Resolution and Absolute Stereochemistry of 6,7-Dimethoxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline. The Crystal Structure of the *R*-Hydrochloride Salt Form

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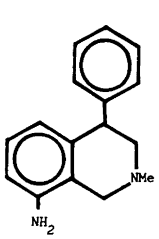
Stereospecific multistep synthesis and resolution of 6,7-dimethoxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline (**3**) has been achieved from its racemic base. The absolute configurations of the optical antipodes converted into their hydrochloride salt forms have been determined by X-ray diffractometric analysis, thus permitting assignment of the antipodes as the (+)-(4*R*)-**3** and (−)-(4*S*)-**3** enantiomers.

The crystal structures of the two enantiomers are related as mirror images and only the (4*R*)-**3** · HCl form has been fully determined by three-dimensional X-ray diffraction. In the solid state, the carbon atoms of the two methoxy groups deviate slightly from the benzene-ring plane and the chirally oriented phenyl substituent is almost perpendicularly tilted out of conjugation with the isoquinoline system.

Examination of the enantiomers in several biochemical tests for 5-HT, NE and DA uptake inhibition–activity revealed an exclusive preference for the (4*S*)-enantiomer. These results are in accord with previous suggestions that the *S*-configurational state of the 4-phenyl substituent is important for biological activity.

The established side effects observed in the use of classical tricyclic antidepressant drugs[1] prompted the search for new structural groups conferring the same psychotropic effect. Of the 'non-classical' antidepressants, Nomifensine (**1**) and Diclofensine (**2**), both members of the 4-phenyltetrahydroisoquinoline group, have found wide use in clinical practice.



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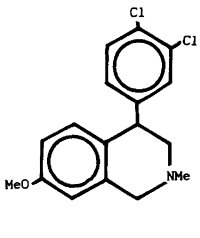

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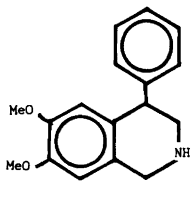

(3)

During the last decade, novel compounds of this group and related structures have been synthesized in the search for new prospective drugs.[2,3] An important feature of the 'non-classical' antidepressants is their enantioselective biological activity, demonstrated in biochemical and pharmacological tests for antidepressant activity. Enantioselective activity has been reported for Nomifensine,[2,4,5] Dichlofensine[6] and other structurally related compounds.[2,3]

In the course of our research concerning the 4-phenyltetrahydroisoquinoline group we have recently synthesized racemic 6,7-dimethoxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline (**3**)[7] and some *N*-derivatives, which all exhibit reuptake inhibition for 5-HT, NE and DA.† The reported dependence, for known antidepressants, of biological activity upon absolute stereochemistry prompted us to investigate the enantiomeric forms of **3** and to establish their absolute configurations by single-crystal X-ray diffraction analysis in order to advance our understanding of the biological enantioselectivity preference.

Experimental

Resolution of 6,7-dimethoxy-4-phenyl-1,2,3,4-tetrahydroisoquinoline (**3**). 16.1 g (0.06 mol) of (±)-**3**, dissolved in 150 ml ethanol were treated with a solution of 23 g (0.06 mol) of (+)-dibenzoyl-D-tartaric acid in 150 ml ethanol at room temperature. Crystallisation continued for 30 h at ambient temperature and proceeded for another 24 h at +8 °C. The crude tartrate (14.8 g) was subjected to a second and third crystallization from ethanol, ratio (g:ml) 1:63 and 1:110, respectively. We obtained 9.3 g of the (−)-**3**-D-tartrate,

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† 5-HT: serotonin, NE: norepinephrine and DA: dopamine.

