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Synthesis, Absolute Configuration and Antimuscarinic Activity of the Enantiomers of [1-(2,2-Diphenyl-[1,3]dioxolan-4-yl)-ethyl]-dimethyl-amine

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Abstract—Methylation of the carbon atom C1 of compound **1**, a potent and not selective muscarinic antagonist, was carried out. The resulting diastereomers were separated and the corresponding racemate further resolved to give four enantiomers, which were tested both as hydrogen oxalate and methiodide salts. The pharmacological results obtained at M_1, M_2 and M_3 muscarinic receptor subtypes, show that methylation at C1, depending on the stereochemistry, increases antagonist potency, having thus the same effect of nitrogen quaternization. These results may well lead to the development of new potent antimuscarinic drugs lacking a cationic head.

Introduction

Compound **1** is a potent muscarinic antagonist[1–3] lacking in significant selectivity.[4] In preceding papers, we reported on some derivatives of this ligand obtained by structure modification carried out in position 2[5–8] and on the nitrogen atom.[9] Here, as a continuation of our research program, we report on the effect of methylation of the carbon atom (C1) alpha to the nitrogen atom.

Chemistry

The synthesis of the compounds used in this study is reported in Scheme 1. Permanganic oxidation of **4** gave the diol **5** as a diastereomeric mixture which was separated by flash chromatography. Each separated diastereomer was then reacted with benzophenone to give the 1,3-dioxolanes **6** and **7** which were aminated with $HN(CH_3)_2$ in a steel bomb at 100 °C to give the diastereomers **2** and **3**.[10] Enantiomeric separations were conveniently achieved by treatment of tertiary amines with D-(+)- and L-(−)-di-*O*,*O*′-*p*-toluyl-tartaric acid (DTTA), in the case of (±)-**2**, and L-(+)- and D-(−)-tartaric acid (TA), in the case of (±)-**3**, followed by fractional crystallization of the diastereomeric salts from ethanol until the melting points and the optical rotations remained constant.[11] Treatment of the salts with 10% NaOH gave the enantiomerically pure free amines. All the tertiary amines, both as a racemate and as pure enantiomer, were transformed into the oxalate or methiodide salts upon treatment with $(COOH)_2$ and CH_3I, respectively.[12]

The absolute configurations were established by means of X-ray crystallography,[13] for one enantioner, as methiodide salt, for each couple. Crystals suitable for X-ray diffraction were grown from 2-propanol solutions. The unit cell of **2**(1*S*,4*R*) contains two crystallographically independent cations, depicted, along with the atom numbering scheme, in Figure 1, and two iodide anions. Both cations display unambiguous *S* and *R* absolute configurations at their two chiral centers, C4 and C18, respectively. In both cases, the H atoms bonded to chiral carbons are in *anti* orientation. The two cations differ mainly in the puckering of dioxolane rings and in the orientation of the phenyl groups with respect to the cycles.

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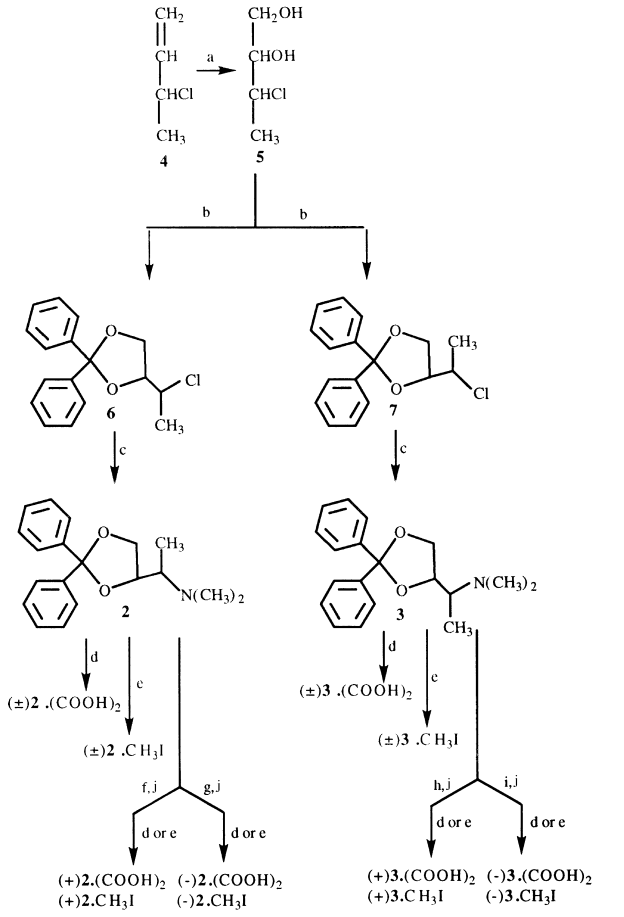


Scheme 1. (a) $KMnO_4$ 1 M, −20 °C→rt; (b) benzophenone, PTSA, reflux; (c) $HN(CH_3)_2$, 100 °C; (d) $(COOH)_2$, anhyd $(C_2H_5)_2O$, rt; (e) CH_3I, anhyd $(C_2H_5)_2O$, rt; (f) D-(+)-DTTA; (g) L-(−)-DTTA; (h) L-(+)-TA; (i) D-(−)-TA; (j) NaOH 10%.

