Conformational Study of 2,4-Diaryl-3-azabicyclo[3.3.1]nonan-9-ones and Their 3-Methyl Derivatives by Quantum Mechanical Calculations, NMR, and X-ray Crystallography

María-Selma Arias,*,† Yves G. Smeyers,‡ María-José Fernández,† Nadine J. Smeyers,† Enrique Gálvez,† Isabel Fonseca,§ and Juliana Sanz-Aparicio§

Departamento de Química Orgánica, Universidad de Alcalá, 28871 Alcalá de Henares, Madrid, Instituto de Estructura de la Materia, CSIC, c/.Serrano 123, 28006 Madrid, Spain, and Instituto Rocasolano, U.E.I. Cristalografía, CSIC, c/.Serrano 119, 28006 Madrid, Spain

Received November 30, 1993•

Some 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ones 1 and their *N*-methyl derivatives 2 have been synthesized and studied by semiempirical quantum mechanical calculations and ^{1}H-NMR spectroscopy (AM1/^{1}H tandem) in order to establish their conformational preferences. The crystal structure of 3-methyl-2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9-one, **2a**, has been determined by X-ray diffraction. It is found that compounds 1 present a CC-α preferred conformation in the gas phase and in $CDCl_3$ solution, while the CC-β form is observed in the solid state. This latter conformation, with the N–H bond in the equatorial position (CC-β), seems to be favored by the formation of intermolecular hydrogen bonds in the crystal. Compounds 2 are practically monoconformational and display a slightly flattened CC conformation with the *N*-methyl group in the equatorial position (CC-β).

Introduction

The conformational properties of substituted bicyclo-[3.3.1]nonanes and heteroanalogs have been extensively studied by different experimental and computational methods[1,2] because of the relation of these compounds with more complex natural and synthetic molecules which possess interesting biological activities. The critical influence of the stereochemical and conformational characteristics on the activity is well known. Thus, several of the structure–activity relationships developed for γ-aminobutyric acid (GABA) agonists and antagonists[3] have been rationalized in terms of the ability of the low-energy conformations to dock optimally on the pharmacophore framework.

As part of a research program aimed at the development of new agonists or antagonists for the $GABA_B$ receptors,[4–6] we have focused on synthetic, structural, and pharmacological studies of some esters derived from the 2,4-diaryl-3-azabicyclo[3.3.1]nonane system, in which the GABA skeleton is included. In these rigid compounds two restricted conformations of the flexible GABA molecule can be mimicked (Figure 1). These conformationally restricted analogs could help us to gain insight into the topography of the receptor.[3]

As far as we are aware, the 2,4-diaryl-3-azabicyclo[3.3.1]-nonan-9-ones and their 3-methyl derivatives have not been studied theoretically. All available data from experiment demonstrate, both in the solid state and in solution, a preference for the chair–chair (CC) conformation, which is additionally stabilized by diequatorial 2- and 4-aryl groups.[1,2,7–10] Accumulating evidence suggests that the relative orientation of the N-substituent is practically fixed in the equatorial position when the substituent is a methyl group.[1,2,7] However, contradictory data and assumptions have been reported for the NH compounds.[8–10]

In order to gather more information about this conformationally restricted bicyclic system, we present in this paper a comparative study of several 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-ones 1 and their 3-methyl derivatives 2, used as synthetic precursors, carried out by semiempirical quantum mechanical calculations and ^{1}H-NMR spectroscopy (300 MHz). In addition, we include the X-ray structure of the 3-methyl-2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9-one, **2a**.

For a systematic study of these compounds, the two forms, chair (C) and boat (B), for each six-membered ring

† Universidad de Alcalá.
‡ Instituto de Estructura de la Materia.
§ Instituto Rocasolano.
• Abstract published in *Advance ACS Abstracts*, April 1, 1994.

