Synthesis, Structural, and Biochemical Study of a Series of Methyl 2,6-Diaryl-1-methyl-4-oxopiperidine-3,5-dicarboxylates and a Series of Methyl 2,4-Diaryl-3,7-dimethyl-9-oxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarboxylates

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A series of methyl-2,6-diaryl-1-methyl-4-oxopiperidine-3,5-dicarboxylates **Ia-c** and 2,4-diaryl-3,7-dimethyl-1,5-dimethoxycarbonyl-9-bispidinones **IIa-c** have been synthesized and studied by ir, ^1H and ^{13}C nmr spectroscopy and the crystal structure of methyl 2,4-diphenyl-3,7-dimethyl-9-oxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarboxylate **(IIa)** has been determined by X-ray diffraction. The enolic form of compound **Ia (I'a)** was also studied.

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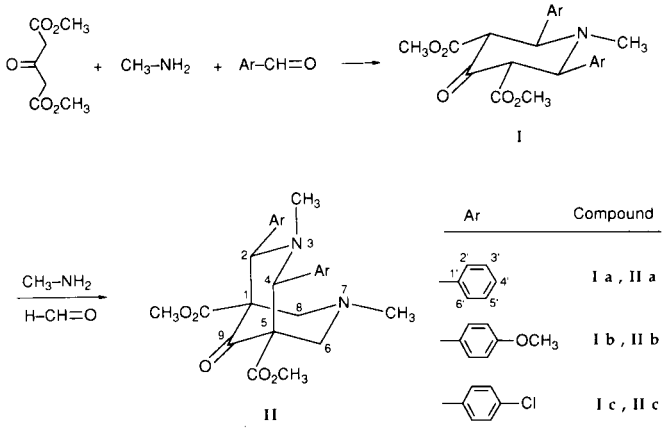
Introduction.

As a part of a research program related to the synthesis and structural study of new $GABA_B$ receptor antagonists, and in connection with our interest in the preparation and structural and pharmacological study of bispidine derivatives [1-4], we have synthesized and studied by ^1H, ^{13}C nmr and ir spectroscopy a series of methyl-2,6-diaryl-1-methyl-4-oxopiperidine-3,5-dicarboxylates (compounds **Ia-c**), and a series of 2,4-diaryl-3,7-dimethyl-1,5-dimethoxycarbonyl-9-bispidinones (compounds **IIa-c**, Scheme 1). In order to determine the preferred conformation of **II** both in solution and in the solid state, the crystal structure of 2,4-diphenyl-3,7-dimethyl-1,5-dimethoxycarbonyl-9-bispidinone **(IIa)** has also been determined.

Scheme 1



In the case of compounds **I**, the enol tautomer of **Ia (I'a)** intramolecularly hydrogen bonded, was also studied.

Results and Discussion.

Compounds **Ia-c** were prepared as shown in Scheme 1, from the reaction of methyl-3-oxoglutarate with methylamine and the corresponding aldehyde in methanol. By treatment of the corresponding **I** with formaldehyde and methylamine in methanol [5] compounds **II** were obtained.

Compounds **Ia-c**.

Infrared Spectra.

Table 1 shows the infrared frequencies and the corresponding assignments of the bands appearing in the OH, C=O and C=C stretching regions of compounds **Ia-c**.

Table 1

Infrared Frequencies (cm^{-1}) of Compounds Ia-c, IIa-c (Potassium Bromide)

Compound	ν (OH)	ν (C=O) ester	ν (C=O) keto
Ia		1753	1719
I'a	3416	1738	
		1655	
Ib		1737	1715
Ic		1738	1718
IIa		1742	1717
IIb		1738	1723
IIc		1736	1702

