Synthesis and Structural, Conformational, and Pharmacological Study of Some Esters Derived from 3-Phenethyl-3-azabicyclo[3.2.1]octan-8-β-ol and the Corresponding *N*-Endo-methyl Quaternary Derivatives

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Abstract □ A series of 8-β-acyloxy-3-phenethyl-3-azabicyclo[3.2.1]octane and its *N*-endo methiodides were synthesized and studied by ^1H and ^{13}C NMR spectroscopy, and the crystal structure of 8-β-*p*-chlorobenzoyloxy-3-phenethyl-3-azabicyclo[3.2.1]octane methiodide (**2c**) was determined by X-ray diffraction. In $CDCl_3$ solution, **1b–1e** display the same preferred conformation. The cyclopentane and piperidine rings adopt an envelope conformation flattened at C-8 and a distorted chair conformation puckered at C-8 and flattened at N-3, respectively, with the N-substituent in the equatorial position with respect to the piperidine ring. In all cases, methylation takes place from the endo position. The ability of the title compounds to antagonize the acetylcholine-induced contraction of guinea pig ileum is also reported. An initial structure–activity relationship is proposed.

The synthesis, the ^1H NMR, ^{13}C NMR, X-ray diffraction data, and the pharmacological study of several potential anticholinergic esters derived from condensed piperidine bi- and tricyclanols have been reported previously.[1–6] In order to gain additional information concerning the effects of stereochemical factors on anticholinergic activity, and in connection with our interest in the preparation and the structural study of 3-azabicyclo[3.2.1]octane derivatives,[7–9] we synthesized a new series of esters derived from the 3-azabicyclo [3.2.1]octan-8-β-ol (Scheme I) that is structurally related to the tropane skeleton (Figure 1). The structural, conformational, and pharmacological study of **1b–1e** and several *N*-endo-methyl quaternary derivatives (**2a–2d**) has been carried out with the objective to explore the structure–activity relationship.

Results

Chemistry—3-Phenethyl-3-azabicyclo[3.2.1]octan-8-β-ol (**1a**) was prepared according to the reported procedure.[7] Esterification of **1a** was carried out following conventional procedures. Treatment of the esters **1** with methyl iodide yielded **2a–2d**.

In all cases, the endo-methyl product was obtained. This is not a surprising result because, in 1967, D. R. Brown et al.[10] stated that the tendency to preferred axial or boat-axial quaternization is greater in camphidine (3-azabicyclo[3.2.1]octane) than in simpler piperidines.

The tight $-CH_2-CH_2-$ bridge in camphidines has the effect of projecting the *N*-axial bond away from the piperidine ring, which may partly explain the relatively easier than expected axial quaternization in this system.

By considering that the geometry of the bicyclic skeleton in the quaternization transition state would be similar to that found for **2c** in the crystalline state (Figure 2[11]), it is easy to understand the *N*-endo quaternization in **1**.

Description of the Structure of 2c—The main crystallographic data and the structure determinations are given in Table I.[12–17] Figure 2 shows a view of the molecule and the numbering used in the crystallographic study. The bicyclic system shows a distorted chair-envelope conformation similar to that found for some azabicyclic compounds:[7,8] the six-membered ring is very flattened at the *N*1 atom and puckered at the C4 atom, and the atoms are deviated −0.372(7) and 0.870(9) Å, respectively, from the plane defined by C2, C3, C5, and C6 atoms. This flattening can be explained by the steric effect of methyl groups on H81 and H72. Ring puckering coordinates[18] are Q_T = 0.623(9), $\phi = -179(1)°$, and $\theta = 32.0(7)°$. The five-membered ring is a nearly perfect envelope with the C4 at the flap, being 0.74(1) Å apart from the plane defined by the other four atoms (C3, C5, C7, C8).

