Experimental and Theoretical Structural Study of 2-Pyridyl- and 4-Hydroxyphenyl-1,4-dihydropyridine Derivatives

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A series of substituted 1,4-dihydropyridines (1,4-DHPs) has been synthesised following the well-known Hantzsch's procedure for symmetrical 1,4-DHP. The structures of these compounds have been thoroughly studied by X-ray crystallographic analysis and semiempirical (AM1) calculations. A good agreement is found between the theoretical and experimental results. In all cases, the most stable conformation fulfils all the requirements needed for exhibiting an antagonist calcium effect.

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Introduction.

1,4-Dihydropyridines (1,4-DHPs) such as nifedipine and other related structures are the most important calcium antagonists and are the drugs of choice for the treatment of cardiovascular disorders such as angina and hypertension [1,2]. It is well-established that the calcium antagonistic activity of members of this family is influenced by (a) the presence of the 1,4-DHP moiety, (b) alkyl groups (preferably methyl) attached at the 2 and 6 positions, (c) ester groups at the 3 and 5 positions, (d) an aromatic substituent at position 4 and (e) an H atom on N1 [1,3,4].

All of the nifedipine derivatives examined by single crystal X-ray diffraction [1,5,6] exhibit a flattened-boat conformation of the 1,4-DHP ring with the N atom at the prow and the phenyl ring in a pseudo axial position at the bow. Structure activity studies have demonstrated that flattening of the boat conformation correlates with increased activity, presumably due to the concurrent change in position of the phenyl ring on C4. It has been recently proposed that the antagonist or agonist activity in DHPs is dependent on the absolute configuration at C-4 (*R*- versus *S*-enantiomer) acting as a molecular switch [7].

In the majority of the more than 30 crystal structures of members of the nifedipine family, the ester groups are found to be nearly coplanar with the nearest double bond in the DHP ring, the carbonyl groups being oriented either *cis* (*sp*, synperiplanar) or *trans* (*ap*, antiperiplanar) to that bond [1]. In nifedipine itself, the carbonyl oxygen of the ester groups are *ap* and *sp* and thus point in opposite directions. It is thought that only the *sp* conformation of the ester group permits hydrogen bonding to the carbonyl O atom as acceptor atom when the drug binds to its receptor site [8,9].

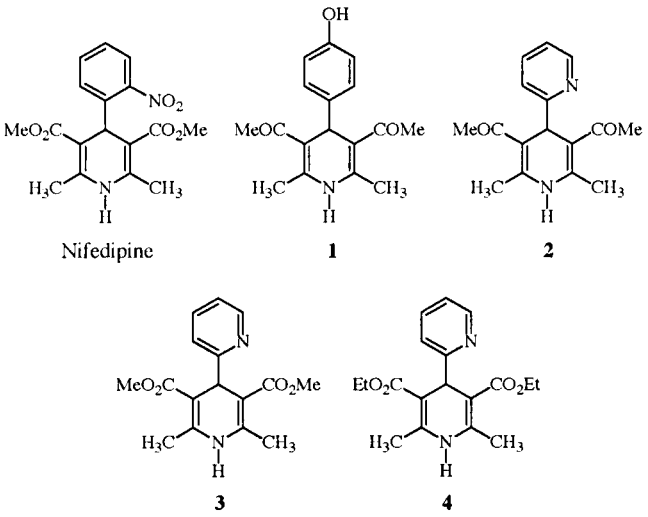
It appears that *o*-phenyl substituted derivatives have a preference for *sp*, *sp* geometry, whereas the non-*o*-substituent derivatives prefer *sp*, *ap* geometry. This is consistent with the thesis that the DHP binding site is non-symmetrical on the receptor, and the probability of the ester groups being *ap*, *sp* oriented when binding is high [6].

The effect of the size of the alkyl substituent in the side chain on the conformation is poorly understood. Variation of the C3 and C5 ester alkyl groups has led to conflicting results. In an early investigation of various DHP derivatives, it was observed that an increase in bulk of the ester side chains led to an increase in activity [10,11]. However, in a series of *meta*-nitrophenyl derivatives, activity appeared to decrease with increasing in the bulk of the ester alkyl groups [12,13]. Furthermore, another investigation revealed that for *ortho*-substituted phenyl derivatives, activity decreased as ester bulk increased and for *meta*-substituted phenyl derivatives, activity increased as ester bulk increased; for *para*-phenyl derivatives, however, activity was always observed to be low no matter what ester groups were present [14].

