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Synthesis, structural and conformational study of some amides derived from 3-methyl-3-azabicyclo[3.2.1]octan-8α(β)-amines

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Abstract

Some amides (**1α**–**7α** and **1β**–**7β**) derived from 3-methyl-3-azabicyclo[3.2.1]octan-8α(β)-amines were synthesized and studied by IR, ^{1}H and ^{13}C NMR spectroscopies. The assignment of all carbon and protons resonances was achieved through the application of one dimensional selective NOE and two dimensional NMR techniques: homonuclear NOESY and heteronuclear ^{1}H–^{13}C gHSQC correlated spectroscopies. Total correlation spectroscopy (TOCSY) experiments were also carried out.

In $CDCl_3$ solution, at room temperature, all compounds adopt a chair-envelope conformation with the *N*–CH_3 group in equatorial disposition. In the α-epimers the piperidine ring is puckered at C8 to relieve the interactions between the amido group and the H6(7)x protons.

α- and β-Epimers show a preferred *trans* disposition for the NH–CO group and free rotation of the NH–CO–R group around the C8–NH bond. Finally, NMR and IR data reveal that compounds **7α** and **7β** adopt in $CDCl_3$ solution a preferred *s-cis* conformation for the O=C–C=C system, the proportion of this conformation increasing when the polarity of the solvent decreases.

Keywords: 3-Methyl-3-azabicyclo[3.2.1]octan-8α(β)-amines derivatives; Amides; Infrared spectroscopy; NMR spectroscopy; Conformational analysis

1. Introduction

Numerous studies have established the importance of nAChRs (nicotinic acetylcholine receptors) within the CNS (central nervous system), in particular their link to higher processes such as memory, cognition, reward and sensory processing [1].

A number of potent azabicyclic aryl amides have been reported as agonists of the nAChRs, many of them being derived from the quinuclidine scaffold [2,3]. The 3-azabicyclo[3.2.1]octane system has not been much used as a basic side chain in such class of ligands.

As a part of a continuing effort to develop novel analgesic agents [4–6] we have synthesized a series of aryl and alkyl amides **1**–**7** (**α** and **β**) containing the 3-methyl-3-azabicyclo[3.2.1]octane system (Scheme 1) to investigate the effect that this basic side chain could exert in their pharmacological properties. For these relatively flexible systems, conformational studies to determine the preferred conformations could be very helpful to establish the structure–activity relationship [5–10].

The assignment of all the carbon and proton resonances was achieved through the application of one dimensional selective NOE (nuclear overhauser effect) and two dimensional NMR techniques: homonuclear NOESY and heteronuclear ^{1}H–^{13}C gHSQC (gradient Heteronuclear Single Quantum Correlations) correlated spectroscopies. TOCSY experiments were also carried out. The existence of *s-cis* and *s-trans* conformations of α,β-unsaturated compounds **7α** and **7β** have been determined with the aid of NOE experiments and solvent effects on the IR carbonyl band.

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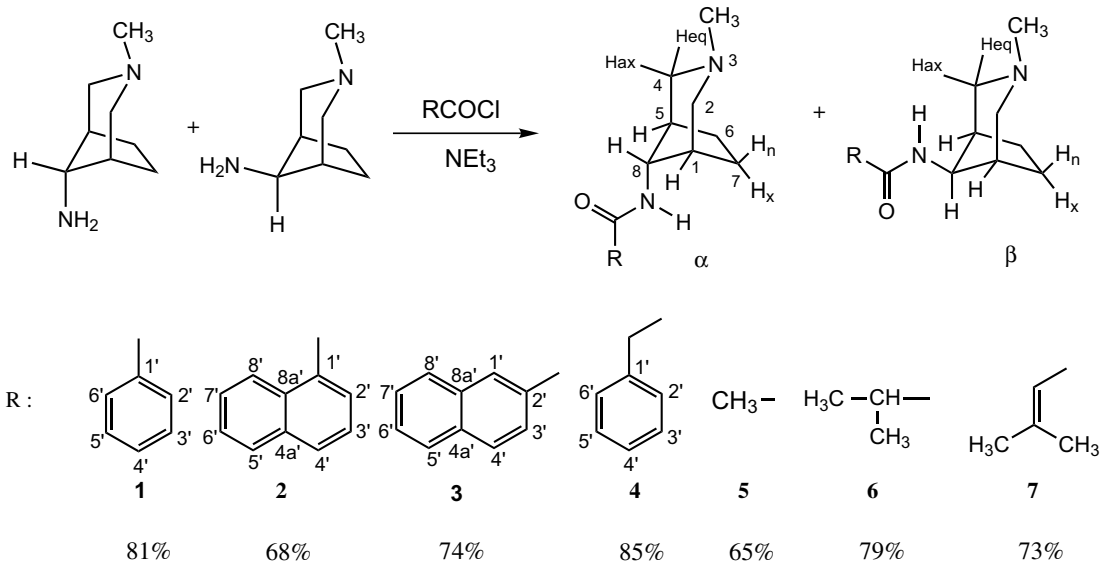

