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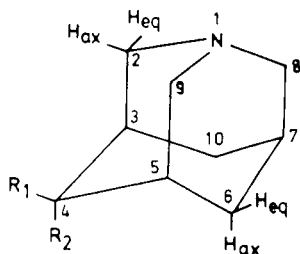
4- α -(or β)-*p*-Chlorobenzoyloxy-1-azaadamantane hydrochloride have been synthesized and studied by ^1H and ^{13}C nmr spectroscopy, and the crystal structure of the α -epimer has been determined by X-ray diffraction. Each ring of the adamantane cage system is a nearly perfect chair, the substituted cyclohexane and piperidine rings, in endo and exo position respectively, having the biggest deviation. From the ^1H and ^{13}C nmr data, several stereoelectronic effects have been deduced.

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Introduction.

In a previous paper [1] we reported the synthesis, ^1H and ^{13}C nmr study of 1-azatricyclo [3.3.1.1³⁻⁷]decane-4- α -(β)-ol **1**, **2** (Scheme I). In anticipation of a subsequent structure-activity relationship study, we report here the structural analysis by several methods of 4- α -(β)-*p*-chlorobenzoyloxy-1-azaadamantane hydrochloride **3**, **4** which are potentially interesting as anticholinergic compounds.

Scheme I



Compound	R ₁	R ₂
1	H	OH
2	OH	H
3	H	OCO-
4	OCO-	H

Results and Discussion.

Description of the Structure of Compound 3.

The important crystallographic data and the structure determination conditions are given in Table 1. Table 2 lists the atomic parameters and Tables 3 and 4 show bond lengths, bond and torsion angles respectively. Several significant torsion angles in which hydrogen atoms are in-

Table 1

Experimental Data and Structure Refinement Procedures

Crystal data

Formula	C16 H18 N O2 CL.HCL
Crystal Habit	White plates
Symmetry	Monoclinic, P2
Unit cell determination:	Least-squares fit from 50 reflexions ($\theta < 45^\circ$)
Unit cell dimensions	11.438(1), 7.052(1), 10.675(1) 90.0, 114.153(3), 90.0
Packing: V(Å ³), Z	785.62(6), 2
Dc(g cm ⁻³), M, F(000)	1.39, 328.24, 344
μ (cm ⁻¹)	38.107

Experimental data

Technique	Four circle diffractometer: Philips PW1100. Bisecting geometry Graphite oriented monochromator: CuK α w/2 θ scans Detector apertures 1 x 1, up θ max 65°
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Number of reflexions:

Measured	1426
Observed	1291 (2 σ (I) criterion)
Range of hkl	-12 12, 0 8, 0 11, (sin θ / λ) max 0.60

Max-min transmission factors: 1.576, 0.575

Solution and refinement

Solution	Direct methods
Refinement	L.S. on Fobs with 1 block
H atoms	Difference synthesis
w-scheme	Empirical as to give no trends in $\langle w \Delta^2 F \rangle$ vs. $\langle F_{obs} \rangle$ and $\langle \sin \theta / \lambda \rangle$ [3]
Final R and Rw	0.046, 0.057
Computer and programs	Vax 11/750, Multan 80 [2], X-ray System [5], Parst [6]
Scattering factors	Int. Tables for X-Ray Crystallography [4]
Anomalous dispersion	Int. Tables for X-Ray Crystallography

Table 2

Coordinates and Equivalent Thermal Parameters as $U_{eq} = (\frac{1}{3}) \cdot \sum(U_{ij} \cdot a_i \cdot a_j \cdot \cos(\alpha_{i,j})) \cdot 10^{*4}$

