Synthesis and Structural Study of 3,4-Dihydro-2(1*H*)-pyridones and Isoxazolo[5,4-*b*]pyridin-6(7*H*)-ones

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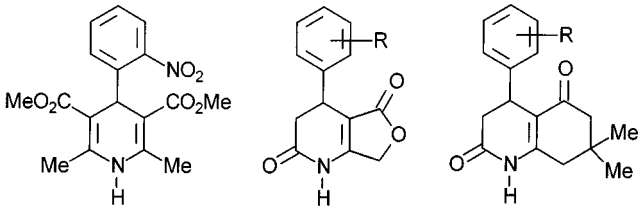
A series of isoxazolo[5,4-*b*]pyridin-6(7*H*)-ones (**8**) have been prepared with a high stereochemical control from the novel 3,4-dihydro-2(1*H*)-pyridones (**7**) by reaction with hydroxylamine hydrochloride and subsequent *5-endo-trig* cyclization. A structural study by X-ray analyses and theoretical calculations (AM1) of both heterocyclic systems (**7** and **8**) shows a favoured conformer with the aryl group on C4 in a pseudoaxial position. The same favoured conformation was found in solution according to NOE experiments and comparison of theoretical and experimental coupling constants.

Introduction

In the last few years, the synthesis and structural characterization of novel analogues of 1,4-dihydropyridine (DHP) calcium-channel modulators has received particular attention due to the pharmacological properties they display.[1−3] In this regard, crystallographic studies have played a very important role for determining receptor−ligand interactions in nifedipine (**1**) and other related 1,4-DHPs.[4,5] Bicyclic analogues have been synthesised to be used as geometrically well-defined rigid structures which are of interest for unravelling the structure-activity relationship for this type of compounds. Furthermore, bicyclic 1,4-DHPs have been reported to retain a remarkable receptor affinity with agonist[6] or antagonist[7−9] effects.

We have recently reported a structural study of furo[3,4-*b*]-2(1*H*)-pyridones (**2**)[10] and 2,5-dioxo-1,2,3,4,5,6,7,8-octahydroquinoline (**3**)[11] as potential calcium-channel modulators. In this regard, it is important to note that 1,4-DHPs fused to a second heterocyclic ring have been less studied in comparison with the huge number of studies carried out on differently substituted monocyclic 1,4-DHPs[12] (Scheme 1).



1 (Nifedipine) **2** **3**

Scheme 1. Nifedipine (**1**), a representative example of calcium antagonist and other related structures **2**, **3**

The absolute configuration at C-4 (*R- versus S*-enantiomer) of 1,4-DHPs is a critical factor for the biological activity as antagonist or agonist of calcium ions.[13] Thus, in order to evaluate the potential interest of novel molecules as calcium-channel modulators, it is important to determine the geometrical parameters in the solid state and in solution.

In this work, we report the synthesis of a series of novel 5-acetyl-4-aryl-3,4-dihydro-6-methyl-2(1*H*)pyridones (**7a−j**) as intermediates for the preparation of isoxazolo[5,4-*b*]pyridin-6(7*H*)-ones (**8**). Both heterocyclic systems (**7** and **8**) have been studied by X-ray analysis and semiempirical calculations in order to determine the most stable conformations in the solid state. ^{1}H NMR NOE experiments have been also carried out, and calculated and experimental coupling constants have been determined to establish the most favoured conformation in solution.

Results and Discussion

The synthesis of novel 5-acetyl-4-aryl-3,4-dihydro-6-methyl-2(1*H*)-pyridones (**7a−j**) has been carried out by re-

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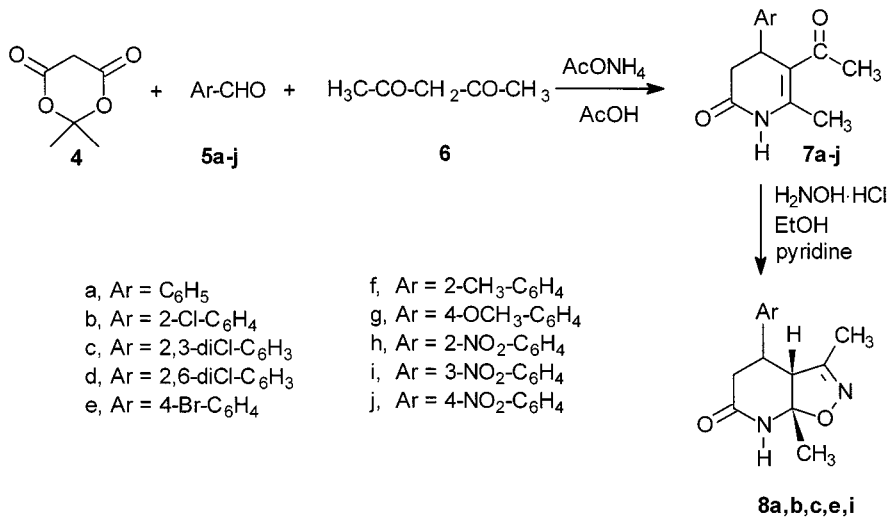
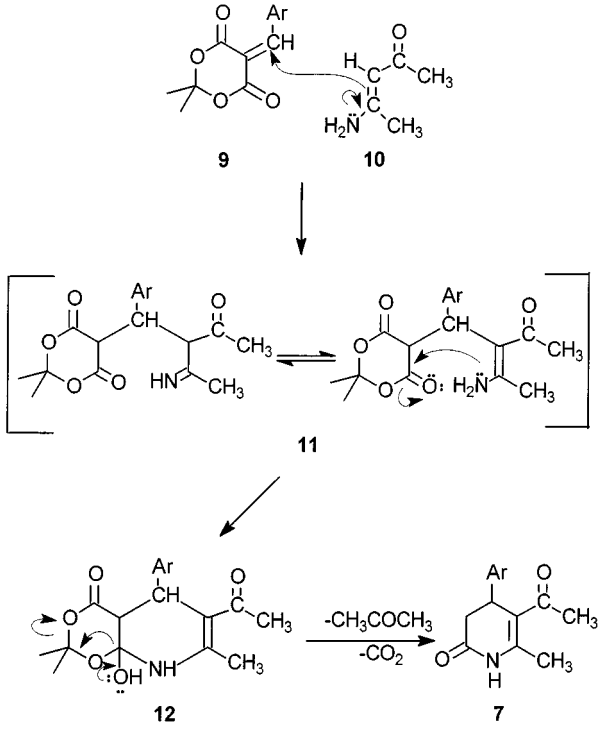


Scheme 2. Synthesis of 3,4-dihydro-2(1*H*)-pyridones **7a−j** and isoxazolo[5,4-*b*]pyridin-6(7*H*)-ones **8a−c**, **e**, **i**

action of equimolar amounts of Meldrum's acid (**4**), acetylacetone (**6**) and different substituted aromatic aldehydes **5** in the presence of ammonium acetate in refluxing acetic acid, by following the procedure recently reported for other 5-alkoxycarbonyl-substituted 3,4-dihydro-2(1*H*)-pyridones[14] (Scheme 2).

The formation of compounds **7a−j** is not straightforward and can be accounted for by considering the strong acidic properties of Meldrum's acid (pK_a = 4.97) which reacts with the aromatic aldehyde to form the Knoevenagel product **9** (Scheme 3). Further reaction with the enamino derivative **10**, generated by nucleophilic addition of ammonia to **6**, yields the nonisolated intermediate **11** which undergoes a 6-*exo*-*trig* cyclization[15] leading to **12**. Subsequent loss of acetone and carbon dioxide yields the 3,4-dihydro-2(1*H*)-pyridones (**7**) as crystalline solids in good yields.



