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Synthesis, structural, conformational and pharmacological study of esters derived from 3-methyl-2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9α-ol as potential analgesics

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ABSTRACT: A series of esters derived from 3-methyl-2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9α-ol (1) was synthesized and studied by ^{1}H and ^{13}C NMR spectroscopy, and the crystal structure of 3-methyl-2,4-diphenyl-9α-(3,5-dimethylbenzoyloxy)-3-azabicyclo[3.3.1]nonane (2) was determined by x-ray diffraction. The compounds studied display in $CDCl_3$ a preferred flattened chair–chair conformation. This bicycle conformation is similar to that found for 2 in the crystal state. Pharmacological assays on mice were performed to evaluate drug-induced behavioral alteration, peripheral or central acute toxicity and analgesic activity. © 1998 John Wiley & Sons, Ltd.

KEYWORDS: 3-methyl-2, 4-diphenyl-3-azabicyclo[3.3.1]nonan-9α-ol esters; analgesics; synthesis; structure; conformation; pharmacological assays

INTRODUCTION

As part of a continuing effort to develop novel analgesic agents analogous to 4-anilidopiperidine,[1] a series of azabicyclic esters were prepared and the analgesic activity of the new compounds was measured.

As the number of surgical outpatients is increasing, agents which can be used in short surgical procedures are in high demand. The 4-anilidopiperidine class of synthetic opioid analgesics is characterized by high potency and rapid onset of action. Fentanyl,[2] the prototype of the series, used concurrently with a skeletal muscle relaxant and an inhalation anaesthetic agent, is widely applied in ambulatory surgeries.

Our intention with the design and synthesis of new analgesic analogues is both to achieve a measurable analgesic activity and to gain a better understanding of the conformational enhancing factors on the opiate receptor affinity. We report here the synthesis and structural analysis, based on ^{1}H and ^{13}C NMR spectroscopy, of a series of esters derived from 3-methyl-2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9α-ol (**2**–**5**). In order to determine their preferred conformation both in solution and in the solid state, the crystal structure of **2** was determined. To complete our studies on these structures, pharmacological testing was also carried out.

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RESULTS AND DISCUSSION

Synthesis

Compounds **2**–**5** were prepared by the two general methods illustrated in Scheme 1. Reaction of 3-methyl-2,4-diphenyl-3-azabicylo[3.3.1]nonan-9α-ol (**1**)[3] with the corresponding acid in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) as catalyst led to the esters **2**, **4** and **5** (method A).[4] Compound **3** was prepared by reaction of **1** with the appropriate acyl chloride (method B).

X-ray diffraction

Compound **2** gave crystalline prisms belonging to the orthorhombic P_{bca} space group. The main crystallographic data and the structure determination procedures are given in Table 1.[5–11] Tables 2 and 3 give bond lengths and bond and torsion angles, respectively. Figure 1 shows a view of the molecule with the numbering used in the crystallographic study.[12]

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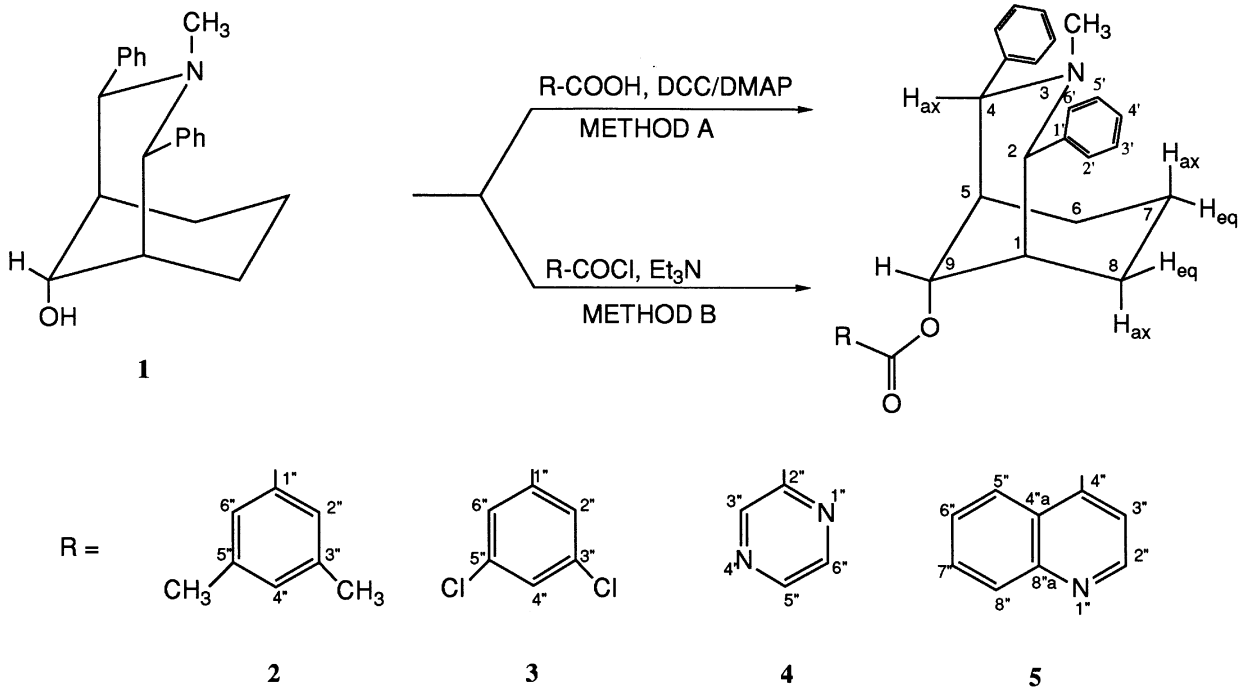

