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Synthesis and structural study of esters derived from 2-methyl-2-azabicyclo[2.2.2]octan-6-*syn*(*anti*)-ols by NMR spectroscopy and x-ray crystallography

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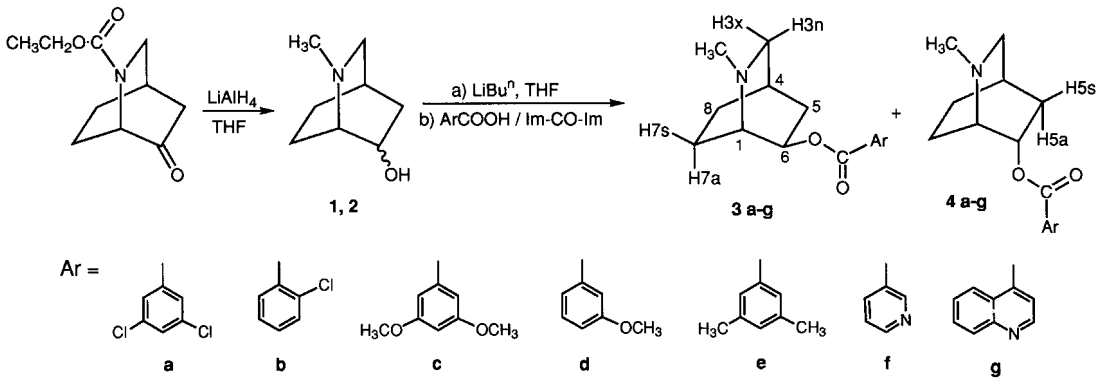
ABSTRACT: A series of esters derived from *syn*- and *anti*-2-methyl-2-azabicyclo[2.2.2]octan-6-ols were synthesized and studied by NMR spectroscopy. The unambiguous assignment of all bicyclic proton and carbon resonances was achieved by the combined analysis of the COSY, ^{1}H–^{13}C correlation spectra and double resonance experiments (spin decoupling). The crystal structure of 6-*anti*-(2-chlorobenzoyloxy)-2-methyl-2-azabicyclo[2.2.2]octane hydrochloride, was determined by x-ray diffraction, which confirmed the configurational assignment. Copyright © 1999 John Wiley & Sons, Ltd.

KEYWORDS: 2-methyl-2-azabicyclo[2.2.[octan-6-ol esters; synthesis; structures; NMR spectroscopy; x-ray crystallography



Scheme 1

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-6-ols have been synthesized. Owing to the complexity of the isoquinuclidine system, its proton magnetic parameters have not been reported, to our knowledge, in sufficient detail.[8,9] In this paper we report the configurational study of compounds **3a–g** and **4a–g** (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 and ^{1}H–^{13}C correlation spectra of **3a** and **4a** and homonuclear spin decoupling experiments in all cases. The crystal structure of 6-*anti*-(2-chlorobenzoyloxy)-2-methyl-2-azabicyclo [2.2.2]octane hydrochloride, **4b·HCl,** was determined by x-ray diffraction.

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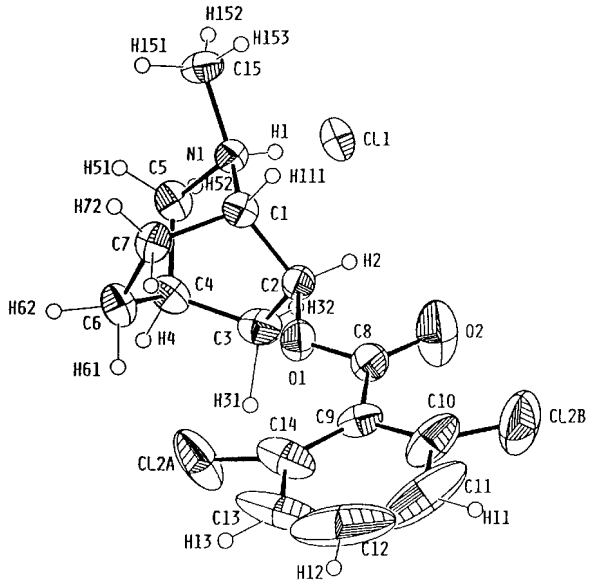

Figure 1. ORTEP[9] plot showing the molecular structure of **4b·HCl** with the atom labeling. Displacement ellipsoids are shown at the 30% probability level.

RESULTS AND DISCUSSION

Synthesis

The requisite alcohols **1** and **2** (Scheme 1) were prepared by reduction with lithium aluminum hydride in tetrahydrofuran of 2-carbethoxy-2-azabicyclo[2.2.2]octan-6-one, which was prepared by the method of Krow *et al*.[10] This method involves addition of benzeneselenyl chloride to 2-carbethoxy-2-azabicyclo[2.2.2]oct-5-ene,[11] followed by dehydrohalogenation and hydrolysis of the derived vinyl selenide to give the 2-carbethoxy-2-azabicyclo[2.2.2]octan-6-one, regioselectively. The synthesis of the new esters **3a–g** and **4a–g** (Scheme 1) was achieved by treatment of the epimeric mixture of the *syn*- and *anti*-2-methyl-2-azabicyclo[2.2.2]octan-6-ols **1** and **2** with the appropriate carboxylic acid in the presence of *N*,*N*′-carbonyldiimidazole. The carboxylic acid was activated as the imidazolide and then treated with the lithium alkoxide, which was generated from the alcohol and *n*-BuLi. 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.**

X-ray crystal structure analysis of 4b·HCl

The ORTEP[12] view of the molecule, together with the atom numbering used in the x-ray analysis, is shown in Fig. 1. Bond lengths and bond angles are given in Table 1. The Cl atom in phenyl ring occupies the two *ortho* positions with occupancy factors of 0.55 (1) and 0.45 (1); the whole ring is disordered into two positions, 180° apart around C-8— C-9, with poor geometry and high thermal parameters for C-11, C-12 and C-13 atoms, as can be seen in Fig. 1. The geometry of the six-membered rings is similar to that found in similar compounds.[13] Pharmacologically interesting[14] are the intramolecular distances of N-1 and O-2 to the centroid of the phenyl ring, 7.198(4) and 3.674(6) Å respectively, and the distance O-2…N-1, which is 4.787(8) Å . The Cl-1 atom supports the whole structure; there is a hydrogen bond with N-1 through H-1 and a series of short contacts (range of distances H…Cl from 2.77 to 3.23 Å) from the Cl-1 atom to the hydrogen of several C atoms in different cells (see Table 1).

