Journal of Molecular Structure, 249 (1991) 203-220
Elsevier Science Publishers B.V., Amsterdam

Synthesis and structural and conformational study of some esters derived from 8-β-hydroxy-3-phenethyl-3-azabicyclico [3.2.1] octan-8-α-carboxylic acid

M. Diez, M.L. Izquierdo, M.S. Arias and E. Galvez[1]
Departamento de Química Orgánica, Universidad de Alcalá de Henares, Madrid (Spain)
E. Matesanz
Instituto de Ciencia de Materiales (sede C) C.S.I.C. Serrano 115 dpdo, 28006 Madrid (Spain)
M. Martinez-Ripoll
Instituto "Rocasolano", UEI Cristalografía, C.S.I.C. Serrano 119, 28006 Madrid (Spain)

(Received 21 February 1991)

Abstract

A series of 8-β-hydroxy-8-α-alkoxycarbonyl-*N*-phenethyl-3-azabicyclo [3.2.1] octane derivatives have been synthesized and studied by IR, ^{1}H and ^{13}C NMR spectroscopy, and the crystal structure of ethyl-8-β-hydroxy-3-phenethyl-3-azabicyclo [3.2.1] octan-8-α-carboxylate (**Va**) has been determined by X-ray diffraction. In deuterochloroform and deuterobenzene the cyclopentane and piperidine rings of the title compounds show an envelope conformation flattened at C8 and a distorted chair conformation puckered at C8 and flattened at N3, respectively, with the *N*-substituent in an equatorial position. These results are in close agreement with that found for compound **Va** in the crystalline state. By comparing the NMR and X-ray parameters of the title compounds with those of the corresponding 8-α-hydroxy-8-β-alkoxycarbonyl-*N*-phenethyl-3-azabicyclo [3.2.1] octane epimers and 3-phenethyl-3-azabicyclo [3.2.1] octan-8-α- (and β)ol, several stereoelectronic effects have been deduced.

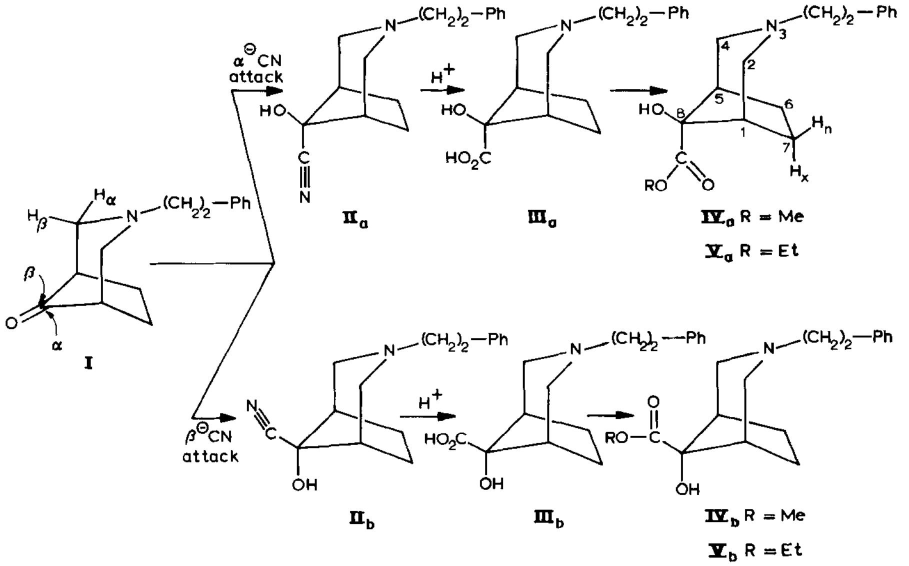
INTRODUCTION

In a previous paper [1] we reported the synthesis, the IR, the ^{1}H and ^{13}C NMR studies and the crystal structure of several esters derived from 8-α-hydroxy-3-phenethyl-3-azabicyclo [3.2.1] octan-8-β-carboxylic acid (compounds **IVb** and **Vb**, Scheme 1), as potential antagonists of the GABA$_B$ receptor. In the same line, we report in this paper the synthesis and structural analysis with the aid of IR and ^{1}H and ^{13}C NMR spectroscopy of a series of 8-α-alkoxycarbonyl-8-β-hydroxy-3-phenethyl-3-azabicyclo [3.2.1] octane derivatives

---

[1] Author to whom correspondence should be addressed.

IVa, **Va** (Scheme 1) with the objective to determine their preferred conformation both in solution and in the solid state, the crystal structure of compound **Va** has also been determined.



Scheme 1.

In order to establish several structural and electronic relationships, the crystal and ^1H and ^{13}C NMR parameters of the 3-phenethyl-3-azabicyclo-[3.2.1]octan-8-α- (and β)ol (compounds **VIIb** and **VIIa**) [2,3] and **Vb** [1] have been taken into account.

SYNTHESIS

The schematic synthesis pathways for **IVa** and **Va** are represented in Scheme 1.

From the reaction of the ketone **I** [4] with ammonium chloride, potassium cyanide in 1,4-dioxane/water (35:10 v/v), maintaining the mixture at room temperature for 5 days, the cyanohydrin **IIb** and the aminonitrile, 8-β-amine-3-phenethyl-3-azabicyclo[3.2.1]octane-8-α-carbonytrile **VI**, were obtained. By treatment of the ketone **I** with ammonium chloride and potassium cyanide in 1,4-dioxane/water (35:1 v/v) at the same molar concentrations as in the case of **IIb** [1], and maintaining the mixture at room temperature for 1 day, the cyanohydrine **IIa** and the aminonitrile **VI** were also obtained. Bearing in mind that the more stable conformation of **I** in solution [4] is as represented in Scheme 1, we postulate that whereas the synthesis of **IIa** is kinetically controlled (the β-attack is more hindered by $H2(4)_{ax}$ than α-attack by $H6(7)_x$, as can be seen with molecular models), the synthesis of **IIb** has thermodynamic control (in the case of **IIa** and **IIb** the most severe steric interaction is exerted by the OH on $H2(4)_{ax}$ as will be shown in the NMR discussion). The more favoured α-hydroxy group solvation would contribute to the thermodynamic control. The fact that only the aminonitrile **VI** was isolated seems to corroborate the above statements.

Compound **IIIa** was prepared by hydrolysis of **IIa**, and compounds **IVa** and **Va** were obtained by esterification of **IIIa**.

EXPERIMENTAL

Crystallographic data for compound **Va** are given in Table 1. Final atomic parameters are given in Table 2. The structural chirality was determined by comparing the 93 most relevant Bijvoet pairs with the conditions $F_o > 10\sigma F_o$ and $|\Delta\ F_c| > 0.05$. This led to an average Bijvoet difference, $\sum|[F_o(+h)-F_o(-h)]-[F_c(+h)-F_c(-h)]|/N$, of 0.292 (0.333 for the wrong enantiomer) and an average Bijvoet ratio, $1+\sum\|[F_o(+h)/F_o(-h)]|/|[F_c(+h)/F_c(-h)]|-1|/N$, of 1.028 (1.032) and to $\sum|[F_o(+h)^2-F_o(-h)^2]-[F_c(+h)^2-F_c(-h)^2]|/\sum|[F_o(+h)^2-F_o(-h)^2]| = 0.934$ (1.086) [8]. Moreover, the technique of determining the chirality, as suggested by Rogers [11], has also been used. Thus, the f'' for the O atoms was allowed to vary in the later stages of the refinement and converged to a value of $\eta = 1.01$.

