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# Synthesis, structural, conformational and pharmacological study of some amides derived from 3-methyl-2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9α-amine

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ABSTRACT

Some mono-substituted amides (**2**–**5**) derived from 3-methyl-2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9α-amine were synthesized and studied by IR, $^{1}H$ and $^{13}C$ NMR spectroscopy. The crystal structure of 3-methyl-2,4-diphenyl-9α-(3,5-dichlorobenzamido)-3-azabicyclo[3.3.1]nonane (**3**) was determined by X-ray diffraction.

NMR data showed that all compounds adopt in $CDCl_3$ a preferred flattened chair–chair conformation with the *N*-$CH_3$ group in equatorial disposition. X-ray data agreed with this conformation in the case of compound **3**.

IR data revealed that compounds **2** and **3** present a C=O···HN intermolecular bond in the solid state. This conclusion was also confirmed by X-ray data of compound **3**. In the case of compound **5**, IR results suggested intermolecular NH···N-heterocyclic bonding. On the contrary, in the pyrazine derivative (**4**), IR, $^{1}H$ and $^{13}C$ NMR data showed the presence of an intramolecular NH···N1″-heterocyclic hydrogen bond in the solid state and solution. Moreover, NMR and IR data showed a preferred *trans* disposition for the NH–C=O group. NMR also revealed free rotation of the –NH–CO–R group around C9–NH bond.

Pharmacological assays on mice were drawn to evaluate analgesic activity.



## 1. Introduction

As continuation of our studies on the synthesis of heterocyclic compounds with potential therapeutic activity, we report in this paper the synthesis and the structural study of a series of amides (**2**–**5**) derived from 3-methyl-2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9α-amine (**1**) by IR and NMR spectroscopy. The unambiguous assignment of all proton and carbon resonances was achieved by double resonance experiments. The structure and conformation of 3-methyl-2,4-diphenyl-9α-(3,5-dichlorobenzamido)-3-azabicyclo[3.3.1]nonane (**3**) in the solid state was determined by X-ray diffraction.

## 2. Experimental

### 2.1. Synthesis

Compounds **2**–**5** were prepared by two general methods illustrated in Scheme 1.

The 3-methyl-2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9α-amine (**1**) was previously synthesized by reduction of the corresponding oxime with sodium in ethanol [1]. Reaction of **1** with the corresponding carboxylic acid in the presence of dicyclohexylcarbodiimide (DCC) and dimethylaminopiridine (DMAP) as catalyst led to the amides (**2**, **4**, **5**) (method A) [2]. Compound **3** was prepared by reaction of the bicyclic amine (**1**) with 2,5-dimethylbenzoyl chloride in presence of triethylamine (method B) [3].

### 2.2. NMR spectra

NMR spectra of compounds **2**–**5** were recorded on a Varian UNITY-300 Spectrometer. The $^{1}H$ NMR spectra of $CDCl_3$ solutions (about 4% w/v) were obtained at 300 MHz using spectral width of 4000 Hz in 24 K memory and acquisition time of 3.0 s over 64 transients. Resolution enhancement (LB = −0.80, GF = 0.60 and GFS = 0.20) was followed by zero filling into 32 K memory prior to Fourier transformations. The double resonance experiments in $CDCl_3$ involved the use of conventional irradiation.

The $^{13}C$ NMR spectra were obtained at 75.429 MHz at a spectral width of 16,501 Hz in 64 K memory, acquisition time of 1s and relaxation delay of 1s, using $CDCl_3$ solutions (20% w/v).

