would more have the character of a hydrogen-bond direction than a specifically defined fixed point.

Acknowledgment. Karin Sabel is gratefully acknowledged for plotting the stereo pictures from the CHEMX system with the Calcomp plotter and Dr. Tor Magnusson for photographing these pictures. Håkan Wikström was the recipient of a Fogarty International Research Fellowship (NIH 1 FO5 TW 03628-01 B15 (AHR)) to study molecular mechanics with Dr. Allinger at the Department of Chemistry, University of Georgia. He was additionally funded by the Swedish Medical Research Council (MFR), Göteborgs Kungliga Vetenskaps- och Vitterhets-Samhälle, Magnus Bergvallus Stiftelse, Stiftelsen Lars Hiertas Minne, Adlebertska Forskningsfonden, Kungliga Vetenskapsakademien, AB Hässle, and Sverige-Amerika Stiftelsen, and all these grants are gratefully acknowledged.

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Registry No. **3a**, 76149-15-0; **4**, 16176-73-1; **5**, 84401-01-4; **10**, 94270-93-6; **10** (*N,N*-dimethyl analog), 109333-99-5; **11** (*N,N*-dimethyl analog), 83343-46-8; **12**-(*S*), 109333-98-4; **13**-(*S*), 109333-97-3; **15**, 68643-08-3.

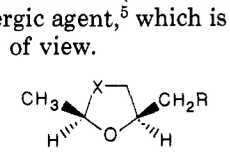
Resolution, Absolute Configuration, and Cholinergic Enantioselectivity of (-)- and (+)-*c*-2-Methyl-*r*-5-[(dimethylamino)methyl]-1,3-oxathiolane *t*-3-Oxide Methiodide and Related Sulfones[1]

E. Teodori,[†] F. Gualtieri,*[†] P. Angeli,[‡] L. Brasili,[‡] and M. Giannella[‡]

Dipartimento di Scienze Farmaceutiche, Università di Firenze, 50121 Firenze, Italy, and Dipartimento di Scienze Chimiche, Università di Camerino, 62032 Camerino, Italy. *Received July 30, 1986*

As a continuation of previous studies on chiral cholinergic agonists carrying a 1,3-oxathiolane nucleus, the enantiomers of *c*-2-methyl-*r*-5-[(dimethylamino)methyl]-1,3-oxathiolane *t*-3-oxide methiodide ((+)- and (-)-**1**) and of *cis*-2-methyl-5-[(dimethylamino)methyl]-1,3-oxathiolane 3,3-dioxide ((+)- and (-)-**2**) were obtained and their absolute configurations established by synthesis. The cholinergic potency of the four isomers was evaluated in vitro on guinea pig ileum and frog rectus abdominis models, and the results show that (-)-**1**, which has the same absolute configuration as L-(+)-muscarine, is a selective and potent muscarinic agent. The (+)-**1** enantiomer is some hundred times less potent than (-)-**1** on the muscarinic guinea pig ileum while, on the same tissue, the corresponding sulfone derivatives ((+)- and (-)-**2**) show no enantioselectivity.

As a continuation of our research on the molecular requirements of the cholinergic receptor recognition site,[2,3] we have recently started the synthesis and study of chiral compounds carrying a 1,3-oxathiolane nucleus. In particular, we have already studied the enantioselectivity of (+)- and (-)-*cis*-2-methyl-5-[(dimethylamino)methyl]-1,3-oxathiolane methiodide (*cis*-oxathiolane).[4] The oxidation product *c*-2-methyl-*r*-5-[(dimethylamino)methyl]-1,3-oxathiolane *t*-3-oxide methiodide (oxathiolane sulfoxide, (±)-**1**) is a potent cholinergic agent,[5] which is rather interesting from many points of view.



(±)-**1**: X = S⟶O; R = $^{+}N(CH_3)_3I^{-}$
(±)-**3**: X = S⟶O; R = $N(CH_3)_2$
(±)-**2**: X = SO_2; R = $^{+}N(CH_3)_3I^{-}$
(±)-**4**: X = SO_2; R = $N(CH_3)_2$

First, the molecular structure of (±)-**1** is very close to that of muscarine, a potent and selective muscarinic agent. Moreover, (±)-**1** shows lower affinity but higher efficacy than the parent compound, a fact that has suggested a role for the sulfoxide function in receptor activation.[6] Finally, *cis*-oxathiolane and oxathiolane sulfoxide behave, pharmacologically speaking, much like the muscarone/muscarine couple[7] whose intriguing structure–activity relationships are not yet clearly understood.[8]

Equally interesting, although much less potent as a muscarinic agonist, is the product of further oxidation of (±)-**1**, *cis*-2-methyl-5-[(dimethylamino)methyl]-1,3-oxathiolane 3,3-dioxide methiodide ((±)-**2**, *cis*-oxathiolane sulfone[5]), which is more potent as a nicotinic agent, the muscarinic selectivity present in (±)-**1** being in this case reversed.