All melting points were taken in open capillary tubes in an Electrothermal IA6304 apparatus, and are uncorrected. The elemental analysis were made in a Perkin-Elmer Elemental Analyzer model 240E. The IR spectra were recorded on a Perkin-Elmer 883 spectrophotometer in the solid state (KBr).

The ^1H NMR spectra of ≈4% (w/v) $CDCl_3$, C_6D_6 or CD_3OD solutions of **II**, **III**, **IV**, **V** and **VI** were recorded at 300 MHz using a Varian UNITY-300 spectrometer. Spectral parameters included sweep widths of 4000 Hz in 24 K memory and acquisition times of 3.0 s over 64 transients. Resolution enhancement using LB = −0.80, GF = 0.50 and GFS = 0.20 was followed by zero filing into 32 K memory prior to Fourier transformations. Conventional irradiation was used for the double resonance experiments.

The homonuclear ^1H chemical shift correlated 2D diagrams were performed by application of the COSY 45 experiment at 300 MHz on a Varian UNITY-300 spectrometer. COSY spectra were run with a 512×512 data matrix using 256 increments in the second dimension and 512 data points in the first dimension. Sine-bell window functions in both dimensions were used. Each experiment involved sixteen scans and two dummy scans with an initial delay of 1 s.

The ^{13}C NMR spectra were obtained at 20 MHz on a Varian FT-80 A (PFT) spectrometer using about 25% (w/v) $CDCl_3$ and DMSO solutions. Two types of spectra were recorded: proton-noise decoupled spectra (to determine the chemical shifts) and off-resonance decoupled spectra (to help assign the sig-

TABLE 1

Experimental data and structure refinement procedures

Crystal data	
Formula	$C_{18}H_{25}O_3N$
Symmetry	Orthorhombic, $P2_12_12_1$
Unit cell determination	Least-squares fit from 68 reflections ($\theta < 44°$)
Unit cell dimensions (Å)	6.2448(2), 8.1062(3), 33.367(4)
(deg.)	90, 90, 90
Packing: V(Å^3), Z	1689.1(2), 4
Dc(g cm^{-3}), M, F(000)	1.1931, 303.400, 656
μ (cm^{-1})	6.101
Experimental data	
Technique	Four circle diffractometer: Philips PW1100 Bisecting geometry Graphite oriented monochromator: CuKα w/2θ scans Detector apertures 1 × 1°, θ_{max} 65°
Number of reflections (including Friedel pairs):	
Measured	3022
Observed	2659 (2σ(I) criterion)
Range of *hkl*	−9 9, −10 10, −38 38, $(\sin\theta/\lambda)_{max}$ 0.562
Solution and refinement	
Solution	Direct methods
Refinement	Least-squares on F_{obs}
Parameters:	
Number of variables	275
Degrees of freedom	2384
Ratio of freedom	9.669
H atoms	difference synthesis
Maximum final shift/error	0.45
w-scheme	empirical as to give no trends in $\langle w\Delta^2F\rangle$ vs. $\langle \lvert F_o \rvert \rangle$ or $\langle \sin\theta/\lambda \rangle$
Final ΔF peaks	0.316 e Å^{-3}
Final R and R_w	0.054, 0.065
Computer and programs	VAX 6000-410, MULTAN80 [5], XRAY76 [6], PESOS [7], CONFAB [8], PARST [9]
Scattering factors	Int. Tables for X-Ray Crystallography [10]
Anomalous dispersion	Int. Tables for X-Ray Crystallography [10]

nals), at a spectral width of 5000 Hz using an acquisition time of 1.638 s, a delay time of 1.640 s and a pulse width of 5 μs.

All measurements were done at 303 K using TMS as the internal reference.

*3-Phenethyl-8-α-cyan-3-azabicyclo[3.2.1]octan-8-β-ol (**IIa**)*

A solution of 3-phenethyl-3-azabicyclo[3.2.1]octan-8-one (3g, 0.013 moles) [1], potassium cyanide (0.845g, 0.013 moles) and ammonium chloride (0.955g,

TABLE 2a

Atomic parameters for non H-atoms. Coordinates and thermal parameters as $U_{eq}=(1/3)\times\sum[U_{ij}a_i^*a_j^*a_ia_j\cos(a_i,a_j)]\times10^3$

Atom	x/a	y/b	z/c	U_{eq}
C1	−0.11557(42)	0.24632(34)	0.18262(7)	48(1)
C2	0.12119(45)	0.26803(38)	0.17066(8)	51(1)
C3	0.14954(50)	0.44110(40)	0.15277(9)	56(1)
N4	0.02340(38)	0.45688(28)	0.11596(7)	54(1)
C5	−0.20037(45)	0.41239(37)	0.12220(9)	54(1)
C6	−0.21471(47)	0.24012(35)	0.14084(8)	50(1)
C7	−0.07190(52)	0.11731(42)	0.11904(9)	61(1)
C8	0.15001(52)	0.13487(43)	0.13881(10)	62(1)
O9	−0.20443(37)	0.37485(26)	0.20607(6)	65(1)
C10	−0.14252(51)	0.08848(37)	0.20683(9)	60(1)
O11	−0.02195(44)	0.04624(32)	0.23314(7)	90(1)
O12	−0.31670(40)	0.00645(30)	0.19801(7)	87(1)
C13	−0.35804(94)	−0.14617(62)	0.22021(15)	112(2)
C14	−0.51706(95)	−0.23941(52)	0.20007(15)	102(2)
C15	0.04311(55)	0.62097(44)	0.09792(10)	65(1)
C16	0.25389(63)	0.63827(50)	0.07604(12)	79(1)
C17	0.27922(52)	0.80034(37)	0.05469(8)	59(1)
C18	0.13856(57)	0.85324(43)	0.02565(10)	71(1)
C19	0.17179(62)	0.99621(46)	0.00424(10)	77(1)
C20	0.34849(74)	1.08907(49)	0.01164(12)	87(1)
C21	0.48998(71)	1.04101(50)	0.04074(12)	90(1)
C22	0.45513(59)	0.89997(47)	0.06210(10)	73(1)

TABLE 2b

Atomic parameters for non H-atoms. Thermal parameters as $\exp[-2\pi^2\sum(U_{ij}a_i^*a_j^*h_ih_j)\times10^3]$