Scheme 1. Synthesis of amides **1–7**(**α** and **β**).

2. Experimental

2.1. Synthesis

The synthesis of compounds **1–7 (α** and **β)** is summarized in Scheme 1.

A solution of a previous synthesized mixture of 3-methyl-3-azabicyclo[3.2.1]octan-8α(β)-amines (2.86 mmol) in dry CH_2Cl_2 (1 mL) was added to a stirred mixture of the corresponding acyl chloride (2.86 mmol) and triethylamine in dry CH_2Cl_2 (1 mL). The reaction mixture was stirring at room temperature for 2–5 h and then was basified with 2.5 N NaOH (1 mL). The organic layer was separated and dried over $MgSO_4$. The solution was concentrated under reduced pressure to give the corresponding mixture of amides (solid/viscous) which was purified by silica gel chromatography using CH_2Cl_2/CH_3OH (ammonia saturated) (92/2).

2.2. NMR and IR spectra

The proton and proton-decoupled ^{13}C NMR spectra were recorded using a Varian UNITY*plus*-5OOFT spectrometer (499.843 MHz for ^1H and 125 MHz for ^{13}C) with PFG, Performa II, WFG, H/C/X PFG NB probe. Measurements were performed for *ca.* 0.03 M solutions of compounds **1–7** in $CDCl_3$. The residual signal of $CDCl_3$ (7.26 ppm) in ^1H NMR and $CDCl_3$ signal (77.00 ppm) in ^{13}C NMR spectra were used as the chemical shift reference. The ^1H, ^{13}C NMR and gHMQC spectra were recorded using the standard Varian software. TOCSY spectra were obtained with a mixing time of 80 ms and NOESY spectra with a mixing time of 500 ms.

The IR spectra of compounds **1–7** were recorded on a Perkin-Elmer FT-IR 1725X spectrophotometer, assisted by a computer, in KBr pellets in the 4000–400 cm^{-1} region and in $CDCl_3$ solution (0.1–0.2 M) in the 4000–900 cm^{-1} region using 0.2 mm NaCl cells. Spectra for very dilute CCl_4 solutions were taken in the 4000–2500 cm^{-1} region with 4 cm quartz cells. Spectra of compound **7** were also registered, at various concentrations, in CCl_4 and $CCl_2{=}CCl_2$. 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

The values of the ^1H NMR chemical shifts are listed in Tables 1 and 2. ^{13}C data are tabulated in Tables 3 and 4.

The ^1H NMR spectra of samples **1–7** in $CDCl_3$ showed two set of signals for the *N*–CH_3, H8, H2(4) and N–H; consequently, it could be deduced that there existed a mixture of two compounds with similar characteristics, one of them in major proportion. To establish the structure of both compounds a deep study for sample **1** (R = Ph) (Fig. 1) has been done.

In sample **1**, the signals corresponding to H8 for both species can be unambiguously assigned owing to their shapes and chemical shifts. They appeared as a doublet of triplets at 4.09 ppm and as a doublet at 3.98 ppm. Saturation of the signal at 4.09 ppm showed NOE enhancements in the two signals at 2.31 ppm and 1.85 ppm. The signals at 4.09, 2.31 and 1.85 ppm, corresponding to the major compound, have been assigned to H8, H1(5) and H6(7)x of the β-epimer, respectively.

On the other hand, saturation of the signal at 3.98 ppm showed NOE enhancement in a signal at 2.29 ppm. The signal at 3.98 ppm has been assigned to H8 whereas the signal at 2.29 ppm is attributed to H1(5) and H2(4)ax (see below), all of them corresponding to the α-epimer.

