and 12.9 Hz, one of 2-CH_2), 8.85 and 9.09 (2 H and 1 H, respectively, each s, 2'-CH, 4'-CH, and 6'-CH). Anal. ($C_{11}H_{15}N_3$·HCl·0.75H_2O) C, H, N.

3-(2-Methyl-1,3-pyrimidin-5-yl)quinuclidine dihydrochloride (40) was prepared from **38** (0.57 g, 2.6 mmol) via **42** using the procedure described for the synthesis of **39**. The product obtained (0.1 g, 19%) was dissolved in MeOH (2 mL), and a solution of ethereal HCl was added to give the dihydrochloride salt: mp 256–258 °C (MeOH/Et_2O); MS m/z 203 (M^+ of free base); ^1H NMR (D_2O) δ 1.84–1.94, 2.06–2.27, and 2.32–2.44 (2 H, 2 H, and 1 H, respectively, each m, 4-CH, 5-CH_2, and 8-CH_2), 2.78 (3 H, s, CH_3), 3.32–3.54, 3.56–3.62, 3.66–3.74, and 3.82–3.90 (4 H, 1 H, 1 H, and 1 H, respectively, each m, 2-CH_2, 3-CH, 6-CH_2, and 7-CH_2), 8.90 (2 H, s, 4'-CH and 6'-CH). Anal. ($C_{12}H_{17}N_3$·2HCl) C, H; N: calcd 52.18; found, 51.58.