We thought it of interest to study the enantioselectivity of the optical isomers of **1** and **2**. To this end it was necessary to obtain the pure enantiomers (+)- and (-)-**1** and (+)- and (-)-**2** and to establish their absolute configurations. This goal was achieved by resolving the racemate of (±)-**3** (the norbase of (±)-**1**) with standard methods, while (+)- and (-)-**2** were obtained by synthesis, which also provided the absolute configurations of the four enantiomers.

Resolution of (±)-3 and Synthesis of (-)- and (+)-1. Resolution was conveniently achieved by treatment of the tertiary amine (±)-**3** with D-(+)- and L-(-)-*O,O'*-di-

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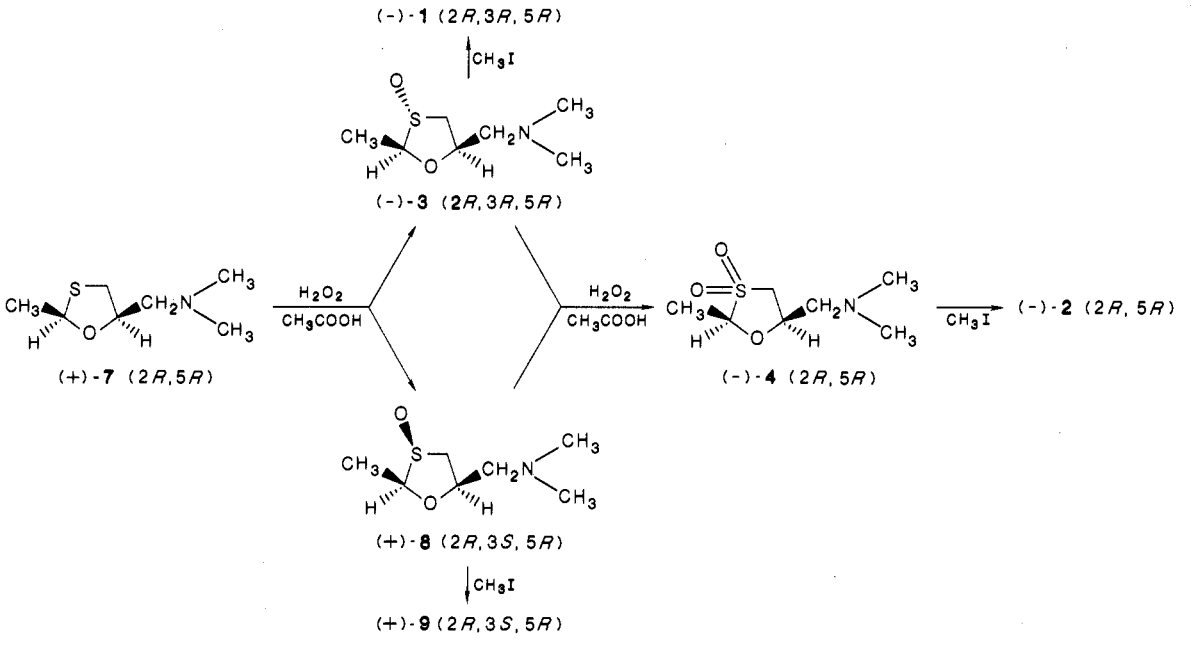
Scheme I



benzoyltartaric acid (D-(+)-DBTA and L-(−)-DBTA) and fractional crystallization of the diastereomeric salts from ethanol. The situation is almost ideal for the resolution of a racemate, as one of the salts is much more soluble and after only two crystallizations a constant rotation is obtained (see the Experimental Section).

The tertiary amines, obtained by treatment with 2.5 N NaOH ((−)-**3** and (+)-**3**), were reacted with CH_3I to give (−)-**1** and (+)-**1**, respectively.

The optical purity of the two enantiomers could not be evaluated directly. In fact the diastereomeric salts of (+)-**3** with L-(−)- and D-(+)-DBTA ((−)-**5** and (+)-**6**) have nearly identical ^1H NMR spectra. In particular, the 2-methyls show identical chemical shifts, so that it was impossible to evaluate the enantiomeric purity this way. Moreover, the shift reagent tris(3-(trifluoroacetyl)-*d*-camphorato)-europium(III) ($Eu(tfc)_3$) failed to discriminate between the two enantiomers.

