

E. Gálvez\*, M. S. Arias, B. Rico and I. Ardid

Departamento de Química Orgánica, Universidad de Alcalá de Henares,  
Madrid, Spain

F. Florencio and J. Sanz

Instituto Rocasolano, Departamento de Rayos-X, C. S. I. C., Serrano 119,  
28006-Madrid, Spain

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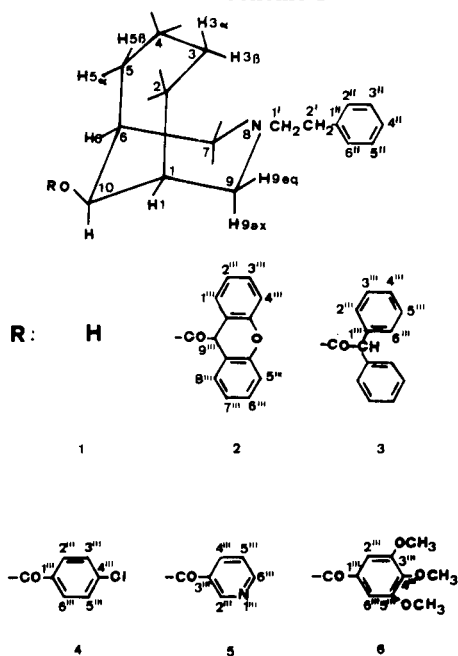
A series of 10 $\alpha$ -acyloxy-*N*-phenethyl-8-azabicyclo[4.3.1]decane derivatives have been synthesized and studied by  $^1\text{H}$  and  $^{13}\text{C}$  nmr spectroscopy, and the crystal structure of *N*-phenethyl-10 $\alpha$ -(*xanten-9'''*-carbonyloxy)bicyclo[4.3.1]decane **2** has been determined by X-ray diffraction. The compounds studied display in deuteriochloroform the same preferred conformation adopted by the piperidine ring as a distorted chair conformation flattened at N-8 with both the phenethyl and acyloxy groups in the equatorial position with respect to the piperidine ring. These results are in close agreement with that found for compound **2** in the crystalline state.

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### Introduction.

In previous papers [1,2] we reported the synthesis, the  $^1\text{H}$  and  $^{13}\text{C}$  nmr studies and the crystal structure of several esters derived from the tropane system as potential anticholinergic compounds. In the same line, we report in this paper the synthesis and structural analysis with the aid of  $^1\text{H}$  and  $^{13}\text{C}$  nmr spectroscopy of a series of 10 $\alpha$ -acyloxy-*N*-phenethyl-8-azabicyclo[4.3.1]decane derivatives **2-6** (Scheme I) with the objective to determine their preferred conformation both in solution and in the solid state, the crystal structure of compound **2** has also been determined. In order to establish several structural and electronic relationships, the  $^1\text{H}$  and  $^{13}\text{C}$  nmr parameters of the corresponding alcohol [3] have also been included.

### Scheme I



### Results and Discussion.

#### Description of the Structure of Compound **2**.

The main crystallographic data and the structure determination conditions are given in Table 1, Table 2 shows the atomic parameters and Table 3 and 4 show bond lengths, bond and torsion angles respectively. Several

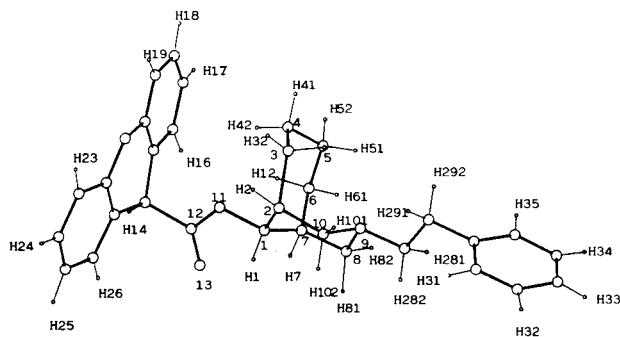


Figure 1. Plutoview of the molecule [9].

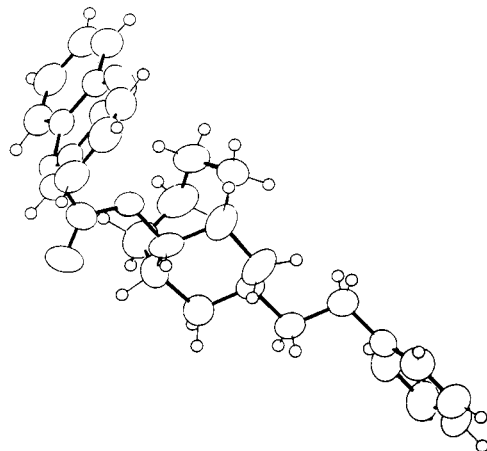


Figure 2. Ortep view of the molecule showing the thermal ellipsoids.