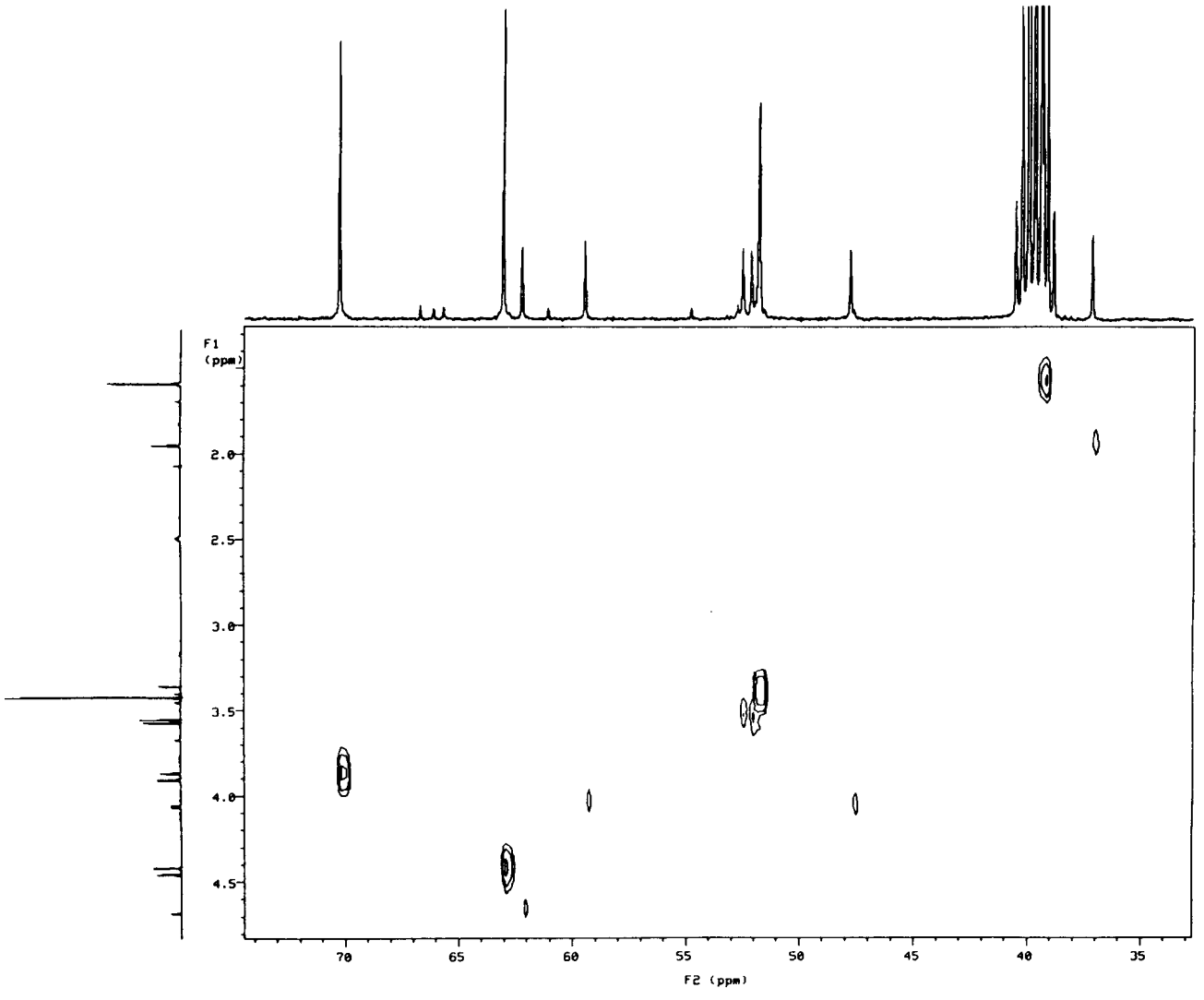


Figure 1

Table 2

^{1}N HMR Chemical Shifts [a] (δ, ppm) and Multiplicities (J, MHz) for compounds **Ia-c**

δ	**Ia**	**Ib**	**Ic**
H2(6) (d)	3.87	3.76	3.92
	J 11.4 Hz	J 11.3 Hz	J 11.5 Hz
H3(5) (d)	4.41	4.34	4.41
N-CH_3 (s)	1.58	1.56	1.58
COO-CH_3 (s)	3.41	3.42	3.44
O-CH_3 (s)		3.72	
H2'(6')	7.43 (m)	7.31 (d)	7.44 (s)
		J 8.2 Hz	
H3'(5')	7.35 (m)	6.89 (d)	7.44 (s)
H4'	7.27 (m)		

[a] Abbreviations: d, doublet; m, multiplet; s, singlet. δ values were deduced by the first order analysis of the spectra, error ±0.05 ppm.

As it has been described in related compounds [5] in **Ia-c** in the solid phase (potassium bromide) the ester carbonyl and the ketone carbonyl free groups absorb at ~1740 and ~1715 cm^{-1} respectively, whereas the conjugated ester carbonyl group (**I'a**) in the solid phase (potassium bromide) shows a band at 1655 cm^{-1}, the very broad absorption band between 2200-3600 cm^{-1} is attributed to the strongly associated OH group.

Furthermore, the presence of "Bohlmann absorption" in the 2800 cm^{-1} region indicates that the *N*-methyl group occupies an equatorial position in the *N*-piperidine chair [1].

NMR Spectra.

The ^{1}H and ^{13}C nmr spectra of compounds **Ia-c** show great similarity (Tables 2-4). Compound **Ia** has been studied in more detail; its proton-coupled ^{13}C nmr spectrum

Table 3

^{1}N HMR Chemical Shifts for Compounds **I'a**

^{1}H Chemical Shifts [a]	δ (ppm)	^{13}C Chemical Shifts [b]	δ (ppm)
H2 (s)	4.67	C2	62.17
H5 (AB system)	4.04	C3	99.37
	J 10 Hz	C4	165.91
H6 (AB system)	4.04	C5	47.79
OH (s)	12.09	C6	59.43
CH_3O (s)	3.54	N-CH_3	37.18
CH_3O (s)	3.56	C'1	138.40, 140.40
N-CH_3	1.94	C(2'-6')	127.36, 127.96
C_6H_5 (m)	7.26		128.11, 128.50
			128.74, 128.98
		CO	170.59, 171.01
		OCH_3	52.09, 52.47

[a] Abbreviations: d, doublet; m, multiplet; s, singlet. δ values were deduced by the first order analysis of the spectra, error ±0.05 ppm. [b] Directly measured on the spectra, error ±0.05.

