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Original paper

Synthesis and structural, conformational and pharmacological study of N-β(or γ)acyloxyalkylnortropinones

Maria L. IZQUIERDO[1], Enrique GALVEZ[1]*, Carolina BURGOS[1], Juan J. VAQUERO[1], Feliciana FLORENCIO[2], Aurelio ORJALES[3] and Ana INNERARITY[3]

[1]*Departamento de Química Orgánica, Universidad de Alcalá de Henares, Madrid,*
[2]*Instituto Rocasolano, Departamento de Rayos-X, CSIC, Serrano 119, 28006 Madrid, and*
[3]*FAES S.A. Aptdo. 555 Bilbao, Spain*

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Summary — A series of *N*-β(or γ)acyloxyalkylnortropinones was synthesized and studied by ^1H and ^{13}C NMR spectroscopies, and the crystal structure of *N*-[β-(diphenylacetyloxy)ethyl] nortropinone **1** was determined by X-ray diffraction. In $CDCl_3$ solution, the compounds studied display the same preferred conformation. The pyrrolidine and piperidone rings adopt a flattened N8 envelope and distorted chair conformation, puckered at N8 and flattened at C3, respectively, with the *N*-substituent in the axial position with respect to the piperidone ring. The ability of the title compounds to antagonize the histamine and acetylcholine-induced contraction of guinea pig ileum is also reported. An initial structure–activity relationship is proposed.

Résumé — **Synthèse et étude structurale, conformationnelle et pharmacologique de *N*-β(ou γ)acyloxyalkylnortropinones.** *On décrit la synthèse et l'étude spectroscopique par techniques de ^1H RMN et de ^{13}C RMN d'une série de* N-β(ou γ)*acyloxyalkylnortropinones. On rapporte aussi la structure cristalline de la nortropinone* ***1*** *en employant des techniques de diffraction des rayons-X. Les noyaux de pyrrolidine et de pipéridone présentent une conformation d'enveloppe aplatie en N8 et de chaise pliée en N8 et aplatie en C3 respectivement, où l'azote porte le substituant en position axiale par rapport au noyau de la pipéridone. Ces composés peuvent jouer un rôle dans l'inhibition de l'action de l'histamine et de l'acétylcholine; nous avons étudié leur pharmacologie sur l'iléon de cobaye. On propose un modèle initial de relation structure–activité.*

tropane derivatives / structural and conformational study / anti-cholinergic

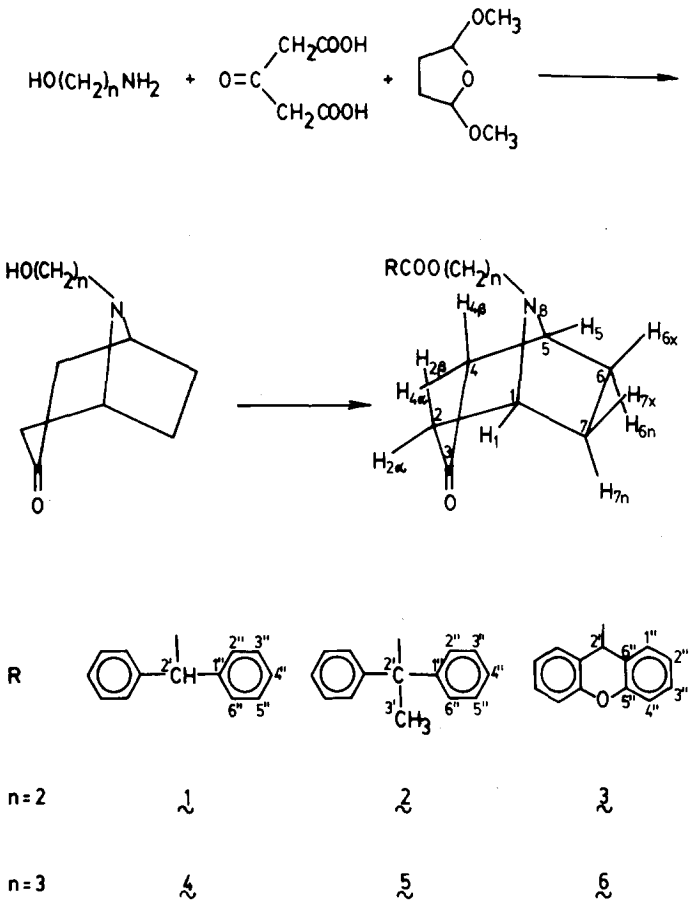
Introduction

In previous papers [1–6], we reported the synthesis, the ^1H NMR, ^{13}C NMR and IR studies and X-ray diffraction data of several potentially pharmacologically interesting tropane derivatives. In order to gain additional information concerning the effects of stereochemical factors on anti-cholinergic activity, we synthesized a new series of tropane derivatives (Scheme 1), in which the conformational flexibility of the cationic head was reduced by incorporation into a ring system. The structural, conformational and pharmacological study of compounds **1–6** has been carried out in order to explore the structure–activity relationship.

