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Synthesis and Crystal Structure of a Novel n-Substituted 1,4-dihydropyridine

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The title compound, $C_{15}H_{16}N_2O_3$, was synthesized, characterized spectroscopically, and finally confirmed by X-ray diffraction studies. The compound crystallizes in the monoclinic space group $P2_1/_n$ with cell parameters $a = 10.314(9)$ Å, $b = 17.976(15)$ Å, $c = 12.762(11)$ Å, $\beta = 113.331(3)^\circ$, $Z = 4$, and $V = 2173(3)$ Å^3. The dihydropyridine ring in the structure is in a flattened-boat conformation. The 2-nitrophenyl ring is orthogonal to the 1,4-dihydropyridine ring. The structure exhibits an intermolecular hydrogen bond of the type C–H···O.

Keywords: 1,4-dihydropyridine; flattened boat; hydrogen bond

INTRODUCTION

The Ca^{2+} channel antagonists are a heterogeneous group of agents possessing a common property, the ability to block current through potential-dependent Ca^{2+} channels [1]. Structurally, a diverse group of organic compounds are known to be calcium channel antagonists. The most potent class of antagonists comprises derivatives of 1,4-dihydropyridines, of which the most widely known agent is

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nifedipine. 1,4-Dihydropyridine (1,4-DHP) moiety is very interesting because of its recognition as a calcium channel antagonist, chemotherapeutic agent for multidrug resistance (MDR) reversal [2] in tumor cells, potent immunomodulator [3], and antitubercular agent [4]. A further study of N-alkylated DHP at the labile hydrogen of the DHP skeleton proved that it is important for MDR reversal in tumor cells, and this has created new interest in N-phenyl substituted 1,4-dihydropyridines [5]. In structure–activity relationships, the effects of substitution on the 1,4-dihydropyridine rings have been meticulously studied [6]. These have indicated specific conformational details that correlate with high binding efficiency [7].

The crystallographic studies of both 1,4-dihydropyridine antagonist and agonist show several common conformational features . The DHP antagonist blocks transmembrane Ca^{2+} influx, thereby causing relaxation of smooth and cardiac muscle [8,9], whereas the DHP agonist produces the opposite pharmacological effect [10,11]. As a part of our ongoing research on such potent molecules, the title compound was synthesized, and the structure of the title compound was established on the basis of Fourier transform infrared (FTIR) absorption spectroscopy, NMR, elemental analysis, and X-ray crystallography.

EXPERIMENTAL

The melting point was determined in an open capillary melting-point apparatus. The FTIR absorption spectrum was recorded on a Shimadzu FTIR-8400 spectrometer (KBr Pellet sample technique, 1000–4000 cm^{-1} frequency ranges. ^1H NMR spectrum was recorded on a Bruker AC 300-MHz FT–NMR spectrometer in Dimethylsulfoxide DMSO-d_6 solution (2.5%). Mass spectra were obtained using a Jeol SX 102/DA6000 spectrometer (for FAB). Elemental analyses were done on a CHN EA 1108 elemental analyser. Analytical thin-layer chromatography (TLC) was performed on 0.25-mm silica-gel plates (Merck 60 F_{254}). The procedure for synthesis is shown in Fig. 1.

Synthesis and Method of Crystallization

The n-substituted-1,4-dihydropyridine was synthesized by refluxing methyl acetoacetate (0.01 mol), 2-anisidine (0.01 mol), and 2-nitro benzaldehyde (0.01 mol) in acetic acid (30 ml) for 10 h. The completion of the reaction was monitored by TLC. The reaction mixture was allowed to cool for 12 h at room temperature. The solid obtained was filtered, washed with cold methanol, dried in a hot-air oven, and recrystallized from dimethylformamide. Yield = 65%, mp 220°C.

