# Enantioselectivity of Muscarinic Antagonists. Isomeric 2-Cyclohexyl-2-phenyl-5-[(dimethylamino)methyl]-1,3-oxathiolane Methiodides[1]

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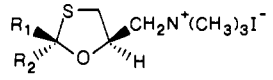
The four isomers of 2-cyclohexyl-2-phenyl-5-[(dimethylamino)methyl]-1,3-oxathiolane methiodide were prepared. Their absolute configuration was attributed by means of X-ray crystallography and circular dichroism. The compounds were tested on rat bladder and guinea pig ileum and heart, and their antimuscarinic potency was evaluated and expressed as $pA_2$. The results show that the introduction of a chiral center into position 2 brings about a small but definite enantioselectivity on rat bladder and guinea pig ileum which is not seen for guinea pig heart. This supports the view that differences exist among the muscarinic receptors of these tissues ($M_2$ receptors). Comparison of the absolute configuration of the antagonists studied in this and in the preceding paper[2] and that of strictly related agonists supports the hypothesis of a common binding site for agonists and antagonists of this kind.

In the previous paper we have emphasized the study of enantioselectivity as a valuable approach to the collecting of information both on the site and interaction mode of receptor ligands and on the identification and characterization of receptor subgroups. In the same paper we reported the synthesis, resolution, absolute configuration, and enantioselectivity of 1,3-oxathiolane antagonists with a chiral center in position 3 and/or 5.[2]

As a continuation of this research we now report the study of 1,3-oxathiolane antagonists carrying chiral centers in positions 2 and 5. To this end we have synthesized the four possible isomers of 2-cyclohexyl-2-phenyl-5-[(dimethylamino)methyl]-1,3-oxathiolane methiodide, namely the enantiomers of compounds **2** and **4**.



(±)-**2**: $R_1 = C_6H_{11}$, $R_2 = C_6H_5$
(±)-**4**: $R_1 = C_6H_5$; $R_2 = C_6H_{11}$

## Chemistry

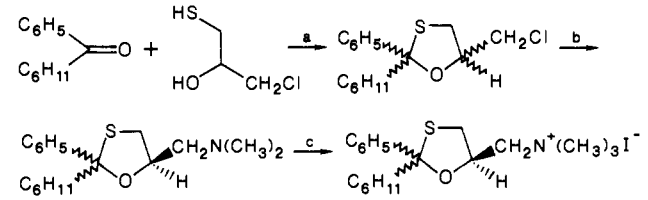
**Structure of the Racemates.** Compounds 1–4 were obtained according to Scheme I. Our research group has already described amine (±)-1 obtained from the more abundant of the two isomers of the intermediate 2-cyclohexyl-2-phenyl-5-(chloromethyl)-1,3-oxathiolane.[3] The isomeric amine (±)-3 was not obtained at that time since the quantity of the corresponding intermediate collected was insufficient.

In the present approach we have preferred to separate the isomeric amines (±)-1 and (±)-3, obtained from the mixture of the corresponding chloromethyl derivatives, by column chromatography. This procedure has allowed us to obtain suitable amounts of (±)-3 and of its methiodide (±)-4.

The configuration reported for amine (±)-1, derived from that of the corresponding chloromethyl derivative,[3] proved to be incorrect when the structures of the *O,O'*-di-*p*-toluoyltartrate [(+)-6] and of the methiodide (+)-4 of the amine (+)-3 were resolved by X-ray crystallography (see Figure 1). In fact, since in this case the 2-phenyl and the 5-side chain appear to be cis, the same groups must be in trans in the isomeric amine (±)-1.

Previous cis attribution had been given by analogy, on the basis of the deshielding effect of the 2-phenyl on the cis 5-proton observed in one of the two 2-phenyl-5-(chloromethyl)-1,3-oxathiolane isomers.[3] The unequivocal attribution now made by means of X-ray crystallography shows that, on the contrary, the effect of the 2-phenyl group on the cis 5-proton in 2,2-disubstituted 1,3-oxathiolane is a shielding one (see Table I). Apparently, the presence of two large groups in position 2 has major consequences on the conformation of the five-membered ring, bringing the 5-proton into the shielding zone of the *cis*-2-phenyl group. This influence is also detectable in $^{13}C$ NMR spectra of compounds 1–4. In fact, while the chemical shifts of the other carbons are nearly identical, carbon 5 is at a higher field in compound (±)-1 and (±)-2 than in compounds (±)-3 and (±)-4 (see Table I). In this case the shielding of the 5-carbon atom of (±)-3 and (±)-4 might be due to a γ-gauche-like interaction between the hydrogen in the 5-position and the 1'-hydrogen of the *cis*-2-cyclohexyl moiety[4] brought closer by the second 2-substituent, as is also suggested by Figure 1b.

**Scheme I**[a]




**1** ($C_6H_5$, $CH_2N(CH_3)_2$: trans) **2** ($C_6H_5$, $CH_2N^+(CH_3)_3I^-$: trans)
**3** ($C_6H_5$, $CH_2N(CH_3)_2$: cis) **4** ($C_6H_5$, $CH_2N^+(CH_3)_3I^-$: cis)

[a] (a) pTSA/xylene; (b) $(CH_3)_2NH$; (c) $CH_3I$.