Table 1

## Experimental Data and Structure Refinement Procedures

<b>Crystal data</b>	
Formula	C <sub>31</sub> H <sub>33</sub> O <sub>3</sub> N
Symmetry	Triclinic, P1
Unit cell determination:	Least-squares fit from 80 reflexions ( $\theta < 45^\circ$ )
Unit cell dimensions	10.811(1), 14.230(1), 8.455(1) 96.266(4), 95.802(3), 77.943(4)
Packing: V (Å <sup>3</sup> ), Z	1260.4(1), 2
Dc(g.cm <sup>-3</sup> ), M, F(000)	1.2321, 467.61, 500
$\mu$ (cm <sup>-1</sup> )	5.832
<b>Experimental data</b>	
Technique	Four circle diffractometer: Philips PW1100, Bisecting geometry, Graphite oriented monochromator: CuK $\alpha$ ~ w/2 scans Detector apertures 1 x 1, up $\theta$ max 65°
Number of reflexions:	
Measured	4283
Observed	3428 (2 $\sigma$ (I) criterion)
Range of hkl	-13 13, -18 18, -10 10, (sin $\theta/\lambda$ ) max. 0.7
<b>Solution and refinement</b>	
Solution	Direct methods and Fourier synthesis
Refinement	L. S. on Fobs with 1 blocks
Parameters:	
Number of variables	409
Degrees of freedom	
Ratio of freedom	
H atoms	Difference Fourier synthesis
Final shift/error	0.02
w-scheme	Empirical as to give no trends in <w $\Delta$ 2F> vs. <Fo> and <sin $\theta/\lambda$ >
Final $\Delta$ F peaks	0.44 e/Å <sup>-3</sup>
Final R and Rw	0.068, 0.079
Computer and programs	Vax 11/750, Multan80 (4), X ray76 (5), Pesos (6), Parst (7)
Scattering factors	International Tables for X-Ray Crystallograph (8)
Anomalous dispersion	International Tables for X-Ray Crystallograph (8)

significant torsion angles in which hydrogen atoms are involved are also given. Figures 1 and 2 show a view of the molecule and the numbering used in the crystallographic study and Figure 3 shows a view of the packing of the molecules in the unit cell.

The piperidine ring adopts a distorted chair conformation in good agreement with the results found in a previous compound [10]. The deviations of C(1) and N(9) from the mean plane through the remaining atoms of the ring are 0.632 (4) and 0.709 (3) Å. The asymmetry parameters [11] are:  $q_2 = 0.077$  (4),  $q_3 = 0.588$  (4),  $QT = 0.593$  (4),  $\phi_2 = 132$  (3) and  $\theta_2 = 4.5$  (4).

In contrast with the previously studied bicyclo[4.3.1]-decane derivative [10], the seven-membered ring presents

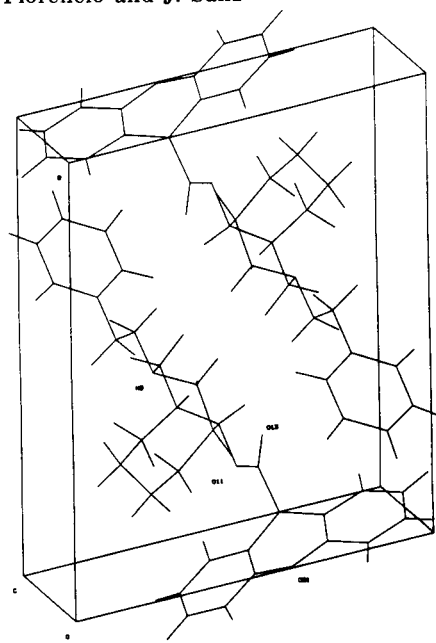


Figure 3. Packing the molecules in the unit cell.