Chemistry

Compounds **1–6** were prepared as shown in Scheme 1. Nortropinones were obtained by the reaction of succindialdehyde generated *in situ* from 2,5-dimethoxytetrahydrofuran, acetonedicarboxylic acid and the corresponding amine hydrochloride following the method described by Robinson-Schöpf [7] and modified by Finlay [8]. Esterification of *N*-β-hydroxyethyl and *N*-γ-hydroxypropylnortropinones was carried out following conventional procedures. The methods of esterification described under Experimental protocols was explored to obtain a better yield than those reported using acid derivatives as esterification reagents.

*Author to whom correspondence should be addressed.
Abbreviations: **DMAP:** 4-(dimethylamino)-pyridine; **DCC:** *N,N'*-dicyclohexylcarbodiimide.



Scheme 1.

Structural study

Description of the structure of compound ***1***

The main crystallographic data and the structure determinations are given in Table I. Table II presents the atomic parameters and Tables III and IV give bond lengths, and bond and torsion angles, respectively; the numbers correspond to those used in Fig. 1. Several significant torsion angles in which hydrogen atoms are involved are also given. Fig. 1 shows the structural formula.

The bicyclic system shows an approximate mirror plane passing through N4, C1, O9 and the middle point of C6–C7 bond. The piperidone ring adopts a distorted chair conformation puckered at N4 and flattened at C1 with displacements of N4 and C1 from the plane through C2, C3, C5 and C8 of 0.88(2) and 0.35(4) Å respectively, as a consequence of the interaction of the C10 methylene and carbonyl groups, respectively, with the bimethylene bridge. The pyrrolidine ring shows a puckered N4 envelope conformation with a deviation of the N4 atom from the plane through C2, C3, C5 and C8 of 0.61(2) Å. The asymmetry parameters [13] are $q_2 = 0.354(4)$, $q_3 = 0.543(4)$, $\psi = 0.1775(7)$, $\theta = 33.1(4)$ for the piperidone ring and $q_2 = 0.401(3)$, $\psi = 0.4(6)$ for the pyrrolidine ring. The acyloxyalkyl group occupies an axial position with respect to the piperidone ring. The phenyl rings are fairly planar with average torsion angles of 0.8°. The intermolecular contacts correspond to Van der Waals interactions.

NMR spectra

The ^1H and ^{13}C NMR data are summarized in Tables V and VI. Assignments of proton and carbon resonances were made on the basis of our previous studies of several tropane systems and literature data [1–6]. In the case of ^{13}C NMR assignments, signal multiplicity obtained from off-resonance decoupled spectra were taken into consideration.

From the ^1H and ^{13}C NMR data of **1–6**, the following general features for the biyclic system were deduced: 1) the pyrrolidine and piperidone rings in these compounds all have a flattened N8 envelope and distorted chair conformation puckered at N8 and flattened at C3, similar to that observed in the crystal structure of **1**; 2) the *N*-group occupies an axial position with respect to the piperidone ring and does not have a preferred conformation. No difference was observed between the compounds with $n = 2$ and $n = 3$.

These conclusions are supported by the following: 1) In the ^1H NMR spectra, the *$w^1/_2$ value for the H1(5) signals of* ~11 Hz corresponds to a tropane system with the piperidine ring in a flattened chair conformation [1, 3, 5, 14]. The JH2(4)–H1(5) values correspond to dihedral angles of ~60°. In all cases JH2(4)$_\beta$–H1(5) is greater than JH2(4)$_\alpha$–H1(5); consequently, the dihedral angle H2(4)$_\alpha$–C–C–H1(5) is greater than H2(4)$_\beta$–H1(5). The regularity of the ^3JH2(4)$_\beta$–H1(5) values in **1–6** reveals that the piperidone ring conformation is not appreciably influenced by the shape and size of the group attached to the piperidone nitrogen atom. In the ^{13}C NMR spectra,

