Synthesis, structural and conformational properties, and gas phase reactivity of 1,4-dihydropyridine ester and ketone derivatives†

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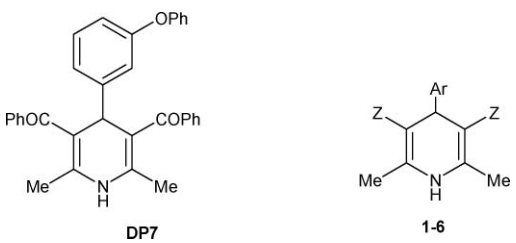
A new series of 4-aryl-2,6-dimethyl-1,4-dihydropyridines, characterized by ester or ketone functions at positions 3 and 5, has been synthesized. Structural and conformational properties, concerning the dihydropyridine ring and the orientation (synplanar/antiperiplanar) of the substituents have been investigated in their crystal structure and in solution by nuclear magnetic resonance. Evaluation of intermolecular and hydrogen bonding interactions as well as packing features, have been also carried out, evidencing interesting packing motifs. Their gas phase reactivity, as protonated and deprotonated molecules, has been investigated by electrospray ionization, high resolution and collision-induced dissociation multiple stage mass spectrometry. Deydrogenation reactions have been observed as a function of the capillary voltage.

Introduction

1,4-Dihydropyridines (1,4-DHPs) are an important class of chemicals widely used as drugs or their precursors.[1] The DHP moiety is common to numerous bioactive compounds such as antihypertensive, vasodilator, antimutagenic and antidiabetic agents.[2,3] Nifedipine, nitrendipine and nimodipine are example of commercially available calcium channel blockers used for the treatment of cardiovascular diseases and containing the DHPs motif.[4,5] 1,4-Dihydropyridines containing different ester moieties and diethyl carbamoyl groups are potential antitubercular agents,[6] while differently functionalized 1,4-DHPs are useful for regeneration of the reduced form of nicotinamide adenine dinucleotide (NADH), an essential compound for living organisms.[7,8] The use of this class of molecules as a scaffold to develop novel antitumor therapies has been recently proposed.[9] For example, the dihydropyridine **DP7** (Scheme 1) has been shown to be a potent inhibitor of P-gb and therefore has potential to become a good candidate in novel treatments for cancers that have developed multi drug resistance (MDR).[10,11]



Scheme 1

Considering the promising activity of **DP7**, we have embarked on a research program aimed at introducing additional diversity in the 1,4-dihydropyridine moiety with the obvious tasks of (*i*) obtaining more powerful P-gp inhibitors; (*ii*) gaining an insight on the tridimensional properties of these products, as their chemical properties are linked to the observed biological activity. Modifications of the aromatic group present at position 4 and/or of the 3,5-diacyl groups were performed to create a small library of compounds (Scheme 1, **1–6**) characterized by either an ester or a ketone functionality at positions 3 and 5.

The conformation of the dihydropyridine ring, the nature of the substituents and their mutual orientation play a key role for the biological activity of 1,4-DHPs. For this reason, a detailed study of the crystal structures of compounds **1**, **2** and **6** has been carried out. We have also studied the gas phase properties and reaction pathways of protonated $[M+H]^+$ and deprotonated $[M-H]^-$ ions produced by **1–6** under electrospray ionization (ESI). This study was then complemented by multistage mass spectrometry (MS^n) experiments and theoretical calculations.

Results and Discussion

Synthetic approach

Compounds **1–6** were prepared according to the classical Hantzsch condensation of one equivalent of an aryl aldehyde with two equivalents of a 1,3-dioxo compound and ammonia, as reported in Scheme 2. Satisfactory yields were obtained for the preparation of esters **1**, **3**, **5** and **6**, whereas compounds **2** and **4** were formed in only modest yields in a complex reaction mixture.

X-Ray crystallography

In the X-ray structures of **1**, **2** and **6** (Fig. 1) the 1,4-DHP ring has a shallow boat conformation. Atoms N(1) and C(4) show small displacements from the base of the boat plane defined by C(2), C(3), C(5) and C(6). As already observed in other 1,4-DHP structures,[12,13] as well as in the present crystal structures, N(1) shows a smaller deviation from that plane (average 0.112(3) Å)

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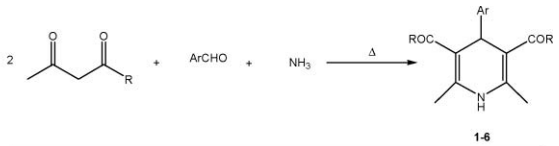
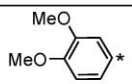
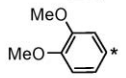
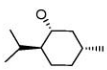
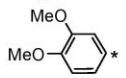


