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Configurational and Conformational Study of New Esters Derived from 2-Methyl-2-azabicyclo[2.2.2]octan-5-*syn*(*anti*)-ols by NMR spectroscopy and X-ray Crystallography—I

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A series of esters derived from *syn*- and *anti*-2-methyl-2-azabicyclo[2.2.2]octan-5-ols were synthesized and studied by ^{1}H, ^{13}C and 2D NMR spectroscopy. The crystal structure of 5-*syn*-(3,5-dichlorobenzoyloxy)-2-methyl-2-azabicyclo[2.2.2]octane was determined by x-ray diffraction. The unambiguous assignment of all bicyclic proton and carbon resonances was achieved by the combined analysis of the ^{1}H–^{13}C correlation spectra and double resonance experiments. The ^{1}H–^{1}H coupling constants are proposed as model values in order to carry out the analysis of other isoquinuclidine derivatives. In order to gain additional information, a conformational analysis using molecular modeling techniques was undertaken. © **1997 John Wiley & Sons, Ltd.**

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Keywords: NMR; ^{1}H NMR; ^{13}C NMR; 5-*syn*(*anti*)-arylcarbonyloxy-2-methyl-2-azabicyclo[2.2.2]octane; ^{1}H–^{1}H coupling constants; conformational analysis

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INTRODUCTION

As part of a research program aimed at the development of new antagonists for the 5-HT$_3$ receptor,[1–7] we are currently involved in studies in which the 2-azabicyclo[2.2.2]octane (isoquinuclidine) ring system is being utilized as a conformationally restricted framework, bearing in mind the importance of conformational effects in the ligand–biological receptor interaction. Thus, a series of new esters derived from *syn*- and *anti*-2-methyl-2-azabicyclo[2.2.2]octan-5-ols were synthesized. Owing to the complexity of the isoquinuclidine system its proton magnetic parameters have not been reported, to our knowledge, in sufficient details.[8,9] In this paper, we report the configurational and conformational study of compounds **1**, **2**, **3a–e** and **4a–e** (Scheme 1) by NMR spectroscopy. The unambiguous assignment of all bicyclic proton and carbon resonances was achieved by the combined analysis of the ^{1}H–^{1}H COSY, ^{1}H–^{13}C correlation spectra of **1** and **2** (epimeric mixture), the ^{1}H–^{13}C correlation spectra of **3a** and **4e** and double resonance experiments in all cases. The ^{1}H–^{1}H coupling constants are proposed as model values in order to carry out the analysis of other isoquinuclidine derivatives. The crystal structure of 5-*syn*-(3,5-dichlorobenzoyloxy)-2-methyl-2-azabicyclo [2.2.2]octane (**3a**) was determined by X-ray diffraction.

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EXPERIMENTAL

The synthesis of **3a–e** and **4a–e** (Scheme 1) was achieved by treatment of the epimeric mixture of the *syn*- and *anti*-2-methyl-2-azabicyclo[2.2.2]octan-5-ols[10] with the appropriate carboxylic acid in the presence of *N*,*N*′-carbonyldiimidazole.[11] The resulting residue was chromatographed on silica gel with the appropriate solvent system to separate the epimeric mixture of the corresponding esters **3** and **4**.

Crystallographic data for **3a** are given in Table 1.[12–16]

All NMR spectra were recorded at 298 K using solutions of about 10 mg of compound in 0.5 ml of $CDCl_3$ and referenced to the corresponding solvent signal (δ^1H 7.26 ppm and δ^{13}C 77.0 ppm). The ^{13}C NMR spectra were obtained on a Varian UNITY-300 spectrometer operating at 75.437 MHz, with a spectral width 16 501 Hz, ^{13}C pulse width 4 μs, acquisition time 1 s and relaxation delay 1 s in 64K memory size. DEPT experiments were performed with standard pulse sequences. The ^{1}H NMR spectra were recorded and double resonance experiments were performed on a Varian UNITY-500 Plus spectrometer operating at 499.81 MHz. Typical spectral parameters were spectral width 5000 Hz, acquisition time 6.5 s, number of data points 65 536, ^{1}H pulse