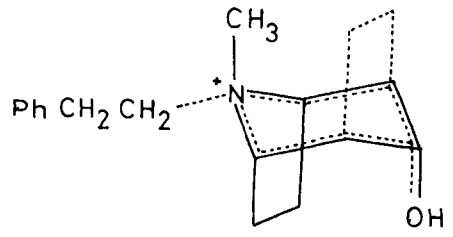

Figure 1—Molecular superposition of atropine and **1a** (dashed line).

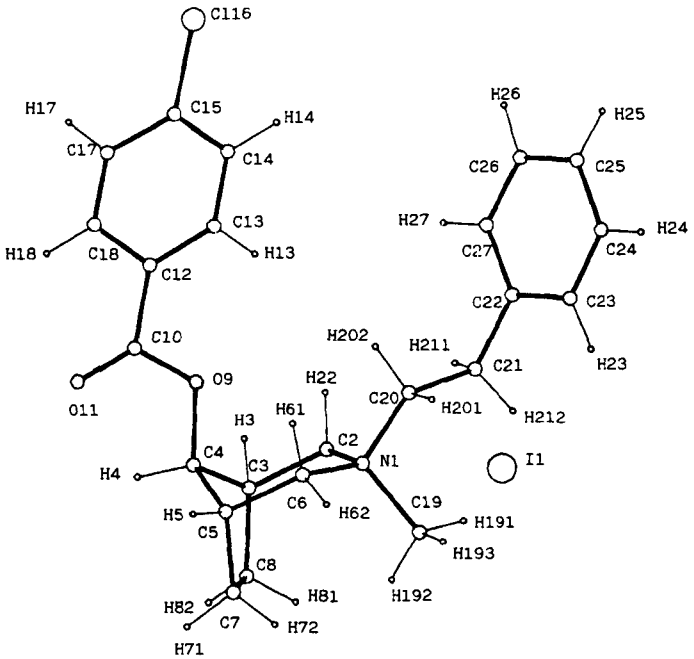

Figure 2—PLUTO view of the molecule showing the atomic numbering (ref 11).

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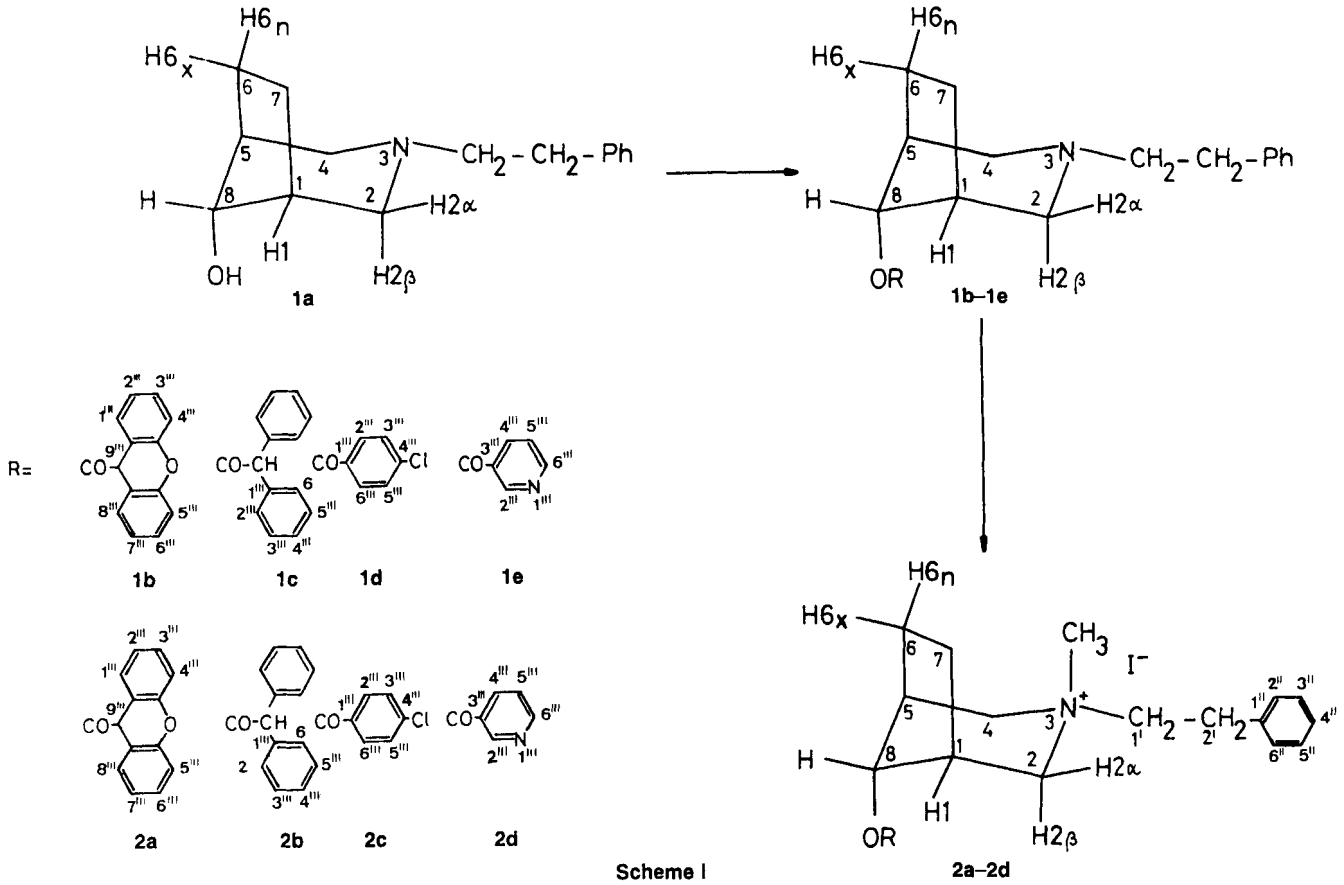