1-6

Compd	R	Ar	Yield %
1	OMe		52
2	Ph		20[a]
3	OMe		70
4	Ph		8[a]
5	OEt		45
6			30

[a] After chromatographic separation

Scheme 2

compared to C(4) (average 0.273(3) Å). The shallowness of the boat is indicated by the puckering parameters (Table 1) that differ from those characterizing an ideal boat ($\theta = 90°$ and $\varphi 2 = n \times 60°$).[14]

The sum of the absolute values of the ring internal torsion angles (P) is another quantitative measure suggested for the evaluation of the flatness of the six-membered ring.[15] These values range from 75.6(4) (**2**) to 89.0(3)° (**1**) (Table 1), indicating a significant amount of flattening from the ideal boat conformation. In nifedipine, a calcium channel blocking drug, the value of P is 72°.[16–19] The phenyl ring at C(4) almost bisects the 1,4-dihydropyridine ring both in **1** and in the two molecules of **6**, while the dihedral angle between the two planes is 76.41(12)° in **2** (Table 2). Similarly to other 1,4-dihydro-pyridine derivatives,[12,18] in all the compounds the two exocyclic substituents at C(3) and C(5) show the opposite orientation with synplanar/antiperiplanar conformation at the two double bonds (Table 2) that imparts chiral character to the 1,4-dihydropyridine ring. **1** and **2** are a racemic mixture in the crystal, as it results by the centrosymmetric space groups ($P2_1/c$ and *Pbca*, respectively) in which they crystallize, while **6** crystallizes in a chiral space group ($P2_1$) (see below). The ester groups in **1** are almost coplanar with the 1,4-DHP ring due to the electron delocalization of the conjugated double bond system involving

Table 1 Geometric and puckering parameters for the 1,4-dihydropyridine ring in compounds **1**, **2** and **6**

Compd	N(1) dev[a]	C(4) dev[a]	*P*[b]	Q(Å)	θ(°)	φ_2 (°)
1	0.117(2)	0.308(2)	89.0(3)	0.253 (2)	72.2(4)	183.4 (4)
2	0.097(2)	0.262(3)	75.6(4)	0.215 (3)	71.9(8)	187.1 (7)
6 (mol A)	0.115(3)	0.262(3)	77.5(5)	0.222 (4)	75.0 (10)	178.1 (10)
6 (mol B)	0.120(3)	0.258(3)	77.3(5)	0.222 (4)	75.6 (10)	178.9 (10)

[a] Deviation (Å) from the least square plane defined by C(2),C(3),C(5), C(6)
[b] P = sum of the absolute values of the ring internal torsion angles of the 1,4-dihydropyridine ring