Table 2

Coordinates and Thermal Parameters as  
 $U_{eq} = (1/3) \cdot \sum |U_{ij} \cdot a_i \cdot a_j \cdot \cos(\alpha_i, \alpha_j)| \cdot 10^{**4}$

Atom	x/a	y/b	z/c	U <sub>eq</sub>
N9	0.2537(2)	0.4747(2)	1.1848(3)	526(9)
O11	0.4328(2)	0.2711(1)	0.8382(3)	600(8)
O13	0.4775(3)	0.3507(2)	0.6433(4)	867(12)
O21	0.5813(2)	0.0249(2)	0.8277(3)	724(10)
C1	0.3997(3)	0.3591(2)	0.9456(5)	612(12)
C2	0.4081(4)	0.3278(3)	1.1135(5)	792(14)
C3	0.3140(5)	0.2535(3)	1.1401(5)	842(18)
C4	0.2170(4)	0.2346(3)	1.0059(6)	797(17)
C5	0.1252(5)	0.3227(3)	0.9536(7)	953(20)
C6	0.1704(5)	0.3786(4)	0.8443(6)	917(19)
C7	0.2769(4)	0.4229(3)	0.8976(4)	727(14)
C8	0.2493(4)	0.5070(3)	1.0269(4)	735(14)
C10	0.3805(4)	0.4209(3)	1.2249(6)	801(15)
C12	0.4718(3)	0.2768(2)	0.6957(4)	565(12)
C14	0.5174(3)	0.1773(2)	0.6128(4)	526(11)
C15	0.4303(3)	0.1095(2)	0.6337(3)	518(10)
C16	0.3105(4)	0.1183(3)	0.5516(4)	669(14)
C17	0.2290(4)	0.0601(3)	0.5792(5)	753(16)
C18	0.2655(4)	-0.0072(3)	0.6884(5)	751(16)
C19	0.3829(4)	-0.0177(3)	0.7686(5)	705(15)
C20	0.4641(3)	0.0402(2)	0.7412(4)	560(11)
C22	0.6749(3)	0.0670(2)	0.7846(4)	583(11)
C23	0.7961(4)	0.0327(3)	0.8510(5)	716(14)
C24	0.8956(4)	0.0698(3)	0.8127(5)	762(15)
C25	0.8748(4)	0.1414(3)	0.7082(5)	740(15)
C26	0.7540(3)	0.1745(2)	0.6444(4)	615(13)
C27	0.6511(3)	0.1389(2)	0.6810(4)	514(10)
C28	0.2203(4)	0.5582(2)	1.3004(4)	613(12)
C29	0.1908(6)	0.5322(3)	1.4586(5)	917(20)
C30	0.1575(4)	0.6193(2)	1.5757(4)	624(13)
C31	0.2459(4)	0.6501(3)	1.6866(5)	739(15)
C32	0.2141(4)	0.7303(3)	1.7917(5)	799(17)
C33	0.0936(4)	0.7818(3)	1.7876(5)	784(16)
C34	0.0056(4)	0.7549(4)	1.6773(5)	839(17)
C35	0.0355(4)	0.6737(3)	1.5721(5)	777(16)

Table 2 (continued)

Atomic Parameters for C31 H33 O3 N  
Coordinates and Thermal Parameters as  
 $\exp[-8.\pi^{**}2.U.(sin(theta)/lambda)**2.10^{**}3$

Atom	x/a	y/b	z/c	U
H1	0.475(5)	0.385(3)	0.952(5)	66(0)
H2	0.465(0)	0.258(0)	1.142(0)	84(0)
H31	0.262(5)	0.291(4)	1.243(7)	88(0)
H32	0.351(5)	0.198(5)	1.150(7)	88(0)
H41	0.166(5)	0.192(4)	1.040(6)	82(0)
H42	0.255(5)	0.200(4)	0.910(7)	82(0)
H51	0.096(6)	0.367(5)	1.061(8)	102(0)
H52	0.049(6)	0.295(4)	0.885(7)	102(0)
H61	0.087(6)	0.436(4)	0.806(7)	99(0)
H62	0.187(6)	0.329(4)	0.734(7)	99(0)
H7	0.297(5)	0.455(4)	0.799(6)	77(0)
H81	0.317(5)	0.561(4)	1.028(6)	78(0)
H82	0.164(5)	0.544(4)	0.999(6)	78(0)
H101	0.398(5)	0.413(4)	1.339(7)	87(0)
H102	0.437(5)	0.467(4)	1.209(7)	87(0)
H14	0.516(0)	0.181(0)	0.493(0)	65(0)
H16	0.283(5)	0.172(4)	0.480(6)	72(0)
H17	0.152(5)	0.065(4)	0.516(7)	81(0)
H18	0.209(5)	-0.049(4)	0.699(6)	79(0)
H19	0.413(5)	-0.060(4)	0.841(6)	75(0)
H23	0.804(5)	-0.017(4)	0.920(6)	76(0)
H24	0.972(5)	0.048(4)	0.856(6)	79(0)
H25	0.942(5)	0.175(4)	0.684(6)	78(0)
H26	0.733(4)	0.222(4)	0.568(6)	67(0)
H281	0.146(5)	0.603(3)	1.256(5)	66(0)
H282	0.287(5)	0.595(3)	1.322(5)	66(0)
H291	0.248(6)	0.484(5)	1.491(7)	95(0)
H292	0.118(6)	0.494(5)	1.436(7)	95(0)
H311	0.333(5)	0.616(4)	1.699(6)	78(0)
H321	0.274(5)	0.755(4)	1.880(7)	83(0)
H33	0.079(5)	0.837(4)	1.864(7)	84(0)
H34	-0.072(6)	0.792(4)	1.685(7)	89(0)
H35	-0.024(5)	0.654(4)	1.515(7)	82(0)