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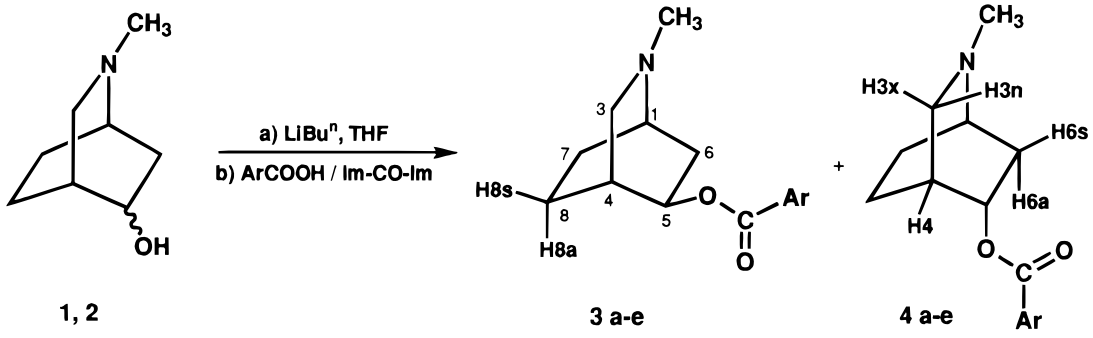

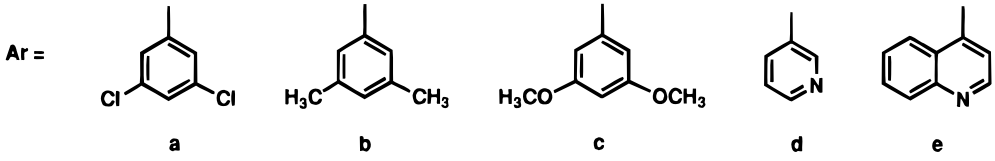

Scheme 1

Table 1. Experimental data and structure refinement procedures for compound 3a

Crystal data	
Formula	$C_{15}H_{17}NO_2Cl_2$
Crystal habit	Colorless prism
Cristal size (mm)	0.16 × 0.20 × 0.27
Symmetry	Monoclinic, $P2_1/n$
Unit cell determination	Least-squares fit from 64 reflections ($\theta < 34°$)
Unit cell dimensions	8.273 (1), 11.486 (1), 15.524 (2) Å, 94.51 (1)°
V (Å^3), Z, D_c (g cm^{-3})	1470.6 (1), 4, 1.42
M, $F(000)$, μ (cm^{-1})	315.22, 660, 40.5
Experimental data	
Technique	Four-circle diffractometer (Seifert XRD3000S) Bisecting geometry Graphite oriented monochromator: Cu Kα $\omega/2\theta$ scans, scan width (°): 1.5 + 0.15 tan θ Detector apertures 2 × 2°, up θ_{max} 65
Number of reflections:	
Measured	2647
Independent	2508
Observed	1845 [2σ (I) criterion]
Range of *hkl*	−10 10, 0 14, 0 18 (sin $\theta/\lambda)_{max.}$ 0.58
Value de R_{int}	0.013
Standard reflections	2 every 100 reflections. No variation
Absorption correction	ψ-Scan, max. and min. corrections 1.49–1.00
Solution and refinement	
Solution	Direct methods
Refinement	Least squares on F_{obs} with 1 block
Number of variables	232
Degrees of freedom	1613
Ratio of freedom	7.8
H atoms	Difference synthesis
Maximum final shift/error	0.009 (z of H4)
W-Scheme	Empirical so as to give no trends $\langle w\Delta^2F\rangle$ *vs.* $\langle\|F_o\|\rangle$ or $\langle\sin\theta/\lambda\rangle$
Max thermal value	0.078 (U11 of O12)
Final ΔF peak	0.48 e Å^{-3}
Extinction correction	None
S, unit weight standard deviation	0.87
Final R and Rw	0.053, 0.058
Computer and programs	VAX 6410, SIR92,[12] XRAY76,[13] PESOS,[14] CSU[15]
Scattering factors	Ref. 16
Anomalous dispersion	Ref. 16

width 10 μs and processed as 128K memory size. The HETCOR spectra of **1**, **2**, **3a** and **4e** were obtained on a Varian UNITY-500 Plus spectrometer, using an acquisition time of 0.088 s, a pulse angle of 90°, a delay of 1 s, an average $^1J_{CH}$ of 140.0 Hz, 256 scans, 256 increments, spectral width 4624.3 Hz in f_1 and 23350.8 Hz in f_2 and an FT size of 1K in f_1 and 8K in f_2.

Molecular modeling was carried out with the Quanta/CHARMm[17] molecular modeling software running on a Silicon Graphics workstation. We derived the structures of **3a**–**e** and **4a**–**e** with full geometry relaxation using the MNDO and AM1[18] Hamiltonian as implemented in MOPAC7.[19] Each of the starting structures was energy minimized using the CHARMm and AM1 methods.

RESULTS AND DISCUSSION

X-ray analysis of 3a

One crystallographically independent molecule forms the asymmetric unit shown in Fig. 1 together with the atomic numbering scheme used in the x-ray analysis. Bond lengths and bond angles are given in Table 2. The van der Waals interactions together with the hydrogen contacts listed in Table 2 determine the crystal packing.