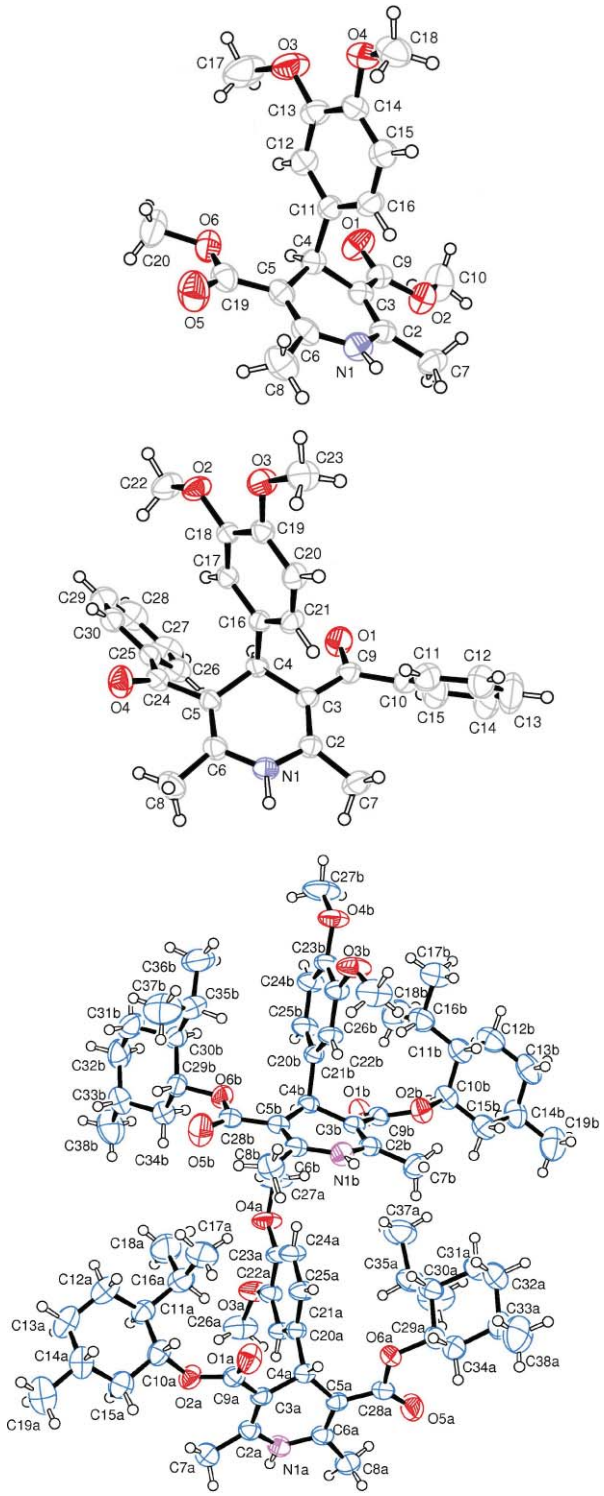


Fig. 1 ORTEP view of the crystal structures of **1** (top), **2** (middle), and of the two molecules constituting the asymmetric unit of **6** (bottom). Ellipsoids enclose 50% probability.

C(2)–C(3)–C(9)–O(1) and C(6)–C(5)–C(19)–O(5) (Table 2). When the substituents of the exocyclic carbonyl or carboxy groups are larger than a methyl group, the steric hindrance plays a key role on the conformational features. The orientation of the cyclohexyl group is very similar in the two molecules of the asymmetric unit

Table 2 Significant torsion and dihedral angles (°) in compounds **1**, **2** and **6**

Compd	C(2)═C(3)–C(9)═O(1)	C(6)═C(5)–C═O	Φ[a]	Δ[a]	Π[a]
1	177.1(2)	8.8(3)	87.69(9)	—	—
2	153.7(3)	43.4(4)	76.41 (12)	74.43 (15)	59.44(13)
6 (molA)	150.4(4)	1.8(6)	87.97 (18)	54.87 (18)	85.54(19)
6 (molB)	149.7(4)	1.8(6)	88.18 (18)	55.29 (18)	85.47(19)

[a] Φ = dihedral angle between the 4-aryl and the 1,4-dihydropyridine ring; Δ = dihedral angle between 1,4-DHP and the ap-Ph/cHex; Π = dihedral angle between 1,4-DHP and the sp-Ph/cHex

of **6** and close to the orientation of the phenyl ring in **2**. The ring bound to the *syn* periplanar ester (in **6**) or to the carbonyl group (in **2**) is almost perpendicular to the 1,4-DHP ring, while when the ring is bound to the *anti* periplanar ester/carbonyl group its orientation is further from perpendicularity (Table 2). The *m*-methoxy group in the dimethoxyphenyl ring has a different orientation in the three crystal structures. In fact in both the molecules of **6** it is directed over the 1,4-DHP ring and it has a *anti* periplanar orientation with respect to the C(4)–H bond.

In contrast, in both **1** and **2** the *m*-methoxy group is directed away from the 1,4-DHP ring with a *syn* periplanar orientation with respect to the C(4)–H bond.

It is worth noting that in the two molecules of **6** the isopropyl groups are oriented towards the centroid of the phenyl ring at position 4 of the 1,4-DHP, thus forming C–H···π···H–C interactions[20] (Fig. 2). These interactions produce conformational rigidity for the phenyl ring that imparts chiral character to **6**. Conformational rigidity seems to occur also in solution. In fact this feature, together with the different orientation of the carboxy groups, causes the two methyl groups in position 2 and 6 of the 1,4-DHP ring, as well as those of the isopropyl group, to produce

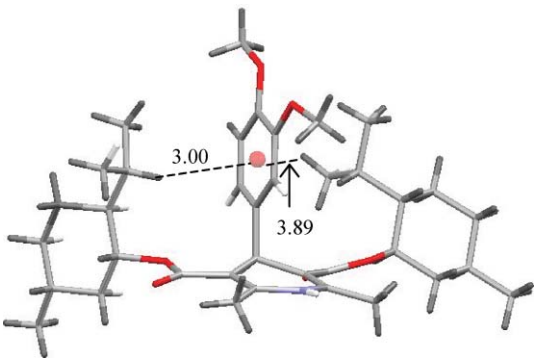


Fig. 2 C–H···π interactions in one molecule of the asymmetric unit of **6**. Distances are in Å.

different ^{1}H and ^{13}C NMR signals. On the other hand, this effect is absent in the case of the remaining 1,4-DHP (**1–5**).

