.367(3)
C5–C13	1.453(3)
C6–C8	1.498(3)
C9–O10	1.205(3)
C9–O11	1.345(3)
O11–C12	1.432(3)
C13–O14	1.228(3)
C13–C15	1.466(4)
C16–C21	1.386(4)
C16–C17	1.387(4)
C17–C18	1.386(4)
C18–C19	1.373(5)
C19–C20	1.364(6)
C20–C21	1.389(5)

Crystal Structure Determination

A single crystal of the title compound with dimensions 0.30 × 0.25 × 0.25 mm was chosen for the X-ray diffraction study. The data were collected on a DIPLabo Image Plate system equipped with a normal focus, 3KW sealed X-ray source (graphite monochromated Mo K_α). The crystal to detector distance was fixed at 120 mm with the detector area of 441 × 240 mm^2. Thirty six frames of data were collected at room temperature by the oscillation method. Each exposure of the image plate was set to 400 s. Successive frames were scanned in steps of 5° per minute with an oscillation range of 5°. Image processing and data reduction were done using Denzo [43]. The reflections were merged with Scalepack [44]. All the frames could be indexed using a monoclinic lattice. Absorption correction was not applied. The structure was solved by direct

Table 3 Bond angles (°)

Atoms	Angle
C6–N1–C2	124.74(2)
C3–C2–N1	118.5(2)
C3–C2–C7	128.1(2)
N1–C2–C7	113.4(2)
C2–C3–C9	121.5(2)
C2–C3–C4	119.46(2)
C9–C3–C4	118.78(2)
C3–C4–C16	112.37(2)
C3–C4–C5	111.42(2)
C16–C4–C5	109.53(2)
C6–C5–C13	125.41(2)
C6–C5–C4	118.84(2)
C13–C5–C4	115.75(2)
C5–C6–N1	118.12(2)
C5–C6–C8	128.8(2)
N1–C6–C8	113.1(2)
O10–C9–O11	121.4(2)
O10–C9–C3	126.9(2)
O11–C9–C3	111.6(2)
C9–O11–C12	116.7(2)
O14–C13–C5	119.9(2)
O14–C13–C15	117.5(2)
C5–C13–C15	122.6(2)
C21–C16–C17	118.7(3)
C21–C16–C4	120.3(2)
C17–C16–C4	121.0(2)
C18–C17–C16	120.2(3)
C19–C18–C17	120.6(3)
C20–C19–C18	119.7(3)
C19–C20–C21	120.5(3)
C16–C21–C20	120.3(3)

methods using SHELXS-97 [45]. Least-squares refinement using SHELXL-97 [45] with isotropic temperature factors for all the non-hydrogen atoms converged the residual R_1 to 0.0770.

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. The hydrogen atoms were allowed to ride on their parent atoms. After eight cycles of refinement the residual converged to 0.0642. The details of crystal data and refinement are given in Table 1. Tables 2 and 3 give the list of bond lengths and bond angles, respectively, which are in good agreement with the standard values. Table 4 gives atomic coordinates and equivalent thermal parameters of the non-hydrogen atoms and Table 5 gives hydrogen-bonding geometry. The ORTEP of the molecule with thermal ellipsoids drawn at 50% probability is shown in Fig. 2.

In the title compound the pyridine ring shows boat conformation. The dihedral angle between the least squares plane of pyridine and phenyl ring is 85.92(13) Å. For N1–C2–C3–C7–C9–O10–O11–C12 and C4–C16–C17–C18–C19–C20–C21, the dihedral angle is 86.13(11) Å. The atoms C4 and N1 deviates from Cremer and Pople plane by 0.204(3) angstrom and 0.134(2) Å, defined by the atoms N1–C2–C3–C4–C5–C6. Pukering parameters also confirms the structure, $Q = 0.306$ Å, $\theta = 106.4(4)°$ and $\phi = 4.3(5)°$. The torsion angle about C3–C9–O11–C12 being −177.8(2)° and that about C4–C5–C13–C15 being 173.7(3)° shows *anti-periplanar* and *anti-periplanar* conformation. The atoms C3–C4–C16–C17 gives *syn-clinal* conformation with a value of 36.5(3)°. The structure exhibits inter-molecular hydrogen bonds of the type N–H···O. N1–H1···O14 has a length of 2.903(3) Å with an angle of 177° along with the symmetry codes $x, -1 + y, z$, respectively. It has also intra-molecular hydrogen bonds of the type C7–H7C···O10 which has a length of 2.862(3) Å and an angle of 103°. The stability of the crystal structure can be accounted for by these hydrogen bonds.

