Resolution, Absolute Stereochemistry and Enantiospecificity of 4-(4-bromophenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline. The Crystal and Molecular Structures of the Racemic and 4R-Enantiomeric Hydrochloride Salt Forms

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The crystal structures and absolute stereochemistry of the ($\pm$)-racemic and ($-$)-enantiomeric hydrochlorides of 4-(4-bromophenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline have been determined by single-crystal X-ray diffraction methods. Crystal data: I. ($\pm$)-(4RS)-4, monoclinic, $P2_1/n$, $a = 10.754(3)$, $b = 11.271(2)$, $c = 12.459(3)$ Å, $\beta = 104.33(2)°$, $Z = 4$, $R = 0.030$ for 1921 reflections. II. ($-$)-(4R)-4, orthorhombic, $P2_12_12_1$, $a = 10.988(2)$, $b = 11.566(1)$, $c = 11.892(2)$ Å, $Z = 4$, $R = 0.035$ for 1043 reflections. X-Ray intensity measurements of anomalously scattered reflections established the absolute configuration of the ($-$)-enantiomer to be 4R. Only small conformational differences between the two crystal forms examined were observed. The intramolecular bond lengths and angles have expected values, and the Br-phenyl planes, in both structures, are almost perpendicular to the isoquinoline ring. In the solid state there are no intermolecular hydrogen bonds except N–H$\cdots$Cl salt bridge interactions, while the remaining intermolecular forces are of normal or weak van der Waals' character. In the crystal structure of the racemic form, the molecules are more closely packed than in the optically active 4R form. In both isomers the conformation of the piperidine ring is best described as a half-chair with the Br-phenyl group and N-methyl substituent equatorially positioned. The chiral hydrogen, H(4) and the N-methyl proton, H(2) are both axially oriented. Examination of the racemic and resolved isomers in the inhibition of stress-induced stomach ulcers reveals a high degree of enantiospecificity. The activity resides mainly in the S form.

The isoquinoline moiety is a new and promising member of 'non-classical' antidepressants with a wide use in clinical practice as a dopamine (DA-D1) antagonist. Nomifensine, 8-amino-2-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline (1) which is the parent compound in this series, is also known to be an effective inhibitor of norepinephrine (NE) re-uptake but to exert little antagonistic effect on serotonin (5-HT).[1] Recently a new pharmacological profile of some antidepressants of this group has been established, namely an antiulcer effect, especially strong against stress-induced peptic ulcers.[2,3] For an improved characterization of the enhanced biological enantiospecific activities of the 4-phenylisoquinoline compounds with respect to the absolute configurations of the enantiomers, a more careful investigation of the correlation between structural and biological data is required. Despite the interest medicinal chemistry would have in different aspects of relationships between chirality and biological activity, few studies have been performed where the activities of both a racemic compound and its enantiomers have been correlated with the differences in their molecular structures.

To elucidate further the structure–activity relationship of potent antidepressants and antiulcer drugs related to Nomifensine (1), a series of halogenated (F,Cl,Br) phenyl analogues have been synthesized and tested biochemically for re-uptake inhibition activity towards DA, NE and 5-HT as well as for antidepressant and antiulcer ac-

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(1)   (3)   (4)
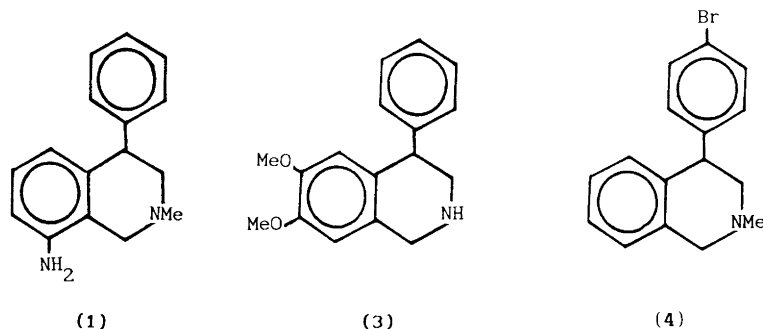
tivity.[4] The most active compounds are the Br-analogues. As a continuation of the project, we now report the resolution and enantiospecific antiulcer activity of the title compound **4** together with a comparison between the crystal structures of the racemic, **4RS** and enantiomeric, **4R** forms. Recently the resolution and absolute stereochemistry of the closely related hydrochloride of the dimethoxy-demethyl compounds (±)-(4RS)-**3**[5,6] and (+)-(4R)-**3**[7,8] have been reported. The observed positive sign of the specific rotation of plane-polarized light[9] and the established 4R absolute configuration of **3** contrasts with the observed but reversed optical preference, (-)-(4R), found in **4**.

Experimental

Resolution of 4-(4-bromophenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (4). To a solution of 9.0 g (0.03 mol) (±)-**4** in 90 ml ethanol was added a solution of 10.75 g (0.03 mol) of (+)-O,O'-dibenzoyl-D-tartaric acid in 90 ml ethanol. Crystallization proceeded for 6 h at room temperature and for another 20 h at 6–8°C. The crude tartrate (9.5 g), with m.p. 115–119°C and $[\alpha]_D^{20} = + 68.10°$ ($c = 0.25$, MeOH), was subjected to a second and third recrystallization from ethanol, ratio (g:ml) 1:20 and 1:35, respectively. The isolated (+)-4-D-tartrate weighed 8.2 g (87%) and had m.p. 120–124°C, $[\alpha]_D^{20} = + 82.38°$ ($c = 0.25$, MeOH). After treatment of the tartrate with aqueous ammonia, the free base was extracted with chloroform. The chloroform solution was dried with magnesium sulphate, and the solvent was evaporated off *in vacuo*. A batch of 3.7 g (82%) of the free base (+)-**4** with $[\alpha]_D^{20} = + 34.72°$ ($c = 0.25$, CHCl₃) was isolated. The base was treated with ether–HCl to give 3.8 g of (+)-4·HCl with m.p. 222–224°C and $[\alpha]_D^{20} = + 27.23°$ ($c = 0.25$, MeOH).

