Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

(2*RS*,4*RS*)-7-Fluoro-2-(2-phenylethyl)-2,3,4,5-tetrahydro-1*H*-1,4-epoxy-1-benzazepine and (2*RS*,4*RS*)-7-chloro-2-(2-phenylethyl)-2,3,4,5-tetrahydro-1*H*-1,4-epoxy-1-benzazepine are isomorphous but not strictly isostructural

Maria C. Blanco,[a] Alirio Palma,[a] Justo Cobo[b] and Christopher Glidewell[c]*

[a]Laboratorio de Síntesis Orgánica, Escuela de Química, Universidad Industrial de Santander, AA 678 Bucaramanga, Colombia, [b]Departamento de Química Inorgánica y Orgánica, Universidad de Jaén, 23071 Jaén, Spain, and [c]School of Chemistry, University of St Andrews, Fife KY16 9ST, Scotland
Correspondence e-mail: cg@st-andrews.ac.uk

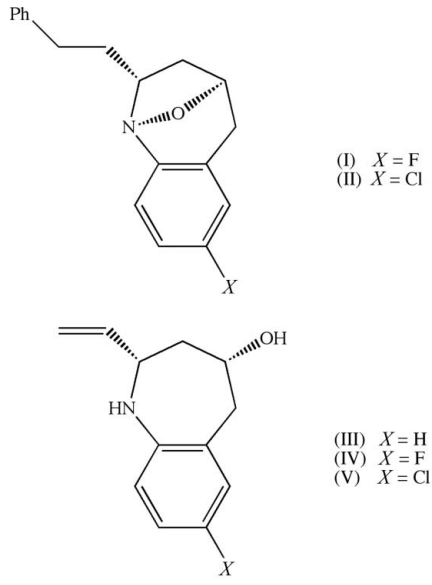
Received 12 April 2012
Accepted 16 April 2012
Online 20 April 2012

(2*RS*,4*RS*)-7-Fluoro-2-(2-phenylethyl)-2,3,4,5-tetrahydro-1*H*-1,4-epoxy-1-benzazepine, $C_{18}H_{18}FNO$, (I), and (2*RS*,4*RS*)-7-chloro-2-(2-phenylethyl)-2,3,4,5-tetrahydro-1*H*-1,4-epoxy-1-benzazepine, $C_{18}H_{18}ClNO$, (II), are isomorphous but not strictly isostructural, as the slight differences in the unit-cell dimensions and molecular conformations are sufficient to preclude, in the structure of (I), the direction-specific intermolecular interactions present in the structure of (II), where the molecules are linked into sheets by a combination of C—H···N and C—H···π(arene) hydrogen bonds.

Comment

We report here the structures of the two title compounds, (I) and (II) (Figs. 1 and 2), which we compare with their 2-styryl analogues (Acosta *et al.*, 2008). The present work forms part of a continuing study of the structures of substituted tetrahydro-1,4-epoxy-1-benzazepines (Acosta *et al.*, 2008, 2010*a*,*b*; Blanco *et al.*, 2008, 2009, 2012; Gómez *et al.*, 2008, 2009, 2010; Palma *et al.*, 2009; Sanabria *et al.*, 2010). Compounds (I) and (II) were prepared by appropriate modification of the method reported previously (Acosta *et al.*, 2008). The importance of compounds of this general type arises from their high potential value as anti-Chagasic and antileishmanicidal agents (Gómez-Ayala *et al.*, 2010).

Compounds (I) and (II) are isomorphous, although with modest differences between the corresponding pairs of unit-cell dimensions. Thus, for example, the *a* repeat distance is greater in (II) than in (I) by *ca* 4.8%, while the *b* repeat distance is smaller in (II) by *ca* 2.7%. Both compounds crystallize as true racemates in the space group $P2_1/c$ and they are approximately isostructural, in that each structure can be refined using the atomic coordinates of the other as the starting point, provided that allowance is made for the presence in (I) of a 7-fluoro substituent as opposed to a 7-chloro substituent in (II).



There are, however, some detailed differences between the molecular conformations of (I) and (II), in particular the conformation of the 2-phenylethyl side chain and its orientation relative to the rest of the molecule, as indicated by the values of the torsion angles C2—C21—C22—C221 and C21—C22—C221—C222 (Table 1; Figs. 1 and 2). On the other hand, the conformations of the heterobicyclic ring systems, as shown by the values (Table 1) of the ring-puckering parameters (Cremer & Pople, 1975), are very similar. In each of (I) and (II), the five-membered ring adopts the half-chair conformation, for which the ideal value of the puckering angle φ_2 is $(36k + 18)^\circ$, where *k* represents an integer. The conformations of the six-membered rings are intermediate between the envelope form, for which the idealized puckering angles are $\theta = 54.7^\circ$ and $\varphi = (60k)^\circ$, and the half-chair form, where the idealized puckering angles are $\theta = 50.8^\circ$ and $\varphi = (60k + 30)^\circ$, where *k* again represents an integer.