Table 1
^{1}H NMR chemical shifts (δ, ppm) for **1α–7α** epimers in $CDCl_3$ at 500 MHz

	1α	**2α**	**3α**	**4α**	**5α**	**6α**	**7α**
H8 (d)	3.98	4.06	3.97	3.69	3.73	3.70	3.74
H2(4)ax (d)	2.29	2.30	[a]	2.11	2.14	[a]	2.09
H2(4)eq (dd)	2.77	2.77	2.74	2.61	2.67	2.65	2.64
H1(5) brs	2.29	2.30	[a]	2.18	2.11	[a]	2.09
H6(7)x/n (m)	1.80	1.74	1.81	1.68	1.70	1.73	1.69
N–CH_3 (s)	2.23	2.27	2.26	2.00	2.20	2.19	2.18
NH brs	5.92	5.20 (d)	6.25	5.14	5.30	5.68	5.28
Ph–CH_2 (s)	–	–	–	3.53	–	–	–
CO–CH_3 (s)	–	–	–	–	1.94	–	–
CH(CH_3)$_2$ (m)	–	–	–	–	–	2.21	–
CH(CH_3)$_2$ (d)	–	–	–	–	–	1.09	–
CH=C(CH_3)$_2$ (s)	–	–	–	–	–	–	5.49 5.78[b]
CH=C(CH_3)$_2$	–	–	–	–	–	–	1.77 (s)[c] 2.09 (s)
H1′		–	8.28 (s)	–	–	–	–
H2′	7.75 (dd)	7.88 (dd)	–	7.38 (m)	–	–	–
H3′	7.47 (m)	7.54 (td)	7.94 (d)	7.31 (m)	–	–	–
H4′	7.47 (m)	7.93 (d)	7.88 (d)	7.31 (m)	–	–	–
H5′	7.47 (m)	7.88 (dd)	7.85 (dd)	7.31 (m)	–	–	–
H6′	7.75 (dd)	7.54 (td)	7.55 (t)	7.38 (m)	–	–	–
H7′	–	7.63 (d)	7.55 (td)	–	–	–	–
H8′	–	8.30 (dd)	7.85 (dd)	–	–	–	–

Abbreviations: brs, broad singlet; d, doublet; dd, doublet of doublets; m, multiplet; s, singlet; t, triplet; td, triplet of doublets.
[a] Not determined.
[b] *s-trans* conformation.
[c] CH_3 in *cis* disposition with respect to the vinyl proton.

Table 2
^{1}H NMR chemical shifts (δ, ppm) for **1β–7β** epimers in $CDCl_3$ at 500 MHz

	1β	**2β**	**3β**	**4β**	**5β**	**6β**	**7β**
H8 (td)	4.09	4.18	4.10	3.81	3.86	3.82	3.86
H2(4)ax (d)	2.32	2.36	2.33	1.70	2.19	2.15	2.18
H2(4)eq (dd)	2.65	2.62	2.62	2.39	2.55	2.53	2.50
H1(5) brs	2.31	2.30	2.27	2.00	2.11	2.11	2.09
H6(7)x/n (m)	1.85	1.85	1.84	1.68	1.70	1.73	1.71
N–CH_3 (s)	2.25	2.24	2.27	2.00	2.23	2.21	2.19
NH brs	6.47	6.26 (d)	6.59 (d)	5.55	5.71	5.68	5.64
Ph–CH_2 (s)	–	–	–	3.61	–	–	–
CO–CH_3 (s)	–	–	–	–	2.03	–	–
CH(CH_3)$_2$ (m)	–	–	–	–	–	2.39	–
CH(CH_3)$_2$ (d)	–	–	–	–	–	1.15	–
CH=C(CH_3)$_2$ (s)	–	–	–	–	–	–	5.60 5.74[a]
CH=C(CH_3)$_2$	–	–	–	–	–	–	1.80 (s)[b] 2.11 (s)
H1′	–	–	8.28 (s)	–	–	–	–
H2′	7.69 (dd)	7.88 (dd)	–	7.38 (m)	–	–	–
H3′	7.47 (m)	7.54 (td)	7.94 (d)	7.31 (m)	–	–	–
H4′	7.47 (m)	7.93 (d)	7.88 (d)	7.31 (m)	–	–	–
H5′	7.47 (m)	7.88 (dd)	7.85 (dd)	7.31 (m)	–	–	–
H6′	7.69 (dd)	7.54 (td)	7.55 (t)	7.38 (m)	–	–	–
H7′	–	7.63 (d)	7.55 (td)	–	–	–	–
H8′	–	8.30 (dd)	7.85 (dd)		–	–	–