**Resolution of the Racemates.** Both racemic amines (±)-1 and (±)-3 were resolved by fractional crystallization from ethanol of the diastereomeric salts formed with D-(+)- and L-(−)-*O,O'*-di-*p*-toluoyltartaric acids.

**Absolute Configuration.** The absolute configurations of (+)- and (−)-3 have been established by means of X-ray crystallography. The method of Bijvoet[5] on methiodide (+)-4 did not give a clear-cut answer to the absolute configuration of the compound. However, resolution of the structure of the enantiomeric salt of (+)-3 with (*S,S*)-*O,O'*-di-*p*-toluoyltartaric acid [(+)-6] gave the absolute configuration of (+)-3 (2*R*,5*R*) (Figure 1).

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(1) Part 28 of the series: Molecular Requirements of the Recognition Site of Cholinergic Receptors. For part 27, see ref 2.
(2) Romanelli, M. N.; Teodori, E.; Gualtieri, F.; Brasili, L.; Angeli, P. *J. Med. Chem.*, preceding paper in this issue.
(3) Angeli, P.; Giannella, M.; Pigini, M.; Gualtieri, F.; Teodori, E.; Valsecchi, B.; Gaviraghi, G. *Eur. J. Med. Chem.* **1985**, *20*, 517.
(4) Teodori, E.; Melani, F.; Gualtieri, F. *J. Heterocycl. Chem.* **1986**, *23*, 1487.
(5) Bijvoet, J. M.; Peerdeman, A. F.; Van Bommel, A. J. *Nature (London)* **1951**, *168*, 271.

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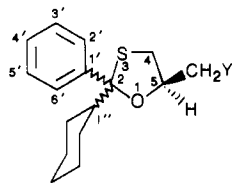
**Table I**



| no. | isomer[d] | Y | mp, °C | NMR, δ $^1$H | NMR, δ $^{13}$C |
|---|---|---|---|---|---|
| (±)-1 | $C_6H_5$ trans | $N(CH_3)_2$ | *a* | ($CDCl_3$): 0.86–2.10 (m, 11 H, cyclohexyl), 2.29 (s, 6 H, $NMe_2$), 2.53–3.10 (m, 4 H, $CH_2N$ and 4-$H_2$), 4.10 (m, 1 H, 5-H), 7.16–7.59 (m, 5 H, aromatics) | ($CDCl_3$): 26.05–28.49 (cyclohexyl except C-1″, 36.79 (C-4), 45.90 ($NMe_2$), 49.61 (C-1″), 62.17 ($CH_2N$), 79.82 (C-5), 102.95 (C-2), 126.44 (C-3′, C-5′), 126.72 (C-4′), 127.28 (C-2′, C-6′), 144.81 (C-1′) |
| (±)-2 | $C_6H_5$ trans | $^+N(CH_3)_3I^-$ | 205–8[b] (EtOH) | (DMSO-$d_6$): 3.24 (s, 9 H, $NMe_3$), 4.36 (m, 1 H, 5-H) | (DMSO-$d_6$): 25.59–28.30 (cyclohexyl except C-1″), 35.91 (C-4), 49.37 (C-1″), 53.56 ($NMe_3$), 67.08 ($CH_2N$), 75.85 (C-5), 103.87 (C-2), 126.03 (C-3′, C-5′), 127.30 (C-4′), 127.86 (C-2′, C-6′), 143.77 (C-1′) |
| (±)-3 | $C_6H_5$ cis | $N(CH_3)_2$ | *c* | ($CDCl_3$): 0.81–2.21 (m, 11 H, cyclohexyl), 2.28 (s, 6 H, $NMe_2$), 2.45 (d, 2 H, $CH_2N$), 2.55–3.25 (m, 2 H, 4-$H_2$), 4.53 (m, 1 H, 5-H), 7.13–7.57 (m, 5 H, aromatics) | ($CDCl_3$): 26.01–28.64 (cyclohexyl except C-1″), 36.49 (C-4), 45.91 ($NMe_2$), 50.02 (C-1″), 62.85 ($CH_2N$), 82.56 (C-5), 102.91 (C-2), 126.50 (C-3′, C-5′), 126.59 (C-4′), 126.84 (C-2′, C-6′), 144.91 (C-1′) |
| (±)-4 | $C_6H_5$ cis | $^+N(CH_3)_3I^-$ | 216–18 (EtOH) | (DMSO-$d_6$): 3.30 (s, 9 H, $NMe_3$), 4.83 (m, 1 H, 5-H) | (DMSO-$d_6$): 25.46–28.70 (cyclohexyl except C-1″), 35.26 (C-4), 48.71 (C-1″), 53.52 ($NMe_3$), 67.65 ($CH_2N$), 77.38 (C-5), 103.42 (C-2), 126.29 (C-3′, C-5′), 127.02 (C-4′), 127.24 (C-2′, C-6′), 143.40 (C-1′) |

[a] The hydrochloride melts at 236 °C (EtOH). [b] Angeli[3] reports 206–208 °C. [c] The hydrochloride melts at 220 °C (EtOH). [d] Stereochemistry is referred to the 5-side chain.