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Registry No. **8a**, 32111-21-0; **8b**, 58139-06-3; **8c**, 58139-08-5; **8d**, 58139-03-0; **8e**, 99968-71-5; **8f**, 59021-15-7; **8g**, 99969-02-5; **8h**, 125060-83-5; **8i**, 98140-48-8; **8j**, 137696-69-6; **8k**, 137741-99-2; **8l**, 125060-68-6; **8m**, 137696-68-5; **8n**, 125060-66-4; **8o**, 125060-75-5; **9b**, 137696-70-9; **10b**·HCl, 137696-74-3; **11b**, 137696-76-5; **12a**, 125059-50-9; **12a**·HCl, 125060-03-9; **12b**, 125059-52-1; **12b** 1.5 oxalate, 137696-85-6; **12c**, 125059-69-0; **12c**·2HCl, 125060-18-6; **12d**, 125059-53-2; **12d**·2HCl, 125060-05-1; **12e**, 137696-86-7; **12e** 1.5 oxalate, 137696-87-8; **12**, 137696-88-9; **12f** oxalate, 137696-89-0; **13a**, 135276-26-5; **13e**, 137696-73-2; **13f**, 137696-71-0; **14a**, 137696-72-1; **15e**, 137696-75-4; **15o**, 137696-77-6; **17a**, 135276-28-7; **17a**·2HCl, 137696-90-3; **17b**, 137696-91-4; **17b**·2.1HCl, 137696-92-5; **17c**, 137696-93-6; **17c**·2HCl, 125060-43-7; **17d**, 137696-94-7; **17d**·2HCl, 137696-95-8; **17e**, 125085-90-7; **17e** oxalate, 137696-96-9; **17f**, 125060-35-7; **17f** oxalate, 125060-36-8; **17g**, 137696-97-0; **17g**·2HCl, 125060-48-2; **17h**, 137696-98-1; **17h**·HCl, 137696-99-2; **17i**, 125060-88-0; **17i** 2 oxalate, 125060-89-1; **17j**, 137697-00-8; **17j**·HCl, 137697-01-9; **17k**, 137697-02-0; **17k**·HCl, 137697-03-1; **17l**, 137697-04-2; **17l** 1.5 oxalate, 137697-05-3; **17m**, 137697-06-4; **17m**·1.5HCl, 137697-07-5; **17n**, 137697-08-6; **17n**·2.5HCl, 137697-09-7; **17o**, 137697-10-0; **17o**·2HCl, 125060-39-1; **18a**, 135276-29-8; **18a**·1.5HCl, 137697-11-1; **18b**, 125060-22-2; **18b** 1.5 oxalate, 125060-23-3; **18c**, 125060-54-0; **18c**·1.4HCl, 137697-12-2; **18d**, 137697-13-3; **18d**·1.5HCl, 137697-14-4; **18e**, 125060-54-0; **18e** oxalate, 137697-15-5; **18f**, 125060-37-9; **18f** oxalate, 125060-38-0; **18g**, 137697-16-6; **18g**·2.1HCl, 137697-17-7; **18h**, 137697-18-8; **18h**·2HCl, 125060-53-9; **18i**, 125060-41-5; **18i**·2.1HCl, 137697-19-9; **18j**, 137697-20-2; **18j**·1.1HCl, 137697-21-3; **18k**, 137697-22-4; **18k**·HCl, 137697-23-5; **18l**, 137697-24-6; **18l**·HCl, 125060-29-9; **18m**, 137697-25-7; **18m**·1.2HCl, 125060-33-5; **18n**, 137697-26-8; **18n**·2.4HCl, 137697-27-9; **18o**, 137697-28-0; **18o**·HCl, 125060-40-4; **19a**, 137697-29-1; **19a**·2HCl, 137697-30-4; **19d**, 137697-31-5; **19d**·2HCl, 125060-30-2; **20a**, 137697-32-6; **20a** oxalate, 137697-33-7; **20d**, 137697-34-8; **20d**·1.4HCl, 137697-35-9; **21**, 121564-88-3; **22**, 38206-86-9; **23**, 137696-78-7; **24**, 137696-79-8; **25b**, 125076-10-0; **25b** oxalate, 125076-11-1; **26**, 125059-87-2; **26**·HCl, 125060-44-8; **27a**, 137697-38-2; **27a** oxalate, 137697-39-3; **27b**, 137697-40-6; **27b** oxalate, 137697-41-7; **28**, 137697-44-0; **28**·HCl, 125060-90-4; **29**, 137697-42-8; **29** oxalate, 137697-43-9; **30**, 137697-45-1; **30** oxalate, 137697-46-2; **31**, 137697-47-3; **31** oxalate, 137697-48-4; **32**, 125059-54-3; **32**·2HBr, 125060-06-2; **33**, 137696-84-5; **34**, 137718-39-9; **34**·2HCl, 137697-49-5; **37**, 125059-59-8; **38**, 137696-80-1; **39**, 125059-60-1; **39**·HCl, 125060-09-5; **40**, 125059-61-2; **40**·2HCl, 125060-10-8; **41**, 137696-81-2; **41**·HCl, 137696-83-4; **42**, 137696-82-3; **43**, 137697-36-0; **43**·HCl, 137697-37-1; 2,6-dichloropyrazine, 4774-14-5; 2,6-diiodopyrazine, 58138-79-7; quinuclidin-3-one, 3731-38-2; 1-azabicyclo[2.2.1]heptan-3-one, 21472-89-9; 1-azabicyclo[3.2.1]octan-6-one, 45675-76-1; 3,6-dichloropyridazine, 141-30-0; 5-bromopyridine, 4595-59-9; 2-methyl-5-bromo-1,3-pyrimidine, 7752-78-5.

Supplementary Material Available: Table of microanalytical data for novel compounds and table of HRMS data for novel compounds (4 pages). Ordering information is given on any current masthead page.

Conformational Studies of Muscarone Analogues: X-ray Analysis and Molecular Mechanics Calculations†

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The X-ray structure of muscarone analogues **3** and **4** was determined and compared with that of muscarone (**1**, iodide and picrate salts), muscarine **2**, dioxolane **5**, oxathiolane **6**, and tetrahydrofuran **7**. In order to better define the pharmacological stereoselectivity of muscarone, the conformational profiles of compounds **1**, **2**, **3**, and **5** were analyzed using Allinger's MM2(85) program or, in the case of **4**, by ^1H NMR spectroscopy. The conformation of the ring in **1** proved similar to that of the other derivatives. MM2 calculations predicted a preferred gauche arrangement of the side chain for **1** and its analogues; such an arrangement was also observed in the solid state of muscarone picrate. Thus, the antiperiplanar arrangement reported for crystalline muscarone iodide appears to be due to crystallographic packing forces. As a consequence, the rationalization of the pharmacological profile of **1** based on the antiperiplanar arrangement is now highly questionable. The lack of stereoselectivity of **4** can be attributed to the absence of a stereocenter at C-2 whereas, in our opinion, there are currently no sound explanations for the low values of eudismic ratios for the muscarone enantiomers.