Table 4

^{13}C HMR Chemical Shifts [a] (δ, ppm) for Compounds **Ia-c**

δ	**Ia**	**Ib**	**Ic**
C2(6)	70.22	69.61	69.15
C3(5)	62.98	63.08	62.70
N-CH_3	39.32	39.09	39.20
COO-CH_3	51.77	51.70	51.92
O-CH_3		55.13	
COO-CH_3	167.46	167.54	167.30
C=O	198.92	199.07	198.45
C1'	140.50	132.43	139.50
C2'(6')	128.69	129.15	129.92
C3'(5')	128.06	113.99	128.80
C4'	128.25	158.93	132.72

[a] Directly measured on the spectra, error ±0.05.

and heteronuclear proton-carbon shift correlation spectrum (Figure 1) were used to provide the required information.

Conformational Study.

From the ^{1}H and ^{13}C nmr data of **Ia-c** was deduced that the piperidine ring adopts (as expected) a chair conformation with the *N*-methyl, aryl and methoxycarbonyl groups in equatorial positions.

These conclusions are supported by the following observations: the ^{3}J H2(6)-H3(5) of ~11 Hz accounts for a dihedral angle H2(6)-C-C-H3(5) of ~180°. For an axial disposition of the *N*-methyl group, a syn-diaxial effect would be exerted on H3(5) and consequently the δ C3(5) values would be shifted to higher field; at this point it is neces-

Table 5

Experimental Data and Structure Refinement Procedures

Crystal Data		
Formula		$C_{25}H_{28}O_5N_2$
Symmetry		Orthorhombic, Pnma
Unit cell determination		Least squares fit from 25 rf/Ins.
Unit cell dimensions (Å)		8.122(1), 21.315(6), 13.359(2)
Packing	V(Å^{-3}), Z	2313(1), 4
	Dc(g.cm^{-3}), M,F(000)	1.254, 436.6, 928.0
	μ(cm^{-1})	0.819
Experimental Data		
Technique		Four circle diffractometer: EnrafNonius CAD-4. Bisecting geometry graphite monochromator: MoKα ω/2θ scans
Number of reflections measured		3796
Independent/Observed		2107 (I>2σ(I) criterion)
Range of hkl		0 to 11, 0 to 29, 0 to 18
Standard reflections		2 reflections every 120 minutes, no variation
Solution and refinement		
Solution		Direct methods [8-10]
Refinement		Least squares on Fobs.
Paremeters	number of variables	180
	H atoms	Fourier diference synthesis, exception H of the methyl groups
Maximum final shift/error		0.03
w-scheme		w = 4 (Fobs)^2/[sigma(Fobs)^2]^2
Final ΔF peaks		0.21 eÅ^{-3}
Final R and Rw		R = 0.053, Rw = 0.057
Computer and Programs		
Computer		Micro Vax II
Structure determination package		Enraf-Nonius/SDP
Programs		[8,9]