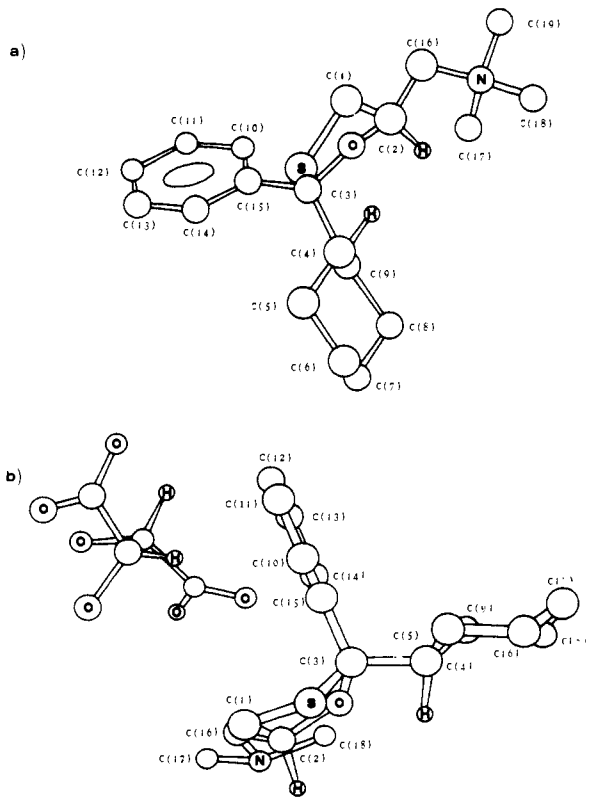


**Figure 1.** X-ray-derived crystal structure of (+)-4 (a) and (+)-6 (b) showing D-(+)-*O,O′*-di-*p*-toluoyltartaric acid (*S,S*) and (+)-3 with a 2*R*,5*R* configuration.

A similar approach was not possible for (+)- and (−)-5 or (+)- and (−)-2 because of crystal problems. Nevertheless, CD spectra allowed attributions of the absolute configuration of (+)- and (−)-1. In fact, it can be seen from

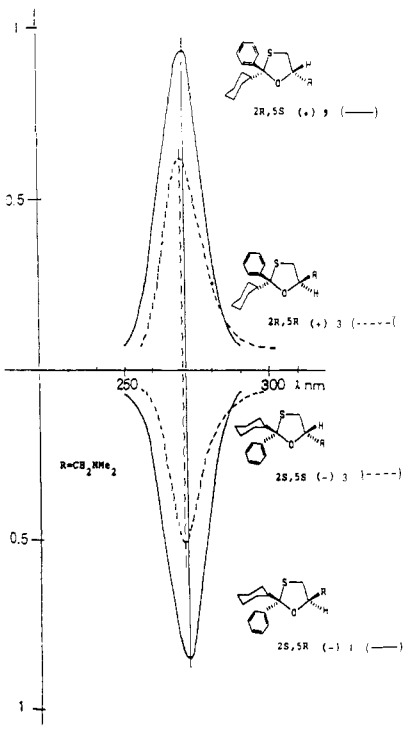
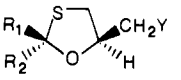



**Figure 2.** CD spectra of the amines (+)- and (−)-1 and of the amines (+)- and (−)-3.

Table II (compounds (+)-3 and (+)-4) that a positive Cotton effect corresponds to a *R* configuration of the carbon in position 2 which is the one having a greater influence on the transition of the neighboring sulfur atom;[6]

(6) Teodori, E.; Gualtieri, F.; Angeli, P.; Brasili, L.; Giannella, M.; Pigini, M. *J. Med. Chem.* **1986**, *29*, 1610.

**Table II**



| no. | $R_1$ | $R_2$ | Y | mp, °C | $[\alpha]^{20}_D$,[a] deg | CD,[b] λ (Δε) | absolute config[c] |
|---|---|---|---|---|---|---|---|
| (+)-1 | $C_6H_{11}$ | $C_6H_5$ | $N(CH_3)_2$ | | +127.1 | 270 (+0.93) | 2*R*,5*S* |
| (−)-1 | | | | | −130.6 | 271 (−0.85) | 2*S*,5*R* |
| (+)-2 | | | $N(CH_3)_3I^-$ | 219–220[d] | +55.8 | 254 (+1.19) | 2*R*,5*S* |
| (−)-2 | | | | 219–220[d] | −53.9 | 254 (−0.99) | 2*S*,5*R* |
| (+)-3 | $C_6H_5$ | $C_6H_{11}$ | $N(CH_3)_2$ | | +101.6 | 269 (+0.62) | 2*R*,5*R* |
| (−)-3 | | | | | −96.5 | 271 (−0.51) | 2*S*,5*S* |
| (+)-4 | | | $N(CH_3)_3I^-$ | 218–219[e] | +98.1 | 253 (+0.78) | 2*R*,5*R* |
| (−)-4 | | | | 218–219[e] | −96.2 | 253 (−0.96) | 2*S*,5*S* |

[a] The solvent is $CHCl_3$ for the bases and $CH_3OH$ for the salts. [b] The same solvents used for $[\alpha]^{20}_D$. [c] The configurations were established by means of X-ray diffraction for (+)- and (−)-4 and by means of CD for (+)- and (−)-2. [d] The racemate melts at 205–206 °C. [e] The racemate melts at 216–218 °C.