Abbreviations: brs, broad singlet; d, doublet; dd, doublet of doublets; m, multiplet; s, singlet; t, triplet; td, triplet of doublets.
[a] *s-trans* conformation.
[b] CH_3 in *cis* disposition with respect to the vinyl proton.

The assignment of the signals corresponding to the N–H, C2, C6(7) and phenyl protons of both epimers were based on the NOE enhancements as well as on the observed correlations on the NOESY spectra.

Table 3
^{13}C chemical shifts (δ, ppm) for compounds **1α**–**7α**, DCl_3

	1α	2α	3α	4α	5α	6α	7α
C8	60.21	60.30	60.19	59.59	59.79	59.48	59.43
C2(4)	61.40	61.45	61.38	61.24	61.40	61.36	61.50
C1(5)	39.78	39.89	39.75	39.49	39.62	39.57	39.80
C6(7)	26.30	26.41	26.38	26.04	26.11	26.15	26.28
N–CH_3	45.22	45.33	45.44	45.16	45.17	45.15	45.25
C=O	167.25	168.99	167.66	170.50	169.63	176.47	166.52
Ph–CH_2	–	–	–	44.04	–	–	–
CO–CH_3	–	–	–	–	23.36	–	–
$CH(CH_3)_2$	–	–	–	–	–	35.47	–
$CH(CH_3)_2$	–	–	–	–	–	19.51	–
$CH{=}C(CH_3)_2$	–	–	–	–	–	–	118.63
$CH{=}C(CH_3)_2$	–	–	–	–	–	–	150.20
$CH{=}C(CH_3)_2$	–	–	–	–	–	–	19.57
							27.01[a]
C1′	134.91	134.77	129.14	135.01	–	–	–
C2′	126.74	127.06	132.85	127.29	–	–	–
C3′	128.52	126.38	123.67	128.63	–	–	–
C4′	131.31	130.44	128.00	129.10	–	–	–
C4a′	–	133.58	132.21	–	–	–	–
C5′	128.52	128.23	127.93	–	–	–	–
C6′	126.74	125.27	128.00	–	–	–	–
C7′	–	130.44	127.50	–	–	–	–
C8′	–	124.69	128.83	–	–	–	–
C8a′	–	130.01	134.96	–	–	–	–

[a] CH_3 in *cis* disposition with respect to the vinyl proton.

Table 4
^{13}C chemical shifts (δ, ppm) for compounds**1β**–**7β**, in $CDCl_3$

	1β	2β	3β	4β	5β	6β	7β
C8	51.81	52.03	60.19	51.06	51.46	51.08	51.08
C2(4)	55.62	55.58	55.60	55.19	55.27	55.35	55.48
C1(5)	36.67	36.76	36.83	36.43	36.39	36.39	36.59
C6(7)	26.40	26.49	26.38	26.23	26.22	26.24	26.36
N–CH_3	45.87	45.85	46.03	45.60	45.67	45.74	45.78
C=O	167.11	168.16	167.66	170.50	169.90	176.57	166.69
Ph–CH_2	–	–	–	44.04	–	–	–
CO–CH_3	–	–	–	–	23.36	–	–
$CH(CH_3)_2$	–	–	–	–	–	35.47	–
$CH(CH_3)_2$	–	–	–	–	–	19.51	–
$CH{=}C(CH_3)_2$	–	–	–	–	–	–	118.65
$CH{=}C(CH_3)_2$	–	–	–	–	–	–	150.61
$CH{=}C(CH_3)_2$	–	–	–	–	–	–	19.71
							27.04[a]
C1′	134.91	134.77	129.14	135.01	–	–	–
C2′	126.74	127.06	132.85	127.29	–	–	–
C3′	128.52	126.38	123.67	128.63	–	–	–
C4′	131.31	130.44	128.00	129.10	–	–	–
C4a′	–	133.58	132.21	–	–	–	–
C5′	128.52	128.23	127.93	–	–	–	–
C6′	126.74	125.27	128.00	–	–	–	–
C7′	–	130.44	127.50	–	–	–	–
C8′	–	124.69	128.83	–	–	–	–
C8a′	–	130.01	134.96	–	–	–	–

[a] CH_3 in *cis* disposition with respect to the vinyl proton.