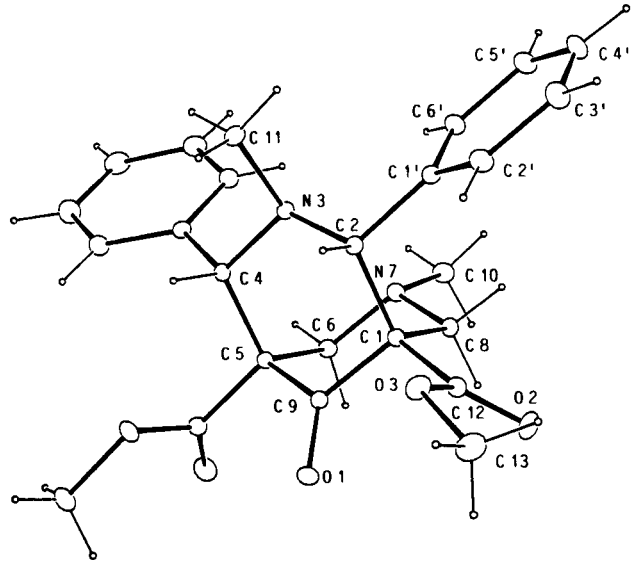


Figure 2

Table 6

Atomic Parameters

Atom	x	y	z	B(A2)
O1	0.4204(2)	0.250	0.1505(1)	3.39(4)
C9	0.3008(3)	0.250	0.0966(2)	2.47(4)
C1	0.2131(2)	0.19115(8)	0.0618(1)	2.52(3)
C8	0.0388(2)	0.19401(9)	0.1091(1)	2.94(3)
N7	-0.0464(2)	0.250	0.0755 (2)	3.03(4)
N3	0.1580(2)	0.250	-0.1006(2)	2.65(4)
C2	0.2142(2)	0.19056(8)	-0.0559(1)	2.58(3)
C11	0.2007(4)	0.250	-0.2075(2)	3.64(6)
C10	-0.2188(3)	0.250	0.1061(2)	4.18(7)
C9	-0.3053(2)	0.13504(9)	0.1055(1)	3.08(4)
O2	0.2612(2)	0.10620(7)	0.1772(1)	4.81(3)
O3	0.4456(2)	0.12363(6)	0.0569(1)	3.97(3)
C13	0.5493(3)	0.0752(1)	0.0989(2)	5.27(5)
C1'	0.1072(2)	0.13681(9)	-0.0939(1)	3.01(3)
C2'	0.1748(3)	0.0780(1)	-0.1112(2)	4.23(4)
C3'	0.0746(3)	0.0287(1)	-0.1413(2)	5.60(6)
C4'	-0.0898(3)	0.0378(1)	-0.1565(2)	5.52(6)
C5'	-0.1587(3)	0.0961(1)	-0.1410(2)	4.83(5)
C6'	-0.0600(2)	0.14547(9)	-0.1097(2)	3.75(4)
H81	-0.024	0.155	0.087	0.0
H82	0.050	0.190	0.184	0.0
H2	0.326	0.184	-0.084	0.0
H111	0.318(3)	0.250	-0.215(2)	0.1
H112	0.162(2)	0.2115(7)	-0.239(1)	0.1
H101	-0.271(2)	0.2144(7)	0.078(1)	0.0
H102	-0.235(3)	0.250	0.186(2)	0.0
H131	0.646	0.071	0.060	0.1
H132	0.579	0.087	0.165	0.1
H133	0.490	0.037	0.100	0.1
H2'	0.293(2)	0.0719(8)	-0.102(1)	0.1
H3'	0.121(2)	-0.0122(8)	-0.155(1)	0.1
H4'	-0.150(2)	0.0045(8)	-0.174(1)	0.1
H5'	-0.280(2)	0.1043(8)	-0.150(1)	0.1
H6'	-0.108(2)	-0.1829(8)	-0.099(1)	0.0

Standard atoms were refined isotopicaly. Anisotopically refined atoms are given in the form of the isotropic equivalent displacement parameter defined as: $(4/3)\bullet[a^2\bullet B(1,1)+b^2\bullet B(2,2)+c^2\bullet B(3,3)+ab(\cos\gamma)\bullet B(1,2)+ac(\cos\beta)\bullet B(1,3)+bc(\cos\alpha)\bullet B(2,3)]$.

sary to remark that the δ C3(5) values of **Ia-c** are quite similar to the δ C2(4) values of compounds **IIa-c** in which, the N-CH_3 group occupies an equatorial disposition (see later).

Finally, the unusual high field value of δ N-CH_3 in the compounds **Ia-c** can be attributed to π-anisotropic field exerted by the vicinal aryl groups.

Structural and Conformational Study of Compound **I'a**.

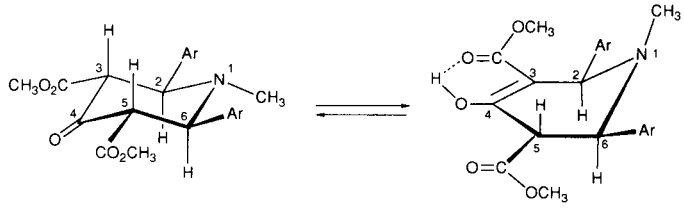
From the ^1H and ^{13}C data of compounds **I'a** (Table 3), we propose for this compound the structure represented in Scheme 2 in which the piperidine ring adopts a pseudo-chair conformation with the C-6-phenyl and C-5-methoxycarbonyl groups in equatorial position and the C-2-phenyl group in equatorial position.

Table 7

Bond Lengths (Å)

Atom 1	Atom 2	Distance	Atom 1	Atom 2	Distance
O1	C9	1.209(3)	C2	H21	0.995(2)
C9	C1	1.516(2)	C11	H111	0.96(2)
C1	C8	1.551(2)	C11	H112	0.97(2)
C1	C2	1.572(2)	C10	H101	0.95(1)
C1	C12	1.527(2)	C10	H102	1.07(2)
C8	N7	1.451(2)	C12	O2	1.194(2)
C8	H81	1.023(2)	C12	O3	1.333(2)
C8	H82	1.013(2)	O3	C13	1.446(2)
N7	C10	1.458(3)	C13	H131	0.946(2)
N3	C2	1.473(2)	C13	H132	0.952 (2)
N3	C11	1.470(2)	C13	H133	0.945(2)
C2	C1'	1.525(2)	C1'	C2'	1.388(3)
C1'	C6'	1.386(3)	C2'	C3'	1.389(3)
C2'	H2'	0.98(2)	C3'	C4'	1.364(4)
C3'	H3'	0.97(2)	C4'	C5'	1.379(3)
C4'	H4'	0.89(2)	C5'	C6'	1.387(3)
C5'	H5'	1.01(2)	C6'	H6'	0.90(2)

Scheme 2



Ia I'a

These conclusions are sustantiated as follows: The low field of the δ OH signal ~12 ppm accounts for a proton intramolecularly bonded. The ^3J H5-H6 ~10 Hz is due to the *trans*-coplanar position between H5 and H6. The size and shape of multiplets corresponding to the phenyl rings are attributed to the structural non-equivalence of them. The above exposed structural conclusions are similar to that described previously for related compounds [5-7].

