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Three styryl-substituted tetrahydro-1,4-epoxy-1-benzazepines: configurations, conformations and hydrogen-bonded chains

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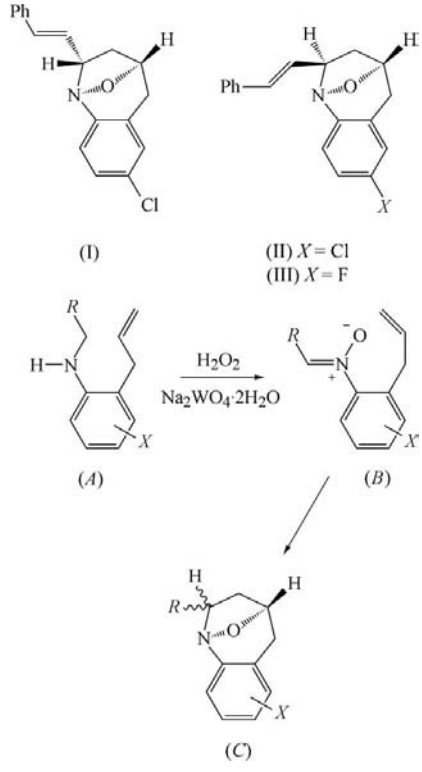
(2*SR*,4*RS*)-7-Chloro-2-*exo*-[(*E*)-styryl]-2,3,4,5-tetrahydro-1*H*-1,4-epoxy-1-benzazepine, $C_{18}H_{16}ClNO$, (I), crystallizes as a racemic twin in the space group $P2_1$ and the molecules are linked into a chain of edge-fused $R_3^3(9)$ rings by a combination of C—H···O and C—H···N hydrogen bonds. The diastereoisomer (2*RS*,4*RS*)-7-chloro-2-*endo*-[(*E*)-styryl]-2,3,4,5-tetrahydro-1*H*-1,4-epoxy-1-benzazepine, (II), also crystallizes as a racemic twin, but in the space group $P2_12_12_1$, and a two-centre C—H···N hydrogen bond and a three-centre C—H···(O,N) hydrogen bond combine to link the molecules into a complex chain of rings. In (2*R*,4*R*)-7-fluoro-2-*endo*-[(*E*)-styryl]-2,3,4,5-tetrahydro-1*H*-1,4-epoxy-1-benzazepine, $C_{18}H_{16}FNO$, (III), which is not isomorphous with (II), the molecules are linked by a single C—H···O hydrogen bond into simple chains, but the molecular arrangements in (II) and (III) are nonetheless very similar. The significance of this study lies in its observation of the variations in molecular configuration and conformation, and in the variation in the supramolecular aggregation, consequent upon modest changes in the peripheral substituents.

Comment

The tetrahydro-1-benzazepine system is an important pharmacophore in drug discovery and many of its derivatives exhibit a broad spectrum of biological activity (Zuccotto *et al.*, 2001; Fabio *et al.*, 2003; Zhao *et al.*, 2003; Seto *et al.*, 2005; Shimada *et al.*, 2005; Kunick *et al.*, 2006). Accordingly, a number of synthetic methods have recently been developed for the synthesis of new derivatives of this heterocyclic system (Fujita *et al.*, 2004; Ikemoto *et al.*, 2005; Qadir *et al.*, 2005). In this context, we have recently developed a simple and efficient synthetic pathway to obtain new 2-aryltetrahydro-1,4-epoxy-1-benzazepines and 2-aryltetrahydro-1,4-epoxynaphtho[1,2-*b*]-azepines and their reduced amino alcohols from readily available 2-allyl-*N*-benzylanilines and naphthylamines, respectively (Gómez *et al.*, 2006; Yépez *et al.*, 2006). Compounds of this type show promising action against *Trypanosoma cruzi* and *Leishmania chagasi* parasites (Palma *et al.*, 2008).