m.p. 175–177 °C. After treatment of the tartrate with aqueous ammonia, then extraction with chloroform, drying with magnesium sulphate and evaporation of the solvent to dryness, 3.8 g (23 %) of the free base (−)-**3**, $[\alpha]_D^{20} = -37.8°$ (c = 0.25, MeOH), were isolated. The base was treated with ether–HCl to give 4.3 g of (−)-**3** · HCl, m.p. 207–210 °C (decomp.). The combined ethanol filtrates were evaporated *in vacuo*, treated with aqueous ammonia, extracted with chloroform and, after drying ($MgSO_4$), the chloroform was again evaporated off. The crude base obtained, 11.2 g, was dissolved in 150 ml of ethanol, and a solution of an equivalent amount (16 g) of (−)-dibenzoyl-D-tartaric acid in 180 ml ethanol was added. The solution was left to stand for 36 h at ambient temperature, and then for another 24 h at +8 °C. The isolated salt weighed 15.2 g. After the second and third recrystallization from ethanol, 7.4 g (38 %) of (+)-**3**-tartrate, m.p. 174–177 °C was isolated. The free base was isolated as described above, 4.0 g (23 %) of (+)-(**3**), $[\alpha]_D^{20} = +38.6°$ (c = 0.25, MeOH). From the hydrochloride colourless crystals were obtained, m.p. 208–210 °C (decomp.). Further recrystallizations of samples of isolated diastereoisomeric salts induced only insignificant changes in their m.p. and optical rotation. The total yield of pure enantiomers attained by the method described was 48 % of the initial (±)-**3**.

Crystal data. (+)-(4*R*)-**3** · HCl, (4*R*)-6,7-dimethyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline hydrochloride, $C_{17}H_{19}NO_2 \cdot HCl$, M_r = 305.80, monoclinic, $P2_1$, Z = 2, a = 13.369(2), b = 5.455(2), c = 11.171(3) Å, β = 95.80(2)°, V = 810.5(4) Å^3, D_x = 1.25 g cm^{-3}, λ(Mo K_α) = 0.7107 Å, μ = 2.36 cm^{-1}, F(000) = 324, room temperature, R = 0.0488 and R_w = 0.0416 for 1082 unique observed reflections.

Data collection and processing. Colourless crystals of the hydrochloride salt of (4*R*)-**3** were grown by slow evaporation from a methanol solution. A crystal with the approximate dimensions 0.14×0.46×0.16 mm and the morphological crystal faces |100|, |010| and |001| was selected for the three-dimensional X-ray diffraction work. 2563 independent reflection intensities were measured at room temperature with graphite monochromatized Mo K_α-radiation on a Philips PW1100 four-circle diffractometer, utilizing the ω-2θ scan technique up to 2θ ≤ 64°. The *hkl*-index range covered was $0 \le h \le 20$, $0 \le k \le 9$ and $0 \le l \le \pm 17$. 1082 reflections with $I \ge 3\sigma(I)$ were considered as observed and were used in the subsequent structure determination and refinement procedures. Three reference reflections, monitored periodically every second hour, did not show any significant structural deterioration during the data collection. Systematically absent reflections indicated the monoclinic space group $P2_1$ with two formula units in the unit cell. The measured intensities were corrected for background, Lorentz, polarization and absorption effects. The transmission factor range of the X-ray beam was 0.965–0.975, and the number of selected sampling points applied in the absorption correction was 4×8×4. Accurate unit-cell parameters were determined by a least-squares fit based on 21 well-centred strong reflections measured in the 2θ-range: 25–35°.

Structure solution and refinement. The crystal structure of (4*R*)-**3** · HCl was solved by direct methods, utilizing the SHELXS 86[8] program system. The initial structural model, first comprising 15 of 21 non-H atoms, was completed subsequently from difference electron-density maps. The structure was refined by the full-matrix least-squares technique with the SHELX 76[9] system, minimizing the function $\Sigma w(|F_o| - |F_c|)^2$. The weighting scheme used for the final refinement was $w^{-1} = \sigma^2(F_o) + 0.0002(F_o)^2$, where σ is the standard deviation of observed amplitudes based on counting statistics. All H-atoms were positioned geometrically after each cycle, with a restricted bond length of 1.08 Å. The two methyl groups were treated as rigid groups with free rotation around the C–C bond. *Non*-H atoms were refined anisotropically and the H-atoms were included with three different isotropic factors, for methyl-H, phenyl-H and general-H. The final discrepancy indices converged to the values R = 0.0488 and R_w = 0.0416 for 198 variables and 1082 reflections. Largest shift/e.s.d. was 0.11, average value 0.04. The residual maximum and minimum heights in the final difference Fourier synthesis were 0.40 and −0.45 e Å^{-3}, respectively. Atomic scattering factors for non-H atoms were taken from the SHELX 76 program package.[9] Fractional coordinates of non-H atoms with equivalent isotropic thermal parameters are shown in Table 1.