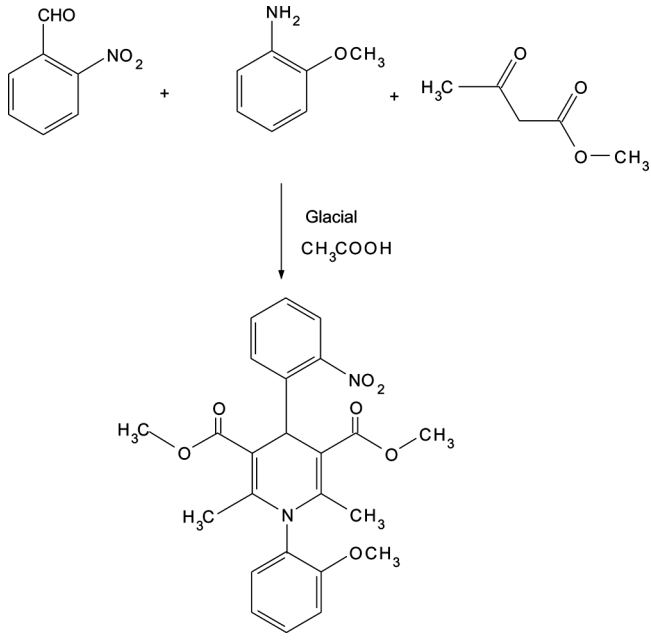

FIGURE 1 Reaction scheme.

IR: 1703 cm^{-1} (C=O str.), 1265 cm^{-1} (C–O–C, str.), 3010 cm^{-1} (aromatic C–H str.), 1652 cm^{-1} (aromatic C=C str.), 2910 cm^{-1} (CH3 symmetric str.), 2845 cm^{-1} (CH_3 asymmetric str). ^{1}H NMR: 2.21δ ppm (3H, s), 2.32δ ppm (3H, s), 3.48δ ppm (6H, s), 3.58δ ppm (3H, s), 5.45δ ppm (1H, s), 6.92δ ppm (1H, d), 7.04δ ppm (1H, t), 7.12δ ppm (1H, t), 7.17δ ppm (1H, d), 7.56δ ppm (1H, d), 7.72δ ppm (1H, t), 7.78δ ppm (1H, t), 7.88δ ppm (1H, d). Mass: 453 (M^{+1}), 390, 374, 330, 300, 148, 92, 77. C,H,N analysis: Calculated %: C (63.71), H (5.35), N (6.19) Found %: C (63.74), H (5.34), N (6.17).

The compound (2 g) was taken in mixture of 10 ml of dimethylformamide and 5 ml of ethanol. Charcoal (2 g) was added, and the solution was heated for 4 min. The solution was filtered while hot through Whatmann no. 42 filter paper in a corkable 50-ml conical flask. The flask was corked and kept for several days. Light yellow crystals were grown by the thin-film evaporation technique.

Crystal Structure Determination

A single crystal of the title compound with dimensions $0.3 \times 0.27 \times 0.25$ mm was chosen for an X-ray diffraction study. The data were

collected on a DIPLabo Image Plate system equipped with a normal-focus, 3-kW, sealed X-ray source (graphite monochromated MoK_α). The crystal-to-detector distance is fixed at 120 mm with a detector area of $441 \times 240\,mm^2$. Thirty-six frames of data were collected at room temperature by the oscillation method. Each exposure of the image plate was set to a period of 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 [12]. The reflections were merged with Scalepack [13]. All of the frames could be indexed using a primitive monoclinic lattice. The structure was solved by direct methods using SHELXS-97 [14]. All of the nonhydrogen atoms were revealed in the first Fourier map itself. Least-squares refinement using SHELXL-97 [15] with isotropic temperature factors for all the nonhydrogen atoms converged the residual $R1$ to 0.1866. Subsequent refinements were carried out with anisotropic thermal parameters for nonhydrogen atoms. After eight cycles of refinement, the residuals converged to 0.0887. The hydrogen atoms were fixed at chemically acceptable positions and were allowed to ride on their parent atoms. The details of crystal data and refinement are given in Table l.[†] Table 2 gives the atomic coordinates and equivalent thermal parameters of the nonhydrogen atoms. Tables 3 and 4 give the list of bond lengths and bond angles, respectively, which are in good agreement with the standard values. Figure 2 is the ORTEP [16] diagram of the molecule with thermal ellipsoids drawn at 30% probability.

A study of torsion angles, asymmetric parameters, and least squares plane calculations revealed that the 1,4-dihydropyridine ring in the structure is in a flattened-boat conformation with the atoms N1 and C4 lying at 0.076(3) Å and 0.117(3) Å from the least squares plane defined by the atoms C2/C3/C5/C6. The torsion angle values C3–C4–C5–C6 $= -20.24°$ and C2–C3–C4–C5 $= 16.12°$ is higher in the 1,4-dihydropyridine ring, indicating that there is greater puckering at C4 than at N1. The degrees of ring distortions at N1 and C4 are directly reflected on the magnitude of torsion angles emanating from these two atoms. The 2-nitrophenyl ring is positioned pseudo-axially, as indicated by the average magnitude of the C6–C5–C4–C25 torsion angle value of 101.3° with respect to the C4 position of the dihydropyridine ring. Another conformation of the planarity of the 1,4-dihydropyridine ring is the sum of magnitudes of the six intraring torsion

[†]CCDC 621009 contains the supplementary crystallographic data for this article. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033; E-mail: deposit@ccdc.cam.ac.uk.