ATOM	X/A	Y/B	Z/C	U _{eq}
CL1	0.4171(1)	0.1381(23)	1.1095(1)	594(5)
CL2	-0.0811(1)	0.1372(24)	-0.2869(1)	707(6)
O1	0.1393(3)	0.1270(26)	0.3895(3)	555(14)
O2	-0.0687(3)	0.1494(29)	0.3480(3)	636(16)
N	0.3719(3)	0.1386(30)	0.8109(4)	487(14)
C1	0.4933(4)	0.1346(32)	0.7866(5)	561(19)
C2	0.4553(4)	0.1352(28)	0.6328(5)	545(19)
C3	0.3772(13)	-0.0383(27)	0.5697(12)	624(46)
C4	0.2564(10)	-0.0374(26)	0.5963(11)	520(41)
C5	0.1768(4)	0.1525(0)	0.5375(5)	509(20)
C6	0.2576(11)	0.3152(26)	0.5978(14)	530(50)
C7	0.3784(11)	0.3165(27)	0.5664(14)	532(47)
C8	0.2929(12)	-0.0362(28)	0.7536(11)	535(39)
C9	0.2976(11)	0.3139(28)	0.7494(14)	542(44)
C20	0.0145(4)	0.1399(27)	0.3068(4)	453(16)
C21	-0.0066(3)	0.1416(32)	0.1601(4)	414(15)
C22	-0.1317(4)	0.1460(32)	0.0604(5)	545(18)
C23	-0.1542(5)	0.1289(30)	-0.0762(5)	618(22)
C24	-0.0525(4)	0.1444(31)	-0.1137(4)	485(17)
C25	0.0713(4)	0.1405(33)	-0.0171(5)	533(18)
C26	0.0942(4)	0.1429(30)	0.1194(5)	519(18)

Coordinates and Thermal Parameters as $EXP(-8 \cdot \pi^2 \cdot U \cdot (\sin(\theta)/\lambda)^2) \cdot 10^{*3}$

ATOM	X/A	Y/B	Z/C	U
H1	0.398(6)	0.102(13)	0.919(6)	48(0)
H11	0.553(0)	0.024(0)	0.838(0)	57(0)
H12	0.520(7)	0.249(12)	0.820(8)	57(0)
H21	0.542(6)	0.135(16)	0.627(6)	51(0)
H31	0.436(8)	-0.142(16)	0.625(10)	57(0)
H32	0.355(11)	-0.029(16)	0.468(12)	57(0)
H41	0.224(14)	-0.144(21)	0.561(16)	53(0)
H51	0.098(6)	0.172(13)	0.556(6)	50(0)
H61	0.190(15)	0.430(21)	0.564(16)	53(0)
H71	0.349(10)	0.323(16)	0.454(10)	58(0)
H72	0.416(8)	0.450(16)	0.597(10)	58(0)
H81	0.211(9)	-0.047(14)	0.777(9)	62(0)
H82	0.346(10)	-0.138(19)	0.797(13)	62(0)
H91	0.361(8)	0.422(17)	0.804(11)	47(0)
H92	0.224(9)	0.297(13)	0.769(7)	47(0)
H221	-0.205(6)	0.104(13)	0.089(6)	52(0)
H231	-0.248(6)	0.133(13)	-0.160(7)	62(0)
H251	0.132(6)	0.102(12)	-0.056(6)	53(0)
H261	0.178(6)	0.125(13)	0.191(6)	52(0)

Table 3

Bond Distances (Å)

CL2-C24	1.742(5)	O1-C5	1.469(6)
O1-C20	1.340(5)	O2-C20	1.202(7)
N-C1	1.514(7)	N-C8	1.502(25)
N-C9	1.492(25)	C1-C2	1.516(8)
C2-C3	1.502(24)	C2-C7	1.549(23)
C3-C4	1.521(21)	C4-C5	1.596(16)
C4-C8	1.556(17)	C5-C6	1.448(16)
C6-C7	1.550(21)	C6-C9	1.490(20)
C20-C21	1.483(6)	C21-C22	1.391(5)
C21-C26	1.388(7)	C22-C23	1.378(8)
C23-C24	1.380(9)	C24-C25	1.369(5)
C25-C26	1.371(7)		

Table 4

Bond Angles (°)