The singlet at 2.00–2.27 ppm has been assigned to the *N*–CH_3 protons in all compounds, in an equatorial disposition. The chemical shifts are similar to the reported values found in equatorial *N*–CH_3 substituted related compounds [5–7,11].

Furthermore, in epimer **1β** saturation of the proton of the N–H group (6.47 ppm) showed NOE enhancements in the signals 4.09 (H8), 2.32, 2.31 and 7.69 ppm. The three last signals must correspond to H2(4)ax, H1(5) and H2′(6′), respectively (Fig. 1). The broad signal at 1.85 ppm can be

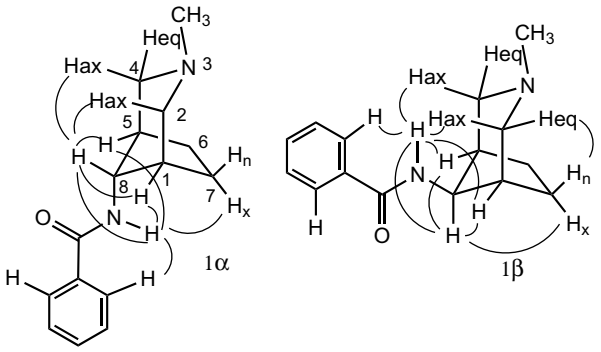

Fig. 1. NOE enhancements in compounds **1α** and **1β**.

assigned to H6(7)n due to a clear correlation signal in the NOESY spectrum with the signal at 2.65, which corresponds to H2(4)eq. Moreover, the signal at 1.85 ppm shows correlation in the NOESY spectrum with H8; therefore, it must also be assigned to H6(7)x, as said above.

For epimer **1α**, saturation of the proton of the N–H group (5.92 ppm) showed NOE enhancements in the signals at 3.98 (H8), 2.29, 1.80 and 7.75 ppm. The last three signals are assigned to H1(5), H6(7)x and H2′(6′), respectively. It can be noted, through the NOESY correlation peak with H8, that the signal at 2.29 ppm assigned to H1(5) can also be attributed to H2(4)ax. Finally, the signal at 2.77 ppm is assigned to H2(4)eq due to the COSY cross peak with H2(4)ax.

Bearing in mind the similarity of the ^{1}H NMR spectra for the amide mixture **1** and the other mixtures (**2**–**7**), the complete assignment of the individual protons for the bicyclic system of the amides **2α**–**7α** (Table 1) and the amides **2β**–**7β** (Table 2) has been made.

The ^{13}C NMR spectra of samples **1**–**7** also showed two sets of signals for the bicyclic system and the C=O group. The results are in agreement with the existence of both α- and β-epimers. Once the resonances of the respective protons were established, the analysis of the gHMQC spectra allowed the distinction between the chemical shift values of the carbons of each epimer. Substituents and electronic effects were also taken into consideration. Tables 3 and 4 show the assignment of ^{13}C NMR chemical shifts.

3.1.2. Conformational study

From the ^{1}H and ^{13}C NMR data, we propose that compounds **1α**–**7α** and **1β**–**7β** in $CDCl_3$ solution adopt a chair-envelope conformation with the *N*–CH_3 in equatorial disposition [7].

In compounds **1α**–**7α**, ^{3}JH8–H1(5) was not observed; consequently the dihedral angle H8–C–C–H1(5) is ~90° according to the Karplus relationship [12]. This fact indicates that the piperidine ring is puckered at C8, probably to relieve the interactions between the amido group and the H6(7)x protons. On the other hand, in compounds **1β**–**7β**, the values of the coupling constants ^{3}JH8–H1(5) ~5 Hz are consistent with dihedral angles H8–C–C–H1(5) of 60°. This value corresponds to a non-distorted piperidine ring [12].