Scheme 3. Mechanism of formation for compounds **7**

The FT-IR spectra of compounds **7a−j** show the NH group at around 3230 cm^{-1} and the two carbonyl groups at ca. 1695 and 1670 cm^{-1}. The ^{1}H NMR spectra show the two protons on C3 as a part of an AMX system which was confirmed by a doublet of doublets at δ = 4.2−4.8 corresponding to the proton on C4 due to the splitting by coupling with the protons on C3 ($J_{3a,4} \approx 7.0$ Hz and $J_{3b,4} \approx 1.0$ Hz). This last coupling suggests a *trans*-diaxial configuration between the proton on C4 and one of the protons on C3. The two methyl groups appear as singlets at δ ≈ 2.3 (CH_3−C6) and δ ≈ 2.0 (CH_3−CO). The signals in the ^{1}H and ^{13}C NMR spectra were unambiguously assigned by HMQC, HMBC, DEPT, NOE and COSY experiments (see Experimental Section).

The ^{13}C NMR spectra of **7a−j** show the signals of the olefinic carbons C5 (δ ≈ 112) and C6 (δ ≈ 150) at unusually low and high δ values, respectively. This finding has been previously observed in other related molecules[16] and clearly indicates a *push-pull* effect due to the electronic behaviour of the substituents on both carbons.

Isoxazolo[5,4-*b*]pyridin-6(7*H*)-ones (**8**) were prepared from **7** by reaction with hydroxylamine hydrochloride and pyridine in refluxing dry ethanol for 48 hours (see Experimental Section). It is worth noting that two tetrahydro derivatives, related to those described in this work, have been previously reported in a patent,[17] although in very low yields.

The 1,3-dipolar cycloaddition of nitrile oxides to 5-unsubstituted 1,4-DHP derivatives has been reported as the most versatile procedure for the preparation of isoxazolo[5,4-*b*]pyridines.[18] Interestingly, the reaction occurs with a high stereochemical control affording only a single isomer. The same stereochemical result was obtained by cyclization reaction from the oxime derivatives.[18] We have used the cyclization reaction for the preparation of a new series of 4-aryl-3a,4,5,7a-tetrahydro-3,7a-dimethylisoxazolo[5,4-*b*]pyridin-6(7*H*)-ones (**8**) whose structural study has

been thoroughly carried out by X-ray analysis, theoretical calculations, NOE experiments and the experimental determination of coupling constants. The formation of bicyclic compounds (**8**) can be accounted for by the formation of a Schiff's base and subsequent nucleophilic attack of the hydroxylic oxygen to the olefinic carbon in a 5-*endo-trig* process.[15]

Compounds **8** show the presence of the NH and C=O groups at ca. 3190 and 1670 cm^{-1}, respectively, in the FT-IR spectra. The ^1H NMR spectra reveal the presence of the proton on C4 ($\delta \approx 3.7-3.8$) as a pseudo-quadruplet by coupling with the proton on C3a ($\delta \approx 3.4$) ($J_{3a,4} \approx 4$ Hz) and the two protons on C5 ($\delta \approx 2.4$) ($J_{5,4} \approx 4.9$ Hz). The two methyl groups appear now at $\delta \approx 1.9$ (CH_3-C3) and $\delta \approx 1.3$ (CH_3-C7a). The ^{13}C NMR spectra show the signals corresponding to the carbons of the bicyclic systems at $\delta = 169$ (CO), 157 (C3), 93 (C7a), 53 (C3a), 35 (C4), 33 (C5), 25 (CH_3-C7a) and 12 (CH_3-C3). All the signals in the ^1H and ^{13}C NMR spectra were also unambiguously assigned by HMQC, HMBC, DEPT, NOE and COSY experiments (see Experimental Section).

We have previously confirmed that semiempirical calculations at the AM1 level (see Experimental Section) reproduce adequately the geometry of 3,4-dihydropyridones.[10,14] Therefore, we have used the AM1 method to find out the stability of the several conformers of compounds **7** and **8**. Compounds **7** present two favoured conformations, labelled **I** when the aryl substituent at C4 lies in a pseudoaxial position, and **II** when it lies in a pseudoequatorial position. Both conformations (**I** and **II**) show a pyridone ring in a screw-boat conformation with the aryl group near to the orthogonal disposition to the pyridone ring pseudoplane.

The calculated AM1 heats of formation for a wide variety of compounds **7** reveal that conformation **I** is about 1−2 kcal/mol more stable than conformation **II**. It is worth mentioning that these findings are in perfect agreement with those previously reported for related 3,4-dihydropyridones.[10,14]

The X-ray analysis of compound **7i** (Figure 1) reveals that it crystallizes with two independent molecules in the asymmetric unit (Table 1). The molecules are held together by means of a hydrogen bond of the type N−H···O (Table 2). The crystal structure is stabilized by means of this hydrogen bond and contacts of the form C−H···O, reported in Table 2. Figure 2 shows the crystal packing diagram of the two independent molecules in the unit cell.

The X-ray structure of **7i** shows that, in each independent molecule, the pyridone ring displays a screw-boat conformation with puckering parameters[19] $Q = 0.408(4)$Å, $\varphi = 117.3(6)°$ and $= 321.6(6)°$ for molecule A and $Q = 0.417(4)$Å, $\varphi = 116.4(5)°$ and $= 323.1(6)°$ for molecule B. Rotational symmetry is dominant with a pseudo-twofold axis intercepting the C3A−C4A and C6A−N1A bonds (C3B−C4B, C6B−N1B for molecule B). The phenyl ring is found in a pseudoaxial position, in a near orthogonal disposition to the mean plane of the pyridone ring. The nitro substituent on the phenyl ring is synperiplanar to the H atom attached to C4A (C4B) of the pyridone ring, as

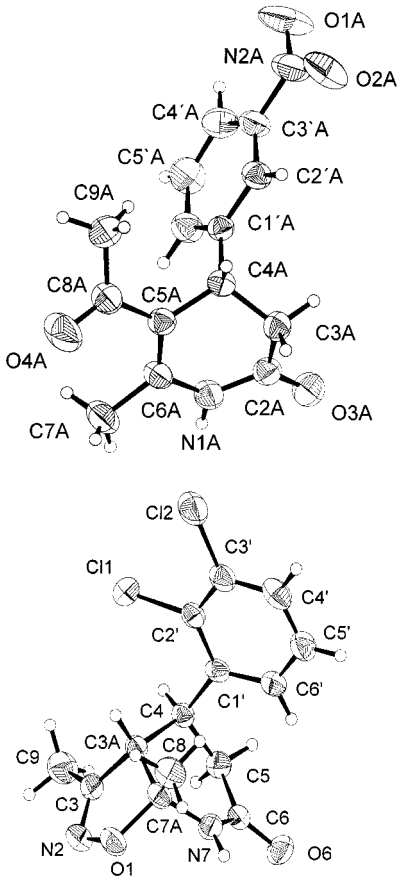


Figure 1. Perspective view of one independent molecule of **7i** (molecule A) and compound **8c** showing the atom numbering scheme for both compounds; displacement ellipsoids are shown at the 50% probability level; H atoms are of arbitrary radii

found in previously reported conformations of the pyridone moiety of related structures.[20,21] The geometrical features predicted by AM1 calculations and determined by X-ray analysis for compound **7i** (molecules A and B) are listed in Table 2, which shows the most relevant bond lengths, valence angles, and dihedral angles.

As shown in Table 2, the values calculated for conformation **I** are in agreement with those found by X-ray analysis, although the AM1 calculations overestimate the N1−C2 and C5−C6 distances and C3−C4−C5 angle, and underestimate the C4−C5 distance and C2−N1−C6 angle. In addition, the X-ray structure shows a more pronounced screw-boat conformation of the dihydropyridone ring according to the internal dihedral angles of the dihydropyridone ring ($\Sigma|\rho|$).[5]

We have also determined the most favourable conformation in solution by using NOE experiments and coupling constants. NOE experiments upon irradiation of the methyl group (Me−C6), NH, H3a, H3b and H4 protons clearly indicate that conformer **I** with the phenyl group on C4 in a pseudoaxial position is also present in solution. Thus, as representative examples, irradiation of NH showed an NOE effect on H6′ as well as on Me−C6, and when Me−C6 was irradiated, a strong NOE effect was observed on H1 and a weak one on H6′.