NMR study

^{1}H NMR (500 MHz) and ^{13}C NMR (75 or 125 MHz) spectroscopy were used to provide the information given in Tables 2–4. The proton magnetic parameters were deduced by analysis of the spectra measured at 500 MHz, taking into account the coupling modifications observed in the different irradiation experiments.

Compounds 3a–g. All the *syn* esters show similar features in their ^{1}H NMR spectra. The signals corresponding to the bicyclic system protons are well differentiated. The respective multiplets are due to one proton, except those assigned to H-7a and H-8a, which overlap. The interpretation of these spectra is based on the unambiguous assignment of the most deshielded signal in the aliphatic region. Thus, for **3a,** based on the deshielding effect of the nitrogen atom and on the observed coupling interactions, the signals at 2.80, 3.04 and 2.51 ppm are respectively assigned to H-1 and to the geminated H-3 protons. The analysis of the COSY map (Fig. 2) shows correlations between H-6 and H-1, between H-6 and the geminated protons H-5 and between H-1 and the geminated protons H-7. The last signals are assigned to the geminated protons H-8. The stereospecific assignments of geminated protons is based on long-range ^4J coupling interactions appearing in the COSY map, namely between H-3x, H-5a (2.51, 2.20 ppm) and H-3n, H-8a (3.04, 1.45 ppm).[15,16] Finally, H-7s is more deshielded than H-7a owing to their respective positions with respect to the nitrogen atom.[17,18]

Bearing in mind the similarity of the ^{1}H NMR spectra for the *syn* esters **3a–g** and the successive spin decoupling experiments performed in all cases, a similar behavior can be assumed. This allows the complete and unambiguous assignment of the individual protons for the bicyclic system of *syn* esters **3a–g.**

For the assignment of the ^{13}C NMR chemical shifts, the similarity of the spectra for compounds **3a–g,** the analysis of the DEPT experiments performed in all cases and the HETCOR spectrum of **3a** (Fig. 3) were taken into consideration. Moreover, the heteronuclear ^{1}H–^{13}C

Table 1. Bond distances and bond angles with e.s.d. values in parentheses

Bond distances (Å)			
N1—C1	1.502 (7)	O1—C8	1.305 (8)
N1—C5	1.515 (7)	C8—O2	1.201 (9)
N1—C15	1.480 (8)	C8—C9	1.477 (8)
C1—C2	1.522 (8)	C9—C10	1.397 (11)
C1—C7	1.522 (8)	C9—C14	1.361 (11)
C2—C3	1.527 (9)	C10—C11	1.427 (22)
C2—O1	1.448 (7)	C10—C12B	1.417 (11)
C3—C4	1.522 (9)	C11—C12	1.380 (30)
C4—C5	1.512 (8)	C12—C13	1.202 (34)
C4—C6	1.520 (9)	C13—C14	1.394 (13)
C6—C7	1.540 (8)	C14—C12A	1.536 (11)
Bond angles (°)			
C5—N1—C15	111.6 (5)	C2—O1—C8	119.3 (5)
C1—N1—C15	113.8 (4)	O1—C8—C9	113.9 (5)
C1—N1—C5	109.7 (4)	O1—C8—O2	122.3 (6)
N1—C1—C7	110.2 (4)	O2—C8—C9	123.6 (6)
N1—C1—C2	105.3 (4)	C8—C9—C1	126.1 (6)
C2—C1—C7	111.4 (4)	C8—C9—C10	118.4 (6)
C1—C2—O1	105.4 (4)	C10—C9—C14	115.5 (7)
C1—C2—C3	108.6 (5)	C9—C10—C12B	130.1 (7)
C3—C2—O1	109.8 (5)	C9—C10—C11	119 (1)
C2—C3—C4	109.9 (5)	C11—C10—C12B	110 (1)
C3—C4—C6	108.6 (5)	C10—C11—C12	118 (2)
C3—C4—C5	109.9 (5)	C11—C12—C13	124 (2)
C5—C4—C6	108.4 (5)	C12—C13—C14	120 (1)
N1—C5—C4	108.3 (4)	C9—C14—C13	123.2 (7)
C4—C6—C7	108.5 (5)	C13—C14—C12A	108.0 (9)
C1—C7—C6	108.9 (5)	C9—C14—C12A	128.4 (7)

Short contacts involving C-11 atom

X—H···Y[a]	X—H	H···Y	X···Y	X—H···Y
N1—H···C1[b]	0.77 (8)	2.23 (8)	3.007 (5)	177 (7)
C2—H2···C1	0.87 (9)	3.05 (9)	3.608 (5)	124 (7)
C3—H32···C1	0.95 (7)	3.10 (7)	3.807 (6)	132 (6)
C5—H52···C1	0.88 (8)	3.23 (7)	3.650 (7)	112 (5)
C5—H51···C1 (i)	1.01 (7)	3.17 (7)	4.086 (7)	151 (4)
C7—H72···C1 (i)	0.90 (10)	2.98 (10)	3.696 (6)	138 (7)
C15—H151···C1 (i)	1.04 (9)	2.83 (9)	3.810 (7)	157 (6)
C1—H111···C1 (ii)	0.91 (6)	2.78 (6)	3.602 (5)	150 (4)
C4—H4···C1 (iii)	1.08 (8)	2.92 (8)	3.710 (6)	130 (5)
C12—H12···C1 (iv)	1.09 (–)	2.77 (–)	3.789 (17)	156 (–)[c]

[a] Symmetry code: (i) $-x+1+1/2$, $y+1/2$, z; (ii) $-x+1+1/2$, $-y$, $z+1/2$; (iii) $-x+1+1/2$, $-y$, z; (iv) $x+1/2$, y, $-z+1+1/2$.
[b] Hydrogen bonding.
[c] (—) No e.s.d. as H-12 was kept fixed in the refinement.

correlated spectrum confirms the previous proton assignments.

