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Structural Study of 3-Azabicyclo[3.3.1]nonane Derivatives Functionalized at 1 and/or 9-Positions by Molecular Mechanics Calculations and NMR Spectroscopy

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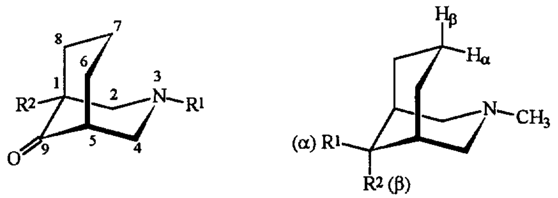
Abstract: Some 3-azabicyclo[3.3.1]nonan-9-ones, **1-3**, 1-alkoxycarbonyl derivates, **4**, **5** and α and β 3-methyl-3-azabicyclo[3.3.1]nonan-9-ols, **6**, **7**, have been studied by means of the molecular mechanics (MMX) method and ^1H, ^{13}C-NMR spectroscopy. Experimental data fit well with theoretical calculations. It is found that the conformational behaviour of the bicyclic system is governed mainly by steric factors and a flattened chair-chair conformation bearing the N-substituent in the equatorial position (CC-β) is always preferred. A monoconformational character can be reasonably assumed except for 3-methyl-3-azabicyclo[3.3.1]nonan-9β-ol, **7**, in non polar solvents where the BC-α form should amount to about 15% of the equilibrium mixture. © 1997 Elsevier Science Ltd.

A wide expansion has been observed in the search for new serotonin 5-HT$_3$ receptor antagonists because of the great number of their potential applications in therapy.[1] Several potent and selective 5-HT$_3$ receptor antagonists -ondansetron, granisetron, renzapride- have been shown to be highly effective inhibitors of chemotherapy or radiation-induced emesis in cancer patiens.[2] Further applications in the treatment of various central nervous system disorders are being currently investigated.[1c, 3]

On the basis of the structures of known ligands, three structural features were shown to contribute to binding to 5-HT$_3$ receptors: a basic-nitrogen, an aromatic ring and a linking group capable of H-bonding interactions (e.g. acyl functional group).[1c, 4] The replacement of one moiety with a bioequivalent has played an important role in the development of new and novel agents from existing ones. Thus, both the affinity and the selectivity for 5-HT$_3$ sites can be modulated by conformational restriction of the basic-nitrogen side chain in the form of an azabicyclic system.[1c, 4a-g, 5-7]

Taking into account that granatane, 1- and 3-azabicyclo[3.3.1]nonane systems are structurally related and the two former skeletons are present in potent 5-HT$_3$ receptor antagonists[1c, 4a-g] -such as granisetron and renzapride-, we turned our attention to the synthesis, structural and pharmacological studies of some 3-methyl-3-azabicyclo[3.3.1]nonane analogues. We present in this paper a comparative study of the azabicyclo derivatives **1-7** (Scheme 1), performed with the aid of theoretical molecular mechanics (MM) calculations and NMR spectroscopy, in order to gather an accurate description of their conformational behaviour. A knowledge of the structural features of these conformationally restricted bicyclic systems can be important to understand the behaviour and activity of natural and synthetic more complex derivatives.

The bicyclo[3.3.1]nonane derivatives can be described by the conformational equilibrium between three groups of conformations: chair-chair (CC), chair-boat (CB, BC) and boat-boat (BB, t-BB). Most of the calculated data available were obtained using MM methods and the predictions are rather reliable if the conformational preferences are governed mainly by steric factors.[8, 9] Nevertheless, a very careful analysis is necessary in making predictions for molecules bearing several substituents and/or heteroatoms since different factors can cause opposite effects and their conformational behaviour are strongly influenced by specific intra and intermolecular interactions (e.g. dipole-dipole and hydrogen bonding). Consequently, the preferred conformation in solution can depend on the polarity and nature of the solvent and can differ from the observed in the solid state.[8, 9]



1, $R^1 = R^2 = H$
2, $R^1 = CH_3, R^2 = H$
3, **2**·H^+ (N)
4, $R^1 = CH_3, R^2 = CO_2CH_3$
5, $R^1 = CH_3, R^2 = CO_2CH_2CH_3$