Nevertheless, the already mentioned large differences in solubility of the two diastereomeric salts and the fact that CD spectra of (−)- and (+)-**3** are symmetrical (see Figure 1) are indications that the enantiomeric purity of the compounds obtained by resolution of the racemate is close to 100%.

Absolute Configuration of (−)- and (+)-1 and of (−)- and (+)-2. The absolute configuration of (−)- and (+)-**1** was established through the tertiary amines (−)- and (+)-**3**. These compounds can in fact be obtained by oxidation of the corresponding (+)- and (−)-*cis*-2-methyl-5-[(dimethylamino)methyl]-1,3-oxathiolane ((+)- and (−)-**7**), whose absolute configurations were known.[4] As shown in Scheme I, the transformation of the prochiral sulfide function of **7** into the chiral sulfoxide gives the two diastereomeric products **3** and **8** in a 4:1 ratio, respectively. The major product (**3**) has the sulfoxide oxygen trans to the C-5 side chain, and the product mixture can be separated by column chromatography.[5] When the reaction was carried out on (+)-**7** (which has a 2*R*,5*R* configuration), the (−)-**3** enantiomer was obtained, thus showing that its absolute configuration is 2*R*,3*R*,5*R*. Accordingly, the diastereomeric compound (+)-**8** has the 2*R*,3*S*,5*R* configuration.

Further oxidation of (−)-**3** (or (+)-**8**) under the same conditions but for a longer time gave (−)-*cis*-2-methyl-5-[(dimethylamino)methyl]-1,3-oxathiolane 3,3-dioxide ((−)-**4**), whose absolute configuration is therefore 2*R*,5*R*. The (−)-**7** enantiomer gives the corresponding enantiomers (+)-**3**, (+)-**4**, and (−)-**8**.

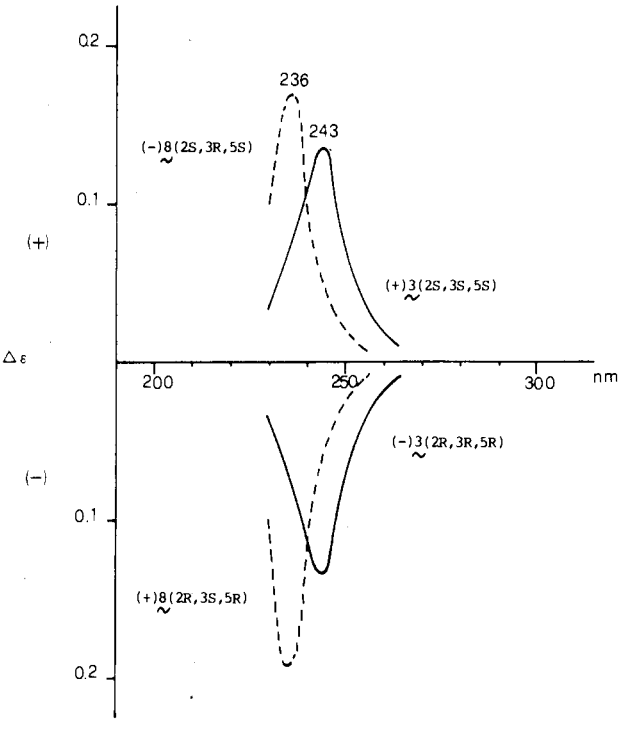


Figure 1. CD curves (EtOH) of (+)- and (−)-**3** and of (+)- and (−)-**8**.

As far as the optical purity of these compounds is concerned, it is important to note that the optical rotation of (−)- and (+)-**3** obtained by synthesis is slightly lower than that of the enantiomers obtained by resolution of the racemate. Since the optical purity of the starting materials ((+)- and (−)-**7** respectively) is about 98%,[4] this well supports our opinion, which has been already discussed, that optical purity of the enantiomers obtained by resolution of the racemate is close to 100%. For the same reason the optical purity of (+)- and (−)-**4** and (+)- and (−)-**8**, which were obtained only by synthesis, must be around 98%.