Table 3

Bond Distances (Å)

N9-C8	1.451(5)	C15-C16	1.395(5)
N9-C10	1.450(5)	C15-C20	1.382(4)
N9-C28	1.462(4)	C16-C17	1.381(7)
O11-C1	1.466(4)	C17-C18	1.374(6)
O11-C12	1.332(4)	C18-C19	1.364(6)
O13-C12	1.200(5)	C19-C20	1.375(6)
O21-C20	1.385(4)	C22-C23	1.384(5)
O21-C22	1.374(5)	C22-C27	1.387(5)
C1-C2	1.522(6)	C23-C24	1.374(7)
C1-C7	1.490(5)	C24-C25	1.389(6)
C2-C3	1.658(7)	C25-C26	1.369(5)
C2-C10	1.533(6)	C26-C27	1.388(5)
C3-C4	1.508(7)	C28-C29	1.507(6)
C4-C5	1.506(6)	C29-C30	1.505(5)
C5-C6	1.463(8)	C30-C31	1.374(6)
C6-C7	1.436(7)	C30-C35	1.382(5)
C7-C8	1.532(5)	C31-C32	1.374(6)
C12-C14	1.518(4)	C32-C33	1.354(6)
C14-C15	1.515(5)	C33-C34	1.347(6)
C14-C27	1.513(4)	C34-C35	1.382(6)

Table 4

Bond Angles (°)

C10-N9-C28	111.0(3)	C16-C15-C20	117.6(3)
C8-N9-C28	109.5(2)	C15-C16-C17	120.6(3)
C8-N9-C10	108.7(3)	C16-C17-C18	120.0(4)
C1-O11-C12	119.6(2)	C17-C18-C19	120.3(4)
C20-O21-C22	118.6(3)	C18-C19-C20	119.7(4)
O11-C1-C7	114.4(3)	C15-C20-C19	121.8(3)
O11-C1-C2	106.9(3)	O21-C20-C19	116.0(3)
C2-C1-C7	114.1(3)	O21-C20-C15	122.3(3)
C1-C2-C10	106.1(3)	O21-C22-C27	122.9(3)
C1-C2-C3	115.6(3)	O21-C22-C23	115.7(3)
C3-C2-C10	111.2(3)	C23-C22-C27	121.4(3)
C2-C3-C4	117.9(4)	C22-C23-C24	119.5(4)
C3-C4-C5	115.2(4)	C23-C24-C25	120.3(4)
C4-C5-C6	116.4(4)	C24-C25-C26	119.2(4)
C5-C6-C7	118.8(4)	C25-C26-C27	122.1(3)
C1-C7-C6	118.0(3)	C22-C27-C26	117.4(3)
C6-C7-C8	114.2(4)	C14-C27-C26	121.9(3)
C1-C7-C8	108.7(3)	C14-C27-C22	120.7(3)
N9-C8-C7	112.5(3)	N9-C28-C29	113.5(3)
N9-C10-C2	110.2(3)	C28-C29-C30	112.4(3)
O11-C12-O13	124.6(3)	C29-C30-C35	120.5(4)
O13-C12-C14	124.0(3)	C29-C30-C31	122.4(4)
O11-C12-C14	111.2(3)	C31-C30-C35	117.1(3)
C12-C14-C27	108.2(2)	C30-C31-C32	121.6(4)
C12-C14-C15	111.2(3)	C31-C32-C33	120.3(4)
C15-C14-C27	110.9(2)	C32-C33-C34	119.4(4)
C14-C15-C20	121.1(3)	C33-C34-C35	121.0(4)
C14-C15-C16	121.2(3)	C30-C35-C34	120.5(4)

Table 4 (continued)

Torsion Angles (°)

