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Three aryl-substituted tetrahydro-1,4-epoxy-1-benzazepines: hydrogen-bonded structures in two or three dimensions

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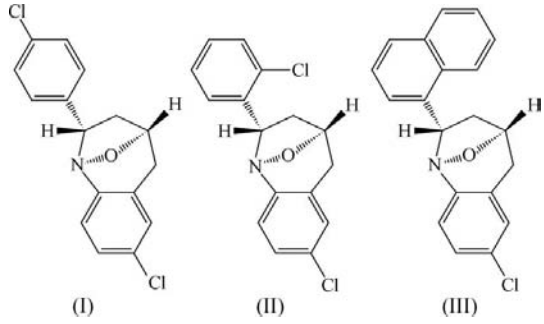
In (2*SR*,4*RS*)-7-chloro-2-*exo*-(4-chlorophenyl)-2,3,4,5-tetrahydro-1*H*-1,4-epoxy-1-benzazepine, $C_{16}H_{13}Cl_2NO$, (I), the molecules are linked by a combination of C—H···O and C—H···N hydrogen bonds into a chain of edge-fused $R_3^3(12)$ rings. The isomeric compound (2*S*,4*R*)-7-chloro-2-*exo*-(2-chlorophenyl)-2,3,4,5-tetrahydro-1*H*-1,4-epoxy-1-benzazepine, (II), crystallizes as a single 2*S*,4*R* enantiomer and the molecules are linked into a three-dimensional framework structure by two C—H···O hydrogen bonds and one C—H···π(arene) hydrogen bond. The molecules of (2*S*,4*R*)-7-chloro-2-*exo*-(1-naphthyl)-2,3,4,5-tetrahydro-1*H*-1,4-epoxy-1-benzazepine, $C_{20}H_{16}ClNO$, (III), are also linked into a three-dimensional framework structure, here by one C—H···O hydrogen bond and two C—H···π(arene) hydrogen bonds. The significance of this study lies in its observation of the variations in molecular configuration and conformation, and in the variation in the patterns of supramolecular aggregation, consequent upon modest changes in the peripheral substituents.

Comment

In a continuation of our structural study of 2-substituted tetrahydro-1,4-epoxy-1-benzazepines (Acosta *et al.*, 2008), itself part of a programme to identify structurally novel anti-parasitic compounds with new modes of action to combat both *Trypanosoma cruzi* and *Leishmania chagasi* parasites (Gómez *et al.*, 2006; Yépez *et al.*, 2006), we now report the structures of three aryl-substituted examples, *viz.* (I)–(III) (Figs. 1–3).

Compounds (I)–(III) were prepared by the reaction of an appropriately substituted 2-allyl-*N*-benzylaniline or 2-allyl-*N*-(1-naphthylmethyl)aniline with an excess of hydrogen peroxide solution in the presence of catalytic amounts of sodium tungstate, with subsequent internal 1,3-dipolar cycloaddition of the resulting nitrones across the terminal C=C bond of the pendant allylic fragment.



Compound (I) crystallizes as a racemic mixture in the space group $Pna2_1$, while the positional isomers (II) and (III) were both refined as single enantiomorphs with the *R* configuration at atom C4, as indicated by the Flack *x* parameters (Flack, 1983). Accordingly, the reference molecule for the racemic compound, (I), was selected to have the *R* configuration at C4. On this basis, the reference molecules in compounds (I)–(III) all have the *S* configuration at atom C2.

The shapes of the heterobicyclic ring systems in (I)–(III), as defined by the ring-puckering parameters (Cremer & Pople, 1975), are all very similar (Table 1). For the five-membered rings, those in (I) and (II) adopt half-chair conformations, for which the ideal puckering angle φ is $(36k + 18)^\circ$, where *k* represents an integer. For the corresponding ring in (III), 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. The conformations of the six-membered heterocyclic rings are intermediate between a half-

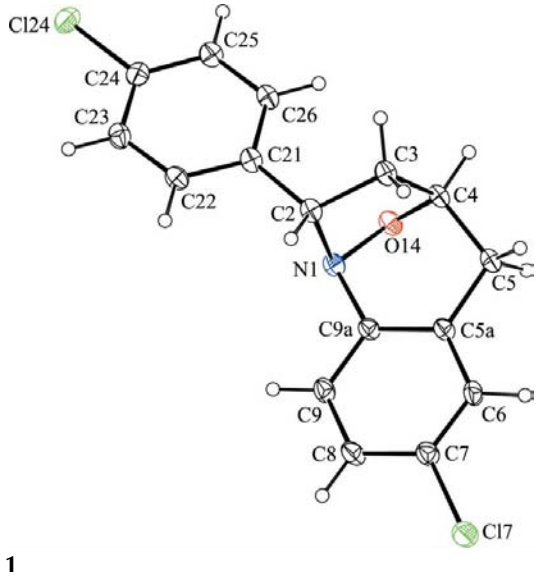


Figure 1
The molecular structure of compound (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