6, $R^1 = OH, R^2 = H$
7, $R^1 = H, R^2 = OH$

Scheme 1

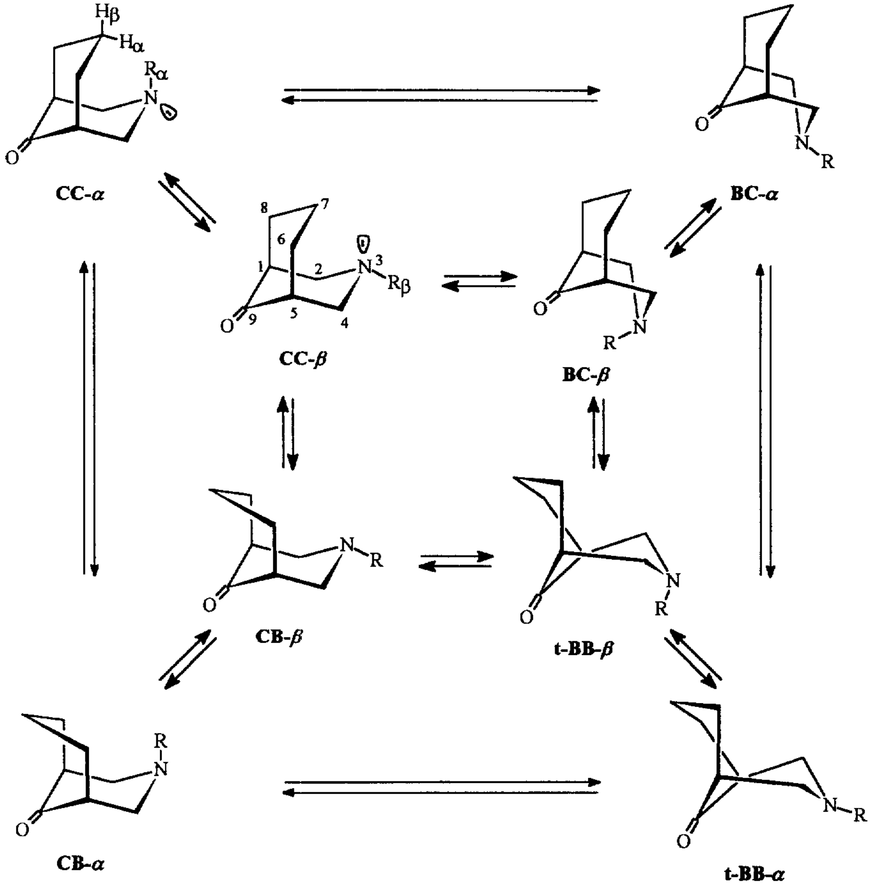
Few data have been found in the literature for these compounds.[8-15] Previous study on the ethyl 3-methyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate (**5**) by ^1H and ^{13}C-NMR spectroscopy showed that this compound adopts in $CDCl_3$ solution a distorted CC conformation with the N-methyl group in the equatorial position.[15] A similar preference is reported for **2**, **6** and **7** on the basis of IR and dipole moment studies.[10, 11] However the AM1 calculations on **1** and its N-methyl analogue **2** indicated a participation of the CB and BC forms around 26 and 48% respectively.[14]

RESULTS AND DISCUSSION

Compounds **1-7** (Scheme 1) were subjected to a systematic study by the molecular mechanics method using the MMX force field[16, 17] (PC-MODEL 386(92) program[18]). Owing to the potential conformational mobility of the bicyclic system and the two spatial orientations of the N-group (3α or *endo* and 3β or *exo* dispositions) by nitrogen inversion, eight conformations, represented in Scheme 2 for the 3-azabicyclo[3.3.1]nonan-9-one (**1**, R = H) and its N-methyl analogue (**2**, $R = CH_3$), were considered. In the case of compounds **4-7** the conformational preferences of the alkoxycarbonyl or hydroxy groups were also explored.

Table 1 shows the relative energies and the conformational populations (N_i) obtained for the eight conformations calculated for the azabicycloketones **1-3** together with the values previously reported for **1** and **2** using the AM1 method.[14] Some characteristic dihedral angles are also tabulated to illustrate the final geometries computed. Concerning the bicyclic system, both theoretical methods predict a preference for a CC conformation. Nevertheless, some differences arise from the comparison of the contributions of the major conformers.

According to MM calculations the 3-methyl-3-azabicyclo[3.3.1]nonan-9-one is practically monoconformational and display a slightly flattened CC conformation with the N-methyl group in the equatorial position (CC-*β*). The energy differences between conformations with an *exo* (*β*) disposition of the N-methyl group and those for *α* forms are in good concordance with previous studies of 3*α* and 3*β* methylbicyclo[3.3.1]nonanes and other derivatives.[8, 9, 19] In the former group, the energy of the CB-*β* form is 2.9 kcal/mol above that of the CC-*β* conformation and the BC-*β* and t-BB-*β* are strongly destabilized. The presence of a 3*α*-methyl group makes the BC-*α* form the lowest in energy while the CC-*α* conformation becomes the most unfavourable in this case.



Scheme 2. Possible conformations of azabicycloketones **1** and **2**.