There is an increasing interest in agents capable of stimulating cholinergic transmission following the evidence that the receptors of the muscarinic system consist of five molecular forms, m_1–m_5,[1,2] and three pharmacological identified subtypes, M_1, M_2, M_3,[3,4] that exhibit different structural, functional and pharmacological properties. Selective ligands are known for the three M_1/m_1–M_3/m_3

† Dedicated to Professor Paolo Grünanger on the occasion of his 65th birthday.

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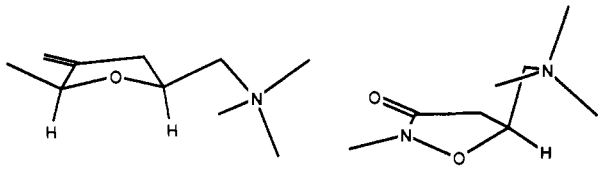
Table I. Muscarinic Potencies of Compounds 1–7[a]

compd	guinea pig		ER[b]	eutomer config	rat	
	atria	ileum			jejunum	bladder
(±)-1	8.62 ± 0.08	9.00 ± 0.07	3.1[c]	2S,5S	7.89 ± 0.03	7.28 ± 0.05
(±)-2	7.23 ± 0.07	7.50 ± 0.05	331[d]	2S,3R,5S	6.81 ± 0.04	6.24 ± 0.05
(±)-3	6.10 ± 0.08	7.38 ± 0.03			6.78 ± 0.03	6.13 ± 0.03
(±)-4	7.62 ± 0.05	7.95 ± 0.03	2.5[e]	5R	7.13 ± 0.03	6.44 ± 0.03
(±)-5	8.02 ± 0.04	8.38 ± 0.06	59[f]	2S,5R[g]	7.58 ± 0.11	6.91 ± 0.05
(±)-6	7.37 ± 0.03	8.23 ± 0.06	170[h]	2R,5R[g]	7.55 ± 0.03	6.64 ± 0.04
(±)-7	5.88 ± 0.06	6.87 ± 0.08			6.19 ± 0.05	5.62 ± 0.03

[a] Potencies are expressed as $-\log EC_{50}$, values taken from refs 18 and 20. [b] Eudismic ratio. [c] Rat ileum, ref 9. [d] Reference 21. [e] Reference 19. [f] Reference 9. [g] Due to the priority rules, enantiomers (2S,5R)-5 and (2R,5R)-6 possess the same spatial arrangement of (2S,5S)-1, (2S,3R,5S)-2, and (5S)-4. [h] Reference 22.

subpopulations of receptors.[5] Nevertheless, there is a demand for compounds having selective central stimulating muscarinic activity due to their therapeutic potential in Alzheimer's disease.[6] Recent papers have reported the synthesis[7,8] of spirocyclic analogues of muscarone 1 which are characterized by a pronounced selectivity for the M_1 subtype.[8] It is noteworthy that the pharmacological profile of 1 differs significantly from that of the major muscarinic agonists,[9,10] i.e. it has been claimed that 1 possesses a reversed enantioselectivity[11] and a low eudismic ratio (ER) (2.4–10.1)[12] in a variety of test preparations.[11,13] Even though it was later demonstrated that the eutomer of muscarone [(−)-1] had chirality at C-2 and C-5 identical to natural muscarine [(+)-2],[14] the low ER values have not been well-rationalized. These aspects have been discussed by different groups and some explanations have been set forth.[11,15–17]



3 4

Figure 1. Plots of compounds 3 and 4 as determined by X-ray crystallography.