The distances deduced from the x-ray data, N2–O12 = 4.99, N2—centroid = 6.39 and O12—centroid = 3.67 A, are within the range values defined for the pharmacophore 5-HT_3 described by Hibert *et al.*[20] The carbonyl group and the aromatic ring deviate from the coplanarity established in that model of pharmacophore by 7.7°.

Spectral analysis and assignment

^{1}H NMR (500 MHz) and ^{13}C NMR (75 or 125 MHz) spectroscopy was used to provide the information given in Tables 3–5. The unambiguous assignment of all bicyclic proton resonances was achieved by the combined use of ^{1}H–^{13}C correlation spectra and double resonance experiments. The proton magnetic parameters were deduced by first-order analysis of the spectra measured at 500 MHz, taking into account the coupling modifications observed in the different double resonance (DR) experiments.

Compounds 3a–e. All the *syn* esters show similar features in their ^{1}H NMR spectra. The signals corresponding to the bicyclic system protons are well differentiated except those assigned to H-4, H-6s and H-7s. The interpretation of these spectra is based on the unambiguous assignment of the signal at lower field to H-5 and the characteristic multiplicity of the H-3 signals.

Thus, for **3a** (^{1}H NMR spectrum, Fig. 2),[21] the saturation of the resonance frequency of H-5 (5.10 ppm) shows that the double doublet of doublets centered at 2.66 ppm becomes a doublet of doublets as result of the loss of the 'W' long-range coupling[22,23] between H-5 and H-3x, while the unaltered doublet of triplets centered at 3.07 ppm corresponds to H-3n. Moreover, the same irradiation modifies the signals at 2.11, 2.02 and 1.96 ppm that correspond to H-6a, H-6s and H-4 protons. The observation (HETCOR, Fig. 3) of a correlation between the two signals centered at 2.11 and 2.02 ppm with the signal at 32.71 ppm leads to the assignment of C-6 protons, and therefore the signal at 1.96 must correspond to H-4.

On saturating the signal assigned to H-3n, the multiplet centered at 1.62 ppm becomes simplified, thus this signal corresponds to H-8a owing to the 'W' long-range coupling between H-3n and H-8a. From the ^{1}H–^{13}C correlation spectra we can now assign the multiplet centered at 1.79 ppm to H-8s, and by exclusion the signals of C-7 and the corresponding protons. The unequivocal assignments of H-6s, H-6a, H-7s and H-7a are based on the coupling constants of H-6a and H-7a from irradiation experiments.

Bearing in mind the similarity of the ^{1}H NMR spectra for the *syn* esters **3a**–e, and the double resonance experiments performed in all cases, a similar behavior can be assumed. This allows the complete and

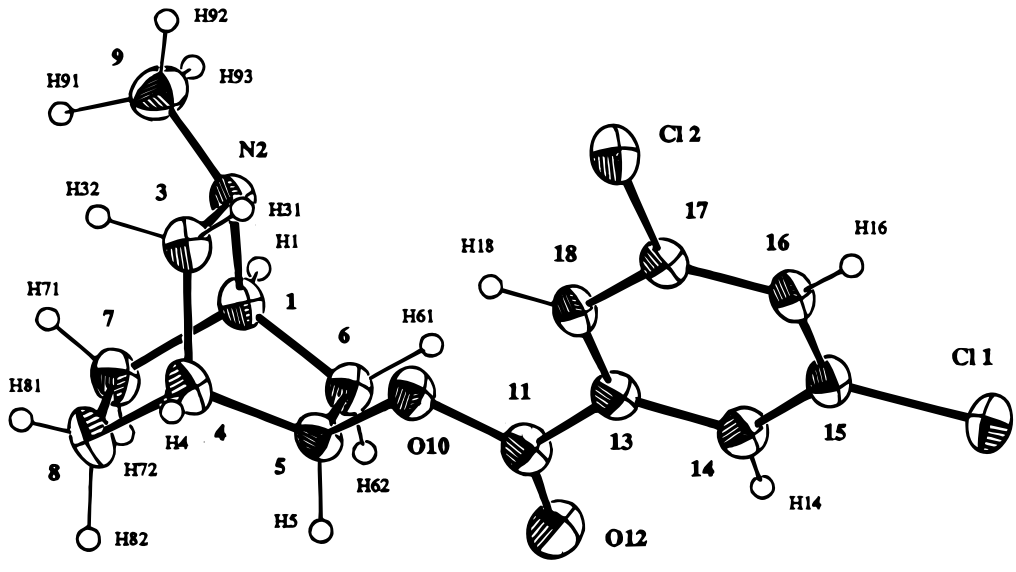

Figure 1. ORTEP view of the molecular structure showing the atomic numbering. Thermal ellipsoids are drawn at the 30% probability level.