The unit cell of **3**(1*S*,4*S*) is built of one crystallographically independent cation, presented in Figure 2, and one iodide anion. The results of the X-ray analysis allowed to assign unambiguous *S* and *S* absolute configurations to C4 and C18 chiral centers (see Fig. 2) present in the cation. The H atoms bonded to chiral carbons display *gauche* conformation, and the puckering of the dioxolane ring is characterized by torsion angles ranging from −42.8(4) to 35.7(4).

In both cases, all bond distances and angles are in the expected ranges and no short van der Waals distances are present in the crystal packing.

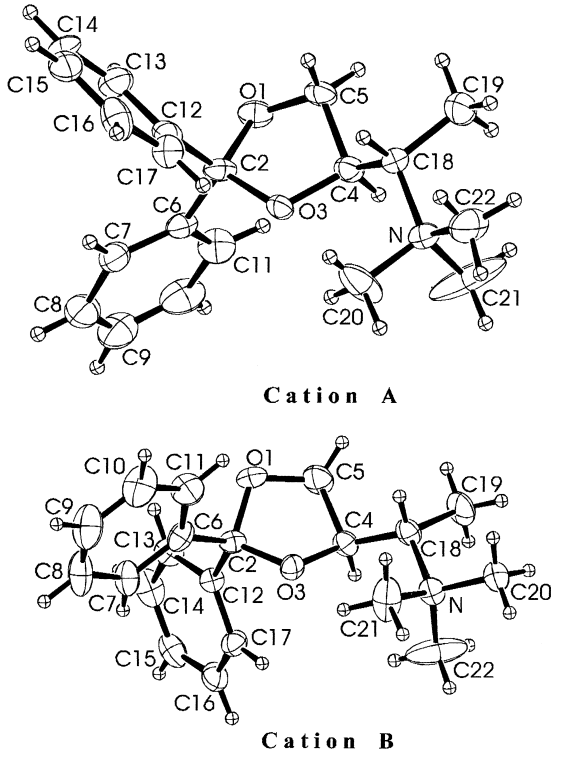


Figure 1. X-ray structure of (−)-**2**(1*S*,4*R*).

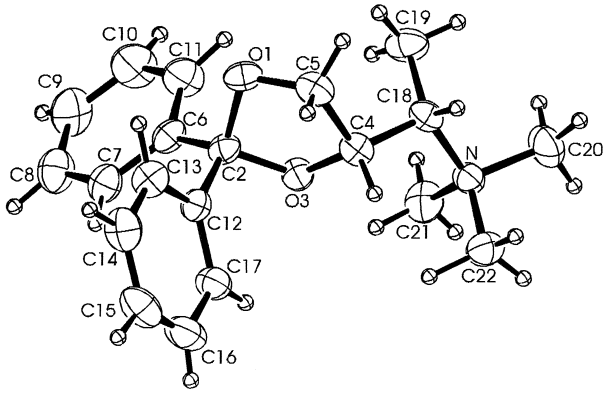


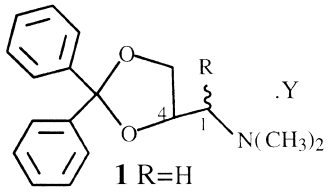
Figure 2. X-ray structure of (+)-**3**(1*S*,4*S*).

Results and Discussion

All the newly-synthesized compounds were tested on three different preparations namely rabbit vas deferens, guinea-pig heart and ileum for M_1, M_2, and M_3 antimuscarinic activity, respectively, following the procedures already described.[4–9,14–16] The results, expressed in terms of pKb,[17] are reported in Table 1. Compounds **2** and **3** behave as competitive antagonists, causing a parallel shift to the right of the agonist dose–response curves (not shown). As already reported, compound **1** is 10-fold more active as methiodide than as hydrogen oxalate salt, at all the three receptor subtypes. Introduction of a methyl group at C1 generates two diastereomers, (±)-**2** and (±)-**3**, which as hydrogen oxalate salts show a significant diastereoselectivity, (±)-**3** being the more potent of the two. However, the diastereoselectivity is lost when the compounds are tested as methiodides. This is the result of a different effect of quaternization of the two diastereomers: in fact while quaternization of (±)-**2** causes an approximately 10-fold increase of activity, quaternization of (±)-**3** does not have any significant effect at M_1 and M_2 subtypes and only a small effect at M_3 subtype.