**Table III.** Antimuscarinic Potency of Compounds 1–4

| | | guinea pig heart | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | rat bladder | | force | | rate | | guinea pig ileum | |
| compd | stereoisomerism | $pA_2$[a] ± SEM | ER[c] | $pA_2$[a] ± SEM | ER[c] | $pA_2$[a] ± SEM | ER[c] | $pA_2$[a] ± SEM | ER[c] |
| (±)-1 | | 7.35 ± 0.09 | | 7.48[b] ± 0.24 | | 7.43[b] ± 0.22 | | 7.92 ± 0.10 | |
| (±)-2 | | 8.05 ± 0.08 | | 8.11 ± 0.05 | | 8.14 ± 0.05 | | 8.26 ± 0.14 | |
| (+)-2 | 2*R*,5*S* | 8.29 ± 0.01 | | 8.10 ± 0.10 | | 8.05 ± 0.07 | | 8.57 ± 0.06 | |
| | | | 5[d] | | 1 | | 1 | | 5[d] |
| (−)-2 | 2*S*,5*R* | 7.61 ± 0.05 | | 8.07 ± 0.04 | | 8.06 ± 0.08 | | 7.86 ± 0.13 | |
| (±)-3 | | 6.91 ± 0.09 | | 6.58[b] ± 0.05 | | 6.79[b] ± 0.16 | | 7.43 ± 0.01 | |
| (±)-4 | | 8.22 ± 0.05 | | 8.13 ± 0.06 | | 7.91 ± 0.06 | | 8.38 ± 0.10 | |
| (+)-4 | 2*R*,5*R* | 8.58 ± 0.07 | | 8.47 ± 0.13 | | 8.35 ± 0.12 | | 8.79 ± 0.09 | |
| | | | 13[d] | | 2 | | 2 | | 9[d] |
| (−)-4 | 2*S*,5*S* | 7.45 ± 0.07 | | 8.16 ± 0.12 | | 7.99 ± 0.11 | | 7.86 ± 0.01 | |
| atropine | | 8.89 ± 0.05 | | 8.95 ± 0.09 | | 9.05 ± 0.10 | | 8.91 ± 0.11 | |

[a] Calculated from the Schild correlation constrained to $n = 1$. Carbachol was used as agonist. Number of replications from six to eight. [b] $-\log K_b$ calculated from the equation $\log (Dr - 1) = \log [ant.] - \log K_b$ at the concentration of $3 \times 10^{-6}$ M, since in these tissues the compound shows a decrease in the maximum effect of carbachol at $1 \times 10^{-5}$ M. [c] Eudismic ratio: ratio between the potency of the more potent and the less potent enantiomer. [d] Significantly different from that of the guinea pig heart ($p < 0.05$).

this relationship must be maintained in the isomeric compounds and as a consequence the 2*R* configuration can be assigned to (+)-1 and (+)-2 and the 2*S* one to compounds (−)-1 and (−)-2 (see Figure 2). Assignment of the absolute configuration in position 5 is then straightforward, the relative stereoisomerism of the substituents in positions 2 and 5 being known.

The same correlation between the absolute configuration in position 2 and the sign of the Cotton effect was found for 2-monosubstituted 1,3-oxathiolanes.[6]

**Optical Purity.** The optical purity of our compounds was established by means of 300-MHz $^1H$ NMR on the salts (+)-5 and (−)-6, monitoring the decrease and disappearance of a suitable signal due to one diastereomer.

As an example, Figure 3 shows the peaks, due to one of the 4-protons of (−)-5, after the first (a), the second (b), and the fourth crystallization (c). No detectable amount of the other diastereomer is left after four crystallizations, so that we can assume an optical purity higher than 99%.

In the same way the optical purity of (−)-6 was checked and was found to be also higher than 99%.

## Results and Discussion

Compounds 1–4 (racemates and enantiomers) were tested for their antimuscarinic potency on rat bladder and guinea pig ileum and heart (rate and force). The results, expressed as $pA_2$ values, are reported in Table III and were obtained through a Schild plot;[7] since in all cases the experimental slope of the straight lines obtained was not significantly different from unity, the $pA_2$ values were calculated, constraining the slope to 1.[8]

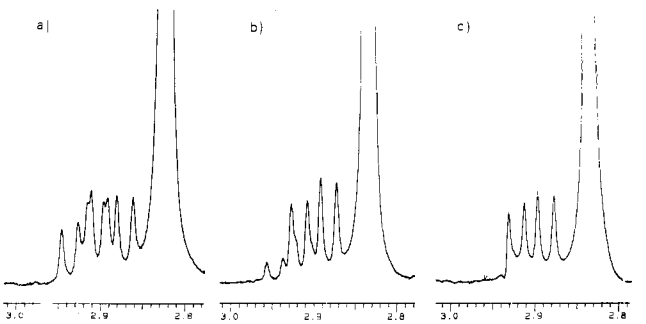



**Figure 3.** 300-MHz $^1H$ NMR spectra of (+)-5 after the first (a), second (b), and fourth crystallization (c).

The tertiary amines (±)-1 and (±)-3 behave as competitive antagonists on rat bladder and guinea pig ileum but do not on guinea pig heart (force and rate), where they induce a reduction of the maximum effect of carbachol at as low a concentration as $10^{-5}$ M. For this reason the values reported for these tissues represent $-\log K_B$ calculated at a concentration of $3 \times 10^{-6}$ M. A noncompetitive action of tertiary amines contrasting with the competitive behavior of the ammonium salts has been already noticed,[9] and makes these compounds of little use in receptor

(7) Arunlakshana, O.; Schild, H. O. *Br. J. Pharmacol.* **1959**, *14*, 48.