Crystal data. (−)-(4*S*)-**3** · HCl, (4*S*)-6,7-dimethyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline hydrochloride, $C_{17}H_{19}NO_2 \cdot HCl$, M_r = 305.80, monoclinic, $P2_1$, Z = 2, a = 13.374(1), b = 5.460(2), c = 11.166(1) Å, β = 95.73(1)°, V = 811.3(3) Å^3, λ(Cu K_α) = 1.5418 Å, room temperature. Diffraction data of the (4*S*)-**3** enantiomer were recorded on a Siemens/Stoe AED2 instrument, running in the ω-2θ mode and using Cu K_α-radiation. The monoclinic unit-cell dimensions, refined from 29 reflections in the 2θ-range 20–48°, together with the observed systematic absences, uniquely revealed the isostructural relationship between the (4*R*)-**3** and (4*S*)-**3** enantiomers.

Determination of the absolute configuration. The absolute stereochemistries of the two optical antipodes (+)-**3** and (−)-**3**, in terms of the *R* and *S* convention, were elucidated by analysis of Bijvoet[10] ratios. The intensities of those Friedel-paired reflections that exhibited the greatest influence of the anomalous scattering effect of the non-H atoms were calculated and selected for measurement. The match between the observed and calculated Bijvoet ratios, defined as: $2(I_{hkl} - I_{\bar{h}\bar{k}\bar{l}})/(I_{hkl} + I_{\bar{h}\bar{k}\bar{l}})$, unequivocally established the (+)-(4*R*)-**3** and (−)-(4*S*)-**3** assignments. The anomalous dispersion correction terms for non-H atoms were taken from Cromer and Liberman.[11] Tables of anisotropic thermal parameters of non-H atoms, fractional co-ordinates of H atoms, full lists of torsion angles and calculated

Table 1. Fractional atomic coordinates of (4*R*)-**3** · HCl with e.s.d.s in parentheses.[a]

Atom	*x*	*y*	*z*	B_{eq}/Å^{2} [b]
Cl	0.8994(1)	−0.1071	0.5438(1)	3.29(4)
C(1)	0.7479(4)	0.4429(12)	0.4347(5)	3.1(2)
N(2)	0.8555(3)	0.3868(13)	0.4177(3)	2.9(1)
C(3)	0.8699(4)	0.3605(15)	0.2884(4)	3.5(2)
C(4)	0.8156(4)	0.1284(12)	0.2382(5)	2.8(2)
C(4A)	0.7070(4)	0.1238(12)	0.2698(5)	2.5(2)
C(5)	0.6366(4)	−0.0341(11)	0.2096(5)	2.8(2)
C(6)	0.5375(4)	−0.0343(11)	0.2327(5)	3.0(2)
O(6)	0.4639(3)	−0.1789(8)	0.1773(4)	4.3(1)
C(61)	0.4935(5)	−0.3732(13)	0.1036(6)	4.4(2)
C(7)	0.5059(4)	0.1330(13)	0.3170(5)	3.0(2)
O(7)	0.4047(3)	0.1316(10)	0.3300(4)	5.1(2)
C(71)	0.3645(5)	0.3499(18)	0.3742(7)	6.8(3)
C(8)	0.5753(4)	0.2824(12)	0.3804(5)	2.9(2)
C(8A)	0.6768(4)	0.2745(12)	0.3587(5)	2.6(2)
C(41)	0.8260(4)	0.1137(13)	0.1038(5)	3.4(2)
C(42)	0.8883(5)	−0.0575(15)	0.0603(6)	5.0(2)
C(43)	0.8987(7)	−0.0675(22)	−0.0632(8)	7.2(3)
C(44)	0.8496(6)	0.0926(22)	−0.1410(7)	6.8(3)
C(45)	0.7865(5)	0.2640(19)	−0.0989(6)	6.4(3)
C(46)	0.7745(4)	0.2744(16)	0.0247(5)	4.7(2)

[a]The *y*-coordinate of the Cl-atom is fixed. Isotropic thermal factors of geometrically calculated hydrogen atoms: methyl-H, phenyl-H and general-H (not listed here) are 7.8(8), 9.3(11) and 4.1(4) Å^{2}, respectively. [b]The equivalent isotropic temperature factors of non-hydrogen atoms are defined as $B_{eq} = 4/3\ \Sigma_i\Sigma_j\beta_{ij}\boldsymbol{a}_i \cdot \boldsymbol{a}_j$.

and observed structure factors are, together with calculated and measured Bijvoet ratios of the (4*R*)-**3** and (4*S*)-**3** enantiomers, available from the authors (B.S. and P.-E.W).