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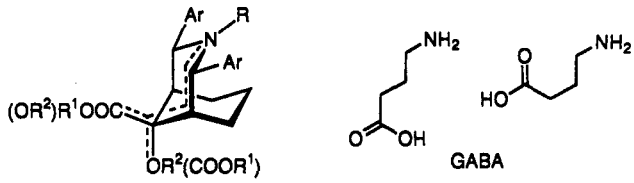
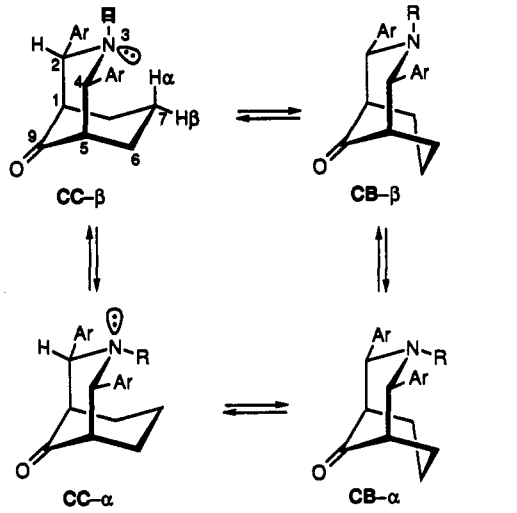


Figure 1. Structure of conformationally restricted analogs of GABA derived from 2,4-diaryl-3-azabicyclo[3.3.1]nonane; the dashed line shows the molecular superpositions of the GABA skeleton.



1a: R=H, Ar=C_6H_5 **2a**: R=CH_3, Ar=C_6H_5
1b: R=H, Ar=p-OCH_3-C_6H_4 **2b**: R=CH_3, Ar=p-OCH_3-C_6H_4
1c: R=H, Ar=p-F-C_6H_4 **2c**: R=CH_3, Ar=p-F-C_6H_4
1d: R=H, Ar=p-CH_3-C_6H_4 **2d**: R=CH_3, Ar=p-CH_3-C_6H_4
1e: R=H, Ar=p-Cl-C_6H_4 **2e**: R=CH_3, Ar=p-Cl-C_6H_4

Figure 2. Possible conformations of azabicycloketones 1 and 2.

as well as the two spatial orientations of the N-group on the piperidone ring (3α and 3β dispositions) must be considered. However, four conformations can be reasonably disregarded according to our previous study[4] on 3-azabicyclo[3.3.1]nonan-9-one, **3**, and its *N*-methyl derivative, **4**, and other data from the literature.[1,2,7-10] Those forms in which the piperidone ring adopts a boat or twist-boat conformation are strongly destabilized by the almost-eclipsed gauche interactions of the aryl groups with the second ring and the aryl/aryl 1,3-diaxial interaction.[2] As a result, these forms are so unfavorable that the conformational behavior of azabicyclo ketones **1** and **2** may be strictly restricted to the four conformations represented in Figure 2. In the present work, the AM1 method has been used to optimize the geometry of these forms to carry out the population analyses and to obtain the atom charges.

Results and Discussion

Table 1 shows the relative formation energies and populations obtained for the four computed conformations of the azabicyclo ketones **1a** and **2a** by the AM1 method (Figure 2). Since a similar trend was found within each of these series, only the data for the significantly populated forms are tabulated for the remaining compounds. This procedure shows the chair–chair conformation (CC) to be the most favorable in all cases, in agreement with previous studies.[1,2,7-10] Results from preliminary studies on the

Table 1. Calculated Relative Formation Energies and Populations of the Conformers of Azabicyclo Ketones 1 and 2

	energy[a]				energy[a]		
compd	conformer	(kcal/mol)	Ni[b]	compd	conformer	(kcal/mol)	Ni[b]
1a	CC-α	0.000	0.814	**2a**	CC-α	6.031	0.000
	CB-α	0.942	0.169		CB-α	3.900	0.001
	CC-β	2.460	0.014		CC-β	0.000	0.916
	CB-β	3.383	0.003		CB-β	1.444	0.083
1b	CC-α	0.000	0.815	**2b**	CC-β	0.000	0.921
	CB-α	0.948	0.162		CB-β	1.474	0.079
1c	CC-α	0.000	0.804	**2c**	CC-β	0.000	0.920
	CB-α	0.925	0.172		CB-β	1.463	0.080
1d	CC-α	0.000	0.814	**2d**	CC-β	0.000	0.916
	CB-α	0.943	0.169		CB-β	1.444	0.083
1e	CC-α	0.000	0.801	**2e**	CC-β	0.000	0.872
	CB-α	0.905	0.177		CB-β	1.149	0.128