Table 1. Crystal analysis parameters at room temperature for **7i** and **8c**

Crystal data	**7i**	**8c**
Formula	$C_{14}H_{14}N_2O_4$	$C_{14}H_{14}Cl_2N_2O_2$
Crystal habit	Colourless	Colourless
Crystal size (mm)	0.46 × 0.14 × 0.06	0.48 × 0.20 × 0.19
Symmetry	Triclinic, $P\bar{1}$	Triclinic, $P\bar{1}$
Unit cell determination	Least-squares fit from 22 reflections	Least-squares fit from 24 reflections
(interval)	($3.7 < \varphi < 27.5°$)	($19 < \varphi < 30°$)
Unit cell dimensions (Å,°)	a = 9.202(1)	a = 7.027(7)
	b = 9.812(1)	b = 8.137(9)
	c = 15.308(1)	c = 12.78(1)
	α = 103.709(7)	α = 83.40(8)
	β = 90.147(7)	β = 75.77(7)
	γ = 103.191(9)	γ = 86.29(8)
Packing: V(Å^3), Z	1305.0(2), 4	703.1(1), 2
D_c (g/cm^3), M.W., F(000)	1.396(3), 274.27, 576	1.479(3), 313.17, 324
μ (mm^{-1})	0.87	0.46
Experimental data		
Technique	Four circle diffractometer	Four circle diffractometer
	Siemens P4	Stoe STADI4
	Graphite monochromator	Graphite monochromator
	ω/2φ scans	ω scans
Radiation, λ	Cu-$K\alpha$, 1.54184	Mo-$K\alpha$, 0.71073
φ_{max}	69.1°	25°
Number of reflections:		
Collected	5668	3135
Independent (R_{int})	4687 (0.02)	2480 (0.03)
Observed, criterion	3081, 4σ(F^2)	1442, 2σ(F^2)
Standard reflections	3, every 100 minutes	2, every 60 minutes
interval		
Decay	No variation	No variation
Absorption correction	ψ scan	ψ scan
Transmission factors:	0.742, 0.637	0.845, 0.805
max., min.		
Solution and refinement		
Solution, program	Direct methods, SHELXS97	
Refinement, program	Least-Squares on F^2, SHELXL97	
Parameters		
Number of variables	366	183
Final <shift/error>	0.001	0.001
Secondary extinction	0.0054(7)	0.0
parameter		
H atoms	Calculated and restrained in the refinement	
Weighting scheme (w)	$[\sigma^2(F_o^2) + (.0843P)^2 + 1.3094P]^{-1}$	$[\sigma^2(F_o^2) + (0.04750P)^2]^{-1}$
where $P = (F_o^2 + 2F_c^2)/3$		
Final R and wR	0.070, 0.256	0.042, 0.098
Goodness of fit	1.22	0.99
ΔF, peaks and hole	0.24, −0.25	0.23, −0.21
(e·Å^{-3})		

The observed conformer in solution has also been confirmed by determining the coupling constants of all the compounds prepared (**7a−j**). The experimental and coupling constants were compared with those calculated by the Karplus[22] and Altona[23] equations, based on the theoretical dihedral angles of the two possible conformers. These data show a very good agreement between the experimental values and those calculated for conformer **I**. Thus, as a selected example, compound **7a** shows experimental coupling constants of $J_{3a,4}$ = 0.9 Hz and $J_{3b,4}$ = 7.5 Hz (calculated J values from Altona's equation: conformation **I**, $J_{3a,4}$ = 1.0 Hz, $J_{3b,4}$ = 6.6 Hz; conformation **II**, $J_{3a,4}$ = 10.5 Hz; $J_{3b,4}$ = 7.0 Hz). The above results strongly support the presence of conformer **I** as the most stable in solution as well as in the solid state.

Structural and conformational studies of the novel compounds **8** were carried out by an X-ray crystallographic analysis of 4-(2′,3′-dichlorophenyl)-3,7a-dimethyl-3a,4,5,7a-tretrahydroisoxazolo[5,4-*b*]pyridin-6(7*H*)-one (**8c**). The most remarkable structural difference of compound **8c** related to the above 3,4-dihydropyridones (**7**) comes from the presence of the isoxazole ring fused to the 3,4-dihydropyridone ring. Compounds **8** present four possible racemic pairs, two with a *cis* ring-fusion and two with a *trans* ring-fusion. AM1 theoretical calculations predict that the stereoisomers with the proton on C3A and the methyl group

Table 2. Most relevant structural features for both conformations (**I** and **II**) of compounds **7i** and **8c** (numbering scheme for each compound is shown in Figure 1); bond lengths are given in Å and angles in degrees (standard deviations in parentheses)

7i Bond lengths	I (AM1)	II (AM1)	X-ray Molecule A	X-ray Molecule B	**8c** Bond lengths	I (AM1)	II (AM1)	X-ray
N1−C2	1.398	1.394	1.357(5)	1.360(6)	O1−N2	1.302	1.305	1.427(4)
C2−C3	1.507	1.507	1.497(6)	1.502(6)	N2−C3	1.319	1.319	1.280(4)
C3−C4	1.526	1.528	1.531(4)	1.528(5)	C3−C3A	1.528	1.529	1.515(4)
C4−C5	1.497	1.494	1.517(5)	1.520(6)	C3A−C7A	1.567	1.574	1.523(4)
C5−C6	1.376	1.369	1.348(5)	1.347(5)	C3A−C4	1.523	1.525	1.542(4)
C6−N1	1.391	1.392	1.398(4)	1.403(5)	C4−C5	1.518	1.524	1.529(4)
C4−C1′	1.504	1.504	1.518(5)	1.521(5)	C5−C6	1.510	1.511	1.501(4)
					C6−N7	1.384	1.381	1.342(4)
					N7−C7A	1.430	1.434	1.460(4)
					C4−C1′	1.501	1.501	1.520(4)
					C7−O1	1.529	1.515	1.452(4)
Valence angles					Bond angles			
C2−N1−C6	122.5	122.2	125.0(3)	124.7(3)	N2−O1−C7A	111.9	111.9	109.0(2)
C3−C4−C5	112.4	113.3	110.1(3)	109.7(3)	O1−N2−C3	112.5	112.6	108.7(3)
N1−C2−O3	119.0	119.1	120.5(4)	120.9(4)	N2−C3−C3A	112.3	112.4	113.0(3)
O4−C8−C5	122.6	122.5	122.2(4)	122.2(4)	C3−C3A−C7A	100.9	100.5	100.6(2)
					C3A−C7A−O1	102.1	102.7	103.1(2)
					C3A−C4−C5	111.2	111.5	109.0(2)
					C6−N7−C7A	124.1	123.2	129.5(3)
					O6−C6−N7	119.2	119.9	121.3(3)
Dihedral angles					Dihedral angles			
N1−C2−C3−C4	−29.6	28.7	−37.2(4)	36.9(5)	N7−C7A−C3A−C4	−9.2	−6.0	−32.8(3)
C2−C3−C4−C5	39.3	-31.2	46.5(4)	−47.4(4)	C7A−C3A−C4−C5	40.8	−32.7	54.6(3)
C3−C4−C5−C6	−26.6	17.6	−28.3(5)	29.1(5)	C3A−C4−C5−C6	−49.0	56.5	−47.4(3)
C4−C5−C6−N1	1.4	1.1	−0.9(5)	1.1(5)	C4−C5−C6−N7	25.8	−42.3	20.3(4)
C5−C6−N1−C2	11.3	−5.5	13.6(6)	−15.1(6)	C5−C6−N7−C7A	8.9	1.3	3.6(4)
C6−N1−C2−C3	3.8	−10.2	6.8(5)	−5.2(5)	C6−N7−C7A−C3A	−17.2	23.5	2.8(4)
Σ|ρ|[a]	111.7	94.3	133.3(5)	134.8(5)	Σ|ρ|[a]	150.9	162.3	161.5
O3−C2−N1−C6	−178.3	172.9	−176.8(4)	177.9(4)	O1−N2−C3−C3A	−0.1	−0.2	−1.7(3)
O4−C8−C5−C6	−1.3	−45.7	19.6(6)	−29.6(6)	C3A−C7A−O1−N2	4.4	1.6	22.8(3)
H31−C3−C4−H4	−80.7	−153.3	−76	75	N2−O1−C7A−N7	−118.2	−121.2	−95.0(2)
H32−C3−C4−H4	37.6	−35.3	41	−42	C3−C3A−C7A−N7	112.9	115.3	93.3(3)
C6−C5−C4−C1′	98.5	140.1	98.1(4)	−96.1(4)	C3−C3A−C4−C5	−74.8	−147.2	−62.7(3)
C6′−C1′−C4−C5	−30.0	−48.8	−30.4(5)	33.4(5)	O1−C7A−N7−C6	96.4	137.3	115.1(3)
					C3A−C4−C1′−C6′	104.5	−122.4	106.2(3)
Hydrogen bonds					Hydrogen bonds			
D H A	D−H	H···A	D···A	D−H···A	D H A	D−H H···A	D···A	D−H···A
N1A−H1A···O3A[i]	0.86	2.17	3.025(4)	178.2	N7−H7···O6[i]	0.86 2.05	2.902(5)	169.3
N1B−H1B···O3B[ii]	0.86	2.20	3.061(4)	178.8				
Short contacts					Short contacts			
D H A	D−H	H···A	D···A	D−H···A	D H A	D−H H···A	D···A	D−H···A
C5′A−14A···O4B[iv]	0.93	2.50	3.382(6)	158.0	C3A−H3A···Cl1[ii]	0.98 2.73	3.354(5)	122.0
C7B−H71B···O4B[iii]	0.96	2.47	2.818(5)	101.2	C4−H4···Cl1[ii]	0.98 2.71	3.058(4)	101.5
C9A−H93A···O3B[iii]	0.96	2.52	3.331(6)	142.2				
Symmetry codes					Symmetry codes			
i: 1 − *x*, −*y*, 1 − *z*					i: −1 − *x*, −*y*, −*z* + 1			
ii: −*x*, −*y*, −*z*					ii: *x*, *y*, *z*			
iii: *x*, *y*, *z*								
iv: 1 + *x*, −1 + *y*, *z*								