The combined ethanol filtrates were evaporated *in vacuo*, treated with aqueous ammonia and extracted with chloroform. After drying (MgSO₄), the chloroform was evaporated off *in vacuo*. The optically impure base, 3.9 g, was dissolved in 40 ml ethanol, and a solution of an equimolecular amount of (-)-O,O'-dibenzoyl-L-tartrate in 40 ml ethanol was added. After 36 h at 6–8°C, 6.2 g crystals with m.p. 116–120°C and

$[\alpha]_D^{20} = - 68.08°$ ($c = 0.25$, MeOH) were obtained. The crude (-)-L-tartrate was recrystallized twice from ethanol, ratio (g:ml) 1:18 and 1:25, respectively, to give 4.8 g crystals with m.p. 121–124°C and $[\alpha]_D^{20} = - 80.89°$ ($c = 0.25$, MeOH). The free base was isolated as described above, 2.3 g (51%) with $[\alpha]_D^{20} = - 32.94°$ ($c = 0.25$, CHCl₃). The hydrochloride weighed 2.4 g and had m.p. 220–223°C and $[\alpha]_D^{20} = - 26.13°$ ($c = 0.25$, MeOH). The total yield of the pure (-)-4·HCl enantiomers obtained by the method described was 67% of the initial (±)-**4**.

Pharmacology. The three hydrochloride forms of (±)-(4RS)-**4**, (-)-(4R)-**4** and (+)-(4S)-**4** were tested for antiulcer activity on an experimental model of a peptic ulcer induced by water-immersion stress according to Takagi, Kasuya and Watanabe.[5] Studies were conducted on 140 male Wistar rats, weighing 250 to 300 g. Before the experiments, the animals were starved for 24 h with free access to water. The compounds were administered orally, dissolved in distilled water, in doses of 0.5, 1.0, 2.0 and 4.0 mg kg⁻¹ 30 min before the immobilization. Dis-

Table 1. Inhibition of stress ulcer by (±)-(4RS)-**4**, (+)-(4S)-**4** and (-)-(4R)-**4** in rats.

Group	Dose (mg kg⁻¹)	Number of animals	Ulcer index, mm mean ± S.E.	Suppression of ulcer index (%)
(4RS)-4 Control	–	10	21.28 ± 1.89	–
	0.5	10	10.76 ± 1.12[a]	– 49.44
	1.0	10	7.01 ± 1.61[a]	– 67.06
	2.0	11	5.03 ± 1.21[a]	– 76.36
	4.0	11	3.31 ± 1.12[a]	– 84.45
(4S)-4	0.5	10	10.42 ± 2.57[b]	– 51.03
	1.0	10	7.11 ± 0.62[a]	– 66.59
	2.0	12	2.98 ± 0.65[a]	– 86.00
	4.0	12	1.47 ± 0.37[a]	– 93.09
(4R)-4	0.5	10	15.02 ± 1.92[b]	– 29.42
	1.0	10	10.26 ± 1.40[a]	– 51.79
	2.0	12	10.02 ± 1.53[a]	– 52.91
	4.0	12	10.86 ± 1.38[a]	– 48.97

[a] Statistical significance compared to controls, $p < 0.001$.
[b] Statistical significance compared to controls, $p < 0.05$.

tilled water was administered to control animals in the same experimental conditions. The destructive changes in the stomach (extracted 6 h after the experiment) are expressed as the mean ulcer index, which represents sum total of the lengths of individual lesions in millimeters, divided by the number of animals in each group $\pm$ the standard error of the mean. Differences were tested for statistical significance by Student's t-test. The data obtained are presented in Table 1.

Crystal data. Structures of the hydrochloride salts of ($\pm$)-4 and (−)-4 were determined by X-ray diffraction. Colourless crystals of suitable size for the X-ray work were obtained after recrystallization from absolute ethanol at room temperature. Many attempts were made to obtain single crystals of good quality of the (−) and (+) isomeric forms. The best crystals were obtained of the (−) isomer, and these were subsequently used in the X-ray experimental work. Crystallographic data and details of the data collections and the structure refinements are summarized in Table 2.

The intensity data sets of ($\pm$)-($4RS$)-4 and (−)-4 were

both collected at 291(1) K on an STOE/AED2 computer-controlled diffractometer, with graphite-monochromatized Cu Kα-radiation, λ = 1.5418 Å. The intensities were measured by the ω–2θ scan technique up to a maximum 2θ value of 140°, $\sin\theta/\lambda$ = 0.6076 Å^{-1}, with stationary background counts recorded on each side of the reflections. The reflection scan width was 1.50° and 1.35° for ($\pm$)-4 and (−)-4, respectively; the $\Delta\omega$ step was 0.03° and min. and max. time per step was 0.5 and 2.0 s for prescanned $I/\sigma(I)$ ratios above 20.0 and 3.0, respectively. The $\sigma(I)$ values were derived from counting statistics. Accurate cell constants and orientation matrices were determined from least-squares refinements which were based on the setting angles of independent and carefully centered reflections. Three standard reflections recorded every 2 h to monitor instrumental and crystal stabilities showed no significant intensity variations. The collected intensities were corrected for Lorentz-polarisation and absorption effects. Empirical absorption corrections were carried out by utilizing a computer program[10] based on psi-scanned reflections. Unique data sets were derived after merging the reflection intensities.

Table 2. Data collection and structure refinement details of the hydrochloride salt of ($4RS$)-4 and ($4R$)-4.