Recently, we have reported the synthesis and conformational study of other 1,4-DHP-based related structures and we found that the data obtained by AM1 calculations compare quite well with the data obtained by X-ray crystallography analysis [15,16], thus validating these theoretical calculations for predicting conformational features of these compounds.

The crystal structure analyses of 3,5-diacetyl-2,6-dimethyl-4-(4'-hydroxyphenyl)-1,4-dihydropyridine monohydrate, (**1**), 3,5-diacetyl-2,6-dimethyl-4-(2-pyridyl)-1,4-dihydropyridine, (**2**), 2,6-dimethyl-3,5-dimethoxycarbonyl-4-(2-pyridyl)-1,4-dihydropyridine, (**3**), and 3,5-diethoxycarbonyl-2,6-dimethyl-4-(2-pyridyl)-1,4-dihydropyridine, (**4**) (Chart 1), were carried out in order to investigate their conformational features and to evaluate structural differences or similarities among these compounds in an attempt to relate these differences to therapeutic potencies. We also describe the synthesis of these compounds, as well as the comparison between the conformations obtained by the quantum chemical calculations at the semiempirical level (AM1) and the results from the X-ray structural analysis.

Chart 1



Nifedipine **1** **2** **3** **4**

Results and Discussion.

The preparation of compounds **1-4** has been carried out by following the well know Hantzch's procedure for symmetrical 1,4-DHP, refluxing the corresponding β-dicarbonyl compound (2 equivalents) with the aromatic aldehyde (1 equivalent) in the presence of ammonia solution in methanol as solvent. These compounds were obtained as crystalline solids and their structure was confirmed by spectroscopic methods.

The molecular structures of four compounds are shown in Figures 1 and 2, together with their atomic labeling schemes. Within experimental error, the bond distances and angles in the common molecular framework of all the four structures are similar (See Tables 1 and 2).

Triggle [8] and Fossheim [17] have published data that suggest that the puckering of the 1,4-DHP ring is related to the activity of the derivative in question. The distortion from planarity of the atoms comprising the DHP ring can be clearly seen from the torsion angles calculated about the ring bonds. The greatest displacement from zero occurs about bonds from N1 and C4, indicating that the greatest degree of puckering occurs at these positions, the distortion being greatest at the C4 position. The magnitude and sign of these torsion angles indicate that both C4 and N1 (Tables 1 and 2) lie above the plane formed by C2, C3, C5 and C6, which imparts a boat-type conformation to the DHP ring (Qt = 0.276(3), Qt = 0.301(2), Qt = 0.200(4), and Qt = 0.206(2) for **1**, **2**, **3** and **4**, respectively). All substituents at positions 2, 3, 5 and 6 in the DHP ring are slightly below this plane.

When the plane of the aromatic ring attached to C4 is perpendicular to the pseudoplane of the base of the DHP boat, activity increases [8,10]. The torsion angle that describes this parameter in compound **1**, is C3-C4-C1'-C2' (or C3-C4-C1'-N2, for **2**, **3**, **4**). The bisection of the aromatic ring with respect to the DHP ring can be expressed as the difference between this torsion angle and the ideal value of 60°. In compound **1** the hydroxyphenyl ring is attached to C4 in a pseudoaxial position and lies in a plane nearly perpendicular to the mean plane of the 1,4-DHP ring (see Table 1 and Figure 1). This compound exhibits a deviation of 6.1(4)° from the ideal value.