The study of crystal packing of **1** and **2** reveals an interesting feature due to molecular associations that yield a one-dimensional extended chain. This chain is characterized as the C(6) packing motif,[19] *via* intermolecular N(1)–H···O(1) hydrogen bonds involving the nitrogen atom of the 1,4-dihydropyridine moiety and the oxygen atom of the carbonyl group in *ap* conformation. The N···O distances are equal to 2.886(2) and 3.012(3) Å in **1** and **2**, respectively (Table 3).

In **2**, two hydrogen bonding interacting molecules are in positions (*x*, *y*, *z*) and (*x*, *1*+*y*, *z*) and, as a consequence, they are coplanar with each other and translated along the *b* axis. In **1**, two adjacent molecules are in positions (*x*, *y*, *z*) and ($\frac{1}{2}$−*x*, −$\frac{1}{2}$+*y*, *z*), thus causing an almost orthogonal orientation of the two molecules (Table 3).

In both the molecules of **6**, the hydrogen bonding pattern is different. In fact the hydrogen bonds involve the nitrogen atom and the oxygen atoms of the *m*- and *p*-methoxy group, thus forming five-membered chelate rings. In the two molecules the N(1)···O(3) distances average 3.133(4) Å while those N(1)···O(4) average 3.065(4) Å (Table 3).

In addition to classical hydrogen bonding interactions, there are several intermolecular interactions, such as –C–H···O interactions. In **2** these involve C(30)–H (*x*,*y*,*z*) that interacts with both O(2) and O(3) of a molecule at *1*−*x*,−*y*,−*z*, thus causing the formation of a chelate five membered ring and a dimeric structure.

Gas phase behavior of protonated and deprotonated molecules

The characterization of the structure and reactivity of cationic and anionic species produced in the gas phase from compounds **1–6** have been carried out by electrospray ionization, using positive and negative mode, and by tandem mass spectrometry through MS^n experiments. Elemental compositions of ions have been attributed by means of high resolution-accurate mass measurements performed with a FT-ICR coupled to an ion trap mass spectrometer. The ESI(+) mass spectra of compounds **1–6** show the presence of $[M+H]^+$ and the adduct $[M+Na]^+$ while fragment ions are undetectable, in agreement with the *soft* nature of electrospray ionization.

An interesting feature is the dehydrogenation process that occurs as a function of the capillary voltage. As an example, in the case of compound **1**, at low capillary voltage values, the ESI(+) mass spectrum shows abundant $[M+H]^+$ ions at *m*/*z* 362. By increasing the capillary voltage, the elimination of two hydrogen atoms occurs yielding ions at *m*/*z* 360. It is likely that the dehydrogenation reaction involves the dihydropyridine ring that is aromatized to a pyridine ring by loss of a molecule of hydrogen. The resulting

Table 3 Intermolecular hydrogen-bonding interactions in compounds **1**, **2** and **6**

#	Donor-H	Acceptor/A	Symmetry	H···A (Å)	D···A (Å)	D–H···A (°)
1	N(1)–H	O(1)	$\frac{1}{2}$−*x*,−$\frac{1}{2}$+*y*, *z*	2.03	2.886 (2)	178
2	N(1)–H	O(1)	*x*, *1*+*y*, *z*	2.12(3)	3.012 (3)	165(2)
6	N(1A)–H	O(3B)	−*1*+*x*,*y*,*1*+*z*	2.44	3.140 (4)	139
	N(1A)–H	O(4B)	−*1*+*x* *y*,*1*+*z*	2.26	3.067 (4)	156
	N(1B)–H	O(3A)	*1*+*x*,*y*,*z*	2.43	3.127 (4)	138
	N(1B)–H	O(4A)	*1*+*x*, *y*, *z*	2.26	3.064 (4)	156

ions are considerably stabilized by their aromatic conjugated system. Elimination of H_2 also occurs under electron ionization of analogous 1,4 dihydropyridines.[21]

Low energy collision induced decompositions of the ions at *m/z* 362 cause fragmentation of the carbomethoxy side chains in positions 3 and 5 with consecutive elimination of two molecules of methanol, yieding ions at *m/z* 330 and 298, respectively.