Atom	$U11$	$U22$	$U33$	$U12$	$U13$	$U23$
C1	46(1)	46(1)	52(1)	−1(1)	−3(1)	−1(1)
C2	41(1)	58(2)	55(1)	−2(1)	−12(1)	2(1)
C3	45(2)	62(2)	63(2)	−9(1)	−7(1)	3(1)
N4	49(1)	52(1)	60(1)	−4(1)	−4(1)	12(1)
C5	41(1)	57(2)	65(2)	−2(1)	−6(1)	9(1)
C6	39(1)	52(2)	59(1)	−4(1)	−12(1)	4(1)
C7	66(2)	58(2)	60(2)	−2(2)	−10(2)	−7(1)
C8	55(2)	61(2)	70(2)	11(2)	−5(2)	−4(2)
O9	65(1)	67(1)	63(1)	5(1)	1(1)	−8(1)
C10	63(2)	59(2)	58(2)	−11(2)	−7(2)	0(1)
O11	88(2)	93(2)	89(1)	−22(2)	−33(1)	38(1)
O12	88(2)	89(2)	85(1)	−44(2)	−28(1)	33(1)
C13	134(4)	106(3)	96(3)	−64(3)	−40(3)	46(3)
C14	134(4)	64(2)	109(3)	−19(3)	−9(3)	10(2)
C15	56(2)	63(2)	77(2)	7(2)	9(2)	10(2)
C16	67(2)	77(2)	92(2)	8(2)	11(2)	20(2)
C17	59(2)	61(2)	59(1)	−2(2)	6(1)	7(1)
C18	66(2)	77(2)	71(2)	−18(2)	−6(2)	5(2)
C19	78(2)	83(2)	69(2)	−5(2)	−15(2)	15(2)
C20	103(3)	72(2)	88(2)	−22(2)	−12(2)	22(2)
C21	89(3)	85(3)	96(2)	−38(3)	−20(2)	8(2)
C22	66(2)	84(2)	70(2)	−8(2)	−14(2)	12(2)

TABLE 2c

Atomic parameters for H-atoms. Coordinates and thermal parameters as $\exp[-8\pi^2 U \sin(\theta/\lambda)^2]$ fixed to $U=0.05$

Atom	x/a	y/b	z/c
H201	0.2104(59)	0.2589(43)	0.1925(10)
H301	0.2926(66)	0.4531(46)	0.1449(10)
H302	0.1160(61)	0.5263(45)	0.1727(10)
H501	−0.2545(60)	0.4042(41)	0.0922(10)
H502	−0.2757(61)	0.4899(45)	0.1402(10)
H601	−0.3557(62)	0.2074(45)	0.1429(10)
H701	−0.0561(60)	0.1393(41)	0.0876(10)
H702	−0.1338(58)	0.0042(46)	0.1226(10)
H801	0.1958(60)	0.0322(44)	0.1520(10)
H802	0.2570(60)	0.1747(43)	0.1180(10)
H901	−0.1181(62)	0.4038(45)	0.2273(11)
H1301	−0.3554(60)	−0.1389(46)	0.2464(11)
H1302	−0.1931(65)	−0.2132(45)	0.2220(10)
H1401	−0.4397(58)	−0.2485(43)	0.1708(10)
H1402	−0.6627(60)	−0.1723(47)	0.2019(10)
H1403	−0.5201(60)	−0.3478(45)	0.2143(9)
H1501	0.0420(60)	0.7171(44)	0.1170(10)
H1502	−0.0819(62)	0.6378(45)	0.0791(10)
H1601	0.2598(62)	0.5327(43)	0.0575(9)
H1602	0.3711(60)	0.6173(48)	0.0957(10)
H1801	0.0159(59)	0.7905(42)	0.0203(10)
H1901	0.0677(58)	1.0344(41)	−0.0173(10)
H2001	0.3637(55)	1.1888(43)	−0.0020(10)
H2101	0.5959(62)	1.1087(47)	0.0441(10)
H2201	0.5625(62)	0.8654(45)	0.0795(10)

0.013 moles) in 1,4-dioxane/water (35:1, 30 ml) was magnetically stirred at room temperature for 24 days then the mixture was poured onto water (50 ml) and the aqueous layer extracted with ethyl ether (4×50 ml). The organic phase was separated, washed with water, dried over magnesium sulphate and the solvent evaporated, the resulting oil was solidified with hexane. The solid was chromatographed on a silica gel column prepacked with hexane. By elution of the column with hexane/ethyl acetate (7:3 v/v), two products were isolated which were identified as the aminonitrile (**VI**) $R_f=0.36$ and the title compound (**IIa**) $R_f=0.5$ in 75% yield, m.p 110–112°C (hexane/acetone). IR (KBr): OH, 3399 cm^{-1}; CN, 2236 cm^{-1}; ^1H NMR, see Table 3; ^{13}C NMR, see Table 4.

Analysis for $C_{16}H_{20}N_2O$. Calc.: C, 74.97; H, 7.86; N, 10.96. Found: C, 74.97; H, 8.00; N, 10.80.

The aminonitrile, 3-phenethyl-8-β-amine-3-azabicyclo[3.2.1]octan-8-α-carbonytrile was obtained in 5% yield, m.p 98–100°C (hexane/acetone). IR (KBr): NH, 3372, 3305 cm^{-1}; CN, 2216 cm^{-1}; ^1H NMR, see Table 3; ^{13}C NMR, see Table 4.

TABLE 3

^{1}H chemical shifts of compounds **IIa-Va** and **VI**[a]

	δ (ppm)				
	II(C_6D_6)	**III**(CD_3OD)	**IV**(C_6D_6)	**V**(C_6D_6)	**VI**($CDCl_3$)
H-6(7)$_n$ (m)[b]	1.60	1.98	1.82	1.84	1.83
H-6(7)$_x$ (m)[b]	1.80	1.98	1.82	1.84	2.01
H-1(5) (brs)	1.80	2.52	2.16	2.18	2.21
	$W_{1/2}\approx 10$Hz	$W_{1/2}\approx 9.5$Hz	$W_{1/2}\approx 8.5$Hz	$W_{1/2}\approx 8$Hz	$W_{1/2}\approx 9.5$Hz
H-2(4)$_\beta$ (dd)	2.08	3.41	2.45	2.43	2.51
H-2(4)$_\alpha$ (d)	2.30	3.61	2.75	2.77	2.78[c]
H-2′ (m)[d]	2.36	3.11	2.59	2.59	2.66
H-1′ (m)[d]	2.50	3.33[e]	2.67	2.67	2.73[c]
Ph (m)[b]	7.10	7.30	7.13	7.24	7.23
OH (brs)				2.35	
CH_3			3.26(s)	0.87(t)	
CH_2-O				3.89(q)	

[a] Abbreviations: br, broad; dd, doublet of doublets; m, multiplet, q, quartet; s, singlet; t, triplet. δ values were deduced by first order analysis of the spectra; error ±0.05 ppm. [b] Multiplets of low resolution; tabulated chemical shifts correspond to the centre of the multiplets. [c] Signals are partially overlapped. [d] H-1′ and H-2′ methylene protons of the phenethyl group appear as a four spin A_2B_2 system. [e] This signal is partially concealed by the solvent signal.