From the data obtained we deduce the existence of free rotation, in $CDCl_3$ solution, of the amido group around the C8–NH bond in both epimers. This conclusion is based on the following experimental data: (a) saturation of the proton of the N–H group showed NOE enhancements in the signals corresponding to H8, H1 and H5; (b) the equivalence of the C2 and C4, and C6 and C7 protons and also of the C2 and C4, and C6 and C7 [13].

The NOESY spectra of epimers **1α** and **1β** showed a clear correlation between N–H and H2′(6′) (Fig. 1) indicating a preferred *trans* form for the –NH–CO group. This *trans* form can also be admitted for **2α**–**7α** and **2β**–**7β** in agreement with IR results (see below).

In the case of the unsaturated compounds **7α** and **7β**, the 2D TOCSY spectrum confirms the assignment of the signals corresponding to each epimer. These compounds can adopt in solution two nearly planar *s-cis* and *s-trans* conformations (Fig. 2). The detailed insight into the conformational equilibrium generated by the C–CO degree freedom was obtained by NOE experiments. We may expect an observable NOE for the vinyl proton with the N–H and CH_3 in the *s-cis* conformation, for both epimers. In the case of an *s-trans* conformation, correlation between the vinyl proton and the CH_3 could only be observed (Fig. 2).

Furthermore, irradiation of the vinyl proton for **7α** (5.49 ppm) showed correlations with the signals at 5.28 and 1.77 ppm. Therefore, these signals must correspond to the N–H and CH_3 groups for the *s-cis* conformation of the O=C–C=C system. In the same experiment, we indirectly achieved saturation of the vinyl proton of the *s-trans* conformer (5.78 ppm) by irradiating the vinyl proton of the *s-cis*-conformer, which then undergoes saturation transfer with the *s-trans* form. This result demonstrates that the equilibrium of conformers is in the slow-exchange regime on the NMR chemical shift time scale but in a fast exchange on the relaxation time scale [14]. The main population of conformers in the equilibrium corresponds to the *s-cis* conformer.

In the case of **7β**, irradiation of the vinyl proton (5.60 ppm) showed correlations with the signals at 5.64 and 1.80 ppm. Therefore, these signals must correspond to the N–H and CH_3 groups for the *s-cis* conformation of the O=C–C=C system. Moreover, when the signal at 5.60 ppm was irradiated, the signal at 5.74 ppm was fully saturated by transfer of saturation. The signal at 5.74 corresponds to the vinyl proton of the *s-trans* form, and the rotation around de C–CO is in a slow-exchange regime on the NMR chemical shift time scale but in a fast exchange on the relaxation time scale as it occurs in the case of **7α**. The main population of conformers in the equilibrium also corresponds to the *s-cis* conformer.

In conclusion, in both epimers there is equilibrium between *s-cis* and *s-trans* conformations, being the most populated, the *s-cis* form. On the other hand, *s-cis*/*s-trans* ratio is higher for **7β**. This fact can be interpreted