1 **2** **3** **4** **5**

Scheme 1.

Table 1. Experimental data and structure refinement procedures

Crystal data:	
Formula	$C_{30}H_{33}NO_2$
Symmetry	Orthorhombic, P_{bca}
Unit cell determination	Least-squares fit from 45 reflections ($\theta < 45°$)
Unit cell dimensions	24.084 (2), 8.941 (1), 22.868 (2) Å 90.0, 90.0, 90.0°
Packing	
V (Å)^3, Z	4924.6 (3), 8
D_o (g cm^{-3}), M, F(000)	1.1859, 439.596, 1888
μ(cm^{-1})	5.358
Experimental data:	
Technique	Philips PW 1100 four-circle diffractometer. Bisecting geometry. Graphite oriented monochromator: Cu Kα $w/2\theta$ scans, scan width 1.5° upto θ_{max} 65°
Number of reflections:	
Measured	4207
Observed	3125 [$3\sigma(I)$ criterion]
Range of *hkl*	0–29, 0–11, 0–27
Solution and refinement:	
Solution	Direct methods
Refinement	Least squares on F_{obs} with one block
H atoms	Difference synthesis
w Scheme	Empirical so as to give no trends in $<w\Delta f>$ vs $<F_{obs}>$ and $<\sin\theta/\lambda>$
Final ΔF peaks	0.2 *e*/ Å^3
Final R and Rw	0.066, 0.073
Computer and programs	Vax 6410, Multan 80,[5] Xtal,[6] Pesos,[7] Xray 80,[8], CSU,[9] Parst[10]
Scattering factors	*International Tables for X-Ray Crystallography*[11]
Anomalous dispersion.	*International Tables for X-Ray Crystallography*[11]

Table 2. Bond lengths (Å) with estimated standard deviations in parentheses

O10—C4	1.453(3)	C14—C15	1.379(6)
O10—C11	1.342(4)	C15—C16	1.395(6)
O12—C11	1.207(3)	C15—C19	1.509(7)
N1—C2	1.474(4)	C16—C17	1.384(6)
N1—C6	1.474(4)	C17—C18	1.388(6)
N1—C33	1.472(4)	C17—C20	1.503(6)
C2—C3	1.544(3)	C21—C22	1.386(5)
C2—C21	1.520(3)	C21—C26	1.384(3)
C3—C4	1.514(4)	C22—C23	1.380(6)
C3—C9	1.531(4)	C23—C24	1.375(6)
C4—C5	1.516(4)	C24—C25	1.380(6)
C5—C6	1.542(3)	C25—C26	1.382(5)
C5—C7	1.540(5)	C27—C28	1.381(5)
C6—C27	1.520(4)	C27—C32	1.393(5)
C7—C8	1.520(6)	C28—C29	1.399(6)
C8—C9	1.530(5)	C29—C30	1.364(7)
C11—C13	1.478(3)	C30—C31	1.369(6)
C13—C14	1.386(4)	C31—C32	1.387(5)
C13—C18	1.391(4)		

Table 3. Bond angles and torsion angles (°) with estimated standard deviations in parentheses

C4—O10—C11	118.5(2)	C14—C13—C18	119.8(3)
C2—N1—C6	114.8(2)	C13—C14—C15	120.8(3)
C2—N1—C33	108.6(2)	C14—C15—C16	118.5(4)
C6—N1—C33	108.9(2)	C14—C15—C19	120.1(4)
N1—C2—C3	114.0(2)	C16—C15—C19	121.4(4)
N1—C2—C21	111.0(2)	C15—C16—C17	122.0(4)
C3—C2—C21	109.6(2)	C16—C17—C18	118.4(4)
C2—C3—C4	107.8(20	C16—C17—C20	121.0(4)
C2—C3—C9	115.4(2)	C18—C17—C20	120.7(4)
C4—C3—C9	110.9(2)	C13—C18—C17	120.6(3)
O10—C4—C3	106.3(2)	C2—C21—C22	118.8(3)
O10—C4—C5	112.1(2)	C2—C21—C26	123.0(2)
C3—C4—C5	108.1(2)	C22—C21—C26	118.1(3)
C4—C5—C6	107.0(2)	C21—C22—C23	120.9(4)
C4—C5—C7	110.2(2)	C22—C23—C24	120.4(4)
C6—C5—C7	116.2(2)	C23—C24—C25	119.4(4)
N1—C6—C5	113.8(2)	C24—C25—C26	120.1(4)
N1—C6—C27	111.6(2)	C21—C26—C25	121.1(3)
C5—C6—C27	109.6(2)	C6—C27—C28	122.5(3)
C5—C7—C8	113.4(3)	C6—C27—C32	118.6(2)
C7—C8—C9	111.9(3)	C28—C27—C32	118.8(3)
C3—C9—C8	112.6(3)	C27—C28—C29	120.0(4)
O10—C11—O12	123.6(3)	C28—C29—C30	120.4(4)
O10—C11—C13	111.0(2)	C29—C30—C31	120.4(4)
O12—C11—C13	125.3(3)	C30—C31—C32	119.9(4)
C11—C13—C14	121.3(3)	C27—C32—C31	120.6(3)
C11—C13—C18	118.9(3)		