TABLE 4

^{13}C chemical shifts (δ, ppm) for compounds **IIa-Va** in $CDCl_3$

	II	**III**[a]	**IV**	**V**
C1-(5)	43.09	38.40	40.50	40.61
C2-(4)	51.68	52.93	53.33	53.44
C6-(7)	24.89	22.99	25.31	25.58
C8	74.28	77.41	80.54	80.64
C1′	58.50	58.15	58.79	58.90
C2′	33.32	29.60	33.90	33.56
$C\equiv N$	122.42			
C=O		173.98	174.96	174.86
CH_3			52.20	14.04
CH_2				61.27
C1″	140.50	137.66	140.60	140.91
C2″(6″)	128.12	129.04	128.11	128.67
C3″(5″)	128.12	128.82	128.74	128.14
C4″	125.78	126.94	125.74	125.73

[a] DMSO.

Analysis for $C_{16}H_{21}N_3$. Calc.: C, 75.26; H, 8.29; N, 16.45. Found: C, 75.15; H, 8.52; N, 16.63.

*8-α-Hydroxy-3-phenethyl-3-azabicyclo[3.2.1]octan-8-β-carboxylic acid hydrochloride (**IIIa**)*

Compound **IIa** (0.5g, 1.6 mmoles) was added portionwise to aqueous HCl (20 ml, 11N) externally cooled at 0 °C, the mixture was magnetically stirred and maintained at 0 °C during this operation. The mixture was stirred at −2 °C for 30 min and kept at −5 °C for 24 h. The solution was refluxed for 6 h, allowed to cool at room temperature and the solvent evaporated under reduced pressure. The solid residue was treated with acetone and filtered. The title compound which was purified by crystallization from ethanol was obtained in 90% yield, m.p. 220–222 °C. IR (KBr): CO, 1726, 1690 cm^{-1}; ^1H NMR, see Table 3; ^{13}C NMR, see Table 4.

Analysis for $C_{16}H_{21}NO_3 \cdot HCl \cdot H_2O$. Calc.: C, 58.23; H, 7.33; N, 4.25. Found: C, 58.12; H, 7.59; N, 4.50.

*General procedure for synthesis of the esters **IVa** and **Va***

Anhydrous hydrogen chloride was bubbled into a solution of **IVa** (0.75g, 24 mmoles) in the corresponding alcohol (25 ml) until saturation, with external cooling and magnetic stirring. The mixture was maintained at 0 °C for 48 h, and refluxed (with anhydrous bubbling HCl) for 2 h. The solution was allowed to cool at room temperature and the solvent removed by evaporation under reduced pressure. The residue was dissolved in cold water (0 °C), made basic with potassium carbonate and extracted with methylene chloride (3 × 25 ml). The organic layer was dried over anhydrous magnesium sulphate and the solvent evaporated under reduced pressure to give a crude ester as a white solid which was purified by crystallization from hexane.

*Methyl-8-β-hydroxy-3-phenethyl-3-azabicyclo[3.2.1]octan-8-α-carboxylate (**IVa**)*

This compound was obtained in 45% yield, m.p. 64–66 °C. IR (KBr): OH, 3460 cm^{-1}; CO, 1736 cm^{-1}; ^1H NMR, see Table 3; ^{13}C NMR, see Table 4.

Analysis for $C_{17}H_{23}NO_3$. Calc.: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.29; H, 8.16; N, 4.81.

*Ethyl-8-β-hydroxy-3-phenethyl-3-azabicyclo[3.2.1]octan-8-α-carboxylate (**Va**)*

This compound was obtained in 50% yield, m.p. 78–80 °C; IR (KBr): OH, 3477 cm^{-1}; CO, 1710 cm^{-1}; ^1H NMR, see Table 3; ^{13}C NMR, see Table 4.

Analysis for $C_{18}H_{25}NO_3$. Calc.: C, 71.25; H, 8.30; N, 4.62. Found: C, 71.52; H, 8.47; N, 4.81.

RESULTS AND DISCUSSION

*Description and discussion of the structure of **Va***

Figure 1 is a view of the molecule showing its absolute chirality and the atomic numbering. Table 5 lists the bond lengths and Table 6 shows the bond and torsional angles. The six-membered ring of the bicycle system adopts a chair conformation similar to that found in a previous compound [2], the asymmetry parameters [12] being $\Phi_2=177(1)$, $\theta_2=165.9(2)$ and Qt=0.673(3), with C1 and N4 at −0.888(2) Å and 0.618(2) Å out of the C2, C3, C5, C6 plane, respectively. The five-membered ring shows an envelope conformation with the C1 atom at the flap (−0.748(2) Å out of the C2, C6, C7, C8 plane), the ring puckering coordinate being $\Phi_2=0.5(3)$.

The molecules are held together by hydrogen bonds (Fig. 2) of the type O9–H901······O11. The geometrical features of these bonds are O9–H901=0.92(3) Å, O9···O11 $(-X,Y+1/2,\ -Z+1/2)=2.836(3)$ Å, H901···O11 $(-X,Y+1/2,-Z+1/2)=1.96(3)$ Å and O9–H901···O11 $(-X,Y+1/2,\ -Z+1/2)=158(3)$.

Taking into account the distances in Table 7, and by considering that (a) in compounds **Va** and **Vb** the O–C=O plane is almost perpendicular to the symmetry plane of the bicycle skeleton (minimal steric hindrance), and (b) the hydrogen bonds in compounds **VIIa** and **VIIb** are intermolecular O–H····N with the electron pair on nitrogen in axial position [2,3], and the hydrogen bonds in compounds **Va** and **Vb** are intermolecular O–H····O=C [1], the following conclusions can be drawn:

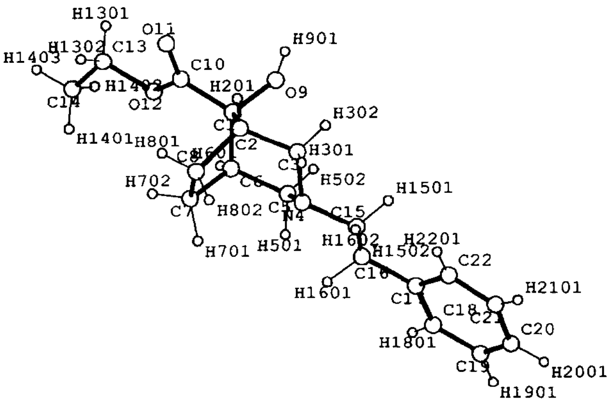


Fig. 1. Perspective view of the molecule showing its absolute chirality.