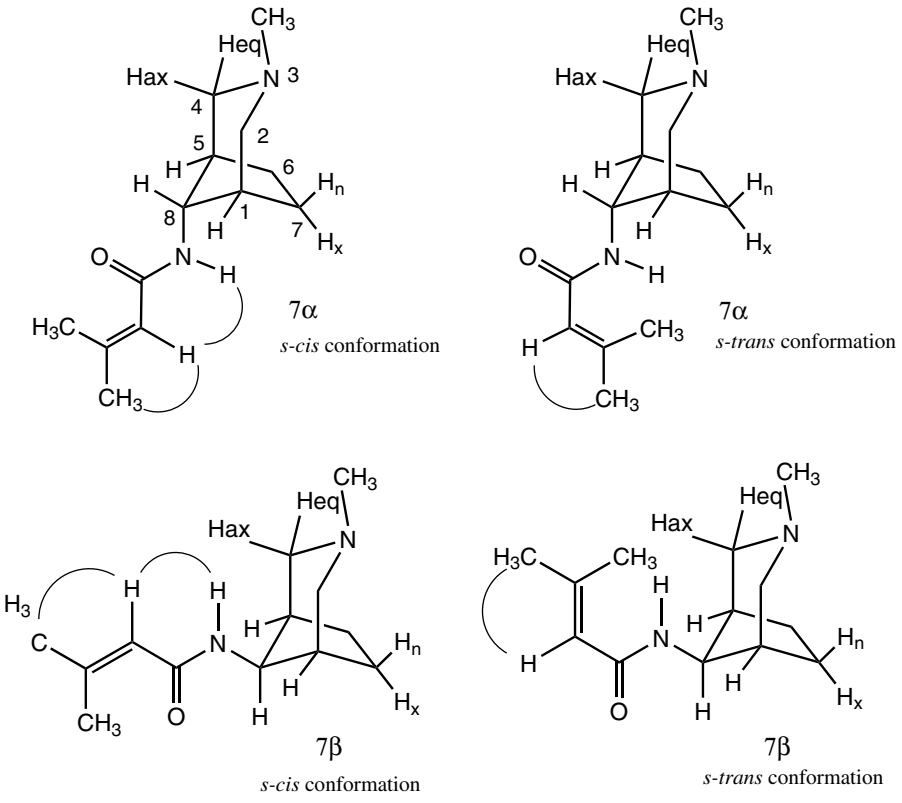

Fig. 2. NOE enhancements in the unsaturated amido moiety in compounds **7α** and **7β**.

as a result of the steric compression, which is present in the *s-trans* conformation of this epimer.

3.2. IR spectra

Contrary to NMR results, the infrared spectra of samples **1**–**7** in our working conditions did not allow showing the presence of the two epimers α and β, which can be attributed to the proximity of the band frequencies [6,15,16].

The infrared spectra of **1**–**7** showed the presence of a strong band at 3320–3270 cm^{-1} in the solid/viscous state (KBr) that is assigned to the stretching vibration of the amide N–H group. Upon dilution this band shifted to 3453–3428 cm^{-1} in $CDCl_3$ (*ca.* 0.1–0.2 M) and to 3457–3438 cm^{-1} in very dilute CCl_4 solution, indicating the presence of intermolecular hydrogen bonding in the solid (or viscous compound) and free NH groups in solution.

In the literature [17], the ν(N–H) band of secondary amides in the 3220–3140 cm^{-1} region in the solid state was assigned to the bonded band of a *cis* complex while a band in the 3340–3270 cm^{-1} was assigned to a *trans* bonded structure. Furthermore, for free N–H groups the frequency ranges given are 3470–3400 for the *trans* and 3440–3420 cm^{-1} for the *cis* structure. Therefore, the above-described solution results reveal that the preferred conformation of compounds **1**–**7** for –NH–CO– is *trans*. The presence of this conformation is confirmed by the results in the 1700–1600 cm^{-1} region (see below). This conclusion also agrees with NMR data in $CDCl_3$.

A weak absorption observed at 3400–3300 cm^{-1}, in some compounds in $CDCl_3$ or CCl_4 solution even at high dilution reveals the presence of intermolecular bonding in our working conditions.

In the carbonyl region compounds **1**–**6** showed two strong bands at 1645–1629 and 1549–1531 cm^{-1} in the solid/viscous state and at 1663–1655 and 1517–1502 cm^{-1} in $CDCl_3$ solution, which are, respectively, assigned to the amide I and amide II bands. These results indicate that C=O groups are implicated in hydrogen bonding with the N–H groups in the solid state (C=O···HN). Moreover, the presence of the amide II band confirms the *trans* conformation of the NH–CO group [18].

In the case of compound **7** two bands were observed in the 1700–1600 cm^{-1} region, at 1671 and 1629 cm^{-1} in KBr. Tentatively, these bands are, respectively, assigned to the out of phase ν(C=O) and in-phase ν(C=C) modes of the O=C–C=C system of the predominant nearly *s-trans* conformation. In $CDCl_3$ solution, the absorption of the C=O band (1664 cm^{-1}) increased whereas the absorption of the C=C band (1637 cm^{-1}) decreased. In accordance with NMR experiments, the infrared results are interpreted on the basis of the predominance of the nearly *s-cis* conformation in $CDCl_3$. In non-polar solvents (CCl_4, CCl_2=CCl_2) changes were produced in the frequencies (at 1673 and 1647 cm^{-1}) and relative intensity of both bands, the C=O absorption prevail-

ing. These results suggest an increase of the *s-cis* conformation in non-polar solvents. The amide II band appeared at 1502–1496 cm^{-1}, the frequencies depending on the medium.

A weak band at 3041 cm^{-1} in the solid state (a very weak shoulder in solution) is assigned to the =CH group stretch in **7**.