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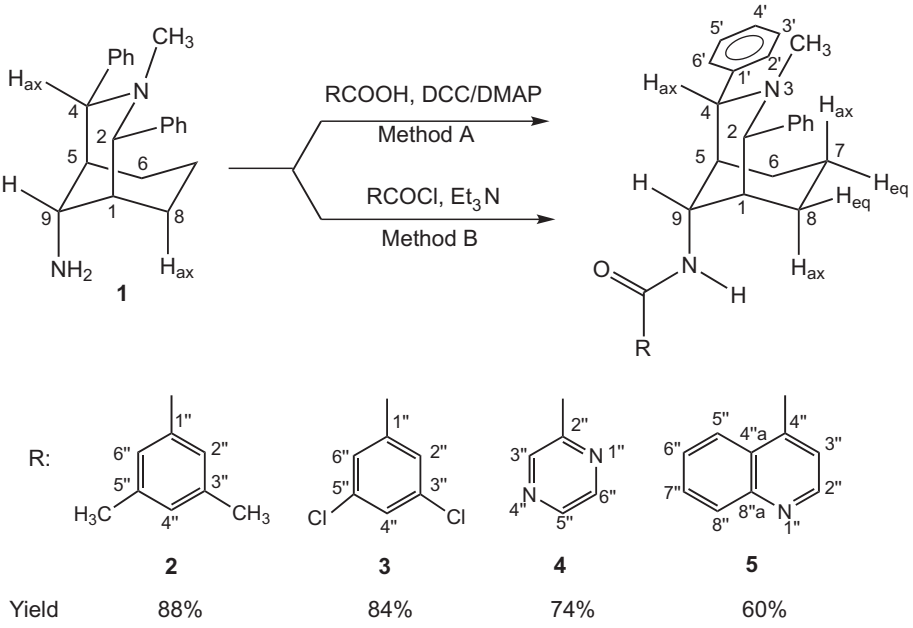


**Scheme 1.** Synthesis of amides 2–5.

*2.3. IR spectra*

The IR spectra for compounds **2–5** were recorded on a Perkin-Elmer FTIR 1725X spectrophotometer, assisted by a computer, in the solid state (KBr) in the 4000–400 $cm^{-1}$ and in $CDCl_3$ solution (≈0.15 M) in the 4000–900 $cm^{-1}$ region using 0.2 mm NaCl cells. Spectra for very dilute $CCl_4$ solution were taken in the 4000–2500 $cm^{-1}$ region with 4 cm quartz cells. The reported wavenumbers are estimated to be accurate to within ±3 $cm^{-1}$.

## 3. Results and discussion

*3.1. NMR spectra*

*3.1.1. Spectral analysis and assignment*

Assignment of proton resonances for compounds **2–5** was made on the basis of our previous studies for related systems [4–9]. The $^1$H NMR spectra of compounds **2–5** showed great similarity in relation to the bicyclic systems. The values of the proton magnetic parameters were deduced by analysis of the respective spin systems and are listed in Table 1.

In the $^1$H NMR spectra of compounds **2–5** the signals corresponding to H9, H1(5), H2(4)$_{ax}$, H7$_{ax}$, the *N*–$CH_3$ group and the aromatic protons appear well differentiated.

The H9 signal is a doublet of triplets owing to the coupling with H1(5) and the amide proton. H2(4)$_{ax}$ signal appears as a doublet due to the coupling with H1(5). The H7ax signal appear as a quartet of triplets because $|^2J(H7_{ax} - H7_{eq})| \approx {}^3J(H6(8)_{ax} - H7_{ax})$.

The H6(8)$_{eq}$, H6(8)$_{ax}$ and H7$_{eq}$ signals are partially overlapped.

To clarify the assignments of the signals and to deduce the proton magnetic parameters, double resonance experiments in $CDCl_3$ for **3** were performed at 300 MHz.

By irradiation of the H7$_{ax}$ signal at 2.62 ppm, the signal corresponding to H6(8)$_{eq}$ simplifies to a doublet with splitting of 13.4 Hz due to the coupling with H6(8)$_{ax}$.

By irradiation of the H1(5) signal at 2.05 ppm, the doublet of triplets corresponding to H9 simplifies to a doublet and the doublet corresponding to H2(4)$_{ax}$ simplifies to a singlet. The triplet of triplets at 1.32 ppm [H6(8)$_{ax}$] becomes a triplet of doublets with splittings of 4.5 and 13.4 Hz due to the couplings with H7$_{eq}$, H6(8)$_{eq}$ and H7$_{ax}$, respectively. The H6(8)$_{eq}$ signal appears as a doublet of doublets with splittings of 5.3 and 13.4 Hz due to the coupling with H7$_{ax}$ and H6(8)$_{ax}$, respectively. The $^3J$ H6(8)$_{eq}$–H7$_{ax}$ is very small and could not be established due to the low resolution of the corresponding signal.

On saturating the H6(8)$_{eq}$ and H7$_{eq}$ signals (1.43–1.45 ppm), H7$_{ax}$ and H6(8)$_{ax}$ simplify to a triplet and an apparent doublet, respectively.