Based on these results, and as part of a programme to identify structurally novel antiparasitic compounds with new modes of action to combat both *T. cruzi* and *L. chagasi*, we have focused our attention on the synthesis of a range of 2-substituted tetrahydro-1,4-epoxy-1-benzazepines. We report here the structures of three styryl-substituted examples, compounds (I)–(III) (Figs. 1–3); in following reports, we deal with aryl-substituted examples (Gómez *et al.*, 2008) and with examples carrying heterocyclic substituents at C2 (Blanco *et al.*, 2008). A search of the Cambridge Structural Database (CSD, Version 5.29 of November 2007; Allen, 2002) found 72 examples of the bicyclic perhydro-1-benzazepine skeleton, which is a substructural fragment of (I)–(III), but found no examples at all of the tetrahydro-1,4-epoxy-1-benzazepine skeleton itself.



The syntheses of compounds (I)–(III) involved treating the corresponding 2-allyl-*N*-cinnamylanilines, (*A*), with an excess of hydrogen peroxide solution in the presence of catalytic amounts of sodium tungstate, and subsequent internal 1,3-dipolar cycloaddition of the resulting nitrones, (*B*), across the terminal C═C bond of the pendant allylic fragment

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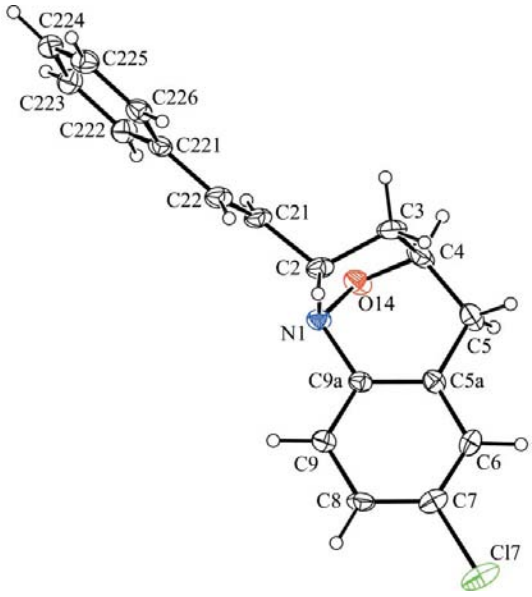

Figure 1
The molecular structure of compound (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

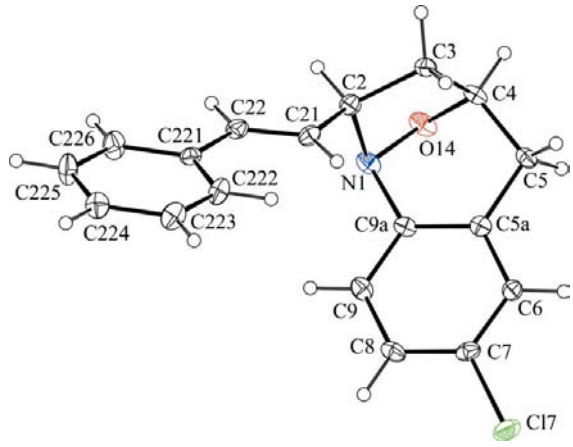

Figure 2
The molecular structure of compound (II), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

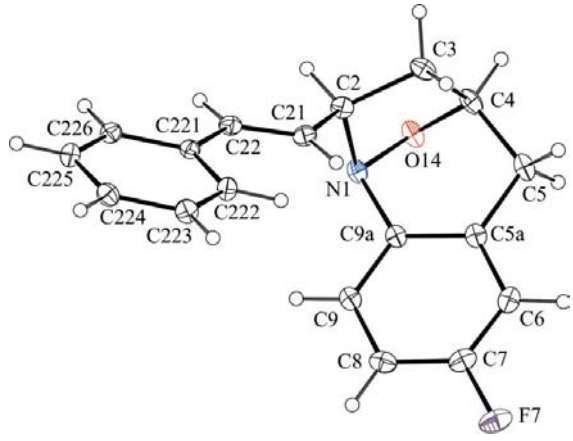

Figure 3
The molecular structure of compound (III), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

connected to the *ortho* position, giving the tricyclic product, (*C*) (see scheme). The 1,3-dipolar cycloaddition of these nitrones resulted in the formation of diastereomeric mixtures of both 2-*exo*- and 2-*endo*-1,4-epoxy-cycloadducts, which were successfully separated by column chromatography.