TABLE 5

Bond distances (Å) of compound **Va**

Parameter	Distance	Parameter	Distance
C1-C2	1.541(3)	C1-C6	1.526(3)
C1-O9	1.416(3)	C1-C10	1.522(4)
C2-H201	0.92 (3)	C2-C3	1.534(4)
C2-C8	1.525(4)	C3-H301	0.93 (4)
C3-H302	0.98 (3)	C3-N4	1.464(3)
N4-C5	1.458(3)	N4-C15	1.465(4)
C5-H501	1.05 (3)	C5-H502	0.98 (3)
C5-C6	1.531(4)	C6-H601	0.92 (3)
C6-C7	1.521(4)	C7-H701	1.06 (3)
C7-H702	1.00 (3)	C7-C8	1.541(4)
C8-H801	0.98 (3)	C8-H802	1.01 (3)
O9-H901	0.92 (3)	C10-O11	1.206(4)
C10-O12	1.308(4)	O12-C13	1.464(5)
C13-H1301	0.87 (3)	C13-H1302	1.16 (3)
C13-C14	1.417(7)	C14-H1401	1.09 (3)
C14-H1402	1.06 (3)	C14-H1403	0.99 (3)
C15-H1501	1.00 (3)	C15-H1502	1.01 (3)
C15-C16	1.511(5)	C16-H1601	1.05 (3)
C16-H1602	0.99 (3)	C16-C17	1.502(4)
C17-C18	1.376(4)	C17-C22	1.385(4)
C18-H1801	0.93 (3)	C18-C19	1.377(4)
C19-H1901	1.01 (3)	C19-C20	1.358(5)
C20-H2001	0.93 (3)	C20-C21	1.369(5)
C21-H2101	0.86 (3)	C21-C22	1.364(5)
C22-H2201	0.92 (3)		

(i) The greater molecular flexibility is shown, as expected, at C–N–C piperidine rest.

(ii) The *N*-piperidine flattening seems not to be affected by the *N*-hydrogen bonding steric requirements.

(iii) In compounds **Va** and **Vb**, similar steric effects exerted by the hydroxy and ethoxycarbonyl groups on $H2(4)_{\beta}$ (or on $H6(7)_{x}$) are observed.

Infrared spectra

The IR spectrum of **Va** in the solid state showed a strong band at 3477 cm^{-1}, which is assigned to the O–H····O stretching vibrations. In the carbonyl region a strong band is observed at 1710 cm^{-1}, which is attributed to the CO hydrogen bonded carbonyl group. These results are according to X-ray data.

Compound **Va** shows characteristic Bohlmann bands in the 2850–2600 cm^{-1} region. These bands are originated by the axially oriented C–H bonds in α-positions in relation to the nitrogen atoms. The strong absorption is in accord-

TABLE 6

Bond angles and torsion angles for compound **Va**

Parameter	Angle	Parameter	Angle
Bond angles (deg.)			
O9-C1-C10	106.3(2)	C6-C1-C10	114.3(2)
C6-C1-O9	111.7(2)	C2-C1-C10	109.8(2)
C2-C1-O9	115.7(2)	C2-C1-C6	99.0(2)
C1-C2-C8	102.2(2)	C1-C2-C3	108.4(2)
C1-C2-H201	111 (2)	C3-C2-C8	111.2(2)
H201-C2-C8	115 (2)	H201-C2-C3	108 (2)
C2-C3-N4	110.1(2)	C2-C3-H302	110 (1)
C2-C3-H301	108 (2)	H302-C3-N4	113 (2)
H301-C3-N4	105 (2)	H301-C3-H302	108 (3)
C3-N4-C15	112.2(2)	C3-N4-C5	111.9(2)
C5-N4-C15	111.3(2)	N4-C5-C6	109.8(2)
N4-C5-H502	112 (2)	N4-C5-H501	100 (1)
H502-C5-C6	107 (2)	H501-C5-C6	107 (1)
H501-C5-H502	117 (2)	C1-C6-C5	108.5(2)
C5-C6-C7	111.6(2)	C5-C6-H601	110 (2)
C1-C6-C7	102.7(2)	C1-C6-H601	109 (2)
H601-C6-C7	113 (2)	C6-C7-C8	105.1(2)
C6-C7-H702	108 (1)	C6-C7-H701	114 (1)
H702-C7-C8	112 (2)	H701-C7-C8	108 (2)
H701-C7-H702	107 (2)	C2-C8-C7	104.9(2)
C7-C8-H802	109 (1)	C7-C8-H801	111 (2)
C2-C8-H802	109 (2)	C2-C8-H801	108 (1)
H801-C8-H802	112 (2)	C1-O9-H901	112 (2)
C1-C10-O12	113.5(2)	C1-C10-O11	123.7(2)
O11-C10-O12	122.5(2)	C10-O12-C13	117.5(3)
O12-C13-C14	109.5(4)	O12-C13-H1302	105 (1)
O12-C13-H1301	116 (2)	H1302-C13-C14	113 (1)
H1301-C13-C14	121 (2)	H1301-C13-H1302	87 (3)
C13-C14-H1403	104 (1)	C13-C14-H1402	107 (2)
C13-C14-H1401	98 (1)	H1402-C14-H1403	113 (2)
H1401-C14-H1403	112 (2)	H1401-C14-H1402	117 (2)
N4-C15-C16	110.8(2)	N4-C15-H1502	108 (2)
N4-C15-H1501	116 (1)	H1502-C15-C16	111 (2)
H1501-C15-C16	103 (2)	H1501-C15-H1502	106 (2)
C15-C16-C17	113.6(3)	C15-C16-H1602	107 (1)
C15-C16-H1601	103 (2)	H1602-C16-C17	112 (2)
H1601-C16-C17	115 (1)	H1601-C16-H1602	102 (2)
C16-C17-C22	120.5(2)	C16-C17-C18	122.6(3)
C18-C17-C22	116.7(2)	C17-C18-C19	122.0(3)
C17-C18-H1801	119 (2)	H1801-C18-C19	118 (2)
C18-C19-C20	119.6(3)	C18-C19-H1901	121 (2)
H1901-C19-C20	118 (1)	C19-C20-C21	119.6(3)
C19-C20-H2001	118 (2)	H2001-C20-C21	121 (2)
C20-C21-C22	120.3(3)	C20-C21-H2101	113 (2)
H2101-C21-C22	125 (2)	C17-C22-C21	121.4(3)
C21-C22-H2201	117 (2)	C17-C22-H2201	120 (2)

TABLE 6 (continued)