The elimination of alcohols, also described for ESI-MS/MS experiments on analogous compounds,[22] can be rationalized by assuming an hydrogen atom transfer from each methyl group at the C-2 and C-6 positions to the methoxy moieties. This should be favored by the *cis* configuration of the disubstituted double bond and by a six-membered transition state, thus resembling an *ortho*-elimination in ionized aromatic systems.[23]

Different structures might be proposed for the ionic species at *m/z* 298, such as a (2,6-dimethylenepiperidine-3,5-diylidene)dimethanone derivative. However, the most reasonable is that in which the 3,5-di(carboxymethyl)-dihydropyridine moiety is converted into a tricyclo decadiene system (Fig. 3). This latter is in agreement with the MS^4 spectrum obtained by selecting the species at *m/z* 298 whose product ions (*m/z* 270 and 256) could be easily formed from the proposed structure (Fig. 3).

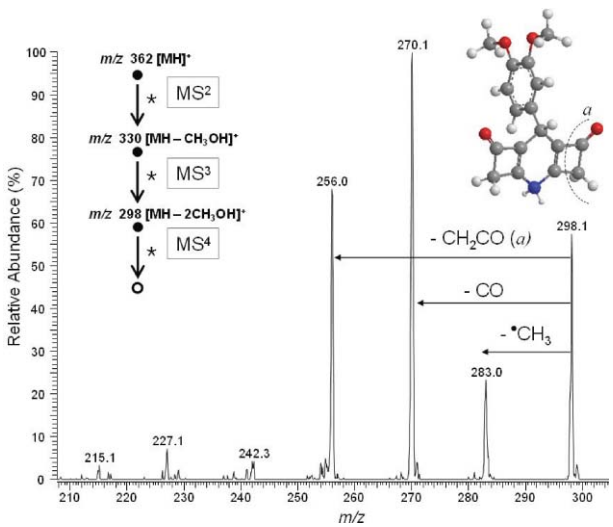


Fig. 3 ESI(+) MS^4 product ion spectrum of the ions at *m/z* 298 obtained by compound **1**. The PM6 energy minimized structure is also depicted.

Also the MS/MS product ion mass spectrum of the oxidized species at *m/z* 360 shows consecutive elimination of two methanol molecules yielding ions at *m/z* 328 and 296, respectively, together with other abundant fragment ions at *m/z* 345 and 330 attributable to $[((M+2H)+H) - CH_3]^{+\bullet}$ and $[((M+2H)+H) - 2\ CH_3]^+$, respectively.

In contrast, CID decompositions of the protonated diketone **2** (*m/z* 454) involve almost exclusively the loss of a 1,2-dimethoxybenzene molecule, yielding ions at *m/z* 316 whose abundance is 100%. Owing to this loss, the pyridine ring gains aromaticity thus forming a thermodynamically stable species. It is worth noting that in the ester derivatives elimination of the aryl group in position 4 occurs to only a minor extent, yielding ions with abundances not higher that 8%. On the other hand, in the keto derivatives, decompositions involving the substituents at position 3 and 5 are only minor processes. As an example, elimination of benzaldehyde from $[\mathbf{2}+H]^+$ produces ions at *m/z* 348 with relative abundance below 5%.

Mass spectrometry has been also used to study the gas phase reactivity of anions derived from compounds **1–6**. To the best of our knowledge, this is the first investigation concerning deprotonated 1,4-dihydropyridines. Their ESI(–) mass spectra show only the species $[M - H]^-$ and $[M+Cl]^-$. When the anions $[M - H]^-$ are submitted to CID experiments, their MS^n spectra show interesting features. In contrast to the protonated molecules, whose gas phase reactions follow few decomposition pathways, deprotonation followed by CID gives a lot of abundant product ions. Most of them are produced by loss of some or all substituents at positions 2, 3, 5, 6 of the heterocyclic ring. Loss of the neutral side chain in position 3 and 5 of the dihydropyridine nucleus from deprotonated **2** yields abundant ions at *m/z* 346 ($[(M–H) – C_6H_5CHO]^-$), while in the case of $[\mathbf{1}\text{-}H]^-$ elimination of $^\bullet OH$, $^\bullet CH_3/CH_3OH$ is observed and it gives ions at *m/z* 328. The decomposition of these two ionic species involves consecutive eliminations of methyl radicals, as confirmed by MS^n experiments. Losses of radical species from even-electron ions are uncommon pathways under electrospray ionization,[24] while for these compounds they produce very abundant species.