Results and discussion

Chemistry. Racemic **3** was obtained as described in Ref. 7. The enantiomers were isolated by treatment of (±)-**3** with an equivalent amount of (+)-dibenzoyl-D-tartaric acid, followed by treatment of the optically impure base with (−)-dibenzoyl-L-tartaric acid. The diastereoisomeric tartrates were recrystallized from ethanol. The resolution was considered complete when the m.p. and the optical resolution did not change between two recrystallisations. The tartrates were then treated with aqueous ammonia to isolate the optically active free bases, (−)-**3** with $[\alpha]_D^{20} = = -37.8°$ (c = 0.25, methanol) and (+)-**3** with $[\alpha]_D^{20} = = +38.6°$ (c = 0.25, methanol).

Further, we tried to establish the enantiomeric purity of (−)-**3** and (+)-**3** by means of their ^{1}H NMR spectra (100 MHz) run with the inclusion of a chiral shift reagent [Eu(hfbc)]. Eu-**3** was added to 0.3 M solutions in $CDCl_3$ of (+)-**3** and (−)-**3**, respectively, until its concentration reached 0.3 M. Under these conditions no shifts in the proton signals were observed, which may be considered an indication of enantiomeric purity. The enantiomers were then transformed into their hydrochloride salts, which were used for biochemical tests and X-ray analysis. Both isomers were tested for re-uptake inhibition of [^{3}H]-5HT into rat brain synaptosomes.[12,13] The results show that (−)-**3** is about ten times as active as (+)-**3**. (IC_{50} = 1.3×10^{-6}, 1.1×10^{-5}, respectively).

X-ray studies. A perspective drawing of the molecular cation with atom numbering is presented in Fig. 1. The hydrogen atoms have been included, and the absolute configuration is 4*R*. Bond lengths and bond angles listed in Table 2 generally conform well with expected values,[14-16] although their estimated standard deviations (e.s.d.s) are somewhat large because of the relatively high thermal motion of the atoms.

Some structural details are noteworthy. The two methoxy oxygen atoms are approximately coplanar with the aromatic benzene ring, thus enabling conjugation of the oxygen electron lone pairs with the aromatic π-system. Only the methoxy carbon atoms C(61) and C(71) are slightly twisted out of the benzene plane. The two distances C(6)–O(6), C(7)–O(7) are 1.360(7) and 1.375(7) Å, and the oxygen atoms are linked to the methyl groups, O(6)–C(61) and O(7)–C(71), by normal single-bond distances, 1.422(7) and 1.416(11) Å, respectively.

Based on the torsion angles, listed in Table 2, the conformation of the six-membered piperidine ring can be described as a half chair with the lowest calculated asymmetry parameter ΔC_2(N2–C3) = 4.6°.[17] As shown in Fig. 1, the phenyl group is almost perpendicularly tilted out of the plane of the isoquinoline system. The dihedral angles between the least-squares planes of the three molecular rings piperidine–benzene, piperidine–phenyl and benzene–phenyl are 7.7(1), 106.1(2) and 105.4(2)°, respectively.

Fig. 2 is a stereoscopic view of the molecular packing, viewed down the *c*-axis. Both hydrogen atoms attached to

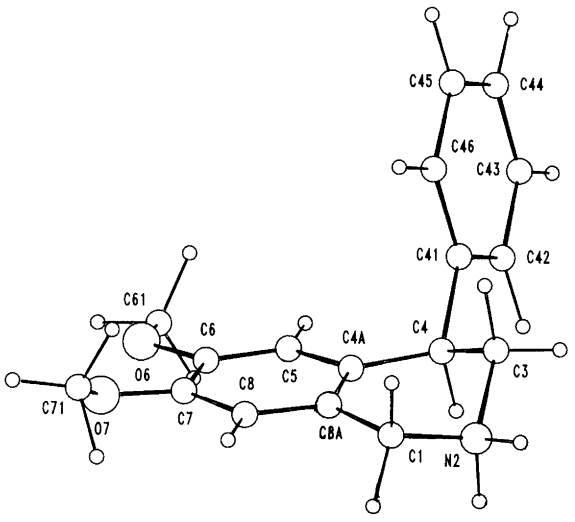

Fig. 1. A perspective view of the molecular cation structure of (4*R*)-**3** · HCl, with atomic numbering system.