Compounds (I) and (II) were both found to crystallize as racemic twins; the reference molecules were selected as those having the *R* configuration at C4. The absolute configuration of (III) was indeterminate, so again the reference molecule was selected as having the *R* configuration at C4. On this basis, (I) has the *S* configuration at C2, while (II) and (III) have the *R* configuration at C2. Compounds (I) and (II) are thus diastereoisomers. However, despite the close similarity between the constitutions of (II) and (III), they are not isomorphous, crystallizing in space groups $P2_12_12_1$ and $P2_1$, respectively.

The shapes of the heterobicyclic ring systems in (I)–(III), as defined by the ring-puckering parameters (Cremer & Pople, 1975), are very similar (Table 1). For the five-membered rings, those in (II) and (III) adopt half-chair conformations, for which the ideal puckering angle φ is $(36k + 18)^\circ$, where k represents zero or an integer. For the corresponding ring in (I), the conformation is intermediate between an envelope form (where the ideal value of φ is $36k^\circ$) and the half-chair form observed in the other examples. In each compound studied here, the conformation of the six-membered heterocyclic ring is intermediate between a half-chair form [where the idealized values of the ring-puckering angles are $\theta = 50.8^\circ$ and $\varphi = (60k + 30)^\circ$] and an envelope form (where the idealized values are $\theta = 54.7^\circ$ and $\varphi = 60k^\circ$).

In the title compounds, the N1—C2—C21—C22 torsion angle (Fig. 1) is 137.8 (3)° in (I), as opposed to −101.4 (3) and −104.56 (10)° in (II) and (III), respectively, possibly associated with the difference in configuration at C2 in (I) on the one hand and in (II) and (III) on the other. In addition, the C21—C22—C221—C222 torsion angle defining the orientation of the terminal aryl group is 22.7 (5)° in (I), as opposed to 3.5 (4)° in (II) and −1.45 (14)° in (III), again highlighting the conformational similarity between (II) and (III).

The hydrogen-bonded supramolecular structures of (I)–(III) are all one-dimensional (Figs. 4–6). In compound (I), molecules related by the 2_1 screw axis along $(\frac{1}{2}, y, \frac{1}{2})$ are linked by two hydrogen bonds (Table 2). C—H···O and C—H···N hydrogen bonds acting individually give rise to *C*(3) and *C*(4) (Bernstein *et al.*, 1995) chains, respectively, while the combination of these two hydrogen bonds generates a chain of edge-fused $R_3^3(9)$ rings (Fig. 4). Although compounds (II) and (III) are not isomorphous, their supramolecular hydrogen-bonded structures show considerable similarity. In compound (II), molecules related by translation along [100] are linked by a combination of one two-centre C—H···N hydrogen bond and one three-centre C—H···(N,O) hydrogen bond (Table 2).

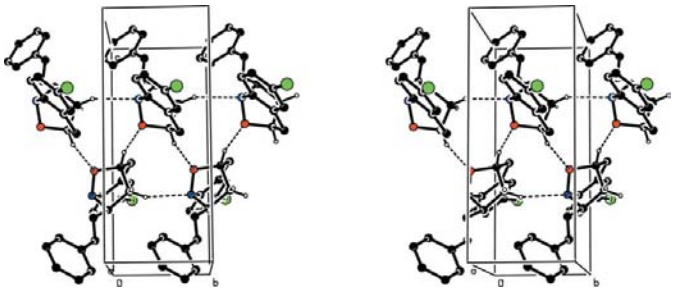

Figure 4
A stereoview of part of the crystal structure of compound (I), showing the formation of a hydrogen-bonded chain of edge-fused $R_3^3(9)$ rings along [010]. For the sake of clarity, H atoms bonded to C atoms which are not involved in the motif shown have been omitted.