Some torsion angles:

O10—C11—C13—C14	11.1(4)
O12—C11—O10—C4	−5.4(4)
O12—C11—C13—C14	−170.6(3)
N1—C2—C21—C22	158.7(3)
N1—C6—C27—C32	−155.9(3)
C3—C4—O10—C11	175.2(2)
C4—O10—C11—C13	173.0(2)

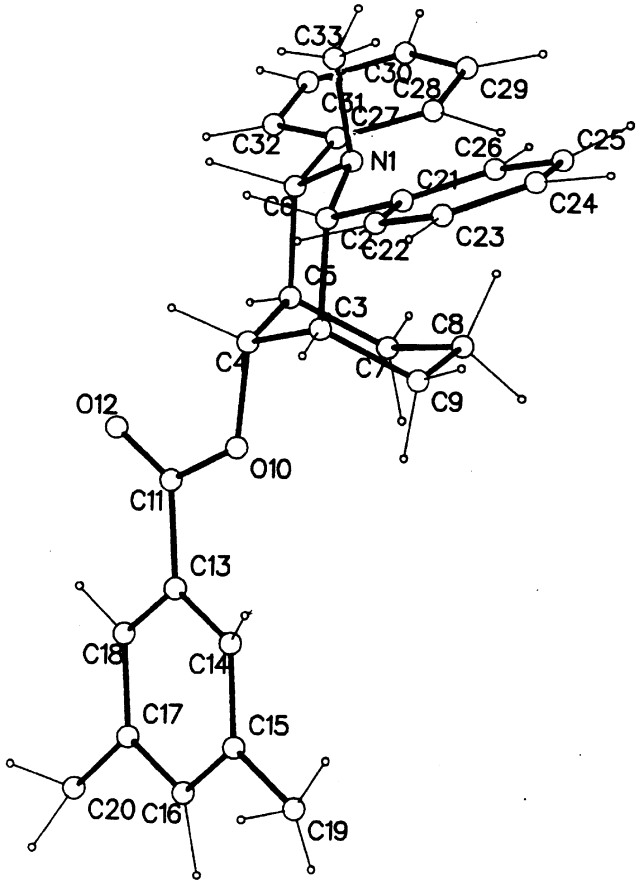

Figure 1. Pluto view of the molecule with the atom labelling used in this section

The bicycle system shows a chair–chair conformation, both chairs being flattened at the N1 and C8 atoms, respectively. The displacement of N1 and C4 from the C2,C3,C5,C6 plane are −0.509(2) and 0.772(3) Å, respectively, and that of C8 and C4 from the plane through C3,C5,C7,C9 are −0.577(3) and 0.733(3) Å. The value for a normal unflattened chair is 0.63 Å. This system presents a pseudo-mirror plane through the N1, C4, C8 and C33 atoms, although the *m*,*m*-dimethylbenzoyloxy moiety deviates from this symmetry with an angle of *ca* 60° between the phenyl ring and the pseudo-mirror plane. The carbonyloxy group is in a plane forming an angle of 11° with the aromatic ring.

Packing in the crystal[13] could be explained in terms of aromatic–aromatic interactions. As can be seen in Table 4 and Figure 2 there is a stacking pattern of the *m*,*m*-dimethylphenyl group (ring 1) along the *b*-axis, which is the shortest in the unit cell. There is also an intermolecular stacking interaction between the two phenyl rings of the bicycle system (rings 2 and 3), defining pairs along the same direction. Along the *a*-and *c*-axes, in contrast, a herringbone motif can be observed in the interactions between pairs of rings 3–1 and 1–2, respectively.