[a] Mean gradient values 0.008–0.01 kcal/mol Å. [b] Populations according to Boltzmann distribution at 300 K.

azabicyclo[3.3.1]nonan-9-one derivatives allow us to suppose that these species are in thermodynamic equilibrium.[4]

For compounds **1** the CC-α form with the N–H bond in the axial position should dominate the conformational equilibrium to the extent of 80–82% at room temperature, followed by the CB-α conformation (0.90–0.95 kcal/mol, 16–18%). The other forms, CC-β and CB-β, with the N–H bond in the equatorial region, should amount to about 2% of the equilibrium mixture, with the CB-β being the most unfavorable.

In the case of the *N*-methyl analogs, **2**, a critical change of the conformational preferences is found. As expected, the α forms are destabilized by the resulting extra steric interactions of the axial *N*-methyl group[1,2,4,7] (Figure 2). According to the AM1 calculations (Table 1) the CC-α conformation does not exist and the CB-α can be practically disregarded. The calculated preference is always for equatorial CH_3 on N: compounds **2** exist with 88–92% in the CC-β conformation, and the CB-β contribution to the 30 °C equilibrium is around 8–13%. The calculations yield much greater energy differences not only between α and β forms but also between the two significant conformers. Thus, a larger monoconformational character can be reasonably assumed for the *N*-methyl derivatives.

The influence of the N-group on the conformational preferences is in good agreement with the previous calculations on 3-azabicyclo[3.3.1]nonan-9-one, **3**, and its N-methyl analog **4** using the same theoretical method.[4] However, some differences arise from the comparison of the contributions of the major conformers. The introduction of the aryl groups in the 2 and 4 equatorial positions of the piperidone ring exert a small effect on the NH derivative **3**, and the ratio of the two significant conformers CC-α:CC-β undergoes a little variation, from 75:25 (**3**) to about 82:18 (**1**). For the *N*-methyl derivatives, on the contrary, a greater increase of the CC-β participation in the conformational equilibrium (48% for **4** *vs* 90% for **2**) is found. This change is achieved by the minimization of the BC-β and CB-α contributions (about 19% for **4**), while the CB-β conformational population remains practically constant. The highest destabilization of the BC-β form is due to the above-mentioned interactions of the aryl groups,[2] while the relative spatial arrangement between the *N*-methyl and the 2,4-diaryl groups seems to be the destabilizing factor of the CB-α form in **2**.

Concerning the bicyclic system, the predominance of the CC conformation agrees with the crystal structure

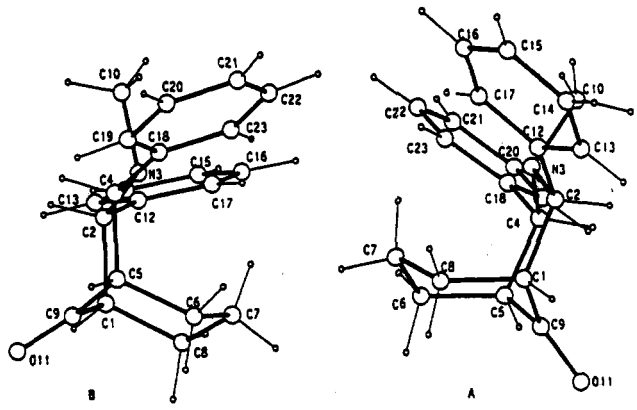


Figure 3. X-ray structure of 2a.

Table 2. Selected Dihedral Angles (deg) for the Significant Conformers of 1a and 2a

	1a		2a		
dihedral angle	CC-α	CB-α	CC-β	CB-β	X-ray
C1C2C4N3[a]	-23.21	-25.76	-25.44	-25.81	
C1C8C6C7[a]	20.76	-24.59	21.98	-25.57	
C2C4N3H(C10)[a]	-80.65	-72.13	176.39	175.90	
N3C2C1C9	53.04	55.60	55.72	56.24	52.0; 53.5
C7C6C5C9	51.21	4.93	52.66	4.33	52.7; 54.1
C1C2N3C4	-45.97	-51.33	-50.75	-51.33	-47.6; -47.7
C1C8C7C6	40.93	-49.08	43.15	-50.70	48.6; 48.7
C1C2C12C13[b]	93.82	80.47	91.85	83.71	81.3; 86.2