Table 2. Bond lengths and bond angles with ESD values in parentheses

Bond lengths (Å)

Cl1—C15	1.742 (4)	C1—C6	1.526 (5)	C11—C13	1.499 (5)
Cl2—C17	1.740 (4)	C1—C7	1.537 (5)	C13—C14	1.390 (5)
O10—C5	1.463 (4)	C3—C4	1.518 (5)	C13—C18	1.383 (5)
O10—C11	1.337 (4)	C4—C5	1.517 (4)	C14—C15	1.379 (5)
O12—C11	1.191 (5)	C4—C8	1.534 (5)	C15—C16	1.375 (5)
N2—C1	1.470 (4)	C5—C6	1.523 (5)	C16—C17	1.385 (5)
N2—C3	1.474 (4)	C7—C8	1.533 (5)	C17—C18	1.387 (5)
N2—C9	1.451 (5)				

Bond angles (°)

C5—O10—C11	116.0 (3)	C4—C8—C7	109.6 (3)
C1—N2—C3	110.3 (2)	O10—C11—O12	124.5 (3)
C1—N2—C9	113.5 (3)	O10—C11—C13	111.4 (3)
C3—N2—C9	112.7 (3)	O12—C11—C13	124.1 (3)
N2—C1—C6	107.1 (3)	C11—C13—C14	117.2 (3)
N2—C1—C7	111.9 (3)	C11—C13—C18	122.3 (3)
C6—C1—C7	109.9 (3)	C14—C13—C18	120.5 (3)
N2—C3—C4	110.6 (3)	C13—C14—C15	119.0 (3)
C3—C4—C5	110.5 (3)	Cl1—C15—C14	118.9 (3)
C3—C4—C8	109.1 (3)	Cl1—C15—C16	119.0 (3)
C5—C4—C8	106.2 (3)	C14—C15—C16	122.2 (3)
O10—C5—C4	107.2 (3)	C15—C16—C17	117.6 (3)
O10—C5—C6	111.4 (3)	Cl2—C17—C16	118.9 (3)
C4—C5—C6	109.6 (3)	Cl2—C17—C18	118.9 (3)
C1—C6—C5	109.2 (3)	C16—C17—C18	122.2 (3)
C1—C7—C8	108.1 (3)	C13—C18—C17	118.5 (3)

Hydrogen contacts (Å, °)

X—H···Y	X—H	X···Y	H···Y	∠X—H···Y
C3—H31···O10	0.97 (5)	2.892 (4)	2.65 (5)	95 (3)
C5—H5···O12	1.00 (5)	2.673 (4)	2.46 (5)	91 (3)
C6—H61···O12	0.98 (5)	3.054 (4)	2.81 (5)	95 (3)
C14—H14···O12	0.89 (5)	2.816 (4)	2.47 (5)	104 (3)
C18—H18···O10	0.92 (5)	2.731 (4)	2.43 (5)	99 (3)
C16—H16···N2[a]	0.96 (5)	3.388 (4)	2.49 (5)	155 (4)

[a] $-x+1, -y+1, -z+1$.

Table 3. ^{1}H chemical shifts (δ, ppm) for compounds 1, 2, 3a–e and 4a–e in $CDCl_3$

		1	3a	3b	3c	3d	3e		2	4a	4b	4c	4d	4e
H-1	(m)	2.50	2.62	2.62	2.61	2.64	2.66	(m)	2.47	2.62	2.58	2.59	2.59	2.63
H-3n	(dt)	3.05	3.07	3.09	3.03	3.08	3.10	(dt)	2.60	2.69	2.64	2.65	2.65	2.72
H-3x	(ddd)	2.41	2.66	2.71	2.73	2.70	2.70	(dd)	2.67	2.85	2.85	2.85	2.83	2.87
H-4	(m)	1.69	1.96	1.96	1.95	1.98	2.06	(m)	1.64	2.03	2.01	2.01	2.02	2.11
H-5a	(m)	3.85	5.10	5.09	5.08	5.15	5.25							
H-5s								(m)	4.06	5.25	5.20	5.21	5.25	5.38
H-6a	(ddd)	1.89	2.11	2.11	2.10	2.12	2.19	(m)	1.26	1.53	1.52	1.52	1.52	1.60
H-6s	(m)	1.79	2.02	2.04	2.04	2.06	2.12	(m)	2.38	2.58	2.54	2.56	2.56	2.64
H-7a	(m)	1.25	1.40	1.42	1.43	1.42	1.45	(m)	1.49	1.62	1.62	1.60	1.59	1.62
H-7s	(m)	1.87	2.00	2.00	1.98	2.00	2.01	(m)	1.87	2.03	1.98	1.99	2.00	2.04
H-8a	(m)	1.40	1.62	1.64	1.63	1.63	1.67	(m)	1.93	1.93	1.97	1.96	1.93	1.96
H-8a	(m)	1.67	1.79	1.78	1.78	1.80	1.83	(m)	1.44	1.62	1.58	1.60	1.59	1.64
N-CH_3	(s)	2.26	2.40	2.41	2.40	2.41	2.41	(s)	2.29	2.36	2.34	2.35	2.33	2.36
H-2′			7.91	7.67	7.21	9.25	7.93			7.89	7.63	7.18	9.20	7.88
H-3′							9.02							9.02
H-4′			7.53	7.18	6.64	8.78				7.55	7.17	6.64	8.75	
H-5′						7.39	8.80						7.38	8.77
H-6′			7.91	7.67	7.21	8.31	7.77			7.89	7.63	7.18	8.27	7.76
H-7′							7.66							7.65
H-8′							8.18							8.17
CH_3	(s)			2.36	3.83						2.35	3.83		