Compounds **IIa-c**.

Description of the Structure of Compound **IIa**.

The main crystallographic data and the structure determination conditions are given in Table 5 [8-10]. Table 6 contains the atomic parameters and Tables 7, 8 and 9 show bond lengths, bond and torsion angles, respectively. Figure 2 displays the structural formula with the numbering used in the crystallographic study, and Figure 3 shows a view of molecular packing.

Table 8

Bond Angles (°)

Atom 1	Atom 2	Atom 3	Angle	Atom 1	Atom 2	Atom 3	Angle
O1	C9	C1	124.1(1)	O3	C13	H131	109.5(2)
C9	C1	C8	105.7(1)	O3	C13	H132	108.8(2)
C9	C1	C2	108.1(1)	O3	C13	H133	109.0(2)
C9	C1	C12	107.5(1)	H131	C13	H132	109.7(2)
C8	C1	C2	114.4(1)	H131	C13	H133	110.2(2)
C8	C1	C12	108.8(1)	H132	C13	H133	109.6(2)
C2	C1	C12	111.9(1)	C2	C1'	C2'	120.6(2)
C1	C8	N7	110.0(1)	C2	C1'	C6'	120.6(2)
C1	C8	H81	107.9(2)	C2'	C1'	C6'	118.8(2)
C1	C8	H82	108.6(1)	C1'	C2'	C3'	120.0(2)
N7	C8	H81	110.1(2)	C1'	C2'	H2'	119.0(1)
N7	C8	H82	115.2(2)	C3'	C2'	H2'	120.8(9)
H81	C8	H82	104.7(2)	C2'	C3'	C4'	120.6(2)
C8	N7	C10	111.8(1)	C2'	C3'	H3'	120.6(9)
C2	N3	C11	108.7(1)	C4'	C3'	H3'	119.0(1)
C1	C2	N3	113.4(1)	C3'	C4'	C5'	120.2(2)
C13	C2	C1'	109.6(2)	C3'	C4'	H4'	117.0(1)
C1	C2	H2	112.6(1)	C5'	C4'	H4'	122.0(1)
N3	C2	C1'	109.6(1)	C4'	C5'	C6'	119.6(2)
N3	C2	H2	105.0(2)	C4'	C5'	H5'	122.3(9)
C1'	C2	H2	106.4(1)	C6'	C5'	H5'	118.0(9)
N3	C11	H111	109.0(1)	C1'	C6'	C5'	120.7(2)
N3	C11	H112	110.4(9)	C1'	C6'	H6'	122.0(1)
H111	C11	H112	106.0(1)	C5'	C6'	H6'	118.0(1)
N7	C10	H101	108.5(9)	C1	C12	O3	112.1(1)
N7	C10	H102	113.0(1)	O2	C12	O3	123.6(2)
H101	C10	H102	110.0(1)	C12	O3	C13	116.1(2)
C1	C12	O2	124.2(2)				

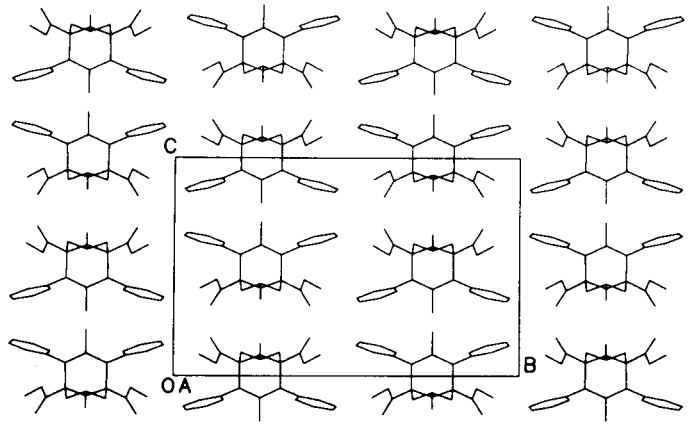


Figure 3

Table 9

Torsion angles (°)