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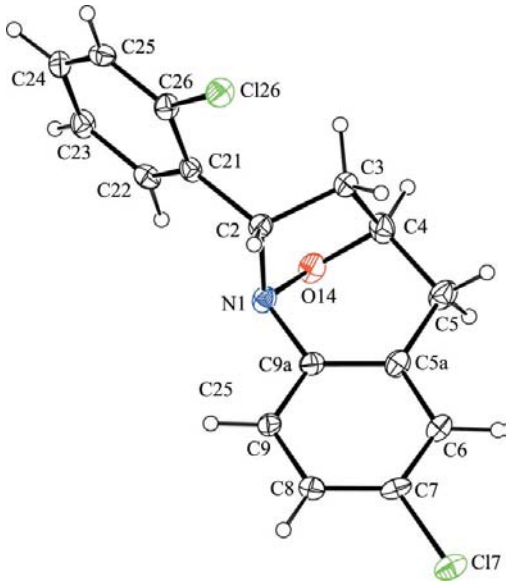

Figure 2
The molecular structure of compound (II), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

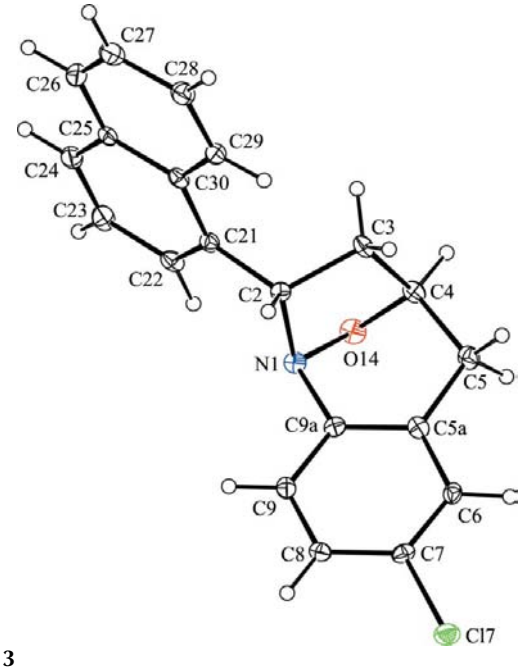

Figure 3
The molecular structure of compound (III), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

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 $\varphi = 60k^\circ$). The values of the N1—C2—C21—C22 torsion angle in (I)–(III), which defines the orientation of the pendent aryl group [94.3 (3), −12.4 (7) and 5.9 (4)°, respectively], are almost certainly dominated by steric factors.

In compound (I), molecules related by the 2_1 screw axis along ($\frac{1}{2}$, $\frac{1}{2}$, z) are linked by one each of C—H···O and C—H···N hydrogen bonds (Table 2). Acting individually, these hydrogen bonds both generate $C(4)$ (Bernstein *et al.*, 1995) chains and in combination they generate a chain of edge-fused $R_3^3(12)$ rings (Fig. 4). A C—H···π(arene) hydrogen bond is also present, but this lies within the chain and hence the dimensionality of the hydrogen-bonded structure is unaffected.

In compound (II), on the other hand, where there are again three hydrogen bonds present in the structure, now one of the C—H···O type and two of the C—H···π(arene) type, the hydrogen bonds give rise to a three-dimensional hydrogen-bonded framework. The formation of this framework is readily analysed in terms of three one-dimensional substructures, each constructed using just one hydrogen bond. The C—H···O hydrogen bond, acting alone, generates a $C(6)$ chain running parallel to the [010] direction, linking molecules related by the 2_1 screw axis along ($\frac{1}{2}$, y, $\frac{1}{4}$). The shorter of the two C—H···π(arene) hydrogen bonds, involving the fused aryl ring as acceptor, forms a chain running parallel to the [100] direction, which consists of molecules related by the 2_1 screw axis along (x, $\frac{1}{4}$, $\frac{1}{2}$). The longer of the C—H···π(arene) hydrogen bonds utilizes the pendent aryl ring as the acceptor, and it generates a chain running parallel to the [001] direction and consisting of molecules related by the 2_1 screw axis along ($\frac{3}{4}$, $\frac{1}{2}$, z). The combination of the chains along [100], [010] and [001] suffices to generate a continuous three-dimensional framework structure. The crystal structure of compound (II) also contains a short intermolecular C—H···Cl contact (Table 2). However, this contact is not likely to be structurally significant, firstly because the C—H bond concerned is of low acidity, and secondly because Cl bonded to C is known to be an extremely poor acceptor of hydrogen bonds, even from O or N (Aakeröy *et al.*, 1999; Brammer *et al.*, 2001; Thallapally & Nangia, 2001).