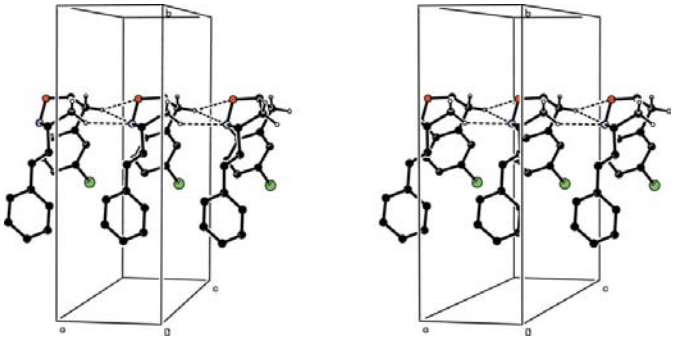

Figure 5
A stereoview of part of the crystal structure of compound (II), showing the formation of a hydrogen-bonded chain of rings along [100]. For the sake of clarity, H atoms bonded to C atoms which are not involved in the motif shown have been omitted.

Although several of the individual components are quite long, the co-operative effect of the three individual components is probably significant. Acting individually, these interactions generate $C(5)$, $C(4)$ and $C(4)$ chains, respectively, while in combination they generate an $R_2^2(7)$ motif divided into $R_1^2(3)$ and $R_2^1(6)$ sectors (Fig. 5). In compound (III), in contrast, molecules related by translation along [100] are linked into simple $C(4)$ chains (Fig. 6) by a single C—H···O hydrogen bond, the donor and acceptor of which correspond exactly to the C—H···O interaction in (III), although this interaction in (III) is characterized by significantly shorter H···O and C···O distances than its counterpart in (II) (Table 2). However, the slightly different mutual orientation of the molecules in (II) and (III) (Figs. 5 and 6) results in H3*B*···N1^{i} and H5*B*···N1^{i} [symmetry code: (i) $1 + x, y, z$] distances in (III) of 3.08 and 2.74 Å, respectively, which are very much longer than the corresponding distances in (II) and well outside the range for effective hydrogen bonding. However, the overall arrangement of the molecules within the chains along [100] is remarkably similar in these two compounds (Figs. 5 and 6).

In summary, we have characterized three compounds containing a heterocyclic ring system whose structural characteristics have not been reported previously, we have analysed their supramolecular aggregation and have found

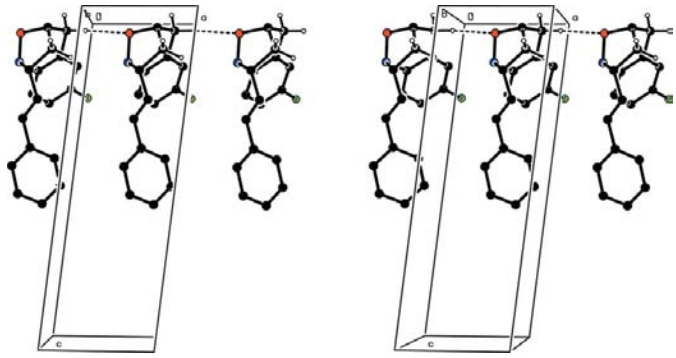

Figure 6
A stereoview of part of the crystal structure of compound (III), showing the formation of a hydrogen-bonded $C(4)$ chain along [100]. For the sake of clarity, only the H atoms bonded to atoms C3 and C5 are shown.

that for compounds (II) and (III), while the crystals are not isomorphous, the molecular arrangements within the crystals are nonetheless very similar.