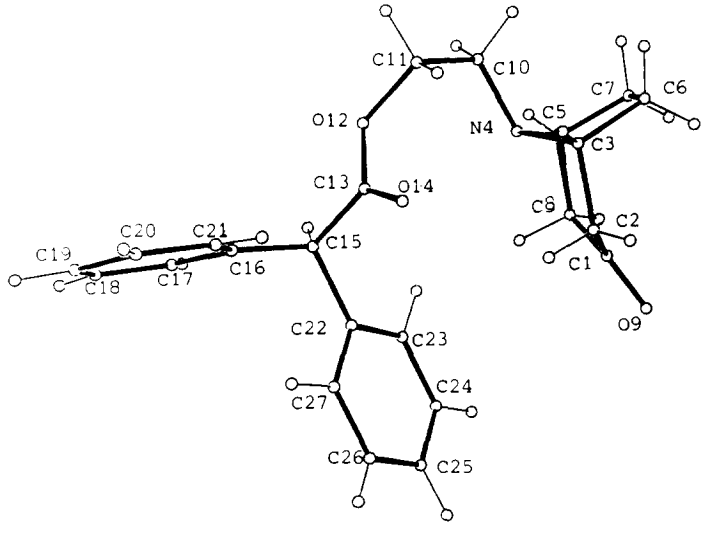


Fig. 1. Structural formula of compound **1**.

Table I. Experimental data and structure refinement procedures.

Crystal data	
formula	$C_{23}H_{25}O_3N$
crystal habit	prismatic
crystal size (mm)	0.15 × 0.20 × 0.30
symmetry	monoclinic, $P2_1/a$
unit cell determination	least-square fit from 56 reflexions (θ 38°)
unit cell dimensions	14.567(7), 13.140(1), 10.153(1) Å, 90.0, 90.09(2), 90.0°
packing: V(Å^3), Z	1943.2(1), 4
Dc(g·cm^{-3}), M, F(OOO)	1.242, 363.46, 776
μ(CuK$_\alpha$) (cm^{-1})	6.17
Experimental data	
technique	four circle diffractometer: Philips PW 1100 bisecting geometry graphite oriented monochromator: CuK$_\alpha$ $\omega/2\theta$ scans detector apertures 1 × 1, up θ_{max} 65° 1.5 min / reflex
number of reflexions:	
measured	3457
independent	3390
observed	2548 (2 σ(I) criterion)
range of *hkl*	0 16, 0 15, −11 11 (sin $\theta/\lambda)_{max}$, 0.60
value of Rint	0.009 variation: 7%
solution and refinement	
solution	direct methods
refinement	L.S. on Fobs with 1 blocks
parameters:	
number of variables	344
degrees of freedom	2204
ratio of freedom	7.4
H atoms	difference synthesis and refined with isotropic temp. factors
final shift / error	0.02
w-scheme	empirical as to give no trends in $<w\Delta^2F>$ vs $<\|F_o\|>$ or $<\sin\theta/\lambda>$
final F peaks	0.11 eÅ^{-3}
final R and Rw	0.061, 0.055
computer and programs	Vax 11 / 750, Multan 80 [9], Xray 76 [10], Pesos [11]
scattering factors	int. tables for X-ray crystallography [12]

Table II. Atomic parameters for non-H atoms.

Atom	*X / A*	*Y / B*	*Z / C*	*Ueq*
C1	0.3161(2)	0.2802(3)	0.6682(5)	884(18)
C2	0.3480(3)	0.3156(3)	0.8019(5)	923(17)
C3	0.4526(2)	0.3345(3)	0.8059(3)	650(12)
N4	0.4716(1)	0.4050(2)	0.6966(2)	468(8)
C5	0.4684(2)	0.3354(3)	0.5831(3)	586(11)
C6	0.5065(3)	0.2369(3)	0.7739(4)	799(15)
C7	0.5174(2)	0.2375(3)	0.6254(4)	736(14)
C8	0.3690(3)	0.3156(3)	0.5524(4)	784(15)
O9	0.2495(2)	0.2254(2)	0.6593(4)	1412(18)
C10	0.5599(2)	0.4582(2)	0.7103(3)	582(11)
C11	0.5518(2)	0.5483(2)	0.8018(4)	635(12)
O12	0.4829(1)	0.6182(1)	0.7495(2)	539(7)
C13	0.4023(2)	0.6223(2)	0.8107(3)	511(10)
O14	0.3849(2)	0.5797(2)	0.9114(2)	797(10)
C15	0.3353(2)	0.6886(2)	0.7336(3)	454(9)
C16	0.3332(2)	0.7969(2)	0.7854(3)	477(10)
C17	0.3182(2)	0.8757(2)	0.6974(3)	564(11)
C18	0.3085(2)	0.9751(3)	0.7415(4)	709(14)
C19	0.3141(3)	0.9967(3)	0.8736(5)	813(16)
C20	0.3307(3)	0.9188(3)	0.9623(4)	812(15)
C21	0.3397(2)	0.8190(3)	0.9191(3)	644(12)
C22	0.2407(2)	0.6400(2)	0.7307(3)	462(9)
C23	0.2224(3)	0.5656(3)	0.6382(4)	789(15)
C24	0.1359(3)	0.5207(3)	0.6324(5)	1016(20)
C25	0.0684(3)	0.5489(3)	0.7143(5)	842(17)
C26	0.0845(2)	0.6230(3)	0.8041(5)	873(17)
C27	0.1710(2)	0.6687(3)	0.8129(4)	698(13)