Concerning the ions at *m/z* 346, two possible structures based on 2-methylene pyridine and on azepine moieties might be proposed. Theoretical calculations show that the former (Fig. 4, top) is more stable than the latter, having a heat of formation,

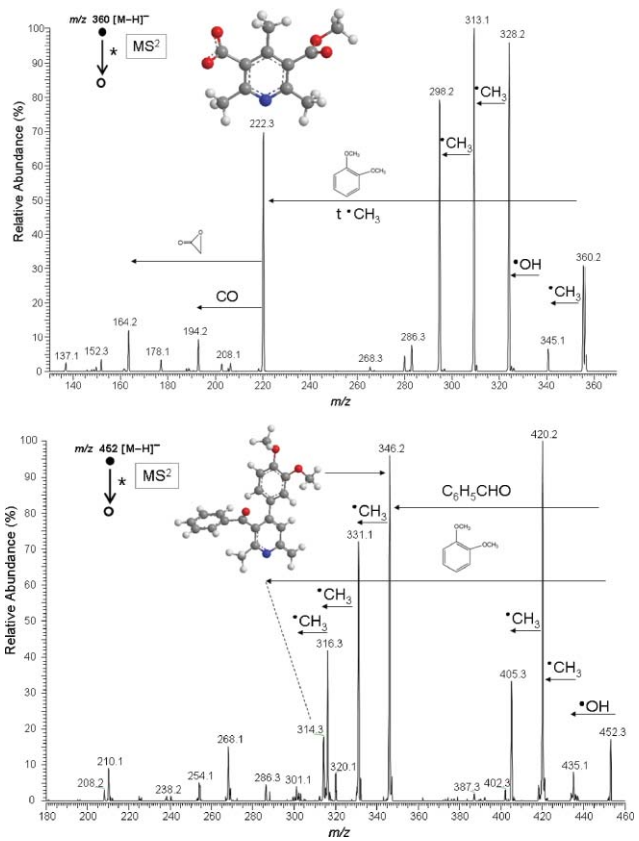


Fig. 4 ESI(–) MS^2 product ion spectra of the species $[M - H]^-$ produced by compounds **1** (top) and **2** (bottom). The arrows indicate reaction pathways confirmed by MS^3 experiments. PM6 energy minimized ion structures for ions at *m/z* 222 (top) and 346 (bottom) are also depicted.

calculated by PM6, 7.3 kcal mol^{-1} less than that calculated for the azepine derivative.

Abundant ions at m/z 420 are present in the CID mass spectrum of [**2**-H]$^-$. (Fig. 4, bottom). They correspond to the loss of 32 u from [M – H]$^-$, easily attributable to CH_3OH. But the radical ions at m/z 435 ([(M–H)–CH_3]$^{-\bullet}$) are also produced. Thus it is likely that ions at m/z 420 may be produced by direct loss of methanol and/or by successive eliminations of $^\bullet CH_3$ and $^\bullet OH$. A two step elimination of methanol is also observed for [**1**-H]$^-$. In fact, under CID conditions, ions at m/z 435 and 420, due to consecutive losses of $^\bullet OH$, from the enol form, and $^\bullet CH_3$, respectively, occur.

Elimination of the neutral substituent at position 4 of the dihydropyridine ring is an important decomposition pathway for [**1**-H]$^-$, yielding ions at m/z 222 (Fig. 4, top). In this case two possible structures, one with the negative charge formally on C(4) and another with it on a carboxy group, after methyl transposition, might be formed. PM6 calculations suggest that the latter (Fig. 4, top) is 53.7 kcal mol^{-1} more stable than the former. Elimination of the neutral aryl substituent at position 4 is only a minor CID reaction pathway for [**2**-H]$^-$. In fact the resulting ions (m/z 314) have relative abundance equal of 15%.

Experimental section

General information

All the solvents were previously dried according to standard procedures. Analytical TLC was performed on silica gel 60 F_{254} plates. Flash column chromatography was carried out on silica gel (0.040–0.063 mm). Melting points were determined on a Kofler hot stage and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 27 °C ($CDCl_3$), unless otherwise stated, on a Bruker Avance 400 instrument operating at 400.13 MHz for ^{1}H and at 100.62 MHz for ^{13}C. The chemical shifts are reported in ppm on the δ scale, using the solvent peak as a reference value. Data are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, m = multiplet, b = broad. J are in Hz.

General procedure for the preparation of the 1,4-dihydropyridines (1–6)

A solution of 1,3-dicarbonyl compound (20 mmol), ammonia 28% (1 mL) and the suitable aldehyde (10 mmol) in ethanol (20 mL) was refluxed for 24 h following the Hantzsch protocol. Evaporation of the solvent gave an oily residue which was column chromatographed using light petroleum/ethyl acetate (4 : 1 v/v) as eluent.

