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

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Abstract

A series of ureas derived from 3-methyl-2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9 α -amine were synthesized and studied by IR, Raman, ¹H and ¹³C NMR spectroscopy. These compounds adopt, in CDCl₃, a preferred flattened chair–chair conformation with the cyclohexane ring more flattened than the piperidine moiety and the N–CH₃ groups in equatorial positions. IR and ¹H and ¹³C NMR data show the presence of two conformations at the urea unity. These results are supported by molecular modeling studies. © 1997 Elsevier Science B.V.

Keywords: 3-Methyl-2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9 α -amine; Vibrational spectroscopy; NMR spectroscopy

1. Introduction

As a part of a research program related to the synthesis and structure of new compounds and in connection with our interest in the preparation and the structural study of 3-methyl-2,4-diphenyl-3azabicyclo[3.3.1]nonane derivatives [1–4], we report in this paper the synthesis and structural analysis carried out with the aid of Raman, IR, ¹H and ¹³C NMR spectroscopy of a series of 3-methyl-2,4-diphenyl-3azabicyclo[3.3.1]nonan-9 α -yl N-heterosubstituted ureas (Scheme 1).

2. Experimental

The IR spectra of compounds 4-7 were recorded on

a Perkin-Elmer FTIR 1725X spectrophotometer, assisted by a computer, in the solid state (KBr) and in CDCl₃ solution (0.04 M) in the 4000–400 cm⁻¹ region using 0.2-mm NaCl cells. Spectra for very dilute CCl₄ solutions were taken in the 4000–2500 cm⁻¹ region with 4-cm quartz cells. The reported wavenumbers are estimated to be accurate to within ± 2 cm⁻¹.

Raman spectra were registered for powdered samples on a Jobin-Yvon Ramanor model U-1000 spectrometer, using the 514.5 nm line from a laser Spectra-Physics model 164. A computer was used for storage, processing and displaying of the signals. The spectra included in this work were obtained from the accumulation of 15 scans.

The ¹H NMR spectra of CDCl₃ solutions (about 4% w/v) of compounds 4–7 were recorded at 300 MHz using a Varian Unity-300 spectrometer. Spectral parameters included sweep width of 4000 Hz in 24K

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memory and acquisition times of 3 s over 64 transients. Resolution enhancement using LB = -0.80, GF = 0.50 and GFS = 0.20 was followed by zero filling into 32K memory prior to Fourier transformations.

The ¹³C NMR spectra were obtained at 75.429 MHz on a Varian Unity-300 spectrometer at a spectral width of 16 501 Hz in 64K memory, acquisition time of 1 s and relaxation delay of 1 s, using CDCl₃ solutions (20% w/v) [5].

Molecular modeling was carried out with the QUANTA/CHARMM molecular modeling package (from Molecular Simulations Inc., 1995), running on a Silicon Graphics workstation. The structures were derived from full geometry relaxation using the AM1 Hamiltonian (Dewar et al., 1995) as implemented in MOPAC 6.

2.1. Synthesis

The ureas 4–7 were synthesized (Scheme 1) from the appropriate heterocyclic amine and 3-methyl-2,4diphenyl-3-azabicyclo[3.3.1]nonan-9 α -amine (3) via *N*-succinimidyl carbamate (2) [5].

3. Results and discussion

3.1. NMR spectra

The ¹H data of compounds 4–7 are summarized in Table 1.

Assignments of proton and carbon resonances have been made on the basis of the literature data for related systems [4,6].

At 300 MHz in CDCl₃ solution the signals due to H9, H2(4)_{ax}, H7_{ax}, H1(5), N-CH₃ and the protons of the phenyl groups appear well differentiated in all cases. Overlapping resonances between H6(8)_{ax}, H6(8)_{eq} and H7_{eq} were observed.

With regard to the ¹³C NMR chemical shifts, substituent steric and electronic effects, signal multiplicity obtained from off-resonance decoupled spectra and our previous studies of related compounds [1] were taken into consideration [5].