In contrast, the AM1 calculations yield much lower energy differences between all the conformations and an unexpectedly large contribution of the CB and BC forms -around 48%-, predicting the greater participation in the equilibrium for the sterically more unfavourable[8, 9] BC-*β* and CB-*α* conformations (about 19% for each one). These findings are also in contradiction with the dipole moment and IR studies of **2**[10] as well as the data reported for related compunds.[8, 9, 19a, 20, 21] Accumulating evidence suggest that the presence of a trigonal atom at the 9- position increase the content of the CB-BC conformers in the equilibrium, while the introduction of a heteroatom at 3- position can somewhat stabilize the CC conformation, being the β position the more favourable for a 3- substituent. Thus, the overall conformational behaviour of **2** will be governed by the balance of these opposite effects and the contribution of the CB and BC forms would be expected to be less than that determined for the bicyclo[3.3.1]nonan-9-one (22% at room temperature)[20] since the first effect is only present in this case.

Table 1. Selected Dihedral Angles (deg), Relative Energies (kcal/mol) and Populations for the Conformations of Azabicycloketones **1-3**.[a]

Compound	Conformation	ω_1	ω_2	ω_3	ω_4	ω_5	ω_6	ω_7	Energy MMX/AM1[b]	Ni MMX/AM1[b]
1	CC-β	-55	55	52	54	-54	-45	174	0.0/3.081	0.97/0.004
	CB-β	-57	57	56	4	-4	52	178	2.9/4.291	0.01/ -
	BC-β	-2	2	-55	56	-56	-49	67	5.7/2.058	- /0.024
	t-BB-β	17	26	-62	26	13	36	59	9.5/5.331	- / -
	CC-α	-54	54	49	53	-53	-43	-75	2.3/0.000	0.02/0.738
	CB-α	-57	57	55	4	-4	51	-67	4.2/0.690	- /0.234
	BC-α	-2	2	-55	56	-56	-49	-177	4.9/4.814	- / -
	t-BB-α	17	26	-63	27	12	36	175	8.8/8.015	- / -
2	CC-β	-56	56	53	54	-54	-45	179	0.0/0.000	0.99/0.485
	CB-β	-58	58	57	4	-4	51	-178	2.8/1.183	0.01/0.066
	BC-β	-1	1	-51	57	-56	-48	77	9.1/0.544	- /0.194
	t-BB-β	19	28	-59	28	10	34	68	12.8/3.701	- / -
	CC-α	-57	40	39	44	-58	-34	-97	14.7/1.528	- /0.037
	CB-α	-53	53	44	9	-9	45	-88	11.5/0.559	- /0.190
	BC-α	-1	1	-56	56	-56	-49	179	5.0/1.695	- /0.028
	t-BB-α	17	24	-64	26	12	36	171	9.1/4.840	- / -
3[c]	CC-β	-54	55	48	54	-53	-47	174	0.0	0.99/
	CB-β	-58	58	55	1	-1	53	-179	2.9	0.01/
	BC-β	-10	10	-40	55	-55	-52	91	5.3	
	t-BB-β	12	37	-49	28	18	34	81	8.0	
	CC-α	-47	44	28	52	-55	-47	-110	4.8	
	CB-α	-50	50	35	2	-2	52	-99	5.9	
	BC-α	-7	7	-47	55	-55	-52	-175	4.5	
	t-BB-α	13	33	-55	27	19	34	178	7.6	

[a] Values calculated using MMX program ($\varepsilon = 1.5$); (ω_1) N3C2C1C9; (ω_2) N3C4C5C9; (ω_3) C1C2N3C4; (ω_4) C9C1C8C7; (ω_5) C9C5C6C7; (ω_6) C1C8C7C6; (ω_7) C1C2N3H for **1** and C1C2N3C10 (C of N-CH_3group) for **2** and **3**. [b] Values obtained by semiempirical quantum mechanical calculations with the AM1 method (ref. 14). [c] In this case, the α/β notation indicates the disposition of the methyl group attached to the nitrogen atom.

The preferred conformation for NH compunds was found to be the CC form as well, but the relative spatial arrangement of the N-H bond is not clear. The question arises whether the CC-α or CC-β form would be the most stable one. For the 3-azabicyclo[3.3.1]nonan-9-one (**1**) the MM calculations (Table 1) indicate a strong preference for the CC-β conformation with the N-H bond in the equatorial position (Schemes 1 and 2) and a small contibution of the CB-β and CC-α forms (1 and 2%). The ratio of the CC-β and CC-α