By irradiation of the H6(8)$_{ax}$ signal (1.32 ppm), H7$_{ax}$ simplifies to a doublet of triplets and H6(8)$_{eq}$ simplifies to an apparent doublet due to the coupling with H7$_{ax}$, $^3J$ H6(8)$_{eq}$-H7$_{eq}$ is very small and only an estimated value (<2 Hz) could be deduced taking into account the $W_{1/2}$ of each line of the doublet.

With all the data the following coupling constants can be deduced:

$^2J$ H6(8)$_{eq}$ − H6(8)$_{ax}$, $^3J$ H6(8)$_{ax}$ − H7$_{ax}$, $^3J$ H6(8)$_{ax}$ − H7$_{eq}$ and $^3J$ H6(8)$_{eq}$ − H7$_{ax}$. The other coupling constants have been measured directly on the spectra. The values are in Table 1.

The singlet at 2.01 ppm has been assigned to the *N*–$CH_3$ protons in all compounds.

The aromatic protons corresponding to the phenyl groups in two and four positions appear unresolved at 7.06–7.90 ppm. With respect to the aryl substituents attached to the amido groups, the *orto* aromatic protons with respect to the nitrogen atoms, in compounds **4** and **5**, appear at higher chemical shifts (9.43–8.74 ppm) in comparison with the other aromatic protons (8.13–7.41 ppm).

For the assignment of the $^{13}$C NMR chemical shifts (Table 2), substituent steric and electronic effects and our previous studies of related compounds [4–9] were taken into consideration.

Regarding the C=O groups, the highest carbon value corresponds to compound **2** where two methyl (electron-donating) substituents are present in the aromatic ring. On the contrary, with the electron-withdrawing substituents (compounds **3–5**) the values of the carbon chemical shifts decrease.

*3.1.2. Conformational study*

We used the NMR technique to analyse the conformations of these compounds and the following general features were deduced:

**Table 1**
$^1$H NMR Chemicals shifts ($\delta$, ppm) and multiplicities ($J$, Hz) for 2–5 in $CDCl_3$.

| $\delta$ (ppm)[a] | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| H9 | 4.58 (dt)<br>$^3J$ H9 − H1(5) = 2.9 | 4.56 (dt)<br>$^3J$ H9 − H1(5) = 3.0 | 4.60 (dt)<br>$^3J$ H9 − H1(5) = 3.2 | 4.73 (dt)<br>$^3J$ H9 − H1(5) = 3.1 |
| H2(4)$_{ax}$ | 3.80 (d)<br>$^3J$ H2(4)$_{ax}$ − H1(5) = 3.4 | 3.79 (d)<br>$^3J$ H2(4)$_{ax}$ − H1(5) = 3.3 | 3.80 (d)<br>$^3J$ H2(4)$_{ax}$ − H1(5) = 3.2 | 3.84 (d)<br>$^3J$ H2(4)$_{ax}$ − H1(5) = 3.2 |
| H7$_{ax}$ | 2.61 (qt)<br>$^3J$ H6(8)$_{ax}$ − H7$_{ax}$ = 14.6<br>$^3J$ H6(8)$_{eq}$ − H7$_{ax}$ = 6.1 | 2.62 (m)<br>$^3J$ H6(8)$_{ax}$ − H7$_{ax}$ = 13.4<br>$^3J$ H6(8)$_{eq}$ − H7$_{ax}$ = 5.3 | 2.61 (qt)<br>$^3J$ H6(8)$_{ax}$ − H7$_{ax}$[b]<br>$^3J$ H6(8)$_{eq}$ − H7$_{ax}$[b] | 2.61 (qt)<br>$^3J$ H6(8)$_{ax}$ − H7$_{ax}$ = 13.4<br>$^3J$ H6(8)$_{eq}$ − H7$_{ax}$ = 5.3 |
| N–C*H*$_3$ | 2.01 (s) | 2.01 (s) | 2.01 (s) | 2.01 (s) |
| H1(5) | 2.05 (brs)<br>($W_{1/2}$ ~ 9 Hz) | 2.05 (brs)<br>($W_{1/2}$ ~ 9 Hz) | 2.05 (brs)<br>($W_{1/2}$ ~ 8 Hz) | 2.13 (brs)<br>($W_{1/2}$ ~ 8 Hz) |
| H6(8)$_{ax}$ | 1.35 (tt)<br>$^3J$ H6(8)$_{ax}$ − H1(5) = 4.4 | 1.32 (tt)<br>$^3J$ H6(8)$_{ax}$ − H1(5) = 4.5 | 1.41 (m)<br>$^3J$ H6(8)$_{ax}$ − H1(5)[b] | 1.31 (m)<br>$^3J$ H6(8)$_{ax}$ − H1(5)[b] |
| H7$_{eq}$ | 1.41 (m)<br>$^2J$ H7$_{ax}$ − H7$_{eq}$ = −14.6<br>$^3J$ H6(8)$_{ax}$ − H7$_{eq}$ = 4.4 | 1.43 (m)<br>$^2J$ H7$_{ax}$ − H7$_{eq}$ = −13.4<br>$^3J$ H6(8)$_{ax}$ − H7$_{eq}$ = 4.5 | 1.41 (m)<br>$^2J$ H7$_{ax}$ − H7$_{eq}$[b]<br>$^3J$ H6(8)$_{ax}$ − H7$_{eq}$[b] | 1.36 (m)<br>$^2J$ H7$_{ax}$ − H7$_{eq}$ = −13.4<br>$^3J$ H6(8)$_{ax}$ − H7$_{eq}$[b] |
| H6(8)$_{eq}$ | 1.41 (m)<br>$^2J$ H6(8)$_{ax}$ − H6(8)$_{eq}$ = −14.6<br>$^3J$ H6(8)$_{eq}$ − H1(5)<2[c] | 1.45 (m)<br>$^2J$ H6(8)$_{ax}$ − H6(8)$_{eq}$ = −13.4<br>$^3J$ H6(8)$_{eq}$ − H1(5)<2[c] | 1.41 (m)<br>$^2J$ H6(8)$_{ax}$ − H6(8)$_{eq}$[b]<br>$^3J$ H6(8)$_{ax}$ − H1(5)[b] | 1.50 (m)<br>$^2J$ H6(8)$_{ax}$ − H6(8)$_{eq}$[b]<br>$^3J$ H6(8)$_{ax}$ − H1(5)[b] |
| N*H* | 6.44 (d)<br>$^3J$ H9 − NH = 8.1 | 6.42 (d)<br>$^3J$ H9 − NH = 8.1 | 8.31 (d)<br>$^3J$ H9 − NH = 8.4 | 6.53 (d)<br>$^3J$ H9 − NH = 8.3 |
| C*H*$_3$ | 2.35 (s) | – | – | – |
| H2′–H6′ | 7.06–7.89 | 7.14–7.84 | 7.10–7.90 | 7.22–7.88 |
| H2″ | 7.34 (s) | 7.60 (d)<br>$^4J$ H2″ − H4″ = 1.9 | – | 8.90 (d)<br>$^3J$ H2″ − H3″ = 4.4 |
| H3″ | – | – | 9.43 (d)<br>$^4J$ H3″ − H5″ = 1.6 | 7.41 (d) |
| H4″ | 7.12 (s) | 7.48 (t)<br>$^4J$ H4″ − H6″ = 1.9 | – | – |
| H5″ | – | – | 8.50 (dd)<br>$^3J$ H5″ − H6″ = 2.4 | 8.13 (d)<br>$^3J$ H5″ − H6″ = 8.3 |
| H6″ | 7.34 (s) | 7.60 (d) | 8.74 (d) | 7.60 (ddd)<br>$^3J$ H6″ − H7″ = 7.8<br>$^4J$ H6″ − H8″ = 1.5 |
| H7″ | – | – | – | 7.75 (ddd)<br>$^3J$ H7″ − H8″ = 7.9<br>$^4J$ H5″ − H7″ = 1.5 |
| H8″ | – | – | – | 8,18 (dd)<br>$^5J$ H5″ − H8″ = 1.2 |

The $\delta$ values were deduced from the first order analysis of the corresponding system protons with an error of ±0.05 ppm.
[a] Abbreviations: brs, broad singlet; d, doublet; dd, doublet of doublets; ddd, double doublet of doublets; dt, doublet of triplets; m, multiplet; qt, quartet of triplets; s, singlet; t, triplet; tt, triplet of triplets.
[b] Not determined due to the low resolution of the signal.
[c] A limit value was estimated taking into account the $W_{1/2}$ values of the corresponding signals.