Atom 1	Atom 2	Atom 3	Atom 4	Angle
O1	C9	C1	C8	115.17(23)
O1	C9	C1	C2	-121.90(23)
O1	C9	C1	C12	-0.95(28)
C5	C9	C1	C8	-60.81(19)
C5	C9	C1	C2	62.12(18)
C5	C9	C1	C12	-176.98(14)
C9	C1	C8	N7	59.89(18)
C9	C1	C8	H81	-180.00(40)
C9	C1	C8	H82	-67.01(19)
C2	C1	C8	N7	-58.97(19)
C2	C1	C8	H81	61.16(19)
C2	C1	C8	H82	174.13(15)
C12	C1	C8	N7	175.07(15)
C12	C1	C8	H81	-64.81(18)
C12	C1	C8	H82	48.16(20)
C9	C1	C2	N4	-49.62(19)
C9	C1	C2	C1'	-172.39(14)
C9	C1	C2	H2	69.35(19)
C8	C1	C2	N3	67.87(19)
C8	C1	C2	C1'	-54.90(19)
C8	C1	C2	H2	-173.16(15)
C12	C1	C2	N3	167.78(14)
C12	C1	C2	C1'	69.45(17)
C12	C1	C2	H2	-48.80(20)
C9	C1	C12	O2	101.09(21)
C9	C1	C12	O3	-76.00(19)
C8	C1	C12	O2	-12.95(24)
C8	C1	C12	O3	169.96(14)
C2	C1	C12	O2	-140.35(18)
C2	C1	C12	O3	42.56(19)
C1	C8	N7	C10	171.57(17)
C1	C8	N7	C6	-63.11(19)
H81	C8	N7	C10	52.80(23)
H81	C8	N7	C6	178.12(14)
H82	C8	N7	C10	-65.35(23)
H82	C8	N7	C6	59.97(21)
C11	N3	C2	C1	166.61(16)
C11	N3	C2	C1'	-70.58(20)
C11	N3	C2	H2	43.36(21)
C4	N3	C2	C1	41.78(21)
C4	N3	C2	C1'	164.60(14)
C4	N3	C2	H2	-81.47(18)
C1	C2	C1'	C2'	-90.36(20)
C1	C2	C1'	C6'	88.16(20)
N3	C2	C1'	C2'	144.64(18)
N3	C2	C1'	C6'	-36.84(22)
H2	C2	C1'	C2'	31.64(23)
H2	C2	C1'	C6'	-149.84(17)
C1	C12	O3	C13	174.20(16)
O2	C12	O3	C13	-2.91(27)
C2	C1'	C2'	C3'	176.91(20)
C6'	C1'	C2'	C3'	-1.64(31)
C2	C1'	C6'	C5'	-177.77(18)
C2'	C1'	C6'	C5'	0.78(29)

Table 9 (continued)

Atom 1	Atom 2	Atom 3	Atom 4	Angle
C1'	C2'	C3'	C4'	1.67(36)
C2'	C3'	C4'	C5'	-0.80(39)
C3'	C4'	C5'	C6'	-0.07(38)
C4'	C5'	C6'	C1'	0.08(35)

Table 10

^{1}H NMR Chemical Shifts [a] (δ, ppm) and Multiplicities (J, MHz) for compound **IIa-c**

δ	**IIa**	**IIb**	**IIc**
H2(4) (s)	4.36	4.26	4.41
H6(8) eq (d)	3.06	3.07	3.00
	J 12.7 Hz	J 12.2 Hz	J 12.9 Hz
H6(8) ax (d)	2.47	2.47	2.49
N7-CH_3 (s)	2.29	2.28	2.30
N3-CH_3 (s)	1.72	1.69	1.73
OCH_3 (s)		3.73	
COO-CH_3 (s)	3.64	3.63	3.65
H2' (d)	8.05	7.92	8.03
		J 2',3' 8.4 Hz	J 2',3' 8.4 Hz
		J 2',6' 2.1 Hz	J 2',6' 2.1 Hz
H3'	7.50 (m)	7.06 (d)	7.58 (d)
		J 3',5' 2.7 Hz	J 3',5' 2.3 Hz
H4'	7.31 (m)		
H5'	7.31 (m)	6.82 (d)	7.38 (d)
		J 5',6' 8.4 Hz	J 5',6' 8.4 Hz
H6' (d)	7.05	6.96	7.08

[a] Abbreviations: d, doublet; m, multiplet; s, singlet. δ values were deduced from the corresponing proton first order spectra analysis with an error value of ± 0.05 ppm.

The molecule presents a crystallographic mirror plane defined by O1, C9, N3 and N7 atoms. The *N*-methyl groups equatorially attached to the nitrogen atoms, lie in this plane.

According the the torsion angles, both piperidine rings are in a flattened chair conformation. Such distortion decreases the C9-N7 and C9-N3 nonbonded interactions from the ideal chair value of 2.52 Å to 2.83 Å and 2.87 Å, respectively. The flattening can be expressed in terms of the displacement of C9 and N7 from the least square plane defined by C1, C8, C5 and C6 of -0.716 and 0.692 Å (ring A) and that of C9 and N3 from the mean plane defined by C1, C2, C4 and C5 of -0.715 and 0.459 Å (ring B). Thus, in ring A this displacement is much closer to that of the ideal chair value of 0.73 Å, while ring B is flattened at the N3 atom.