Compounds 4a–g. The ^{1}H NMR spectra of *anti* esters **4a–g** are very similar. The multiplets corresponding to H-6, H-1, H-3n, H-3x and H-5s appear well differentiated in all cases. Other signals, except those of H-5a and H-7s for **4a,** appear partially overlapped. Following a systematic study analogous to that discussed above for **3a–g,** the assignment of the individual proton and carbon atoms for the *anti* esters **4a–g** was carried out with the aid of the COSY and HETCOR spectra of **4a** and the use of spin decoupling and DEPT experiments in all cases. Thus, in the case of **4a,** the analysis of the correlations observed in the COSY spectrum between the C-3 protons (2.61 and 2.76 ppm) with the signals centered at 1.58 ppm (H-5a) and 1.63 ppm (H-8) show the W long-range coupling, and leads to the assignment of H-3x (2.61 ppm) and H-3n (2.76 ppm). The assignment of the C-7 protons (1.79 and 1.91 ppm) and the C-8 protons (multiplet centered at 1.63 ppm) is confirmed on the basis of the decoupling experiments. Hence the irradiation of the resonance

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

Atom	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**		**4a**	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**
H-1 (m)	2.80	2.82	2.83	2.83	2.82	2.83	2.91	(m)	2.80	2.82	2.81	2.81	2.81	2.82	2.88
H-3n (dt)	3.04	3.04	2.94	2.96	3.01	3.01	3.09	(m)	2.76	2.75	2.76	2.76	2.75	2.78	2.79
H-3x (dt)	2.51	2.48	2.66	2.64	2.59	2.58	2.51	(dt)	2.61	2.61	2.61	2.61	2.63	2.60	2.61
H-4 (m)	1.84	1.82	1.84	1.83	1.84	1.85	1.87	(m)	1.82	1.81	1.80	1.80	1.83	1.83	1.84
H-5a (m)	2.20	2.21	2.17	2.18	2.18	2.21	2.27	(m)	1.58	1.62	1.59	1.60	1.59	1.60	1.63
H-5s (m)	1.76	1.78	1.75	1.76	1.76	1.77	1.83	(m)	2.27	2.28	2.27	2.27	2.27	2.29	2.34
H-6a(ddd)	5.04	5.10	5.06	5.07	5.06	5.10	5.20								
H-6s								(m)	5.29	5.32	5.29	5.30	5.28	5.34	5.42
H-7a (m)	1.52	1.53	1.52	1.54	1.53	1.53	1.57	(m)	1.79	1.87	1.88	1.84	1.87	1.84	1.88
H-7s (m)	2.04	2.04	2.02	2.02	2.02	2.05	2.10	(m)	1.91	1.87	1.89	1.89	1.87	1.90	1.88
H-8a (m)	1.46	1.44	1.45	1.48	1.46	1.45	1.49	(m)	1.63	1.62	1.62	1.62	1.63	1.63	1.64
H-8s (m)	1.61	1.61	1.62	1.62	1.62	1.63	1.64	(m)	1.63	1.62	1.62	1.62	1.63	1.63	1.64
N-CH_3(s)	2.44	2.42	2.48	2.48	2.47	2.46	2.45	(s)	2.46	2.46	2.46	2.46	2.47	2.46	2.48
CH_3 (s)			3.82	3.85	2.35						3.83	3.85	2.36		
H-2′	7.94		7.22	7.59	7.68	9.26	7.93		7.87		7.17	7.55	7.63	9.21	7.86
H-3′		7.42					9.00			7.44					9.01
H-4′	7.53	7.38	6.63	7.08	7.16	8.77			7.54	7.40	6.64	7.09	7.18	8.77	
H-5′		7.30		7.33		7.38	8.78			7.31		7.34		7.39	8.78
H-6′	7.94	7.79	7.22	7.66	7.68	8.33	7.75		7.87	7.81	7.17	7.62	7.63	8.28	7.75
H-7′							7.64								7.64
H-8′							8.15								8.18

Table 3. ^{1}H–^{1}H coupling constants (J, Hz) for compounds **3a–g** and **4a–g**