Parameter	Angle	Parameter	Angle
Torsion angles (deg.)			
O9-C1-C10-O11	−82.4(3)	C6-C1-C10-O11	153.8(3)
C2-C1-C10-O11	43.5(3)	O9-C1-C10-O12	93.9(2)
C6-C1-C10-O12	−29.8(3)	C2-C1-C10-O12	−140.1(2)
C6-C1-O9-H901	−160 (2)	C2-C1-O9-H901	−47 (2)
C2-C1-C6-H601	169 (2)	C2-C1-C6-C7	47.9(2)
C10-C1-C6-C5	172.9(2)	O9-C1-C6-C5	52.1(2)
C2-C1-C6-C5	−70.3(2)	C6-C1-C2-C8	−48.0(2)
C6-C1-C2-C3	69.5(2)	C6-C1-C2-H201	−171 (2)
O9-C1-C2-C8	−167.5(2)	O9-C1-C2-C3	−49.9(3)
O9-C1-C2-H201	69 (2)	C10-C1-C2-C8	71.9(2)
C10-C1-C2-C3	−170.4(2)	C10-C1-C2-H201	−51 (2)
O9-C1-C6-C7	170.3(2)	O9-C1-C6-H601	−68 (2)
C10-C1-C6-C7	−68.7(2)	C10-C1-C6-H601	52 (2)
C10-C1-O9-H901	74 (2)	C1-C2-C8-H801	−89 (2)
C1-C2-C8-H802	146 (2)	C1-C2-C8-C7	30.1(2)
C1-C2-C3-H301	−178 (2)	C1-C2-C3-H302	62 (2)
C1-C2-C3-N4	−63.5(2)	C3-C2-C8-H801	154 (2)
H201-C2-C8-H801	31 (3)	C3-C2-C8-H802	31 (2)
H201-C2-C8-H802	−92 (3)	C3-C2-C8-C7	−85.4(2)
H201-C2-C8-C7	151 (2)	H201-C2-C3-H301	60 (3)
H201-C2-C3-H302	−58 (3)	H201-C2-C3-N4	175 (2)
C8-C2-C3-N4	48.1(3)	C8-C2-C3-H302	174 (2)
C8-C2-C3-H301	−66 (2)	C2-C3-N4-C5	53.2(3)
C2-C3-N4-C15	179.3(2)	H302-C3-N4-C5	−71 (2)
H301-C3-N4-C5	170 (2)	H302-C3-N4-C15	54 (2)
H301-C3-N4-C15	−63 (2)	C3-N4-C15-H1501	−40 (2)
C3-N4-C15-H1502	−160 (2)	C3-N4-C15-C16	77.3(3)
C3-N4-C5-H501	−167 (1)	C3-N4-C5-H502	66 (2)
C3-N4-C5-C6	−53.7(3)	C5-N4-C15-H1501	85 (2)
C5-N4-C15-H1502	−34 (2)	C5-N4-C15-C16	−156.2(2)
C15-N4-C5-C6	179.6(2)	C15-N4-C5-H502	−60 (2)
C15-N4-C5-H501	66 (1)	N4-C5-C6-C1	65.2(2)
H502-C5-C6-C1	−57 (2)	H501-C5-C6-C1	174 (1)
N4-C5-C6-H601	−175 (2)	N4-C5-C6-C7	−47.2(3)
H502-C5-C6-H601	61 (3)	H501-C5-C6-H601	−66 (3)
H502-C5-C6-C7	−170 (2)	H501-C5-C6-C7	61 (1)
C5-C6-C7-H701	−33 (2)	C1-C6-C7-H701	−149 (2)
C5-C6-C7-H702	−153 (2)	C1-C6-C7-H702	90 (2)
C5-C6-C7-C8	86.2(2)	C1-C6-C7-C8	−29.8(2)
H601-C6-C7-H701	92 (3)	H601-C6-C7-H702	−27 (3)
H601-C6-C7-C8	−147 (2)	C6-C7-C8-C2	−0.3(3)
H702-C7-C8-C2	−118 (2)	H701-C7-C8-C2	122 (1)
C6-C7-C8-H801	117 (2)	C6-C7-C8-H802	−117 (2)
H702-C7-C8-H801	0 (3)	H701-C7-C8-H801	−119 (2)
H702-C7-C8-H802	124 (3)	H701-C7-C8-H802	5 (2)
C1-C10-O12-C13	−179.1(3)	O11-C10-O12-C13	−2.7(4)
C10-O12-C13-H1301	52 (2)	C10-O12-C13-H1302	−42 (1)
C10-O12-C13-C14	−164.5(3)	O12-C13-C14-H1401	55 (1)

TABLE 6 (continued)

Parameter	Angle	Parameter	Angle
O12-C13-C14-H1402	−66 (2)	O12-C13-C14-H1403	171 (2)
H1302-C13-C14-H1401	−61 (2)	H1301-C13-C14-H1401	−163 (3)
H1302-C13-C14-H1402	175 (2)	H1301-C13-C14-H1402	73 (3)
H1302-C13-C14-H1403	54 (2)	H1301-C13-C14-H1403	−48 (3)
N4-C15-C16-H1601	50 (2)	N4-C15-C16-H1602	−57 (2)
N4-C15-C16-C17	176.5(2)	H1502-C15-C16-H1601	−69 (2)
H1501-C15-C16-H1601	176 (2)	H1502-C15-C16-H1602	−178 (3)
H1501-C15-C16-H1602	67 (3)	H1502-C15-C16-C17	56 (2)
H1501-C15-C16-C17	−57 (2)	C15-C16-C17-C18	−58.4(4)
C15-C16-C17-C22	125.1(3)	H1602-C16-C17-C18	178 (2)
H1601-C16-C17-C18	61 (2)	H1602-C16-C17-C22	2 (2)
H1601-C16-C17-C22	−115 (2)	C16-C17-C22-H2201	2 (2)
C16-C17-C22-C21	174.6(3)	C16-C17-C18-H1801	5 (2)
C16-C17-C18-C19	−175.1(3)	C18-C17-C22-H2201	−173 (2)
C18-C17-C22-C21	−1.9(5)	C22-C17-C18-C19	1.3(5)
C22-C17-C18-H1801	−178 (2)	C17-C18-C19-H1901	179 (2)
C17-C18-C19-C20	0.1(5)	H1801-C18-C19-H1901	0 (3)
H1801-C18-C19-C20	179 (2)	C18-C19-C20-H2001	−176 (2)
C18-C19-C20-C21	−1.0(5)	H1901-C19-C20-H2001	4 (3)
H1901-C19-C20-C21	179 (2)	C19-C20-C21-H2101	−178 (2)
C19-C20-C21-C22	0.4(6)	H2001-C20-C21-H2101	−3 (3)
H2001-C20-C21-C22	175 (2)	C20-C21-C22-C17	1.0(6)
H2101-C21-C22-C17	179 (3)	C20-C21-C22-H2201	173 (2)
H2101-C21-C22-H2201	−8(3)		

TABLE 7

Distances of the N and C(OH) atoms from the four C-atoms plane of the piperidine ring

Compound	Distances (Å)	
	C	N
Va	0.88	0.61
Vb	0.86	0.63
VIIa	0.93	0.71
VIIb	0.90	0.58

ance with the near perfect chair conformation of the C–N–C piperidine group in the solid state (see Table 6), as it was observed in related structures [13].

NMR spectra

Spectral analysis

Assignments of proton and carbon resonances have been made on the basis

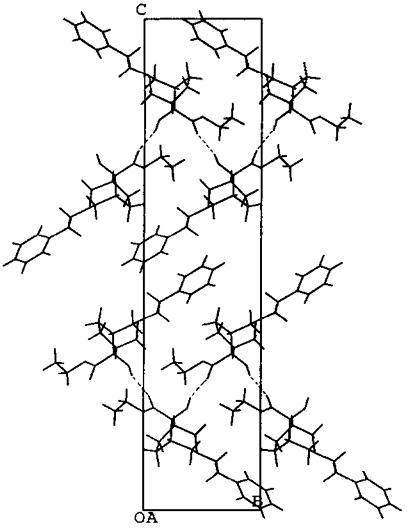


Fig. 2. View of the molecular packing showing the hydrogen interactions.

of the literature data for compounds **IIb–Vb** [1], α- and β-epimers of 3-phenethyl-3-azabicyclo[3.2.1]octan-8-ol [2,3] and related systems [4,14]. **IVa** has been studied in more detail; their 300 MHz ^{1}H NMR spectra, and homonuclear 2D COSY-45 [15,16] of **IVa** were used to provide the required information.