Table I. Muscarinic and Nicotinic Potency of the Enantiomers of 1, 2, and 9[a]

		guinea pig ileum (muscarinic, M)			frog rectus abdominis (nicotinic, N)			muscarinic selectivity	
compd	stereochem	$ED_{50} \pm SE$[b]	EPMR[c]	eudismic ratio	$ED_{50} \pm SE$[b]	EPMR[c]	eudismic ratio	ED_{50}^N/ED_{50}^M	$EPMR^N/EPMR^M$
(±)-1		$1.22 \pm 0.17 \times 10^{-7}$	1.3		$2.3 \pm 1.0 \times 10^{-4}$	45		1920	35
(−)-1	2*R*,3*R*,5*R*	$1.13 \pm 0.21 \times 10^{-7}$	1.2		$1.7 \pm 0.8 \times 10^{-4}$	33		1500	28
				133			3.5		
(+)-1	2*S*,3*S*,5*S*	$1.49 \pm 0.23 \times 10^{-5}$	159		$6.1 \pm 1.0 \times 10^{-4}$	120		41	0.8
(±)-9		$1.96 \pm 1.0 \times 10^{-5}$	209		$2.1 \pm 0.8 \times 10^{-4}$	41		11	0.2
(−)-9	2*S*,3*R*,5*S*	$2.00 \pm 0.56 \times 10^{-5}$	213		$2.6 \pm 0.8 \times 10^{-3}$	510		130	2.4
				3.4			24		
(+)-9	2*R*,3*S*,5*R*	$6.34 \pm 1.69 \times 10^{-5}$	660		$1.1 \pm 0.7 \times 10^{-4}$	21		1.7	0.03
(±)-2		$2.64 \pm 1.0 \times 10^{-5}$	281		$7.2 \pm 1.1 \times 10^{-5}$	15		3.0	0.05
(−)-2	2*R*,5*R*	$1.6 \pm 0.08 \times 10^{-5}$	170		$3.3 \pm 0.8 \times 10^{-5}$	6.5		2.1	0.04
				1			12		
(+)-2	2*S*,5*S*	$1.58 \pm 0.20 \times 10^{-5}$	168		$3.9 \pm 1.0 \times 10^{-4}$	76		24	0.5
carbachol		$9.4 \pm 0.8 \times 10^{-8}$	1		$5.1 \pm 0.6 \times 10^{-6}$	1		54	1
(±)-muscarine		$7.94 \pm 2.0 \times 10^{-8}$	0.8		$>5 \times 10^{-4}$	>95		>6300	>119

[a] All compounds with intrinsic activity (α) equal to 1. The number of replications varies from 8 to 10. [b] The statistical significance of the ED_{50} averages of each pair of enantiomers was estimated by the *t* test at the $p < 0.05$ level. In all cases except (+)- and (−)-2, the averages were significantly different. [c] EPMR = equipotent molar ratios between ED_{50} of compound and ED_{50} of carbachol calculated through to regression of the angular transformate of the fractional effect vs. the log concentrations of the agonists. Figures lower than 1 indicate higher potency while larger numbers indicate lower potency with respect to carbachol.

Chiroptical Properties. While 1,3-oxathiolane 3,3-dioxide compounds **2** and **4** did not show any appreciable Cotton effect up to 230 nm, the 1,3-oxathiolane 3-oxides **1**, **3**, **8**, and **9** showed a small but definite Cotton effect around 240 nm.

Mislow and co-workers[9] have shown that a correlation exists between the absolute configuration of methyl alkyl sulfoxides and their optical activity; in the absence of strongly perturbating groups a *negative* Cotton effect centered at the absorption band near 200 nm correlates with the *R* configuration. This rule was found still to be applicable when the alkyl group itself is also chiral but not strongly perturbating.[10]

However, the rule does not hold any longer when the sulfoxide group is part of a ring system,[11] and Sollman and co-workers[12] actually found that in some 3-thiacholestane oxides a *positive* Cotton effect at 200 nm is related to an *R* configuration of sulfur.

Since our instrument would not give reliable data below 230 nm, we were unable to verify the presence of the 200-nm Cotton effect, and the transition we observed was probably a weaker one that is sometimes found near 230 nm, which is always of opposite sign[13] and therefore may itself be correlated to the absolute configuration.

Our results confirm that Mislow's rule does not apply to cyclic sulfoxides and at the same time show that Sollman's results cannot be extended to our compounds since, for instance (Figure 1), compounds (−)-**3** and (+)-**8**, which have opposite configurations at the sulfur atom, show the same sign of the Cotton effect around 240 nm. It may be that the size of the ring and the presence of other chiral centers do not allow an obvious correlation of CD curves with absolute configuration in the case of cyclic sulfoxides.

When the CD spectra of sulfoxides are compared with those of the previously studied *cis*-oxathiolanes,[4] it is apparent that in the former case a 2*R*,3*R*,5*R* configuration results in a negative Cotton effect while in the latter series a negative Cotton effect is obtained with a 2*R*,5*R* configuration. Again the strongly perturbing sulfoxide function does not allow any correlation between the two series.

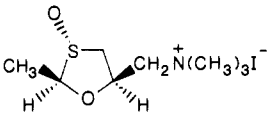
Finally, a correlation seems to exist in the sulfoxide series between a negative Cotton effect and *R* configuration at both the 2- and 5-positions; however, for the reasons mentioned above, the significance of such a correlation may be questioned.