	($4RS$)-4	($4R$)-4
Formula	$C_{16}H_{16}NBr \cdot HCl$	$C_{16}H_{16}NBr \cdot HCl$
Melting point/°C	259–262	220–223
Space group	$P2_1/n$	$P2_12_12_1$
Unit cell dimensions/Å	a= 10.754(3)	a= 10.988(2)
	b= 11.271(2)	b= 11.566(1)
	c= 12.459(3)	c= 11.892(2)
	β = 104.33(2)°	
Unit cell volume/Å^3	1463.2(6)	1511.3(4)
Formula units per unit cell, Z	4	4
Calculated density g cm^{-3})	1.537	1.488
Crystal shape (colourless)	Needle-shaped	Prismatic
Crystal size/mm	0.30×0.22×0.06	0.10×0.11×0.12
Determination of unit cell		
Number of reflections used	21	28
θ-range/°	30–58	42–49
Intensity data		
Range (from–to) in h	−13–13	0–14
k	0–13	0–14
l	0–15	0–13
Number of observed reflections	2950	1786
unique	2643	1584
significant, $I > 3\sigma(I)$	1921	1043
Absorption correction		
Linear absorption coefficient/cm^{-1}	57.8	56.0
Transmission factor range	0.37–0.69	0.31–0.42
Least-squares refinement		
Number of refined parameters	240	177
$\Delta\sigma_{min,max}$/e Å^{-3}	0.1, −0.2	0.2, −0.4
Final agreement factors		
$R = \Sigma|\Delta F|/\Sigma|F_o|$	0.030	0.035
$wR = (\Sigma w|\Delta F|^2/\Sigma w|F_o|^2)^{1/2}$	0.039	0.047

Structure determinations and refinements. The original models of the non-H atoms of the two structures were derived by a combination of direct methods and difference Fourier recycling (MULTAN80).[11] The structures were subsequently refined by full-matrix and weighted least-squares methods (SHELX76)[12] based on structure factors, F. In both structures, the non-H atoms were refined together with their anisotropic displacement parameters. The H-atom positions in the racemic form were all located from a $\Delta\rho$ map and refined individually with isotropic thermal factors. Most of the H-atoms of the (–) isomer were also located from subsequent difference electron density ($\Delta\rho$) maps. As a consequence of the high ratio of the numbers of refined parameters to significantly observed structure factor amplitudes, the H-atoms were

fixed at calculated positions along with two fixed isotropic group temperature factors for the methyl- and general-hydrogen atoms. In the final cycle of each refinement, the maximum shift/e.s.d. for non-H atoms was <0.01, and no significant features in the electron density, $\Delta\rho$ map were observed. Table 3 gives the atomic coordinates of non-H atoms and Table 4 bond distances and angles. In Table 5 some selected torsion angles, dihedral angles between least-squares planes, hydrogen bonds and intermolecular contacts less than 3.6 Å are given. Fig. 1 shows a perspective drawing of the cationic molecule of (–)-(4R)-4 with the adopted numbering scheme; the numbering of the racemic (±)-(4RS)-4 isomer follows the same scheme.

Table 3. Fractional non-H atomic coordinates of the hydrochloride of (4RS)-4 and (4R)-4, with equivalent values of the anisotropic temperature factors. The e.s.d.s are given in parentheses.[a]

Atom	x	y	z	$B_{eq}/\text{Å}^2$
(4RS)-4[b]				
Br	−0.46639(3)	0.87545(3)	0.15158(3)	3.16(1)
Cl	0.29985(10)	0.40458(8)	0.43657(8)	3.76(3)
C(1)	0.3698(4)	0.7266(3)	0.3612(4)	3.20(10)
N(2)	0.2887(3)	0.6279(2)	0.3029(2)	2.63(7)
C(24)	0.3428(5)	0.5826(4)	0.2111(4)	3.86(13)
C(3)	0.1518(3)	0.6644(3)	0.2573(3)	2.72(9)
C(4)	0.0910(3)	0.7039(3)	0.3499(3)	2.35(8)
C(4A)	0.1740(3)	0.7952(3)	0.4242(3)	2.13(8)
C(5)	0.1231(4)	0.8704(3)	0.4912(3)	2.80(9)
C(6)	0.1990(4)	0.9503(3)	0.5617(3)	3.29(10)
C(7)	0.3286(4)	0.9568(4)	0.5671(3)	3.60(11)
C(8)	0.3811(4)	0.8828(3)	0.5023(3)	3.11(9)
C(8A)	0.3048(3)	0.8009(3)	0.4305(3)	2.39(8)
C(41)	−0.0449(3)	0.7476(3)	0.3009(3)	2.30(8)
C(42)	−0.1448(3)	0.7073(3)	0.3436(3)	2.74(9)
C(43)	−0.2697(4)	0.7469(3)	0.3006(3)	2.93(9)
C(44)	−0.2936(3)	0.8268(3)	0.2146(3)	2.50(8)
C(45)	−0.1966(4)	0.8695(3)	0.1702(3)	2.83(9)
C(46)	−0.0726(3)	0.8293(3)	0.2143(3)	2.62(9)
(4R)-4				
Br	−0.1712(1)	−0.1307(1)	0.3499(1)	4.52(2)
Cl	0.4699(2)	0.3236(2)	0.0879(2)	4.36(6)
C(1)	0.5925(8)	0.0089(7)	0.1568(9)	3.8(2)
N(2)	0.5282(7)	0.1060(5)	0.2147(6)	3.7(2)
C(24)	0.6027(10)	0.1522(8)	0.3090(9)	5.0(3)
C(3)	0.4052(8)	0.0699(8)	0.2543(7)	3.6(2)
C(4)	0.3229(8)	0.0335(6)	0.1586(8)	3.4(2)
C(4A)	0.3870(8)	−0.0525(7)	0.0808(7)	3.1(2)
C(5)	0.3229(9)	−0.1207(7)	0.0067(6)	3.7(2)
C(6)	0.3794(9)	−0.1949(8)	−0.0680(8)	4.3(3)
C(7)	0.5060(10)	−0.2006(8)	−0.0678(8)	4.8(3)
C(8)	0.5727(8)	−0.1338(9)	0.0051(8)	4.3(2)
C(8A)	0.5151(8)	−0.0573(7)	0.0796(7)	3.5(2)
C(41)	0.2029(6)	−0.0105(7)	0.2040(7)	2.8(2)
C(42)	0.0955(8)	0.0316(8)	0.1608(9)	4.0(2)
C(43)	−0.0154(8)	−0.0044(8)	0.2030(8)	4.4(2)
C(44)	−0.0170(8)	−0.0847(7)	0.2899(7)	3.7(2)
C(45)	0.0876(7)	−0.1300(8)	0.3345(7)	3.8(2)
C(46)	0.1985(7)	−0.0934(7)	0.2903(7)	3.3(2)