[a] Dihedral angles between the planes defined by the following atoms: C1C2C4 and C2C4N3; C1C8C6 and C8C6C7; C2C4N3 and C4N3H (or C of CH_3 methyl group, C10). The remaining entries correspond to torsion angles. [b] C12 and C13 represent the ipso and ortho carbons of the phenyl groups.

described for 1a,[8,9] 1b,[9] and 1d[9] as well as IR,[7a,8a] ^{1}H,[10a] and ^{13}C-NMR[7b] data. The X-ray crystal structure of 2a was determined by us and confirms the same behavior for the *N*-methyl analogs 2 in the solid state. Compound 2a presents two independent molecules in the asymmetric unit with very similar geometrical features: both chair forms are slightly flattened at N3 and C7 with the *N*-methyl group in the equatorial position (Figure 3, Table 2). The packing of the molecules is governed mainly by van der Waals forces.

The good general agreement between calculated and experimental torsion angles for 2a (Table 2) also supports the correctness of the calculations. The more significant deviations correspond to the dihedral angles C1–C8–C7–C6 and C1–C2–C11–C12, which indicate a large flattening of the cyclohexanone ring and a slightly different orientation of the phenyl groups for the CC-β-computed conformer with respect to the X-ray structure.

In compounds 1, the calculations suggest a clear preference of the N–H bond for occupying an axial position, in contradiction with the more accurate X-ray data published for 1a, b and 1d.[8b,9]

Concerning the NH disposition in compounds 1, the situation is not clear. Thus, for 1a two crystalline modifications have been found as a function of the crystallization solvent: α (polar) and β (nonpolar), and it has been concluded, using IR data, that both modifications differ in the equatorial and axial orientations of the N–H bond.[8a] Although a CC form with an axial disposition of the N–H bond was first proposed for the β polymorphic form,[8a] later studies showed the equatorial position of this bond.[8b,9] The same trend has been found for 1b and 1d in the solid state.[9]

Table 3. Proton Magnetic Parameters for the Azabicyclo Ketones 1 and 2 (300 MHz, $CDCl_3$)[a,b]

	1a	1b[c]	1c	2a	2b[c]	2c
δ(ppm)						
H-1(5) (m)	2.48	2.40	2.43	2.43	2.38	2.39
H-2(4)β (d)	4.41	4.33	4.39	3.74	3.66	3.72
H-6(8)α (m)	1.92	1.93	1.90	1.91	1.94	1.87
H-6(8)β (m)	1.70	1.70	1.71	1.64	1.64	1.65
H-7α (m)	2.91	2.86	2.83	2.92	2.88	2.81
H-7β (m)	1.39	1.37	1.40	1.47	1.46	1.48
NH (s)	1.70	1.84	1.60			
CH_3 (s)				1.98	1.94	1.93
^2J (Hz)						
H 6(8)α–H6(8)β	-14.62	-14.60	-14.60	-14.47	-14.30	-14.65
H7α–H7β	-13.19	-13.20	-13.20	-13.51	-13.41	-13.35
^3J (Hz)						
H1(5)–H2(4)β	2.69	2.69	2.93	3.66	3.42	3.42
H1(5)–H6(8)α	1.95	2.00	1.95	2.56	2.60	2.56
H1(5)–H6(8)β	3.42	3.40	3.42	3.10	3.00	3.10
H6(8)α–H7α	5.98	5.98	6.10	5.46	5.49	5.37
H6(8)α–H7β	1.59	1.50	1.59	1.53	1.50	1.59
H6(8)β–H7α	13.19	13.20	13.20	13.51	13.41	13.35
H6(8)β–H7β	6.30	6.25	6.27	5.68	5.61	5.68

[a] Error, δ ± 0.01 ppm; *J* ± 0.05 Hz. [b] Aromatic protons δ: 1a, 7.55 (d, *J* = 7.57 Hz, 2H), 7.40 (dd, *J* = 7.57 and 7.32 Hz, 2H), 7.31 (t, *J* = 7.32 Hz, 1H); 1b, 7.44, 6.92 (m, AA'MM' system, *J* = 8.79, 2.56 and 0.00 Hz); 1c, 7.51, 7.09 (m, AA'MM'X system due to the fluorine atom, H/H $J_{A,M}$ = 8.79 Hz, H/F *J* = 8.55 and 5.37 Hz); 2a, 7.87–7.12 (m, 5H); 2b, 7.74–6.86 (m, 4H); 2c, 7.80–7.04 (m, 4H). [c] OCH_3, δ: 3.81 (1b), 3.82 (2b).