J	Atoms	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**4a**	**4b**	**4c**	**4d**	**4e**	**4f**	**4g**
2_J	H3n–H3x	9.5	9.5	9.5	9.5	9.5	9.5	9.5	9.7	9.5	9.5	9.6	9.5	9.5	9.5
	H5a–H5s	13.7		13.9	13.5		13.5	13.7	14.2	13.9	13.9	14.1		13.5	14.3
	H7a–H7s	12.7		13.2				13.2	13.9			13.6			
3_J	H1–H6a	2.0	2.2	2.2	2.2	2.2	2.2	2.2							
	H1–H6s								4.1	4.0	4.0	4.1	4.0	4.0	4.0
	H1–H7a	2.0						2.7							
	H1–H7s	3.4						3.4							
	H3n–H4	3.3	2.7	2.6	2.7	2.7	2.7	3.0	2.9	2.9	2.9	2.9		3.3	2.9
	H3x–H4	2.2	2.2	2.6	2.4	2.4	2.4	2.3	2.2	2.0	2.2	2.2	2.2	2.2	2.2
	H4–H5a	3.8		3.4		3.7	3.7	3.7	3.0	2.9	2.9	3.1	2.9	2.9	
	H4–H5s	2.6	2.6	2.7	2.4		2.6	2.5	2.8	2.9					2.6
	H5a–H6a	9.8	9.5	9.8	9.5	9.5	9.5	9.8							
	H5a–H6s								3.0	2.9	2.9	3.1	2.9	2.9	2.9
	H5s–H6a	4.9	4.8	4.4	4.4	4.8	4.8	4.6							
	H5s–H6s								9.5	9.5	9.5	9.2		9.2	9.5
4_J	H3x–H5a	2.2	2.2	2.6	2.4	2.4		2.3	2.2	2.0	2.2	2.1	2.2	2.2	2.2
	H6s–H7s								1.5		1.3	1.5		1.5	1.5

frequency of H-6 shows a simplification of the signals centered at 2.80, 1.58, 1.82 and 1.91 ppm, that correspond to H-1, H-5s and H-5a and H-7s, respectively. The simplification of the signals of H-1 (J = 4.1 Hz), H-5s (J = 9.5 Hz) and H-5a (J = 3.0 Hz) is due to the loss of the corresponding vicinal couplings, while the modification of the signal of H-7s shows the loss of a W long-range coupling (1.5 Hz). This last coupling is the key to distinguish the *syn* from the *anti* esters.

In conclusion, the complete and unambiguous assignment of the individual protons for the isoquinuclidine system of *syn*- and *anti*-6-arylcarbonyloxy-2-methyl-2-azabicyclo[2.2.2]octanes **3a–g** and **4a–g** has been carried out. The x-ray analysis of **4b·HCl** confirms the structure and configuration of these compounds deduced by NMR studies. Molecular modeling (MM) calculations were performed for **4b·HCl.** Selected torsion angles for the AM1 optimized conformation are compared with the corresponding angles from x-ray analysis in Table 5.

From the ^{1}H and ^{13}C NMR data (Tables 2–4) for compounds **3a–g** and **4a–g** it can be deduced that all compounds of the same family show the same orientation of the arylcarbonyloxy group. Also, coplanarity between carbonyl and aryl group in all compounds can be assumed. This coplanarity is also observed in the x-ray and AM1 results. The main difference between the x-ray and MM data consists in the values of dihedral angles implicated in the rotation around C-2—O-1 bond; this

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

Atom	3a	3b	3c	3d	3e	3f	3g	4a	4b	4c	4d	4e	4f	4g
C-1	54.94	54.96	55.56	55.41	54.88	55.29	55.00	53.13	53.20	55.54	55.39	52.98	53.23	53.18
C-3	56.92	56.98	56.99	57.04	57.06	56.65	56.87	55.95	56.12	56.09	56.03	55.80	55.97	55.97
C-4	26.30	26.48	26.35	26.39	26.44	25.67	26.37	26.25	26.35	26.40	26.28	26.05	26.27	26.30
C-5	32.73	32.92	33.27	33.27	33.15	32.59	32.88	33.24	33.36	33.42	33.36	33.07	33.36	33.41
C-6	75.80	75.46	75.20	75.13	74.79	73.72	75.59	71.17	71.03	70.27	70.13	69.52	70.73	71.32
C-7	20.10	20.25	21.51	21.34	21.03	20.25	19.94	17.65	17.77	17.71	17.65	17.53	17.56	17.65
C-8	23.76	23.92	23.48	23.60	23.70	22.90	23.84	24.50	24.50	24.58	24.52	24.21	24.55	24.55
N-CH_3	43.25	43.25	43.76	43.71	45.56	43.32	43.13	42.40	42.47	42.43	42.42	42.13	42.40	42.42
CH_3			54.64	54.73	21.13					53.33	53.24	20.83		
C=O	164.40	165.92	166.36	166.51	166.99	165.05	166.21	163.71	165.34	165.82	165.93	166.04	164.73	165.63
C-1′	133.31	131.17	132.44	131.88	130.40	125.95	135.50	133.43	131.39	132.65	131.92	130.18	126.46	135.23
C-2′	128.15	133.43	107.43	114.30	127.41	150.99	122.14	127.87	133.60	107.33	114.17	126.80	150.82	121.95
C-3′	135.09	130.77	160.53	159.44	137.78		149.70	135.23	130.59	160.72	159.50	137.58		149.73
C-4′	132.63	132.12	105.43	119.15	134.38	153.39		132.66	132.34	105.33	119.08	134.09	153.34	
C-4′a							149.00							149.14
C-5′	135.09	126.43	160.53	129.26	137.78	123.23	129.91	135.23	126.54	160.72	129.34	137.58	123.26	129.64
C-6′	128.15	130.97	107.43	122.17	127.41	137.37	129.55	127.87	131.05	107.33	121.82	126.80	126.46	130.03
C-7′							127.92							128.07
C-8′							125.61							125.52
C-8′a							125.10							125.13

could be explained as follows: in the crystal structure, the packing forces are determinant in the conformation of the benzoyloxy group, but in the MM results, a promediated distance between the carbonyl oxygen atom and H-111 and H-2 (see Fig. 1 for numbering) is preferred.