Table 4. Interaction between phenyl rings in crystal of **2**[a]

Rings[b]	GG′	α	G′P	S′G	β	GP′	SG′	β′	Symmetry		
1 vs 1′	5.2	3	3.4	3.9	99	3.5	3.8	114	$1/2-x$	$-1/2+y$	z
2 vs 3′	4.8	12	3.6	3.7	104	3.6	3.7	99	x	$1+y$	z
3 vs 1′	5.3	58	4.8	3.0	158				$1/2+x$	y	$1/2-z$
1 vs 2′	5.4	70	4.9	3.0	172				$1/2-x$	$1-y$	$-1/2+z$

[a] For each possible Ph···Ph′ interaction the following parameters are given: GG′, the distance between centroids; α, the angle between least-squares planes; G′P, the distance from G′ to the least-square plane of the first ring; S′G, the distance from the closest substituent of the second ring to the centroid of the first one; β, the angle C′—H′···G at this substituent; GP′, SG′ and β′ analogously for the second ring vs the first ring. All distances are in Å and angles in degrees. The symmetry operation refers to the second ring.
[b] Ring 1, C13—C18; ring 2, C21—C26; ring 3, C27—C32.

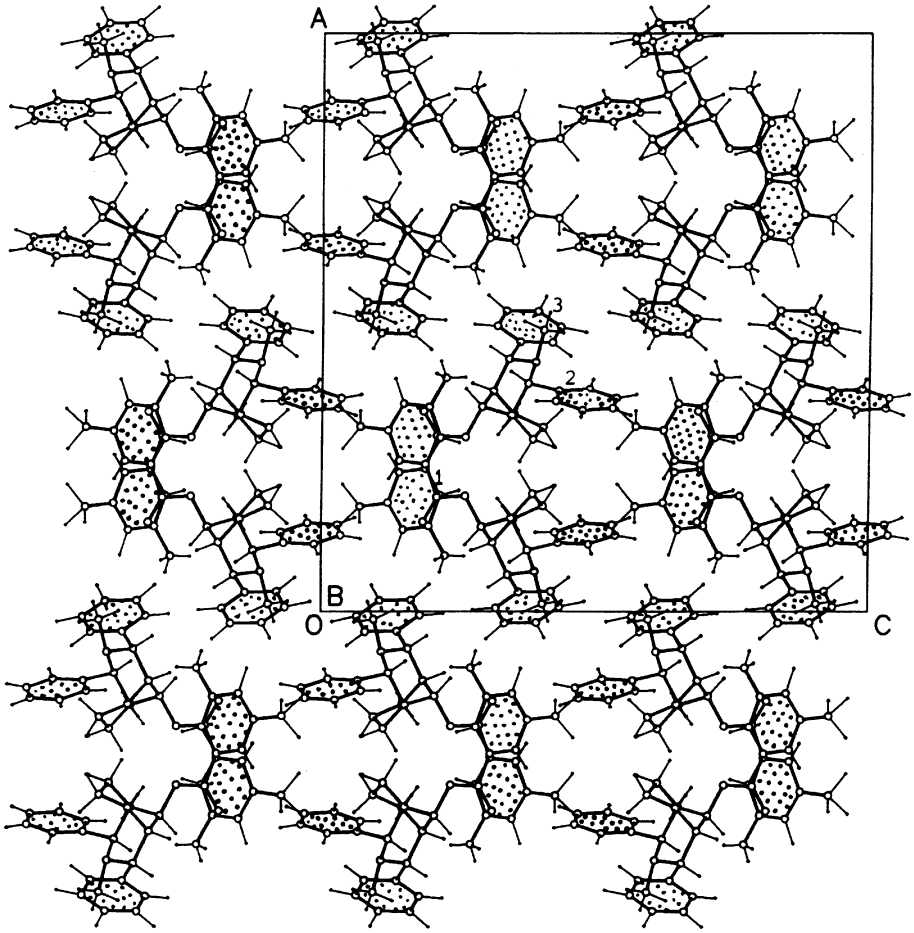

Figure 2. Packing in the unit cell projected on to the *ac* plane. The phenyl rings 1, 2 and 3, involved in the interactions, are dotted and numbered in the asymmetric unit

NMR spectra

The ^{1}H and ^{13}C NMR data for compounds **2–5** are summarized in Tables 5–7.

Assignments of proton and carbon resonances were made on the basis of the literature data for 3-methyl-2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9α-ol[3] and related systems.[14]

Spectral analysis. *^{1}H NMR.* In $CDCl_3$ at 300 MHz, the signals due to H9, $H2(4)_{ax}$, $H7_{ax}$, H1(5) and the methyl group are well differentiated. The H9 signal appears as a triplet due to the vicinal coupling with H1(5). The $H2(4)_{ax}$ signal appears as a doublet due to the vicinal coupling with H1(5), and the $H7_{ax}$ signal as a quartet of triplets because $|^{2}J(H7_{ax} - H7_{eq})| \approx {}^{3}J(H7_{ax} - H6(8)_{ax})$.