C5-O1-C20	117.6(3)	C8-N-C9	111.2(8)
C1-N-C9	109.7(8)	C1-N-C8	110.8(7)
N-C1-C2	107.9(4)	C1-C2-C7	110.8(8)
C1-C2-C3	109.8(8)	C3-C2-C7	110.2(8)
C2-C3-C4	109.3(12)	C3-C4-C8	109.8(10)
C3-C4-C5	110.2(10)	C5-C4-C8	106.1(11)
O1-C5-C4	100.9(6)	C4-C5-C6	109.4(7)
O1-C5-C6	115.3(6)	C5-C6-C9	109.5(12)
C5-C6-C7	111.9(12)	C7-C6-C9	109.3(11)
C2-C7-C6	106.5(12)	N-C8-C4	107.2(12)
N-C9-C6	110.5(13)	O1-C20-O2	123.5(4)
O2-C20-C21	125.1(4)	O1-C20-C21	111.4(4)
C20-C21-C26	122.2(4)	C20-C21-C22	118.7(4)
C22-C21-C26	119.1(4)	C21-C22-C23	119.7(5)
C22-C23-C24	119.0(5)	CL2-C24-C23	119.4(4)
C23-C24-C25	120.9(4)	CL2-C24-C25	119.1(4)
C24-C25-C26	119.3(5)	C21-C26-C25	120.7(4)

Some Torsion Angles (°)

C5-O1-C20-21	171(1)	C5-O1-C20-O2	-9(2)
C20-O1-C5-C4	126(1)	C20-O1-C5-C6	-116(1)
C3-C4-C5-O1	66(1)	C8-C4-C5-O1	-175(1)
O1-C5-C6-C7	-54(1)	O1-C5-C6-C9	-175(1)
O2-C20-C21-C22	-3(2)	O1-C20-C21-C22	177(1)
O2-C20-C21-C26	176(1)	O1-C20-C21-C26	-4(2)
H1-N-C9-H91	65(8)	H1-N-C9-H92	-55(7)
H1-N-C8-H81	63(7)	H1-N-C8-H82	-54(9)
H1-N-Cl-H11	39(4)	H1-N-Cl-H12	-82(7)
H12-C1-C2-H21	76(7)	H11-C1-C2-H21	-56(5)
H21-C2-C7-H71	67(8)	H21-C2-C7-H72	-56(9)
H21-C2-C3-H31	57(8)	H21-C2-C3-H31	-67(9)
H32-C3-C4-H41	68(13)	H31-C3-C4-H41	-66(13)
H41-C4-C8-H81	-65(13)	H41-C4-C8-H52	54(14)
H41-C4-C5-H51	69(13)	H51-C5-C6-H61	-45(10)
H61-C6-C9-H91	-76(11)	H61-C6-C9-H92	58(11)
H61-C6-C7-H71	-59(12)	H61-C6-C7-H72	49(12)
H221-C22-C23-H231	27(7)	H251-C25-C26-H261	10(8)

volved are also given. Figure 1 displays the structural formula with the numbering used in the crystallographic study.

The adamantane cage system has mean bonds lengths of 1.52(2) Å and internal bonds angles of 109.4(9)°, in good agreement with those in similar molecules [7,8]. It is only slightly distorted from ideal, the overall mean torsion angles being 61(1)°. Therefore, each ring is a nearly perfect chair, but the C5 atom is more deviated from the plane through C4, C6, C8, C9, (0.743(5) Å), than from the plane through C3, C4, C6, C7, (0.688(5) Å), as a consequence of the *p*-chlorobenzoyloxy position on the C5 atom, the substituted cyclohexane and piperidine rings, in *endo* and *exo* positions respectively, having the largest deviation.