conformations undergoes a little variation with different effective dielectric constants (from 97:2 for ε=1.5 to 92:7 for ε=80 at room temperature), while the CB-β conformational population remains practically constant. Reverse results were obtained by the AM1 method. This procedure showed that the CC-α form with the N-H bond in the axial position should dominate the conformational equilibrium to the extent of 74% followed by the CB-α confomation (23%). The other forms, CC-β and BC-β, with the N-H bond in the equatorial region, should amount to about 3% of the equilibrium mixture. Considering that the MM method gives a best description of the conformational preferences of **2**, the CC-β conformation might probably be the lowest in energy for **1** while the contribution of the CB and BC forms may be negligible. Furthermore, theoretical results indicate that nitrogen inversion in **1** through the interconversion between the CC-β and CC-α forms requires a low additional cost (about 2.3 kcal/mol by the MM approach and 3.1 kcal/mol by the AM1 procedure). Therefore, it seems that the energy to be gained by intermolecular attractive interactions[8,9] (i.e. hydrogen bond) could be sufficient to change the spatial preference of the N-H bond. These features provide a reasonable support for the crystal structure described for related compounds and the observation in solution of the N-H hydrogen inversion depending upon the solvent.[8,9]

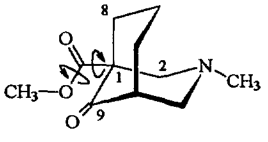
On the other hand, the greater geometry distortion was found in the conformations calculated by the AM1 method[14] (strong flattening of the rings in a chair conformation), probably to relieve the repulsive steric interactions present in all these forms.[8,9] This feature and/or an underestimation of the above-mentioned interactions could explain the different conformational preferences predicted for **1** and **2**. As a result, the contribution of the CB, BC forms would be overestimated[22] and the enviroment of the nitrogen atom should be roughly reproduced. Studies of related compounds using the same theoretical method have shown similar trends.[23,24] In light of these findings, the conformational behaviour of the remaining compounds **3-7** (Scheme 1) were studied by means of the MM method.

The MM calculations show that the ammonium cation **3** (Scheme 1, Table 1) should exist predominantly in a CC conformation with the N-methyl group in the equatorial position (β) and the N-H bond in the axial region (α). The same preference was found for the 3-methyl-1-phenyl-3-azabicyclo[3.3.1]nonan-9-one hydrochloride in the solid state (X-ray data).[25] The protonation of the nitrogen atom leads, as expected, to a greater flattening of the piperidone ring. According to this procedure the energy difference between the CC-β and CB-β forms of the compounds **1-3** (Table 1) is independent of the nature of the nitrogen substituents.

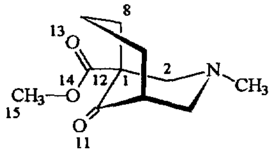
Similary, the CC-β conformation has the lowest strain energy for the ketoesters **4** and **5** and the azabicyclanols **6** and **7**, as was previously suggested.[10-12,15] Relative steric energies and populations for the significant conformations are collected in Tables 2 and 3.

The introduction of an alkoxycarbonyl group at the 1-position does not influence significantly the conformational behaviour of the bicyclic system. Thus, the relative stability of the eight conformations computed for **4** and **5** and their geometries are similar to those predicted for the azabicycloketone **2**. The substituent only exerts a small effect on the energy difference between these forms, depending on its spatial disposition. The conformational preferences of the alkoxycarbonyl moiety were checked for each conformation of the bicyclic system by rotation around the C1-C12, C12-O14 and O14-C15 (in the case of **5**) bonds (Table 2). This study shows that the relative orientation around the C12-O14 rotational fragment is practically fixed with values of the dihedral angles C1-C12-O14-C15 and O13-C12-O14-C15 about 180 and 0°. The rotational system C1-C12 can adopt two spatial arrangements, denoted as **A** and **B**, where the carbonyl group is almost eclipsed with the bicyclic carbons C2 (C2-C1-C12-O13 (ω_3)≈ -5°) or C8 (C8-C1-C12-O13 (ω_4)≈ 8°), respectively; the alternative conformation in which the carbonyl group would be eclipsed with C9 does not

Table 2. Relative Steric Energies (kcal/mol), Populations and Selected Dihedral Angles (deg) for the Significant Conformations of **4** and **5**.[a]

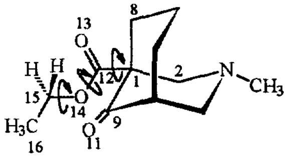


4, CC-β



4, CB-β

	A	B	A	B
C8C1C12O14 (ω_1)	-61	-171	-60	-169
C2C1C12O13 (ω_3)	-5	-116	-3	-112
C8C1C12O13 (ω_4)	120	8	120	11
C9C1C12O13 (ω_5)	-120	124	-118	130
Energy	0.15	0.00	2.28	3.79
N_i	0.43	0.56	0.01	-