Scheme I

Ring puckering coordinates are $Q_T = 0.502(9)$, and $\phi = -146(1)°$. The bicyclic system has a pseudo mirror plane passing through N1-C4 atoms. The O9 and C19 atoms also lie in this plane. The *p*-chlorobenzoyloxy and the methyl groups are in axial and pseudo-axial positions, respectively, while the phenethyl group is in a pseudo-equatorial position with respect to the piperidine ring.

Nuclear Magnetic Resonance Spectra—The ^1H and ^{13}C NMR spectra of **1b–1e** and **2a–2d** show a great similarity. Assignments of proton and carbon resonances were made from the data of **1a**.[7]

In the case of the ^{13}C NMR spectra, substituent steric and electronic effects on ^{13}C chemical shifts[19] and signal multiplicity obtained from off-resonance decoupled spectra were taken into consideration.

The ^1H and ^{13}C NMR data of **1d** and **2c** are summarized in Tables II and III, respectively, as representative compounds of the two series studied.

Conformational Study—*Compounds **1b–1e***—From the ^1H and ^{13}C NMR data of **1b–1e**, the following general features for the bicyclic system were deduced: the cyclopentane and piperidine rings adopt an envelope conformation flattened at C8 and a distorted chair conformation puckered at C8 and flattened at N3 respectively, with the N-substituent in the equatorial position with respect to the piperidine ring. These conclusions are supported by the following results. (*1*) In the ^1H NMR spectra, the range of values of $\omega 1/2$ of 9–10 Hz of H1(5) is in a good agreement with previously reported values for a chair conformation in related bicyclic systems.[7,8,20,21] (*2*) It was found that in all cases, the following relations are present: $^3JH2(4)_\beta$—H1(5) ≃ $^3JH2(4)_\alpha$—H1(5) and $^3JH8$-H1(5) ≃ 5Hz. Hence, the dihedral angles $H2(4)_\alpha$—C—C—H1(5) and $H2(4)_\beta$—C—C—H1(5) should have similar values and H8—C—C—H1(5) must be <60° according to the Karplus relationship.[22] (*3*) In the ^{13}C NMR spectra, the chair conformation adopted by the piperidine ring is confirmed by the C2(4) chemical shifts (Table III). For a boat conformation, these carbon signals would be shifted to higher field because of the steric compressing effect due to the eclipsing between $H2(4)_\beta$ and H1(5) atoms.[20,21,23–25] (*4*) The chemical shift of C1′ of the phenethyl group is in agreement with an equatorial disposition of the N-substituent.[26,27]