EXPERIMENTAL

General. Melting points are uncorrected. The mass spectra were obtained with a Hewlett-Packard Model 5988 spectrometer (EI, 70 eV). The IR spectra were measured as KBr pellets on a Perkin-Elmer Model 883 spectrophotometer. Results obtained in the elemental analysis (C, H, N) of compounds were within $\pm 0.4\%$ of theoretical values. 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 13C spectra were obtained on a Varian UNITY-300 spectrometer operating at 75.437 MHz. DEPT experiments were performed with standard pulse sequences. The ^{1}H spectra and double resonance experiments (homonuclear spin decoupling) were registered on a Varian UNITY-500 Plus spectrometer operating at 499.81 MHz. The COSY and HETCOR spectra were obtained on a Varian UNITY-500 Plus spectrometer.

Molecular modeling was carried out with Quanta/CHARMm[19] software running on a Silicon Graphics workstation. The starting molecular structure of **4b·HCl** was obtained from the x-ray crystallographic study. The structure was optimized by semiempirical molecular orbital calculations using the AM1[20] Hamiltonian as implemented in MOPAC 7.[21]

Synthesis of syn- and anti-2-methyl-2-azabicyclo-[2.2.2]octan-6-ols 1 and 2. To a stirred suspension of 1.28 g (34 mmol) of lithium aluminum hydride in dry THF (20 ml), under argon at 0 °C, was added dropwise a solution of 6.68 g (34 mmol) of 2-carbethoxy-2-azabicyclo[2.2.2]octan-6-one[10] in 10 ml of dry THF. The mixture was stirred under reflux for 5 h, then cooled to near 0 °C and quenched by successive addition of (1.3 ml) of water and 1.3 ml of 15% aqueous sodium hydroxide, and stirring was continued at room temperature for 30 min. Filtration and concentration under reduced pressure yielded a mixture of alcohols **1** and **2** (4.42 g, 93% combined yield). ^{1}H NMR indicated a 40:60 ratio of **1:2.** IR (NaCl, film), 3356 cm^{-1}; MS, *m/z* 141 (M^+, 14%), 97 (29), 96 (57), 94 (38), 82 (100), 70 (40), 68 (42), 57 (66), 56 (25), 55 (49), 54 (28), 53 (26). **1:** ^{1}H NMR (δ), 1.29 (1H, m, H-7a), 1.39 (1H, m, H5s), 1.50 (2H, m, H-8), 1.63 (1H, m, H-4), 1.95 (1H, m, H-5a), 1.99 (1H, m, H-7s), 2.14 (1H, dt, J = 9.6, 2.1 Hz, H-3x), 2.31 (3H, s, Me), 2.39 (1H, m, H-1), 3.06 (1H, ddd, J = 9.6, 3.8 Hz, 2.7, H-3n), 3.67 (1H, m, H-6a); ^{13}C NMR (δ), 17.80 (C-7), 24.74 (C-8), 26.53 (C-4), 36.79 (C-5), 42.67 (Me), 56.94 (C-3), 57.67 (C-1), 68.69 (C-6). **2:** ^{1}H NMR (δ), 1.31 (1H, m, H-5a), 1.50 (2H, m, H-8), 1.67 (1H, m, H-4), 1.75 (1H, m, H-7s), 1.80 (1H, m, H-7a), 2.04 (1H, m, H5s), 2.37 (3H, s, Me), 2.43 (1H, m, H-1), 2.44 (1H, dt, J = 9.6 Hz, 2.1, H-3x), 2.65 (1H, dt, J = 9.6, 2.7 Hz, H-3n), 4.10 (1H, m, H-6a); ^{13}C NMR (δ), 16.22 (C-7), 24.74 (C-8), 26.53 (C-4), 36.01 (C-5), 42.55 (Me), 55.99 (C-3), 56.35 (C-1), 66.62 (C-6).

Synthesis of syn- and anti-6-arylcarbonyloxy-2-methyl-2-azabicyclo[2.2.2]octanes/General procedure. A solution of *n*-BuLi (1.6 M solution in hexane, 0.88 ml,