Coordinates and thermal parameters as $Ueq = (1/3)\cdot\text{sum}[Uij\cdot ai^*\cdot aj^*\cdot ai\cdot aj\cdot\cos(ai, aj)]\cdot 10^4$.

Table III. Bond distances (Å).

C 1–C2	1.508(8)	C 1–C8	1.481(7)
C 1–O9	1.212(5)	C 2–C3	1.544(6)
C 3–C6	1.538(6)	N 4–C5	1.472(4)
N 4–C10	1.471(4)	C 5–C7	1.533(5)
C 5–C8	1.503(5)	C 6–C7	1.516(6)
C10–C11	1.510(5)	C11–O12	1.461(4)
O12–C13	1.330(4)	C13–O14	1.193(4)
C15–C22	1.519(4)	C16–C17	1.386(5)
C16–C21	1.391(5)	C17–C18	1.388(5)
C18–C19	1.373(7)	C19–C20	1.384(7)
C20–C21	1.389(6)	C22–C23	1.380(5)
C22–C27	1.369(5)	C23–C24	1.393(7)
C24–C25	1.341(7)	C25–C26	1.355(7)
C26–C27	1.398(5)		

the chair conformation adopted by the piperidone ring is confirmed by the δC2(4) values (Table VI). For a boat conformation, these carbon signals would be shifted to higher fields as a result of the steric compressing effect due to the eclipsing between the $C2(4)_\beta$ and C1(5) hydrogen atoms [1, 3, 15, 16].

2) For compounds **1–6** δC2(4) values are nearly the same. The chemical shifts of C6(7) are not affected by the substituents on the nitrogen atom. These facts can be justified by considering that the conformer with the nitrogen substituent in an axial position with respect to the 6-membered ring is the most favorable, in agreement with previous observations [16–18].

The patterns of the CH_2-O and CH_2-N triplets and the phenyl protons in the ^1H NMR spectra of **1–6** accounts for several preferred conformations of the acyloxyalkyl group.

The results obtained by X-ray diffraction of **1** are in good agreement with the ^1H and ^{13}C NMR conclusions except for the disposition of the *N*-substituent; the *N*-equatorial conformation in the crystalline state is probably due to packing forces.

Pharmacology

Anti-histaminic and anti-cholinergic *in vitro* properties of compounds **1**, **3**, **4** and **6** were evaluated on isolated guinea pig ileum. Atropine and diphenydramine were used as reference compounds.

Results of these experiments are summarized in Table VII. Compounds **1**, **3**, **4** and **6** at high concentrations were found to possess some degree of antagonism against histamine and acetylcholine by inhibiting the contractions induced by them. IC_{50} values were practically the same for the compounds with both histamine and acetylcholine and

Table IV. Bond angles (°) and torsion angles (°).