Table 4 Atomic coordinates and equivalent thermal parameters of the non-hydrogen atoms

Atom	*x*	*y*	*z*	U_{eq}
N1	0.2716(2)	0.8068(3)	0.4695(9)	0.0521(6)
C2	0.3415(3)	0.8376(3)	0.4259(1)	0.0487(6)
C3	0.3391(2)	1.0083(3)	0.40167(1)	0.0459(6)
C4	0.2470(3)	1.1532(3)	0.4172(1)	0.0460(6)
C5	0.2275(2)	1.1171(3)	0.4821(1)	0.0447(6)
C6	0.2290(2)	0.9409(3)	0.5027(1)	0.0462(6)
C7	0.4132(3)	0.6716(3)	0.4118(1)	0.0634(7)
C8	0.1907(3)	0.8690(4)	0.5585(1)	0.0617(7)
C9	0.4131(2)	1.0517(3)	0.3562(1)	0.0513(6)
O10	0.4779(2)	0.9474(3)	0.3338(1)	0.0777(7)
O11	0.4010(2)	1.2296(3)	0.3402(1)	0.0764(7)
C12	0.4651(4)	1.2870(5)	0.2940(2)	0.0947(1)
C13	0.2072(3)	1.2776(3)	0.5168(1)	0.0504(6)
O14	0.2212(2)	1.4304(2)	0.4968(9)	0.0719(6)
C15	0.1726(4)	1.2660(5)	0.5764(2)	0.0826(1)
C16	0.1004(3)	1.1705(3)	0.3647(1)	0.0526(7)
C17	0.0290(3)	1.0182(4)	0.3321(1)	0.0670(8)
C18	−0.1060(3)	1.0358(6)	0.2861(1)	0.0891(1)
C19	−0.1708(4)	1.2036(7)	0.2726(2)	0.0926(1)
C20	−0.1014(4)	1.3543(6)	0.3044(2)	0.0934(1)
C21	0.0344(3)	1.3393(4)	0.3503(1)	0.0740(9)

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

Table 5 Hydrogen-bonding geometry (Å°)

D–H···A	D–H	H–A	D–A	D–H···A	Symmetry codes
N(1)–H(1)···O(14)	0.86	2.04	2.903(3)	177	$x, -1 + y, z$
C(4)–H(4)···O(11)	0.98	2.34	2.694(3)	100	
C(4)–H(4)···O(14)	0.98	2.37	2.752(3)	102	
C(7)–H(7C)···O(10)	0.96	2.15	2.862(3)	130	

Note: D–H and H–A distances are essentially standard values and are not derived from the experiment

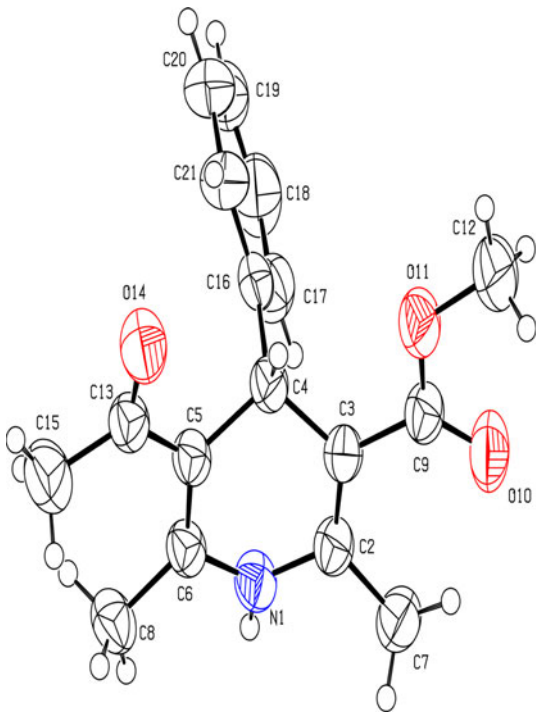


Fig. 2 ORTEP of the molecule with 50% probability

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