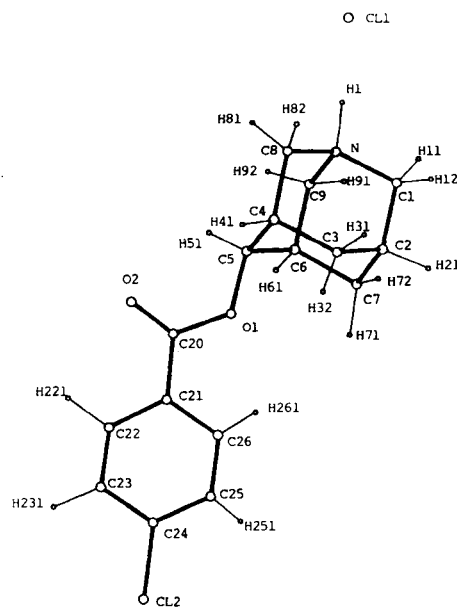


Figure 1

There is a pseudo mirror plane through the adamantane skeleton defined by N, Cl, C2, C5 and Cl1 atoms; the *p*-chlorobenzoic group lies nearly in this plane, with atoms being deviated from 0.10(2) Å (C26) to 0.30(2) Å (C23). The planarity data are given in Table 5.

The chloride ion is situated at 3.013(4) Å from the N atom, with a H1...Cl1 distance of 1.97 Å and a N-H1...Cl1 angle of 157°, the N-H distance being 1.10(7) Å.

The ester group presents a mean torsion angle of 3(2)° in the C20-C21 bond, as expected in view of the *p*-substitution. Consequently the C20-C21 linkage exhibits partial double bond character, as does the C20-O1 bond.

The crystal packing diagram displayed in Figure 2 shows that molecules are situated along the C axis, there-

Table 5

Deviations (Å) of Atoms from the Adamantane Mirror Plane Through N C1 C2 C5 CL1

N*	0.013(21)	C3	1.260(20)	O1	0.191(20)	C21	0.148(23)
C5*	-0.005(0)	C7	-1.243(20)	C20	0.151(20)	C22	0.168(22)
C2*	0.003(20)	C4	1.301(20)	O2	0.118(20)	C23	0.299(21)
C1*	-0.008(20)	C6	-1.184(20)	CL2	0.211(17)	C24	0.148(22)
CL1*	-0.003(20)	C8	1.277(20)			C25	0.125(23)
		C9	-1.192(20)			C26	0.098(21)

Table 6

¹H NMR Chemical Shifts (δ, ppm) and Multiplicities (J, MHz) for Compounds **3** and **4**, in Deuteriochloroform at 360 MHz

Compound	3	4
H2 (9) ax	3.60 (m)	3.78 (d) ² J 12.6
H2 (9) eq	3.60 (m)	3.40 (d)
H3 (5)	2.53 (s)	2.48 (s)
H4	5.33 (s)	5.33 (s)
H6 (10) ax	2.38 (d) ² J 13.4	2.15 (m)
H6 (10) eq	1.94 (d)	2.15 (m)
H7	2.30 (s)	2.30 (s)
H8	3.51 (s)	3.51 (s)
H2' (6')	8.00 (d) ² J 8.1	7.96 (d) ² J 8.6
H3' (5')	7.47 (d)	7.47 (d)

[a] The abbreviations: d, doublet; m, multiplet; s, singlet.

fore perpendicularly to the helicoidal axis. They are linked only by Van der Waals forces.

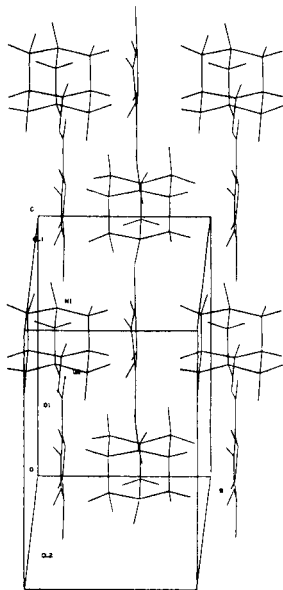


Figure 2

NMR Spectra.

The ¹H and ¹³C nmr data of **3,4** are shown in Table 6 and Table 7. Assignments of proton and carbon resonances were made from literature data of compounds **1** and **2** [1] and several monoaza bicyclic derivatives [9]. In the case of ¹³C nmr assignments, substituent steric and electronic effects on ¹³C chemical shifts [10,11] and signal multiplicity obtained from off-resonance decoupled spectra were taken into consideration.