The crystallization behaviour of (I) and (II) may be contrasted with that of the 2-styryl analogues (Acosta *et al.*, 2008), the molecular constitutions of which differ from those of (I) and (II) only by having two fewer H atoms in the hydrocarbyl side chain. The 2-styryl compounds crystallize in different crystal systems, both in Sohnke space groups and neither of them as a true racemate, although their method of synthesis is expected to lead to the formation of racemic mixtures (Acosta *et al.*, 2008). The 2-styryl analogue of (I) crystallizes as a single enantiomorph in the space group $P2_1$, *i.e.* as a conglomerate, while the 2-styryl analogue of (II) crystallizes as an inversion twin in the space group $P2_12_12_1$. Hence, these two styryl compounds are neither isomorphous with one another nor with their 2-phenylethyl analogues.

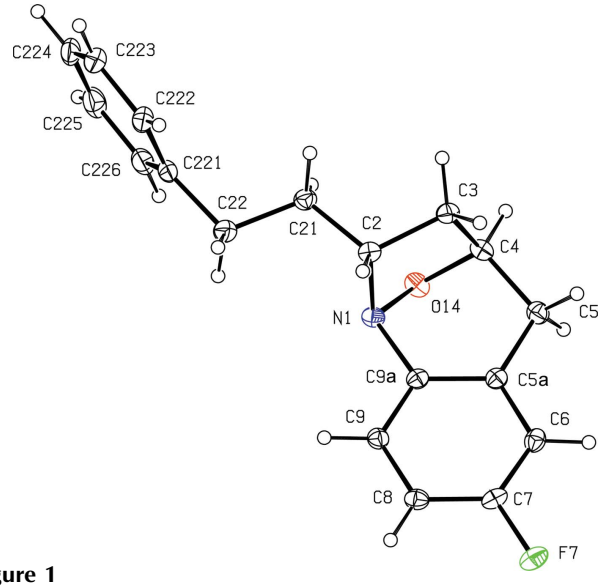


Figure 1
The molecular structure of the (2*R*,4*R*) enantiomer of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level.

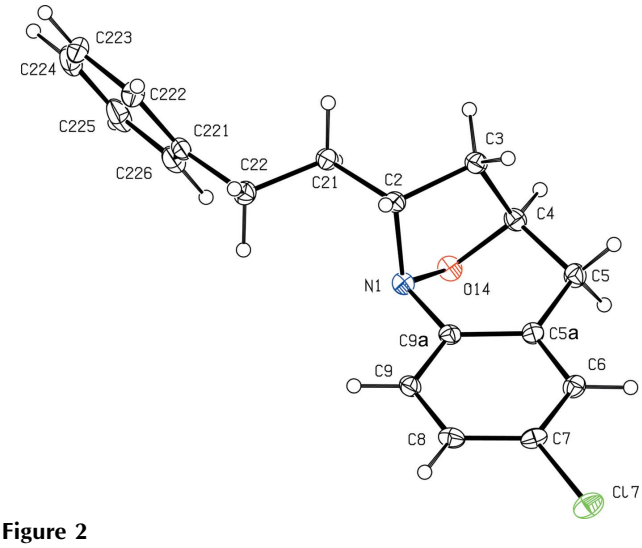


Figure 2
The molecular structure of the (2*R*,4*R*) enantiomer of (II), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level.

In the crystal structure of (II), molecules are linked into sheets by a combination of C—H···N and C—H···π(arene) hydrogen bonds (Table 2), and the formation of this hydrogen-bonded sheet can be readily analysed in terms of two substructures (Ferguson *et al.*, 1998*a*,*b*; Gregson *et al.*, 2000), each in the form of a simple chain. Molecules of (II) related by the 2_1 axis along (1, *y*, $\frac{1}{4}$) are linked by C—H···N hydrogen bonds to form a *C*(9) (Bernstein *et al.*, 1995) chain running parallel to the [010] direction (Fig. 3). In addition, molecules related by translation along [100] are linked by a C—H···π(arene) interaction to form a second chain motif, and the combination of chains along [100] and [010] leads to the formation of a sheet lying parallel to (001) in the form of a (4,4) net containing just one type of ring (Fig. 3).