Hence, a good agreement of the preferred conformation for the bicyclic system of **1b–1e** with regard to **1a** in solution and in the solid state[7] has been observed. Moreover, the global minimum energy conformer deduced by Molecular Mechanics Method (MM2) for **1a**[9] is the same as that found in solution and in the solid state.

*Compounds **2a–2d***—From the ^1H NMR and ^{13}C NMR data of **2a–2d** it can be deduced that the preferred conformation in $CDCl_3$ solution is analogous to that observed for **1b–1e**, but the flattening at C2(4) seems to be more pronounced than that observed in **1b–1e** in order to relieve the steric effect exerted by the endo-methyl group on H6(7)n. Compounds **2a–2d** show analogous conformation in solution to that found for **2c** in the crystal state for the bicyclic system. These conclusions are supported by similar arguments to those discussed for **1b–1e**. However, it is necessary to remark the increased values of $\omega 1/2$ of H1(5) in **2a–2d** (≃13 Hz) with respect to the same values in **1b–1e** (≃10 Hz). This fact confirms a greater flattening of the piperidine ring in **2a–2d**.

Pharmacology—Anticholinergic in vitro properties of **1b**, **1c**, **1e**, and **2a–2d** were evaluated on isolated guinea pig ileum preparations. Atropine was used as reference compound. Results of these experiments are summarized in Table IV. All compounds studied presented some degree of potency in the inhibition of contractions induced by acetylcholine in the guinea pig ileum preparation. Compounds **1b**, **2a**, and **2c** were more potent than the rest of the compounds and their IC_{50} values were 3.39×10^{-7}, 2.67×10^{-6}, and 5.39×10^{-7} M, respectively. The IC_{50} values of most of the compounds studied against acetylcholine were near 10^{-5} M or higher.

Discussion

In our previous study about the structural and M_2-antagonist properties[28–33] of some *N*-β (or γ)-acyloxyalkylnortropinones and norgranatanones[2,6] we concluded that pharmacological action of these compounds would be explained in terms of the shape and size of the cationic head that would hinder an adequate interaction with the anionic site of

Table I—Experimental Data and Structure Refinement Procedures

Parameter	Data/Procedure
Crystal Data	
Formula	$C_{23}H_{27}NO_2Cl1$
Crystal size, mm	0.23 × 0.33 × 0.30
Symmetry	Monoclinic, P21
Unit cell determination	Least-squares fit from 45 reflexions ($\theta < 43°$)
Unit cell dimensions, Å	7.249(1), 18.330(6), 9.021(1) 90.0, 110.8(1), 90.0
Packing	
V(A^3), Z	1120.7(3), 2
Dc(g · cm^{-3}), M, F(000)	1.4138, 477.031, 672
μ, cm^{-1}	14.271
Experimental data	
Technique	Four circle diffractometer: Enraf-Nonius CAD 4 Bisecting geometry Graphite oriented monochomator: MoKα $\omega/2\theta$ scans Detector apertures 1 × 1, up θmax. 29°
Number of reflexions	
Measured	3041
Observed	2643 ($1 > 2\sigma(1)$ criterion)
Range of hkl	0 9, 0 25, −12 12, (sinθ/λ)max 0.70
Max-min transmission factors	1.337, 0.710[a]
Solution and refinement	
Solution	Direct methods
Refinement	L.S. on Fobs with 1 block
Number of variables	252
H atoms	Difference Fourier synthesis
Final shift/error	0.07
W-scheme	Empirical as to give no trends in $\langle\omega\Delta^2F\rangle$ versus $\langle Fo\rangle$ and $\langle\sin\theta/\lambda\rangle$
Final R and Rw	0.057, 0.075
Computer and programs	VAX 11/750, Multan80,[b] X-ray76,[c] Pesos,[d] Parst[e]
Scattering factors	Int. Tables X-ray Crystallography[f]
Anomalous dispersion	Int. Tables X-ray crystallography[f]