3.2. Conformational study

From the ¹H NMR and ¹³C NMR data of

Table 1 ¹H NMR chemical shifts (δ /ppm) and multiplicities (J/Hz) for compounds 4–7^a

	4	5	6	7	
	11	п	I	II	II
H9	4.39 m	4.34 m	4.37 m	4.32 m	4.37 t ³ /3.9
H2(4) _{ax}	3.69 d ³ J2.9	3.67 d ³ J3.4	3.69 d	3.65 d	3.68 d ³ J2.9
H7 _{ax}	2.50 m	2.60 m	2.50 m	2.50 m	2.60 m
N-CH ₃	1.95 s	1.94 s	1.94 s	1.92 s	1.95 s
H1(5)	2.05 brs	2.00 brs	1.96	1.88	2.04 brs
	$W_{1/2} \approx 9 \text{ Hz}$	$W_{1/2} \approx 9 \text{ Hz}$	$W_{1/2} \approx 10 \text{ Hz}$	$W_{1/2} \approx 10 \text{ Hz}$	$W_{1/2} \approx 9 \text{ Hz}$
H6(8) _{ax}	1.45 m	1.5 m	1.2–1.4 m	1.2–1.4 m	1.45 m
H7 _{eq}	1.45 m	1.5 m	1.2–1.4 m	1.2–1.4 m	1.45 m
H6(8) _{eq}	1.45 m	1.5 m	1.2–1.4 m	1.2–1.4 m	1.45 m
H2'-H6' (m)	7.00-7.48	7.04-7.46	7.00-7.44	7.00-7.44	7.00-7.46
	7.60-7.86	7.64-7.84	7.62-7.80	7.62-7.80	7.66-7.84
H4″	7.65 d ³ J8.3	7.28 d ³ J3.9	-	-	7.52 dd ${}^{3}J8.6$
H5″	7.34 t ³ <i>J</i> 7.6	6.79 d	6.79 d	6.79 d	7.04 td ³ /2 4
H6″	7.22 t ³ J7.6	-	7.14 t	7.14 t	_
H7″	7.71 d	_	7.24 d	7.24 d	7.37 dd
NH	10-11 br	10-11 br	6.75 d	10-11 br	10-11 br
CH ₃	-	_	3.85 s	3.85 s	_

^a Abbreviations: br, broad; d, doublet; dd, doublet of doublets; m, multiplet; qt, quartet of triplets; s, singlet; t, triplet; td, triplet of doublets. Values of δ were deduced from the first-order analysis of the corresponding system protons with an error of ± 0.05 ppm.

compounds 4–7 the following general features for the bicyclic system were deduced:

- 1. These compounds adopt in CDCl₃ solution a flattened chair-chair conformation.
- 2. The cyclohexane ring is more flattened than the piperidine moiety.
- 3. The N-CH₃ groups are in equatorial positions.

These conclusions are supported by the following: In the ¹H NMR spectra, the range of values for $W_{1/2}$ of H1(5) is between 9 and 10 Hz which is in good agreement with previously reported values for a flattened chair-chair conformation in related bicyclic systems [1,6]. For a boat disposition of one of these rings, the signal corresponding to H1(5) would be an unresolved doublet with a coupling constant of about 18 Hz [7].

The ${}^{3}JH2(4)_{ax}-H1(5) \approx 3$ Hz accounts for a dihedral angle about 60°.

The twin-chair conformation is unambiguously confirmed by the ¹³C spectrum and its comparison

with the corresponding amine [5] and related systems [6]. Bearing in mind the similarity of the chemical shift of C7 for the amine and compounds 4-7 (20.23-20.42) [5], it is clear that these compounds should adopt the same preferred conformation in solution, a flattened chair-chair form.

The N-CH₃ ¹³C chemical shift of compounds 4-7 of about 44 ppm [5] is the same value as those found in equatorial N-CH₃ substituted piperidines [1,8].

In compounds 4–7, $\Delta\delta(H7_{ax}[4-7] - H7_{eq}[4-7]) \approx$ 1.1 ppm was attributed to the field effect exerted by the nitrogen lone pair on H7_{ax}.

We used NMR, IR and computational techniques to analyze the conformations of these compounds.

Compounds 4–7 can adopt four conformations (I– IV) due to the restricted rotation around the C–N bonds (Scheme 2). Molecular modeling studies (AM1 calculations) show that conformation III has the highest energy probably due to steric hinderance. On the contrary, conformation II is the most stable followed by conformations I and IV.



Scheme 2.

In Fig. 1 the conformations I, II and IV for compound 5 are shown. It is important to note that in conformation II there is an intramolecular hydrogen bond between N-H and the nitrogen of the heterocyclic ring. Bearing in mind the results obtained, we studied the conformations of ureas 4-7 from ¹H and ¹³C NMR data.

In the ¹H NMR spectra for 4-7 there are two

signals for the following protons: N-CH₃, H9, H1(5), H2(4)_{ax} and the N-H attached to the bicyclic system. Consequently, two conformations are present in CDCl₃ solution. This result has also been observed in DMSO- d_6 solution. The proportions of these two conformations depend on the nature of the heterocyclic ring.