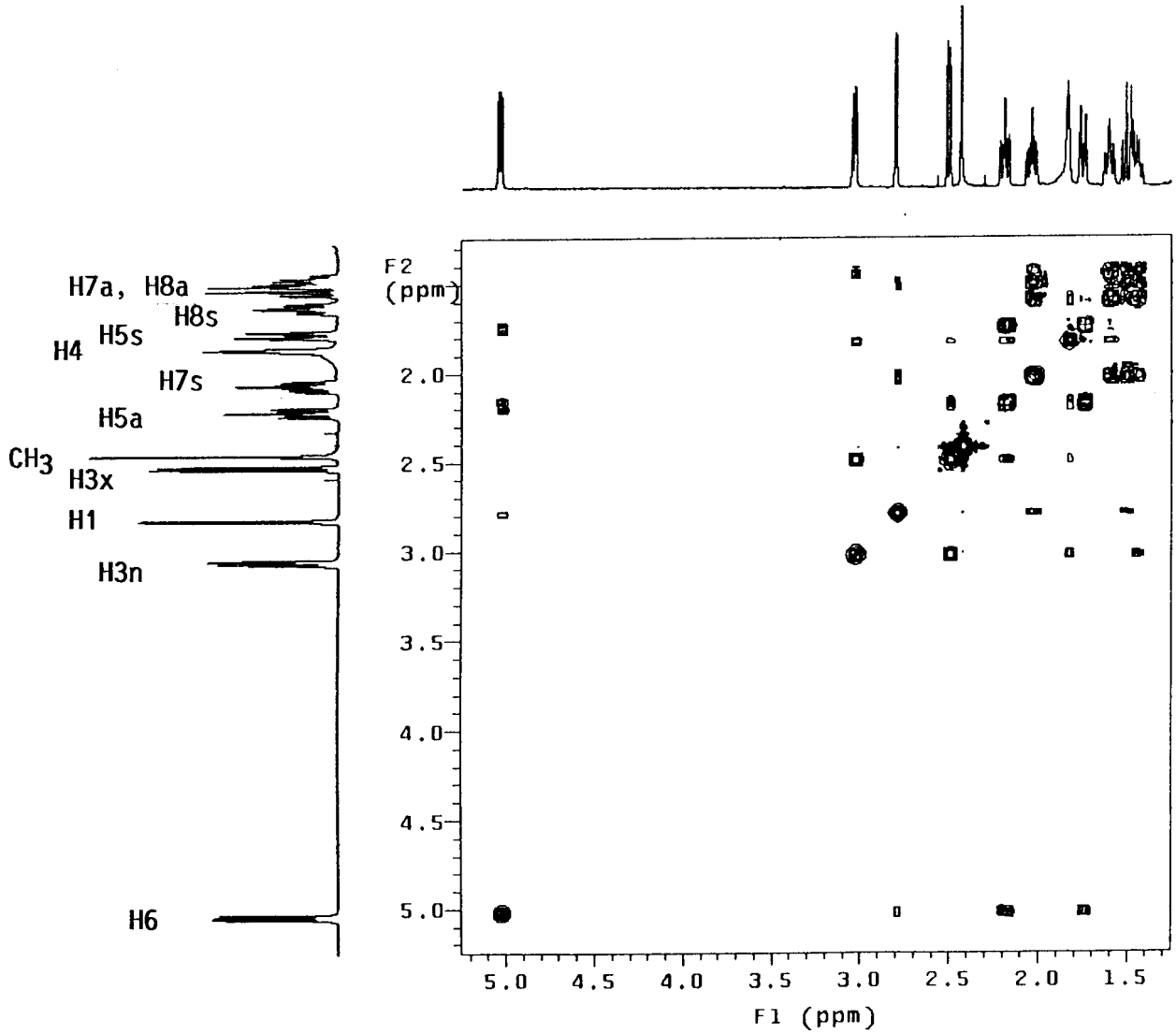

Figure 2. ^{1}H–^{1}H COSY spectrum of **3a** (aliphatic region)

1.42 mmol) was added dropwise to a solution of the epimeric mixture of alcohols **1** and **2** (200 mg, 1.42 mmol) in dry THF (5 ml) at 0 °C under argon. The mixture was stirred at the same temperature for 30 min. To the reaction mixture was added dropwise a solution containing the appropriate imidazolide prepared by the following method: *N,N′*-carbonyldiimidazole (CDI) (229 mg, 1.42 mmol) was added to a solution of the corresponding carboxylic acid (1.42 mmol) in dry THF (5 ml); the mixture was stirred at room temperature under argon for 2 h. The whole was stirred at room temperature under argon for 48 h. Then 100 ml of methylene chloride were added, and the mixture was washed successively with a saturated aqueous solution of $NaHCO_3$ (25 ml) and brine (3×25 ml), dried over $MgSO_4$, filtered and the filtrate concentrated under reduced pressure to give a mixture of the corresponding epimeric esters **3** and **4.** The resulting residue was then chromatographed on silica gel with the appropriate solvent system to separate the epimeric mixture of the desired esters **3a–g** and **4a–g.** After this separation, each epimer was converted into its hydrochloride salt and crystallized.

syn- and anti-6-(3,5-dichlorobenzoyloxy)-2-methyl-2-azabicyclo[2.2.2]octanes (3a, 4a). Colorless oil; yield 54%. The crude mixture of epimers was chromatographed by eluting with hexane–acetone–triethylamine (9.3:0.2:0.5), affording first the *syn* epimer **3a,** MS, *m/z* 315 (M^+, 5%), 173 (11), 147 (13), 145 (20), 140 (100), 124 (16), 110 (11), 109 (17), 97 (30), 96 (42), 94 (19); converted into its hydrochloride and crystallized from acetone, m.p. 232–233 °C; IR (KBr), 1728 cm^{-1}; and second the *anti* epimer **4a,** MS, *m/z* 315 (M^+, 6%), 173 (13), 147 (16), 145 (26), 140 (100), 124 (22), 110 (11), 108 (26), 98 (24), 96 (36), 94 (18), 82 (32); converted into its hydrochloride and crystallized from acetone, m.p. 223–224 °C (decomp.); IR (KBr), 1727 cm^{-1}.

syn- and anti-6-(2-chlorobenzoyloxy)-2-methyl-2-azabicyclo[2.2.2]octanes (3b, 4b). Colorless oil; yield 48%.