Resolution of the racemates (±)-**2** and (±)-**3** afforded two couples of enantiomers, (+)-**2**(1*R*,4*S*)/(−)-**2**(1*S*,4*R*) and (−)-**3**(1*R*,4*R*)/(+)-**3**(1*S*,4*S*) which, in the same way

Table 1. Antimuscarinic activity (pKb) of compounds **1**, **2** and **3**



1 R=H

2, **3** R=CH_3

Compound	Y	pKb M_1	Eu	pKb M_2	Eu	pKb M_3	Eu
1	$(COOH)_2$	7.15±0.12		7.11±0.03		6.72±0.08	
1	CH_3I	8.36±0.07		8.29±0.06		7.91±0.07	
(±)-**2**	$(COOH)_2$	6.95±0.20		7.20±0.05		6.96±0.01	
(+)-**2** (1*R*,4*S*)	$(COOH)_2$	6.52±0.14		6.41±0.06		6.41±0.12	
			3		9		6
(−)-**2** (1*S*,4*R*)	$(COOH)_2$	6.94±0.01		7.35±0.08		7.19±0.25	
(±)-**2**	CH_3I	7.82±0.08		8.07±0.14		7.92±0.16	
(+)-**2** (1*R*,4*S*)	CH_3I	8.24±0.14		7.53±0.02		7.51±0.02	
			13		5		3
(−)-**2** (1*S*,4*R*)	CH_3I	7.12±0.13		8.21±0.24		8.00±0.20	
(±)-**3**	$(COOH)_2$	8.11±0.06		8.03±0.04		7.94±0.12	
(−)-**3** (1*R*,4*R*)	$(COOH)_2$	6.83±0.12		7.47±0.04		7.45±0.22	
			43		8		30
(+)-**3** (1*S*,4*S*)	$(COOH)_2$	8.46±0.10		8.39±0.16		8.92±0.05	
(±)-**3**	CH_3I	8.01±0.11		8.22±0.11		8.30±0.11	
(−)-**3** (1*R*,4*R*)	CH_3I	8.23±0.08		8.38±0.14		8.40±0.07	
			6		4		4
(+)-**3** (1*S*,4*S*)	CH_3I	7.47±0.24		7.82±0.06		7.85±0.06	

as the diastereomers, were tested as hydrogen oxalate and methiodide salts. Considering first the oxalate salts, it can be seen that the couple of enantiomers that displays the highest eudismic ratio (Eu) is the (−)-**3**(1*R*,4*R*)/(+)-**3** (1*S*,4*S*), the eutomer being the enantiomer (+)-**3**(1*S*,4*S*). The other couple (+)-**2**(1*R*,4*S*)/(−)-**2**(1*S*,4*R*) displays much lower Eu values with the eutomer being the enantiomer (−)-**2**(1*S*,4*R*). Within the methiodide series, both Eu values are decreased but, surprisingly, for the couple (−)-**3**(1*R*,4*R*)/(+)-**3**(1*S*,4*S*) a reversal of enantioselectivity is observed with the eutomer being the enantiomer (−)-**3**(1*R*,4*R*). For the other couple (+)-**2**(1*R*,4*S*), (−)-**2**(1*S*,4*R*), only at M_1 is a reversal of enantioselectivity seen. This, again, is the result of a different effect of quaternization that causes an increase of affinity by the enantiomers (+)-**2**(1*R*,4*S*), (−)-**2**(1*S*,4*R*) and (−)-**3**(1*R*,4*R*) while a decrease is observed by the enantiomer (+)-**2**(1*S*,4*S*).

In conclusion, the present investigation shows that a methyl group appropriately oriented on C1 of compound **1** increases antimuscarinic activity at three receptor subtypes, up to the same level of quaternization. Quaternization of the corresponding derivative decreases activity, indicating that spatial orientation of the methyl group, which contributes to enhance affinity, negatively affects the binding of the cationic head. These results may well lead to the development of new antimuscarinic drugs lacking the cationic head which often represents a limitation in drug therapy.