As in compound (II), the structure of (III) contains one C—H···O hydrogen bond and two C—H···π(arene) hydrogen bonds and, again, these link the molecules into a three-dimensional framework. However, the detailed construction of this framework differs from that in (II), and there are two readily identified substructures in the structure of (III), one of which is one-dimensional and the other two-dimensional. The two-dimensional substructure is built from the two C—

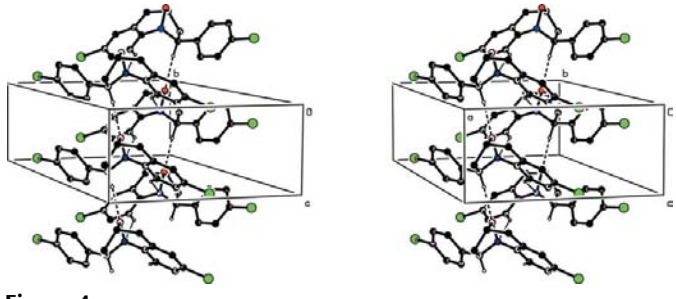

Figure 4
A stereoview of part of the crystal structure of compound (I), showing the formation of a hydrogen-bonded chain of $R_3^3(12)$ rings along [001]. For the sake of clarity, H atoms bonded to C atoms which are not involved in the motif shown have been omitted.

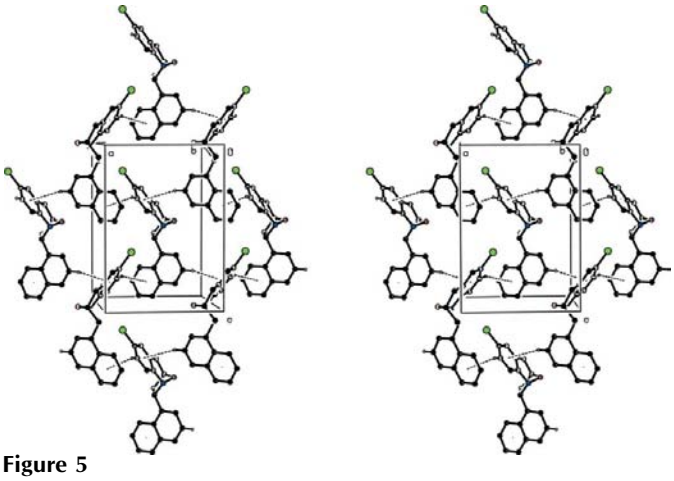

Figure 5
A stereoview of part of the crystal structure of compound (III), showing the formation of a sheet parallel to (010) built from two C—H···π(arene) hydrogen bonds. For the sake of clarity, H atoms bonded to C atoms which are not involved in the motif shown have been omitted.

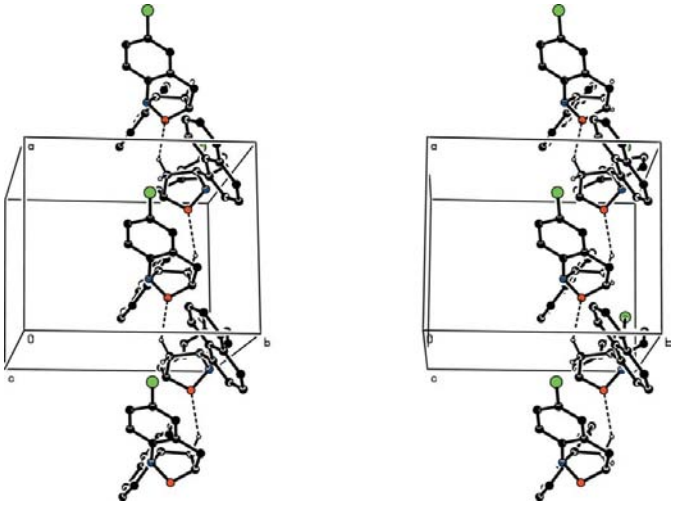

Figure 6
A stereoview of part of the crystal structure of compound (III), showing the formation of a $C(4)$ chain along [100] built from C—H···O hydrogen bonds. For the sake of clarity, H atoms bonded to C atoms which are not involved in the motif shown have been omitted.