Results and Discussion

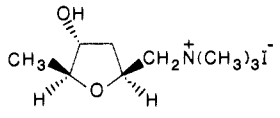
The activity of the compounds obtained in vitro in the guinea pig ileum (muscarinic, M) and frog rectus abdominis (nicotinic, N) models is reported in Table I. Potency is expressed as EPMR (equipotent molar ratio, ED_{50} of test compound/ED_{50} of carbachol), where carbachol was used as the reference compound. In the same table, muscarinic selectivity is reported as the ED_{50} ratio (ED_{50}^N/ED_{50}^M) and as the EPMR ratio ($EPMR^N/EPMR^M$). The latter value is apparently more meaningful since it takes into account the fact that nicotinic receptors usually require higher doses of agonist in order to be activated. The statistical significance of the ED_{50} averages of each pair of enantiomers was estimated by the *t* test at the $p < 0.05$ level. In all cases except (+)- and (−)-**2**, the averages were significantly different. As a consequence, all parameters derived from ED_{50}'s (EPMR, eudismic ratio, and muscarinic selectivity) appear to be statistically sound.

Compound (−)-1 is the most potent and selective muscarinic agonist while compound (−)-**2** is more potent and selective as a nicotinic agonist; all other isomeric compounds show low or very low potency and selectivity.

The data reported in the table show that only *c*-2-methyl-*r*-5-[(dimethylamino)methyl]-1,3-oxathiolane *t*-3-oxide methiodide (**1**) has a high enantioselectivity on guinea pig ileum and that the most potent enantiomer ((−)-1) has an absolute configuration (2*R*,3*R*,5*R*) that is identical with that of L-(+)-muscarine (2*S*,3*R*,5*S*).



(2*R*,3*R*,5*R*)-(−)-oxathiolane sulfoxide ((−)-1)



(2*S*,3*R*,5*S*)-L-(+)-muscarine

Enantioselectivity on the same tissue is reduced dramatically when the sulfoxide function is cis with regard

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to the 2- and 5-substituents (**9**) and disappears when the sulfoxide function is oxidized to the sulfone (**2**).

The enantioselectivity of 1 is considerably reduced also when the nicotinic activity is considered. On the other hand, a small increase in enantioselectivity on frog rectus abdominis is found for compounds **9** and **2**. These results suggest that the function in position 3 is critical for the interaction with the muscarinic receptor, while being unimportant for the nicotinic one. In fact, the simple inversion of chirality at position 3, as in compounds (−)-**1** (2*R*,3*R*,5*R*) and (+)-**9** (2*R*,3*S*,5*R*), results in a drop in muscarinic potency of about 600 times whereas nicotinic potency is maintained practically unchanged.

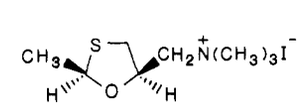
On the other hand, chirality at positions 2 and 5 is still of some importance since in all cases the 2*R*,5*R* isomers are more potent as nicotinic agonists than the 2*S*,5*S* counterparts, just as happens for the muscarinic activity of **2**.

It is therefore confirmed that the functionality in position 3 of muscarine-like compounds can identify in the recognition site of the muscarinic receptor a subsite that is unique and can suitably be called the "muscarinic subsite", as we have already proposed in studying the racemates.[3,5] As a consequence, differences in the corresponding region of the agonist molecules can lead to compounds of different selectivity toward the two receptor subclasses.

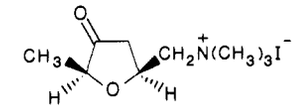
The lack of enantioselectivity of **2** on guinea pig ileum is very interesting since the same happens for muscarone.[14] In both cases there is a dipole that lies more or less on the plane of the pentatomic cycle (unlike muscarine and oxathiolane sulfoxide, where the dipole has a trans orientation), and in both cases there is no enantioselectivity or specificity toward the muscarinic receptor. However, compound **2** is much less potent than muscarone; this could be due to the fact that **2**, unlike muscarone, has a sulfur–oxygen group in a cis position with regard to the groups in 2 and 5, a feature that seems to be unaccepted by the muscarinic recognition site, as the already discussed drop in muscarinic potency (+)-**9** as compared to (−)-**1** would seem to confirm.