On the other hand, the IR spectra in solution of azabicyclo ketones 2, for which Ar = phenyl or para-substituted phenyl, have been interpreted[7a] by assuming an intermolecular association in nonpolar solvents through the CC-α conformation, with a more favorable orientation of the lone pair for an attractive interaction (i.e., an intermolecular hydrogen bond) between the carbonyl carbon and the amino group. Nevertheless, in protic solvents an equilibrium mixture of CC-α and CC-β forms has been proposed because both can be solvated without any preference.

To our knowledge, the limited ^{1}H-NMR data reported for these azabicyclo ketones are mainly devoted to the ^{1}H chemical shifts of 1.[10] To obtain additional information, compounds 1a–c and 2a–c were studied in depth by ^{1}H-NMR ($CDCl_3$, 300 MHz). The unambiguous assignment of all bicyclic proton resonances was achieved by the combined use of 2D NMR techniques[11] (COSY and ^{1}H–^{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 3.

With regard to the chemical shifts, the most relevant difference between the two series corresponds to H2(4)β protons, whose signal appears at higher field in 2 (Δδ H2-(4)β ≈ −0.7 ppm), in consonance with the Mulliken partial charges on H2(4)β atoms encountered for the preferred conformations of 1a (CC-α, ρ = 0.109) and 2a (CC-β, ρ = 0.069). This can be related to σ-electron delocalization of the nitrogen lone pair in trans coplanar C2(4)–H bonds[12] for 2 and the lack of this relative orientation for 1, in agreement with the calculated preferences: CC-α (axial N–H bond) for 1 and CC-β (equatorial *N*-methyl) for 2. The results of the calculations also account for the β-deshielding effect[7b] exerted by the *N*-methyl group on

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Table 4. Model Vicinal Coupling Constants (in Hz) Calculated from Haasnoot *et al.*'s[a] Equations for 1a and 1b[b]

coupling constants	1a			2a			
	CC-α	CB-α	av[c]	CC-β	CB-β	av[c]	X-ray
H1(5)-H2(4)β	2.9	2.6	2.8	3.2	3.1	3.2	3.8
H1(5)-H6(8)α	2.2	2.8	2.3	2.3	3.1	2.4	2.6
H1(5)-H6(8)β	4.6	10.3	5.6	4.3	10.3	4.8	4.0
H6(8)α-H7α	7.0	5.3	6.7	6.4	5.0	6.3	5.5
H6(8)α-H7β	1.0	12.9	3.0	1.1	13.1	2.1	1.5
H6(8)β-H7α	11.7	1.8	9.9	12.2	1.9	11.3	13.0
H6(8)β-H7β	6.7	5.1	6.4	6.2	4.8	6.1	5.0

[a] Reference 13. [b] The vicinal coupling constants for the individual conformations (CC-α, CB-α, CC-β, CB-β and the solid state structure, see Figures 2 and 3) were calculated from the medium values of the corresponding dihedral angles; thus, in the first entry the medium value of the H1–C1–C2–H2β and H4β–C4–C5–H5 dihedral angles was taken. [c] Population-weighted values.

the C2(4) chemical shift (partial charges on C2(4): ρ = 0.025 (**1a**) and 0.033 (**2a**)).

On the other hand, experimental coupling constants (Table 3) point out that **1** exhibits the greater flattening of the cyclohexanone ring. Again, these data might be related to the predominance of the CC-α conformation for these compounds: the cyclohexanone ring is distorted in order to avoid the repulsive interaction N3–H···C7–H7α.

Vicinal coupling constants were also empirically estimated, in the computed conformers of **1a** and **2a**, and in the solid structure of **2a** by using the equation proposed by Haasnoot *et al.*[13] (Table 4). Although calculated and experimental values (Table 3) do not agree well, probably due to errors in the calculation method and/or some inadequacy in Haasnoot's equation for these systems, the predicted values follow the same trend and support the previous hypothesis.