[a] Sum of the modular values of internal dihedral angles of dihydropyridone ring.[5]

on C7A in a *cis* disposition (**8c$_1$** and **8c$_2$**) are more stable ($\Delta E \approx 6$ kcal/mol) than those showing a *trans* configuration (**8c$_3$** and **8c$_4$**) (Figure 3). Each stereoisomer presents both pseudoaxial (**I**) and pseudoequatorial (**II**) conformations at C4. The calculated heat of formation for the most stable isomers shows that **8c$_1$** (**I**) is 0.9 kcal/mol more stable than **8c$_1$** (**II**), and that **8c$_1$** (**I**) 5.1 kcal/mol more stable than **8c$_2$** (**I**) (Figure 3).

An X-ray analysis carried out on compound **8c** (Figure 1) reveals that the isomer **8c$_1$** (**I**) was also found in the crystal.

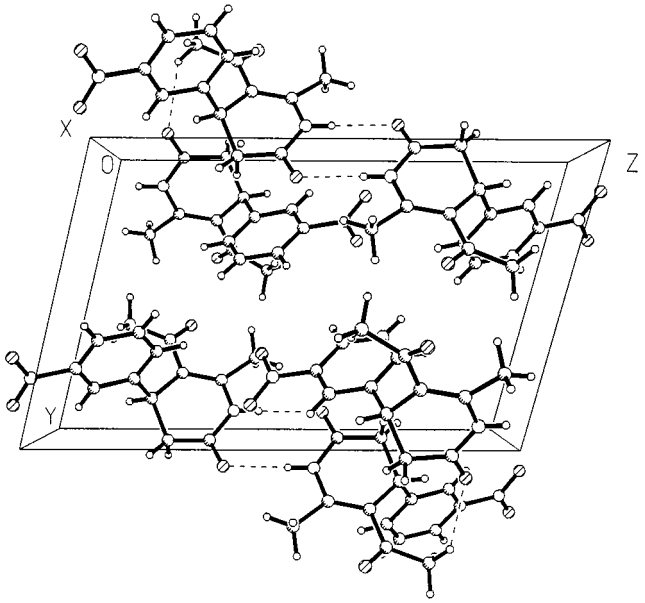


Figure 2. Packing diagram of compound **7i** with hydrogen bonds and intermolecular short contacts indicated by dashed lines; atoms are of arbitrary radii

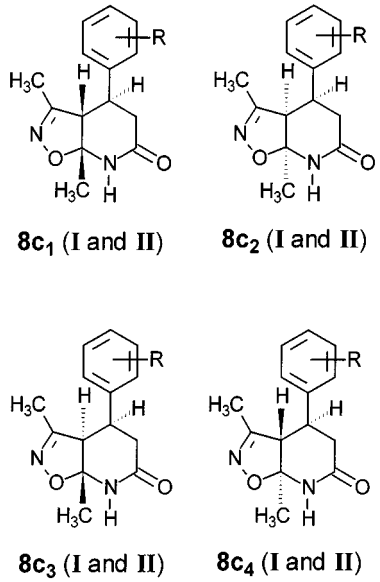


Figure 3. Stereoisomers of compound **8c** showing *cis* ring fusion (**8c**$_1$, **8c**$_2$) and *trans* ring fusion (**8c**$_3$, **8c**$_4$)

These findings confirm that only one isomer is formed in the cyclization reaction which presents the same stereochemistry as that found for other related structures.[18] The molecular structure of compound **8c** is shown in Figure 1 and its most relevant structural features are collected in Table 2 together with those predicted by AM1 calculations (**8c**$_1$**I** and **8c**$_1$**II**) for comparison purposes. In **8c** the conformation of the pyridone ring is between that of an envelope and a half chair with puckering parameters[19] Q = 0.454(3)Å, θ = 53.4(4)° and φ = −12.3(4)°. The dihydroisoxazole ring has an envelope conformation with C7A pointing up and puckering parameters Q = 0.228(3)Å, and φ = 3.9(7)°. In contrast to the above-mentioned 3,4-dihydropyridones (**7**), the phenyl group on C4 does not bisect the 2-pyridone ring (C6′−C1′−C4−C5: 16.3 (4)°). This finding is in agreement with the X-ray data previously reported for related structures.[18] Finally, a planar geometry for the ring nitrogen was observed, which indicates an sp^2 character. The molecules of **8c** form centrosymmetric dimers by means of a hydrogen bond of the type N−H···O. In addition, the packing of the molecules is governed also by C−H···Cl contacts (Table 2). Figure 4 shows the crystal packing diagram.