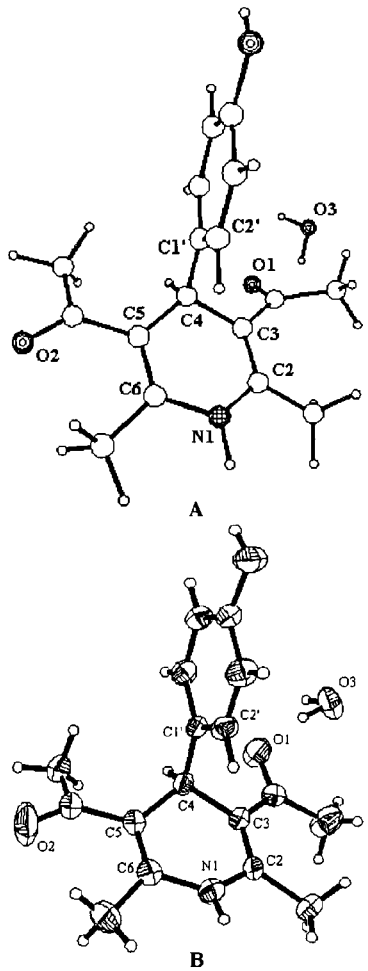


Figure 1. Semiempirical (AM1) geometry (**A**) and X-ray structure (**B**) of compound **1** showing the numbering scheme.

AM1 calculations show a boat conformation for the 1,4-dihydropyridine ring with a pseudoaxial orientation of the aryl group.

Table 1. Most Relevant Bond Distances, Valence Angles and Dihedral Angles for compound **1**. Bond distances are given in Å and angles in degrees. (Standard deviations in parenthesis). The numbering scheme is shown in Figure 1.

1	AM1	X-ray
Bond Distances.		
N1-C2	1.395	1.384 (4)
C2-C3	1.373	1.347 (5)
C3-C4	1.500	1.528 (4)
C4-C5	1.504	1.524 (4)
C5-C6	1.363	1.360 (4)
C6-N1	1.398	1.377 (4)
Valence Angles.		
C2-N1-C6	120.26	124.1 (3)
C3-C4-C5	112.26	111.0 (2)
O1-C-C3	122.58	122.6 (3)
O2-C-C5	121.31	119.0 (3)
Dihedral Angles		
N1-C2-C3-C4	1.5	6.6 (4)
C2-C3-C4-C5	-15.6	-25.4 (4)
C3-C4-C5-C6	16.9	26.6 (4)
C4-C5-C6-N1	-3.3	-8.8 (5)
C5-C6-N1-C2	-13.7	-13.8 (5)
C6-N1-C2-C3	15.2	14.9 (5)
Σ|ρ|	66.2	96.15
C2-C3-C5-C6	-0.7	-0.5
C4-C3-C2-C6	10.1	13.6
N1-C2-C3-C5	-6.1	-7.5
O1-C-C3-C2	13.8	20.8 (5)
O2-C-C5-C6	129.1	-177.9 (3)
C2-C3-C4-C1'	-106.7	-98.9 (4)
C2'-C1'-C4-C3	-75.8	66.1 (4)

Table 2. Most Relevant Bond Distances, Valence Angles and Dihedral Angles for compounds **2, 3, 4**. Bond distances are given in Å and angles in degrees. (Standard deviations in parenthesis). The numbering scheme is shown in Figure 2.

	2		**3**		**4**	
	AM1	X-ray	AM1	X-ray	AM1	X-ray
Bond distances						
N1-C2	1.395	1.379 (2)	1.390	1.377 (6)	1.392	1.372 (3)
C2-C3	1.363	1.359 (2)	1.374	1.357 (6)	1.373	1.354 (3)
C3-C4	1.501	1.527 (2)	1.499	1.535 (6)	1.506	1.521 (3)
C4-C5	1.498	1.522 (2)	1.499	1.514 (6)	1.494	1,520 (3)
C5-C6	1.377	1.361 (2)	1.374	1.365 (6)	1.373	1.358 (3)
C6-N1	1.388	1.377 (2)	1.390	1.376 (6)	1.391	1.385 (3)
Valence Angles						
C2-N1-C6	121.10	123.7 (1)		123.9 (4)	121.4	124.2 (2)
C3-C4-C5	112.50	111.3 (1)	111.1	111.0 (4)	111.3	111.6 (2)
O1-C-C3	121.60	119.1 (1)	128.8	127.8 (4)	128.4	122.4 (2)
O2-C-C5	122.80	122.3 (1)	128.8	128.1 (4)	127.2	127.4 (2)
Dihedral Angles						
N1-C2-C3-C4	3.1	10.5 (2)	-9.6	-7.3 (7)	-9.7	-7.1 (3)
C2-C3-C4-C5	18.0	29.6 (2)	25.5	19.8 (6)	24.8	20.2 (2)
C3-C4-C5-C6	-20.6	-27.8 (2)	-25.4	-19.0 (6)	-24.6	-19.4 (3)
C4-C5-C6-N1	8.5	6.2 (2)	9.5	5.8 (7)	9.5	5.5 (3)
C5-C6-N1-C2	8.4	15.8 (2)	9.2	9.8 (7)	9.2	10.5 (3)
C6-N1-C2-C3	-11.2	-13.9 (2)	-9.2	-8.8(7)	-8.7	-9.7 (3)
Σ|ρ|	69.8	104.60	88.4	70.38	86.5	72.40
O1-C-C3-C2	-123.4	172.9 (2)	7.5	0.6 (8)	171.4	168.3 (2)
O2-C-C5-C6	-10.5	20.0 (2)	-7.6	4.7 (8)	6.4	1.5 (4)
C2-C3-C4-C2'	-104.9	-96.8 (2)	-95.7	-105.6(5)	-96.6	-105.4 (2)
N1'-C2'-C4-C5	-56.0	-52.2 (2)	61.8	-56.6 (5)	-81.7	-61.5 (2)