**Table 2**
$^{13}$C Chemicals shifts ($\delta$, ppm) for 2–5 in $CDCl_3$.

| $\delta$ (ppm)[a] | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| C9 | 52.62 | 53.20 | 52.50 | 53.20 |
| C2(4) | 73.89 | 73.86 | 73.87 | 73.88 |
| N–C*H*$_3$ | 44.18 | 44.16 | 44.18 | 44.16 |
| C1(5) | 40.12 | 39.94 | 40.15 | 40.09 |
| C7 | 20.26 | 20.13 | 20.29 | 20.14 |
| C6(8) | 20.72 | 20.66 | 20.59 | 20.63 |
| *C*H$_3$ | 21.23 | – | – | – |
| *C*=O | 167.23 | 164.28 | 162.17 | 166.58 |
| C1′ | 142.90 | 142.84 | 142.77 | 142.61 |
| C2′(6′) | 127.50[b] | [c] | 127.08[b] | 127.20[b] |
| C3′(5′) | 128.24 | 128.28 | 128.22 | 128.33 |
| C4′ | 126.68 | 126.84 | 126.73 | 126.86 |
| C1″ | 135.08 | 137.84 | – | – |
| C2″ | 124.54 | 125.48 | 142.48 | 149.55 |
| C3″ | 138.32 | 135.53 | 147.25 | 118.34 |
| C4″ | 132.99 | 131.33 | – | 129.64 |
| C4″a | – | – | – | 124.48 |
| C5″ | 138.32 | 135.53 | 144.36[d] | 125.07 |
| C6″ | 124.54 | 125.48 | 144.56[d] | 125.07 |
| C7″ | – | – | – | 130.21 |
| C8″ | – | – | – | 130.21 |
| C8″a | – | – | – | [c] |

[a] Error of ±0.05 ppm.
[b] Broad signal.
[c] Not determined owing to the low resolution of the signal.
[d] These values may be interchanged.

- In $CDCl_3$ solution, these compounds adopt a flattened chair–chair conformation with the *N*–$CH_3$ groups in equatorial positions.
- The cyclohexane ring is more flattened than the piperidine moiety.
- The phenyl groups are near coplanar with respect to C–H2(4)$_{ax}$; the shapes of the multiplets due to proton aromatic signals account for a distinct conformation of the phenyl groups (due to restricted phenyl spinning).
- The conjugated amido group lies in a plane nearly coincident with the symmetry plane of the bicycle; in this conformation, the carbonyl group occupies a *cis* disposition with respect to H9, therefore the amido group is in a *trans* form.
- Free rotation of the amido group around the C9–NH bond can be deduced.
- $^1$H NMR data indicate an intramolecular hydrogen bond N–H···N1″-heterocyclic in compound **4** in $CDCl_3$ solution.

These conclusions are supported by the following experimental data:

In the $^1$H NMR spectra, the $W_{1/2}$ value (8–9 Hz) for the H1(5) signals is in agreement with previously reported values for a flattened chair–chair conformation in related bicyclic systems [4–9].

For a boat disposition of one of these rings, the signal corresponding to H1(5) would be an apparent doublet with a coupling constant about 18 Hz [10].

In all cases, the $^2J$[H2(4)$_{ax}$ – H1(5)] value of *ca.* 3 Hz accounts for a dihedral angle of about 60° according to the Karplus relationship [11]. In compounds **2**, **3**, $^3J$ [H2(4)$_{ax}$ – H1(5)] ≈ 3.3 Hz is smaller than $^3J$ [H6(8)$_{ax}$ – H1(5)] ≈ 4.5 Hz and consequently the H2(4)$_{ax}$–C–C–H1(5) dihedral angle is greater than H6(8)$_{ax}$–C–C–H1(5); this fact is in close agreement with a flattened chair conformation for the cyclohexane ring. Moreover, $^3J$ [H6(8)$_{ax}$ – H1(5)] ≈ 4.5 Hz is greater than $^3J$ [H6(8)$_{eq}$ – H1(5)] (<2) and $^3J$ [H6(8)$_{ax}$ – H7$_{eq}$] ≈ 4.5 Hz is greater than $^3$J[H6(8)$_{eq}$ – H7$_{eq}$] (<2); therefore, the H6(8)$_{eq}$–C–C–H1(5) and H6(8)$_{eq}$–C–C–H7$_{eq}$ dihedral angles are greater than H6(8)$_{ax}$–C–C–H1(5) and H6(8)$_{ax}$–C–C–H7$_{eq}$, respectively; these results confirm the distortion of the cyclohexane ring.