Finally, characteristic aromatic bands are observed in samples **1**–**4** in the expected regions. In the same way methyl and *iso*-propyl group bands can be detected in the spectra of **5** and **6**, respectively.

4. Conclusions

A series of amides (**1α**–**7α** and **1β**–**7β**) derived from 3-methyl-3-azabicyclo[3.2.1]octan-8α(β)-amines have been synthesized and studied by IR and NMR spectroscopy.

The NMR data reveal that in $CDCl_3$ solution the amides adopt a preferred chair-envelope conformation with the *N*–CH_3 substituent in an equatorial position with respect to the chair piperidine ring. Besides, free rotation of the amido group around the C8–NH bond and a preferred *trans* form for the –NH–CO group has been deduced. The most relevant conformational difference between α- and β-epimers is the distortion of the piperidine ring in α- epimers.

NMR and IR data indicate that in $CDCl_3$ solution the α,β-unsaturated amides **7α** and **7β** are in equilibrium between *s-cis* and *s-trans* conformations, being the most populated, the *s-cis* form. The proportion of the *s-cis* conformation increases when the polarity of the solvent decreases. The relative population of both conformations (*s-cis*/*s-trans*) is higher for **7β** due to the steric compression present on the *s-trans* conformation.

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References

[1] D.P. Walker, D.G. Wishka, D.W. Piotrowski, et al., Bioorg. Med. Chem. 14 (2006) 8219, and references therein.
[2] A.L. Bodnar, L.A. Cortés-Burgos, K.K. Cook, et al., J. Med. Chem. 48 (2005) 905.
[3] S.R. Baker, J. Boot, M. Brunavs, et al., Bioorg. Med. Chem. Lett. 15 (2005) 4727.
[4] E. Gálvez-Ruano, I. Iriepa-Canalda, A. Morreale, K.B. Lipkowitz, J. Comput-Aided Mol. Des. 13 (1999) 57.
[5] I. Iriepa, B. Gil-Alberdi, E. Gálvez, J. Sanz-Aparicio, I. Fonseca, A. Orjales, A. Berisa, L. Labeaga, J. Phys. Org. 11 (1998) 125.
[6] I. Iriepa, B. Gil-Alberdi, E. Gálvez, M.J. Herranz, J. Bellanato, P. Carmona, A. Orjales, A. Berisa, L. Labeaga, J. Mol. Struct. 482-483 (1999) 425.
[7] I. Iriepa, A.I. Madrid, A. Morreale, E. Gálvez, J. Bellanato, J. Mol. Struct. 651-653 (2003) 585.
[8] I. Iriepa, F.J. Villasante, E. Gálvez, L. Labeaga, A. Innerarity, A. Orjales, Bioorg. Med. Chem. Lett. 12 (2002) 189.
[9] A. Morreale, E. Gálvez-Ruano, I. Iriepa-Canalda, D.B. Boyd, J. Med. Chem. 41 (1998) 2029.
[10] A. Morreale, I. Iriepa, E. Gálvez, Current. Med. Chem. 9 (2002) 99.
[11] E. Gálvez, M.S. Arias, J. Bellanato, J.V. García-Ramos, F. Florencio, P. Smith-Verdier, S. García-Blanco, J. Mol. Struct. 127 (1985) 185.
[12] M. Karplus, J. Am. Chem. Soc. 85 (1963) 2870.
[13] I. Iriepa, A.I. Madrid, E. Gálvez, J. Bellanato, J. Mol. Struct. 787 (2006) 8.
[14] L. Kozersky, B. Kwiecien, P. Krajewsky, et al., New J. Chem. 26 (2002) 1060.
[15] B. Gil-Alberdi, Thesis, University of Alcalá, Madrid, 1996.
[16] I. Iriepa, F.J. Villasante, E. Gálvez, J. Bellanato, J. Mol. Struct. 509 (1999) 105.
[17] S.S. Parker, Applications of Infrared Spectroscopy, in: Biochemistry Biology and Medicine, Adam Hilger, London, 1971, pp. 165–171, and references therein.
[18] L.J. Bellamy, second ed., The Infrared Spectra of Complex Molecules, Vol. II, Chapman and Hall, London and New York, 1980, pp. 280–281, and references therein.