5, CC-β

	A-1	A-2	A-3	B-1	B-2	B-3
C8C1C12O14 (ω_1)	-62	-61	-62	-173	-174	-175
C2C1C12O13 (ω_3)	-6	-5	-6	-118	-119	-121
C8C1C12O13 (ω_4)	119	120	118	7	6	4
C9C1C12O13 (ω_5)	-121	-120	-122	122	122	120
C12O14C15C16 (ω_7)	179	83	-83	179	83	-83
Energy	0.10	0.13	0.25	0.00	0.15	0.08
N_i	0.17	0.16	0.13	0.20	0.16	0.18

[a] Values obtained for ε= 1.5. In all cases the dihedral angles C1O12O14C15 (ω_2) and O13C12O14C15 (ω_6) have similar values (180 ± 2 and 0 ± 2°, respectively).

exist due to the destabilizing through-space interaction of the lone electron pairs of oxygen atoms (O13 and O11) (see Figure 1). Moreover, the energy content of the three staggered dispositions around the O14-C15 bond in **5** is very close (Table 2). The **B** orientation is preferred for the CC-β, BC-β and BC-α forms, while the **A** disposition becomes somewhat stabilized for the other conformations. According to the MM calculations, indicated for **4** in Table 2, the CC-β to CB-β interconversion could be facilitate by the simultaneous change in the spatial orientation of the alkoxycarbonyl group from **B** to **A** diposition.

In any case, the contribution of the CB-β form can be reasonably disregarded. Thus, the ketoesters **4** and

Table 3. Relative Steric Energies (kcal/mol) and Populations for the Selected Conformations of **6** and **7**.[a]

Conformation	**6**			**7**		
	Energy	N_i	HO11C9H9(°)	Energy[b]	N_i[b]	HO11C9H9(°)
CC-β	0.00	1.00	54/-53	0.00 (0.00)	1.00 (0.96)	50/-51
CB-β	5.16	-	38/-39	4.36 (4.37)	-	52/-50
BC-α	5.44	-	52/-51	6.32 (1.83)	- (0.04)[c]	180

[a] Values obtained for $\varepsilon = 1.5$. [b] The values computed considering the formation of an intramolecular hidrogen bond (N ······ H-O) and $\varepsilon = 1$ are given in parentheses. [c] d(N3 ---- HO11) = 1.95 Å.

5 can be described by a slightly flattened chair-chair conformation with the N-CH_3 group in the β-position. The alkoxycarbonyl group at 1-position can adopt two spatial arrangements, with practically the same contribution, by rotation around the C1-C12 bond. A stereo-view of these conformations is represented in Figure 2 for **5**. Similar conclusion was reached for **5** on the basis of ^1H and ^{13}C-NMR data.[15]

Regarding the theoretical values, shown in Table 3 for the most stable conformations of the azabicyclanols **6** and **7** , the presence of an α or β 9-hydroxy group increases the energy content of the CB-β form being closer to the BC-α conformation. These data correspond to the most favourable disposition of the hydroxy group and indicate that the O-H bond can adopt two symmetric and isoenergetic gauche dispositions with repect to H-9, except for the BC-α form of **7** in which an anti orientation is preferred.

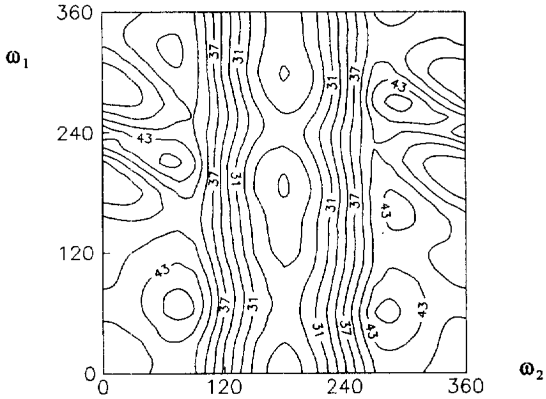
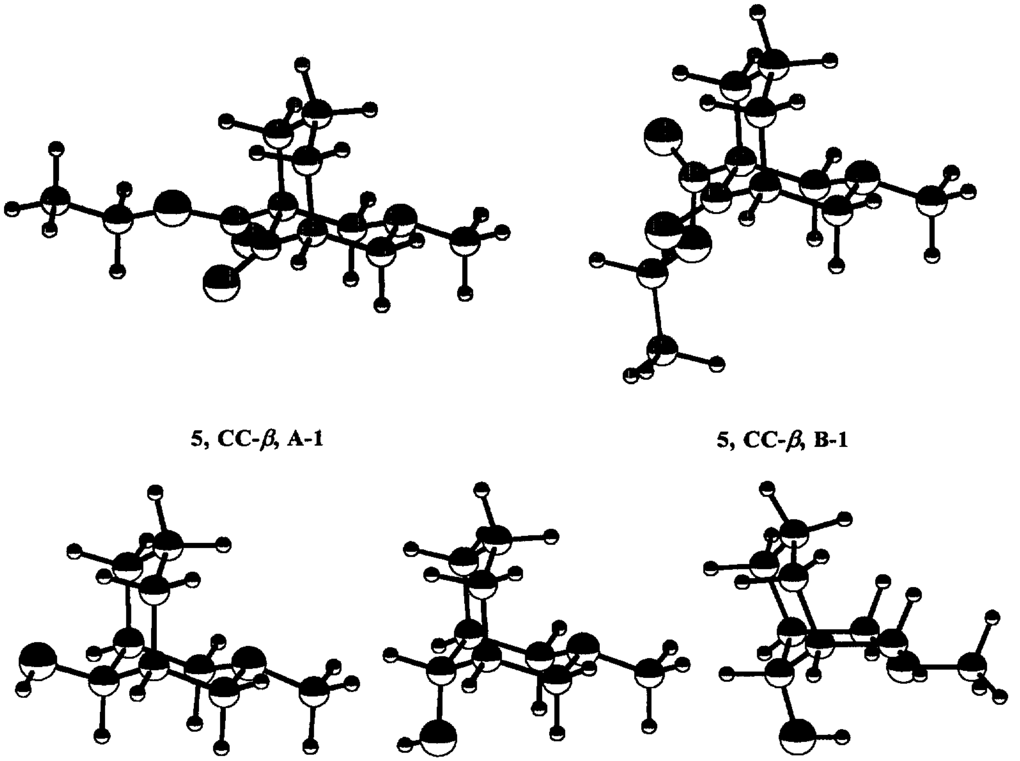