Bond angles (°)				Torsion angles (°)			
C8–C1–O9	123.0(5)	C2–C1–O9	119.8(5)	C3–N4–C10–C11	– 81.4(3)	N4–C10–C11–O12	– 59.1(4)
C2–C1–C8	117.2(4)	C1–C2–C3	112.1(4)	C10–C11–O12–C13	106.6(3)	C11–O12–C13–O14	6.7(5)
C2–C3–C6	111.4(3)	C2–C3–N4	105.5(3)	C11–O12–C13–C15	–173.0(3)	O12–C13–C15–C16	– 95.8(3)
N4–C3–C6	105.6(3)	C3–N4–C10	113.2(3)	O12–C13–C15–C22	138.0(3)	O14–C13–C15–C16	84.5(4)
C3–N4–C5	101.2(2)	C5–N4–C10	113.4(2)	O14–C13–C15–C22	– 41.7(4)	C13–C15–C22–C23	– 82.8(4)
N4–C5–C8	107.4(3)	N4–C5–C7	106.7(3)	C13–C15–C16–C17	146.7(3)		
C7–C5–C8	111.2(3)	C3–C6–C7	105.1(3)				
C5–C7–C6	103.5(3)	C1–C8–C5	113.0(4)	H22–C2–C3–H31	57.7(3)	H21–C2–C3–H31	– 54.5(7)
N4–C10–C11	111.2(3)	C10–C11–O12	108.9(3)	H31–C3–C6–H61	84.8(7)	H31–C3–C6–H62	– 38.9(7)
C11–O12–C13	117.5(2)	O12–C13–C15	110.4(3)	H51–C5–C8–H81	– 59.7(2)	H51–C5–C8–H82	63.7(3)
O12–C13–O14	124.8(3)	O14–C13–C15	124.8(3)	H51–C5–C7–H71	26.5(0)	H51–C5–C7–H72	– 90.6(0)
C13–C15–C22	110.5(2)	C13–C15–C16	111.8(2)	H62–C6–C7–H71	0.3(5)	H61–C6–C7–H71	–120.5(6)
C16–C15–C22	112.5(2)	C15–C16–C21	122.2(3)	H62–C6–C7–H72	120.0(4)	H61–C6–C7–H72	– 0.9(6)
C15–C16–C17	118.7(3)	C17–C16–C21	118.9(3)	H102–C10–C11–H111	53.8(7)	H101–C10–C11–H111	– 56.7(9)
C16–C17–C18	120.8(4)	C17–C18–C19	120.2(4)	H102–C10–C11–H112	– 65.6(8)	H101–C10–C11–H112	–176.2(9)
C18–C19–C20	119.6(4)	C19–C20–C21	120.5(4)	H171–C17–C18–H181	6.6(2)	H181–C18–C19–H191	0.5(8)
C16–C21–C20	120.0(3)	C15–C22–C27	123.1(3)	H191–C19–C20–H201	– 3.7(2)	H201–C20–C21–H211	5.0(9)
C15–C22–C23	119.0(3)	C23–C22–C27	117.9(3)	H231–C23–C24–H241	– 3.7(6)	H241–C24–C25–H251	– 1.5(5)
C22–C23–C24	120.2(4)	C23–C24–C25	121.3(5)	H251–C25–C26–H261	2.2(8)	H261–C26–C27–H271	– 5.6(5)
C24–C25–C26	119.4(4)	C25–C26–C27	120.4(4)				
C22–C27–C26	120.8(4)						

no significant differences among them were observed. The reference compounds in each case were always more active than the test substances.

As a general conclusion, according to the results obtained, compounds **1**, **3**, **4** and **6** did not show specific inhibitory activity against isolated guinea pig ileum contractions induced by histamine and acetylcholine.

Discussion

A variety of techniques have been used in attempts to elucidate the receptor-bound conformation of muscarinic agonists and antagonists [19]. Despite these efforts, the active conformation of structurally flexible muscarinic ligands remains unclear [19].

From a number of X-ray diffraction studies of muscarinic agonists, Baker *et al.* [20] have suggested a range of 70° for both conformational dihedral angles τ_2 (NCCO) and τ_1 (CCOC) in the favored agonist conformation. For acetylcholine (Fig. 2), from a theoretical model and for the same angles, Schulman *et al.* [21] postulate the values of 189° and 132° for τ_1 and τ_2, respectively. The τ_1 value proposed for 3-hydroxyquinuclidinyl acetate is −71° [22].

The N−O distance for the *exo*- and *endo*-methyl conformations of tropine are ≃3.8 Å. The corresponding distance for 3-quinuclidinol was ~3.5 Å [23]. These compounds fit the simple distance geometry pharmacophore constraints established previously for the acetylcholine receptor [24]. The distance from the protonated nitrogen to the center of the nearest phenyl ring in the first M_1 selective muscarinic receptor antagonist (pirenzepine) [25], is 6−7 Å in the energetically favorable conformation [26]. (It must be noted that receptors responsible for smooth muscle contraction have a low affinity for pirenzepine [27].)