In the light of these results we feel that the very puzzling inversion of the eudismic ratio of muscarone as compared to muscarine[8,15] should be regarded with some care. This ratio, although remarkably constant in different tissues,[16,17] is in fact very small (~2.5), and its significance as supporting evidence for a possible inversion of stereochemistry in the binding of muscarone as compared to muscarine might have been overestimated.[18-20] This view finds some backing in the fact that the most potent isomer of *cis*-oxathiolane,[5] whose pharmacological behavior is close to that of muscarone, shows an absolute configuration identical with that of L-(+)-muscarine and (−)-oxathiolane sulfoxide.

The finding that enantioselectivity is high for *cis*-oxathiolane and very low for muscarone remains to be explained.



cis-oxathiolane



muscarone

Experimental Section

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 using Me_4Si or DSS as internal standard. Chromatographic separations were performed on a silica gel column (Kieselgel 40, 0.063–0.200 mm, Merck). Where analyses are indicated by 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.

Chemistry. (±)-*c*-2-Methyl-*r*-5-[(dimethylamino)methyl]-1,3-oxathiolane *t*-3-Oxide[21] ((±)-3). The tertiary amine (±)-**3** was obtained as described previously.[5] If the oxidation is performed on pure *cis*-2-methyl-5-[(dimethylamino)methyl]-1,3-oxathiolane ((±)-**7**, obtained as described before[4]), the number of isomers present in the mixture reduces to two and column chromatography will be much easier.

When 55.6 mg of (±)-**3** in $CDCl_3$ was added with increasing amounts of $Eu(tfc)_3$ (till a maximum of 143.7 mg), no evident resolution of any signal of the racemate occurred.

Resolution of (±)-3. Compound (±)-**3** (1.6 g) and 3.4 g of D-(+)-*O*,*O*′-dibenzoyltartaric acid (D-(+)-DBTA) were dissolved in 15 mL of anhydrous ethanol and left at room temperature overnight. The solid obtained ((+)-**5**) was crystallized twice, and the melting point and optical rotation remained nearly constant: yield 1.3 g; $[\alpha]^{20}_D$ +41.5° (EtOH); mp 152–155 °C; NMR (Me_2SO-d_6) δ 1.52 (d, 3, 2-CH_3), 2.3–3.5 (m, 4, 4-H_2 and 5-CH_2), 2.65 (s, 6, $N(CH_3)_2$), 4.55 (q, 1, 2-H), 4.78 (m, 1, 5-H), 5.80 (s, 2, CHO), 7.3–8.6 (m, 10, aromatics), 8.32 (s, 2, OH and NH). Anal. ($C_{25}H_{29}NO_{10}S$) C, H, N.

The salt was dissolved in H_2O and the solution made alkaline with 2.5 N NaOH; $CHCl_3$ extraction afforded 0.35 g of (−)-**3**: $[\alpha]^{20}_D$ −109.5° (EtOH); CD (EtOH) λ 243 nm, $\Delta\epsilon$ = −0.129. The IR and ^{1}H NMR spectra of (−)-**3** are identical with those of the racemate.[5]

The tertiary amine obtained from the mother liquor of (+)-**5** was treated with L-(−)-DBTA under the same conditions as described above, and the salt obtained ((−)-**5**) was crystallized twice from anhydrous ethanol: yield 1.28 g; $[\alpha]^{20}_D$ −40.9° (EtOH); mp 151–153 °C; ^{1}H NMR identical with those of the enantiomeric salt. Anal. ($C_{25}H_{29}NO_{10}S$) C, H, N.

The salt, treated as described above, gave 0.32 g of (+)-**3**: $[\alpha]^{20}_D$ +108.8° (EtOH); CD (EtOH) λ 243 nm, $\Delta\epsilon$ = +0.133. IR and ^{1}H NMR spectra are identical with those of the enantiomer.

To look for possible differences between the enantiomeric salts, which would allow evaluation of optical purity, we reacted (+)-**3** with an equimolecular amount of D-(+)-DBTA in anhydrous EtOH. The product ((+)-**6**) was so soluble in this solvent that it was isolated by evaporation and recrystallization from CH_3CN: $[\alpha]^{20}_D$ +97.3° (EtOH); mp 55–57 °C. This compound shows a ^{1}H NMR spectrum practically identical with that of diastereomeric (−)-**5**; in particular, the 2-CH_3 signals have the same chemical shift,

(14) The muscarinic potencies of the two enantiomers of muscarone on rabbit ileum referred to acetylcholine are as follows: D-(−)-muscarone (2*R*,5*R*), EPMR = 0.06; L-(+)-muscarone (2*S*,5*S*), EPMR = 0.15. The eudismic ratio is therefore 2.5. See ref 8, 16.