Table 2. Bond distances, bond angles, selected torsion angles and hydrogen bonding scheme of (4*R*)-**3** · HCl. The e.s.d.s are given in parentheses.

Bond lengths/Å

C(1)–N(2)	1.501(6)	O(6)–C(61)	1.422(8)
C(1)–C(8A)	1.518(8)	C(7)–O(7)	1.375(7)
N(2)–C(3)	1.484(6)	C(7)–C(8)	1.376(8)
C(3)–C(4)	1.537(10)	O(7)–C(71)	1.416(11)
C(4)–C(4A)	1.528(8)	C(8)–C(8A)	1.403(8)
C(4)–C(41)	1.524(8)	C(41)–C(42)	1.372(10)
C(4A)–C(5)	1.397(8)	C(41)–C(46)	1.379(9)
C(4A)–C(8A)	1.381(8)	C(42)–C(43)	1.401(12)
C(5)–C(6)	1.375(8)	C(43)–C(44)	1.354(14)
C(6)–O(6)	1.360(7)	C(44)–C(45)	1.374(14)
C(6)–C(7)	1.407(9)	C(45)–C046)	1.407(9)

Bond angles/°

N(2)–C(1)–C(8A)	111.1(4)	C(6)–C(7)–O(7)	115.6(5)
C(1)–N(2)–C(3)	111.2(4)	O(7)–C(7)–C(8)	124.6(5)
N(2)–C(3)–C(4)	109.4(4)	C(7)–O(7)–C(71)	116.4(6)
C(3)–C(4)–C(41)	108.4(5)	C(7)–C(8)–C(8A)	120.4(5)
C(3)–C(4)–C(4A)	110.7(5)	C(4A)–C(8A)–C(8)	120.1(5)
C(4A)–C(4)–C(41)	114.2(4)	C(1)–C(8A)–C(8)	116.5(5)
C(4)–C(4A)–C(8A)	120.7(5)	C(1)–C(8A)–C(4A)	123.4(5)
C(4)–C(4A)–C(5)	120.6(5)	C(4)–C(41)–C(46)	120.6(6)
C(5)–C(4A)–C(8A)	118.7(5)	C(4)–C(41)–C(42)	120.2(6)
C(4A)–C(5)–C(6)	121.7(5)	C(42)–C(41)–C(46)	119.1(6)
C(5)–C(6)–C(7)	119.0(5)	C(41)–C(42)–C(43)	112.0(7)
C(5)–C(6)–O(6)	125.5(5)	C(42)–C(43)–C(44)	121.2(9)
O(6)–C(6)–C(7)	115.4(5)	C(43)–C(44)–C(45)	119.6(8)
C(6)–O(6)–C(61)	117.7(4)	C(44)–C(45)–C(46)	119.9(8)
C(6)–C(7)–C(8)	119.8(5)	C(41)–C(46)–C(45)	120.3(7)

Torsion angles/°

N(2)–C(1)–C(8A)–C(4A)	−11.4(8)
C(8A)–C(1)–N(2)–C(3)	46.6(6)
C(1)–N(2)–C(3)–C(4)	−68.0(6)
N(2)–C(3)–C(4)–C(4A)	50.6(6)
N(2)–C(3)–C(4)–C(41)	176.6(5)
C(3)–C(4)–C(4A)–C(8A)	−16.5(8)
C(4)–C(4A)–C(8A)–C(1)	−3.1(8)

H-bonding parameters/Å.

Donor-H[a]	Donor··Acceptor	H··Acceptor	<Donor-H··Acceptor	Symmetry[b]
N(2)–H(2A) 1.08(1)	N(2)··Cl 3.069(6)	H(2A)··Cl 1.99(1)	N(2)–H(2A)··Cl 173.1(4)°	(*x*, *y*, *z*)
N(2)–H(2B) 1.08(1)	N(2)··Cl 3.128(6)	H(2B)··Cl 2.19(1)	N(2)–H(2B)··Cl 143.4(4)°	(*x*, *y* + 1, *z*)

[a]H-atoms are in fixed positions. [b]Transition symmetries (in parentheses) refer to the Cl-atom.

the protonated nitrogen, N(2), are involved in hydrogen bonding to the Cl anion, linking translated cationic molecules parallel to the short *b*-axis (cf. Table 2). The hydrogen bonding scheme is further stabilized by a short interatomic Cl···N contact, 3.261(4) Å in the direction of the *a*-axis, thus involving adjacent molecules related by the crystallographic twofold screw. Apart from these contacts, the molecules are held together by weak π-electron overlap and ordinary van der Waals forces.