In compounds **2, 3** and **4** the α-pyridyl ring is attached to C4 in a pseudo-axial position and lies in a plane nearly perpendicular to the mean plane of the 1,4-DHP ring. These compounds exhibit a deviation of 7.8(2)°, 8.2(5)° and 3.8(2)° from the ideal value, respectively. The torsion angles predicted by AM1 agree well with those in the crystal structure (see Table 2).

In compounds **2, 3** and **4**, the most stable conformation corresponds to the heteroatom (N) being synperiplanar to the H atom H(4) of the 1,4-DHP ring. This is in agreement with the previously reported conformation of the 1,4-DHP moiety [18]. Semiempirical calculations predict in all cases this conformation to be 1 kcal/mol more stable than the antiperiplanar, which agrees with their determined crystal structures.

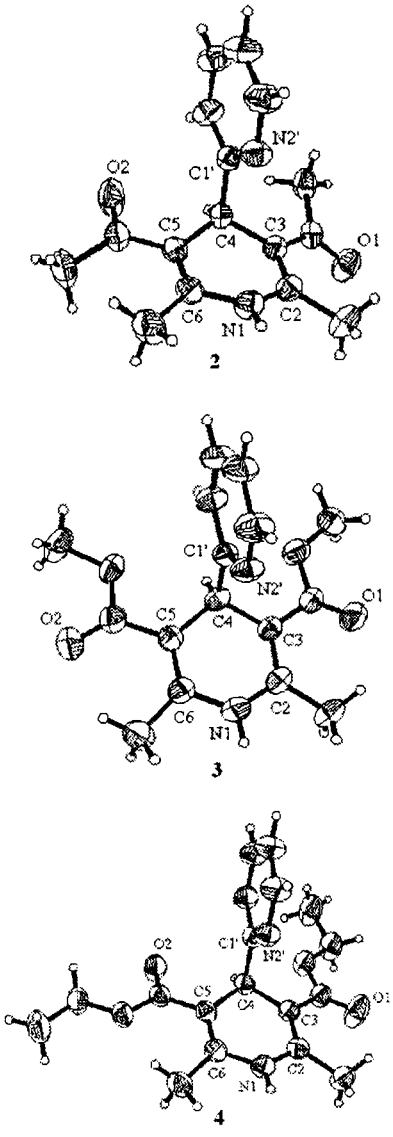


Figure 2. X ray structure of compounds **2**, **3**, and **4** showing the numbering scheme.

The sum, $\Sigma|\rho|$, of the absolute values of the internal torsion angles of the DHP ring is a measure of its planarity (Table 3). Published structure activity ratios indicate that increased planarity of this ring ($\Sigma|\rho|$ tending to zero) correlates with higher activity of the compound. Larger $\Sigma|\rho|$ values are observed, in general, for parent compounds with a nitro group in the *meta* position. This is an indication of the decreased planarity of the DHP ring and hence the lower activity of compounds with a *meta* substituent. Deviations from planarity in the DHP ring, defined as the sum of the numeric values of the six intra-ring torsion angles, range from 52.1° to 112.5° in the investigated nifedipine derivatives [19]. Compound **1** exhibits a $\Sigma|\rho|$ of 96.2(4)°, **2**, 104.6(2)°, **3**, 70.3(6)° and **4**, 72.4(3)°. Hence the methoxycarbonyl group causes the least deviation from planarity of the DHP ring.