The *N*–CH$_3$ $^{13}$C chemical shifts of compounds **2**–**5** of about 44 ppm (Table 2) agree with the values found in equatorial *N*–CH$_3$ substituted piperidines [4–9,12].

Furthermore, in the $^{13}$C NMR spectra, the twin-chair conformation is confirmed by the C2(4) (73.86–73.89 ppm) and C6(8) (20.59–20.72 ppm) chemical shifts in agreement with previous work [4–9]. For a boat conformation, the carbon signals would be shifted to a higher field because of the steric compressing effect due to the eclipsing between H2(4)$_{ax}$ – H1(5) and H6(8)$_{ax}$ – H1(5) hydrogen atoms.

In addition, by comparing the NMR results of the α-epimers (**2**–**5**) with those of their corresponding β-epimers [5], we can deduce that they adopt similar preferred conformations with some slightly differences. The values Δδ C2(4)(**2**–**5**)–C2(4)(β-epimers) ≈ 5 ppm and Δδ C6(8)(β-epimers)-C6(8)(**2**–**5**) ≈ 7 ppm can be attributed to the steric *syn*-diaxial effect exerted by the axial amido group on H2(4)$_{ax}$ for β-epimers and on H6(8)$_{ax}$ for α-epimers (**2**–**5**). Besides, the effect on H6(8)$_{ax}$ is greater for α-epimers due to greater distortion of the cyclohexane ring in comparison with the piperidine one.

The Δδ H6(8)$_{eq}$(β-epimers) – H6(8)$_{eq}$(α-epimers) ≈ 0.2 ppm is attributed to the W arrangement of the equatorial protons with respect to the amido group in the first case; consequently, these protons would be more sensitive to the inductive deshielding effect [13].

Owing to the small differences in the chemical shifts of the H7$_{ax}$ and H2(4)$_{ax}$ among compounds **2**–**5** and related systems [4–8], we can conclude that the positions adopted by the phenyl groups in **2**–**5** will be the same as those found in the related systems, with near coplanarity with respect to C–H2(4)$_{ax}$ as it was also observed in the crystal structure of **3**.

The differences Δδ[H2(4)$_{ax}$(**2**–**5**) – H2(4)$_{ax}$(**1**)(3.59 ppm)] ≈ 0.2 ppm and Δδ [H6(8)$_{ax}$(**2**–**5**) – H6(8)$_{ax}$(**1**)(1.49 ppm)] ≈ 0.1 ppm can be attributed not only to the σ-effect exerted by the amido group, but also to the decreasing anisotropic effect exerted by the lone pair of the nitrogen atom when the amino group changes into an amido group [4].

The Δδ [H9(**2**–**5**) – H9(**1**)(3.27 ppm)] value of 1.5 ppm can be partially attributed to the π deshielding effect exerted by the carbonyl group over H9, confirming the *cis* disposition between this group and H9.

The equivalence of the C1 and C5 protons and C6 and C8 protons and also of the C1 and C5, and C6 and C8 accounts for free rotation of the amido group around the C9-NH group [14,15].

In compound **4**, the signal corresponding to the N–H amide proton appears as a doublet centered at 8.3 ppm while in compounds **2**, **3** and **5** the doublet appears at 6.4–6.5 ppm. This fact indicates that the amide proton is hydrogen bonded in $CDCl_3$ solution (see IR results), in this case forming a five member ring through an intramolecular bond with the vicinal heterocyclic nitrogen (N1″, Scheme 1).

Moreover, the Δδ [H6(8)$_{ax}$(**4**)-H6(8)$_{ax}$(**2, 3, 5**)] value (≈0.1 ppm) and the fact that H6(8)$_{ax}$ and H6(8)$_{eq}$ are isochronous for compound **4** (see Table 1) can be attributed to the anisotropic effect exerted by the intramolecularly bonded pyrazine moiety over H6(8)$_{ax}$.