Figure 1. Torsional energy surface obtained by driving C8C1C12O14 (ω_1) and C1C12O14C15 (ω_2) in the CC-β conformation of **4**; intervals of 10°; energies in kcal/mol.

As expected, the BC-α conformation of **7** is stabilized by intramolecular O-H····N bonding and its participation is calculated around 4% for a value of the effective dielectric constant $\varepsilon=1$. An increase of ε decrease the contribution of this stabilizing factor while a variation of ε does not change the conformational preferences of **6**. Owing to the limitation of the MM methods for the study of hydrogen bonds (in general, they are not sufficiently strong),[16] the content of this form in the equilibrium might be higher. Nevertheless, the conformational behaviour of **7** must be always governed mainly by the CC-β conformation, according to the IR data.[11] The most stable conformations of **6** and **7** are represented in Figure 2.



5, **CC-β, A-1**

5, **CC-β, B-1**

6, **CC-β**

7, **CC-β**

7, **BC-α**

Figure 2. PLUTO view of the most stable conformations of **5** - **7**.

To obtain additional information, compounds **2**, **6** and **7** were studied in depth by ^1H and ^{13}C-NMR. The unambiguous assignment of all bicylic proton and carbon resonances was achieved by the combined use of 2D NMR techniques[26] (COSY and ^1H-^{13}C correlation spectra) and double-resonance experiments. The values of the proton magnetic parameters were deduced by analysis of the respective spin systems and are listed in Table 4 along with the carbon chemical shifts.

Concerning the ^{13}C chemical shifts (Table 4) the magnitude and close similarity of the C-7 and N-CH_3 support the assumption that these compounds exist very largely in double chair forms with the N-CH_3 group in the equatorial (β) position.[15, 27, 28] Assuming a CC conformation, the configuration at C-9 in the epimeric azabicyclanols **6** and **7** can be readily inferred on the basis of the upfield shifting γ-gauche effect[27, 28] exerted by the hydroxy group on the C-2(4) and C-6(8) atoms. Comparing the chemical shifts of C-2(4) and C-6(8) (Table 4) it is evident that the OH group must be equatorial (α) with repect to the piperidine ring in **6** and axial (β) in **7**. The value of the γ-gauche effect of the OH group -ca. 6.7ppm- is similar to that reported for the 3-phenethyl analogues[28] and 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ols and their 3-methyl derivatives.[27] Moreover, the deshielding of H-6(8)β in **6** and H-2(4)β in **7** -Table 4, around 0.4 ppm- also supports the

Table 4. ^{1}H and ^{13}C Parameters for the Azabicycloketone **2** and the Epimeric Azabicyclanols **6** and **7**.[a]