(8) Mackay, D. *J. Pharm. Pharmacol.* **1978**, *30*, 312.

(9) Ensing, K.; de Zeeuw, R. A. *Pharm. Res.* **1986**, *3*, 327.

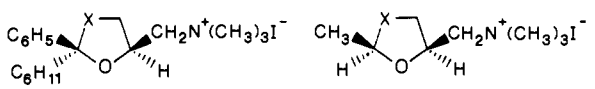
studies. In our case the norbases were some 3–6 times less potent that the corresponding quaternary salts.

It was expected that introduction of a chiral center close to the hydrophobic groups in position 2, which determine the main part of the interaction energy, would introduce some enantioselectivity in the molecule that shows no enantioselectivity when symmetrically substituted in position 2.[2]

This is indeed the case for the rat bladder and guinea pig ileum where a small but significant stereoselectivity is present. On the other hand, on guinea pig heart the stereoselectivity remains very low or totally absent. As for the compounds studied in the preceding paper,[2] the enantioselectivity of **2** and **4** is low if compared to that of the corresponding agonists;[4] however, it points in the same direction, and **2** and **4** seem to discriminate between ileum and heart, thus supporting the view that differences exist among the muscarinic receptors of these two issues ($M_2$ receptors).[10]

As far as tissue selectivity is concerned, compounds **2** and **4** (racemates and enantiomers) do not show any differentiation of the tissues studied when the criterion of Furchgott[11] is followed (differences of at least 0.5 in $-\log K_B$). In this they differ from the corresponding agonist *c*-2-methyl-*r*-5-[(dimethylamino)methyl]-1,3-oxathiolane methiodide, which was able to discriminate between ileum and heart (the (−) enantiomer being better than the racemate).[12] We thus have the confirmation that evaluation of enantioselectivity can give information that neither the racemate nor the single enantiomers can.

The order of potency of the four stereoisomers is (on guinea pig ileum) (+)-**4** (2*R*,5*R*) > (+)-**2** (2*R*,5*S*) > (−)-**2** (2*S*,5*R*) ≥ (−)-**4** (2*S*,5*S*). This is more or less the order of potencies found by Brimblecombe[13] and Triggle[14] for the corresponding isosteric 1,3-dioxolanes. It is remarkable that the most potent enantiomers of the corresponding agonists of both series have, notwithstanding the different notation, the same absolute stereochemistry of the most potent antagonists.




X = O (2*S*, 5*R*) X = S (2*R*, 5*R*) X = O (2*S*, 5*R*) X = S (2*R*, 5*R*)

This might support the view that agonists and antagonists of this kind interact with a common binding site on the receptor molecule. However, considering these data for 1,3-dioxolanes, Triggle[14] suspended his judgement on the basis of the slightness of the differences among the potencies of the various isomers. Brimblecombe,[15] on the other hand, arguing that it is the configuration of C-5 that cholinergic potency depends on, whereas in the anticholinergic drugs the configuration at C-5 is of little importance and anticholinergic potency depends only on configuration at C-2, reached the conclusion that agonists and antagonists of this class act at different sites of the receptor.

Actually, the prevalence of chirality at C-2 over that at C-5 only means that, for antagonists, hydrophobic interactions are much more important than electrostatic interactions and that the reverse is true for agonists; it says nothing about the actual site of binding of the two kinds of ligands. Only the comparison of the overall chirality of agonists and antagonists can be meaningful in this respect, so the conclusion of the Brimblecombe does not seem completely justified.

Our results show that the identity of stereochemical features for agonists and antagonists of this kind is not coincidental. Moreover, the differences among the 1,3-oxathiolane isomers are somehow larger and allow a more confident interpretation. Finally, the finding that also for 1,3-oxathiolane sulfoxides the absolute stereochemistry of agonists and antagonists is identical[2] seems to indicate that agonists and antagonists of this kind interact with the same receptor binding site.

A serious objection to this hypothesis is that the enantioselectivity of agonists is much larger than that of antagonists.[16]

A simple explanation is however possible, admitting that antagonists interact with the same site as agonists but induce, mainly through the strong interactions of their hydrophobic bulky groups, a conformational change in the receptor molecule which eventually results in a looser contact of the hydrophilic part of the molecule (the ring and the side chain in position 5) and in a lower enantioselectivity (wedgelike action).

Of course, as discussed in the preceding paper,[2] a fortuitous coincidence of the stereochemical demands of totally different binding sites of agonists and antagonists cannot be ruled out and more work will be necessary to clarify this point. However, having synthesized and characterized all four isomers of 2-cyclohexyl-2-phenyl-5-[(dimethylamino)methyl]-1,3-oxathiolane methiodide, the way is now open for the synthesis and study of the corresponding oxathiolane sulfoxides which, having a third chiral center in the molecule, should bring us more valuable information on the stereoisomerism of interaction.

## Experimental Section

**Chemistry.** All melting points were taken on a Büchi apparatus and are uncorrected. Infrared spectra were recorded with a Perkin-Elmer 337 spectrophotometer in Nujol mull for solids and neat for liquids. $^1$H NMR spectra were measured on a Varian EM 360L spectrometer with $Me_4Si$ or DSS as internal standards, except those of the salts **5** and **6**, which were recorded on a Varian VXR 300 spectrometer. Chromatographic separations were performed on a silica gel column (Kieselgel 40, 0.063–0.200 mm, Merck). Where analyses are indicated with symbols, the analytical results are within ±0.4% of the theoretical values. Optical activity was measured at a concentration of 1 g/100 mL (*c* 1) with a Perkin-Elmer 241 polarimeter with an accuracy of ±0.5°. CD was measured at a concentration of 1 mg/mL with a JASCO J 500 C spectropolarimeter.