For a series of compounds investigated by Triggle and coworkers [8], the authors noted an apparent correlation between activity (as measured by IC_{50} for tonic CD response in guinea pig ileal longitudinal muscle) and the planarity of the DHP ring (as indicated by θ_{ave}, the average of the absolute value of the torsion angles C2-C3-C4-C5 and C3-C4-C5-C6). The value $\theta_{ave} < 15°$corresponds to the most potent compounds in that series. In compound **1** θ_{ave} is 26.0(5)°, and 28.7(2)° in **2**, which is in the range of the least active compounds studied by Triggle's group, whereas compounds **3** and **4** are closer to the limiting value (θ_{ave} is 19.4(6)° and 19.8(3)°, respectively).

Table 3. Structural parameters (°) for compounds **1**, **2**, **3**, **4**.

Compound	$\Sigma\|\rho\|$	Deviation	Ester conformation	θ_{ave}
1	96.2(4)	6.1(4)	*ap sp*	26.0(5)
2	104.6(2)	7.8(2)	*sp ap*	28.7(2)
3	70.3(6)	8.2(5)	*sp sp*	19.4(6)
4	72.4(3)	3.8(2)	*sp ap*	19.8(3)

The bond lengths and valence angles in the 1,4-DHP ring of these structures are generally close to those found in related compounds [20,21]. The mean value of the C=C in the 1,4-DHP ring is in the range of 1.353Å and 1.360Å, which is closer to that found by Krajewski [20] in a related compound (1.365Å) and greater than the 1.32Å value found in *N*-benzyl-1,4-dihydronicotinamide [21]. Although the geometrical features predicted by AM1 calculations compared quite well with the experimental data, AM1 calculations overestimate the double bond distance values and underestimate the single bond distance.

Practically the same C=O bond lengths are observed for both carbonyl groups in all compounds of this series. AM1 calculations and X-ray data show that the conjugated carbonyl group is coplanar with the endocyclic double bonds according to the obtained values of the dihedral angles (O1-C-C3-C2 and O2-C-C5-C6).

In compounds **1**, **2** and **4**, both carbonyl substituted groups are directed counter to one another showing that there is no symmetry element in the molecule. In compound **1** the oxygen in the carbonyl groups are twisted in opposite direction (C3 *ap* and C5 *sp*) to the ring double bonds, similar to that of nifedipine. In compounds **2** and **4** the alkoxycarbonyl groups show the same orientation of the carbonyl groups (C3 *sp*, C5 *ap*), which is the opposite of compound **1**. In compound **3** the methoxycarbonyl groups are twisted in the same direction, both being *sp* to the ring double bonds. This conformation (designated *sp*, *sp*) has also been found in felodipine and other DHP structures [8,19,22], although the conformation where the carbonyl groups are twisted in opposite direction (*ap*, *sp*) occurs most frequently. AM1 calculations for **1**, **2** and **4**, found a local minimum with *sp/ap* arrangement and found for compound **3** that the *sp/sp* arrangement is 2 kcal/mol more stable than *ap/sp*.

It may be that the *ap*, *sp* conformation is favoured statistically as it can be achieved in two ways. The fact that both conformations are observed in a variety of crystalline environments strongly suggests that they do not differ much in terms of energy. Therefore, it is expected that the conformation with the highest receptor affinity can be adopted in all compounds. This solid-state conformational difference between the compounds should therefore be irrelevant to questions concerning their pharmacological activity [19].

In each of the crystal structures previously reported having a phenyl substituent on C4, the hydrogen on N1 participates in an intermolecular hydrogen bond with the neighbouring carbonyl oxygen. This is not the case for compound **1**, where the hydrogen bonds between the hydroxyl group in *para* position of the phenyl ring, one of the carbonyl groups and the crystallized water molecule make the hydrogen bonding pattern more complex than in the other crystal structures in this series and in related compounds previously reported [23]. The water molecule participates in three hydrogen bonds (Table 4). It is acceptor when it is involved in hydrogen bonding to a neighbouring 1,4-DHP molecule by means of a strong hydrogen bond to the amino group, and a donor in the hydrogen bonds to O3' and O1 of the carbonyl and hydroxy groups, respectively. An intermolecular hydrogen bond is also formed between the O2 carbonyl and the O1 hydroxy group of the neighbouring molecule.