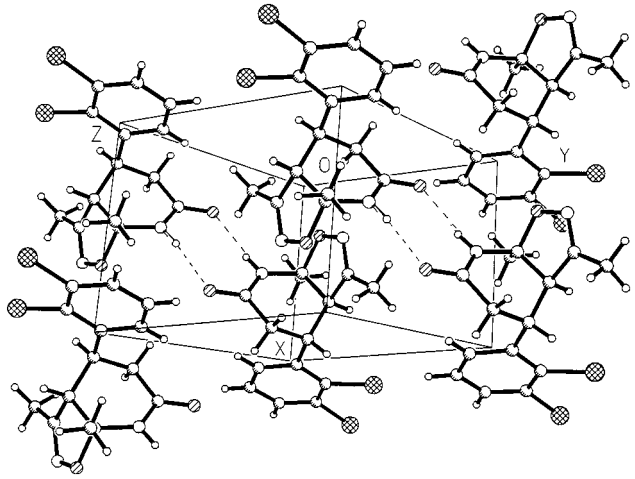


Figure 4. Packing diagram of compound **8c** as hydrogen-bonded dimer indicated by dashed lines; atoms are of arbitrary radii

It is important to note that large differences were found between the calculated (AM1) and observed structural features for compound **8c**, which showed a screw-boat conformation. These discrepancies were especially significant for the dihedral angles (see Table 2). In order to determine the conformation of compound **8c** in solution, NOE experiments and coupling constant determinations were carried out. Taking into account the distances between nonbonding atoms involved in the observed NOEs for both favoured conformations **I** and **II**, and considering that only those of less than 4 Å can be detected, it is possible to establish the most favoured conformation present in solution. The proximity observed between protons NH, CH_3−C7a, H3a and H6′ is in agreement with the observed NOE effects, thus supporting that conformation **I** is also found in solution. This result was confirmed by a comparison of the experimental coupling constants between the protons on C5, C4 and C3a, and those calculated from the Karplus[22] and Altona[23] equations by using the theoretical dihedral angles of conformations **I** and **II**.

In Table 3 the calculated coupling constants for three different compounds are presented, along with the experimental values. Comparison of the values in Table 3 clearly indicates that conformation **I** is also present in solution, thus supporting the above NOE effects.

Conclusions

In summary, we have carried out the synthesis of a series of novel 5-acetyl-4-aryl-3,4-dihydro-6-methyl-2(1*H*)-pyridones (**7a−j**) as interesting precursors for the preparation

Table 3. Experimental and calculated vicinal coupling constants for compounds **8a**, **8c** and **8i**

Compound		$^3J_{HH}$ Karplus			$^3J_{HH}$ Altona			$^3J_{HH}$ exp.	
		$J_{5a,4}$	$J_{5b,4}$	$J_{3a,4}$	$J_{5a,4}$	$J_{5b,4}$	$J_{3a,4}$	$J_{5b,4}$[a]	$J_{3a,4}$
8a$_1$	I	2.7	6.0	2.1	0.5	5.0	1.6	5.0	3.9
	II	13.0	4.2	10.6	12.3	3.5	10.1		
8c$_1$	I	2.6	6.3	2.1	0.5	5.3	1.6	4.9	4.1
	II	13.0	4.2	10.7	12.3	3.4	10.3		
8i$_1$	I	2.8	5.8	2.1	0.5	4.8	1.6	5.0	4.1
	II	13.0	4.3	10.5	12.3	3.5	10.1		

[a] Protons on C5 appear as a sole doublet by coupling with H4.

of novel 4-aryl-3a,4,5,7a-tetrahydro-3,7a-dimethylisoxazolo[5,4-*b*]pyridin-6(7*H*)-ones (**8a,b,c,e,i**). The formation of compounds **8** from **7** occurs in a stereospecific way leading to a single isomer. A structural study by X-ray analysis on both systems (**7** and **8**) reveals a favoured conformation (**I**) in the solid state in which the aryl group on C4 lies in a pseudoaxial position. Theoretical calculations (AM1) show a reasonable correlation for **7** and a large discrepancy for **8** related to the X-ray structures.

We have also determined by theoretical and experimental methods (NOE, coupling constants) the favoured conformation in solution for both systems (**7** and **8**). Either in the solid state or in solution, conformation **I** was the most stable. Interestingly, the observed conformation **I** is similar to that found for active calcium-channel modulators.

The structural and conformational features of 1,4-DHPs have been mainly determined by X-ray analysis in the search for improving the structure-activity relationship. In this regard, the data reported in this work on 3,4-dihydropyridones (**7**) and, particularly, on the less studied bicyclic systems (**8**), are of interest for a further study of receptor−ligand interactions.

Experimental Section

Melting points were determined in a capillary tube in an Electrothermal C14500 apparatus and are uncorrected. The NMR spectra were recorded on a Bruker DPX300 spectrometer [300 MHz (^{1}H) and 75.47 MHz (^{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 Shimadzu FT-IR 8300 instrument as potassium bromide pellets. Mass spectra were obtained with a Hewlett Packard 5989 A machine. Microanalyses were performed in a Perkin−Elmer 2400 CHN 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 with hexane/ethyl acetate (8:2) 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 used. Semiempirical AM1 calculations[24] were carried out by using the MOPAC[25] molecular orbitals set. Previously, the molecular geometry were optimised by using Allinger's Molecular Mechanics[26] with PCMODEL program.[27]

5-Acetyl-4-Aryl-3,4-dihydro-6-methyl-2(1*H*)-pyridone (7). − General Procedure: A mixture of the appropriate aromatic aldehyde (40 mmol), Meldrum's acid (40 mmol), acetylacetone (40 mmol) and ammonium acetate (42 mmol) in acetic acid (40 mL) was heated at reflux for 10 h and then poured into ice-water. The solid that precipitated was collected by filtration. Further purification was accomplished by recrystallization from ethanol.

5-Acetyl-3,4-dihydro-6-methyl-4-phenyl-2(1*H*)-pyridone (7a): Following the general procedure, reaction with **5a** (4.24 g, 40 mmol) gave **7a**, 59% yield; m.p. 195−196 °C. − $C_{14}H_{15}NO_2$ (229.3): calcd. C 73.34, H 6.59, N 6.11; found C 73.53, H 6.41, N 6.21. − EI-MS: *m*/*z* = 229 (88) [M$^+$], 214 (35), 186 (66), 131 (100), 91 (42), 77 (39). − ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 9.97 (s, 1 H, NH), 7.50−7.22 (m, 5 H, Ph), 4.30 (dd, *J* = 7.5 Hz, *J* = 0.9 Hz, 1 H, H-4), 2.94 (dd, *J* = 16.5 Hz, *J* = 7.5 Hz, 1 H, H-3a), 2.40 (dd, *J* = 16.5 Hz, *J* = 0.9 Hz, 1 H, H-3b), 2.34 (s, 3 H, CH$_3$), 2.01 (s, 3 H, CH$_3$). − ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 197.1 (CO), 170.1 (C2), 148.8 (C6), 144.8 (C1′), 128.2 (C2′, C6′), 126.5 (C4′), 123.4 (C3′, C5′), 114.2 (C5), 38.2 (C3), 38.5 (C4), 30.7 (CH$_3$−CO), 19.7 (CH$_3$−C6). − IR (KBr): ṽ = 3220 (NH), 1700 (C=O), 1680 (C=O), 1600 (C=C) cm^{-1}.

5-Acetyl-4-(2′-chlorophenyl)-3,4-dihydro-6-methyl-2(1*H*)-pyridone (7b): Following the general procedure, reaction with **5b** (5.62 g, 40 mmol) gave **7b**, 74% yield; m.p. 188−189 °C. − $C_{14}H_{14}ClNO_2$ (263.7): calcd. C 63.76, H 5.35, N 5.31; found C 63.50, H 5.46, N 5.49. − EI-MS: *m*/*z* = 263/265 (3/1) [M$^+$], 248/250 (9/3), 228 (100) [M$^+$ − Cl], 220/222 (17/5), 165/167 (27/8). − ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 9.98 (s, 1 H, NH), 7.43 (d, 1 H, H3′), 7.22 (t, 1 H, H4′), 7.19 (t, 1 H, H5′), 7.06 (d, 1 H, H6′), 4.58 (dd, *J* = 7.3 Hz, *J* = 1.1 Hz, 1 H, H-4), 2.94 (dd, *J* = 16.5 Hz, *J* = 7.3 Hz, 1 H, H-3a), 2.40 (dd, *J* = 16.5 Hz, *J* = 1.1 Hz, 1 H, H-3b), 2.34 (s, 3 H, CH$_3$), 1.97 (s, 3 H, CH$_3$). − ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 197.1 (CO), 170.1 (C2), 148.8 (C6), 138.1 (C1′), 132.2 (C2′), 129.9 (C3′), 128.7 (C4′), 127.6 (C5′), 127.5 (C6′), 114.2 (C5), 38.2 (C3), 38.5 (C4), 30.7 (CH$_3$−CO), 19.7 (CH$_3$−C6). − IR (KBr): ṽ = 3234 (NH), 1697 (C=O), 1672 (C=O), 1619 (C=C) cm^{-1}.