TABLE 1 Crystal Data and Structure Refinement

Parameter	Value
Empirical formula	$C_{24}H_{24}N_2O_7$
Formula weight	452.45
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Cell dimensions	$a = 10.314(9)$ Å
	$b = 17.976(15)$ Å
	$c = 12.762(11)$ Å
	$\beta = 113.331(3)^\circ$
Volume	2173(3) Å^3
Z	4
Density (calculated)	1.383 Mg/m^3
Absorption coefficient	0.103 mm^{-1}
F_{000}	952
Crystal size	$0.3 \times 0.27 \times 0.25$ mm
Theta range for data collection	2.07° to 25.03°
Index ranges	$-12 \le h \le 12$
	$-21 \le k \le 21$
	$-15 \le l \le 15$
Reflections collected	7330
Independent reflections	3826 [R(int) = 0.0277]
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3826/0/304
Goodness of fit on F^2	1.080
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0887$, $wR2 = 0.2419$
R indices (all data)	$R1 = 0.1199$, $wR2 = 0.2915$
Extinction coefficient	0.038(7)
Largest diff. peak and hole	0.626 and -0.404 e.Å^{-3}

angles, ΣP, around the ring. For the compound under study, ΣP is 63.55°. This value is a bit low when compared to the corresponding value of 72° reported for nifedipine drug molecule [17]. Such a mild flattening might have significant implications for the pharmacological potency of the title compound as a calcium channel antagonist, because Fossheim [18] has suggested that the most active compounds in the nifedipine and nisoldipine series possess the shallowest boat conformations. The dihedral angle between the nitrophenyl ring and the dihydropyridine ring is 87.01(16)°, implying that the nitrophenyl ring is nearly orthogonal to the dihydropyridine ring. The dihedral angle between the dihydropyridine ring and the methoxyphenyl ring is 84.64(16)°. These values are comparable with the corresponding

TABLE 2 Atomic Coordinates and Equivalent Thermal Parameters of the Nonhydrogen Atoms

Atom	x	y	z	U_{eq}
N1	−0.0421(3)	0.0768(2)	0.2109(2)	0.0625(7)
C2	0.0080(3)	0.1057(2)	0.1322(2)	0.0608(8)
C3	0.1113(3)	0.0700(2)	0.1128(2)	0.0571(7)
C4	0.1820(3)	0.0002(2)	0.1778(2)	0.0568(7)
C5	0.0945(3)	−0.0340(2)	0.2380(2)	0.0567(7)
C6	−0.0023(3)	0.0063(2)	0.2602(3)	0.0611(8)
C7	−0.0742(4)	−0.0185(2)	0.3357(3)	0.0793(1)
C8	−0.0646(3)	0.1751(2)	0.0722(3)	0.0750(9)
C9	−0.1338(3)	0.1227(2)	0.2461(3)	0.0664(8)
C10	−0.0741(4)	0.1642(2)	0.3456(3)	0.0722(9)
C11	−0.1581(4)	0.2087(2)	0.3813(4)	0.0823(1)
C12	−0.3012(5)	0.2127(2)	0.3158(4)	0.0880(2)
C13	−0.3620(4)	0.1702(2)	0.2176(3)	0.086(2)
C14	−0.2772(3)	0.1265(2)	0.1834(3)	0.0733(9)
O15	0.0688(2)	0.1564(2)	0.4035(2)	0.0874(8)
C16	0.1359(5)	0.1990(2)	0.5052(3)	0.1001(2)
C17	0.1697(4)	0.1001(2)	0.0334(3)	0.0652(8)
O18	0.1482(4)	0.1603(2)	−0.0118(3)	0.1290(2)
O19	0.2557(3)	0.0529(2)	0.0147(2)	0.0837(8)
C20	0.3289(5)	0.0791(2)	−0.0526(4)	0.093(2)
C21	0.1199(3)	−0.1120(2)	0.2719(3)	0.0656(8)
O22	0.0671(3)	−0.1483(2)	0.3247(3)	0.1060(2)
O23	0.2109(3)	−0.1440(2)	0.2351(2)	0.0791(8)
C24	0.2327(5)	−0.2229(2)	0.2552(5)	0.1030(2)
C25	0.3307(3)	0.0190(2)	0.2664(2)	0.0596(8)
C26	0.3458(4)	0.0800(2)	0.3371(3)	0.0698(9)
C27	0.4742(4)	0.1008(2)	0.4208(3)	0.0860(2)
C28	0.5933(4)	0.0599(3)	0.4385(3)	0.0930(2)
C29	0.5835(4)	−0.0020(3)	0.3738(3)	0.0870(2)
C30	0.4548(3)	−0.0214(2)	0.2877(3)	0.0701(9)
N31	0.4575(3)	−0.0878(2)	0.2207(3)	0.0822(9)
O32	0.5279(3)	−0.1415(2)	0.2742(3)	0.1220(2)
O33	0.3944(3)	−0.0877(2)	0.1177(2)	0.0928(9)