[a] Reference 12. [b] Reference 13. [c] Reference 14. [d] Reference 15. [e] Reference 16. [f] Reference 17.

the receptor. In the present study, information about the head group geometry with regard to anticholinergic action is provided by the evaluation of several esters of 3-phenethyl-3-azabicyclo[3.2.1]octan-8-β-ol which possess a conformationally rigid azabicyclic ring (**1a**) cationic head group that is sterically related to tropine, the cationic head group of atropine.

Taking into account our previous molecular mechanics calculations (MM2 program) about the conformational preferences of **1a**[9] and the results obtained through molecular modelling studies by F. I. Carrol et al.[34] for tropine and 3-quinuclidinol, the fact that structures like **1** and **2** do not lead to anticholinergics better than atropine would be explained in terms of the size of the phenethyl group, which would hinder the adequate interaction with the anionic site of the receptor.

Experimental Section

All melting points were taken in open capillary tubes and are uncorrected. Infrared spectra were determined on a Perkin-Elmer 883 spectrophotometer. The ^{1}H NMR spectra were recorded on a Brucker WM 360 spectrometer operating at 360 MHz, and the ^{13}C NMR spectra were determined on a Brucker WP 80 spectrometer operating at 20 MHz. Noise decoupled and single frequency off resonance decoupled spectra were obtained. The elemental analyses were determined using a Perkin-Elmer elemental analyzer (Model 240B).

Synthesis of the Esters (1b–1e): General Procedure—*Method A*—A solution of DCC (*N,N'*-dicyclohexylcarbodiimide; 2.5 mmol) and DMAP (4-dimethylaminopyridine; 0.2 mmol) in anhydrous methylene chloride (5 mL) was added in a dropwise manner to a stirred solution of 3-phenethyl-3-azabicyclo[3.2.1]octan-8-β-ol[7] (2 mmol) and the corresponding acid (2 mmol) in anhydrous methylene chloride (10 mL). The mixture was stirred at room temperature for 4 h. Then, the reaction mixture was filtered, the solvent was removed under reduced pressure, the residual oil was treated with ethyl ether, and the filtrate was evaporated under reduced pressure.

Method B—A solution of the acyl chloride (2 mmol), triethylamine (2 mmol), and 3-phenethyl-3-azabicyclo[3.2.1]octan-8-β-ol[7] (2 mmol) in anhydrous methylene chloride (10 mL) was stirred at room temperature for 3 h. The reaction mixture was washed with aqueous potassium carbonate and extracted with methylene chloride (4 × 50 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure.

*8-β-(Xanten-9‴-carbonyloxy)-N-phenethyl-3-azabicyclo[3.2.1]octane (**1b**)*—This compound was obtained (method A) in 75% yield, mp 90–92 °C (from hexane); IR (KBr): ν CO, 1710 cm^{-1}.

Anal.—Calc. for $C_{29}H_{29}NO_3$: C, 79.24; H, 6.65; N, 3.18. Found: C, 79.58; H, 7.03; N, 3.35.

*8-β-(Diphenylacetoxy)-N-phenethyl-3-azabicyclo[3.2.1]octane (**1c**)*—This compound was obtained (method A) in 75% yield, mp 77–79 °C (from hexane); IR (KBr): ν CO, 1720 cm^{-1}.

Anal.—Calc. for $C_{29}H_{31}NO_2$: C, 81.84; H, 7.34; N, 3.29. Found: C, 82.04; H, 7.22; N, 3.56.