5-Acetyl-4-(2′,3′-dichlorophenyl)-3,4-dihydro-6-methyl-2(1*H*)-pyridone (7c): Following the general procedure, reaction with **5c** (7.00 g, 40 mmol) gave **7c**, 70% yield; m.p. 237−238 °C. − $C_{14}H_{13}Cl_2NO_2$ (298.2): calcd. C 56.40, H 4.39, N 4.70; found C, 56.27, H 4.61; N 4.79. − EI-MS: *m*/*z* = 297/299/301 (< 1) [M$^+$], 282/284/286 (8/5/1), 262/264 (100/40) [M$^+$ − Cl], 254/256/258 (10/6/1), 220/222 (40/14), 199/201/203 (15/10/2). − ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 10.0 (s, 1 H, NH), 7.54 (dd, *J* = 9.7 Hz, *J* = 1.8 Hz, 1 H, H4′), 7.26 (t, *J* = 9.7 Hz, 1 H, H5′), 7.02 (dd, *J* = 9.7 Hz, *J* = 1.8 Hz, 1 H, H6′), 4.54 (dd, *J* = 7.3 Hz, *J* = 1.1 Hz, 1 H, H-4), 2.99 (dd, *J* = 16.1 Hz, *J* = 7.3 Hz, 1 H, H-3a), 2.33 (dd, *J* = 16.1 Hz, *J* = 1.1 Hz, 1 H, H-3b), 2.30 (s, 3 H, CH$_3$), 1.99 (s, 3 H, CH$_3$). − ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 195.9 (CO), 168.6 (C2), 148.5 (C6), 140.8 (C1′), 132.2 (C3′), 130.0 (C2′), 129.1 (C4′) 128.3 (C5′), 125.9 (C6′), 112.7 (C5), 36.2 (C3), 35.9 (C4), 29.2 (CH$_3$−CO), 18.6 (CH$_3$−C6). − IR (KBr): ṽ = 3222 (NH), 1695 (C=O), 1676 (C=O), 1593 (C=C) cm^{-1}.

5-Acetyl-4-(2′,6′-dichlorophenyl)-3,4-dihydro-6-methyl-2(1*H*)-pyridone (7d): Following the general procedure, reaction with **5d** (7.0 g, 40 mmol) gave **7d**, 69% yield; m.p. 165−166 °C. − $C_{14}H_{13}Cl_2NO_2$ (298.2): calcd. C 56.40, H 4.39, N 4.70; found C 56.62, H 4.21, N 4.82. − EI-MS: *m*/*z* = 297/299/301 (8/5/1) [M$^+$], 282/284/286 (9/6/1), 262/264 (100/38) [M$^+$ − Cl], 254/256/258 (17/13/3), 220/222 (48/17), 199/201/203 (18/29/13). − ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 9.87 (s, 1 H, NH), 7.27−7.40 (m, 2 H, H3′, H5′), 7.22 (t, *J* = 7.0 Hz, 1 H, H4′), 4.50 (dd, *J* = 6.5 Hz,

J = 1.0 Hz, 1 H, H-4), 2.92 (dd, J = 16.5 Hz, J = 6.5 Hz, 1 H, H-3a), 2.49 (dd, J = 16.5 Hz, J = 1.0 Hz, 1 H, H-3b), 2.11 (s, 3 H, CH_3), 1.94 (s, 3 H, CH_3). − ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 197.8 (CO), 169.3 (C2), 143.7 (C6), 139.1 (C1′), 132.1 (C4′), 130.7, 130.2 (C3′, C5′), 129.8 (C2′, C6′), 115.2 (C5), 36.6 (C4), 33.9 (C3), 30.0 (CH_3−CO), 18.7 (CH_3−C6). − IR (KBr): ṽ =3220 (NH), 1685 (C=O), 1668 (C=O), 1618 (C=C) cm^{-1}.

5-Acetyl-4-(4′-bromophenyl)-3,4-dihydro-6-methyl-2(1*H*)-pyridone (7e): Following the general procedure, reaction with **5e** (7.44 g, 40 mmol) gave **7e**, 67% yield; m.p. 156−157 °C. − $C_{14}H_{14}BrNO_2$ (308.2): calcd. C 54.56, H 4.56, N 4.55; found C 54.62, H 4.67, N 4.67. − EI-MS: m/z = 307/309 (95/90) [M$^+$], 292/294 (50/48), 264/266 (79/76), 228 (100) [M$^+$ − Br$^{\cdot+}$], 209/211 (41/38). − ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 9.90 (s, 1 H, NH), 7.49 (d, J = 8.4 Hz, 2 H, H3′, H5′), 7.13 (d, J = 8.4 Hz, 2 H, H2′, H6′), 4.17 (dd, J = 6.9 Hz, J = 1.1 Hz, 1 H, H-4), 2.92 (dd, J = 15.9 Hz, J = 6.9 Hz, 1 H, H-3a), 2.39 (dd, J = 15.9 Hz, J = 1.1 Hz, 1 H, H-3b), 2.29 (s, 3 H, CH_3), 2.02 (s, 3 H, CH_3). − ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 197.6 (CO), 170.1 (C2), 148.6 (C6), 142.3 (C1′), 132.5 (C3′, C5′), 129.9 (C2′, C6′), 120.7 (C4′), 114.4 (C5), 39.5 (C3), 38.3 (C4), 30.5 (CH_3−CO), 19.7 (CH_3−C6). − IR (KBr): ṽ = 3207 (NH), 1687 (C=O), 1670 (C=O), 1590 (C=C) cm^{-1}.

5-Acetyl-3,4-dihydro-6-methyl-4-(2′-methylphenyl)-2(1*H*)-pyridone (7f): Following the general procedure, reaction with **5f** (4.80 g, 40 mmol) gave **7f**, 55% yield; m.p. 184−186 °C. − $C_{15}H_{17}NO_2$ (243.3): calcd. C 74.05, H 7.04, N 5.76; found C 74.22, H 6.97, N 5.88. − EI-MS: m/z = 243 (45) [M$^+$], 228 (100) [M$^+$ − CH_3], 200 (42), 145 (35). − ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 9.89 (s, 1 H, NH), 7.21 (d, 1 H), 7.11 (d, 2 H), 6.91 (d, 1 H), 4.32 (dd, J = 7.1 Hz, J = 1.0 Hz, 1 H, H-4), 2.91 (dd, J = 15.7 Hz, J = 7.1 Hz, 1 H, H-3a), 2.37 (s, 3 H, CH_3), 2.32 (s, 3 H, CH_3), 2.25 (dd, J = 15.7 Hz, J = 1.0 Hz, 1 H, H-3b), 1.91 (s, 3 H, CH_3). − ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 197.8 (CO), 170.1 (C2), 148.3 (C6), 140.4 (C1′), 135.9 (C2′), 131.8 (C6′) 127.7 (C4′), 127.2 (C5′), 126.2 (C3′), 114.7 (C5), 37.8 (C3), 35.5 (C4), 29.9 (CH_3−CO), 19.7 (CH_3), 19.5 (CH_3). − IR (KBr): ṽ = 3139 (NH), 1697 (C=O), 1672 (C=O), 1598 (C=C) cm^{-1}.