With respect to the carboxylate groups, the bond length C12-O2 [1.194(2)Å] corresponds clearly to a double bond, while C12-O3 [1.333(2)Å] and C13-O3 [1.446(3)Å] show single bonds values, as it could be expected.

Dihedral angles between the planes P1 (C1, C2, C4, C5), P2 (C1, N7, C6, C9) and P3 (C14 to C19) are: P1-P2 95 (7), P1-P3 99.85 (7) and P2-P3 5.75 (33)°.

Infrared Spectra.

Table 1 shows the infrared frequencies and the corresponding assignments. The presence of strong Bohlman's bands in the 2600-2800 cm^{-1} region indicates that the *N*-methyl groups occupy an equatorial position in the double-chair bispidine skeleton in close agreement with the X-ray results for **IIa**.

NMR Spectra.

The assignment of proton and carbon resonances has been made on the basis of double resonance experiments and heteronuclear proton-carbon shift correlation spectra of **IIa-c** (Tables 10 and 11). The signals of all the protons appear well differentiated in the spectra. H6(8) eq signals correspond to protons "gauche" to the nitrogen electron pair. H6(8) axial signals appear at higher field due mainly, to the σ-electron deslocalization of the nitrogen lone pair in trans-coplanar bonds [1].

Table 11

^{13}C NMR Chemical Shifts [a] (δ, ppm) for compound IIa-c

δ	IIa	IIb	IIc
C2(4)	72.14	71.69	71.30
C1(5)	63.00	63.22	62.81
C6(8)	59.99	59.98	59.85
N3-CH_3	42.76	42.61	42.61
N7-CH_3	44.09	44.13	44.06
COO-CH_3	52.30	52.26	52.48
O-CH_3		55.15	
C=O	204.26	204.44	203.72
COO-CH_3	167.94	168.09	165.75
C1'	138.54	130.45	137.41
C2'	128.78	129.94	130.70
C3'	128.78	114.78	129.04
C4'	128.35	159.11	132.93
C5'	128.46	113.15	128.48
C6'	128.56	129.65	130.35

[a] Directly measured on the spectra, error ±0.05.

The C6(8) and N7-CH_3 ^{13}C chemical shifts of compounds **IIa-c** are consistent with the N7-CH_3 group occupying the equatorial position of a flattened chair bispidine ring [1].

Conformational Study.

From the facts above exposed, it can be deduced that compounds **IIa-c** adopt in DMSO-d_6 solution a flattened chair-chair conformation with the *N*-methyl groups in the equatorial position. It seems to be interesting to remark that in compounds **IIa-c** the aryl groups occupy a near coplanar position with respect to H2(4), this fact is confirmed by the following: The H2' and H3' signals are shifted to lower field (~ 1 and 0.3 ppm respectively) due to the σ-deshielding effect exerted by the N-lone pairs (see Table 10). The N-CH_3 and H2(4) protons are shielded and deshielded respectively by the aryl groups.

In summary, several points of evidence lead to establish that compounds **IIa-c** adopt in DMSO solution a conformation similar to that deduced for compound **IIa** in the crystal state.

Binding Study of Compounds **Ib,c** and **IIa-c**.

Binding experiments of GABA to the $GABA_B$ receptors in crude rat synaptosomal brain membranes were performed as described by Hill and Bowery [11]. The effective dossage (ED_{50}) was 3 x 10^{-7} *M*.

The studied compounds, like possible $GABA_B$ antagonists, had been tested in a decreasing concentrations range from 3 x 10^{-8} to 10^{-5} *M*. No one of them could carry out more than 15% of the ^3H-GABA bound to the $GABA_B$ receptor. Those results were the average from two duplicate experiences.

EXPERIMENTAL

All melting points were taken in open capillary tubes and are uncorrected. Infrared spectra were determined using a Perkin-Elmer 883 spectrophotometer in dimethyl sulfoxide-d_6. The ^1H and ^{13}C nmr spectra were recorded on a Varian UNITY-300 spectrometer. The ^1H nmr spectra were obtained at 300 MHz using spectral width of 8000 Hz and acquisition time of 3.0 s over 64 transients. LB = -0.8, GF = 0.6 and GFS = 0.2 were used for resolution enhancement. Conventional irradiation was used for the double resonance experiments. The ^{13}C nmr spectra were recorded at 75 MHz. The spectral parameters included spectral width of 20000 Hz, acquisition time of 1.0 s, delay time 1.0 and pulse width 4 μs. The heteronuclear (XHCORD) shift correlation experiments were performed by using standard Varian pulse sequences [14,15]. Elemental analysis were made in a Perkin-Elmer Analyzer 240B.

Synthesis of Compounds **Ia-c**. General Procedure.

To a mixture of methyl 3-oxoglutarate (0.02 mole) and the corresponding aldehyde (0.041 mole) externally cooled (0°), a solution of 33% methanolic methylamine (0.021 mole) was added. The resulting mixture was maintained at 4° for 24 hours. Then, methanol was added to the solution, and the crystals obtained were washed and recrystallized from methanol.