[a] $B_{eq} = \frac{4}{3}\,\Sigma_i\Sigma_j\beta_{ij}a_ia_j$. [b] The coordinates of the racemate refer to the 4R-configurational form.

Table 4. Intramolecular bond distances and bond angles with e.s.d.s in parentheses.

	(4*RS*)-4[a]	(4*R*)-4[b]
Distance/Å		
Br—C(44)	1.910(3)	1.914(9)
C(1)—N(2)	1.488(5)	1.495(11)
C(1)—C(8A)	1.495(6)	1.468(13)
N(2)—C(24)	1.497(6)	1.488(12)
N(2)—C(3)	1.498(4)	1.490(11)
C(3)—C(4)	1.525(6)	1.513(12)
C(4)—C(4A)	1.518(4)	1.530(12)
C(4)—C(41)	1.520(4)	1.513(11)
C(4A)—C(5)	1.392(5)	1.376(12)
C(4A)—C(8A)	1.391(5)	1.409(12)
C(5)—C(6)	1.376(5)	1.382(12)
C(6)—C(7)	1.381(6)	1.392(15)
C(7)—C(8)	1.375(6)	1.374(14)
C(8)—C(8A)	1.401(5)	1.402(13)
C(41)—C(42)	1.389(5)	1.376(12)
C(42)—C(43)	1.390(5)	1.383(13)
C(43)—C(44)	1.374(5)	1.390(12)
C(44)—C(45)	1.382(6)	1.370(11)
C(45)—C(46)	1.387(5)	1.392(11)
C(41)—C(46)	1.393(5)	1.406(11)
Bond angle/°		
N(2)—C(1)—C(8A)	113.5(3)	113.9(7)
C(1)—N(2)—C(3)	112.5(3)	111.4(6)
C(1)—N(2)—C(24)	109.7(3)	110.9(7)
C(24)—N(2)—C(3)	109.6(3)	111.2(7)
N(2)—C(3)—C(4)	111.0(3)	112.5(7)
C(3)—C(4)—C(41)	109.9(3)	110.3(7)
C(3)—C(4)—C(4A)	111.2(3)	111.1(7)
C(4A)—C(4)—C(41)	112.7(3)	113.5(6)
C(4)—C(4A)—C(8A)	119.9(3)	119.5(7)
C(4)—C(4A)—C(5)	121.4(3)	121.6(8)
C(5)—C(4A)—C(8A)	118.7(3)	118.8(8)
C(4A)—C(5)—C(6)	121.5(4)	122.5(9)
C(5)—C(6)—C(7)	119.8(4)	118.5(9)
C(6)—C(7)—C(8)	119.7(4)	120.5(9)
C(7)—C(8)—C(8A)	121.0(4)	120.9(9)
C(4A)—C(8A)—C(8)	119.4(3)	118.8(8)
C(1)—C(8A)—C(8)	117.0(3)	117.6(8)
C(1)—C(8A)—C(4A)	123.6(3)	123.5(8)
C(4)—C(41)—C(46)	121.7(3)	121.3(7)
C(4)—C(41)—C(42)	119.9(3)	119.7(7)
C(42)—C(41)—C(46)	118.4(3)	119.0(7)
C(41)—C(42)—C(43)	120.8(3)	120.9(8)
C(42)—C(43)—C(44)	119.2(4)	118.8(8)
Br—C(44)—C(43)	118.9(3)	118.3(7)
C(43)—C(44)—C(45)	121.8(4)	122.2(8)
Br—C(44)—C(45)	119.3(3)	119.5(7)
C(44)—C(45)—C(46)	118.3(3)	118.2(8)
C(41)—C(46)—C(45)	121.5(3)	120.8(7)

[a] H-positions which are refined individually range between 0.89 and 1.05 Å with an average value of 0.98 Å. [b] H-atoms assumed in geometrically fixed positions with C—H = 1.08 Å.

Determination of the absolute configuration. The absolute stereochemistry of (–)-**4** hydrochloride was determined by measuring Bijvoet differences with Cu Kα-radiation. Classical Bijvoet[13] ratios, defined as: $2(I_{hkl} - I_{\overline{hkl}})/(I_{hkl} + I_{\overline{hkl}})$ were calculated for reflections with θ less than 36°.
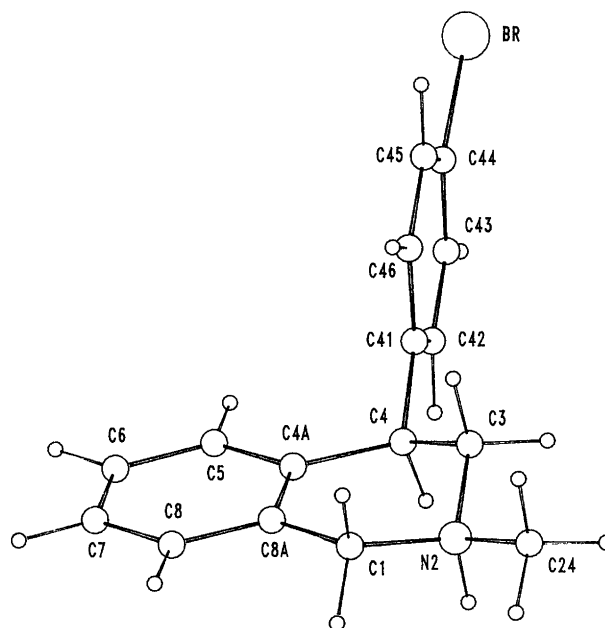

Fig. 1. Molecular structure and atomic labeling scheme of (4*R*)-**4**. The numbering of the racemic isomer, (4*RS*)-**4**, follows the same scheme.