C10-N9-C28-C29	-74.20(0)
C8-N9-C28-C29	165.81(0)
C28-N9-C10-C2	173.71(0)
C8-N9-C10-C2	-65.81(0)
C28-N9-C8-C7	-177.16(0)
C10-N9-C8-C7	61.41(0)
C1-O11-C12-C14	172.55(0)
C1-O11-C12-O13	-3.18(0)
C12-O11-C1-C7	73.57(0)
C12-O11-C1-C2	-159.11(0)
O11-C1-C7-C8	175.34(0)
O11-C1-C7-C6	43.19(0)
O11-C1-C2-C3	-59.27(0)
O11-C1-C2-C10	176.91(0)
C2-C1-C7-C8	51.78(0)
C2-C1-C7-C6	-80.37(0)
C7-C1-C2-C10	-55.59(0)
C7-C1-C2-C3	68.23(0)
C1-C2-C10-N9	61.45(0)
C3-C2-C10-N9	-65.07(0)
C1-C2-C3-C4	-8.30(1)
C10-C2-C3-C4	112.81(0)
C2-C3-C4-C5	-57.75(1)
C3-C4-C5-C6	81.38(1)
C4-C5-C6-C7	-62.74(0)
C5-C6-C7-C1	60.29(1)
C5-C6-C7-C8	-69.33(1)
C1-C7-C8-N9	-53.62(0)
C6-C7-C8-N9	80.48(0)
O13-C12-C14-C15	-142.27(0)
O11-C12-C14-C15	41.98(0)

O13-C12-C14-C27	95.7 (0)
O11-C12-C14-C27	-80.05(0)
N9-C28-C29-C30	179.60(0)
C28-C29-C30-C31	-94.89(0)
H1-C1-C7-H7	45.05(4)
H1-C1-C2-H2	-84.11(3)
H2-C2-C10-H101	-15.93(4)
H2-C2-C10-H102	99.98(4)
H42-C4-C5-H51	-170.80(5)
H41-C4-C5-H51	77.38(5)
H42-C4-C5-H52	69.18(5)
H41-C4-C5-H52	-42.64(5)
H7-C7-C8-H81	-39.33(4)
H7-C7-C8-H82	76.05(4)

a distorted chair conformation, according to the torsion angles of the preferred forms given by Hendrickson [12] and consequently, a mirror symmetry is dominant ( $\Delta C6 = 0.041$  (2),  $\Delta C3 = 0.0088$  (1) [13]. There are four axial differentiated substituent positions in a cycloheptane ring with a chair conformation [12] and that named as 3a, the one found here, is the least energetically preferred because of the steric hindrance produced by the short 3a, 3a and 1a, 3a distances (in this case O11....H42 = 2.51 (6) and O11....H62 = 2.70 (6) Å respectively).

The two substituents are in equatorial positions with respect to the piperidine ring.

The three condensed rings are not in a plane, the angle

between both phenyl groups being 13.9 (1)°. The central ring shows a flattened boat conformation, O21 and C14 being at 0.132 (3) and 0.212 (3) Å respectively from the mean plane defined by the other four atoms. The assymetry parameters [11] are: Q2 = 0.197 (3), Q3 = -0.032 (3), QT = 0.200 (3),  $\phi = -176.9$  (9) and  $\theta = 99.2$  (8).

The carbonyloxy group presents a well defined double bond at C12-O13 (C12-O13 = 1.200 (5) Å) although some  $\pi$ -electron contribution (conjugation) can be observed along the C12-O11 bond (O11-C12 = 1.332 (4) Å) C12 atom is the most deviated from the plane defined by O11, C12, C13 and C14 atoms (0.023 (3) Å). As it could be expected, the C1-O11 and C14-C12 distances correspond to single C-O and C-C bonds, 1.465 (6) and 1.517 (7) Å respectively.

The molecules are held together by Van der Waals forces and there are no significative intermolecular distances.

#### NMR Spectra.

The  $^1\text{H}$  and  $^{13}\text{C}$  nmr data of **1-6** are summarized in Tables 5, 6 and 7; assignments of protons and carbon resonances were made from the literature data of compound **1** [3], and several monoaza and diazabicyclo derivatives [14-16]. In the case of the  $^{13}\text{C}$  nmr assignments,

Table 5

$^1\text{H-NMR}$  Chemical Shifts ( $\delta$ ) for Compounds **1-6** (Deuteriochloroform, 360 MHz)