Table II. Selected Geometrical Data from Crystallographic Analysis of Compounds 1–7

compd	Q	ϕ_2	τ	$d_{1,7}$ (Å)	$d_{7,8}$ (Å)	ref
1[a]	0.33	343	+157	3.69	6.01	23
1*[b]	0.32	335	+69	3.07	5.39	23
2	0.26	301	+73	3.07	5.40	24
3	0.40	346	+84	3.22	5.61	c
4	0.26	163	+61	3.07	4.86	c
5	0.23	99	+94	3.20	4.84	25
6	0.46	354	+77	3.16	5.49	26
7	0.14	279	+68	3.09	5.22	27

[a] Muscarone iodide. [b] Muscarone picrate. [c] This work.

In connection with an ongoing research program on the topography of the cholinergic recognition sites, we prepared and tested the muscarone analogues 3 and 4 in order to study the direct influence of the polarity of the carbonyl group of 1 on the biological activity and selectivity.[18] We also prepared and tested the two enantiomers of 4.[19] Table I reports the potencies and the ER's of muscarone 1,[20] its analogues 3[19] and 4,[19] the structurally related muscarine 2,[20,21] *cis*-dioxolane 5,[20,9] *cis*-oxathiolane 6,[22] and tetrahydrofuran 7.[18] All the derivatives are potent mus-

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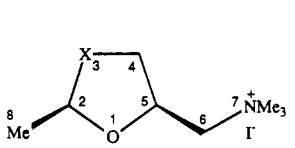
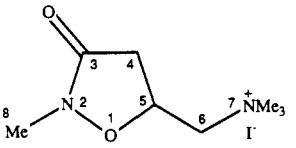
carinic agonists but, whereas muscarone 1 and its analogue 4 show low ER values, the other partners are characterized by high eudismic ratios. Furthermore, compound 4 has a reversed enantioselectivity with the 5*R* enantiomer acting as the eutomer (Table I). Since the pharmacological profile of muscarone has also been rationalized on the basis of its conformation in the solid state,[15] we became interested in the conformational preferences of 3 and 4. This paper deals with the X-ray analysis of compounds 3 and 4 and a study of the conformational profile of compounds 1–7,





4

1: X = C=O
2: X = CHOH (*trans*)
3: X = C=CH_2
5: X = O
6: X = S
7: X = CH_2

carried out through molecular mechanics calculations and ^{1}H NMR spectroscopy.

Results and Discussion

As shown in Table I, the moiety X, located at the 3-position of the heterocyclic ring, is responsible for the modulation of the potency and the selectivity of the muscarinic ligands 1–7. Its influence might be exerted either directly, i.e. it might be due to the electronic nature of the group, its orientation, etc. or indirectly through changes of the conformation of the entire molecule. This indirect influence is analyzed in the present paper through a detailed study of the conformational profile of the five-membered ring as well as the side chain bearing the ammonium group.

In Figure 1 structures of compounds 3 and 4 are reported, derived from the X-ray coordinates. Hydrogens have been omitted for clarity with the exception of H-2 and H-5. Table II reports the main geometrical data for 3 and 4 which are compared with those reported for 1,[23] 2,[24] 5,[25] 6,[26] 7.[27] The conformation of the ring is expressed as the amplitude Q and phase ϕ_2[28] whereas the orientation of the ammonium group is characterized by the value of the dihedral angle O1–C5–C6–N7 (τ). The phase value indicates that while the ring assumes very similar conformations in compounds 1, 2, 3, and 6 (ϕ_2: 301°–354°; ^{1}E–E_5 conformations, Table II) and a conformation close to them in 7 (ϕ_2: 279°), it is differently puckered in 4 (ϕ_2: 163°; $^5T_1$ conformation) and 5 (ϕ_2: 99°; $^3T_4$ conformation). Furthermore, the value of τ shows that all the compounds crystallize with the ammonium group (N7) gauche to the ring oxygen (O1) (τ = +61° – +94°). The sole exception is represented by muscarone 1 where the N7 and O1 moieties assume an antiperiplanar arrangement (τ = +157°).