values of 83.94° and 84.94° reported earlier [19]. The torsion angle values of −134.9(3)° and −73.9(4)° for C3–C4–C25–C30 and C5–C4–C25–C26, respectively, determine the conformation of the junction between the nitrophenyl and the dihydropyridine ring. The other structural aspect is the conformation of the carbethoxy groups on the dihydropyridine ring. Each carbethoxy group is oriented in a *cis* conformation with respect to the adjacent C=C bond as indicated by the torsion angle values of 9.08(59)° and −3.19(55)°, respectively, for

TABLE 3 Bond Lengths (Å)

Atoms	Length
N1–C2	1.399(4)
N1–C6	1.403(4)
N1–C9	1.453(4)
C2–C3	1.349(4)
C2–C8	1.500(4)
C3–C17	1.472(4)
C3–C4	1.521(4)
C4–C5	1.526(4)
C4–C25	1.540(4)
C5–C6	1.350(4)
C5–C21	1.460(4)
C6–C7	1.498(4)
C9–C14	1.376(4)
C9–C10	1.389(5)
C10–O15	1.369(4)
C10–C11	1.383(5)
C11–C12	1.381(6)
C12–C13	1.388(6)
C13–C14	1.370(5)
O15–C16	1.428(4)
C17–O18	1.205(4)
C17–O19	1.316(4)
O19–C20	1.429(4)
C21–O22	1.211(4)
C21–O23	1.335(4)
O23–C24	1.444(4)
C25–C26	1.390(4)
C25–C30	1.400(4)
C26–C27	1.384(5)
C27–C28	1.372(6)
C28–C29	1.365(6)
C29–C30	1.391(5)
C30–N31	1.475(5)
N31–O33	1.214(4)
N31–O32	1.237(4)

C2–C3–C19–O18 and C6–C5–C21–O22. The molecule exhibits *trans*/*trans* conformation. The torsion angle values observed in the latter are −171.7(3)° and 175.2(3)°, respectively, for C2–C3–C17–O19 and C6–C5–C21–O23. Similar conformation was observed in the molecule reported earlier [19]. The methoxy group lies in the plane of the phenyl ring as indicated by the torsion angle value of −2.3(5)° for C11–C10–O15–C16. The nitro group is twisted out of the plane of the phenyl ring as indicated by the torsion angle values of 41.56(49)° and 43.13(52)°,

TABLE 4 Bond Angles (°)

Atoms	Angle
C2–N1–C6	122.1(2)
C2–N1–C9	118.8(2)
C6–N1–C9	119.0(3)
C3–C2–N1	119.9(3)
C3–C2–C8	124.9(3)
N1–C2–C8	115.1(3)
C2–C3–C17	121.3(3)
C2–C3–C4	122.4(3)
C17–C3–C4	116.1(3)
C3–C4–C5	110.7(2)
C3–C4–C25	110.1(2)
C5–C4–C25	109.6(2)
C6–C5–C21	120.8(3)
C6–C5–C4	121.7(3)
C21–C5–C4	117.5(3)
C5–C6–N1	119.9(3)
C5–C6–C7	124.9(3)
N1–C6–C7	115.2(3)
C14–C9–C10	119.3(3)
C14–C9–N1	122.0(3)
C10–C9–N1	118.6(3)
O15–C10–C11	124.2(3)
O15–C10–C9	115.6(3)
C11–C10–C9	120.2(3)
C12–C11–C10	119.4(4)
C11–C12–C13	120.6(3)
C14–C13–C12	119.1(4)
C13–C14–C9	121.2(3)
C10–O15–C16	117.8(3)
O18–C17–O19	120.2(3)
O18–C17–C3	127.7(3)
O19–C17–C3	112.1(3)
C17–O19–C20	116.8(3)
O22–C21–O23	119.8(3)
O22–C21–C5	128.0(3)
O23–C21–C5	112.2(3)
C21–O23–C24	116.2(3)
C26–C25–C30	115.0(3)
C26–C25–C4	118.2(3)
C30–C25–C4	126.7(3)
C27–C26–C25	122.8(3)
C28–C27–C26	120.1(4)
C29–C28–C27	119.4(4)
C28–C29–C30	120.0(4)
C29–C30–C25	122.5(3)