(ppm) [a]	1	2	3	4	5	6
H-2 (5) $_{\alpha}$ (m)	1.49	1.16	1.23	1.64	1.65	1.57
H-2 (5) $_{\beta}$ (m)	1.49	1.58	1.37	1.64	1.65	1.57
H-3 (4) $_{\alpha}$ (m)	1.79	1.36	1.58	1.87	1.90	1.84
H-3 (4) $_{\beta}$ (m)	1.79	1.36	1.58	1.87	1.90	1.84
H-1 (6) (brs)	2.06	2.05	2.14	2.37	2.39	2.30
	(w $_{1/2}$ 9 Hz)	(w $_{1/2}$ 13 Hz)	(w $_{1/2}$ 13 Hz)	(w $_{1/2}$ 13 Hz)	(w $_{1/2}$ 13 Hz)	(w $_{1/2}$ 13 Hz)
H-7 (9) $_{ax}$ (dd)	2.01 [b]	2.07 [b]	2.10 [b]	2.27	2.29	2.22
H-7 (9) $_{eq}$ (dd) [c]	2.68	2.64	2.65	2.81	2.82	2.75
H-10 (t)	3.85	4.85	4.99	5.23	5.28	5.15
H-2' (m) [d]	2.42	2.41	2.40	2.53	2.54	2.47
H-1' (m) [d]	2.70	2.70	2.67	2.79	2.79	2.73
Ph (m)	7.16	7.19	7.18	7.28	7.25	7.18
H-1'''						
H-2'''				8.00 [e]	9.28 (s)	7.28 (s)
H-3'''		7.19 (m)	7.18 (m)	7.43 [e]		
H-4'''					8.32 (d)	
H-5'''				7.43 [e]	7.41 (dd)	
H-6'''				8.00 [e]	8.79 (d)	7.28 (s)
H-9'''		4.98 (s)				
-CH-			4.97 (s) [f]			
-OCH <sub>3</sub>						3.84 (s)

[a] Abbreviations: d, doublet; dd, doublet of doublets; m, multiplet; s, singlet, t, triplet. Values deduced from the first order analysis of the spectra, error  $\pm 0.05$  ppm. For multiplets the tabulated chemical shifts correspond to the centre of the signals. [b] This signal overlaps partially with the broad singlet corresponding to H-1 (6). [c] This signal appears as an apparent broadened doublet, except for 1, and overlaps with H-1 signal in all the cases. [d] H-1 and H-2 methylene protons of phenethyl group appear as a four spin A<sub>2</sub>B<sub>2</sub> system. [e] Aromatic protons of the *p*-chlorophenyl moiety appear as a four spin AA'XX' system. [f] Partially overlapped with the corresponding to H-10.

Table 6

<sup>1</sup>H-NMR Coupling Constants (J) for Compounds 1-6 (Deuteriochloroform, 360 MHz)

J (Hz) [a]	1	2	3	4	5	6
H7 (9) <sub>ax</sub> -H7 (9) <sub>eq</sub>	-10.6	-11.4	-11.4	-11.5	-11.5	-11.4
H7 (9) <sub>ax</sub> -H1 (6)	2.9	3.0	4.0	2.7	3.0	2.7
H7 (9) <sub>eq</sub> -H1 (6)	2.2	2	2	2	2	2
H10-H1 (6)	5.1	5.4	5.6	5.2	5.7	5.6
H1'-H2'	7.8	7.7	7.7	7.6	7.6	7.7
H2'''-H3'''				8.4		
H4'''-H5'''					7.8	
H5'''-H6'''					4.8	

[a] Values deduced from the first order analysis of the spectra; error  $\pm 0.5$  Hz, except for the cases where a limit value was estimated on the basis of the  $w_{1/2}$  of the respective signals.

Table 7

<sup>13</sup>C-NMR Chemical Shifts ( $\delta$ ) for Compounds 1-6 (Deuteriochloroform)

(ppm)	1	2	3	4	5	6
C-1 (6)	38.45	35.65	35.80	36.02	36.02	36.03
C-2 (5)	31.24	31.40	31.56	31.69	31.74	31.91
C-3 (4)	26.85	26.19	26.41	26.90	26.85	26.41
C-7 (9)	60.42	60.10	60.25	60.29	60.22	60.27
C-10	72.01	78.60	78.45	78.66	79.00	78.26
C-1'	59.98	59.82	59.86	59.92	59.87	59.83
C-2'	33.96	33.89	33.93	33.99	33.94	33.98
C=O				165.04	164.60	165.43
C-1''	140.77	140.63	138.70	140.71	140.65	140.70
C-2'' (6'') [a]	128.19	128.96	128.53	128.76	128.73	128.73
C-3'' (5'') [a]	128.66	128.81	128.25	128.76	128.31	128.30
C-4''	125.76	125.81	125.84	125.92	126.77	125.90
C-1'''		128.20	138.79	128.31		125.90
C-2'''		123.20	128.69	128.76	153.33	107.08
C-3'''		128.65	128.69	131.03	125.92	153.03
C-4'''		116.91	127.17	139.30	137.04	140.70
C-5'''		116.91	128.69	131.03	123.31	
C-6'''		128.65	128.69	128.76	151.04	107.08
C-7'''		123.20				
C-8'''		128.20				
C-9'''		46.23				
-CH-			57.74			
-OCH <sub>3</sub>						56.21 60.89

[a] Signal may be interchanged.

substituent steric and electronic effects on the <sup>13</sup>C chemical shifts [17,18] and signal multiplicity obtained from off resonance decoupled spectra were taken into consideration.