Moreover, ¹H NMR spectra of compounds 4-7



Fig. 1. Conformations for compound 5 obtained by AM1 calculations.

Table 2 Infrared and Raman frequencies (cm^{-1}) of compounds $4-7^{a,b}$

Compound 4	Medium KBr	ν(N-H) ^c	ν (N-H) ^d 3409 vw 3370 vw	<i>ν</i> (N-H) ^е 3241 w	ν(C=O) 1708 s, sh 1680 vs	Heterocyclic ring		Others	
						1600 m	1535 vs	1574 sh	1564 sh
	Solid		f	f	1706 vw	1599 ^g	<i>1535</i> m	1580 vw	1565 w
	CDCl ₃	3416 vw		3231 w 3200 sh	1705 sh 1693 sh 1675 s	1601 m	1535 vs	1573 sh	1565 s
	CCl_4	3430 vw 3418 sh		3234 w	h	h	h	h	h
5	KBr		3410 sh 3380 vw	3256 w	1700 sh 1676 s	1600 sh	1551 s		
	CDCI ₃	3415 w		3249 w 3238 w 3195 sh	1698 sh 1673 s	1598 m	1553 s		
	CCI ₄	3436 w 3423 sh		3256 w-m	h	h	h		
6	KBr		3395 w	3242 w	1702 s, sh 1680 s	1 60 0 m	1537 vs	1573 s	1560 sh
	CDCl ₃	3443 w 3422 w	3360 sh	3245 sh 3215 w	1693 s 1673 s	1600 m	1537 s-vs	1574 s	1560 sh
	CCl_4	3448 sh 3435 w	3360 sh	3226 w	h	h	h	h	h
7	KBr		3416 sh 3377 w	3249 w	1706 sh 1686 s	1610 m	1546 vs	1574 sh	
	Solid		ſ	f	ſ	1600 ^g	<i>1554</i> m	<i>1573</i> w–m	
	CDCl ₃	3415 w	3340 sh	3238 w 3209 sh	1702 m 1674 s	1611 m	1542 s	1575 s	1563 sh
	CCl ₄	3429 w 3420 sh		3275 sh 3242 w 3217 sh	h	h	h	h	h

^a Raman frequencies are given in italics.

^b Abbreviations: s, strong; m, medium; w, weak; sh, shoulder; v, very.

^c Free NH group.

^d Weakly intermolecularly bonded NH group and/or overtones.

^e Intramolecularly bonded NH group.

^f Not observed.

^g Contribution of a phenyl ring band.

^h Not measured.

show two signals for the N–H attached to the bicyclic system, one at 10–11 ppm as a very broad singlet corresponding to one proton, and consequently, this N–H is bonded in solution forming an intramolecular hydrogen bond. This conclusion is also supported by IR studies. There is another signal (doublet) at 6.75 ppm corresponding to a non-bonded N–H of another conformation. The N–H attached to the heterocyclic ring is overlapped by other signals.

We propose that compounds 4–7 adopt in $CDCl_3$ solution two conformations I and II, the main conformation (II) being the most stable ($\approx 90\%$)

for compounds 4, 5 and 7. Compound 6 adopts the conformations I and II in approximately the same proportion. These results agree with those obtained from molecular modeling and IR studies (see below).

Additional molecular modeling studies will be carried out in order to determine the rotational barrier energy around the C-N bonds.

3.3. Vibrational spectra

Table 2 shows the most characteristic IR and Raman frequencies (cm^{-1}) and the corresponding

assignments in the N-H and double bond stretching regions.

From IR data in the solid state and in solution the presence of an intramolecular hydrogen bond can be clearly deduced. This hydrogen bond is formed between the NH group and the basic nitrogen atom of the heterocyclic ring. Besides the band at 3260-3215 cm⁻¹ assigned to the hydrogen bond, two bands appeared at 3448-3418 cm⁻¹ in very dilute CCl₄ solution which are caused by free NH groups. The higher frequency band is tentatively assigned to a free NH-trans mode suggesting, according to NMR results, the presence of a small proportion of conformation I (or IV) in CCl_4 . The spectrum of 6 in CDCl₃ solution also presented two free NH bands, indicating that the relative proportion of conformation I is greater in this case than in the other three compounds, where only one band was observed.

The existence of at least two conformations is supported by the presence of two carbonyl bands in the solid and in solution, the band at lower frequency (bonded CO group) being stronger. Moreover, this result suggests that the predominant conformations are I and II.

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