^{13}C NMR chemical shifts of compounds (**II–V**) are listed in Table 4. Substituent steric and electronic effects on ^{13}C chemical shifts [17,18], signal multiplicity obtained from off-resonance decoupled spectra and our previously reported values for related bicyclic systems [1–4,14] were taken into consideration.

^{1}H NMR spectra

Overlapping resonances between different signals were observed for all the compounds in the solvents employed to record their ^{1}H NMR spectra (Tables 3 and 8).

In order to clarify the assignment of the signals and to deduce the proton magnetic parameters, the homonuclear 2D COSY spectrum [15,16] in C_6D_6 for **IVa** was recorded. The contour plots of the 300 MHz proton COSY spectra is shown in Fig. 3 (the aromatic proton region is omitted).

The cross-connectivity patterns were analyzed taking into account that the non-resolvable wide singlet at 2.16 ppm can be unambiguously assigned to bridgehead H1(5) protons. By considering the correlations, the following can be established: the doublet of doublets centred at 2.45 ppm due to two protons with a correlation with H1(5) and a stronger correlation with the doublet at 2.75 ppm (two protons), must correspond to H2(4)$_\beta$, and the signal at 2.75

TABLE 8

Coupling constants deduced from the analysis of the ^1H NMR spectra of compounds **IIa**–**Va** and **VI**[a]

	J(Hz)				
	II(C_6D_6)	III(CD_3OD)	IV(C_6D_6)	V(C_6D_6)	VI($CDCl_3$)
H2(4)$_\alpha$-H2(4)$_\beta$	−11	−12.0	−10.5	−10.5	−10.9
H2(4)$_\beta$-H1(5)	3	3.1	3.6	3.9	3.5
H1′-H2′	7.8	7.5	7.8	7.6	7.6
CH_3-CH_2				7.1	

[a] Error ±0.2 Hz.

^{3}JH2(4)$_\alpha$-H1(5) could not be established, only a slight broadening of the H2(4)$_\alpha$ signal has been observed.

ppm corresponds to H2(4)$_\alpha$. In this signal no cross-peak with H1(5) is observed, and that is in agreement with the small value for ^{3}JH2(4)$_\alpha$-H1(5). The non-resolved singlet at 1.82 ppm due to four protons correlates with H1(5), and must correspond to H6(7)$_x$ and H6(7)$_n$.

Conformational study

*Compound **IIa***

The ^1H and ^{13}C parameters are in rather good agreement with previously reported values for compound **VIIa** [2] in which the cyclopentane and piperidine rings have a flattened C8 envelope and distorted chair conformation puckered at C8 and flattened at N3 respectively.

In compound IIa ^{3}JH2(4)$_\beta$-H1(5) is greater than ^{3}JH2(4)$_\alpha$-H1(5) and consequently the dihedral angle H2(4)$_\beta$-C-C-H1(5) is smaller than H2(4)$_\alpha$-C-C-H1(5) according to the Karplus relationship [19]. This is also more consistent with a chair flattened conformation than with a boat conformation for the piperidine ring, since in the latter form the signal corresponding to H1(5) should appear as an apparent doublet, a common feature in previously reported systems that adopt the boat conformation [13].

The following differences:

$\Delta\delta$C2(4)(**IIb**[1]) − C2(4)(**VIIb**[3]) = −2.12 ppm

$\Delta\delta$C2(4)(**IIb**) − C2(4)(**IIa**) = 4.61 ppm

$\Delta\delta$C2(4)(**VIIb**) − C2(4)(**VIIa**[2]) = 6.09 ppm

account for a greater syn-diaxial steric compressing effect, exerted by the OH group on H2(4)$_\beta$, than the same effect exerted by the CN group; as was pos-

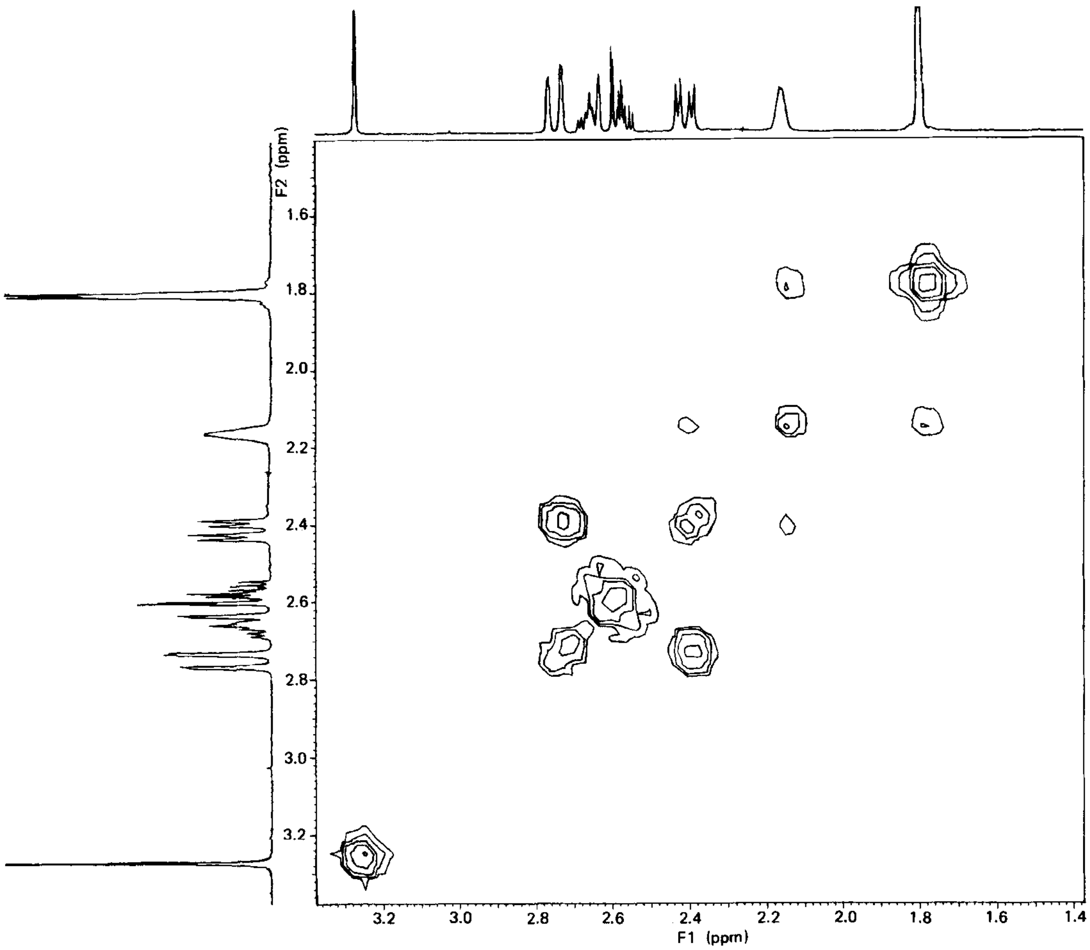


Fig. 3. Contour plots of 300 MHz proton COSY spectrum of **IVa** in C_6D_6 (the aromatic part is omitted).

tulated in the synthetic discussion. As was expected the same effect is not observed on $H6(7)_x$.