The absolute configuration ascertained by X-ray diffraction analysis, via the anomalous dispersion technique, established the (+)-(4*R*)-**3** and (−)-(4*S*)-**3** relationship. The determination of the absolute configuration in terms of the *R* and *S* convention instead of the (+) and (−) optical antipodes is of particular importance, since conflicting observations are found in the literature concerning the optical and absolute stereoselectivity for this type of compound. The observed (−)-(4*S*) preference of **3** is in contrast with

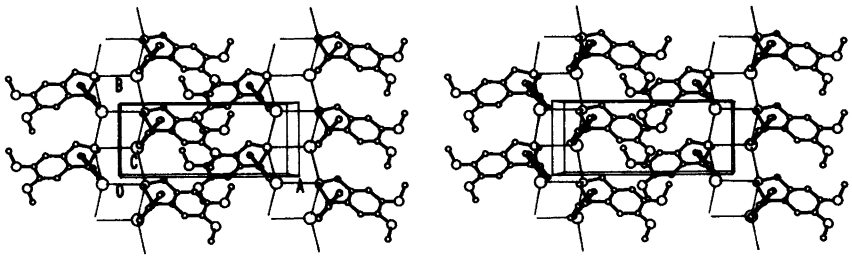

Fig. 2. A stereoscopic packing diagram of (4*R*)-**3** · HCl viewed down the *c*-axis. The Cl atoms are marked with large open circles and the interatomic distances (less than 3.3 Å) with thin lines. The crystal packing is dominated by infinite ··Cl–H–N–H··Cl·· hydrogen-bond chains along the short *b*-axis. The molecules related by the crystallographic twofold screw are further stabilized by short Cl··N contacts along the *a*-axis. The H-atoms are omitted for clarity.

the established (+)-(4*S*) relationship found in Nomifensine (**1**)[2] and Diclofensine (**2**)[6] but is quite in agreement with the (−)-(4*S*) stereoselectivity observed in Latifine.[15] Interestingly, specific rotation spectra of Nomifensine entities have shown that small changes of the *N*-substituent in the piperidine rings may cause a change in the direction of the optical rotation.[2] Observations from the closely related benzazepine family have also shown that the sign of rotation may even be inverted with the change of solvent.[18]

The crystal and molecular structure of the racemic (±)-**3** · HCl compound[19] has also been determined. This crystal form contains two independent molecules, **A** and **B**, in the asymmetric unit. The most important structural difference between these two conformers is associated with the orientation of the 4-phenyl ring. In Fig. 3, a conformational overlay of the *R*-stereoisomers of the racemate and the (4*R*)-**3** conformer is shown, illustrating the close structural relationship between the phenyl rings of (4*R*)-**3** and the racemic molecule **B**. This orientation of the phenyl ring can, with confidence, be accepted to be close to the optimum geometry of the free molecule. A detailed comparison of the various X-ray conformers reveals differences. In Table 3 some selected geometrical parameters of (4*R*)-**3** and the *R*-configurational forms of (±)-**3** are listed. The two methoxy carbon atoms, C(61) and C(71) of (4*R*)-**3** are significantly displaced from the benzene plane, in marked contrast with the coplanarity of the methoxy groups in the racemic conformers. Additionally, the displacement of the carbon atom, C(3) is significantly different. The conformational variation elucidated in the two crystal forms is probably caused by differences in crystal packing and hydrogen bonding.