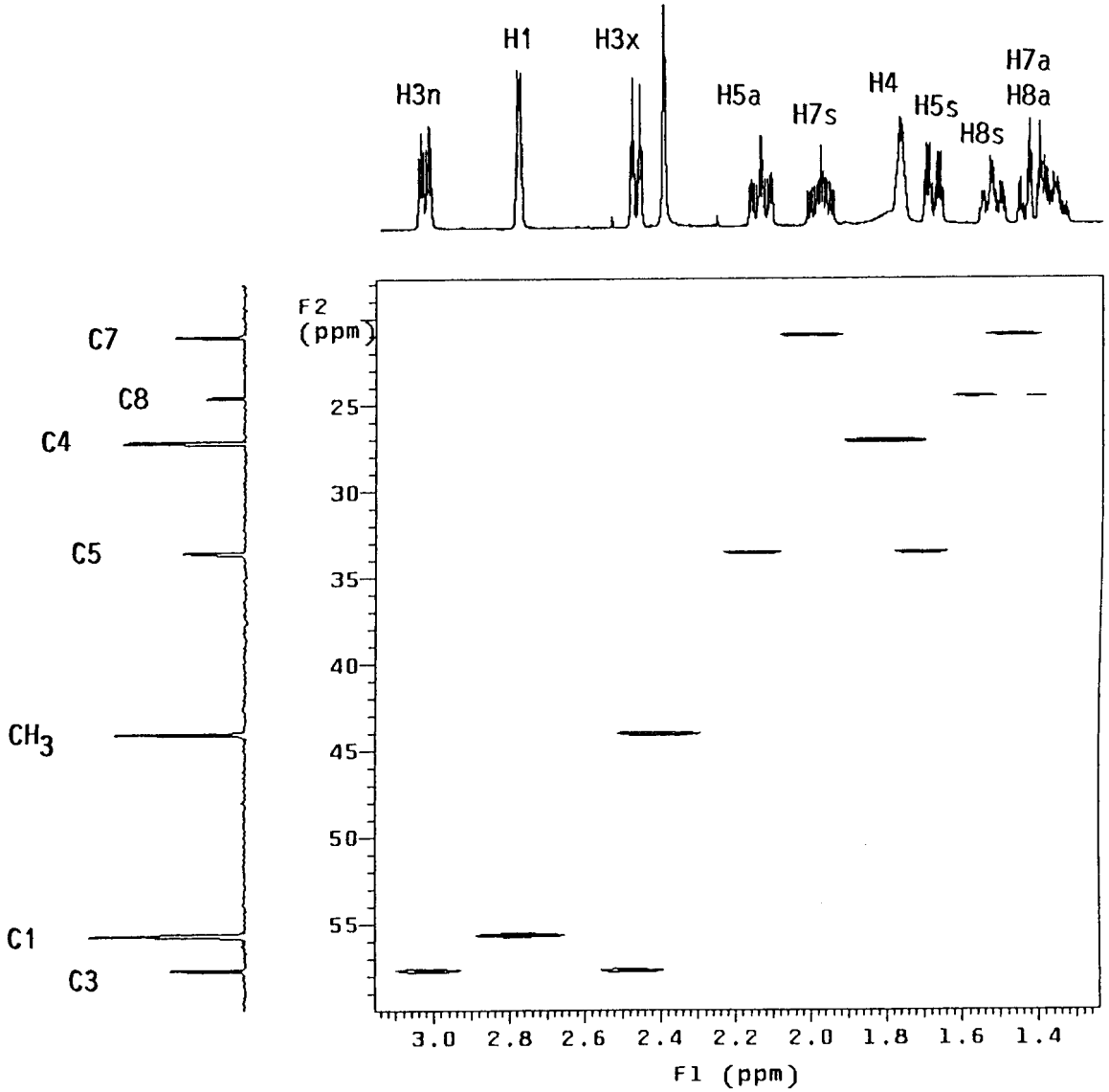

Figure 3. Expansion of ^{1}H–^{13}C HETCOR spectrum of **3a**

The crude mixture of epimers was chromatographed by eluting with hexane–acetone–triethylamine (9.6:0.2:0.2), affording first the *syn* epimer **3b,** MS, *m/z* 280 (M^+, 2%), 141 (24), 140 (82), 139 (53), 113 (23), 111 (72), 96 (31), 94 (27), 82 (100), 75 (59), 70 (20); converted into its hydrochloride and crystallized from acetone, m.p. 191–192 °C; IR (KBr), 1724 cm^{-1}; and second the *anti* epimer **4b,** MS, *m/z* 280 (M^+, 2%), 140 (100), 139 (24), 101 (29), 97 (21), 96 (30), 82 (25), 59 (87), 58 (37); converted into its hydrochloride and crystallized from acetone, m.p. 211–212 °C (decomp.); IR (KBr), 1725 cm^{-1}.

syn- and anti-6-(3,5-dimethoxybenzoyloxy)-2-methyl-2-azabicyclo[2.2.2]octanes (3c, 4c). Colorless oil; yield 56%. The crude mixture of epimers was chromatographed by eluting with hexane–acetone–triethylamine (7:2:1), affording first the *syn* epimer **3c,** MS, *m/z* 305 (M^+, 27%), 165 (57), 140 (100), 137 (29), 124 (19), 122 (30), 97 (28), 96 (39), 94 (25), 82 (29), 70 (17); converted into its hydrochloride and crystallized from ethanol–diethyl ether, m.p. 161–63 °C; IR (KBr), 1708 cm^{-1}; and second the *anti* epimer **4c,** MS, *m/z* 305 (M^+, 29%), 165 (50), 140 (100), 137 (31), 124 (18), 122 (30), 97 (37), 94 (21), 82 (20), 70 (19); converted into its hydrochloride and crystallized from acetone–diethyl ether, m.p. 214–16 °C; IR (KBr), 1720 cm^{-1}.

syn- and anti-6-(3-methoxybenzoyloxy)-2-methyl-2-azabicyclo[2.2.2]octanes (3d, 4d). Colorless oil; yield 51%. The crude mixture of epimers was chromatographed by eluting with diethyl ether–triethylamine (9.9:0.1), affording first the *syn* epimer **3d,** MS, *m/z* 275 (M^+, 20%), 140 (100), 124 (27), 97 (28), 96 (38), 94 (23), 82 (29), 77 (25), 70 (20); converted into its hydrochloride and crystallized from hexane–ethyl acetate, m.p. 104–10 °C (decomp.); IR (film), 1714 cm^{-1}; and second the