The geometric parameters (Table 2) for the intermolecular contacts in the structure of (I), which correspond to hydrogen bonds in the structure of (II), show some significantly longer distances, particularly for the H···*A* contacts. Thus, for example, while the H···N distance in the C—H···N hydrogen bond in (II) is well below the sum of the van der Waals radii for H and N (2.64 Å; Bondi, 1964; Rowland & Taylor, 1996), the corresponding distance in (I) is markedly greater than this van der Waals sum. At the same time, the C—H···N angle in (I) is *ca* 40° smaller than that in (II) and this angle in itself would be sufficient to raise doubts about the structural significance of this contact (*cf.* Wood *et al.*, 2009), irrespective of the H···*A* distance. In a similar way, the H···*A* and *D*···*A* distances for the C—H···π(arene) contact are much longer for (I) than for (II). Hence, the modest differences in unit-cell dimensions and atomic coordinates between (I) and (II) are sufficient to render the contacts in (I), which correspond to the hydrogen bonds in (II), far too long to be regarded as hydrogen bonds or as structurally significant. It is for this reason that the isomorphous compounds (I) and (II) are not strictly isostructural, but only approximately so.

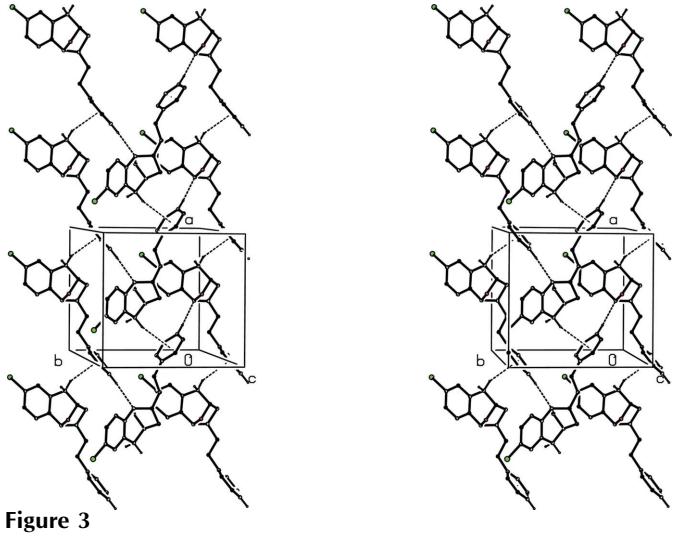


Figure 3
A stereoview of part of the crystal structure of (II), showing the formation of a hydrogen-bonded (dashed lines) sheet parallel to (001). For the sake of clarity, H atoms bonded to C atoms which are not involved in the motifs shown have been omitted.

We have recently reported a similar phenomenon in a series of isomorphous 4-hydroxy-2-vinyl-2,3,4,5-tetrahydro-1-benzazepines, (III)–(V) (Acosta *et al.*, 2009) (see Scheme), where modest but monotonic changes in all of the unit-cell dimensions from (III) *via* (IV) to (V) are sufficient to preclude, in the structure of (V), the occurrence of one of the hydrogen bonds present in the structures of (III) and (IV).

Experimental

For the synthesis of (I) and (II), sodium tungstate dihydrate (10 mol% $Na_2WO_4{\cdot}2H_2O$), followed by 30% aqueous hydrogen peroxide solution (12 mmol), were added to a stirred and cooled (ice-bath) solution of the appropriate substituted 2-allyl-*N*-(3-phenylpropyl)aniline (4 mmol) in methanol (30 ml). The resulting mixtures

were stirred at 273 K for 2–8 h, and then at ambient temperature for an additional 12–20 h (the progress of the reactions was monitored by thin-layer chromatography). Each mixture was filtered and then extracted with ethyl acetate (2 × 50 ml) and, for each, the combined extracts were dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and toluene (30 ml) was added to the organic residue. The resulting solution was heated under reflux for 6–8 h. After cooling each solution to ambient temperature, the solvent was removed under reduced pressure and the crude products were purified by column chromatography on silica gel using heptane–ethyl acetate (compositions 50:1 to 10:1 *v*/*v*) as eluant. Slow evaporation of the appropriate chromatographic fractions, at ambient temperature and exposed to air, gave colourless crystals suitable for single-crystal X-ray diffraction. Compound (I): yield 42%, m.p. 371 K; MS (70 eV) *m*/*z* (%): 283 (M^+, 15), 266 (2), 253 (1), 148 (18), 136 (100), 122 (18), 91 (48). Compound (II), yield 32%, m.p. 374 K; MS (70 eV) *m*/*z* (%): 299 (M^+, ^{35}Cl, 15), 282 (3), 269 (1), 164 (12), 152 (100), 138 (15), 91 (67).