Acknowledgements

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10. ^{1}H NMR ($CDCl_3$) of compound **2**: δ 0.92 (d, 3H), 2.40 (s, 6H), 2.80 (m, 1H), 3.76 (t, 1H), 4.05 (t, 1H), 4.19 (q, 1H), 7.45 (m, 10H); and **3**: δ 1.12 (d, 3H), 2.22 (s, 6H), 2.63 (m, 1H), 3.92 (m, 1H), 4.10 (m, 2H), 4.19 (q, 1H), 7.42 (m, 10H).
11. Optical rotation and melting point for enantiomers **2** and **3** as tartarate salts: **2**-(1*R*,4*S*) $[\alpha]_D^{20}$ +97.11 (CH_3OH); mp 174–176 °C; **2**-(1*S*,4*R*) $[\alpha]_D^{20}$ −97.02 (CH_3OH); mp 174–175 °C; **3**-(1*R*,4*R*) $[\alpha]_D^{20}$ −8.5 (CH_3OH); mp 170–172 °C; **3**-(1*S*,4*S*) $[\alpha]_D^{20}$ +8.5 (CH_3OH); mp 171–173 °C.
12. Characterization of compounds **2** and **3**. (±)-**2**·$(COOH)_2$: mp 96–99 °C; ^{1}H NMR (DMSO-d_6) δ 1.12 (d, 3H), 2.79 (s, 6H), 3.47 (m, 1H), 3.83 (t, 1H), 4.15 (t, 1H), 4.30 (m, 1H), 7.41 (m, 10H); (±)-**3**·$(COOH)_2$: mp 145–148 °C; ^{1}H NMR (DMSO-d_6) δ 1.35 (d, 3H), 2.72 (s, 6H), 3.49 (m, 1H), 3.97 (m, 2H), 4.56 (m, 1H), 4.30 (m, 1H), 7.41 (m, 10H); (±)-**2**·CH_3I: mp 228–230 °C; ^{1}H NMR (DMSO-d_6) δ 1.26 (d, 3H), 2.87 (s, 9H), 3.47 (q, 1H), 3.90 (m, 1H), 4.24 (m, 1H), 4.37 (m, 1H), 7.60 (m, 10H); (±)-**3**·CH_3I: mp 186–188 °C; ^{1}H NMR (DMSO-d_6) δ

1.26 (d, 3H), 2.87 (s, 9H), 3.60 (q, 1H), 3.94 (m, 1H), 4.11 (m, 1H), 4.74 (m, 1H), 7.58 (m, 10H); (+)-**2**·$(COOH)_2$: mp 102–105 °C; (−)-**2**·$(COOH)_2$: mp 101–103 °C; (+)-**2**·CH_3I: $[\alpha]_D^{20}$ +11.92 (CH_3OH); mp 223–225 °C; (−)-**2**·CH_3I: $[\alpha]_D^{20}$ −11.64 (CH_3OH); mp 224–226 °C; (+)-**3**·$(COOH)_2$: mp 167–169 °C; (−)-**3**·$(COOH)_2$: mp 168–170 °C; (+)-**3**·CH_3I: $[\alpha]_D^{20}$ +30.73 (CH_3OH); mp 201–203 °C; (−)-**3**·CH_3I: $[\alpha]_D^{20}$ −30.54 (CH_3OH); mp 202–204 °C.

13. Diffractometric data were collected at room temperature in the range $2 \leq \theta \leq 27°$, including Friedel pairs. Intensities were corrected for Lorentz and polarization effects, and an absorption correction, based on empirical scan, was applied to data. The structure was solved by direct methods (SHELX86 program), and was refined through full matrix least-squares calculations based on F^2 (SHELXL93 program). All non-H atoms were refined anisotropically; H atoms were constrained to ride in ideal positions on their bonded atoms.

Crystal data for compound **2**(1*S*,4*R*). $C_{20}H_{26}INO_2$, M = 439.32, monoclinic, a = 13.941(3), b = 7.429(1), c = 20.866(3) Å, β = 105.49(1)°, V = 2082.5(6) Å^3, space group $P2_1$, Z = 4, D_c = 1.401 Mg/m^3, μ(Mo-K_α) = 1.548 mm^{-1}, $F(000)$ = 888; approximate crystal dimensions 0.30×0.18×0.15 mm.

The absolute configuration was determined by refinement on Flack parameter, whose final value was 0.00(4). The final agreement factors were R = 0.0487 and wR^2 = 0.1235 for 462 parameters and 7043 observed reflections. The largest peak and hole differences were 1.148 and −0.922 e Å^3.

Crystal data for compound **3**(1*S*,4*S*). $C_{20}H_{26}INO_2$, M = 439.32, monoclinic, a = 9.075(1), b = 10.045(1), c = 10.983(2) Å, β = 90.22(1)°, V = 1002.1(5) Å^3, space group $P2_1$, Z = 2, D_c = 1.457 Mg/m^3, μ(Mo-K_α) = 1.610 mm^{-1}, $F(000)$ = 444; approximate crystal dimensions 0.33×0.25×0.22 mm.

The absolute configuration was determined by refinement on Flack parameter, whose final value was 0.00(2). The final agreement factors were R = 0.0277 and wR^2 = 0.0650 for 300 parameters and 3077 observed reflections. The largest peak and hole differences were 0.549 and −0.431 e Å^3.

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