***c*-2-Cyclohexyl-2-phenyl-*r*-5-[(dimethylamino)methyl]-1,3-oxathiolane [(±)-1] and 2-Cyclohexyl-*c*-2-phenyl-*r*-5-[(dimethylamino)methyl]-1,3-oxathiolane [(±)-3].** 2-Cyclohexyl-2-phenyl-5-(chloromethyl)-1,3-oxathiolane, as a 85:15 mixture of the two possible isomers, was obtained as described before[3] and reacted with an excess of dimethylamine in a sealed tube at 100 °C for 7 days. Evaporation of the excess of the amine gave a semisolid residue that was dissolved in $CHCl_3$ and washed

(10) Eglen, R. M.; Whiting, R. L. *J. Autonom. Pharmacol.* **1986**, *5*, 323.
(11) Furchgott, R. F. *Handbook of Experimental Pharmacology*; Blaschko, H., Muscholl, E., Eds.; Springer-Verlag: Berlin, 1972; p 283.
(12) Angeli, P.; Brasili, L.; Gualtieri, F.; Teodori, E. *International Symposium on Muscarinic Cholinergic Mechanisms*; Cohen, S., Sokolovsky, M., Eds.; Freund: London, 1986; p 24.
(13) Brimblecombe, R. W.; Inch, T. D. *J. Pharm. Pharmacol.* **1970**, *22*, 881.
(14) Chang, K. J.; Deth, R. C.; Triggle, D. J. *J. Med. Chem.* **1972**, *15*, 243.
(15) Brimblecombe, R. W.; Green, D.; Inch, T. D. *J. Pharm. Pharmacol.* **1970**, *22*, 951.
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with water. Evaporation of the dried ($Na_2SO_4$) solvent gave an oil (83% yield) that was column chromatographed with a mixture of petroleum ether, diethyl ether, dichloromethane, isopropyl alcohol, and triethylamine (50:20:20:9:1) as eluent.

The first fraction (85% of the total) was **c-2-cyclohexyl-2-phenyl-r-5-[(dimethylamino)methyl]-1,3-oxathiolane [(±)-1].**[3]

The second fraction (15% of the total) was **2-cyclohexyl-c-2-phenyl-r-5-[(dimethylamino)methyl]-1,3-oxathiolane** [(±)-3]. Anal. ($C_{18}H_{27}NOS$) C, H, N. The chemical and physical characteristics of the two compounds are reported in Table I.

**c-2-Cyclohexyl-2-phenyl-r-5-[(dimethylamino)methyl]-1,3-oxathiolane Methiodide [(±)-2] and 2-Cyclohexyl-c-2-phenyl-r-5-[(dimethylamino)methyl]-1,3-oxathiolane Methiodide [(±)-4].** Amine (±)-1 (1.0 g) was dissolved in dry ethyl ether (30 mL), methyl iodide (3 mL) was added, and the solution was left at room temperature overnight. The white solid obtained, (±)-2, was crystallized from absolute ethanol.[3]

In the same way and starting from (±)-3, compound (±)-4 was obtained. Anal. ($C_{19}H_{30}INOS$) C, H, N.

The chemical and physical characteristics of the two compounds are reported in Table I.

**Resolution of (±)-1.** A solution of (±)-1 (1.0 g) in 95% ethanol (8 mL) was added to a solution of L-(−)-*O,O'*-di-*p*-toluoyltartaric acid (*R,R*) (1.33 g) in 95% ethanol (12 mL).

After a few hours at room temperature, the salt crystallized as white crystals. The crystallization was repeated four times to constant optical rotation. Yield 0.98 g; mp 147–148 °C; $[\alpha]^{20}_D$ −124.4° (MeOH). Anal. ($C_{18}H_{27}NOS{\cdot}C_{20}H_{18}O_8$) C, H, N.

The salt obtained, (−)-5, was treated with a solution of 10% NaOH and extracted with ether to give 0.35 g of (−)-1 as a thick oil.

The base obtained from the mother liquors (0.73 g) was dissolved in ethanol (6 mL) and treated with a solution of D-(+)-*O,O'*-di-*p*-toluoyltartaric acid (*S,S*) (0.97 g) in ethanol (8 mL). After six crystallizations, the salt (+)-5 melted at 149–150 °C; $[\alpha]^{20}_D$ +118.4° (MeOH); yield 0.73 g. Anal. ($C_{18}H_{27}NOS{\cdot}C_{20}H_{18}O_8$) C, H, N.

Compound (+)-5, treated as described above, gave 0.30 g of (+)-1 as a thick oil.

IR and $^1H$ and $^{13}C$ NMR spectra are identical with those of the racemate. Chemical and physical characteristics of (+)- and (−)-1 are reported in Table II.

**(+)- and (−)-c-2-Cyclohexyl-2-phenyl-r-5-[(dimethylamino)methyl]-1,3-oxathiolane Methiodides [(+)-2 and (−)-2].** Via the procedure described before and starting with (+)-1, compound (+)-2 was obtained in 95% yield.

In the same way, starting from (−)-1, compound (−)-2 was obtained in 90% yield.