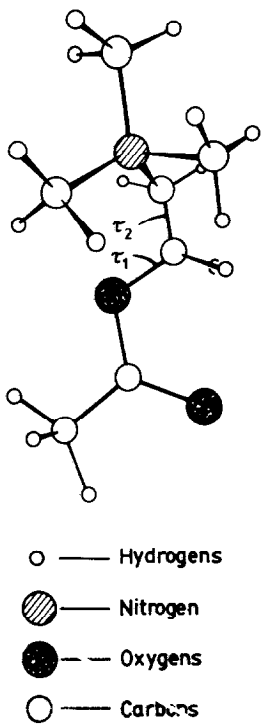


Fig. 2. Acetylcholine.

In the case of compound **1**, τ_1 = 106.57°, τ_2 = −59.09°, N−O distance = 2.853(?) Å and the distances between the nitrogen atom and the center of the phenyl rings are

Table V. ^{1}H NMR chemical shifts (δ, ppm) and multiplicities (*J*, Hz) for compounds **1**−**6**.[a,b]

	1[c]	2	3	4	5	6
H1(5)	3.4 brs $w_{1/2}$ 11	3.3 brs $w_{1/2}$ 10	3.2 brs $w_{1/2}$ 10	3.3 brs $w_{1/2}$ 12	3.3 brs $w_{1/2}$ 10	3.3 brs $w_{1/2}$ 11
H2(4)$_\beta$	2.5 dd ^2J 15.9 ^3J 4.0	2.5 dd ^2J 15.0 ^3J 4.2	2.4 dd ^2J 13.6 ^3J 4.2	2.5 dd ^2J 15.6 ^3J 4.3	2.6 dd* ^2J 15.0	2.5 dd ^2J 15.6 ^3J 4.2
H2(4)$_\alpha$	2.1 d	2.0 dd ^3J 1.5	2.0 d	2.1 dd ^3J 1.2	2.1 dd**	2.1 dd ^3J 1.2
H6(7)$_x$	1.9 m	1.9 m	1.9 m	1.9 m	1.9 m	1.9 m
H6(7)$_n$	1.5 m	1.5 m	1.5 m	1.5 m	1.6 m	1.5 m
Hα	2.8 t ^3J 5.6	2.7 t ^3J 5.4	2.6 t ^3J 6.0	2.5 t ^3J 6.6	2.4 t ^3J 7.0	2.3 t ^3J 7.0
Hβ	4.3 t	4.3 t	4.2 t	1.8 q*	1.8 q*	1.8 q
Hγ				4.3 t ^3J 6.0	4.3 t ^3J 6.0	4.1 t ^3J 6.0
H2′	5.0 s		5.0 s	5.0 s		5.0 s
H3′		1.9 s			1.9 s	
Aromatic	7.3 m	7.3 brs	7.2 m	7.3 brs	7.3 brs	7.2 m

[a]Spectra recorded in $CDCl_3$.
[b]Abbreviations: s, singlet; brs, broad singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet.
[c]Spectra recorded at 360 MHz.
*Not resolved.

Table VI. ^{13}C NMR chemical shifts (δ^a, ppm) for compounds **1**–**6**.

	1	2	3	4	5	6
C1(5)	59.39	59.43	59.54	58.76	58.70	58.75
C2(4)	47.58	47.62	47.68	47.46	47.29	47.33
C6(7)	27.78	27.82	27.78	27.86	27.83	27.91
C3	209.09	209.12	209.07	209.17	208.54	209.34
Cα	49.26	49.22	49.22	46.68	46.50	46.85
Cβ	64.32	64.84	65.27	28.30	28.08	28.20
Cγ				63.19	63.13	63.40
C=O(0)	172.13	174.79	171.38	172.22	174.54	171.53
C2′	57.30	56.64	45.74	57.32	56.64	46.31
C3′		27.21			27.15	
C1″	138.68	144.43	129.00	138.79	144.56	128.88
C2″	128.61*	128.01	123.28	128.57*	127.98	123.26
C3″	128.15*	128.01	129.00	128.08*	127.98	129.06
C4″	127.21	126.77	116.97	127.23	126.71	116.97
C5″	128.15*	128.01	151.46	128.08*	127.98	151.46
C6″	128.61*	128.01	118.59	128.57*	127.98	118.71

[a]Directly measured on the spectra.
*Values may be interchanged.