To clarify the assignment of the signals and to deduce

Table 5. ^{1}H chemical shifts (δ, ppm) for compounds **2**–**5**[a]

	2	**3**	**4**	**5**
H9	5.42(t)	5.43(t)	5.56(t)	5.59(t)
$H2(4)_{ax}$	3.76(d)	3.74(d)	3.77(d)	3.80(d)
$H7_{ax}$	2.6(qt)	2.61(qt)	2.59(qt)	2.63(qt)
N-CH_3	2.35(s)	2.0(s)	2.0(s)	2.02(s)
H1(5)	2.17(brs) ($W_{1/2}$≈8.6 Hz)	2.17(brs) ($W_{1/2}$≈8.8 Hz)	2.22(brs) ($W_{1/2}$≈8.5 Hz)	2.26(brs) ($W_{1/2}$≈8.4 Hz)
$H6(8)_{ax}$	1.74(tt)	1.62(tt)	1.67(m)	1.66(tt)
$H7_{eq}$	–[b]	–[b]	1.46(m)	–[b]
$H6(8)_{eq}$	1.37(dd)	1.38(dd)	1.39(dd)	1.42(dd)
H2′–H6′(m)	7.14–7.45	7.14–7.46	7.14–7.46	7.14–7.47
			7.72–7.90	7.72–7.89
H2″	7.65(d)	7.89(d)		9.0(d)
H3″			9.29(s)	7.92(d)
H4″	7.17(d)	7.53(t)		
H5″			8.74(s)	8.20(dd)
H6″	7.65(d)	7.89(d)	8.74(s)	7.67[c](ddd)
H7″				7.79[c](ddd)
H8″				8.81(dd)

[a] Abbreviations: brs, broad singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; m, multiplet; q, quartet; qt, quartet of triplets; s, singlet; t, triplet; tt, triplet of triplets. The δ values were deduced from the first-order analysis of the corresponding system protons with an error of ± 0.05 ppm.
[b] These chemical shifts were not determined owing to the low resolution of the signal.
[c] These values may be interchanged.

Table 6. Coupling constants (J, Hz) deduced from the analysis of the ^{1}H NMR spectra of compounds **2**–**5**[a]

	2	**3**	**4**	**5**
H9–H1(5)	3.7	3.4	3.7	3.7
$H2(4)_{ax}$–H1(5)	3.2	2.9	2.9	2.9
$H6(8)_{ax}$–H1(5)	4.7	–[b]	4.5	4.9
$H6(8)_{ax}$–$H6(8)_{eq}$	−13.5	−14.2	−13.9	−13.7
$H6(8)_{ax}$–$H7_{ax}$	13.1	12.7	13.2	13.7
$H6(8)_{ax}$–$H7_{eq}$	4.7	–[b]	5.4	5.4
$H6(8)_{eq}$–H1(5)	<2[c]	<2[c]	<2[c]	<2[c]
$H6(8)_{eq}$–$H7_{ax}$	5.5	5.1	–[b]	5.6
$H6(8)_{eq}$–$H7_{eq}$	<2[c]	<2[c]	<2[c]	<2[c]
$H7_{ax}$–$H7_{eq}$	−13.1	−12.7	−13.2	−13.7
H2″–H3″				4.6
H2″–H4″	0.5	1.9		
H3″–H5″			0.5	
H4″–H6″	0.5	1.9		
H5″–H6″				8.5
H5″–H7″				1.46
H5″–H8″				
H6″–H7″				6.8
H6″–H8″				1.46
H7″–H8″				8.5

[a] Values deduced from the first-order analysis of the corresponding system protons. Error ± 0.05 Hz.
[b] Not determined owing to the low resolution of the signal.
[c] Approximate value.

Table 7. ^{13}C chemical shifts (δ, ppm) for compounds **2**–**5**[a]

	2	**3**	**4**	**5**
C9 (d)	76.21	77.56	77.99	77.82
C2(4) (d)	73.08	72.99	72.96	73.14
N-CH_3 (c)	44.04	43.98	43.97	44.02
C1(5) (d)	40.21	40.09	40.09	40.19
C7 (t)	20.48	20.34	20.34	20.37
C6(8) (t)	20.68	20.65	20.61	20.72
CH_3 (c)	21.20			
C=O (s)	166.23	163.50	163.19	165.46
C1′ (s)	142.61	142.28	142.28	142.31
C2′(6′)	–[b]	127.04[c] (d)	128.15	127.5[c] (d)
C3′(5′) (d)	128.20	128.26	128.26	128.27
C4′(d)	126.71	126.84	126.85	126.92
C1″	130.58 (s)	132.60 (s)		
C2″	127.23 (d)	127.90 (d)	143.98 (s)	149.60 (d)
C3″	137.99 (s)	135.90 (s)	146.05 (d)	122.07 (d)
C4″	134.56 (d)	133.30 (d)		135.49 (s)
C4″a				126.61 (s)
C5″	137.99 (s)	135.29 (s)	147.44 (d)	125.57[d] (d)
C6″	127.23 (d)	127.91 (d)	144.68 (d)	125.20[d] (d)
C7″				129.88 (d)
C8″				129.88 (d)
C8″a				148.92 (s)