A total of 15 reflections well spread over the θ-range, which exhibited the greatest anomalous scattering effects were selected for careful X-ray intensity remeasurement under the same conditions. Based on the match between calculated and observed Bijvoet ratios, all measured reflections established the (–)-(4*R*)-configurational assignment. The anomalous dispersion correction terms were those reported by Cromer and Liberman.[14] Lists of calculated and observed Bijvoet ratios of the (4*R*)-**4** enantiomer, tables of fractional H-atom coordinates, anisotropic thermal factors of non-H atoms, calculated and observed structure factors and full lists of torsion angles of the two hydrochloride salts (4*RS*)-**4** and (4*R*)-**4** are available from one of the authors (B.S.).

Results and discussion

Chemistry. The synthesis and biological testing of the racemic form of 4-(4-bromophenyl)-2-methyl-1,2,3,4-tetraisoquinoline (**4**) has been previously reported.[4] The (+)-(4*S*)-**4** and (–)-(4*R*)-**4** enantiomers were isolated by treatment of (±)-**4** with an equimolecular amount of dibenzoyl-D-tartaric acid in ethanol, followed by treatment of the optically impure base with dibenzoyl-L-tartaric acid. The resolution of the two enantiomers was considered complete when the m.p. and the optical rotation did not change between two recrystallizations. The optical purity of the bases was checked by means of their ¹H NMR spectra recorded in the presence of the chiral shift reagent Eu(hfbc)₃. No additional splitting of the proton signals was observed, which indicated enantiomeric

Table 5. Endocyclic torsion angles of the piperidine ring, dihedral angles between molecular least-squares planes, H-bonding and intermolecular close contacts of non-H atoms shorter than 3.6 Å. Compared values greater than 3.6 Å are marked*.

	(4RS)-4[a]	(4R)-4
Torsion angle/°		
C(1)–N(2)–C(3)–C(4)	−61.2(4)	−61.4(9)
N(2)–C(3)–C(4)–C(4A)	50.9(4)	49.1(9)
C(3)–C(4)–C(4A)–C(8A)	−23.4(4)	−21.5(11)
C(4)–C(4A)–C(8A)–C(1)	4.4(5)	5.7(13)
C(4A)–C(8A)–C(1)–N(2)	−12.5(5)	−16.3(12)
C(8A)–C(1)–N(2)–C(3)	40.5(4)	43.0(10)
N(2)–C(3)–C(4)–C(41)	176.5(3)	175.8(6)
C(4A)–C(4)–C(41)–C(42)	−103.6(4)	−104.7(9)
Dihedral angle/°		
Piperidine–benzene	3.9(1)	3.9(3)
Piperidine–phenyl	93.7(1)	93.9(2)
Benzene–phenyl	92.2(1)	94.4(2)

Compound	Donor–H N(2)–H(N2)	Donor···Acceptor N(2)···Cl	H···Acceptor H(N2)···Cl	<Donor–H···Acceptor N(2)–H(N2)···Cl
H-bonding parameters (Å and °).				
(4RS)-4	1.01(6)	3.004(3)	2.01(6)	165(5)
(4R)-4[b]	1.08	3.004(7)	1.96	161

Intermolecular contacts/Å	(4RS)-4	(4R)-4
Br···Cl[c]	3.496(2)[i]	3.406(3)[i']
C5···C24	3.558(6)[ii]	3.52(1)[ii']
C6···C24	*3.636(6)[ii]	3.56(1)[ii']
C4A···C45	3.558(5)[iii]	*3.62(1)[iii']
C5···C44	3.500(5)[iii]	*4.10(1)[iii']
C5···C46	*4.359(5)[iii]	3.58(1)[iii']
C8···C46	3.506(5)[iii]	*4.72(1)[iii']
C8A···C45	3.554(5)[iii]	*3.80(1)[iii']

[a] The torsion angles of the racemic R-configurational form is given. [b] H-atoms in fixed positions. [c] Transition symmetry code: (4RS)-4: (i) −x−¹/₂,y+¹/₂,−z+¹/₂; (ii) −x+¹/₂,y+¹/₂,−z+¹/₂; (iii)x+¹/₂,−y+³/₂,z+¹/₂. (4R)−4: (i') −x,y−¹/₂,−z+¹/₂; (ii') −x+1,y−¹/₂,−z+¹/₂; (iii') −x+¹/₂,−y,z−¹/₂.

purity. The optically active bases were then converted into their hydrochloride salts, which were used for X-ray analysis and pharmacological testing.

Pharmacology. The established antiulcer effect of 4, as can be seen from Table 1, is much higher than that of Nomifensine[2,7] and nearly as strong as the effect of Gas-trofensine, AN₅.[2,3,15] These facts demonstrate once again the positive influence on the biological activity of a halo-substituent in the 4-position of the 4-phenyl group. It is obvious, from the comparative study of the three forms of 4, that the antiulcer effect is highly enantiospecific and that the antiulcer effect of the racemate is due mainly to the 4S-enantiomeric content. These results correlate well with our previous data for enantiospecificity of the com-pounds in inhibiting the development of peptic ulcers.[2] The considerably higher biological activity of 4, when compared with the structurally similar dimethoxytetrahy-droquinoline 3 might be explained both by the presence of a halogen substituent and also by a more favorable

conformation in its interaction with the corresponding re-ceptor systems.