H···π(arene) interactions. The hydrogen bond in which the pendent naphthyl substituent is the acceptor generates a chain along ($\frac{3}{4}$, $\frac{1}{2}$, z), while that having the fused aryl ring as acceptor forms a chain along ($\frac{1}{4}$, $\frac{1}{2}$, z), and the combination of these two hydrogen bonds thus generates a sheet parallel to (010) (Fig. 5). Two sheets of this type, containing the 2_1 axes at $y = 0$ and $y = \frac{1}{2}$, respectively, pass through each unit cell and they are linked by the one-dimensional substructure. This substructure is built using the C—H···O hydrogen bond, which links into a $C(4)$ chain (Fig. 6) the molecules related by the 2_1 screw axis along (x, $\frac{3}{4}$, $\frac{1}{2}$). Atom C3 in the molecule at (x, y, z) acts as hydrogen-bond donor to atom O14 in the molecule at ($\frac{1}{2} + x$, $\frac{3}{2} - y$, $1 - z$). Since these two molecules are components of different (010) sheets, the effect of this $C(4)$ chain is to link the sheets into a continuous three-dimensional framework structure.

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) in methanol (40 ml). The resulting mixtures were then stirred at ambient temperature for periods ranging from 48 to 72 h. Each mixture was 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 7 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 46%, m.p. 406–407 K; MS (70 eV) *m*/*z* (%): 305 (M^+, ^{35}Cl, 31), 288 (12), 276 (3), 262 (5), 164 (7), 138 (100), 125 (13), 111 (5). Analysis found: C 63.0, H 4.5, N 4.7%; $C_{16}H_{13}Cl_2NO$ requires: C 62.8, H 4.3, N 4.6%. For (II): colourless crystals, yield 50%, m.p. 440–442 K; MS (70 eV) *m*/*z* (%): 305 (M^+, ^{35}Cl, 21), 288 (7), 276 (1), 262 (1), 164 (6), 138 (100), 125 (13), 111 (4). Analysis found: C 62.5, H 4.6, N 4.4%; $C_{16}H_{13}Cl_2NO$ requires: C 62.8, H 4.3, N, 4.6%. For (III): colourless crystals, yield 60%, m.p. 469–470 K; MS (70 eV) *m*/*z* (%): 321 (M^+, ^{35}Cl, 20), 304 (10), 292 (6), 278 (6), 154 (100), 153 (75), 139 (33), 138 (35), 127 (20). Analysis found: C 74.9, H 4.9, N 4.5%; $C_{20}H_{16}ClNO$ requires: C 74.7, H 5.0, N 4.4%.

Compound (I)

Crystal data

$C_{16}H_{13}Cl_2NO$
$M_r = 306.17$
Orthorhombic, $Pna2_1$
$a = 11.9348$ (11) Å
$b = 21.617$ (2) Å
$c = 5.3024$ (6) Å
$V = 1368.0$ (2) Å^3
$Z = 4$
Mo $K\alpha$ radiation
$\mu = 0.47$ mm^{-1}
$T = 120$ (2) K
0.45 × 0.27 × 0.05 mm

Data collection

Bruker–Nonius KappaCCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
$T_{min} = 0.817$, $T_{max} = 0.977$
12986 measured reflections
3116 independent reflections
2124 reflections with $I > 2\sigma(I)$
$R_{int} = 0.058$

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.045$
$wR(F^2) = 0.104$
$S = 1.05$
3116 reflections
181 parameters
1 restraint
H-atom parameters constrained
$\Delta\rho_{max} = 0.30$ e Å^{-3}
$\Delta\rho_{min} = -0.30$ e Å^{-3}
Absolute structure: Flack (1983), with 1380 Friedel pairs
Flack parameter: 0.09 (9)

Compound (II)

Crystal data

$C_{16}H_{13}Cl_2NO$
$M_r = 306.17$
Orthorhombic, $P2_12_12_1$
$a = 7.4328$ (11) Å
$b = 12.3746$ (16) Å
$c = 14.9187$ (19) Å
$V = 1372.2$ (3) Å^3
$Z = 4$
Mo $K\alpha$ radiation
$\mu = 0.47$ mm^{-1}
$T = 120$ (2) K
0.27 × 0.10 × 0.07 mm

Data collection

Bruker–Nonius KappaCCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
T_{min} = 0.926, T_{max} = 0.968
12048 measured reflections
3131 independent reflections
1541 reflections with $I > 2\sigma(I)$
R_{int} = 0.147