Table 4. ^1H–^1H coupling constants (J, Hz) for compounds 1, 2, 3a–e and 4a–e

	1	3a	3b	3c	3d	3e	2	4a	4b	4c	4d	4e
						^2J						
H3n–H3x	10.8	10.5	10.3	10.3	10.5	10.5	10.4	10.7	10.7	10.6	10.7	10.5
H6s–H6a	14.1	14.3	14.7	14.7	14.7	14.5	12.5	14.3	14.2			
H7s–H7a	13.2	13.1	12.8	12.8	13.4	13.4						
H8s–H8a		13.6	13.6		13.6	13.6						
						^3J						
H3n–H4	2.6	2.4	2.6	2.6	2.6	2.6	2.0	2.4	2.4	2.4	2.4	2.4
H3x–H4	2.0	2.6	2.6	2.6	2.6	2.6	2.9	2.9	3.2	3.3	3.1	3.1
H4–H5		3.1	2.9	2.9	3.0	2.9			3.4			2.9
H5–H6a	9.2	9.5	9.2	9.2	9.2	9.5	1.9	2.9	3.2			
H5–H6s	3.0	4.0	4.4	4.4	4.1	4.4	9.2	9.3	9.3			9.3
H6a–H1	2.4	2.6	2.6	2.6	2.6	2.6	3.5	2.4	2.6			
H6s–H1	3.0	2.6			2.6	3.0		2.9	3.2			
H7a–H1		2.1	2.2	2.2	2.3	2.3		2.4	2.4			
H7a–H8a		11.3	11.0	11.0	11.4	11.3			10.7			
H7a–H8s		5.0	5.1	5.1	5.0	5.0		5.1	3.9			
H7s–H8s		11.1	11.0	10.6	11.3	11.3			11.2			
H7s–H8a		4.4	4.4		4.5	4.6						
H7s–H1		2.4			2.4							
H8a–H4		2.9	2.9		2.9	2.6						2.9
H8s–H4		3.6	3.5		3.5	3.5			3.4			2.9
						^4J						
H3n–H8a	2.6	2.6	2.6	2.6	2.6	2.6	2.6	2.4	2.4	2.4	2.4	2.4
H3x–H5	1.3	1.5	1.5	1.5	1.5	1.5						
H5–H8s									1.5			1.5
H6s–H7s	3.0				2.6			2.5	3.2			

unambiguous assignment of the individual protons for the bicyclic system of *syn* esters **3a–e**.

For the assignment of the ^{13}C NMR chemical shifts, the similarity of the spectra for compounds **3a–e**, the analysis of the DEPT experiments performed in all cases and the HETCOR spectrum of **3a** were taken into consideration.

Compounds 4a–e. All ^1H NMR spectra of *anti* esters **4a–e** are very similar. The multiplets corresponding to H-5, H-3x and H-3n appear well differentiated in all cases. Following a systematic study analogous to that discussed above for **3a–e**, the assignment of the individual protons and carbon atoms for the *anti* esters **4a–e** was carried out by the combined use of DR experiments,

Table 5. ^{13}C chemical shifts (δ, ppm) for compounds 1, 2, 3a–e and 4a–e in $CDCl_3$