*8-β-(4‴-Chlorobenzoyloxy)-N-phenethyl-3-azabicyclo[3.2.1]octane (**1d**)*—This compound was obtained (method B) and purified on a silica gel column. Elution of the column with hexane:ethyl acetate (9:1, v/v) gave the desired ester in 74% yield, mp 105–107 °C (from hexane); IR (KBr): ν CO 1710 cm^{-1}; ^{1}H NMR (see Table II); ^{13}C NMR (see Table III).

Anal.—Calc. for: $C_{22}H_{24}ClNO_2$: C, 71.43; H, 6.54; N, 3.79 Found: C, 71.23; H, 6.28; N, 3.83.

*8-β-(3‴-Pyridincarbonyloxy)-N-phenethyl-3-azabicyclo[3.2.1]octane (**1e**)*—This compound was obtained (method A) and purified on a silica gel column. Elution of the column with hexane:ethyl acetate (7:3, v/v) gave the desired ester in 70% yield, mp 51–53 °C (from hexane); IR (KBr): ν CO, 1720 cm^{-1}.

Anal.—Calc. for: $C_{21}H_{24}N_2O_2$: C, 74.96; H, 7.19; N, 8.32. Found: C, 75.18; H, 7.32; N, 8.63.

Synthesis of the Methiodides (2a–2d): General Procedure—A solution of 8-β-acyloxy-*N*-phenethyl-3-azabicyclo[3.2.1]octane (1 mmol) in acetone (for **2d**, in ethanol; 5 mL) containing excess CH_3I was heated under reflux for 24 h. The methiodide was isolated by filtration.

*8-β-(Xanthen-9‴-carbonyloxy)-N-phenethyl-3-azabicyclo[3.2.1]octane Methiodide (**2a**)*—This compound was obtained in 68% yield, mp 180–182 °C (from isopropanol); IR (KBr): ν CO, 1735 cm^{-1}.

Anal.—Calc. for: $C_{30}H_{32}INO_3$: C, 62.05; H, 5.55; N, 2.41. Found: C, 61.94; H, 5.45; N, 2.27.

*8-β-(Diphenylacetoxy)-N-phenethyl-3-azabicyclo[3.2.1]octane Methiodide (**2b**)*—This compound was obtained in 70% yield, mp 180–183 °C (from isopropanol); IR (KBr): ν CO, 1730 cm^{-1}.

Anal.—Calc. for: $C_{30}H_{34}INO_2$: C, 63.59; H, 6.05; N, 2.47. Found: C, 63.21; H, 6.14; N, 2.60.

*8-β-(4‴-Chlorobenzoyloxy)-N-phenethyl-3-azabicyclo[3.2.1]octane Methiodide (**2c**)*—This compound was obtained in 63% yield, mp 185–187 °C (from absolute ethanol); IR (KBr): ν CO, 1730 cm^{-1}. ^{1}H NMR (see Table II); ^{13}C NMR (see Table III).

Anal.—Calc. for: $C_{23}H_{27}ClINO_2$: C, 53.97; H, 5.32; N, 2.74 Found: C, 54.18; H, 5.03; N, 3.01.

*8-β-(3‴-Pyridincarbonyloxy)-N-phenethyl-3-azabicyclo[3.2.1]octane Dimethiodide (**2d**)*—This compound was obtained in 80% yield, mp 225–228 °C; IR (KBr): ν CO, 1725 cm^{-1}.

Anal.—Calc. for: $C_{23}H_{30}I_2N_2O_2$: C, 44.53; H, 4.87; N, 4.52 Found: C, 44.25; H, 5.03; N, 4.18.