Dimethyl 4-(3,4-dimethoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (1). Reagents: acetylacetone and 3,4-dimethoxybenzaldehyde according to the procedure reported by Ohsumi *et al.*[25] m.p. 144–146 °C (ethanol) (lit: 146–147 °C).

(4-(3,4-dimethoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-diyl)-bis(phenylmethanone) (2). Reagents: benzoylacetone and 3,4-dimethoxybenzaldehyde., m.p. 221–223 °C (methanol). ^{1}H NMR ($CDCl_3$): δ 1.99 (s, 6H, 2CH_3), 3.64, 3.80 (2 s, 6H, 2CH_3), 3.64, 3.80 (2 s, 6H, 2 OCH_3), 5.13 (s, 1H, CH), 5.65 (s, 1H, NH), 6.35 (s, 1H), 6.60–6.62 (d, 1H), 6.69–6.71 (d, J = 8.2 Hz, 2H), 7.36–7.47 (m, 6H, Ph), 7,47–7,59 (m, 4H, Ph). ^{13}C NMR 19.0, 43.2, 54.3, 54.7, 110.0, 111.1, 113.4, 118.8, 119.0, 128.6, 128.8, 131.2, 137.6, 139.0, 147.8, 148.1, 197.9. ESI-MS: m/z 476 [M+Na]$^+$. Anal. Calcd for: $C_{29}H_{27}NO_4$: C, 76.80; H, 6.00; N, 3.09. Found: C, 77.04; H, 5.92; N, 2.87.

Dimethyl 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (3). Reagents: acetylacetone and 1,4-benzodioxane-6-carboxaldehyde, m.p. 223–225 °C (ethanol). ^{1}H NMR ($CDCl_3$). δ 2.35 (s, 6H, 3 CH_3), 3.68 (s, 6H, 3 CH_3), 3.68 (s, 6H, 2 OCH_3), 4.25 (s, 4H, 2 OCH_2), 4.92 (s, 1H, CH), 5.68 (s, 1H, NH), 6.70–6.79 (m, 3H, Ph). ESI-MS: m/z 382 [M+Na]$^+$. Anal. Calcd. for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.69; H, 6.04; N, 3.81.

Dimethyl 4-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (4). Reagents: benzoylacetone and 1,4-benzodioxane-6-carboxaldehyde, m.p. 244–246 °C (ethanol). ^{1}H NMR ($CDCl_3$). δ 1.99 (s, 6H, 2 CH_3), 4.18 (s, 4H, 2 CH_2), 5.02 (s, 1H, CH), 5.60 (s, 1H, NH), 6.36–6.39 (dd, J = 8.0, 2.0, 1H), 6.53 (d, J = 2.0, 1H), 6.62 (d, J = 8.0 Hz, 1H), 7.36–7.40 (m, 4H, Ph), 7.45–7.49 (m, 2H), 7.59–7.62 (m, 4H). ESI-MS: m/z 452 [M+H]$^+$. Anal. Calcd. for $C_{29}H_{25}NO_4$: C, 77.14; H, 5.58; N, 3.10. Found: C, 77.33; H, 5.60; N, 2.97.

Diethyl 4-(1*H*-indol-4-yl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (5). Reagents: indole-4-carboxaldehyde and ethylacetate, m.p. 176–178 °C (methanol). ^{1}H NMR ($CDCl_3$): δ 1.12 (t, J = 6.8, 6H, 2CH_3), 2.36 (s, 6H, 2 CH_3), 3.93–4.07 (ABq, J = 10.8, 6.8 Hz, 4H, 2CH_2), 5.46 (s, 1H, CH), 5.61 (s, 1H, NH), 6.81–6.83, 7.07–7.08, 7.17–7.21 (m 5H, indole), 8.03 (s, 1H); ^{13}C NMR ($CDCl_3$): 13.20, 18.58, 36.47, 58.56, 101.99, 107.89, 118.99, 120.87, 122.16. Anal. Calcd. for $C_{21}H_{24}N_2O_4$: C, 68.46; H, 6.57; N, 7.60. Found: C, 68.38; H, 6.53; N, 7.76. ESI-MS: m/z 391 [M+Na]$^+$.