Table 7

Carbon-13 Chemical Shifts (δ, ppm) for Compounds **3** and **4**, in Dimethylsulfoxide-d₆ at 90 MHz

Compound	3	4
C2 (9)	53.52	49.98
C3 (5)	29.19	29.46
C4	72.10	72.10
C6 (10)	27.38	31.27
C7	24.31	24.04
C8	54.68	54.54
C1'	128.55	128.55
C2' (6')	131.28	131.50
C3' (5')	129.09	128.87
C4'	138.64	138.64
C=O (O)	163.97	163.97

From the ¹H and ¹³C nmr data (Tables 6 and 7) of compounds **3** and **4**, the following conclusions can be obtained:

a) The $\Delta\delta$ C2(9)**3** - C2(9)**4** = 3.54 ppm and $\Delta\delta$ C6(10)**4** - C6(10)**3** = 3.89 ppm are attributed as in the case of the alcohols **1** and **2** to the anisotropic and steric syn-diaxial effect exerted by the oxygen (C-O-C) atom on H2(9) and H6(10) respectively. These differences are less than that found in compounds **1** and **2** ($\Delta\delta$ C2(9)**1** - C2(9)**2** = 5.58, $\Delta\delta$ C6(10)**2** - C6(10)**1** = 5.27 ppm) [1], this fact is explained in terms of the decreased electron density at the oxygen (C-O-C) atom as it was pointed out in the X-ray study. The $\Delta\delta$ H2(9)_{ax}**4** - H2(9)_{ax}**3** \cong 0.18 ppm and $\Delta\delta$ H6(10)_{ax}**3** - H6(10)_{ax}**4** \cong 0.22 ppm are explained in the same line.

These differences, as expected, are less than that found in compounds **1** and **2**.

b) δ H2(9)_{ax}**3** > δ H2(9)_{eq}**4** and δ H6(10)_{eq}**4** > δ H6(10)_{ax}**3**, this is attributed, as in the case of compounds **1** and **2**, to the **W** arrangement of the equatorial proton with respect to the electron-withdrawing group.

The conjugation between the carbonyl and the phenyl group in **3** and **4** is confirmed by the δ C values.

Hence, good agreement of the preferred conformation of the acyloxy group of **3** in solution and in the solid state has been observed.

With the objective to establish a possible structure-activity relationship, the N-O (alc.) distance (3.8 Å in tropine [12]) and the distance from the nitrogen to the center of the phenyl ring (6.7 Å in pirenzepine [13]) have been calculated from the X-ray coordinates of **3**, 4.2(1) Å and 7.8(2) Å respectively, with the assumption that the preferred conformation for the linkage of **3** with the muscarinic receptor would be the same, as that found from X-ray data.

EXPERIMENTAL

Infrared spectra were determined using a Perkin-Elmer 883 spectrophotometer. The ¹H and ¹³C nmr spectra were recorded on a Bruker WM 360 spectrometer at 360 and 90 MHz, respectively. The elemental analysis were made in a Perkin-Elmer Elemental Analyzer model 240B.

4- α -(β)-*p*-Chlorobenzoyloxy-1-azaadamantane Hydrochlorides **3,4**.

A solution of 4-chlorobenzoyl chloride (164 mg, 0.94 mmole) and the epimeric mixture of **1** and **2** (143.8 mg, 0.94 mmole) [1] in dry pyridine was stirred at reflux for 16 hours. The reaction mixture was concentrated *in vacuo* to dryness. The solid obtained was washed with ethyl acetate and crystallized from 2-propanol to yield 244.2 mg (79%); ir (potassium

bromide): ν CO 1721 cm⁻¹.

Anal. Calcd. for C₁₆H₁₉Cl₂NO₂: C, 58.55; H, 5.83; N, 4.27. Found: C, 58.30; H, 5.67; N, 4.40.

After fractional crystallizations from ethanol compounds **3** and **4** were separated; pmr: (see Table 6); cmr: (see Table 7).

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