[a] Abbreviations: d, doublet; s, singlet. The δ values were deduced from the first-order analysis of the corresponding system protons with an error of ± 0.05 ppm.
[b] Not determined owing to the low resolution of the signal.
[c] Broad signal.
[d] These values may be interchanged (C5″ for C6″).

the proton magnetic parameters, double resonance experiments in deuteriochloroform for **5** were performed at 300 MHz. By irradiation of the H1(5) signal at 2.26 ppm, both the triplet and doublet corresponding to H9 and $H2(4)_{ax}$, respectively, simplify to singlets and the unresolved triplet of triplets at 1.66 ppm [$H6(8)_{ax}$] becomes a triplet of doublets with splittings of 5.4 and 13.7 Hz due to the couplings with $H7_{eq}$, $H6(8)_{eq}$ and $H7_{ax}$, respectively.

The $H6(8)_{eq}$ signal appears as a doublet of doublets

with splittings of 5.6 and 13.7 Hz due to the couplings with $H7_{ax}$ and $H6(8)_{ax}$, which is confirmed by saturating the $H7_{ax}$ signal at 2.63 ppm, whereupon the $H6(8)_{eq}$ signal collapses to a doublet with a splitting of 13.7 Hz.

On saturating the $H6(8)_{eq}$ and $H7_{eq}$ signals at 1.42 ppm, $H7_{ax}$, H1(5) and $H6(8)_{ax}$ simplify to a doublet, quadruplet and apparent doublet, respectively.

In summary, the following constants can be deduced:

$$^2J[H6(8)_{eq} - H6(8)_{ax}],\ ^3J[H6(8)_{ax} - H7_{ax}],$$

$$^3J[H6(8)_{ax} - H7_{eq}],\ \text{and}\ ^3J[H6(8)_{eq} - H7_{ax}].$$

^{13}C NMR. Chemical shifts and signal assignment of compounds **2**–**5** are listed in Table 7. Substituent steric and electronic effects on ^{13}C chemical shifts, and signal multiplicity obtained from off-resonance decoupled spectra from our previous studies of related compounds were taken into consideration.[3]

Conformational study. From the ^1H and ^{13}C NMR data for **2**–**5**, the following general features may be deduced:

(a) the bicyclic system exists predominantly in a flattened chair–chair conformation;
(b) the cyclohexane ring is more flattened than the piperidine moiety;
(c) the *N*-CH_3 group is an in equatorial position with respect to the piperidine ring;
(d) the phenyl groups are nearly coplanar with respect to $H2(4)_{ax}$; the shape of the multiplets due to proton aromatic signals accounts for a distinct conformation of phenyl groups (due to restricted phenyl spinning);
(e) the conjugated benzoyloxy group lies in a plane nearly coincident with respect to the symmetry plane of the bicycle; in this conformation, the carbonyl group occupies a *cis* disposition with respect to H9.

These conclusions are supported by the following observations. In the ^1H NMR spectra, the $W_{1/2}$ value for the H1(5) signals (*ca* 8–9 Hz) is in agreement with previously reported values for a flattened chair–chair conformation in related bicyclic systems.[14–19] For a boat disposition of one of these rings, the signal corresponding to H1(5) would be an unresolved doublet with a coupling constant about 18 Hz.[1]

In all cases, the ^3J [$H2(4)_{ax}$–H1(5)] value of *ca* 3 Hz accounts for a dihedral angle of about 60° according to the Karplus relationship.[20] In componds **2–5,** ^3J [$H2(4)_{ax}$–H1(5)] is smaller than ^3J [$H6(8)_{ax}$–H1(5)] and consequently the $H2(4)_{ax}$—C—C—H1(5) dihedral angle is greater than $H6(8)_{ax}$—C—C—H1(5); this is in close agreement with a flattened chair conformation for the cyclohexane ring. On the other hand, ^3J [$H6(8)_{ax}$–H1(5)] is greater than ^3J [$H6(8)_{eq}$–H1(5)] and ^3J [$H6(8)_{ax}$–$H7_{eq}$] is greater than ^3J [$H6(8)_{eq}$–$H7_{eq}$]; therefore, the $H6(8)_{eq}$—C—C—H1(5) and $H6(8)_{eq}$—C—C—$H7_{eq}$ dihedral angles are greater than $H6(8)_{ax}$—C—C—H1(5) and $H6(8)_{ax}$—C—C—$H7_{eq}$, respectively; this confirms the distortion of the cyclohexane ring.

In the ^{13}C NMR spectra, the twin-chair conformation is confirmed by the C2(4) and C6(8) chemical shifts[21] (Table 7). For a boat conformation, the carbon signals would be shifted to a higher field because of the steric compressing effect due to the eclipsing between $H2(4)_{ax}$–H1(5) and $H6(8)_{ax}$–H1(5) hydrogen atoms.

In all cases, $\Delta\delta$ [$H7_{ax}$ (**2**–**5**)−$H7_{eq}$ (**2**–**5**)] ≈ 1.2 ppm was attributed to the field effect exerted by the nitrogen lone pair on $H7_{ax}$.