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(21) Stereochemistry is assigned relative to the C-5 substituent in accordance with IUPAC (IUPAC *Nomenclature of Organic Chemistry*; Pergamon: New York, 1979; Section E-2.3.3, p 478); the symbols mean *c* = cis, and *t* = trans with respect to the reference (*r*). *Chemical Abstracts* nomenclature is different in that the α/β system is followed. Accordingly, compound (±)-**3** should be named 2α-methyl-5α-[(dimethylamino)methyl]-1,3-oxathiolane 3β-oxide.

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thus preventing the checking of the enantiomeric purity of (−)- and (+)-**3** by this method.

(−)-*c*-2-Methyl-*r*-5-[(dimethylamino)methyl]-1,3-oxathiolane *c*-3-Oxide Methiodide ((−)-1). An excess of MeI (1 mL) was added to a solution of (−)-**3** (0.3 g) in anhydrous ether (20 mL), and the reaction mixture was left at room temperature overnight. The white solid obtained was crystallized from absolute ethanol: yield 90%; mp 195–196 °C (lit.[5] mp 172–174 °C for the racemate); $[\alpha]^{20}_D$ −48.4° (EtOH); CD (EtOH) λ 245 nm, $\Delta\epsilon$ = −0.153. The IR and ^{1}H NMR spectra are identical with those of the racemate.

In the same way, starting from (+)-**3**, we obtained (+)-**1**: yield 90%; mp 194–195 °C; $[\alpha]^{20}_D$ +48.2° (EtOH); CD (EtOH) λ 245 nm, $\Delta\epsilon$ = +0.132. The IR and ^{1}H NMR spectra are identical with those of the enantiomer.

(2*R*,3*R*,5*R*)-*c*-2-Methyl-*r*-5-[(dimethylamino)methyl]-1,3-oxathiolane *t*-3-Oxide ((−)-3). To a sample of 1 g of (+)-**7**, obtained as described before,[4] in 5 mL of CH_3COOH was added 2.5 mL of cold 30% H_2O_2. After 0.5 h at room temperature, the reaction mixture was made alkaline with 10% NaOH and extracted with $CHCl_3$ to give 1.1 g of a mixture (oil), which was chromatographed on a silica gel column with $CHCl_3$–petroleum ether–absolute ethanol–concentrated NH_4OH (340:60:65:8) as eluent.

The first fraction (R_f 0.60) was **(2*R*,3*R*,5*R*)-*c*-2-methyl-*r*-5-[(dimethylamino)methyl]-1,3-oxathiolane *t*-3-oxide ((−)-3)**: yield 0.7 g; $[\alpha]^{20}_D$ −108.0° (EtOH); CD (EtOH) λ 243 nm, $\Delta\epsilon$ = −0.110.

The compound is in every respect identical with that obtained by resolution of the racemate; treated with CH_3I, as described above, it gave **(2*R*,3*R*,5*R*)-*c*-2-methyl-*r*-5-[(dimethylamino)methyl]-1,3-oxathiolane *t*-3-oxide methiodide ((−)-1)**: $[\alpha]^{20}_D$ −48.0° (EtOH).

The second fraction (R_f 0.26) was **(2*R*,3*S*,5*R*)-*c*-2-methyl-*r*-5-[(dimethylamino)methyl]-1,3-oxathiolane *c*-3-oxide ((+)-8)**: yield 0.25 g; $[\alpha]^{20}_D$ +8.0° (EtOH); CD (EtOH) λ 236 nm, $\Delta\epsilon$ = −0.191. It shows the same IR and ^{1}H NMR spectra as the racemate.[5]

(2*S*,3*S*,5*S*)-*c*-2-Methyl-*r*-5-[(dimethylamino)methyl]-1,3-oxathiolane *t*-3-Oxide ((+)-3). With the same procedure described for (−)-**3** and starting from (−)-**7**, we obtained (+)-**3**, (+)-**1**, and (−)-**8**. **(2*S*,3*S*,5*S*)-*c*-2-Methyl-*r*-5-[(dimethylamino)methyl]-1,3-oxathiolane *t*-3-oxide ((+)-3)**: $[\alpha]^{20}_D$ +108.3° (EtOH); CD (EtOH) λ 243 nm, $\Delta\epsilon$ = +0.118.

The compound is in every respect identical with that obtained by resolution of the racemate; treated with CH_3I as described above, it gave **(2*S*,3*S*,5*S*)-*c*-2-methyl-*r*-5-[(dimethylamino)methyl]-1,3-oxathiolane *t*-3-oxide ((+)-1)**: $[\alpha]^{20}_D$ +47.7° (EtOH).