Table 5. Selected torsion angles (°) for **4b·HCl**

Dihedral angle	X-ray	MM	Dihedral angle	X-ray	MM
C1—C2—O1—C8	−125.5	−79.9	C3—C2—O1—C8	117.7	162.4
C2—O1—C8—O2	3.8	8.6	C2—O1—C8—C9	179.1	−172.4
O1—C8—C9—C14	7.1	−0.3	O2—C8—C9—C10	2.6	−2.1
C1—N1—C5—C4	−20.0	−11.9	C1—C2—C3—C4	−10.3	−7.3
C4—C6—C7—C1	−15.3	−10.1	C2—C3—C4—C5	64.5	62.8
C5—N1—C1—C7	−46.4	−51.5	C5—N1—C1—C2	73.8	67.8
C2—C3—C4—C6	−54.0	−56.1	C3—C4—C5—N1	−46.7	−52.7
N1—C1—C2—C3	−54.8	−56.9	N1—C1—C7—C6	66.9	65.2
N1—C1—C2—O1	−172.4	−173.5	C7—C1—C2—O1	−53.0	−53.3
C15—N1—C5—C4	−147.1	−137.0	C15—N1—C1—C2	−160.3	−167.1

anti epimer **4d,** MS, *m/z* 275 (M^+, 17%), 140 (100), 124 (23), 97 (31), 96 (45), 94 (24), 82 (44), 77 (32), 70 (22); converted into its hydrochloride and crystallized from hexane–ethyl acetate, m.p. 132–135 °C; IR (KBr), 1720 cm^{-1}.

syn- and anti-6-(3,5-dimethylbenzoyloxy)-2-methyl-2-azabicyclo[2.2.2]octanes (3e, 4e). Colorless oil; yield 43%. The crude mixture of epimers was chromatographed by eluting with hexane–acetone–triethylamine (9:0.5:0.5), affording first the *syn* epimer **3e,** MS, *m/z* 273 (M^+, 18%), 140 (100), 97 (28), 96 (39), 94 (26), 82 (27), 79 (25), 77 (24), 70 (24); converted into its hydrochloride and crystallized from hexane–acetone, m.p. 176–180 °C; IR (KBr), 1720 cm^{-1}; and second the *anti* epimer **4e,** MS, *m/z* 273 (M^+, 29%), 140 (100), 105 (25), 97 (32), 96 (41), 94 (25), 82 (37), 79 (34), 77 (31), 70 (25); converted into its hydrochloride and crystallized from hexane–acetone, m.p. 206–209 °C; IR (KBr), 1720 cm^{-1}.

syn- and anti-6-(3-piyridincarbonyloxy)-2-methyl-2-azabicyclo[2.2.2]octanes (3f, 4f). Colorless oil; yield 47%. The crude mixture of epimers was chromatographed by eluting with ethyl acetate–ethanol–triethylamine (9.6:0.2:0.2), affording first the *anti* epimer **4f,** MS, *m/z* 246 (M^+, 18%), 140 (100), 124 (29), 97 (28), 96 (49), 94 (25), 82 (82), 78 (48), 70 (24); converted into its hydrochloride and crystallized from acetone–propan-2-ol, m.p. 176–177 °C; IR (KBr), 1710 cm^{-1}; and second the *syn* epimer **3f,** MS, *m/z* 246 (M^+, 18%), 140 (100), 124 (21), 97 (29), 96 (43), 94 (23), 82 (42), 78 (44), 70 (27); converted into its hydrochloride and crystallized from acetone–propan-2-ol, m.p. 181–186 °C; IR (KBr), 1730 cm^{-1}.

syn- and anti-6-(4-quinolincarbonyloxy)-2-methyl-2-azabicyclo[2.2.2]octanes (3g, 4g). Colorless oil; yield 60%. The crude mixture of epimers was chromatographed by eluting with ethyl acetate–acetone–triethylamine (8.5:1:0.5), affording first the *anti* epimer **4g,** MS, *m/z* 296 (M^+, 19%), 141 (9), 140 (100), 128 (18), 125 (7), 101 (12), 97 (10), 96 (15), 82 (8), 70 (24); converted into its hydrochloride and crystallized from acetone–ethanol, m.p. 140–143 °C (decomp.); IR (KBr), 1720 cm^{-1}; and second the *syn* epimer **3g,** MS, *m/z* 296 (M^+, 10%), 140 (100), 128 (67), 101 (55), 96 (32), 94 (24), 82 (70), 75 (33), 70 (24); converted into its hydrochloride and crystallized from acetone–ethanol, m.p. 171–173 °C; IR (KBr), 1719 cm^{-1}.

Crystal data for 4b·HCl. A plate, colorless crystal was used to collect the experimental data on a four-circle Philips PW1100 automatic diffractometer with Cu Kα (λ = 1.5418 Å) radiation and a graphite oriented monochromator. Formula, $C_{15}H_{18}NO_2Cl{\cdot}HCl$; M_r, 316.219; crystal size, 0.40 × 0.27 × 0.10 mm. Lattice parameters were refined using 82 reflections, $12 < 2\theta < 88°$. The crystal is orthorhombic, space group *Pbca*, with a = 24.418(2), b = 13.283(1), c = 9.661(1) Å, Z = 8; 2668 reflections were measured in the range $2 < \theta < 65°$; two standard reflections, measured every 90 min, showed no intensity variation; 2055 were considered observed with the $I > 2\sigma(I)$ criterion. Lorentz and polarization corrections were applied. All calculations were performed on a VAX 6410 computer. The structure was solved by direct methods using SIR92[22] and Fourier synthesis; subsequents calculations used XRAY80[23] with full-matrix least-squares refinement on F magnitudes. All the non-H atoms were refined anisotropically. All H atoms, except H-32, H-153 and those of the phenyl ring, were located from a difference synthesis and refined isotropically. After several cycles of refinement, H-11, H-12 and H-13 and the thermal parameter of C-12 were maintained fixed. An empirical weighting scheme was applied as to give no trends in $< w\Delta^2F > vs < |F_o| >$ and $< \sin\theta/\lambda >$, PESOS;[24] ratio of maximum shift/σ = 0.039; 245 parameters refined. Maximum and minimum peak heights in the difference Fourier map were 0.72 and −0.84 e $Å^{-3}$, respectively; S = 2.767. Final R factors were R = 0.087, R_w = 0.107. All geometrical calculations were performed by using PARST.[25] Atomic scattering factors were taken from the *International Tables for X-Ray Crystallography.*[26]

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