Experimental

For the preparation of compounds (I)–(III), sodium tungstate dihydrate, $Na_2WO_4{\cdot}2H_2O$ (5 mol%), followed by 30% aqueous hydrogen peroxide solution (0.30 mol), were added to a stirred solution of the appropriately substituted 2-allylaniline (0.10 mol; see scheme in *Comment*) in methanol (40 ml). The resulting mixtures were then stirred at ambient temperature for periods ranging from 8 to 72 h. Each mixture was then filtered and the solvent removed under reduced pressure. Toluene (50 ml) was added to the solid residue and the resulting solution was heated under reflux for periods ranging from 3 to 10 h. After cooling each solution to ambient temperature, the solvent was removed under reduced pressure and the crude product was purified by chromatography on silica using heptane–ethyl acetate (compositions ranged from 10:1 to 60:1 *v*/*v*) as eluent. Crystallization from heptane gave crystals of compounds (I)–(III) suitable for single-crystal X-ray diffraction. For (I): colourless crystals, yield 54%, m.p. 415–416 K; MS (70 eV) *m*/*z* (%): 297 (M^+, ^{35}Cl, 75), 296 (7), 280 (36), 267 (11), 164 (32), 139 (71), 138 (100), 130 (96), 129 (77), 128 (41), 112 (25). Analysis found: C 72.4, H 5.8, N 4.5%; $C_{18}H_{16}ClNO$ requires: C 72.6, H 5.4, N 4.7%. For (II): colourless crystals, yield 25%, m.p. 403–404 K; MS (70 eV) *m*/*z* (%): 297 (M^+, ^{35}Cl, 67), 296 (11), 280 (36), 267 (11), 164 (27), 139 (72), 138 (100), 130 (95), 129 (76), 128 (44), 112 (23). Analysis found: C 72.9, H 5.1, N 4.5%; $C_{18}H_{16}ClNO$ requires: C 72.6, H 5.4, N 4.7%. For (III): orange crystals, yield 20%, m.p. 407–408 K; MS (70 eV) *m*/*z* (%): 281 (M^+, 64), 280 (41), 264 (33), 251 (12), 148 (29), 130 (62), 129 (58), 128 (33), 123 (56), 122 (100), 96 (30). Analysis found: C 76.6, H 5.9, N 4.8%; $C_{18}H_{16}FNO$ requires: C 76.8, H 5.7, N 5.0%.

Compound (I)

Crystal data

$C_{18}H_{16}ClNO$
$M_r = 297.77$
Monoclinic, $P2_1$
$a = 10.5798$ (8) Å
$b = 5.3448$ (10) Å
$c = 12.873$ (3) Å
$\beta = 90.204$ (12)°
$V = 727.9$ (2) Å^3
$Z = 2$
Mo $K\alpha$ radiation
$\mu = 0.26$ mm^{-1}
$T = 120$ (2) K
0.45 × 0.15 × 0.08 mm

Data collection

Bruker–Nonius KappaCCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
T_{min} = 0.924, T_{max} = 0.979
17564 measured reflections
3305 independent reflections
2033 reflections with $I > 2\sigma(I)$
R_{int} = 0.083

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.050
$wR(F^2)$ = 0.120
S = 1.04
3305 reflections
191 parameters
1 restraint
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.31 e Å^{-3}
$\Delta\rho_{min}$ = −0.33 e Å^{-3}
Absolute structure: Flack (1983), with 1460 Friedel pairs
Flack parameter: 0.32 (9)

Compound (II)

Crystal data

$C_{18}H_{16}ClNO$
M_r = 297.77
Orthorhombic, $P2_12_12_1$
a = 5.2855 (10) Å
b = 15.649 (2) Å
c = 17.880 (3) Å
V = 1478.9 (4) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.26 mm^{-1}
T = 120 (2) K
0.36 × 0.27 × 0.14 mm

Data collection

Bruker–Nonius KappaCCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
T_{min} = 0.929, T_{max} = 0.965
32581 measured reflections
3384 independent reflections
2525 reflections with $I > 2\sigma(I)$
R_{int} = 0.063