(2*S*,3*R*,5*S*)-*c*-2-Methyl-*r*-5-[(dimethylamino)methyl]-1,3-oxathiolane *c*-3-oxide ((−)-8): $[\alpha]^{20}_D$ −7.6° (EtOH); CD (EtOH) λ 236 nm, $\Delta\epsilon$ = +0.164. The compound shows IR and ^{1}H NMR spectra identical with those of the enantiomer.

(2*R*,3*S*,5*R*)-*c*-2-Methyl-*r*-5-[(dimethylamino)methyl]-1,3-oxathiolane *c*-3-Oxide Methiodide ((+)-9). Using the same procedure described for (−)-**1** and starting from (+)-**8**, we obtained compound (+)-**9** in 90% yield: mp 152–154 °C (lit.[5] mp 165–168 °C for the racemate); $[\alpha]^{20}_D$ +29.6° (EtOH); CD (EtOH) λ 243 nm; $\Delta\epsilon$ = −0.127. The IR and ^{1}H NMR spectra are identical with those of the racemate.

In the same way, starting from (−)-**8**, we obtained **(2*S*,3*R*,5*S*)-*c*-2-methyl-*r*-5-[(dimethylamino)methyl]-1,3-oxathiolane *c*-3-oxide methiodide ((−)-9)** in 90% yield: mp 153–154 °C; $[\alpha]^{20}_D$ −29.0° (EtOH); CD (EtOH) λ 243 nm; $\Delta\epsilon$ = +0.144. IR and ^{1}H NMR spectra are identical with those of the enantiomer.

(2*R*,5*R*)-*cis*-2-Methyl-5-[(dimethylamino)methyl]-1,3-oxathiolane 3,3-Dioxide ((−)-4). To a sample of 1.0 g of (−)-**3** (or (+)-**8**) in CH_3COOH (5 mL) was added 2.5 mL of 30% H_2O_2, and the solution was left at room temperature for 24 h. The reaction mixture was made alkaline with $NaHCO_3$ and extracted with $CHCl_3$ to give 0.8 g of an oil, which was purified from some starting material through column chromatography, with the same eluent as used for (−)-**3**: yield 0.65 g; $[\alpha]^{20}_D$ −42.0° (EtOH). The IR and ^{1}H NMR spectra are identical with those of the racemate.

In the same way, starting from (+)-**3** (or (−)-**8**), we obtained **(2*S*,5*S*)-*cis*-2-methyl-5-[(dimethylamino)methyl]-1,3-oxathiolane 3,3-dioxide ((+)-4)**: $[\alpha]^{20}_D$ +41.2° (EtOH). IR and ^{1}H NMR spectra are identical with those of the enantiomer.

(2*R*,5*R*)-*cis*-2-Methyl-5-[(dimethylamino)methyl]-1,3-oxathiolane 3,3-Dioxide Methiodide ((−)-2). Using the same procedure as described for (−)-**1**, and starting from (−)-**4**, we obtained compound (−)-**2** in 90° yield: mp 201–202 °C (lit.[5] mp 178–180 °C for the racemate); $[\alpha]^{20}_D$ −12.5° (EtOH). IR and ^{1}H NMR spectra are identical with those of the racemate.

In the same way, starting from (+)-**4**, we obtained **(2*S*,5*S*)-*cis*-2-methyl-5-[(dimethylamino)methyl]-1,3-oxathiolane 3,3-dioxide methiodide ((+)-2)** in 90% yield: mp 200–202 °C; $[\alpha]^{20}_D$ +11.9° (EtOH). IR and ^{1}H NMR spectra are identical with those of the enantiomer.

Pharmacology. The protocols used to obtained the results shown in Table I on guinea pig ileum and frog rectus abdominis have been previously reported.[4]

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Registry No. (±)-**1**, 109280-12-8; (+)-**1**, 109280-06-0; (−)-**1**, 109280-05-9; (±)-**2**, 98311-68-3; (+)-**2**, 109280-11-7; (−)-**2**, 109280-10-6; (±)-**3**, 109280-01-5; (+)-**3**, 109280-03-7; (−)-**3**, 109280-02-6; (+)-**4**, 109280-09-3; (−)-**4**, 109280-14-0; (+)-**5**, 109361-01-5; (−)-**5**, 109361-02-6; (+)-**6**, 109361-03-7; (+)-**7**, 103066-62-2; (−)-**7**, 103066-64-4; (+)-**8**, 109280-04-8; (−)-**8**, 109280-07-1; (±)-**9**, 109280-13-9; (+)-**9**, 109361-04-8; (−)-**9**, 109280-08-2.

Additions and Corrections

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Page 233. Drug **4** (dopexamine) should not be included in Table I since it is predominantly a β_2-adrenergic receptor agonist and DA_1-dopaminergic receptor agonist with only very weak activity at β_1-adrenergic receptors.