Molecular description. The molecular conformations of the cations in the crystal structures of the isomeric (4RS)-4 and (4R)-4 hydrochloride forms are illustrated in Fig. 2(a), where a superposition of their common R-configurational forms is presented. The graphical over-lay clearly reveals the minor conformational difference which is restricted to the Br-phenyl rings. The angle be-tween the two Br-phenyl planes is approximately 2°, as evaluated from the dihedral angles given in Table 5. In Fig. 2(b) a molecular overlay between the mirror-image R and S forms of the racemic salt is also illustrated, show-ing the diverging orientations of the Br-phenyl rings. A comparison between the structures of the crystalline forms of compound 4 shows that the molecular bond lengths and bond angles have expected values that agree to within experimental error. The conformation of the het-erocyclic piperidine rings is best described as half-chair
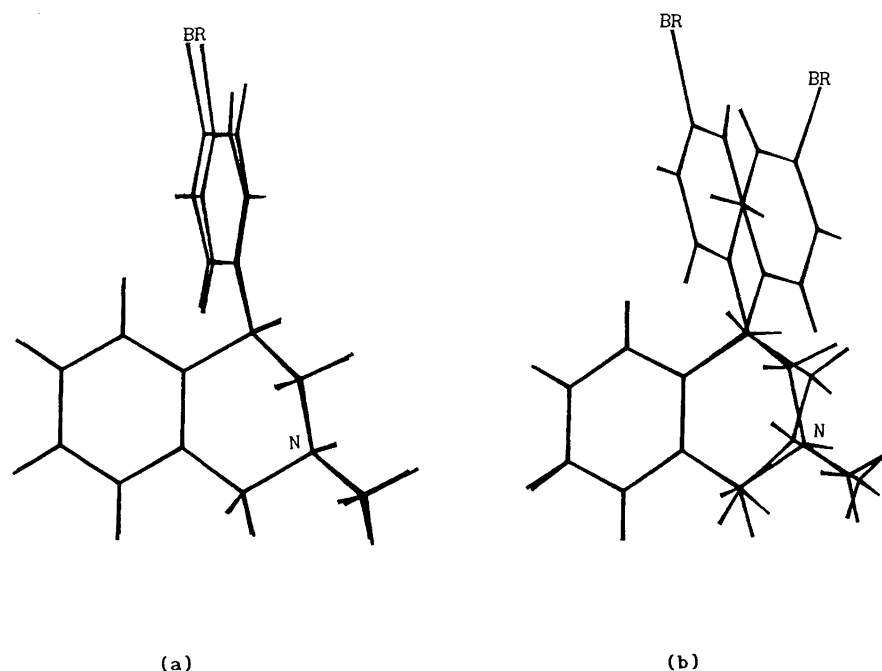
(a)   (b)

Fig. 2. (a) Molecular conformational overlay of the *R*-chiral form of (4*RS*)-4 and (4*R*)-4 (Br-phenyl ring: right), revealing the close relationship between the adopted molecular conformations in the two crystal forms. (b) Superposition of the *R* and *S* (Br-phenyl ring: right) forms of (4*RS*)-4. The distances between equivalent atoms are N2–N2: 0.45, C3–C3: 0.90, C41–C41: 1.39 and Br–Br: 5.93 Å.

with the lowest asymmetry parameters,[16] ΔC_2(N2–C3): 10.7° and 5.6° for (4*RS*)-4 and (4*R*)-4, respectively.

The established biological activity of compound **4** is mainly due to the *S*-configurational state. The atomic positions of the *R*-enantiomeric form, exhibited in Fig. 1, may be compared with those of the mirror-image *S*-chiral form of the racemate shown in Fig. 3. Notable from this figure is the pseudo-equatorial orientations of the Br-phenyl ring and the *N*-methyl substituent and, further, the axial orientations of H(4) and the *N*-methyl proton, H(2).
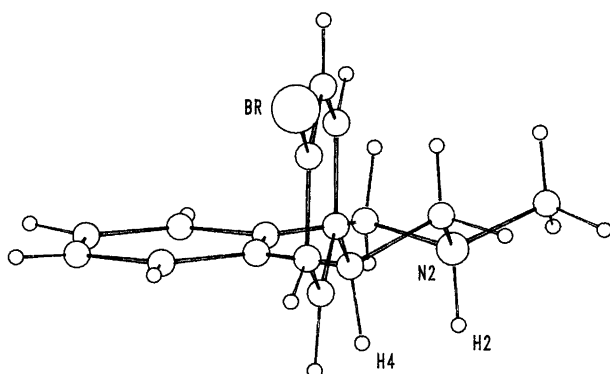

Fig. 3. The 4*S*-configurational form of the racemate, (4*RS*)-4. The chiral hydrogen, H4 (*axial*) and the N-proton, H2 (*axial*) are labeled. Notable is the pseudo-*equatorial* orientations of the *N*-methyl substituent and the aromatic Br-phenyl group. The conformation of the piperidine-ring is *half-chair*.