			6 (9α-OH)		**7** (9β-OH)	
		2 (CDCl$_3$)	CDCl$_3$	CD$_3$OD	CDCl$_3$	CD$_3$OD
^{1}H δ(ppm)	H-1(5)(m)[b]	2.20	1.74	1.71	1.90	1.76
	H-2(4)α(dd)	3.06	2.87	2.89	2.47	2.55
	H-2(4)β(ddd)	2.50	2.20	2.22	2.60(dd)	2.58
	H-6(8)α(m)	2.14	1.53	1.47	1.81	1.84
	H-6(8)β(m)	1.97	1.94	2.03	1.58	1.66
	H-7α(m)	2.78	2.42	2.45	2.24	2.42
	H-7β((m)	1.44	1.39	1.36	1.35	1.33
	H-9(t)	-	3.68	3.64	3.59	3.62
	CH$_3$-N(s)	2.19	2.11	2.11	2.15	2.11
^{3}J (H,H) (Hz)	H1(5)-H2(4)α	2.56	2.56	2.56	2.56	2.35
	H1(5)-H2(4)β	3.20	2.56	2.56	4.40	3.21
	H1(5)-H6(8)α	2.10	2.93	3.32	3.30	3.21
	H1(5)-H6(8)β	4.76	3.85	4.49	3.67	4.17
	H6(8)α-H7α	6.10	6.23	6.41	5.87	6.20
	H6(8)α-H7β	2.20	1.47	2.20	1.47	1.50
	H6(8)β-H7α	12.65	13.18	13.25	13.18	13.25
	H6(8)β-H7β	6.04	6.23	6.41	6.04	6.20
	H1(5)-H9	-	3.66	3.63	3.30	3.31
^{2}J (H,H) (Hz)	H2(4)α-H2(4)β	-11.90	-11.72	-11.76	-11.72	-11.01
	H6(8)α-H6(8)β	-14.20	-14.28	-13.90	-14.28	-14.11
	H7α-H7β	-13.18	-12.82	-13.25	-13.55	-13.25
|^{4}J (H,H)| (Hz)	H2(4)β-H6(8)β	1.56	2.20	1.92	-	1.50
^{13}C δ(ppm)	C-1(5)	47.87	35.65	36.84	35.68	37.59
	C-2(4)	62.75	61.39	62.54	54.27	55.94
	C-6(8)	34.85	24.42	25.47	30.73	32.58
	C-7	21.09	21.11	22.19	19.10	22.07
	C-9	218.60	72.03	72.61	70.54	71.55
	CH$_3$-N	45.03	46.02	46.50	46.28	47.04

[a] Error, ^{1}H δ ± 0.01ppm; J ± 0.05Hz; ^{13}C δ ± 0.02ppm. [b] Ill-resolved multiplet.

correctness of this assignment.[28] On the contrary, the signals of H-6(8)α and H-2(4)α are shifted downfield (0.3-0.4 ppm) in **7** and **6**, respectively. This trend could be adscribed to the W-arrangement between these protons and the OH group.[29]

The vicinal coupling constants are very useful magnetic parameters for the conformational analysis of the bicyclic system owing to their strong dependence on the dihedral angles. By that, these parameters were empirically estimated in the most significant conformations computed for **2**, **5-7** by using the equation proposed by Haasnoot *et al.*[30] (Table 5) and compared with those deduced from the analysis of the spectra (Table 4). In general, the experimental values are more consistent with those calculated for a CC-β conformation flattened at N3 and C7 in which the cyclohexanic ring exhibits the greater distortion from the

Table 5. Model Vicinal Coupling Constants (in Hz) Calculated from Haasnoot *et al's*[a] Equations for **2** and **5-7**.

Coupling Constants	2			5		6	7	
	CC-β	CB-β	BC-α	CC-β	exp[b]	CC-β	CC-β	BC-α
H1(5)-H2(4)α	2.1	2.2	4.1	2.1	2.20	2.3	2.3	3.7
H1(5)-H2(4)β	3.7	3.5	9.8	3.7	3.65	3.5	3.6	9.8
H1(5)-H6(8)α	2.4	3.5	2.5	2.4	2.43	2.6	2.6	2.7
H1(5)-H6(8)β	4.2	10.4	4.1	4.2	4.77	4.1	4.0	3.8
H6(8)α-H7α	5.7	4.7	4.8	5.7	6.02;6.03	5.9	5.7	4.9
H6(8)α-H7β	1.6	12.7	2.0	1.6	2.92;3.05	1.5	1.5	2.0
H6(8)β-H7α	12.1	2.2	12.6	12.1	12.36;12.28	11.9	12.0	12.6
H6(8)β-H7β	5.5	4.4	4.7	5.4;5.9	6.30;6.29	5.8	5.9	4.9
H1(5)-H9						3.5	3.1	3.2

[a] Reference 30. [b] Reference 15.

ideal geometry. Again, these data support the previous hypothesis. The more significant deviation corresponds to the value of ^{3}J H1(5)-H2(4)β for 7 in CDCl$_3$ -4.40 Hz-, greater than that observed in CD$_3$OD -3.21 Hz-. This variation might be related to the contribution of the BC-α form stabilized in non polar solvents by intramolecular O-H····N bonding which is lack in protic solvents, where this form can be in fact disregarded as was discussed above. MM calculations estimate its participation in the conformational equilibrium around 4% and the population-weighted values for the vicinal coupling constants are practically similar to those calculated for the CC-β form. Nevertheless, the experimental value of ^{3}J H1(5)-H2(4)β accounts for a higher contribution in CDCl$_3$. A lesser effect is observed for ^{3}J H1(5)-H2(4)α due to the closer values of this coupling constant in both CC-β and BC-α forms (Table 5). From these data, a limiting value of the BC-α contribution around 15 % was deduced for the 3-methyl-3-azabicyclo[3.3.1]nonan-9β-ol (7) in CDCl$_3$ solution.