5-Acetyl-3,4-dihydro-4-(4′-methoxyphenyl)-6-methyl-2(1*H*)-pyridone (7g): Following the general procedure, reaction with **5g** (5.44 g, 40 mmol) gave **7g**, 55% yield; m.p. 201−202 °C. − $C_{15}H_{17}NO_3$ (259.3): calcd. C 69.48, H 6.61, N 5.40; found C 69.62, H 6.41, N 5.62. − EI-MS: m/z = 259 (54) [M$^+$], 244 (14), 228 (21), 216 (45), 161 (100). − ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 9.96 (s, 1 H, NH), 7.01 (d, J = 8.1 Hz, 2 H, H3′, H5′), 6.80 (d, J = 8.1 Hz, 2 H, H2′, H6′), 4.28 (dd, J = 7.1 Hz, J = 0.9 Hz, 1 H, H-4), 3.66 (s, 3 H, OCH_3), 2.87 (dd, J = 16.5 Hz, J = 7.1 Hz, 1 H, H-3a), 2.38 (dd, J = 16.5 Hz, J = 0.9 Hz, 1 H, H-3b), 2.30 (s, 3 H, CH_3), 1.89 (s, 3 H, CH_3). − ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 196.8 (CO), 169.8 (C2), 148.1 (C6), 157.8 (C4′), 134.7 (C1′), 127.5 (C2′, C6′), 114.2 (C5), 113.9 (C3′, C5′), 55.3 (OCH_3), 37.8 (C3), 35.4 (C4), 29.8 (CH_3−CO), 19.6 (CH_3−C6). − IR (KBr): ṽ = 3210 (NH), 1690 (C=O), 1660 (C=O), 1600 (C=C) cm^{-1}.

5-Acetyl-3,4-dihydro-6-methyl-4-(2′-nitrophenyl)-2(1*H*)-pyridone (7h): Following the general procedure, reaction with **5h** (6.04 g, 40 mmol) gave **7h**, 64% yield; m.p. 189−191 °C. − $C_{15}H_{17}NO_3$ (259.3): calcd. C 69.48, H 6.61, N 5.40; found C 69.62, H 6.41, N 5.62. − EI-MS: m/z = 274 (40) [M$^+$], 257 (100), 244 (80), 259 (50), 228 (7), 231 (20). − ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 9.98 (s, 1 H, NH), 7.95 (dd, J = 8 Hz, J = 1.3 Hz, 1 H, H3′), 7.55 (t, J = 7.5 Hz, 1 H, H5′), 7.43 (t, J = 7.9 Hz, 1 H, H4′), 7.25 (dd, J = 7.7 Hz, J = 1.3 Hz, 1 H, H6′), 4.85 (dd, J = 7.5 Hz, J = 16.9 Hz, 1 H, H-4), 2.94 (dd, J = 16.9 Hz, J = 7.5 Hz, 1 H, H-3a), 2.40 (dd, J = 16.9 Hz, J = 1.0 Hz, 1 H, H-3b), 2.34 (s, 3 H, CH_3), 2.34 (s, 3 H, CH_3). − ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 197.3 (CO), 170.1 (C2), 148.8 (C6), 147.2 (C2′), 135.5 (C1′), 133.7 (C5′), 128.6 (C4′), 128.4 (C6′), 114.2 (C5), 38.2 (C3), 3.2 (C4), 30.1 (CH_3−CO), 19.7 (CH_3−C6). − IR (KBr): ṽ = 3228(NH), 1699 (C=O), 1673 (C=O), 1600 (C=C) 1525, 1350 (NO_2) cm^{-1}.

5-Acetyl-3,4-dihydro-6-methyl-4-(3′-nitrophenyl)-2(1*H*)-pyridone (7i): Following the general procedure, reaction with **5i** (6.04 g, 40 mmol) gave **7i** (Table 1), 68% yield; m.p. 180−182 °C. − $C_{14}H_{14}N_2O_4$ (274.3): calcd. C 61.31, H 5.14, N 10.21; found C 61.28, H 5.09, N 10.15. − EI-MS: m/z = 274 (22) [M$^+$], 257 (100), 244 (81), 228 (12), 176 (21). − ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 10.02 (s, 1 H, NH), 8.08 (m, 1 H, H4′), 8.02 (br s, 1 H, H2′), 7.59−7.65 (m, 2 H, H5′, H6′), 4.38 (dd, J = 7.5 Hz, J = 1.0 Hz, 1 H, H-4), 2.97 (dd, J = 15.8 Hz, J = 7.5 Hz, 1 H, H-3a), 2.47 (dd, J = 15.8 Hz, J = 1.0 Hz, 1 H, H-3b), 2.34 (s, 3 H, CH_3), 2.07 (s, 3 H, CH_3). − ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 197.0 (CO), 169.8 (C2), 148.8 (C6), 146.6 (C3′), 143.2 (C1′), 133.2 (C6′), 130.2 (C5′), 122.6 (C4′), 121.8 (C2′), 114.6 (C5), 38.6 (C4), 38.3 (C3), 30.7 (CH_3−CO), 19.7 (CH_3−C6). − IR (KBr): ṽ = 3238 (NH), 1693 (C=O), 1680 (C=O), 1602 (C=C) 1525, 1380 (NO_2) cm^{-1}.

5-Acetyl-3,4-dihydro-6-methyl-4-(4′-nitrophenyl)-2(1*H*)-pyridone (7j): Following the general procedure, reaction with **5j** (6.04 g, 40 mmol) gave **7j**, 75% yield; m.p. 139−140 °C. − $C_{14}H_{14}N_2O_4$ (274.3): calcd. C 61.31, H 5.14, N 10.21; found C 61.47, H 5.27, N 10.44. − EI-MS: m/z = 274 (100) [M$^+$], 259 (79), 231 (89), 176 (83). − ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 9.98 (s, 1 H, NH), 8.15 (d, J = 8.2 Hz, 2 H, H3′, H5′), 7.45 (d, J = 8.2 Hz, 2 H, H2′, H6′), 4.35 (dd, J = 6.9 Hz, J = 1.0 Hz, 1 H, H-4), 2.99 (dd, J = 16.3 Hz, J = 6.9 Hz, 1 H, H-3a), 2.42 (dd, J = 16.3 Hz, J = 1.0 Hz, 1 H, H-3b), 2.35 (s, 3 H, CH_3), 2.05 (s, 3 H, CH_3). − ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 197.3 (CO), 169.9 (C2), 151.1 (C1′), 148.9 (C5), 147.3 (C4′), 129.1 (C2′, C6′), 128.8 (C3′, C5′), 114.2 (C6), 39.1 (C3), 38.7 (C4), 30.7 (CH_3−CO), 19.8 (CH_3−C6). − IR (KBr): ṽ = 3235 (NH), 1701 (C=O), 1670 (C=O), 1615 (C=C), 1521, 1348 (NO_2) cm^{-1}.

4-Aryl-3a,4,5,7a-tetrahydro-3,7a-dimethylisoxazolo[5,4-*b*]pyridin-6(7*H*)-ones (8). − General Procedure: A mixture of the appropriate 2(1*H*)pyridone **7** (3.5 mmol), hydroxylamine hydrochloride (3.7 mmol), and 0.5 mL of pyridine in 40 mL of dry ethanol was heated at reflux for 48 h and then poured into ice-water. The solid that precipitated was collected by filtration. Further purification was accomplished by recrystallization from ethanol.

3a,4,5,7a-Tetrahydro-3,7a-dimethyl-4-phenylisoxazolo[5,4-*b*]pyridin-6(7*H*)-one (8a): Following the general procedure, reaction with **7a** gave **8a**, 36% yield; m.p. 192−193 °C. − $C_{14}H_{16}N_2O_2$ (244.3): calcd. C 68.83, H 6.60, N 11.47; found C 68.98, H 6.72, N 11.57. − EI-MS: m/z = 244 (30) [M$^+$], 224 (5), 187 (100), 172 (20), 110 (40), 96 (50). − ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 8.70 (s, 1 H, NH), 7.40−7.20 (m, 5 H, Ph), 3.72 (q, J = 5.0 Hz, J = 3.9 Hz, 1 H, H-4), 3.38 (d, J = 3.9 Hz, 1 H, H-3a), 2.42 (d, J = 5.0 Hz, 2 H, H-5), 1.89 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3). − ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 169.7 (CO), 156.8 (C3), 144.7 (C1′), 127.2 (2C), 126.9, 126.5 (2C), 93.4 (C7a), 54.5 (C3a), 34.4 (C4), 33.5 (C5), 25.7 (CH_3−C7a), 12.2 (CH_3−C3). − IR (KBr): ṽ = 3180 (NH), 1680 (C=O), 1600 (C=C) cm^{-1}.