Table III. Relative Energies (kcal/mol), Equilibrium Percentages, and Selected Geometrical Data for Calculated Conformations of Compounds 1, 2, 3, and 5

conformn	E_{rel}	equil %	Q	ϕ_2	τ	τ'[a]
1A	0.00	95.8	0.35	344	+77	–
1B	1.86	4.2	0.34	353	+163	–
2A	0.00	43.7	0.39	322	+78	+177
2B	0.03	41.5	0.39	321	+78	+68
2C	0.77	11.9	0.39	323	+78	–58
2D	2.08	1.3	0.38	16	+161	+68
2E	2.12	1.2	0.38	15	+161	+177
2F	2.83	0.4	0.38	15	+162	–59
3A	0.00	97.1	0.37	329	+77	–
3B	2.09	2.9	0.36	332	+155	–
5A	0.00	90.1	0.42	31	+74	–
5B	1.31	9.9	0.42	29	+164	–

[a] τ': dihedral angle C2–C3–O–H.

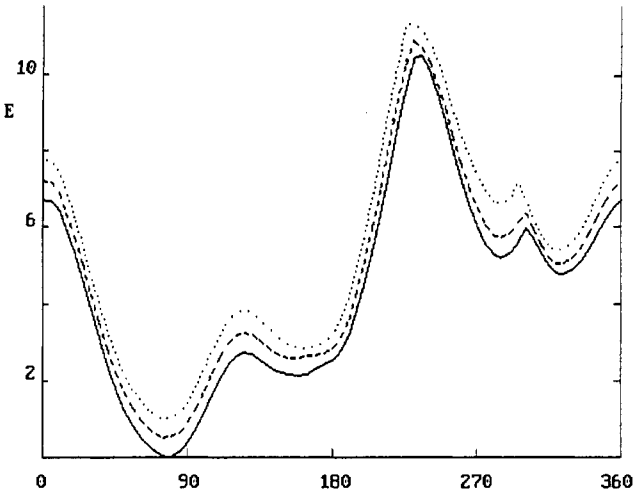


Figure 2. Conformational energy E_{rel} (kcal/mol) of compounds 1 (···), 2 (—), and 3 (- - -) as a function of the torsional angle O1–C5–C6–N7 (τ). For a better comparison of the profiles the E = 0 coordinate of 1 and 3 has been shifted by +1 and +0.5 kcal/mol, respectively.

An alternative manner to describe and compare the geometry of muscarinic ligands consists in the evaluation of the interatomic distances among the three major centers of interaction: the ammonium nitrogen, the ring oxygen, and the terminal methyl carbon atom. Table II reports the O1–N7 and N7–C8 distances ($d_{1,7}$ and $d_{7,8}$) for the set of compounds 1–7. The distance $d_{1,7}$ is almost the same (3.1–3.2 Å) for all of the compounds but 1 in which case it is higher (3.69 Å). The parameter $d_{7,8}$ lies in the range 5.2–5.6 Å for 2, 3, 6, and 7 but is smaller in 4 (4.86 Å) and 5 (4.84 Å) and greater in 1 (6.01 Å). Since the anomalous values of $d_{1,7}$ and $d_{7,8}$ in 1, 4, 5 parallel the anomalous values of ϕ_2 and τ, in the following discussion we will make use of these two latter parameters.