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.047
$wR(F^2)$ = 0.084
S = 1.12
3384 reflections
191 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.24 e Å^{-3}
$\Delta\rho_{min}$ = −0.22 e Å^{-3}
Absolute structure: Flack (1983), with 1401 Friedel pairs
Flack parameter: 0.44 (8)

Compound (III)

Crystal data

$C_{18}H_{16}FNO$
M_r = 281.32
Monoclinic, $P2_1$
a = 5.4172 (2) Å
b = 8.0164 (6) Å
c = 16.2310 (11) Å
β = 96.745 (4)°
V = 699.98 (8) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.09 mm^{-1}
T = 120 (2) K
0.23 × 0.21 × 0.15 mm

Data collection

Bruker–Nonius KappaCCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
T_{min} = 0.970, T_{max} = 0.986
16046 measured reflections
1715 independent reflections
1510 reflections with $I > 2\sigma(I)$
R_{int} = 0.034

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.035
$wR(F^2)$ = 0.083
S = 1.17
1715 reflections
190 parameters
1 restraint
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.17 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}

Table 1
Ring-puckering parameters (Å, °) for compounds (I)–(III).

Puckering parameters for five-membered rings are defined for the atom sequence O14—N1—C2—C3—C4. Puckering parameters for six-membered rings are defined for the atom sequence O14—N1—C9a—C5a—C5—C4.

Compound	Five-membered ring		Six-membered ring		
	Q_2	φ_2	Q	θ	φ
(I)	0.430 (3)	190.2 (5)	0.604 (3)	50.3 (3)	348.1 (4)
(II)	0.457 (2)	197.0 (3)	0.622 (2)	51.4 (2)	345.9 (3)
(III)	0.453 (2)	197.9 (2)	0.616 (2)	50.6 (2)	344.7 (2)

Table 2
Hydrogen-bond parameters (Å, °) for compounds (I)–(III).

Compound	D—H···A	D—H	H···A	D···A	D—H···A
(I)	C3—H3*B*···N1^{i}	0.99	2.57	3.507 (5)	158
	C4—H4···O14^{ii}	1.00	2.35	3.318 (4)	163
(II)	C3—H3*B*···N1^{iii}	0.99	2.61	3.443 (3)	142
	C5—H5*B*···N1^{iii}	0.99	2.54	3.434 (3)	151
	C5—H5*B*···O14^{iii}	0.99	2.60	3.496 (3)	151
(III)	C5—H5*B*···O14^{iv}	0.99	2.33	3.316 (3)	176

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

The space group $P2_12_12_1$ was uniquely assigned from the systematic absences for compound (II). For compounds (I) and (III), the systematic absences permitted $P2_1$ or $P2_1/m$ as possible space groups; in both cases, $P2_1$ was selected and confirmed by the subsequent structure analyses. All H atoms were located in difference maps and then treated as riding atoms in geometrically idealized positions, with C—H = 0.95 (aromatic, heteroaromatic and alkene), 0.99 (CH_2) or 1.00 Å (aliphatic CH) and with U_{iso}(H) = 1.2U_{eq}(C). In the absence of significant resonant scattering in (III), the Flack parameter (Flack, 1983) was indeterminate (Flack & Bernardinelli, 2000), and hence Friedel-equivalent reflections were merged prior to the final refinements; the reference molecule in (III) was set to have the *R* configuration at atom C4. Compounds (I) and (II) crystallized as racemic twins and were refined using the TWIN and BASF instructions in *SHELXL97* (Sheldrick, 2008), giving a twin fraction of 0.32 (9)/0.68 (9) in (I) and 0.44 (8)/0.56 (8) in (II), and again the reference molecules were chosen as those having the *R* configuration at atom C4.

For all 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: *OSCAIL* (McArdle, 2003) and *SHELXL97* (Sheldrick, 2008); molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL97* and *PRPKAPPA* (Ferguson, 1999).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GG3177). Services for accessing these data are described at the back of the journal.

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