The IR and $^1H$ and $^{13}C$ NMR spectra are identical with those of the racemate. The chemical and physical characteristics of the two compounds are reported in Table II.

**Resolution of (±)-3.** Via the procedure described above, 1.29 g of (±)-3 was treated with 1.27 g of L-(−)-*O,O'*-di-*p*-toluoyltartaric acid (*R,R*) to give, after five crystallizations, 0.8 g of the diastereomeric salt (−)-6: mp 151–152 °C; $[\alpha]^{20}_D$ −132.5° (MeOH). Anal. ($C_{18}H_{27}NOS{\cdot}C_{20}H_{18}O_8$) C, H, N. A 0.32-g sample of (−)-3 was obtained from (−)-6 as a thick oil.

The base obtained from the mother liquors, treated with D-(+)-*O,O'*-di-*p*-toluoyltartaric acid (*S,S*) gave 0.86 g of (+)-6, which melts at 149–150 °C; $[\alpha]^{20}_D$ +138.4° (MeOH). Anal. ($C_{18}H_{27}NOS{\cdot}C_{20}H_{18}O_8$) C, H, N.

The salt (+)-6, treated with NaOH as described above, gave 0.33 g of (+)-3 as a thick oil.

The IR and $^1H$ and $^{13}C$ NMR spectra are identical with those of the racemate. The chemical and physical characteristics of (+)- and (−)-3 are reported in Table II.

**(+)- and (−)-2-Cyclohexyl-c-2-phenyl-r-5-[(dimethylamino)methyl]-1,3-oxathiolane Methiodides [(+)-4 and (−)-4].** Via the procedure already described and starting from (+)-3, compound (+)-4 was obtained in 85% yield.

In the same way, starting from (−)-3, compound (−)-4 was obtained in 85% yield.

The IR and $^1H$ and $^{13}C$ NMR spectra are identical with those of the racemate. The chemical and physical characteristics of the compounds are reported in Table II.

Table IV

| | (+)-6 | (+)-4 |
|---|---|---|
| Fw | 708.8 | 447.2 |
| space group | $p2_1$ | $p2_1$ |
| a, Å | 9.256 (2) | 11.981 (2) |
| b, Å | 25.115 (3) | 12.734 (2) |
| c, Å | 7.943 (2) | 6.901 (1) |
| $\beta$, deg | 94.6 (1) | 98.1 (1) |
| $V$, Å$^3$ | 1840.5 | 1042.4 |
| $Z$ | 2 | 2 |
| $d_{calcd}$, g cm$^{-3}$ | 1.279 | 1.425 |
| $\mu$(Mo K$\alpha$), cm$^{-1}$ | 1.04 | 15.15 |
| radiation | Mo | Mo |
| scan mode | $\theta/2\theta$ | $\theta/2\theta$ |
| scan width, deg in $\omega$ | 1.2 | 1.2 |
| scan speed, deg (in $\omega$) min$^{-1}$ | 1 | 0.67 |
| $2\theta$ range, deg | 4–56 | 4–56 |
| no. unique reflections | 4547 | 2620 |
| max shift of parameters | 0.87 | 0.55 |
| $R$ | 0.0488 | 0.0293[a] |
| no. of reflections for R | 3439 | 2513 |

[a] The $R$ value for the enantiomeric (−)-4 is 0.0314.

**Crystallographic Work.** Crystals of (+)-6 and (+)-4, suitable for X-ray diffraction studies, were grown from 95% and absolute ethanol, respectively. The structures of (+)-6 and (+)-4 are given in Figure 1. Measurements of diffraction were carried out on a Philips PW 1100 diffractometer, using graphite-monochromated Mo K$\alpha$ radiation ($\lambda$ = 0.7107 Å). The unit cell dimension were obtained from least squares of 25, $2\theta$ values between 14° and 30°.

Three reference reflections monitored showed no significant deterioration during data collection. Corrections were made for Lorentz and polarization factors but not for absorption. Only reflections with $I \geq 3\sigma(I)$ were considered. The crystal data and experimental details are summarized in Table IV. The structure of (+)-6 was resolved by the direct-method technique and that of (+)-4 by the heavy atom technique;[17] after least-squares refinement of the weighted coordinates, the Fourier method revealed the remaining non-hydrogen atoms. The atomic parameters of non-hydrogen atoms were refined anisotropically by the blocked diagonal least-squares method in both cases. The quantity monitored was $\sum w(|F_o| - |F_c|)^2$, with $w = 1$ and $1/[\sigma^2(F_o) + 0.004F^2]$, respectively. The majority of hydrogen atoms were obtained on a difference Fourier map and the remaining ones by calculation; the latter were not refined. The final atomic parameters for (+)-6 and (+)-4 are given in the supplementary material. The Bijvoet method was used to establish the absolute configuration of (+)-4 from the anomalous scattering due to the I atom, with use of Mo radiation. However the $R$ value for a *R,R* configuration for (+)-4 (0.0293) is not sufficiently lower than that of the enantiomer [(−)-4; R = 0.0314] to unequivocally regard the configuration as established. Even the collection of a second set of *h,k,l* data did not provide suitable values of Bijvoet pairs for the sound attribution of the absolute configuration.