	1	3a	3b	3c	3d	3e	2	4a	4b	4c	4d	4e
C-1	51.50	50.93	50.99	50.98	50.90	50.96	51.84	51.38	51.43	51.45	51.33	51.35
C-3	50.75	51.42	51.45	51.39	51.31	51.45	55.17	54.61	54.73	54.75	54.59	54.65
C-4	32.27	30.65	30.69	30.74	30.62	30.62	33.46	30.33	30.33	30.36	30.30	30.36
C-5	67.63	72.79	71.34	71.84	72.22	72.86	67.82	73.14	71.71	72.15	72.58	73.24
C-6	36.13	32.71	32.32	31.99	32.37	32.66	35.38	32.08	31.93	32.04	32.03	32.19
C-7	21.27	22.15	22.07	22.02	22.00	22.10	23.14	23.77	24.06	24.03	23.82	23.78
C-8	22.36	22.58	23.07	23.42	22.78	22.58	17.36	18.24	18.26	18.31	18.21	18.33
N-CH_3	45.52	42.98	42.98	42.93	42.91	42.92	42.81	42.91	42.93	42.95	42.88	42.90
C=O		163.92	166.63	166.01	164.95	165.93		163.76	166.41	165.87	164.76	165.75
C-1′		133.53	130.47	132.56	126.44	135.31		133.46	130.49	132.57	126.41	135.28
C-2′		127.96	127.24	107.31	153.34	122.17		127.87	127.12	107.14	153.30	121.99
C-3′		135.20	137.90	160.60		149.78		135.23	137.90	160.61		149.75
C-4′		132.61	134.48	105.30	150.94			132.66	134.43	105.22	150.79	
C-4′a						149.09						149.09
C-5′		135.20	137.90	160.60	123.21	130.04		135.23	137.90	160.61	123.21	130.02
C-6′		127.96	127.24	107.31	137.03	129.65		127.87	127.12	107.24	136.90	129.69
C-7′						128.09						128.09
C-8′						125.57						125.49
C-8′a						125.14						125.09
CH_3			21.15	55.57					21.15	55.56		