6.947 Å and 5.257 Å, respectively, in the crystalline state. As was deduced from the NMR studies of compounds **1**–**3**, the acyloxyethyl group seems to have several preferred conformations in solution and, consequently, the steric requirements presented above would be met in compounds **1**–**3**, as can be seen with molecular models.

By considering that the transition from full to partial agonism or antagonism was related to increased size of the terminal (acyl) group, it could be expected for compounds **1**–**3** to exhibit partial competitive antagonism.

In vitro pharmacological testing demonstrated that compounds **1** and **3** non-competitively inhibited acetylcholine-induced contractions of guinea pig ileum (Table VII).

Taking into account the previous literature data suggesting that efficacy at muscarinic receptors is critically dependent upon the size of the amino group [28], the non-competitive action of compounds **1** and **3** would be explained in terms of the shape and size of the cationic head, which would hinder the adequate interaction with the anionic site of the receptor. The carbonyl group would also interact unfavorably. The fact that compounds **4** and **6** have anti-cholinergic activities similar to those of **1** and **3** could be attributed to the same steric factors.

Table VII. Activities of the compounds **1, 3, 4** and **6** and diphenhydramine and atropine in the inhibition of contractions induced by acetylcholine and histamine in the isolated guinea pig ileum assay.[a]

Compd.	IC_{50} (M)[b]	
	histamine	acetylcholine
1	1.66×10^{-5}	1.89×10^{-5}
3	2.20×10^{-5}	9.32×10^{-6}
4	2.20×10^{-5}	2.77×10^{-5}
6	2.10×10^{-5}	1.10×10^{-5}
Diphenhydramine	1.52×10^{-7}	
Atropine		3.31×10^{-9}

[a]Data in this table represent the means of 3–4 measurements.
[b]IC_{50}: concentration required for 50% inhibition of the response elicited by the submaximal dose of acetylcholine (1.6×10^{-7} M) or histamine (6.4×10^{-7} M).

Experimental protocols

Chemistry

All melting points were taken in open capillary tubes and are uncorrected. Infrared spectra were determined using a Perkin–Elmer 1310 spectrophotometer. The ^1H NMR spectra were recorded using a Varian EM390 operating at 90 MHz. The ^{13}C NMR spectra were determined on a Varian FT80 spectrometer operating at 20 MHz. Noise-decoupled and single frequency off-resonance-decoupled spectra were obtained. The elemental analyses were made in a Perkin–Elmer Elemental Analyzer model 240B.

*Synthesis of the esters **1**–**6***
General procedure. To a stirred solution of the corresponding *N*-substituted nortropinone (4 mmol) and the acid (4 mmol) in anhydrous methylene chloride (10 ml), was added dropwise a solution of DCC (5 mmol) and DMAP (0.4 mmol) in anhydrous methylene chloride (5 ml). The mixture was stirred at room temperature for 3 h. Then, the reaction mixture was filtered, the solvent removed *in vacuo* and the residual oil was treated with ethyl ether. The ethereal suspension thus formed was filtered and the filtrate evaporated under reduced pressure. The residual oil was purified on a silica gel column prepacked in hexane. Elution of the column with ethyl acetate–hexane (7:3) gave the desired ester as an oil which was crystallized from hexane (except compound **5**).

*N-[β-(Diphenylacetyloxy)ethyl]nortropinone **1***
This compound was obtained in 61% yield; mp: 62–63°C. IR(KBr) ν CO 1710 cm^{-1}. ^1H NMR (Table V). ^{13}C NMR (Table VI). Anal. calcd. for $C_{23}H_{25}NO_3$: C: 76.01; H: 6.93; N: 3.99; found: C: 76.16; H: 7.02;N: 3.60.

*N-[β(α,α-Diphenylpropionyloxy)ethyl]nortropinone **2***
This compound was obtained in 60% yield; mp: 96–98°C. IR(KBr) ν CO 1715 cm^{-1}. ^1H NMR (Table V); ^{13}C NMR (Table VI). Anal. calcd. for $C_{24}H_{27}NO_3$: C: 76.36; H: 7.20; N: 3.71; found: C: 76.33; H: 7.08; N: 3.99

N-*[β-(Xanten-9-carbonyloxy)ethyl]nortropinone* **3**
This compound was obtained in 70% yield; mp: 96–98°C. IR(KBr) ν CO 1710 cm^{-1}. ^1H NMR (Table V); ^{13}C NMR (Table VI). Anal. calcd. for $C_{23}H_{23}NO_4$: C: 73.19; H: 6.14; N: 3.71; found: C: 73.40; H: 6.52; N: 3.68.