For compounds **1** the contribution of the CB-α conformation could not be asserted experimentally. Evidence was not found by ^{1}H-NMR even at 203 K in CD_2Cl_2. Moreover, the reasonably good agreement between the observed values for the vicinal coupling constants of the cyclohexanone system protons and those calculated for the CC-α form (Tables 3 and 4) indicates that these azabicyclo ketones can be considered virtually monoconformational in solution. These findings suppose that the CB forms may be even more energetically unfavorable than calculated by the AM1 approach. The same trend has been reported by Ferguson *et al.*[14] for the boat forms of six-membered rings using ab initio calculations at the 3-21G level.

Theoretical results indicate that nitrogen inversion in **1** through a change from CC-β to CC-α, in which the equatorial N–H bond is sterically more accessible, requires an additional cost of about 2.5 kcal/mol. Therefore, it seems that the heat of formation of an intermolecular hydrogen bond[15] could be sufficient to shift the conformational equilibrium toward this conformation. This feature provides a reasonable support for the crystal structure of **1** and agrees with the observation of a polymorphous transformation of the β-crystal of **1a** by thermographic analysis.[8a] In addition, different dispositions of the N-substituents both in the solid state and in solution have been described for related compounds and this behavior has been ascribed to the hydrogen bonding network in the crystal structures.[2,6]

Conclusions

In summary, the AM1 calculations satisfactorily reproduce the conformational preferences of the azabicyclo ketones **1** and **2**, both in $CDCl_3$ solution and in the crystalline state. Compounds **2** are practically monoconformational and always prefer a slightly flattened CC conformation having the *N*-methyl group in the equatorial position. In the case of **1** a clear predominance of the CC form with an axial disposition of the N–H bond (CC-α) is found in the gas phase (theoretical calculations) and in $CDCl_3$ solution while, in the solid state, this bond occupies the equatorial region (CC-β form). Theoretical results account for the formation of an intermolecular hydrogen bond as the probable reason for this nitrogen inversion.

Experimental Section

General. The melting points are uncorrected. The mass spectra were obtained with a Hewlett-Packard 5988 spectrometer (EI, 70 eV). The IR spectra were measured as KBr pellets on a Perkin-Elmer 883 spectrophotometer. All NMR spectra (^{1}H, ^{13}C, COSY-45 and XHCORD) were recorded on a Varian UNITY-300 spectrometer in $CDCl_3$ (CD_2Cl_2 for ^{1}H of **1** at 203 K); resolution enhancement was applied to deduce the proton magnetic parameters.

X-ray Analysis. The main crystallographic data and the structure determination conditions for compound **2a** are listed in Table 5.[30]

Computational Details. Owing to the large size of the azabicyclo ketones **1** and **2**, a semiempirical quantum mechanical method, at the Hartree–Fock level, was employed for the computation of the formation energy of each conformer. An analytical procedure of energy minimization, as a function of all the molecular parameters, was applied to determine the optimal structure. The AM1 method was chosen because this procedure leads to rather reliable predictions of the main features of polycyclic molecules[4,21-23] and describes reasonably well the hydrogen bonds when geometrical structural requirements might allow their formation.[24] As the AM1 method is implemented in the MOPAC program (version 6.1), molecular structure optimization and analysis of the critical points properties on the potential energy hypersurface were carried out simultaneously. The optimization was performed by using an analytic gradient minimization method (*BFGS*, precise option).[25] Furthermore, the above analytic method implemented with the extrapolation

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Table 5. Crystal Data, Data Collection and Structure Refinement