The <sup>1</sup>H and <sup>13</sup>C parameters corresponding to the piperidine ring of 1-6 are in good agreement with previously reported values for related bicyclic systems in which the piperidine ring has a distorted chair conformation flattened at N8 [3,14-16]. In all cases, the coupling constants have practically the same values and <sup>3</sup>JH7 (9)<sub>ax</sub>-H1 (5) is greater than <sup>3</sup>JH7 (9)<sub>eq</sub>-H1 (5) and consequently the dihedral angle H7 (9)<sub>eq</sub>-C-C-H1 (5) is greater than H7 (9)<sub>ax</sub>-C-C-H1 (5) ac-

ording 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 latter form should not only give a value of *ca.* 10 Hz for <sup>3</sup>JH7 (9) <sub>$\beta$</sub> -H1 (5) but also the signal corresponding to H1 (5) should appear as an apparent doublet, a common feature in previously reported systems that adopt the boat conformation [14]. The <sup>3</sup>JH1 (6)-H10 value of  $\approx 5$  Hz amounts for a dihedral angle  $\approx 50^\circ$  according to the Karplus relationship [19].

The chemical shift of C1' of the phenethyl group is in agreement with an equatorial disposition of the *N*-substituent [14].

In all the compounds studied, the  $\delta$  C values are similar to the corresponding  $\delta$  C values observed in the alcohol 1 (Table 7) except the  $\delta$  C10 values ( $\Delta\delta$  C10 (1)-C10 (2-6)  $\approx -6.5$  ppm) and  $\delta$  C1 (6) values ( $\Delta\delta$  C1 (6) (1)-C1 (6) (2-6)  $\approx 2.5$  ppm), these differences can be attributed to the increased electronic attracting effect due to the acyloxy group [17]. This argument can be applied to explain  $\Delta\delta$  H10 (1)-H10 (2-6)  $\approx -1$  ppm although a field effect of the carbonyl group on H10 cannot be discarded.

The  $\Delta\delta$  H1 (6) (4-6)-H1 (6) (2,3)  $\approx 0.3$  ppm,  $\Delta\delta$  H7 (9)<sub>ax</sub> (4-6)-H7 (9)<sub>ax</sub> (2,3)  $\approx 0.2$  ppm,  $\Delta\delta$  H7 (9)<sub>eq</sub> (4-6)-H7 (9)<sub>eq</sub> (2,3)  $\approx 0.2$  ppm and  $\Delta\delta$  H10 (4-6)-H10 (2,3)  $\approx 0.4$  ppm are attributed to the more electronic attracting effect exerted by the oxygen atom conjugated with the  $\pi$ -acyl system. The  $\Delta\delta$  H2 (5) <sub>$\beta$</sub>  (2)-H2 (5) <sub>$\alpha$</sub>  (2)  $\approx 0.40$  ppm can be attributed to the field effect exerted by the  $\pi$ -acyl system.

Antihistaminic and anticholinergic *in vitro* properties of compound 2 were evaluated on the isolated guinea pig ileum. Atropine and diphenhydramine were used as reference compounds. *In vitro* pharmacological testing demonstrated that compound 2 noncompetitively inhibited acetylcholine induced contraction of guinea pig ileum tissue. The N-O distance for the exo and endo-methyl conformations of tropine are  $\approx 3.8$  Å. The corresponding distance for 3-quinuclidinol was  $\approx 3.5$  Å [20]. These compounds fit the simple distance geometric pharmacophore, constraints established previously for the acetylcholine receptor [21]. The distance from the protonated nitrogen to the center of the nearest phenyl ring in the first M1 selective muscarinic receptor antagonist (pirenzepine) [22] amounts 6-7 Å in the energetically favoured conformation [23].