### 3.2. IR spectra

Table 3 shows the infrared frequencies ($cm^{-1}$) with the corresponding assignments of the bands appearing in the NH and double bond stretching regions.

Compound **2** in the solid state (KBr) showed a medium infrared band at 3283 $cm^{-1}$ which is assigned to the intermolecularly bonded NH group (see later). This band shifted to 3455 $cm^{-1}$ and 3462 $cm^{-1}$ in $CDCl_3$ (0.06 M) and in $CCl_4$ (0.0003 M), respectively, due to the formation of free N–H groups. However, a small proportion of bonded molecules remained even at high dilution. In the literature [16] the *ν* (N–H) band of secondary amides in the 3340–3270 $cm^{-1}$ region in the solid state was assigned to a *trans* bonded structure while a band in the 3220–3140 $cm^{-1}$ region was attributed to the bonded band of a *cis* complex. Moreover, for free N–H groups the frequency ranges given are 3470 $cm^{-1}$ for the *trans* and 3440–3420 $cm^{-1}$ for the *cis* structure. Therefore, in accordance with $^1$H NMR data, IR results for compound **2** reveal that the preferred conformation of this compound for the –NH–CO– system is *trans*.

In KBr two bands appeared in the carbonyl amide region at 1637 and 1622 $cm^{-1}$ and upon dilution in $CDCl_3$ a strong band appeared at 1652 $cm^{-1}$, indicating that C=O groups are implicated in intermolecular hydrogen bonding with N–H groups (NH···O=C). In the related β-compound the intermolecular hydrogen bond was confirmed by the results obtained by cooling the sample at the liquid air temperature which showed a decrease of both N–H and C=O stretching frequencies, as expected [5].

A very strong band at 1534 $cm^{-1}$ (1510 $cm^{-1}$ in $CDCl_3$) is assigned to the amide II band and according to the literature the presence of this band confirms the *trans* conformation of the –NH–CO– system [17].

In the case of compound **3** the infrared spectrum in the solid state showed a *ν* (N–H) medium intensity band at 3279 $cm^{-1}$, which was shifted to 3449 $cm^{-1}$ in $CDCl_3$ and to 3457 $cm^{-1}$ in $CCl_4$. In the carbonyl amide region two bands appeared in the spectrum of the solid at 1639 and 1617 $cm^{-1}$ and one band at 1663 $cm^{-1}$ in $CDCl_3$ solution. These results agree with results for compound **2** and are interpreted in the same way. Furthermore, X-ray data confirm the *trans* NH–CO structure and the presence of a double NH···O=C hydrogen bond amide system defining chains along the *z* axis in the crystal (d N···O = 2.930 (5) Å; d O···H = 2.1 (1) Å; <N–H···O=C = 155 (5)°).

Contrary to the infrared results obtained for compounds **2** and **3**, in the case of **4** the *ν* N–H stretching frequency at 3404 $cm^{-1}$ in the solid did not change much upon dilution in $CDCl_3$ (3401 $cm^{-1}$) or $CCl_4$ (3411 $cm^{-1}$), indicating the existence of intramolecular bonding, in this case between the NH group and the vicinal heterocyclic nitrogen (NH···N), forming a five member ring as it has also been deduced from $^1$H NMR results (see before). Consequently, the amide I band (1681 $cm^{-1}$ in KBr) did not increase on dilution in $CDCl_3$ (1671 $cm^{-1}$). The intramolecular bond was also present in the related β-epimer, this conclusion being confirmed by cooling the solid sample at the liquid air temperature: no change was observed in the NH and C=O stretching frequencies [5].