4-(2′-Chlorophenyl)-3a,4,5,7a-tetrahydro-3,7a-dimethylisoxazolo-[5,4-*b*]pyridin-6(7*H*)-one (8b): Following the general procedure, reaction with **7b** gave **8b**, 45% yield; m.p. 166−167 °C. − $C_{14}H_{15}ClN_2O_2$ (278.7) calcd. C 60.33, H 5.42, N 10.05; found C

60.50, H 5.66, N 10.18. − EI-MS: *m/z* = 278/280 (30/10) [M^+], 261/263 (9/3), 221/223 (100/35), 204/206 (30/10), 110 (30), 96 (70). − ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 8.72 (s, 1 H, NH), 7.53 (d, 1 H, H3′), 7.40−7.22 (m, 3 H, H4′, H5′, H6′), 3.77 (q, *J* = 4.9 Hz, *J* = 4.1 Hz, 1 H, H-4), 3.42 (d, *J* = 4.1 Hz, 1 H, H-3a), 2.43 (d, *J* = 4.95 Hz, 2 H, H-5), 1.90 (s, 3 H, CH_3) and 1.34 (s, 3 H, CH_3). − ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 169.8 (CO), 157.5 (C3), 138.3 (C2′), 129.9 (C1′), 129.1 (C5′), 128.9, 128.1, 127.6 (aryl), 93.3 (C7a), 54.3 (C3a), 34.2 (C4), 33.3 (C5), 25.7 (CH_3−C7a), 12.3 (CH_3−C3). − IR (KBr): ṽ = 3200 (NH), 1700 (C=O), 1600 (C=C) cm^{-1}.

4-(2′,3′-Dichlorophenyl)-3,7a-dimethyl-3a,4,5,7a-tetrahydroisoxazolo[5,4-*b*]pyridin-6(7 *H*)-one (8c): Following the general procedure, reaction with **7c** gave **8c** (Table 1), 60% yield; m.p. 242−243 °C. − $C_{14}H_{14}Cl_2N_2O_2$ (313.2): calcd. C 53.69, H 4.51, N 8.94; found C 53.50, H 4.46, N 8.49. − EI-MS: *m/z* = 312/314/316 (26/18/4) [M^+], 295/297/299 (10/6/1), 255/257/259 (100/70/17), 240/242 (36/24), 110 (36), 96 (74). − ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 8.73 (s, 1 H, NH), 7.61 (dd, *J* = 8.0 Hz, *J* = 1.2 Hz, 1 H, H4′), 7.41 (t, *J* = 8.0 Hz, 1 H, H5′), 7.22 (dd, *J* = 8.0 Hz, *J* = 1.2 Hz, 1 H, H6′), 3.79 (q, *J* = 4.9 Hz, *J* = 4.1 Hz, 1 H, H-4), 3.38 (d, *J* = 4.1 Hz, 1 H, H-3a), 2.43 (d, *J* = 4.9 Hz, 2 H, H-5), 1.90 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3). − ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 169.5 (CO), 157.2 (C3), 140.8 (C1′), 132.2 (C3′), 130.6 (C2′), 129.2 (C4′), 128.2 (C5′), 126.5 (C6′), 93.1 (C7a), 53.9 (C3a), 35.0 (C4), 33.1 (C5), 25.6 (CH_3−C7a), 12.1 (CH_3−C3). − IR (KBr): ṽ = 3188 (NH), 1670 (C=O), 1583 (C=C) cm^{-1}.

4-(4′-Bromophenyl)-3a,4,5,7a-tetrahydro-3,7a-dimethylisoxazolo[5,4-*b*]pyridin-6(7*H*)-one (8e): Following the general procedure, reaction with **7e** gave **8e**, 61% yield; m.p. 196−197 °C. − $C_{14}H_{15}BrN_2O_2$ (323.2): calcd. C 52.03, H 4.48, N 8.67; found C 52.16, H 4.56, N 8.49. − EI-MS: *m/z* = 323/325 (30/28) [M^+], 305/307 (10/8), 265/267 (100/96), 244 (20), 251/253 (20/18), 231 (10), 110) (30), 96 (30). − ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 8.72 (s, 1 H, NH), 7.58 (d, *J* = 8.2 Hz, 2 H, H3′, H5′), 7.22 (d, *J* = 8.2 Hz, 2 H, H2′, H6′), 3.75 (q, *J* = 4.9 Hz, *J* = 4.1 Hz, 1 H, H-4), 3.38 (d, *J* = 4.1 Hz, 1 H, H-3a), 2.40 (d, *J* = 4.9 Hz, 2 H, H-5), 1.90 (s, 3 H, CH_3), 1.33 (s, 3 H, CH_3). − ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 169.8 (CO), 157.8 (C3), 143.4 (C1′), 131.5 (C3′, C5′), 130.0 (C2′, C6′), 121.2 (C4′), 93.7 (C7a), 54.6 (C3a), 34.8 (C4), 34.1 (C5), 25.9 (CH_3−C7a), 12.5 (CH_3−C3). − IR (KBr): ṽ = 3200 (NH), 1675 (C=O), 1600 (C=C) cm^{-1}.

3a,4,5,7a-Tetrahydro-3,7a-dimethyl-4-(3′-nitrophenyl)isoxazolo[5,4-*b*]pyridin-6(7*H*)-one (8i): Following the general procedure, reaction with **7i** gave **8i**, 63% yield; m.p. 168−170 °C. − $C_{14}H_{15}N_3O_4$ (289.3): calcd. C 58.13, H 5.23, N 14.53; found C 58.30, H 5.38, N 14.62. − EI-MS: *m/z* = 289 (20) [M^+], 272 (10), 259 (80), 243 (12), 232 (100), 217 (17), 110 (27). − ^{1}H NMR ([D$_6$]DMSO, 300 MHz): δ = 8.90 (s, 1 H, NH), 8.02 (s, 1 H, H2′), 8.12 (m, 1 H, H6′), 7.55−7.50 (m, 2 H, H4′, H5′), 3.68 (q, *J* = 5.0 Hz, *J* = 4.1 Hz, 1 H, H-4), 3.59 (d, *J* = 4.1 Hz, 1 H, H-3a), 2.54 (d, *J* = 5.0 Hz, 2 H, H-5), 1.89 (s, 3 H, CH_3), 1.30 (s, 3 H, CH_3). − ^{13}C NMR ([D$_6$]DMSO, 75 MHz): δ = 169.7 (CO), 157.7 (C3), 147.9 (C3′), 143.6 (C1′), 134.2 (C6′), 130.1 (C5′), 122.0 (C4′), 121.2 (C2′), 93.2 (C7a), 55.4 (C3a), 36.3 (C4), 33.9 (C5), 25.8 (CH_3−C7a), 12.4 (CH_3−C3). − IR (KBr): ṽ = 3260 (NH), 1685 (C=O), 1600 (C=C), 1550, 1348 (NO_2) cm^{-1}.

Crystals of **7i** and **8c** were grown by slow evaporation from ethanol. 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 U_{eq} of their parent atoms. Programs used: data collection for **7i**: XSCANS,[28] cell refinement: XSCANS,[28] data reduction: XSCANS,[28] (for **8c**: data collection: DIF4,[29] cell refinement: DIF4,[29] data reduction: REDU4,[30] and EMPIR.[31]). Program used to solve both structures: SHELXS97.[32] Program used to refine both structures: SHELXL97.[33] Molecular graphics: DIAMOND.[34] Software used to prepare material for publication: PLATON.[35]

Crystallographic data (excluding structure factors) for the structure(s) included in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-134980 **(7i)** and -134981 **(8c)**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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