Methyl 2,6-Diphenyl-1-methyl-4-oxopiperidine-3,5-dicarboxylate (**Ia**).

This compound had mp 136-137°, yield 74%; ir (Table 1); ^{1}H nmr (Tables 2,3); ^{13}C nmr (Tables 3,4).

Anal. Calcd. for $C_{22}H_{23}NO_5$: C, 69.28; H, 6.08; N, 3.67. Found: C, 68.93; H, 6.18; N, 3.46.

Methyl 2,6-Bis(*p*-methoxyphenyl)-1-methyl-4-oxopiperidine-3,5-dicarboxylate (**Ib**).

This compound had mp 151-152°, yield 44%; ir (Table 1); ^{1}H nmr (Table 2); ^{13}C nmr (Table 4).

Anal. Calcd. for $C_{24}H_{27}NO_7$: C, 65.29; H, 6.16; N, 3.17. Found: C, 65.38; H, 6.17; N, 3.15.

Methyl 2,6-Bis(*p*-chlorophenyl)-1-methyl-4-oxopiperidine-3,5-dicarboxylate (**Ic**).

This compound had mp 156-157°, yield 22%; ir (Table 1); ^{1}H nmr (Table 2); ^{13}C nmr (Table 4).

Anal. Calcd. for $C_{22}H_{21}NO_5Cl_2$: C, 58.68; H, 4.70; N, 3.11. Found: C, 59.06; H, 4.74; N, 2.93.

Synthesis of Compounds **IIa-c**. General Procedure.

To a warmed solution of the corresponding **I** (0.004 mole) in absolute methanol (20 ml) a 40% formaldehyde (0.0021 mole) and 33% methanolic methylamine (0.0032 mole) was added.

Methyl 3,7-Dimethyl-2,4-diphenyl-9-oxo-3,7-diazabicyclo[3.3.1]-nonane-1,5-dicarboxylate (**IIa**).

The mixture was maintained 48 hours at room temperature and the crystals obtained were filtered, washed and recrystallized from methanol, mp 184-185°, yield 60%; ir (Table 1); ^{1}H nmr (Table 10); ^{13}C nmr (Table 11).

Anal. Calcd. for $C_{25}H_{28}N_2O_5$: C, 68.79; H, 6.46; N, 6.42. Found: C, 68.57; H, 6.42; N, 6.27.

Methyl 3,7-Dimethyl-2,4-bis(*p*-methoxyphenyl)-9-oxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarboxylate (**IIb**).

The mixture was stirred at room temperature 72 hours and purified on a silica-gel column, using ethyl acetate-hexane (5:5) as eluent. The product was precipitated with hexane and recrystallized from methanol, mp 192-193°, yield 48%; ir (Table 1); ^{1}H nmr (Table 10); ^{13}C nmr (Table 11).

Anal. Calcd. for $C_{27}H_{32}N_2O_7$: C, 65.31; H, 6.50; N, 5.64. Found: C, 65.01; H, 6.43; N, 5.54.

Methyl 3,7-Dimethyl-2,4-bis(*p*-chlorophenyl)-9-oxo-3,7-diazabicyclo[3.3.1]nonane-1,5-dicarboxylate (**IIc**).

The mixture was maintained at 4° for 48 hours and a mixture of **Ic** and **IIc** was obtained. This mixture was chromatographed on a silica-gel column, using ethyl acetate-hexane (2:8) as the eluent. Then it was recrystallized from methanol, mp 197-199°, yield 10%; ir (Table 1); ^{1}H nmr (Table 10); ^{13}C nmr (Table 11).

Anal. Calcd. for $C_{25}H_{26}N_2O_5Cl_2$: C, 59.41; H, 5.19; N, 5.54. Found: C, 59.64; H, 5.20; N, 5.54.

Biochemistry Assay.

All compounds were dissolved in DMSO 100 times higher concentration than the amounts used in the incubation assay. Crude synaptosomal brain membranes were prepared as described previously Zukin *et al.* [12]. Protein assay was carried out by the method of Bradford [13] using bovine serum albumin as a standard.

The $GABA_B$ binding assay was performed in rat synaptic membranes essentially as described Hill and Bowery [11] with minor modifications. Briefly: 200 μg of membrane proteins were incubated with 10 n*M* ^{3}H-GABA, isoguvacine (as $GABA_A$ receptor blocker) and increasing concentrations (10 nM^{-3} μM) unlabelled GABA in 50 m*M* Tris/2.5 m*M* calcium chloride. The incubation was carried out at 25° for 10 minutes. The reaction was stopped by centrifugation at 14,000 x g for 10 minutes. The pellet was disrupted in 1*N* sodium hydroxide and the radioactivity measured. Specific $GABA_B$ binding was estimated as the difference between 'total binding' and 'non-specific binding' (binding in the presence of 100 μM unlabelled GABA).

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