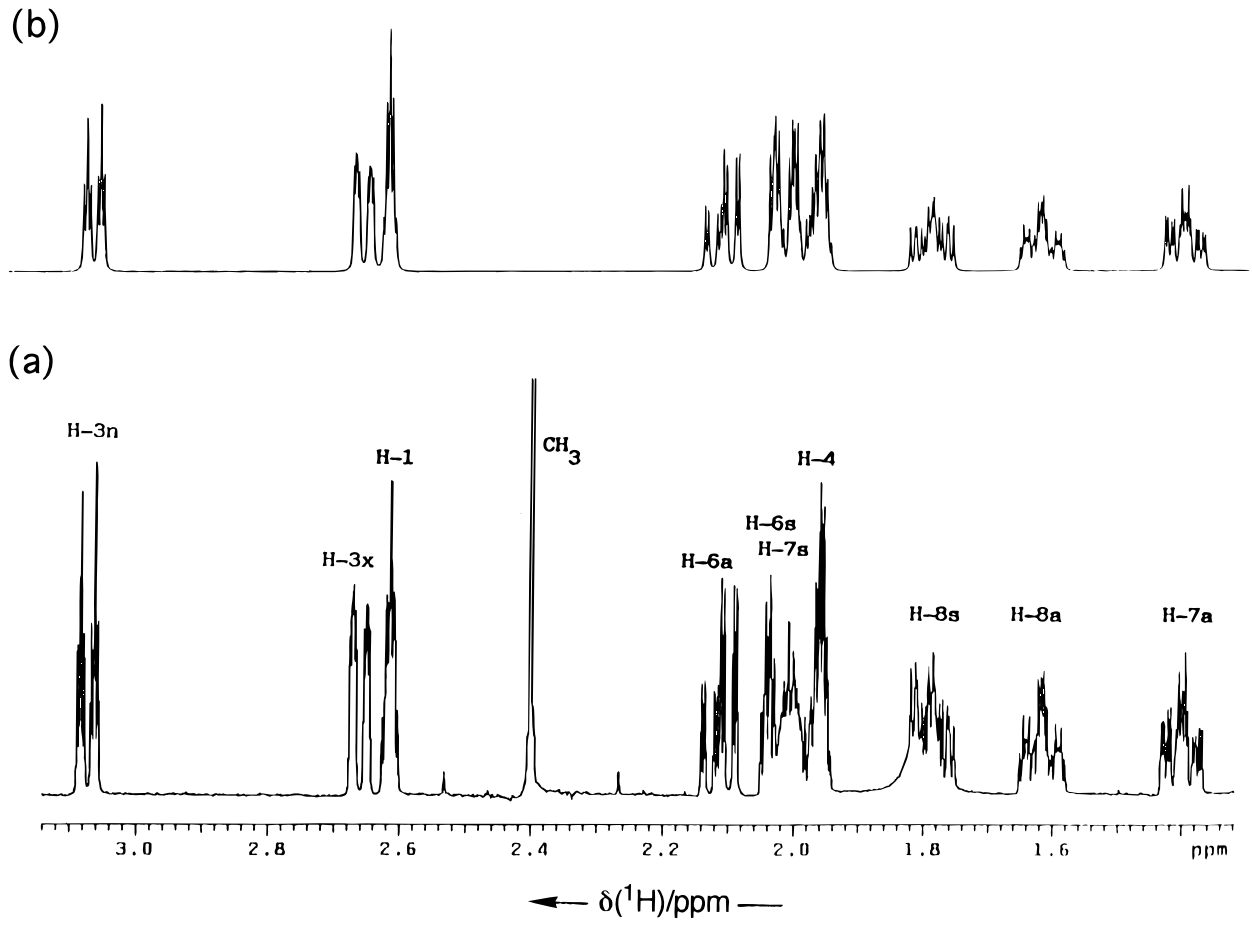

Figure 2. (a) Partial 500 MHz ^{1}H spectrum of **3a**; (b) simulated spectrum.

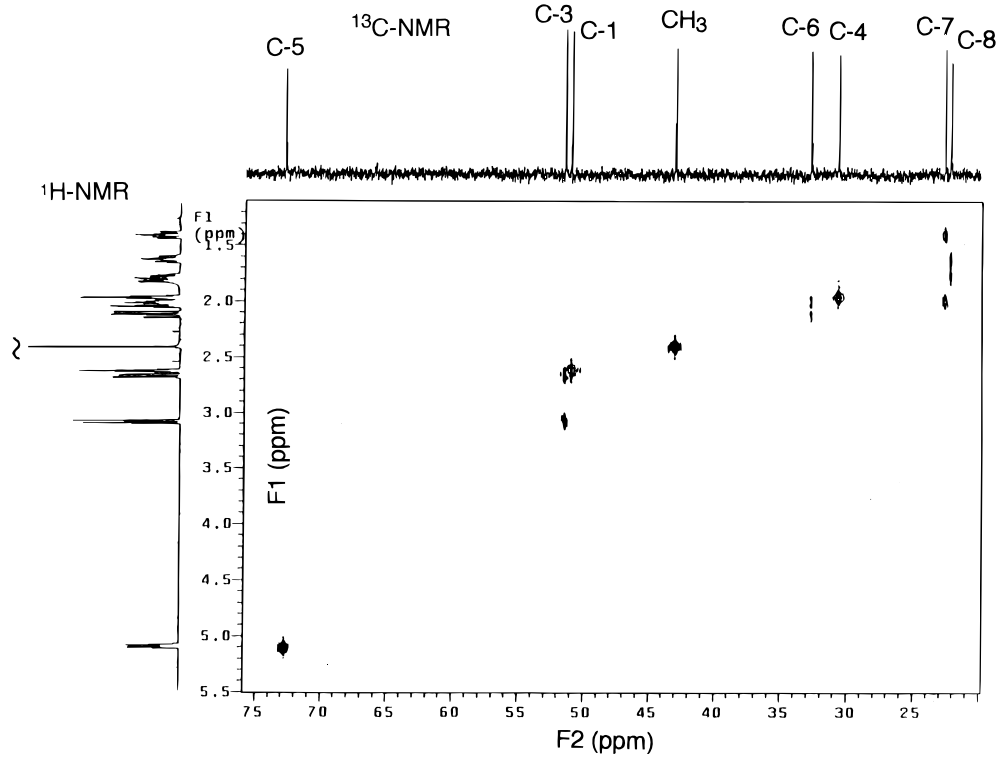

Figure 3. ^{1}H–^{13}C correlated spectrum of **3a** (the aromatic region is omitted).

Table 6. Selected torsion angles (°) for compound 3a

Dihedral angle	X-ray	MM	Dihedral angle	X-ray	MM
Cl1—C15—C14—C13	−177.7	−179.9	Cl2—C17—C18—C13	179.3	179.9
C4—C5—H10—C11	166.3	153.9	C6—C5—O10—C11	−73.9	−87.6
O12—C11—O10—C5	0.1	−0.3	O12—C11—C13—C14	7.7	0.1
C5—O10—C11—C13	179.0	179.3	O12—C11—C13—C18	−173.8	179.7
N2—C1—C6—C5	59.9	58.5	N2—C1—C7—C8	−63.7	−60.0
N2—C3—C4—C5	51.1	56.5	N2—C3—C4—C8	−65.3	−62.0
C4—C3—N2—C9	139.4	144.6	C7—C1—N2—C9	−75.1	−83.3
C6—C1—N2—C9	164.5	158.0	C1—N2—C3—C4	11.5	4.9
C1—C6—C5—C4	1.9	1.7	C1—C7—C8—C4	8.6	3.0

DEPT experiments in ^{13}C and the HETCOR spectrum of **4e**.