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 distal ileum ~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, 126.9; KCl, 2.68; $CaCl_2$, 1.80; $MgCl_2$, 1.05;

Table II—Proton Magnetic Parameters for 1d and 2c

Chemical Shift[a]	δ, ppm		Coupling Constants[b]	J, Hz	
	1d	2c		1d	2c
$H6(7)_x$(m)	1.70	2.13	$H2(4)_\alpha$-$H2(4)_\beta$	−10.7	−12.8
$H6(7)_n$(m)	1.70	2.13	H8-H1 (5)	4.8	5.0
H1(5) (brs)	2.26	2.73	H1′-H2′	7.6	—
	W½ ≃ 10 Hz	W½ ≃ 13 Hz	H2‴-H3‴	8.5[f]	7.7[f]
$H2(4)_\beta$(d)	2.52	4.10	H5‴-H6‴	8.5[f]	7.7[f]
$H2(4)_\alpha$(d)	2.56	3.73	—	—	—
H8 (t)	4.91	5.00	—	—	—
H1′ (m)[c]	2.71	3.86	—	—	—
H2′ (m)[c]	2.56	3.23	—	—	—
CH_3 (s)	—	3.80	—	—	—
Ar (m)[d]	7.24–7.12	7.32–7.20	—	—	—
H2‴ (6‴)[e]	7.95	7.94	—	—	—
H3‴ (5‴)[e]	7.34	7.43	—	—	—

[a] Spectra recorded at 360 MHz in $CDCl_3$; abbreviations: d, doublet; dd, doublet of doublets; m, multiplet; s, singlet; t, triplet; brs, broad singlet; tabulated chemical shifts correspond to the center of the multiplet, except for the aromatic protons in which the interval is given; error: ±0.05 ppm; the $H6(7)_x$ and $H6(7)_n$ signals overlap. [b] Error: ±0.5 Hz. [c] These protons appear as a four spin A_2B_2 system. [d] These protons appear as a low resolution four spin AA′BB′ system. [e] H2‴(6‴) and H3‴(5‴) appear as a four spin system AA′XX′. [f] This value was assigned assuming that $^3JH2''' - H5''' = {}^3JH3''' - H6''' \simeq 0$ Hz

Table III—Carbon-13 Chemical Shifts for 1d and 2c

Group	Chemical Shift, ppm[a]	
	1d	2c
C1(5)	36.51	35.73
C2(4)	53.14	63.87
C6(7)	24.78	22.44
C8	75.37	73.99
C1′	59.67	70.87
C2′	33.53	29.19
C=O	165.10	164.24
$-CH_3$	—	54.83
C1″	140.86	134.92
C2″(6″)[b]	128.12	129.05
C3″(5″)[b]	128.21	128.98
C4″	125.85	127.23
C1‴	128.00	127.38
C2‴(6‴)	130.95	128.98
C3‴(5‴)	129.13	130.98
C4‴	139.30	140.43

[a] Measured in $CDCl_3$. [b] Signal may be interchanged.

Table IV—Activities of 1b, 1c, 1e, and 2a–2d and Atropine in the Inhibition of Contractions Induced by Acetylcholine in the Isolated Guinea[a]

Drug	Acetylcholine
	IC_{50}, M[b]
1b	3.39×10^{-7}
1c	$>10^{-5}$
1e	$>10^{-5}$
2a	2.67×10^{-6}
2b	9.92×10^{-6}
2c	5.39×10^{-7}
2d	$>10^{-4}$
Atropine	3.31×10^{-9}

[a] Data in this table represent the mean from two measurements. [b] Concentration required for 50% inhibition of the response elicited by the submaximal dose of acethylcholine (1.28×10^{-6} M).

$NaHCO_3$, 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).

Anticholinergic Activity—A dose–response curve for acetylcholine chloride was determined with concentrations ranging from 1×10^{-8} to 5.12×10^{-6} M at a rate factor of 2. The tissue, after washing with Tyrode's solution, was allowed to equilibrate. Ten minutes later, a second dose–response curve was determined and again the tissue was washed and allowed to equilibrate. After equilibration, submaximal doses of acetylcholine chloride 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 concentrations of the products studied were added to the preparation 5 min before the addition of the submaximal concentration of acetylcholine chloride. Ten minutes 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 are reported as percentage of inhibition of the maximal response obtained with submaximal concentration of acetylcholine chloride. By regression analysis, the dose which elicits 50% inhibition of the maximal possible contraction (IC_{50}) was determined.

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