In compound **5** the spectrum of the solid showed a *ν* N–H band at about 3330 $cm^{-1}$ and a strong band at 1658 $cm^{-1}$ with a shoulder at about 1640 $cm^{-1}$. The *ν* N–H band was shifted to 3437 $cm^{-1}$ in $CDCl_3$ and to 3445 $cm^{-1}$ in $CCl_4$. However, the amide I band (1658 $cm^{-1}$) did not change much in $CDCl_3$ (1662 $cm^{-1}$) and the frequency of the amide II band was 1515 $cm^{-1}$ in both media. As

**Table 3**
Infrared frequencies ($cm^{-1}$) of compounds 2–5.

| Compound | Medium | *v* (N–H) free | Bonded | Amide I | Ring | Amide II |
|---|---|---|---|---|---|---|
| 2 | KBr | | 3283 m[a] | 1637 m<br>1622 s | 1601 s[b]<br>1595 s[b] | 1534 vs |
| | $CDCl_3$ | 3455 w | 3320 vvw | 1652 s-vs | 1604 s[b] | 1510 vs |
| | $CCl_4$ | 3462 w | 3322 vvw | [c] | [c] | [c] |
| 3 | KBr | | 3279 m | 1639 s<br>1617 vs | 1602 vw[b]<br>1566 vs[b] | 1540 vs |
| | $CDCl_3$ | 3449 w | 3330 vvw | 1663 s | 1601 vw[b]<br>1568 s | 1509 vs |
| | $CCl_4$ | 3457 w | 3340 vvw | [c] | [c] | [c] |
| 4 | KBr | | 3404 w-m[d] | 1681 vs | 1628 w[e]<br>1601 vw[e]<br>1578 w[e] | 1520 vs |
| | $CDCl_3$ | | 3401 w[d] | 1671 vs | 1601 w[e]<br>1580 w[e] | 1529 sh<br>1523 vs |
| | $CCl_4$ | | 3411 w-m[d] | [c] | [c] | [c] |
| 5 | KBr | | 3330 w | 1658 vs<br>1640 sh | 1602 vw[e]<br>1585 w[e]<br>1496 s[e] | 1515 s |
| | $CDCl_3$ | 3437 w | 3323 vvw | 1662 s | 1602 w[e]<br>1584 w[e]<br>1497 s[e] | 1515 vs |
| | $CCl_4$ | 3445 w | 3335 vvw | [c] | [c] | [c] |

[a] Abbreviations; s, strong; m, medium; w. weak, v, very; sh, shoulder.
[b] Aromatic ring.
[c] Not measured.
[d] Intramolecular bond.
[e] Heterocycle.

in the related β-epimer [5] infrared results of **5** suggest intermolecular bonding between the N–H and the basic nitrogen of the quinoline ring (NH···N) in the solid state.

### 3.3. Pharmacology

Pharmacology assays on mice were performed with compounds **2**–**5** to evaluate drug-induced gross behavioral alteration. Both the writhing test [18] and hot-plate test [19] were applied to evaluate analgesic activity.

With respect to the analgesic activity, compounds **2**–**4** [10 mg $Kg^{-1}$ (i.p)] showed a partial antinociceptive effect in the acetic acid writhing test in the mouse but this appeared to be non-statistically significant activity when we compared it with the degree of protection afforded by acetylsalicylic acid [200 mg $Kg^{-1}$ (p.o.)] or diclofenac [10 mg $kg^{-1}$ (p.o)]. However, compound **5** [10 mg $Kg^{-1}$ (i.p.)] showed a statistically significant activity with a degree of protection similar to acetylsalicylic acid or diclofenac. When the hot-plate test was used, compounds **2**–**5** did not achieve the grade of activity showed by morphine [8 mg $Kg^{-1}$ (i.p.)]. These results indicate that compound **5** would exhibit peripheral but no significant central analgesic effect.

## 4. Conclusions

Some amides (**2**–**5**) derived from 3-methyl-2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9α-amine have been synthesized and studied by IR and NMR spectroscopies.

The $^1H$ and $^{13}C$ NMR data revealed that in $CDCl_3$ solution the amides adopt a preferred chair–chair conformation with the *N*–$CH_3$ substituent in an equatorial position. X-ray data for compound **3** agreed with this conclusion. Besides, free rotation of the amido group around the C9–NH bond and a preferred *trans* form for the –NH–CO– system have been deduced.

X-ray data for compound **3** and IR data for **2** and **3** revealed the presence of intermolecular C═O···HN bonds in the solid state. On the contrary, IR results for compound **5** suggested NH···N-heterocyclic intermolecular bonding.

Compound **4** shows the presence of an intramolecular NH···N1″-heterocyclic hydrogen bond in the solid state and in non-polar solvents.

With respect to the analgesic activity, compound **5** is the most active compound showing peripheral effect, although non-significant central effect.

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