Compound (I)

Crystal data

$C_{18}H_{18}FNO$
M_r = 283.33
Monoclinic, $P2_1/c$
a = 9.6285 (4) Å
b = 11.2875 (5) Å
c = 13.5147 (6) Å
β = 99.565 (3)°
V = 1448.38 (11) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.09 mm^{-1}
T = 120 K
0.45 × 0.31 × 0.16 mm

Data collection

Bruker–Nonius KappaCCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
T_{min} = 0.961, T_{max} = 0.986
20017 measured reflections
3324 independent reflections
2004 reflections with $I > 2\sigma(I)$
R_{int} = 0.068

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.049
$wR(F^2)$ = 0.117
S = 1.04
3324 reflections
190 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.20 e Å^{-3}
$\Delta\rho_{min}$ = −0.22 e Å^{-3}

Compound (II)

Crystal data

$C_{18}H_{18}ClNO$
M_r = 299.78
Monoclinic, $P2_1/c$
a = 10.0891 (10) Å
b = 10.981 (2) Å
c = 13.7952 (18) Å
β = 92.771 (11)°
V = 1526.6 (4) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.25 mm^{-1}
T = 120 K
0.32 × 0.26 × 0.20 mm

Data collection

Bruker–Nonius KappaCCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
T_{min} = 0.925, T_{max} = 0.952
22115 measured reflections
3506 independent reflections
2409 reflections with $I > 2\sigma(I)$
R_{int} = 0.055

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.047
$wR(F^2)$ = 0.104
S = 1.05
3506 reflections
190 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.25 e Å^{-3}
$\Delta\rho_{min}$ = −0.31 e Å^{-3}

Table 1
Selected geometric parameters (Å, °) for (I) and (II).

Ring-puckering angles in the five-membered rings refer to the atom sequence O14—N1—C2—C3—C4, those in the six-membered rings refer to the atom sequence O14—N1—C9a—C5a—C5—C4 and those in the seven-membered rings refer to the atom sequence N1—C2—C3—C4—C5—C5a—C9a.

(*a*) Torsion angles

Parameter	(I)	(II)
N1—C2—C21—C22	68.0 (2)	67.6 (2)
C2—C21—C22—C221	177.41 (15)	−177.52 (16)
C21—C22—C2221—C222	−87.2 (2)	−103.9 (2)

(*b*) Ring-puckering parameters

(i) Five-membered rings

Compound	Q_2	φ_2
(I)	0.4409 (17)	196.2 (2)
(II)	0.4498 (7)	196.5 (2)

(ii) Six-membered rings

Compound	Q	θ	φ
(I)	0.6234 (16)	52.04 (16)	346.9 (2)
(II)	0.6325 (17)	53.54 (16)	347.2 (2)

(iii) Seven-membered rings

Compound	Q	φ_2	φ_3
(I)	1.1031 (18)	196.89 (10)	119.2 (3)
(II)	1.0877 (18)	196.26 (11)	117.9 (3)

Table 2
Parameters (Å, °) for hydrogen bonds in (II) and the corresponding intramolecular contacts in (I).

Cg represents the centroid of the C221–C226 ring.

Compound	D—H···A	D—H	H···A	D···A	D—H···A
(II)	C5—H5B···Cg^{i}	0.99	2.85	3.721 (2)	148
	C224—H224···N1^{ii}	0.95	2.53	3.481 (3)	176
(I)	C5—H5B···Cg^{i}	0.99	3.79	4.635 (3)	145
	C224—H224···N1^{ii}	0.95	2.80	3.567 (3)	138

Symmetry codes: (i) $x-1, y, z$; (ii) $-x+2, y-\frac{1}{2}, -z+\frac{1}{2}$.

All H atoms were located in difference maps and then treated as riding in geometrically idealized positions, with C—H = 0.95 (aromatic), 0.99 (CH_2) or 1.00 Å (aliphatic CH), and with U_{iso}(H) = 1.2U_{eq}(C). In each compound, the reference molecule was selected to have the *R* configuration at atom C4, and on this basis, the configuration at atom C2 is also *R*. The centrosymmetric space group thus accommodates equal numbers of the (2*R*,4*R*) and (2*S*,4*S*) enantiomers in each unit cell.

For both compounds, data collection: *COLLECT* (Nonius, 1999); cell refinement: *DIRAX*/*LSQ* (Duisenberg *et al.*, 2000); data reduction: *EVALCCD* (Duisenberg *et al.*, 2003); program(s) used to solve structure: *SIR2004* (Burla *et al.*, 2005); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *PLATON* (Spek, 2009); software used to prepare material for publication: *SHELXL97* and *PLATON*.

The authors thank the Centro de Instrumentación Científico-Técnica of the Universidad de Jaén and the staff for the

data collection. JC thanks the Consejería de Innovación, Ciencia y Empresa (Junta de Andalucía, Spain) for financial support. Financial support from COLCIENCIAS (grant No. 1102-521-28229) is gratefully appreciated by AP and MCB.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK3435). Services for accessing these data are described at the back of the journal.

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