The major differences between the series of *syn* and *anti* esters are due to the different disposition of H-5. Taking the spectrum of **4e** as an example: (i) the unequivocal assignment of the H-3n and H-3x resonances is made owing to the different multiplicity of these signals. Taking into account the long-range coupling between H-3n and H-8a, the doublet of triplets centered at 2.72 ppm must be assigned to H-3n. The doublet of doublets centered at 2.87 ppm must correspond to H-3x; this proton presents a geminal coupling with H-3n (10.5 Hz) and a vicinal coupling with H-4 (3.1 Hz), but no long-range coupling due to the *anti* disposition of the arylcarbonyloxy group. (ii) The saturation of the resonance frequency of H-5 shows a simplification of the signals centered at 2.11, 1.64, 2.64 and 1.60 ppm, that must correspond to H-4, H-8s and C-6 protons. The simplification of the signals of H-4, H-6s and H-6a is due to the loss of the corresponding vicinal coupling, while the modification of the signal of H-8s shows the loss of a 'W' long-range coupling. The assignment of the H-8s resonance of 1.68 ppm is confirmed on the basis of its correlation with H-8a and C-8 signals in the HECTOR spectrum.

The magnetic parameters for alcohols **1** and **2** (Table 3–5) were based on the analysis of ^{1}H–^{1}H COSY and ^{1}H–^{13}C correlation spectra of the epimeric mixture and double resonance experiments, and taking into account the data deduced for the ester derivatives discussed above.

Conformational study

There are several trends in the chemical shifts of certain protons and carbons in this series of compounds, as described below.

(i) $\Delta\delta$ C-8(**3a**–**e**) − C-8(**4a**–**e**) ≈ 4–5 ppm can be attributed to the *syn*-diaxial steric effect exerted by the arylcarbonyloxy group in the *anti* epimer. $\Delta\delta$ H-8a(**4a**–**e**) − H-8a(**3a**–**e**) ≈ 0.3 ppm is justified in the same way, and by the field effect exerted by the *O*COAr in the *anti* epimer. Moreover, $\Delta\delta$ H-8s(**3a**–**e**) − H-8s(**4a**–**e**) ≈ 0.2 ppm can be interpreted bearing in mind the 'W' disposition of the *O*COAr moiety with respect to H-8s in the *anti* isomer.[24,25]

(ii) Similarly, $\Delta\delta$ C-3(**4a**–**e**) − C-3(**3a**–**e**) ≈ 3 ppm is attributed to *γ-gauche* effect exerted by the arylcarbonyloxy group in the *syn* epimer. The value of $\Delta\delta$ H-3n(**3a**–**e**) − H-3n(**4a**–**e**) ≈ 0.35 ppm is in accord with the steric and field effect of the *O*COAr group as in the case of H-8s. Also, a low-field shift of 0.15 ppm is observed for H-3x in the *anti* epimer respect to the *syn* epimer, due to the 'W' relative disposition of the functional group.

(iii) It is of interest that the protons eclipsed with the electron-attracting functional group (OH or *O*COAr) resonate at lower chemical shifts than do the geminal partners *trans* to the substituent. This is the case of H-6s in the *syn* epimer and H-6a in the *anti* epimer, that show an upfield shift of 0.5 and 0.6 ppm, respectively, *vs.* the same protons in the opposite epimers. These data are in fairly good agreement with those found for 7-monosubstituted dibenzobicyclo[2.2.2]octanes.[26]

From the ^{1}H and ^{13}C NMR data (Table 3–5) of **3a**–**e** and **4a**–**e**, it can be deduced that all compounds of the same family show the same orientation of the arylcarbonyloxy group and also coplanarity for that group in all compounds can be assumed. Furthermore, the chemical shifts of H-5 in both families of epimers are similar, which suggests the same relative orientation with respect to C=O group in both series.

In order to obtain an insight into the conformation of these compounds, molecular modeling (MM) calculations were performed for **3** and **4** with the CH_3–N orientation at *endo* and *exo* positions. The lowest CHARMm and AM1 energy conformations for these compounds are almost identical. Selected torsion angles for the lowest energy conformation of **3a** with an *exo* position of the CH_3–N group are given in Table 6, and they are compared with the corresponding angles from x-ray analysis, no significant deviations being observed. From MM studies, a similar disposition of the arylcarbonyloxy group in each family of compounds, with the two possible orientations of the *N*-Me group, is observed. In all cases, the relative orientation of the H-5 with respect of the carbonyl group is the same.

Taking into account the above discussion, we propose that for **3a**–**e** and **4a**–**e**, the preferred conformation in $CDCl_3$ solution is similar to that deduced from CHARMm and AM1 calculations, and in the case of **3a** also similar to that deduced from x-ray study, with respect to the disposition of the arylcarbonyloxy group.

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