The minor variations from one system to another (Table 4) may be due to the different nature and spatial disposition of the functional groups which lead to variable distortion of the CC-β conformation.[8, 9] MM calculations do not reproduce these small changes, predicting practically the same geometric features and vicinal coupling constants (Table 5).

CONCLUSIONS

In summary, the molecular mechanics approach (MMX force field) satisfactorily reproduces the conformational behaviour of the 3-azabicyclo[3.3.1]nonane derivatives **1-7**. These compounds always prefer a chair-chair conformation flattened at N3 and C7, bearing the N-substituent in the equatorial position (CC-β). In the case of the 3-azabicyclo[3.3.1]nonan-9-one (**1**), the nitrogen inversion through the interconversion between the CC-β and CC-α forms requires a low additional cost (about 2.3 kcal/mol), suggesting that the spatial preference of the N-H bond might be governed in solution by the solute-solvent interactions. The 3-methyl-3azabicyclo[3.3.1]nonan-9β-ol (**7**) adopts in CD$_3$OD solution a CC-β conformation, while in non polar solvents (CDCl$_3$) the contribution of the BC-α form -stabilized by intramolecular O-H·····N bonding- is estimated around 15%. The other compounds are practically monoconformational. In the ketoesters **4** and **5**, both theoretical and experimental data account for two spatial arrangements, with practically the same contribution, for the alkoxycarbonyl moiety.

EXPERIMENTAL

General. The IR spectra were measured as KBr pellets on a Perkin-Elmer 883 spectrophotometer. All NMR spectra (^1H, ^{13}C, double resonance experiments, DEPT, COSY-45 and HETCOR) were recorded on a varian UNITY-300 spectrometer in $CDCl_3$ and/or CD_3OD at 298°K; resolution enhancement was applied to deduce the proton magnetic parameters.

Synthesis. Compounds **2**,[31, 32] **6** and **7**[11] were obtained as reported earlier. Thus, the hydrolysis of the ethyl 3-methyl-9-oxo-3-azabicyclo[3.3.1]nonane-1-carboxylate (**5**)[15, 32] with 25% HCl gave an oil residue which solidified by treatment with acetone-diethyl ether. The product was recrystallized from methanol and the analytical and spectroscopic data showed that its structure corresponds to the carboxylic acid hydrochloride having the 9-oxo group as hydrate (this feature is described by first time). Decarboxylation of this intermediate with 50% H_2SO_4 yielded the azabicycloketone **2** pure (46%). Reduction of **2** with $NaBH_4$ in dry 2-propanol led to a mixture of the two epimeric azabicyclanols **6** and **7** (α:β ratio, 59:41). Silical gel chromatography using ethyl acetate as eluent provided samples with 92% and 85% (by ^1H-NMR) of **6** (α) and **7**(β), respectively. The synthetized compunds gave satisfactory microanalytical data[11, 31, 32] and IR spectra.[10, 11, 32] The ^1H and ^{13}C magnetic parameters are collected in Table 4.

9,9-Dihydroxy-3-methyl-3-azabicyclo[3.3.1]nonane-1-carboxylic acid hydrochloride: 58%; mp 152-5°C; IR (KBr) 3347, 3164, 2566, 2444, 1691 cm^{-1}; ^1H-NMR (CD_3OD) δ 3.67(dd, J= -13.2 and 1.5 Hz, 1H), 3.48 (dd, J= -13.2 and 2.2 Hz, 1H), 3.45 (dt, J= -12.8 and 1.8 Hz, 1H), 3.16 (ddd, J= -12.8, 3.7 and 1.8 Hz, 1H), 2.81(s, 3H), 2.28(m, 2H), 2.07(m,1H), 1.76(m,4H); ^{13}C-NMR (CD_3OD) δ 176.22, 96.28, 58.47, 57.84, 47.23, 34.16, 32.46, 26.30, 19.47. Anal. Calcd for $C_{10}H_{18}NO_4Cl$ (251.70): C, 47.72; H, 7.21; N, 5.56. Found: C, 47.52; H, 7.16; N, 5.49.

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