*Compounds **IVa** and **Va***

In $CDCl_3$ solution. In this case, the ^{13}C parameters are in rather good correlation with those reported for compounds **IIa** and **VIIa** [2] and by consequence, it seems that compounds **IVa** and **Va** show the same conformation in $CDCl_3$ solution for the bicycle system as that proposed for **IIa** and **VIa**.

The following differences:

$\Delta\delta$C2(4)(**IVb**, **Vb**[1]) – C2(4)(**VIIb**[3]) = –2.3 ppm

$\Delta\delta$C2(4)(**IVa**, **Va**) – C2(4)(**IVb**, **Vb**[1]) = –2.7 ppm

$\Delta\delta$C2(4)(**VIIb**) – C2(4)(**VIIa**[2]) = 6.09 ppm

$\Delta\delta$C2(4)(**IVa**, **Va**) – C2(4)(**VIIa**[2]) = 1 ppm

account for a greater syn-diaxial steric compressing effect, exerted by the OH group on $H2(4)_\beta$, than the same effect exerted by the COOR group.

Δ[($\Delta\delta$C2(4) (**IIb**) – C2(4) (**IIa**)) – ($\Delta\delta$C2(4) (**IVb**, **Vb**) – C2(4) (**IVa**, **Va**))] ≈ 2 ppm is due to the greater syn-diaxial effect exerted by the COOR group with respect to the same effect exerted by the CN group on $H2(4)_\beta$.

δC6(7) (**VIIa**) ≈ δC6(7) (**VIIb**) ≈ δC6(7) (**IIa**, **IVa**, **Va**) ≈ δC6(7) (**IIb**, **IVb**, **Vb**) and consequently the syn compressing steric effect of OH, CN or COOR groups seems not to operate on $H6(7)_x$.

The chemical shift of C-1′ (≈58 ppm) of the phenethyl group for **IVa**, **Va** is in agreement with an equatorial disposition of the *N*-substituent [13].

In C_6D_6 solution. In this case, the arguments for the δ ^1H parameters are similar as those above exposed for compound **IIa**.

By comparing the ^1H and ^{13}C parameters for compound **IIIa**·HCl in CD_3OD solution with those found for **IIa**, it can be deduced that the preferred conformation adopted by the bicycle system is similar to that found for **IIa**.

In all the cases studied, the *N*-ethylene and aromatic proton resonances were complex multiplets, accounting for a preferred conformation (or conformations) of the phenethyl group.

Hence, good agreement of the preferred conformation of compounds **IIa**, **IVa** and **Va** in $CDCl_3$ and C_6D_6 solutions, and **IIIa** in CD_3OD solution, and in the solid state for compound **IVa** has been observed. The cyclopentane and piperidine rings adopt an envelope conformation flattened at C8 and a distorted chair conformation puckered at C8 and flattened at N3, respectively, with the *N*-substituent in the equatorial position.

The unique difference between crystal and solute conformations is the conformation of the ethoxycarbonyl group, which in the solid state seems to be governed by the intermolecular hydrogen bonds.

ACKNOWLEDGEMENT

We thank the Comisión Interministerial de Ciencia y Energía (Grant FAR-0440) for support of this research.

REFERENCES

1 M. Díez, M.L. Izquierdo, E. Gálvez, M.S. Arias, I. Fonseca and J. Sanz, J. Mol. Struct., 246 (1990) 339.
2 M.S. Arias, E. Gálvez, I. Ardid, J. Bellanato, J.V. García-Ramos, F. Florencio and S. García-Blanco, J. Mol. Struct., 161 (1987) 151.
3 E. Gálvez, M.S. Arias, I. Ardid, F. Florencio, J. Sanz, J. Bellanato and J.V. García-Ramos, J. Mol. Struct., 196 (1989) 307.
4 E. Gálvez, I. Ardid, L. Fuentes, F. Florencio and S. García-Blanco, J. Mol. Struct., 142 (1986) 411.
5 P. Main, S.J. Fiske, S.E. Hull, L. Lessinger, G. Germain, J.P. Declercq and M.M. Woolfson, MULTAN, A System of Computer Programs for the Automatic Solution of Crystal Structures from X-Ray Diffraction Data, Universities of York, England and Louvain, Belgium, 1980.
6 J.P. Stewart, P.A. Machin, C.W. Dickinson, H.L. Ammon, H. Heck and H. Flack, The X-RAY 76 System, Technical Report TR-446, Computer Science Center, University of Maryland, College Park, MD, 1976.
7 M. Martínez-Ripoll and F.H. Cano, PESOS: A Computer Program for the Automatic Treatment of Weighting Schemes, Instituto Rocasolano C.S.I.C., Madrid, 1975.
8 M. Martínez-Ripoll and J. Fayos, Z. Kristallogr., 152 (1980) 189.
9 M. Nardelli, Comput. Chem., 7 (1983) 95.
10 International Tables for X-ray Crystallography, Vol. 4, Kynoch Press, Birmingham, UK, 1974.
11 A. Rogers, Acta Crystallogr. Sect. A, 37 (1981) 734.
12 D. Cremer and J.A. Pople, J. Am. Chem. Soc., 97 (1975) 1354.
13 E. Gálvez, M.S. Arias, J. Bellanato, J.V. García Ramos, F. Florencio, P. Smith-Verdier and S. García-Blanco, J. Mol. Struct., 127 (1985) 185, and references cited therein.
14 M.L. Izquierdo, M.S. Arias, E. Gálvez, B. Rico, I. Ardid, J. Sanz, I. Fonseca, A. Orjales and A. Innerarity, J. Pharm. Sci., in press.
15 A. Bax and R. Freeman, J. Magn. Reson., 44 (1981) 542.
16 A.E. Derome, Modern NMR Techniques for Chemistry Research, Pergamon, Oxford, 1987.
17 F.W. Wehrli and A.P. Marchand, Interpretation of ^{13}C NMR spectra, 2nd Edn., New York, 1988.
18 E. Breitmeier and W. Voelter, ^{13}C NMR spectroscopy. Methods and Application in Organic Chemistry, 2nd Edn., Verlag Chemie, Weinheim, 1978.
19 C.A.G. Haasnoot, F.A.A.M. de Leeuw and C. Altona, Tetrahedron, 36 (1980) 2783.