An exception to the characteristic N1-H···O=C bonding type is observed in β-pyridyl analogues [20,24], where the hydrogen acceptor is in the pyridine ring nitrogen. This is also the case found in this α-pyridyl compounds, where the molecules are held together by this interaction forming dimers. The differences in the hydrogen bonding parameters found for various compounds of this class are insignificant, indicating that the degree of ring puckering does not influence the strength of the interaction at N1.

Table 4. Hydrogen-bonding geometry (Å, °). W, refers to water molecule.

Compound 1				
D-H	*D...A*	*H...A*	*D-H...A*	
O2-H1W	O2...O3'	H1W...O3'	O2-H1W...O3'	(i)
1.022(3)	2.841(3)	1.825(2)	172.2(2)	
O1-H1	O1...O5'	H1...O5'	O1-H1...O5'	(ii)
0.820(2)	2.727(4)	1.936(3)	161.7(2)	
N1-H1	N1...O4	H1...O4	N1-H1...O4	(iii)
0.860(3)	2.896(4)	2.058(3)	164.7(2)	
O4-H2W	O4...O1	H2W...O1	O4-H2W...O1	(iv)
0.999(3)	2.867(4)	1.870(3)	176.2(2)	
Symmetry:				
(i) x, y, z; (ii) -x+1, y+1/2, -z+1/2; (iii) -x, y-1/2, -z-1/2; (iv) x-1, y, z.				
Compound 2				
D-H	*D...A*	*H...A*	*D-H...A*	
N1-H1	N1...N2	H1...N2	N1-H1...N2	
0.860(1)	3.071(2)	2.215(1)	173.27(9)	
Symmetry: -x+1, -y+1, -z				
Compound 3				
D-H	*D...A*	*H...A*	*D-H...A*	
N1-H1	N1...N2	H1...N2	N1-H1...N2	
0.860(4)	2.972(5)	2.115(4)	175.0(3)	
Symmetry: -x+1, -y+1, -z+1				
Compound 4				
D-H	*D...A*	*H...A*	*D-H...A*	
N 1-H1	N1...N2	H1...N2	N1-H1...N2	
0.860(2)	2.962(2)	2.102(2)	178.1(1)	
Symmetry: -x+1, -y+1, -z+1				

In summary, we have carried out a structural study by X-ray analysis and semiempirical (AM1) calculations of 1,4-dihydropyridine derivatives. Both methods show a boat conformation for the 1,4-dihydropyridine ring with a pseudoaxial orientation of the aryl group in position 4. The conformational features reported for 1,4-DHP calcium modulators are preserved for the compounds presented in this work, which indicate the potential activity of these compounds as biologically active systems.

EXPERIMENTAL

Melting points were determined in a capillary tube in an Electrothermal C14500 apparatus and are uncorrected. The nmr spectra were recorded on a Bruker AC spectrometer operating at 250 MHz for ^1H and 62.0 MHz for ^{13}C. Chemical shifts are given as δ values against tetramethylsilane as the internal standard and *J* values are given in Hz. The ir spectra were measured with a Bruker IRS48 instrument as potassium bromide pellets. Mass spectra were obtained with a Hewlett Packard 5890 instrument. Microanalyses were performed by the Servicio de Microanálisis of Universidad Complutense de Madrid. The reactions were monitored by tlc performed on silica-gel plates (Merck $60F_{250}$) and using benzene:methanol (2:1) as the eluent. Commercially available starting materials and reagents were purchased from commercial sources (BDH and Fluka) and were used without further purification. Aromatic aldehydes were distilled before use.

Semiempirical AM1 calculations [25] were carried out by using the MOPAC [26] program. Previously, the molecular geometries were optimised by using Allinger's Molecular Mechanics [27] with PCMODEL program [28]. Calculations were performed on a PC 486/33 computer.

Crystals of each compound were grown by slow evaporation of ethanol solutions. The crystallographic and experimental data for these materials are summarized in Table 5. Measurements were carried out using a Siemens P3/R3 single crystal four-circle diffractometer. Detailed crystallographic data have been deposited at the Cambridge Crystallographic Data Centre and are available on request.

Table 5. X-ray Crystallographic data for compounds **1**, **2**, **3**, **4**.