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.061
$wR(F^2)$ = 0.153
S = 1.05
3131 reflections
181 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.38 e Å^{-3}
$\Delta\rho_{min}$ = −0.48 e Å^{-3}
Absolute structure: Flack (1983), with 1316 Friedel pairs
Flack parameter: 0.01 (15)

Compound (III)

Crystal data

$C_{20}H_{16}ClNO$
M_r = 321.79
Orthorhombic, $P2_12_12_1$
a = 9.6174 (18) Å
b = 11.558 (3) Å
c = 13.465 (4) Å
V = 1496.7 (7) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.26 mm^{-1}
T = 120 (2) K
0.32 × 0.08 × 0.06 mm

Data collection

Bruker–Nonius KappaCCD area-detector diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2003)
T_{min} = 0.956, T_{max} = 0.985
16825 measured reflections
3418 independent reflections
2460 reflections with $I > 2\sigma(I)$
R_{int} = 0.085

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.054
$wR(F^2)$ = 0.114
S = 1.10
3418 reflections
208 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.30 e Å^{-3}
$\Delta\rho_{min}$ = −0.33 e Å^{-3}
Absolute structure: Flack (1983), with 1446 Friedel pairs
Flack parameter: 0.01 (9)

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)	0.447 (3)	197.4 (4)	0.618 (3)	51.0 (3)	341.9 (4)
(II)	0.436 (6)	195.7 (8)	0.620 (5)	51.3 (5)	344.5 (7)
(III)	0.440 (3)	188.7 (4)	0.630 (3)	54.7 (3)	347.5 (4)

Unique assignments of space groups were made from the systematic absences for compounds (II) and (III), both $P2_12_12_1$. For compound (I), the systematic absences permitted $Pna2_1$ or $Pnam$ (= $Pnma$, No. 62) as possible space groups; $Pna2_1$ was selected and confirmed by the structure analysis. 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). Compounds (II) and (III) were refined as single enantiomorphs, in each case having the *R* configuration at atom C4, as suggested by the values of the Flack *x* parameter (Flack, 1983; Flack & Bernardinelli, 1999). However, particularly for compound (II), the enantiomorph-discriminating power (Flack & Bernardinelli, 2000) is not high. The reference molecule in the racemic compound, (I), was chosen as that having the *R* configuration at atom C4; here the correct orientation of the structure with respect to the polar-axis direction was established by means of the Flack *x* parameter. Compound (II) diffracted rather weakly, with only *ca* 49% of the reflections labelled 'observed', even at 120 K.

Table 2
Parameters (Å, °) for hydrogen bonds and short intermolecular contacts in compounds (I)–(III).

*Cg*1, *Cg*2 and *Cg*3 represent the centroids of the rings C21–C26, C5a/C6–C9/C9a and C25–C30, respectively.

Compound	D—H···A	D—H	H···A	D···A	D—H···A
(I)	C2—H2···O14^{i}	1.00	2.29	3.287 (4)	173
	C9—H9···N1^{ii}	0.95	2.50	3.328 (4)	145
	C8—H8···*Cg*1^{ii}	0.95	2.72	3.615 (4)	157
(II)	C8—H8···O14^{iii}	0.95	2.36	3.190 (6)	146
	C6—H6···*Cg*1^{iv}	0.95	2.82	3.619 (6)	143
	C25—H25···*Cg*2^{v}	0.95	2.60	3.410 (6)	143
	C4—H4···Cl7^{vi}	1.00	2.79	3.654 (6)	145
(III)	C3—H3*B*···O14^{vii}	0.99	2.48	3.338 (4)	145
	C8—H8···*Cg*3^{iv}	0.95	2.81	3.658 (4)	149
	C23—H23···*Cg*2^{viii}	0.95	2.80	3.702 (4)	158

Symmetry codes: (i) $x, y, 1+z$; (ii) $1-x, 1-y, \frac{1}{2}+z$; (iii) $1-x, -\frac{1}{2}+y, \frac{1}{2}-z$; (iv) $\frac{3}{2}-x, 1-y, -\frac{1}{2}+z$; (v) $-\frac{1}{2}+x, \frac{1}{2}-y, 1-z$; (vi) $2-x, \frac{1}{2}+y, \frac{1}{2}-z$; (vii) $\frac{1}{2}+x, \frac{3}{2}-y, 1-z$; (viii) $\frac{1}{2}-x, 1-y, \frac{1}{2}+z$.

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: LN3112). Services for accessing these data are described at the back of the journal.

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