In various antidepressants the strict positional complementarity requirements at the receptors for the location of the nitrogen atom and the aromatic substituents make these changeable parameters very important. In the *rectus*, (4*R*)-**3** and *racemic*, (±)-**3** conformers the intramolecular distances from the nitrogen atom N(2) to the centre of the the benzene ring range between 3.68 and 3.76 Å and the distance from N(2) to the phenyl ring-centre between 5.02 and 5.10 Å. In the (4*R*)-**3** conformer the out-of-planarity distance from the N(2) atom to the phenyl plane is 1.46 Å and in the two independent molecules **A** and **B** of the (±)-**3** form the displacement values are 0.87 and 1.85 Å, respectively. These distances are quite typical for semi-rigid tetraisoquinoline compounds, but they are also closely re-

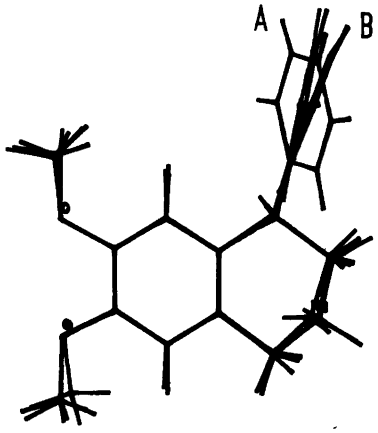

Fig. 3. X-Ray conformational overlay of the observed (*R*)-conformers of (4*R*)-**3** and (±)-**3**. The two independent molecules in the racemic form are designated **A** and **B**.

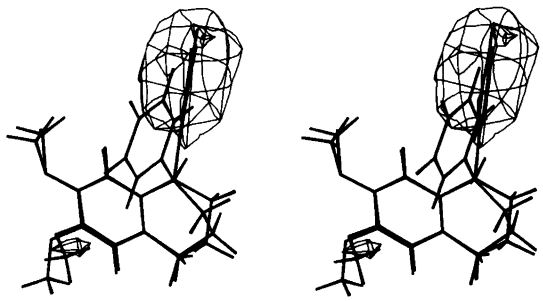

Fig. 4. Stereoscopic view showing the molecular overlay of the (4*R*)- and (4*S*)-enantiomeric forms of **3**. The excess volume of the (4*S*)-enantiomer is indicated with residual van der Waals contours.

Table 3. Selected topographical features of the hydrochloride salts of (4*R*)-**3** and (±)-**3**, showing some atomic distances from the benzene ring plane, dihedral angles between the piperidine-, benzene- and phenyl- least-squares planes and calculated asymmetry parameters of the piperidine ring.

	(4*R*)-**3** · HCl	(±)-**3** · HCl	
		Molecule **A**[a]	Molecule **B**[a]
Atomic distances from benzene plane/Å			
O(6)	−0.03	−0.04	−0.04
C(61)	−0.26	−0.12	0.13
O(7)	0.08	−0.01	−0.03
C(71)	0.65	−0.03	0.04
C(1)	−0.08	−0.08	−0.01
N(2)	−0.34	−0.69	−0.44
C(3)	0.53	0.04	0.25
C(4)	0.11	−0.07	−0.03
Dihedral angles between planes/°			
Piperidine–benzene	7.7(1)	8.8(3)	4.9(3)
Piperidine–phenyl	106.1(2)	91.1(3)	107.6(3)
Benzene–phenyl	105.4(2)	95.7(3)	103.4(3)
Calculated asymmetry parameters/°[b] of the piperidine ring			
	ΔC_2(C2–N3) = 4.6	ΔC_s(N2) = 11.0	ΔC_2(C2–N3) = 4.5

[a] *R*-configurational forms. Positive sign when the atoms of the (4*R*) chirally oriented phenyl ring are above the benzene (paper) plane (*cf.* Fig. 1). The e.s.d.s of the distances are less than 0.01 Å. [b] The piperidine ring conformation is (4*R*)-**3** and (±)**3**: molecule **B**, is best described as half chair; (±)-**3**: molecule **B**, as a sofa or half boat (Duax, Weeks & Rohrer, 1976).

lated to the corresponding phenyl distances in agonistic compounds such as (*R*)-apomorphine[20] (Two independent molecules, *N*-aromatic ring-centre: 5.1 Å; *N*-aromatic ring-plane: 1.2 and 0.9 Å, respectively) and dopamine[21] (*N*-aromatic ring-centre: 5.1 Å; *N*-aromatic ring-plane 1.6 Å). The biochemical antidepressant activity of **3** is restricted to the (4*S*)-enantiomer. Fig. 4 shows a stereoscopic view of the molecular overlay of the (4*S*)-**3** and (4*R*)-**3** configurational states, mapping the divergent orientations of the phenyl substituents.

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