The axial H(2) orientation is most probably a consequence of the preferred equatorial methylation of the heterocyclic nitrogen atom. Interestingly, conformation–activity studies of closely related tetrahydroisoquinoline derivatives[17] (N in the 3-position) show that an axial orientation of the nitrogen lone pair (or ammonium hydrogen) may be necessary for receptor interaction if the nitrogen atom is alkylated. The nitrogen H(2) atom in the crystal structures of (4*RS*)-4 and (4*R*)-4 is the only proton involved in hydrogen bonding, salt-bridging the cationic molecule and the chloride anion. In the crystal structures of the less active, protonated form of the dimethoxydemethyl compound **3**,[3,4] it is observed that not only the aromatic phenyl ring but also the position of the nitrogen is flexible. The piperidine rings of the two independent crystal conformers A and B of the racemic hydrochloride salt of (4*RS*)-3 adopt a sofa and a half-chair conformation, respectively. The two NH₂-hydrogens in these conformations are connected to the nitrogen atom in a pseudo-axial and equatorial manner, and both protons are involved in hydrogen bonding to adjacent anionic chloride atoms. In Fig. 4 the *S*-configurational forms of the two independent crystal conformers A and B of the dimethoxydemethyl compound (4*RS*)-3 have been superimposed on the *S*-chiral form of (4*RS*)-4. A close relationship between the low-energy half-chair conformers in the vicinity of the nitrogen atom is observed.

In structure–activity relationship studies, where attempts are made to correlate the structural requirements for antagonistic potency of dopamine-like derivatives, the
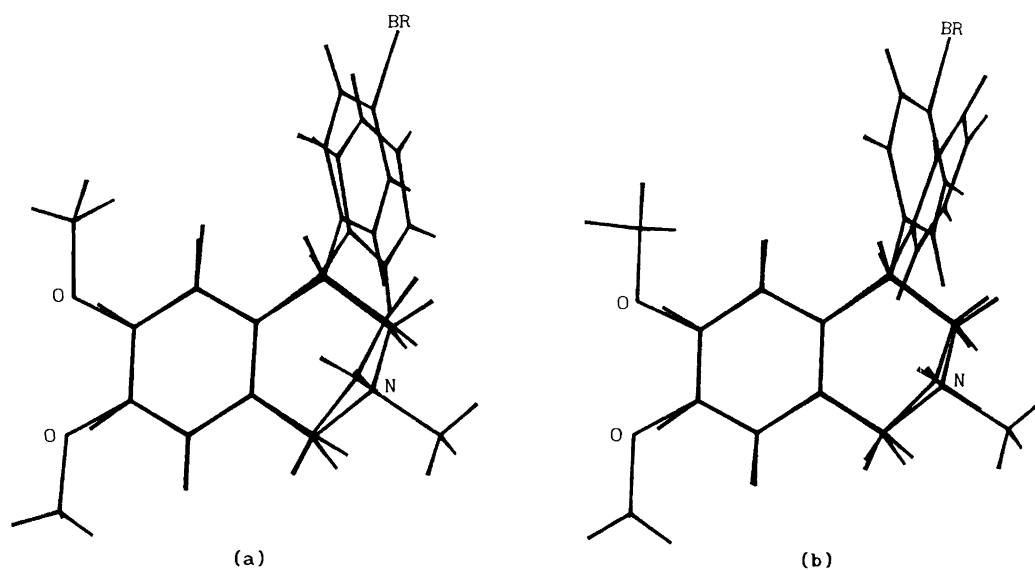
Fig. 4. Superposition of the 4S-chiral form of (a) (4RS)-4 and (4RS)-3 (mol A). Deviating distances N2–N2: 0.50, C3–C3: 0.43, C41–C41: 0.34 and C44–C44: 1.09 Å; (b) (4RS)-4 and (4RS)-3 (mol B). Deviating distances N2–N2: 0.23, C3–C3: 0.20, C41–C41: 0.25 and C44–C44: 0.95 Å.

distance of the heterocyclic nitrogen from the benzene aromatic plane to the aromatic benzene- and phenyl-ring centers are commonly studied parameters. These distances are found to be some of the most sensitive and most highly correlated structural parameters of the biological activity.[17] In the semi-rigid half-chair conformation of the tetraisoquinoline molecule, as observed in (4RS)-4 and (4R)-4, the two carbon atoms C(4) and C(1) are situated less than 0.06 Å from the benzene plane,

while the N(2) and C(3) atoms are positioned on each side of the expanded isoquinoline plane. As compared with the molecular S-configurational form of compound 4 shown in Fig. 3, where the aromatic benzene ring has been oriented to the left and the Br-phenyl ring is directed towards the reader, the N(2) atom is located 0.223(3) and 0.288(7) Å below and the C(3) atom 0.458(4) and 0.381(9) Å above the isoquinoline plane. Furthermore, the intramolecular distances from the nitrogen atom to
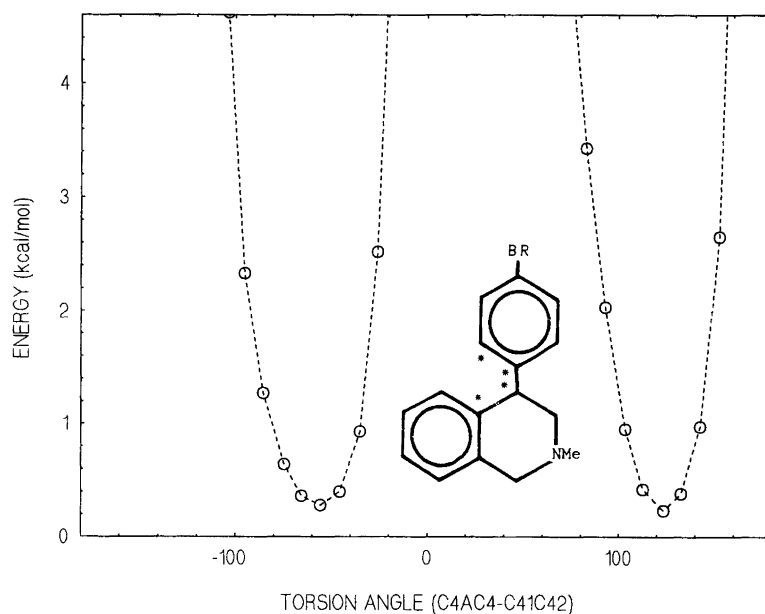

TORSION ANGLE (C4AC4-C41C42)

Fig. 5. MM2(87) diagram showing the final steric energy as a function of the torsion angle which influences the Br-phenyl ring orientation. The observed torsional angle in the solid state of the racemic 4S form is τ(C4A–C4–C41–C42) = 103.6°, [τ(C4A–C4–C41–C46) = −76.4°].