N-*[γ-(Diphenylacetyloxy)propyl]nortropinone* **4**
This compound was obtained in 73% yield; mp: 60–62°C. IR(KBr) ν CO 1715 cm^{-1}. ^1H NMR (Table V); ^{13}C NMR (Table VI). Anal. calcd. for $C_{24}H_{27}NO_3$: C: 76.38; H: 7.21; N: 3.71; found: C: 76.69; H: 7.27; N: 3.63.

N-*[γ-(α,α-Diphenylpropionyloxy)propyl]nortropinone* **5**
This compound was obtained in 60% yield (oil). IR (film) ν CO 1710 cm^{-1}. ^1H NMR (Table V); ^{13}C NMR (Table VI). Hydroiodide derivative: mp: 180–182°C (from acetone–hexane). Anal. calcd. for $C_{25}H_{30}INO_3$: C: 57.81; H: 5.82; N: 2.70; found: C: 57.68; H: 5.83; N: 2.64.

N-*[γ-(Xanten-9-carbonyloxy)propyl]nortropinone* **6**
This compound was obtained in 80% yield; mp: 78–79°C. IR(KBr) ν CO 1710 cm^{-1}. ^1H NMR (Table V); ^{13}C NMR (Table VI). Anal. calcd. for $C_{24}H_{25}NO_4$: C: 73.65; H: 6.39; N: 3.58; found: C: 73.30; H: 6.45; N: 3.70.

Pharmacological methods

General tissue preparation
Distal ileum was obtained from male albino guinea pigs (300–500 g). All animals were fasted overnight and killed by cervical dislocation and then exanguinated by cutting the jugular vein. Segments of the distal ileum, approximately 20 cm, long were excised 5 cm above the ileocecal junction and immediately placed in aerated Tyrode's solution of the following composition (mM): NaCl 136.9, KCl 2.68, $CaCl_2$ 1.80, $MgCl_2$ 1.05, $NaHCO_3$ 11.90, NaH_2PO_4 0.42 and glucose 5.55.

Segments of ileum, 25 mm long, were suspended in a 20 ml organ bath containing an appropriate solution which was kept at 37°C and aerated with O_2 containing 5% CO_2. Contractions were recorded isotonically at a loading tension of 1.2 g using an electromechanical transducer (HSE MOD 368) connected to a polygraph (Linear Corder Mark VII).

Anti-histaminic activity
A dose–response curve for histamine dihydrochloride was determined with concentrations ranging from 2.5×10^{-9}–2.56×10^{-6} M at a rate factor of 2 and the tissue after washing with Tyrode's solution, was allowed to equilibrate. 10 min later, a second dose–response curve was determined and again the tissue washed and allowed to equilibrate. After equilibration, submaximal doses of histamine dihydrochloride were added to the bath at 10 min intervals until a constant response was obtained. This contraction (in mm) was taken as the 100% value.

The preparation was then pretreated with increasing doses of the products being studied 5 min before the addition of submaximal concentrations of histamine dihydrochloride. 10 min after each dose level addition, a submaximal concentration of the agonist was always added in order to check that the 100% contraction value was reached.

Results were obtained as the percent of inhibition of the maximal response obtained with submaximal concentration of histamine dihydrochloride. The dose which elicits 50% inhibition of the maximal possible contraction (IC_{50}) was determined by regression analysis.

Anti-cholinergic activity
A dose–response curve for acetylcholine hydrochloride was determined with concentrations ranging from 1×10^{-8}–5.12×10^{-6} M at a rate factor of 2 and the tissue after washing with Tyrode's solution was allowed to equilibrate. 10 min later, a second dose–response curve was determined and again the tissue washed and allowed to equilibrate. After equilibration, submaximal doses of acetylcholine hydrochloride were added to the bath at 10 min intervals until a constant response was obtained. This contraction (in mm) was taken as the 100% value.

The preparation was then pretreated with increasing doses of the compounds being studied 5 min before the addition of submaximal concentrations of acetylcholine hydrochloride. 10 min after each dose level addition, a submaximal concentration of the agonist was always added in order to check that the 100% contraction value was reached.

Results were obtained as the percent inhibition of the maximal response obtained with the submaximal concentration of acetylcholine hydrochloride. The dose which elicits 50% inhibition of the maximal possible contraction (IC_{50}) was determined by regression analysis.

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