Bis((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)-4-(3,4-dimethoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate (6). Reagents: 3,4-dimethoxybenzaldehyde and (–)menthol acetoacetate, m.p. 191–193 °C (methanol). ^{1}H NMR ($CDCl_3$): δ 0.43, 0.57, 0.68, 0.77, 0.79, 0.80, 0.82 (6d, J = 10.8, 18H, 6 CH_3), 0.73–1.95 (m, 18H, CH/CH_2), 2.22, 2.33 (2 s, 6H, 2 CH_3), 3.75, 3.77 (2 s, 6H, 2 OCH_3), 4.62, 4.58 (2td, J = 10.8, 4.4, 2 OCH), 4.91 (s, 1H, CH), 5.49 (s, 1H, NH), 6.63–6.70 (m, 2H, Ar), 6.79 (d, J = 2 Hz, 1H, Ar). ^{13}C NMR ($CDCl_3$) 15.63, 16.76, 19.52, 19.70, 20.91, 21.02, 22.07, 22.10, 22.80, 23.80, 25.18, 26.56, 31.41, 31.43, 34.38, 34.46, 38.68, 41.23, 41.47, 47.32, 47.62, 55.76, 55.86, 72.97, 73.68, 103.91, 104.98, 110.77, 111.60, 119.81, 140.58, 142.95, 144.22, 147.27, 148.23, 167.09, 167.34. ESI-MS: m/z 632 [M+Na]$^+$. Anal. Calcd. for $C_{37}H_{55}NO_6$: C, 72.87; H, 9.09; N, 2.30. Found: C, 73.02; H, 8.96; N, 2.41.

X-Ray crystallography

Single crystals of **1**, **2** and **6** were submitted to X-ray data collections by using a Siemens P4 four-circle diffractometer with graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). The structures were solved by direct methods implemented in SIR 2006[26] and in SHELXS-97[27] programs. The refinements were carried out by full-matrix anisotropic least-squares on F^2 for all reflections for non-H atoms by using the SHELXL-97 program.[28]

CCDC-770770, CCDC-770771 and CCDC-770772 contain the supplementary crystallographic data for compounds **1**, **2** and **6**, respectively, described in this paper.†

Mass spectrometry

ESI measurements have been carried out on a LCQ-DECA ion trap (Thermo, Bremen, D) in positive and negative modes. Solutions were introduced into the mass spectrometer using a syringe pump at a flow rate of 5 μL min^{-1}. Operating conditions of the ESI source were: spray voltage (±) 4.5 kV; capillary temperature 200 °C; sheath gas (nitrogen) flow rate, *ca.* 0.75 L min^{-1}. Ultra pure helium was the collision gas and the CID collision energy was in the range 0.5–1.0 eV (laboratory frame).

Elemental compositions of ions have been assigned by accurate mass measurements carried out by using a LTQ-FT ICR mass spectrometer (Thermo, Bremen, D) at resolution (R_{FWHM}) 50,000.

Theoretical calculations

Theoretical calculations has been carried out on different neutral and charged species by using MOPAC Pro version 9.0 and the semiempirical Parameterized Model number 3 (PM6).[29] The starting geometries were those obtained by X-ray crystallography, properly modified for the different chemical species, and they were fully optimized without any constraint by using the Restricted Hartree–Fock (RHF) and the half-electron formalisms for calculations on closed-shell and open-shell species, respectively.

Conclusions

This study has produced a new series of 1,4-dihydropyridine derivatives, functionalized as ketones or esters at positions 3 and 5, whose structural and conformational properties, and gas phase reactivity have been investigated by using X-ray crystallography, nuclear magnetic resonance spectroscopy, mass spectrometry and theoretical calculations. The conformational study of their crystal structures, both concerning the 1,4-dihydropyridine ring and the substituents at positions 3 and 5, as well as the study of intermolecular and hydrogen bonding interactions have added useful information for understanding the features of this class of compounds.

Investigation of the gas phase ion chemistry of the cations and anions derived from protonation or deprotonation of these compounds has been carried out by electrospray and multi-stage (up to MS^4) mass spectrometry. It is of interest the different reactivity shown in collision-induced dissociation experiments as a function of the charge of the species. While the loss of methanol from substituents at position 3 and 5 dominate the CID spectra of protonated diester cations formed from **1** and **3**, for ketone derivatives, elimination of the neutral aryl moiety at position 4 is highly prevalent over all the other gas phase reactions. The occurrence of a dehydrogenation process as a function of the electrospray capillary voltage has been also observed and discussed.

Deprotonated molecules undergo several kinds of gas phase decompositions, most of them involving elimination of radical species. Nevertheless, elimination of the neutral aryl moiety at position 4 is a common process for all deprotonated molecules.

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