Parameter	**1**	**2**	**3**	**4**
Solvent	Ethanol	Ethanol	Ethanol	Ethanol
Empirical formula	$C_{17}H_{19}NO_3 \bullet H_2O$	$C_{16}H_{18}N_2O_2$	$C_{18}H_{22}N_2O_4$	$C_{16}H_{18}N_2O_4$
Formula weight	303.348	270.330	330.383	302.329
Crystal size, mm	0.30x0.30x0.20	0.35x0.35x0.22	0.40x0.30x0.22	0.52x0.15x0.1
Crystal system	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P2_1/c$
a, (Å)	9.2581(7)	7.7465(7)	10.4651(8)	7.3690(10)
b, (Å)	16.1004(13)	9.8984(11)	11.8374(8)	11.2430(6)
c, (Å)	10.8117(9)	18.7789(28)	14.4572(14)	18.8720(14)
β, (°)	103.85(1)	101.79(1)	103.49(1)	98.01(2)
V (Å^3), Z	1564.7(2), 4	1409.5(3), 4	1741.5(3), 4	1548.3(3), 4
D_{calc}, (Mg/m^{-3})	1.2112	1.2739	1.2601	1.2970
Wavelength, (Å)	1.54178	1.54178	1.54178	1.54178
Temperature, K	293(2)	293(2)	293(2)	293(2)
2θ max, (°)	138.26	138.36	138.29	138.38
Limiting indices, *h*	-11, 1	-1, 9	-1, 12	-1, 8
k	-19, 1	-1, 12	-1, 14	-13, 1
l	-11, 13	-22, 22	-17, 17	-22, 22
Reflections collected	3668	3686	4190	4046
Independent reflections	2759	2516	3048	2789
Data/restraints/parameters	2759/0/205	2516/0/186	3048/0/222	1530/0/204
Goodness-of-fit on F^2	1.291	1.043	1.074	1.043
Final *R* indices [I>2σ (I)]	*R* = 0.0476, *wR* = 0.1948	*R* = 0.0422, *wR* = 0.1180	*R* = 0.0524, *wR* = 0.1629	*R* = 0.0655, *wR* = 0.1888
Extinction coefficient	0.005298	0.018857	0.012350	0.006698
Largest diff. peak, eÅ^{-3}	0.24	0.21	0.21	0.35
Largest diff. hole, eÅ^{-3}	-0.24	-0.15	-0.24	-0.24

The structures were solved by direct methods and Fourier synthesis. Non-H atoms were refined anisotropically by full-matrix least-squares techniques. H atoms were calculated geometrically and included in the refinement, but were restrained to ride on their parent atoms. The isotropic displacement parameters of the H atoms were fixed to 1.3 times *Ueq* of their riding atoms. Data collection: XSCANS [29]. Cell refinement XSCANS [29]. Data reduction: XSCANS [29]. Program(s) used to solve structure: SHELXS97 [30]. Program(s) used to refine structure: SHELXL97 [31]. Molecular graphics: DIAMOND [32]. Software used to prepare material for publication: PLATON [33].

3,5-Diacetyl-2,6-dimethyl-4-(4'-hydroxyphenyl)-1,4-dihydropyridine (**1**).

A mixture of *p*-hydroxybenzaldehyde (0.01 mole), acetylacetone (0.02 mole), ammonium hydroxide 30% (2 ml) in 20 ml of methanol was heated at reflux overnight. The solvent was evaporated and the obtained solid was recrystallized from ethyl ether, 22% yield, mp 184–186°; ir (potassium bromide): 3330 (NH), 1660 (C=O), 1560 and 1425 cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6) δ: 9.15 (s, H, OH), 8.80 (1H, s, NH), 6.95 (2H, d, Ph, J = 8.1), 6.60 (2H, d, Ph, J = 8.1), 4.54 (1H, s, CH), 3.45 (6H, s, CH_3) and 2.20 (6H, d, CH_3); ^{13}C nmr (dimethylsulfoxide-d_6) δ: 196.8 (C=O), 155.6 (C2, C6), 143.8 (C1'), 137.8 (C4'), 128.1 (C2', C6'), 114.1 (C3', C5'), 112.9 (C3, C5), 38.1 (C4), 30.0 (C10, C12) and 19.1 (C7, C8); ms: *m/z* 285 (M^+), 284 (M^+-H), 270 (M^+-CH_3), 242 (M^+-$COCH_3$) and 192 (M^+-C_5H_5OH).