(*Continued*)

TABLE 4 Continued

Atoms	Angle
C29–C30–N31	115.4(3)
C25–C30–N31	122.1(3)
O33–N31–O32	123.1(4)
O33–N31–C30	120.1(3)
O32–N31–C30	116.9(3)

respectively, for O32–N31–C30–C29 and O33–N31–C30–C35. The structure exhibits an intermolecular hydrogen bond of the type C−H···O. The intermolecular hydrogen bond C12–H12···O18 has a length of 3.352(6) Å and an angle of 143° with symmetry code $-1/2+x$, $1/2+y$, $1/2+z$. The presence of hydrogen bonding in the crystal structure shows its major role in the calcium channel antagonist effect [20]. The packing of the molecules (Fig. 3) when viewed down the a axis indicates that the molecules are stacked and are linked by the intermolecular hydrogen bond to form a linear polymeric chain.

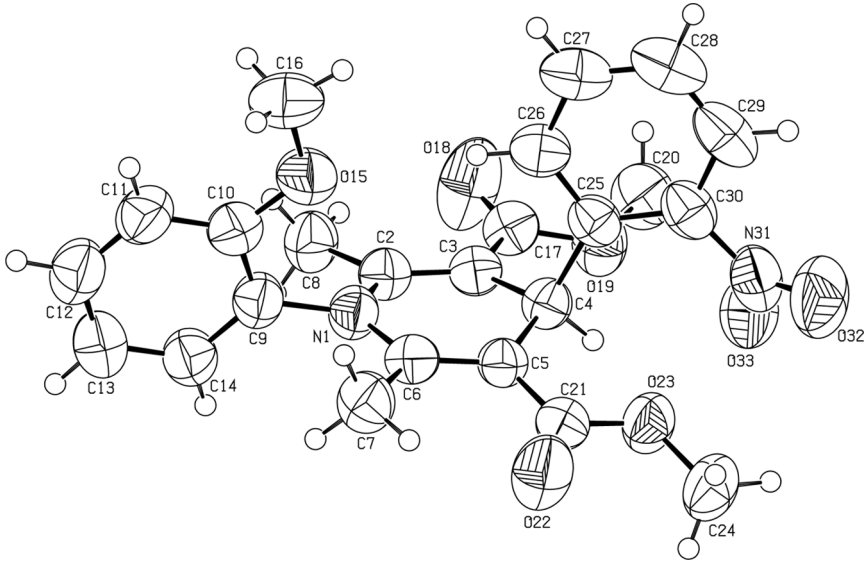

FIGURE 2 ORTEP diagram of the molecule with thermal ellipsoids drawn at 30% probability.

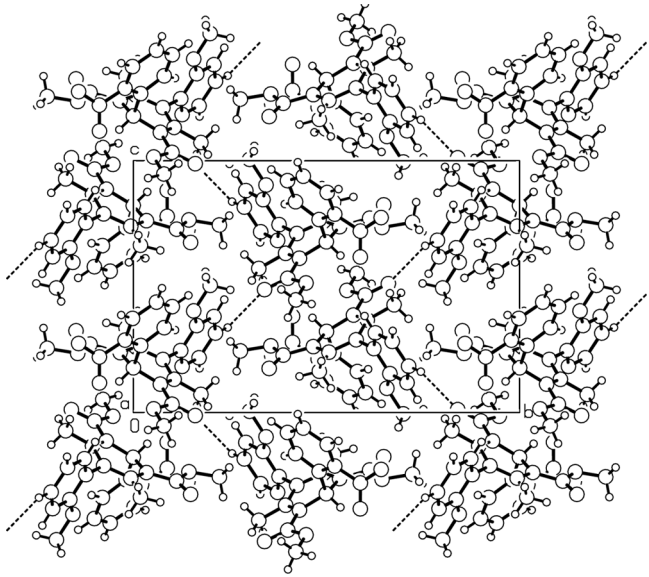

FIGURE 3 Packing diagram of the molecules when viewed down the *a* axis. The dotted lines represents the intermolecular hydrogen bond.

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