The conformation of the side chain was first investigated since its unusual antiperiplanar arrangement in muscarone iodide 1 has been used to explain the low ER values.[15] In order to find out if such a disposition was due to intramolecular forces or could be attributed to crystallographic packing forces, we carried out molecular mechanics calculations on 1 and, comparatively, on 2, 3, and 5. Table III reports the selected geometrical data concerning the conformations which significantly contribute to the overall populations of compounds 1, 2, 3, and 5 determined by exploration of their conformational space with the MM2(85) program.[29] Comparison of the calculated and X-ray data

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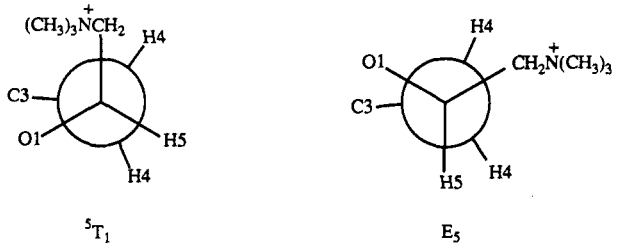

Figure 3. Newman projection along bond C5–C4 of X-ray conformation ($^5T_1$) and proposed solution conformation (E_5) of compound **4**.

for muscarone iodide **1** shows that it crystallizes in the second lower energy minimum (1B). It is worth pointing out that a change of the counterion of **1** from iodide to picrate causes a switch in the conformational preference from antiperiplanar to gauche (τ = +69°, Table II). Interestingly, the solid-state conformation of muscarone picrate corresponds to the calculated global minimum (1A). The conformational behavior around the C5–C6 bond of compounds **1–3** was determined by using the driver option of the MM2 program (5-deg incremental steps). Figure 2 shows that the conformational profiles are quite similar for **1**, **2**, and **3**. Three minima are found higher in energy than the global minimum, and the energy barriers are all comparatively high. In summary, the solid-state conformation of muscarone iodide, which possesses an antiperiplanar orientation of the ammonium group, seems energetically disfavored over the other with the side chain in a gauche arrangement. The difference in energy (about 2 kcal/mol) is probably balanced by more favorable intermolecular interactions.

Compounds **4** and **5** exhibit an anomalous value of ϕ_2. Compound **4** has structural features which might favor a ring conformation different from that of the other compounds under study. In fact, it has two sp^2-hybridized ring atoms, and therefore the four atoms O1, N2, C3, C4 should lie in about the same plane with atom C5 pointing above or below this plane. Such an arrangement gives rise to two ring conformations close to ^5E and to E_5. X-ray analysis shows that the molecule assumes the $^5T_1$ conformation with a pseudoaxial orientation of the CH_2NMe_3 group. This orientation is not disfavored by 1,3-interactions as both the atoms located 1,3 to C5 are sp^2 hybridized. Unfortunately, the lack of parameters for the nitrogen–oxygen bond did not allow us to carry out molecular mechanics calculations on compound **4**.

Information on the conformation of **4** in solution (D_2O) was obtained from the ^1H NMR spectrum. The coupling constants $J_{4a,5}$ and $J_{4b,5}$ are 8.6 and 8.7 Hz, respectively. These data are in sharp contrast with the solid state conformation of **4** ($^5T_1$, Figure 3) in which the dihedral angles H4a–C4–C5–H5 and H4b–C4–C5–H5 are –95° and +25°; in fact, introduction of these two values into the Altona equation[30] gives two calculated constants of 1.5 and 8.7 Hz, respectively. So, the conformational population of **4** in D_2O cannot be described by the only solid-state conformation $^5T_1$. Another conformation, which probably gives a percentage contribution larger than that of the conformation $^5T_1$, should be present. This conformation,

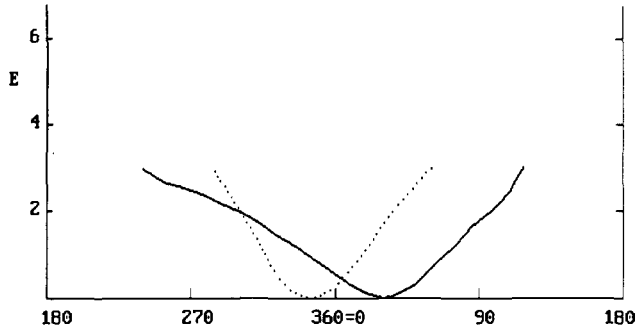

Figure 4. Conformational energy E_{rel} (kcal/mol) of compounds **1** (···) and **5** (—) as a function of the phase ϕ_2.

more compatible with the NMR data, should possess torsional angles between H-5 and the two H-4's of about –20° and –140° (Figure 3). These torsional angles are consistent with a conformation close to E_5 where the ϕ_2 value is 324°, within the range of the other compounds.