Anal. Calcd. For $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.62; H, 6.77; N, 5.08.

Synthesis of 4-(2-Pyridyl)-1,4-dihydropyridine **2**, **3**, **4**.

General procedure.

A mixture of the appropriate dicarbonyl compound (0.02 mole), 2-pyridincarbaldehyde (0.01 mole), ammonium hydroxide 30% (2 ml) in 20 ml of methanol was heated at reflux overnight and then poured into ice water. The solid that precipitated was collected by filtration. Further purification was accomplished by recrystallization from ethanol.

3,5-Diacetyl-2,6-dimethyl-4-(2-pyridyl)-1,4-dihydropyridine (**2**).

This compound was obtained from acetylacetone, following the general procedure, in 73% yield, mp 164–165°; ir (potassium bromide): 3330 (NH), 1720 (C=O), 1620 (C=C), 1490 and 1425 cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6) δ: 8.90 (1H, s, NH), 7.12–8.45 (4H, m, aromatic) 5.20 (1H, s, CH), 3.42 (6H, s, CH_3) and 2.29 (6H, d, CH_3); ^{13}C nmr (dimethylsulfoxide-d_6) δ: 196.9 (C=O), 165.0, 144.4, 136.7, 121.3, 121.0 (aromatic), 148.8 (C2, C6), 110.9 (C3, C5), 42.1 (C4), 29.9 (CH3) and 18.8 (CH3); ms: *m/z* 270 (M^+), 269 (M^+-H), 255 (M^+-CH_3); 227 (M^+-$COCH_3$) and 192 (M^+-NC_5H_5).

Anal. Calcd. For $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 71.22; H, 6.87; N, 10.41.

2,6-Dimethyl-3,5-dimethoxycarbonyl-4-(2-pyridyl)-1,4-dihydropyridine (**3**).

This compound was obtained from methylacetoacetate, following the general procedure, in 71% yield, mp 246–248°; ir (potassium bromide): 3320 (NH), 1690 (C=O), 1620 (C=C), 1490 and 1425 cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6) δ: 8.75 (1H, s, NH), 7.10-8.50 (4H, m, aromatic), 5.05 (1H, s, CH), 3.59 (6H, s, OCH_3) and 2.21 (6H, s, CH_3); ^{13}C nmr (dimethylsulfoxide-d_6) δ: 167.4 (CO_2), 164.8, 146.2, 135.8, 121.3, 121.2 (aromatic), 149.1 (C2,C6), 100.2 (C3,C5), 50.6 (OCH_3), 40.1 (C4) and 18.3 (CH_3); ms: *m/z* 302 (M^+), 287 (M^+-CH_3), 271 (M^+-OCH_3), 243 (M^+ - $COOCH_3$) and 224 (M^+-NC_5H_5).

Anal. Calcd. For $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.67; H, 6.20; N, 9.40.

3,5-Diethoxycarbonyl-2,6-dimethyl-4-(2-pyridyl)-1,4-dihydropyridine (**4**).

This compound was obtained from ethylacetoacetate, following the general procedure, in 63% yield, mp 195-197°; ir (potassium bromide): 3320 (NH), 1685 (C=O), 1620 (C=C), 1490 and 1425 cm^{-1}; ^1H nmr (dimethylsulfoxide-d_6) δ: 8.75 (1H, s, NH), 7.65-8.45 (4H, m, aromatic), 5.05 (1H, s, CH), 1.12 (6H, t, CH_3), 4.05 (4H, q, CH_2) and 2.21 (6H, d, CH_3); ^{13}C nmr (dimethylsulfoxide-d_6) δ: 166.9 (CO_2), 165.1, 145.9, 136.7, 121.8, 121.2 (aromatic), 149.0 (C2, C6), 100.4 (C3-C5), 58.9 (O-CH_2), 42.6 (C4), 18.3 (CH_3) and 14.2 (CH_3); ms: *m/z* 330 (M^+), 329 (M^+-H), 315 (M^+-CH_3), 285 (M^+-OCH_2CH_3) and 252 (M^+-NC_5H_5).

Anal. Calcd. For $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.59; H, 6.82; N, 8.51.

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