The problem was resolved with the resolution of the structure of (+)-6 (Figure 1). As a matter of fact, the absolute configuration of D-(+)-*O,O'*-di-*p*-toluoyltartaric acid (*S,S*) being known, it was possible to establish the absolute configuration of the basic portion of the molecule [(+)-3] which was *R,R*, confirming the indication given by the Bijvoet method.

**Pharmacology.** The protocols used to obtain the results shown in Table III on guinea pig ileum and heart and on rat bladder have been previously reported.[2]

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Research (CNR) and Ministery of Public Education (MPI) of Italy.

**Registry No.** (±)-1, 115114-12-0; (±)-1 (Y = Cl), 115114-14-2; (+)-1, 115114-19-7; (-)-1, 115114-18-6; (±)-2, 115114-16-4; (+)-2, 115114-20-0; (-)-2, 115114-21-1; (±)-3, 115114-13-1; (±)-3 (Y = Cl), 115114-15-3; (+)-3, 101990-97-0; (-)-3, 115114-22-2; (±)-4, 115114-17-5; (+)-4, 101990-80-1; (-)-4, 115114-24-4; (-)-5, 115181-63-0; (+)-5, 115181-64-1; (-)-6, 115181-65-2; (+)-6, 115114-23-3; $C_6H_5COC_6H_{11}$, 712-50-5; (±)-$HSCH_2CH(OH)CH_2Cl$, 115046-74-7; L-(-)-O,O'-di-p-toluoyltartaric acid, 32634-66-5; D-(+)-O,O'-di-p-toluoyltartaric acid, 32634-68-7.

**Supplementary Material Available:** Tables of X-ray parameters for (+)-6 and (+)-4 (7 pages). Ordering information is given on any current masthead page.

# Substituted Benzamides with Conformationally Restricted Side Chains. 2. Indolizidine Derivatives as Central Dopamine Receptor Antagonists

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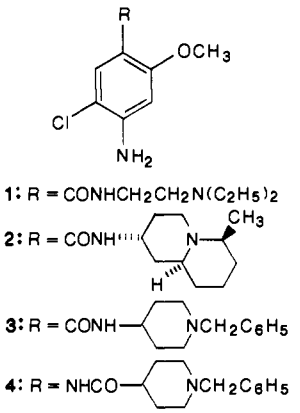
The substituted benzamides metoclopramide (1) and clebopride (3) are stimulants of gastric motility. They are also central dopamine receptor antagonists with 3 being the more potent. This is presumed to be due to an additional interaction of its *N*-benzyl group with the receptor. The effect of restricting the conformation of this group by replacing the *N*-benzylpiperidine side chain of 3 by phenyl-substituted quinolizidines and indolizidines has been investigated. Only the indolizidines had significant activity, the nature of which depended upon the orientation of the phenyl substituent. The 2α-phenyl isomers **5d–h** were potent central dopamine $D_2$ receptor antagonists with **5h** showing selectivity for the limbic system. The 2β-phenyl isomer **5c** was a gastric motility stimulant devoid of significant central dopamine receptor antagonist activity. Implications on receptor models are discussed.

Metoclopramide (1) is a substituted benzamide that is used clinically as a stimulant of upper gastrointestinal motility and as an antiemetic.[1] Its effects on the gastrointestinal tract are believed to be due to a combination of peripheral dopamine receptor antagonism and a potentiation of the cholinergic effects on gut muscle, probably mediated via 5-hydroxytryptamine.[2,3] Metoclopramide has also been shown to have antipsychotic activity at high doses. This activity is thought to be a consequence of its low potency as a central dopamine receptor antagonist.[4] The first paper in this series described how conformational restriction of the (diethylamino)ethyl side chain of 1 gave a compound 2, which was a selective stimulant of upper gastrointestinal motility but devoid of significant dopamine receptor antagonist activity.[5]

The structurally related clebopride (3) has been marketed for the treatment of gut disorders of a psychosomatic origin.[6] It is thought to have similar dual activity to 1 but is a more potent central dopamine receptor antagonist.[7] This greater central potency, both in vivo and in vitro, is probably due to an additional binding interaction of the *N*-benzyl group with central dopamine receptors.[6]

In an earlier study, reversal of the amide linkage of 3 produced a compound, 4, which was found to be a potent central dopamine antagonist but devoid of significant upper gastrointestinal motility activity.[8] The aim of the present work was to investigate the effectiveness of the secondary binding interaction of the *N*-benzyl group by conformationally restricting the side chain of 3 in the form of β-aryl-substituted quinolizidines and indolizidines, compounds **5a-i** (Table I). Inspection of Dreiding models indicated that β-substitution would probably incorporate the more likely binding conformations of the *N*-benzyl group of 3, with only a small increase in the N to aryl distance. The structure–activity relationships of **5a–i** will be discussed, and the results will be interpreted with reference to recent theories on the structural requirements for central dopamine antagonists.[9]




## Chemistry

The synthesis of **5a–d** has been described elsewhere.[10] The indolizidines **5e–i** were prepared by an analogous procedure (Scheme I).

Reaction of the respective aminoindolizidines **10e–i** with 4-(acetylamino)-5-chloro-2-methoxybenzoyl chloride followed by selective base hydrolysis of the 4-acetylamino group gave the indolizidines **5e–i**. The equatorial amines **10e–i** were prepared stereospecifically from the ketones **9e–i** by sodium/pentanol reduction of their oxime derivatives. The ketones **9e–i** themselves were prepared by acid-catalyzed cyclization of the Michael adducts formed

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