The X-ray structure of *cis*-dioxolane **5** shows also an anomalous ϕ_2 value (99°), at variance with molecular mechanics calculations. The calculation gave ϕ_2 equal to 31° (conformation 5A), proximate to the usual range. We traced the energy profile for the pseudorotational path of the ring by calculating the energy of several points in the path through proper use of the driver option of MM2 program (the gauche orientation of the ammonium group was maintained throughout the path). Figure 4 shows the profile of **5** in comparison to that of muscarone **1**. Only the part of the curve representing conformations in the range of 3 kcal/mol greater than the global minimum is reported. The profile of **5** is flatter than that of **1**. About 2 kcal/mol are necessary to force the ring from the minimum (ϕ_2 = 31°) into the solid-state conformation (ϕ_2 = 99°), an energy cost similar to that necessary to reach the solid-state conformation of muscarone iodide. Even easier (1 kcal/mol) is the transformation from the most stable conformation (E_2; ϕ_2 = 31°) to the common one ($^1T_5$; ϕ_2 = 342°). Thus, the presence of two oxygen atoms in the ring apparently increases its conformational mobility.

In summary, the X-ray data of compounds **1–7** show that most of them assume conformations with the ring similarly puckered (ϕ_2: 300–360°) and the side-chain in a gauche arrangement with respect to the ring oxygen. These experimental results confirm the conformational data obtained by molecular mechanics calculations with the major exception of muscarone iodide (**1**) where the calculations predicted the gauche form as the most stable conformation of the side chain whereas the X-ray analysis showed that **1** crystallized in the antiperiplanar arrangement. This case is of particular importance since such an argument has been used to rationalize the peculiar pharmacological profile of **1**, i.e. the low values of eudismic ratio. Here we conclude that there are no strong intramolecular interactions to induce muscarone iodide to crystallize with the side chain in the antiperiplanar disposition since our theoretical results indicate that the gauche conformation is more stable by about 2 kcal/mol and the same conformation was observed in the solid state of muscarone picrate (**1***).[23] Moreover, an inspection of the stereodrawings of muscarone and of its analogues has shown that the ammonium group is in about the plane of the five-membered ring not only when it has an anti orientation but also when it is gauche oriented. Also in this respect muscarone behaves like the other examined muscarinic agonists.

An alternative explanation of the low ER's of **1** could be due to an isomerization of muscarone (cis form) to *allo*-muscarone (trans form) during the biological tests. It

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is well known that the chirality at C-2 strongly influences the enantioselectivity.[9,10] As an example, the two enantiomers of the allo (trans) form of dioxolane 5[9] and oxathiolane 6[22] are almost equipotent, their eudismic ratio is 2.0 and 1.5, respectively. On the same basis, the absence of a stereocenter at C-2 can account for the lack of enantioselectivity of derivative 4. Since the biological tests are performed in a buffer solution, at room temperature and at physiological pH, we recorded the ^{1}H NMR spectrum of 1 in D_2O at room temperature. After several hours, we observed the complete disappearance of the signals corresponding to the two H-4's (2.38 and 2.69 ppm), but there was no change either in the intensity or in the chemical shift (4.04 ppm) of H-2. As a consequence, we exclude this possibility as the explanation of the low values of eudismic ratio. Since the reported values of ER are not accompanied by any indication about the optical purity of the samples, in our opinion it is necessary to collect new pharmacological data on compounds with a well-established enantiomeric excess. Work along this line is in progress and will be published in due course.

Experimental Section

^{1}H NMR spectra of 1 and 4 were recorded on a Bruker AC-E 300 spectrometer. Molecular mechanics calculations were performed with the MM2(85) program[29] obtained from QCPE.