In the case of compound 2, the N-O (ether) distance deduced from X-Ray data, is 4.196 Å, and the distances between the nitrogen atom and the center of the xanthen phenyl rings are 7.038 and 7.794 Å. As it can be deduced from the nmr studies in compounds 2-6, the preferred conformation in solution can be similar to that found for 2 in the crystal state. In consequence the non-competitive action of compound 2 could be explained in terms of the

shape and size of the tetramethylene chain and the phenethyl group, that would hinder an adequate interaction with the anionic site of the receptor. Obviously, further pharmacological studies are necessary to establish the possible structure activity relationships.

## EXPERIMENTAL

All melting points were taken in open capillary tubes and are uncorrected. Infrared spectra were determined using a Perkin-Elmer 883 spectrophotometer. The  $^1\text{H}$  nmr spectra were recorded using a Bruker WM 360 spectrometer at 360 MHz. The  $^{13}\text{C}$  nmr spectra were determined at 20 MHz on a Bruker WP 80 spectrometer. Noise decoupled a single frequency off resonance decoupled spectra were obtained. The elemental analysis was made in a Perkin-Elmer Elemental Analyzer model 240B.

### Synthesis of the Esters 2-6. General Procedure.

A solution of DCC (*N,N*-Dicyclohexylcarbodiimide) (2.5 mmoles) and DMAP (4-(Dimethylamino)pyridine) (0.2 mmoles) in anhydrous methylene chloride (5 ml) was added dropwise to a stirred solution of 8-phenethyl-8-azabicyclo[4.3.1]decane-10 $\alpha$ -ol (2 mmoles) and the corresponding acid (2 mmoles) in anhydrous methylene chloride (10 ml). The mixture was stirred at room temperature for 24 hours. The mixture was filtered. The filtrate was evaporated *in vacuo*, ether was added, the mixture was filtered and the filtrate was evaporated.

10 $\alpha$ -(Xanthen-9''''-carbonyloxy)-*N*-phenethyl-8-azabicyclo[4.3.1]decane (2).

This compound was obtained in 67% yield, mp 113-115° (hexane); ir (potassium bromide):  $\nu$  CO 1730  $\text{cm}^{-1}$ ; pmr: (see Table 5); cmr: (see Table 7).

*Anal.* Calcd. for  $\text{C}_{31}\text{H}_{33}\text{NO}_3$ : C, 79.62; H, 7.11; N, 2.99. Found: C, 79.55; H, 7.17; N, 3.31.

10 $\alpha$ -(Diphenylacetoxy)-*N*-phenethyl-8-azabicyclo[4.3.1]decane (3).

This compound was purified on a silica gel column. Elution of the column with hexane-ethyl acetate (9:1 v/v) gave the desired ester as an oil in 70% yield; ir (film):  $\nu$  CO, 1740  $\text{cm}^{-1}$ ; pmr: (see Table 5); cmr: (see Table 7).

10 $\alpha$ -(4''''-Chlorobenzoyloxy)-*N*-phenethyl-8-azabicyclo[4.3.1]decane (4).

This compound was purified on a silica gel column. Elution of the column with hexane-ethyl acetate (9:1 v/v) gave a residue which was crystallized from hexane in 80% yield, mp 105-107°; ir (potassium bromide):  $\nu$  CO 1725  $\text{cm}^{-1}$ ; pmr (see Table 5); cmr: (see Table 7).

*Anal.* Calcd. for  $\text{C}_{24}\text{H}_{28}\text{ClNO}_2$ : C, 72.25; H, 7.07; N, 3.51. Found: C, 72.43; H, 7.34; N, 3.36.

10 $\alpha$ -(3''''-Pyridincarbonyloxy)-*N*-phenethyl-8-azabicyclo[4.3.1]decane (5).

This compound was obtained in 61% yield, mp 87-89° (hexane); ir (potassium bromide):  $\nu$  CO 1710  $\text{cm}^{-1}$ ; pmr: (see Table 5); cmr: (see Table 7).

*Anal.* Calcd. for  $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_2$ : C, 75.78; H, 7.74; N, 7.68. Found: C, 75.42; H, 8.11; N, 8.00.

10 $\alpha$ -(3''''',4''''',5'''''-Trimethoxybenzoyloxy)-*N*-phenethyl-8-azabicyclo[4.3.1]decane (6).

This compound was obtained in 62% yield, mp 136-138° (hexane); ir (potassium bromide):  $\nu$  CO 1720  $\text{cm}^{-1}$ ; pmr (see Table 5); cmr: (see Table 7).

*Anal.* Calcd. for  $\text{C}_{27}\text{H}_{35}\text{NO}_5$ : C, 71.48; H, 7.78; N, 3.09. Found: C, 71.41; H, 7.87; N, 3.18.

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