The *N*-CH_3 ^{13}C chemical shift of these compounds of about 45 ppm is similar to that found in equatorial *N*-CH_3 substituted piperidines[22] and in **1.**[3] Owing to the small differences in the chemical shifts of the $H7_{ax}$ and $H2(4)_{ax}$ between the alcohol (**1**) and esters (**2**–**5**), we can conclude that the position adopted by the phenyl groups in **2**–**5** will be the same as that found in the alcohol **1,**[3] with near coplanarity with respect to $H2(4)_{ax}$, as was observed in the x-ray structure of **2.**

The differences $\Delta\delta$ [$H2(4)_{ax}$ (**2**–**5**) − $H2(4)_{ax}$ (**1**)] ≈ 0.2 ppm and $\Delta\delta$ [$H6(8)_{ax}$ (**2**–**5**) − $H6(8)_{ax}$ (**1**)] ≈ 0.1 ppm can be attributed not only to the σ-effect exerted by the acyloxy group, but also to the decreasing anisotropic effect exerted by the lone pairs of the oxygen atom when the hydroxyl group changes into an acyloxy group.

The $\Delta\delta$ [H9 (**2**–**5**) − H9 (**1**)] value of 1.5 ppm can be partially attributed to the π deshielding effect exerted for the carbonyl group.

The ^1H and ^{13}C data for the acyloxy groups account for conjugation between the aromatic rings and the carbonyloxy group.

Pharmacology

Pharmacological assays on mice were performed with compounds **2**–**5** to evaluate drug-induced gross behavioral alteration and both the writhing test[23] and hot-plate test[24] were applied to evaluate analgesic activity.

Concerning the behavioral effects, evaluated in mice with the Irwin screening procedure,[25] no peripheral or central toxic signs were observed with **2**–**5** dosed at 10 mg kg^{-1} (i.p.); all the animals appeared normal 24 h after treatment and remained so during the 7 day observation period.

The results of the pharmacological evaluation for analgesic activity are summarized in Table 8. Although all the compounds [10 mg kg^{-1}(i.p.)] show a partial antinociceptive effect in the acetic acid writhing test in the mouse; this appeared to be a non-statistically significant activity when we compared it with the degree of protection afforded by acetylsalicylic acid [200 mg kg^{-1} (p.o.)] or diclofenac [10 mg kg^{-1}(p.o.)].

The same happened when the hot-plate test was used because, although **2**–**5** exhibit some peripheral analgesic

Table 8. Analgesic activity[a] of compounds **2–5,** using as comparators acetylsalicylic acid, diclofenac and morphine

Compound[b]	Writhing test[c]	Hot-plate test[c]
2	−24	+11.2
3	−14	+3
4	−23	+28
5	−29	−7
Acetylsalicylic acid	−53*	n.d.[d]
Diclofenac	−50**	n.d.[d]
Morphine	n.d.	+113.2**

[a] See methods. Statistical significance versus control was evaluated by the Wilcoxon's two-samples test (writhing test) or by Fisher's exact test (hot-plate test).
[b] All compounds administered at 10 mg kg^{-1} (i.p.) except acetylsalicylic acid [200 mg kg (p.o.)] and diclofenac [10 mg kg^{-1}(p.o.)]
[c] *$p < 0.01$; **$p < 0.001$.
[d] Not determined.

effect, they would never achieve the grade of activity showed by morphine [8 mg kg^{-1}(i.p.)].

EXPERIMENTAL

All melting points were measured in open capillary tubes in an Electrothermal IA6304 apparatus, and are uncorrected. Elemental analyses were performed with a Perkin-Elmer Model 240E Elemental Analyzer. IR spectra were recorded on a Perkin-Elmer Model 883 spectrophotometer in the solid state (potassium bromide).

NMR spectra were recorded on a Varian UNITY-300 spectrometer in deuteriochloroform.

The ^{1}H NMR spectra were obtained at 300 MHz using spectral width of 4000 Hz in 24K memory and an acquisition time of 3.0 s over 64 transients. Resolution enhancement using LB = −0.80, GF = 0.50 and GFS = 0.20 was followed by zero filling into 32K memory prior to Fourier transformation. Conventional irradiation was used for the double resonance experiments in the same solvents.

The ^{13}C NMR spectra were obtained at 75.429 MHz on a Varian UNITY-300 spectrometer at a spectral width of 16 501 Hz in 64K memory, an acquisition time of 1 s and a relaxation delay of 1 s. Two types of spectra were recorded: proton-noise decoupled spectra and off-resonance decoupled spectra.