crystal data	
formula	$C_{21}H_{23}NO$
crystal size (mm)	0.30 × 0.31 × 0.23
symmetry	triclinic, P-1
unit cell determin	least-squares fit from 50 reflexions ($15 < 2\theta < 35$)
unit cell dimens (Å)	12.592 (1), 13.251 (2), 13.262 (3), 96.47 (1), 112.85 (1), 116.56 (1)
packing: V (Å^3), Z	1710.4 (3), 4
D_c (g-cm^{-3}), M, $F(000)$	1.1860, 305.419, 656
μ (cm^{-1})	0.672
experimental data	
technique	four-circle diffractometer: ENRAF-NONIUS CAD-4, bisecting geometry, graphite-oriented monochromator: Mo Kα, 0.71070, w/2θ scan
scanning range for θ	$2 < \theta < 28$
no. of reflns	
measured	8197
observed	5203 ($I < 2\sigma(I)$ criterion)
range of hkl	−16/16, −17/17, 0.17
absorption	no correction applied
solution and refinement	
solution	direct methods
refinement	mixed, temp factors of H atoms fixed
variables	553
H atoms	differential Fourier synthesis
w-scheme	empirical as to give no trends in $\langle w\delta^2F\rangle$ vs $\langle\|F_o\|\rangle$ and $\langle\sin\theta/\lambda\rangle$[16]
final max shift/error	0.5
final R and R_w	0.046, 0.056
computer and programs	VAX 11/750, MULTAN80,[17] XRAY80,[18] PARST[19]
scattering factors	*Int. Tables for X-Ray Crystallography*[20]
anomalous dispersion	*Int. Tables for X-Ray Crystallography*[20]

procedure called eigenvector following (option *EF*)[26] was used to lower the mean gradient up to values below 0.01 kcal/mol·Å (or deg).

Synthesis. The azabicyclo ketones **1a–c** and **2a–c** were obtained and purified as reported earlier for **1a**, **1b**, **2a**, and **2b**.[27,28] Thus, compounds **1** were prepared by the Mannich condensation of cyclohexanone, aromatic aldehyde, and ammonium acetate.[27,28] The N-methylation was performed by treatment of **1** with methyl iodide and anhydrous potassium carbonate in acetone.[27] All crystalline compounds (from methanol) gave satisfactory microanalytical data and mps,[27,28] as well as mass,[29] IR,[7a,8a] and ^{13}C NMR[7b] spectra. The ^1H magnetic parameters are collected in Table 3.

2,4-Bis(4-fluorophenyl)-3-azabicyclo[3.3.1]nonan-9-one (1c): 26%; mp 197–8 °C; IR (KBr) 3312, 1707 cm^{-1}; ^{13}C NMR δ 21.07 (C7), 28.88 (C6(8)), 53.87 (C1(5)), 64.12 (C2(4)), 115.42, 128.35, 136.79, 162.17 (Ar, J_{CF} = 21.43, 8.24, 3.30, and 246.13 Hz, respectively), 216.8 (CO); MS m/z (rel intensity) 327 (M^+, 35), 230 (M^+ − 97, 100), 176 (21), 148 (23), 135 (27), 109 (29). Anal. Calcd for $C_{20}H_{19}NOF_2$ (327.37): C, 73.38; H, 5.85; N, 4.28. Found: C, 73.28; H, 6.02; N, 4.57.

2,4-Bis(4-fluorophenyl)-3-methyl-3-azabicyclo[3.3.1]nonan-9-one (2c): 68%; mp 193–4 °C; IR (KBr) 1717 cm^{-1}; ^{13}C NMR δ 20.67 (C7), 29.46 (C6(8)), 43.38 (CH_3), 54.54 (C1(5)), 73.67-(C2(4)), 115.47, 129.06, 136.19, 161.99 (Ar, J_{CF} = 21.36, 9.15, 3.05 and 245.37 Hz, respectively), 216.4 (CO); MS m/z (rel intensity) 341 (M^+, 26), 148 (50), 147 (42), 138 (59), 136 (100), 135 (55), 133 (39), 115 (27), 109 (99), 95 (29). Anal. Calcd for $C_{21}H_{21}NOF_2$ (341.40): C, 73.88; H, 6.20; N, 4.10. Found: C, 73.61; H, 6.08; N, 4.37.

Acknowledgment. We thank Dr. Federico Gago for several helpful comments. This research has been financed in part by the Spanish Comisión Interministerial de Ciencia y Tecnología (Grant FAR-88-0440) and the University of Alcalá de Henares (Madrid, Spain).

Supplementary Material Available: Tables of atomic coordinates, equivalent isotopic displacement coefficients, bond lengths, and bond angles for non H-atoms and a unit cell packing diagram for **2a** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(30) The author has deposited atomic coordinates for **2a** with the Cambridge Crystallographic Data Center. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.