(a)   (b)
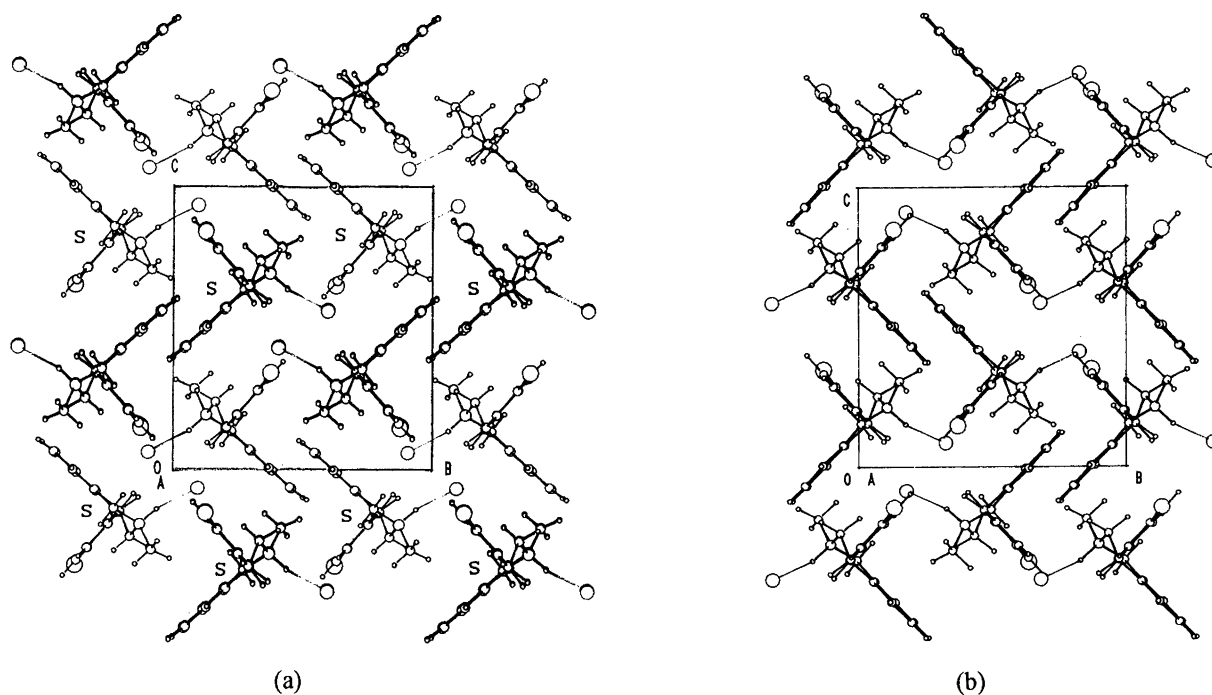
Fig. 6. Molecular packing diagrams for (4*RS*)-**4** (a) and (4*R*)-**4** (b), projected along the *a*-axis. The atoms of the *S*-chiral molecules of the racemate are marked.

the centers of the aromatic benzene and Br-phenyl rings are 3.76 and 5.15 Å; 3.77 and 5.13 Å for (4*RS*)-**4** and (4*R*)-**4**, respectively.

Reported X-ray structures and molecular mechanics calculations of tetrahydroisoquinoline-related derivatives show a significant preference for the aromatic phenyl ring to be pseudo-equatorially attached to the isoquinoline ring system. In the 4*S*-chiral form of 4(*RS*)-**4**, the observed torsion angle in the solid state, which influences the orientation of the Br-phenyl plane, is: τ(C4A–C4–C41–C42) = 103.6° [τ(C4A–C4–C41–C46) = – 76.4°], thus orienting the Br-phenyl plane to be almost perpendicular to the isoquinoline system. Based on the crystal structure coordinates of this conformer, computational molecular mechanics energy calculations [MM2(87)] have been performed where the torsion angle τ(C4A–C4–C41–C42) has been changed systematically.[18] The calculated most favorable low-energy 4*S*-conformer is located at the approximate torsion angles: 120° and – 60°. As shown in Fig. 5, the energy barrier which separates the double minima represents the phenyl plane rotation away from perpendicularity towards coplanarity with the isoquinoline system. The energy of the X-ray 4*S*-conformer is located approximately 1 kcal mol – 1 above the calculated minimum value.

Crystal packing. The packings of the hydrochloride structures of the (4*RS*)-**4** and the (4*R*)-**4** isomers are viewed along the crystallographic *a*-axes in Fig. 6. (4*RS*)-**4** is illustrated on the left and (4*R*)-**4** on the right. The atoms of the racemic *S*-chiral forms are marked, which gives the

possibility of a close comparison of the molecular packing in the two crystal forms. As experienced from other salts of tertiary amines, a single H atom attached to the quaternary N atom cannot establish an extended hydrogen bonding network. Except from the charged hydrogen-bonded salt interactions between the molecular cation and the chloride anion, the two crystal isomers are packed through normal van der Waals' forces. In the racemic salt the molecules are more closely packed than in the (4*R*)-**4** form. The intermolecular contacts between unlike fragments, *e.g.*, the piperidine and Br-phenyl rings, (Table 5) are more numerous in the racemic salt, which is possibly a consequence of more favorable electrostatic interactions between neighboring molecules. The bonding stability of the racemic crystal structure is also consistent with a higher melting point and a higher density (Table 2).

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