Synthesis of the esters 2–5: general procedures. *Method A.* To a stirred solution of 3-methyl-2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9α-o1 (**1**) (3.3 mmol) and the corresponding acid (3.3 mmol) in anhydrous methylene chloride (30 ml) was added dropwise a solution of DCC (3.5 mmol) and DMAP (0.33 mmol) in anhydrous methylene chloride (5 ml). The reaction mixture was stirred at room temperature for 1–3 days then filtered under reduced pressure. The filtrate was concentrated *in vacuo*, diethyl ether was added to the resulting oil, the mixture was filtered and the filtrate was evaporated under reduced pressure. The residual oil was purified on a silica gel column prepacked in a suitable solvent. Elution of the column with ethyl acetate–hexane (4:1, 3:1 and 4:1, v/v, for compounds **2, 4** and **5,** respectively) gave a solid which was crystallized from hexane.

Method B. A solution of the acyl chloride (3.3 mmol), triethylamine (3.3 mmol) and 3-methyl-2,4-diphenyl-3-azabicyclo[3.3.1]nonan-9α-o1 (**1**) (3.3 mmol) in anhydrous methylene chloride (25 ml) were stirred at room temperature for 1–2 days. The reaction mixture was washed with saturated Na_2CO_3 solution and then with water. The organic layer was separated, dried (magnesium sulphate) and the solvent evaporated under reduced pressure. The residual oil was purified on a silica gel column prepacked in a suitable solvent. Elution of the column with ethylcetate–hexane (6:1, v/v) for compound **3** gave a solid which was crystallized from hexane.

3-Methyl-2,4-diphenyl-9α(3,5-dimethylbenzoyloxy)-3-azabicyclo[3.3.1]nonane. (**2**). This compound was obtained (method A) in 74% yield, m.p. 178–179 °C (from light petroleum); IR (KBr): ν CO, 1712 cm^{-1}. Analysis: calculated for $C_{30}H_{33}NO_2$, C 81.97, H 7.57, N 3.19; found, C 81.68, H 7.41, N 3.17%.

3-Methyl-2,4-diphenyl-9α(3,5-dichlorobenzoyloxy)-3-azabicyclo[3.3.1]nonane. (**3**). This compound was obtained (method B) in 52% yield, m.p. 176–177 °C (from hexane); IR (KBr): ν CO, 1725 cm^{-1}. Analysis: calculated for $C_{28}H_{27}NO_2Cl_2$, C 70.00, H 5.67, N 2.92; found, C 70.24, H 5.87, N 2.77%.

3-Methyl-2,4-diphenyl-9α(pirazine-2-carbonyloxy)-3-azabicyclo[3.3.1]nonane. (**4**). This compound was obtained (method A) in 59% yield, m.p. 170–172 °C (from hexane); IR (KBr): ν CO, 1715 cm^{-1}. Analysis: calculated for $C_{26}H_{27}N_3O_2$, C 75.52, H 6.58, N 10.16; found, C 75.30, H 6.74, N 9.92%.

3-Methyl-2,4-diphenyl-9α(quinolin-4-carbonyloxy)-3-azabicyclo[3.3.1]nonane. (**5**). This compound was obtained (method A) in 68% yield, m.p. 151–152 °C (from hexane); IR (KBr): ν CO, 1713 cm^{-1}. Analysis: calculated for $C_{31}H_{30}N_2O_2$, C 80.49, H 6.54, N 6.06; found, C 80.19, H 6.77, N 5.80%.

Pharmacological Methods. Male Albino Swiss mice (18–22 g) were used. The animals were starved for about 15 h before treatment. All the test compounds were administered intraperitoneally in a 5% ethanol–saline solution. The dose employed throughout the pharmacological assays was 10 mg kg^{-1} (10 ml kg^{-1}).

Gross behavioral effects and acute toxicity in mice. Irwin's multi-dimensional screening procedure[24] was used in groups of three mices to evaluate drug-induced behavioral alteration. Testing of mice was performed 30 min, 1 h, 3 h and 24 h after treatment (total observation period 7 days). D-Amphetamine (5 mg kg^{-1}) and diazepam (5 mg kg^{-1}) were used for comparison.

Analgesic activity. 1. Writhing test.[22] Groups of 10 mice were injected intraperitoneally with a 0.75% acetic acid solution (0.01 ml g^{-1}) 30 min after administration of the test compound. The writhing movements of each animal were counted for 20 min. The analgesic effect was expressed as the percentage of protection compared with the control group. Acetylsalicylic acid [200 mg kg^{-1} (p.o.)] and sodium diclofenac [10 mg kg^{-1}(p.o.)], administered 60 min before injection of the irritant, were used as reference standards.

2. Hot plate test.[23] Groups of eight mice were used. They were placed individually on a hot-plate (Socrel, D-537), maintained at 55 ± 0.5 °C, and the time of reaction (end point: licking of the hind paws) was recorded 30 min after administration of the test compound. The mice were removed as soon as they reacted or, if they failed to react, after 60 s. The analgesic effect was expressed as the percentage variation of time compared with the control group. Morphine (8 mg kg^{-1}) was used for comparison.

SUPPLEMENTARY MATERIAL

Data from the crystallographic study of **2** are available from the authors on request.

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