X-ray Analysis. Crystals of 3 and 4, obtained by evaporation of 2-propanol, were mounted on an Enraf-Nonius CAD4 diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å) and using the ω–2θ scan technique. The cell constants were determined from a least-square fit of the setting angles for 25 accurately centered reflections. Three standard reflections, measured every 3500 s of X-ray exposure, showed no intensity decay over the course of data collection. The intensity data were corrected for Lorentz and polarization effects, and an empirical absorption correction was performed [min. trans. 83.9% (89.5%), max. trans. 99.6% (100.0%), av trans. 93.7% (94.7%) for 3 (4)]. The structure was solved by standard heavy atom Patterson methods followed by weighted Fourier synthesis. Refinement was by full-matrix least-squares techniques based on F to minimize the quantity $\Sigma w(|F_o| - |F_c|)^2$ with $w = 1/\sigma^2(F)$. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were included as constant contributions to the structure factors and were not refined.

Compound 3, $C_{10}H_{20}INO$, crystallized in the monoclinic space group $P2_1/n$ (systematic absences $h01$: $h + 1$ = odd; $0k0$: k = odd) with a = 7.486 (1) Å, b = 17.289 (4) Å, c = 9.979 (2) Å, β = 100.91 (2)°, V = 1268.2 (8) Å^3, Z = 4, and d_{calc} = 1.556 g/cm^3. A total of 2215 reflections were measured over the ranges: $4 \le 2\theta \le 50°$, $0 \le h \le +8$, $-20 \le k \le 0$, $-11 \le l \le +11$. Refinement converged to R_1 = 0.035 and R_2 = 0.051.

Compound 4, $C_8H_{17}IN_2O_2 \cdot H_2O$, crystallized in the triclinic space group $P\bar{1}$ with a = 5.763 (1) Å, b = 7.914 (2) Å, c = 14.080 (6) Å, α = 100.71 (3)°, β = 90.46 (2)°, γ = 93.07 (1)°, V = 629.9 (6) Å^3, Z = 2, and d_{calc} = 1.677 g/cm^3. A total of 2211 reflections were measured over the ranges $4 \le 2\theta \le 50°$, $-6 \le h \le +6$, $0 \le k \le 9$, $-16 \le l \le +16$. Refinement converged to R_1 = 0.056 and R_2 = 0.092.

^{1}H NMR spectrum of 1: (D_2O) δ 1.20 (d, J = 6.8 Hz, 3 H, Me), 2.38 (dd, J = 18.4, 10.3 Hz, 1 H, H-4a), 2.69 (dd, J = 18.4, 6.0 Hz, 1 H, H-4b), 3.17 (s, 9 H, NMe_3), 3.63 and 3.65 (AB part of an ABX system, J_{AB} = 14.0, J_{AX} = 10.5, J_{BX} = 0.5 Hz, 2 H, H-6a and H-6b), 4.04 (q, J = 6.8 Hz, 1 H, H-2), 4.80 (m, 1 H, H-5).

^{1}H NMR spectrum of 4: (D_2O) δ 2.71 (dd, J = 17.0, 8.6 Hz, 1 H, H-4a), 3.12 (dd, J = 17.0, 8.7 Hz, 1 H, H-4b), 3.14 (s, 3 H, Me), 3.20 (s, 9 H, NMe_3), 3.60 (dd, J = 14.5, 0.8 Hz, 1 H, H-6a), 3.91 (dd, J = 14.5, 9.8 Hz, 1 H, H-6b), 5.30 (m, 1 H, H-5).

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Registry No. (±)-1, 7524-73-4; (±)-2, 2209-02-1; (±)-3, 137626-50-7; (±)-4, 132016-39-8; (±)-5, 68737-69-9; (±)-6, 84827-19-0; (±)-7, 86156-68-5.

Supplementary Material Available: Tables of X-ray final atomic positional coordinates, atomic thermal parameters, bond distances, and bond angles of compounds 3 and 4 and MM2-calculated atomic coordinates of the minimum energy conformers of compounds 1, 2, 3, and 5 (18 pages). Ordering information is given on any current masthead page.