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Intermolecular interactions in the chiral and racemic forms of 3-hydroxy-2-(1-oxoisoindolin-2-yl)-butanoic acid derived from threonine

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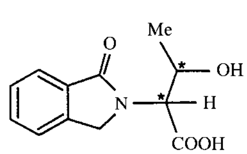
The title compounds, $C_{12}H_{13}NO_4$, are derived from L-threonine and DL-threonine, respectively. Hydrogen bonding in the chiral derivative, (2*S*/3*R*)-3-hydroxy-2-(1-oxoisoindolin-2-yl)butanoic acid, consists of $O-H_{acid}\cdots O_{alkyl}-H\cdots O{=}C_{indole}$ chains [O$\cdots$O 2.659 (3) and 2.718 (3) Å], $Csp^3-H\cdots O$ and three $C-H\cdots\pi_{arene}$ interactions. In the (2*R*,3*S*/2*S*,3*R*) racemate, conventional carboxylic acid hydrogen bonding as cyclical $(O-H\cdots O{=}C)_2$ [graph set $R_2^2(8)$] is present, with $O_{alkyl}-H\cdots O{=}C_{indole}$, $Csp^3-H\cdots O$ and $C-H\cdots\pi_{arene}$ interactions. The COOH group geometry differs between the two forms, with C—O, C═O, C—C—O and C—C═O bond lengths and angles of 1.322 (3) and 1.193 (3) Å, and 109.7 (2) and 125.4 (3)°, respectively, in the chiral structure, and 1.2961 (17) and 1.2210 (18) Å, and 113.29 (12) and 122.63 (13)°, respectively, in the racemate structure. The O—C═O angles of 124.9 (3) and 124.05 (14)° are similar. The differences arise from the contrasting COOH hydrogen-bonding environments in the two structures.

Comment

The study of biologically active molecules is of primary importance in medicinal chemistry. Many inhibitors are based on modified amino acids which incorporate the basic structural features determining normal enzyme–substrate interactions. Phthalimidine (isoindolin-1-one) derivatives often display biological activity as potential anti-inflammatory agents and antipsychotics (Norman *et al.*, 1993; Allin *et al.*, 1996). The majority of structurally determined phthalimidine



(I) = 2*S*/3*R*
(II) = racemate

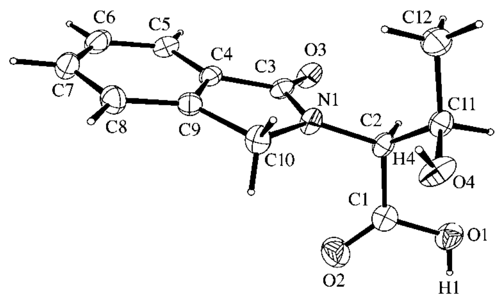


Figure 1
A view of (I) with the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

systems are either *N*-substituted or substituted at the 3-position (McNab *et al.*, 1997; Kundu *et al.*, 1999). Threonine and its derivatives have attracted considerable interest, not least due to the alkyl hydroxy group which can participate in binding, in intermolecular interactions and as a linking group in proteins. The title compounds, (2*S*/3*R*)-3-hydroxy-2-(1-oxoisoindolin-2-yl)butanoic acid, (I), and (2*R*,3*S*/2*S*,3*R*)-3-hydroxy-2-(1-oxo-isoindolin-2-yl)butanoic acid, (II), synthesized from the chiral (L) and racemic (DL) forms of threonine, respectively, constitute part of a study of the hydrogen-bonding interactions and anion recognition properties of synthetic amino acid derivatives (Brady *et al.*, 1998; Dalton *et al.*, 1999; Gallagher & Murphy, 1999; Gallagher *et al.*, 1999).

A view of molecule (I) (*SR* configuration) is shown in Fig. 1 and selected dimensions are given in Table 1. Molecule (II) is depicted similarly in Fig. 2, with selected dimensions in Table 3. The bond lengths and angles in the isoindoline group of both structures are similar to those reported previously (McNab *et al.*, 1997; Kundu *et al.*, 1999) and are in agreement with expected values (Orpen *et al.*, 1994). The angles between the five- and six-membered rings of the isoindoline systems are 0.66 (18)° in (I) and 1.13 (11)° in (II), and the maximum deviation from planarity for an atom in either ring plane is 0.0179 (17) Å for N1 in (I) and 0.0168 (9) Å for N1 in (II), with the carbonyl O3 atom 0.071 (4) Å from the C_4N ring plane in (I) and 0.061 (2) Å in (II). The carboxylic acid CCO_2 plane is almost perpendicular to the C_4N ring plane

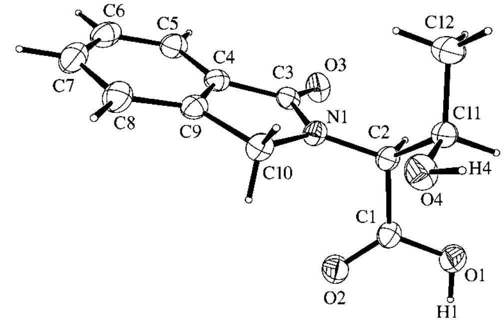


Figure 2
A view of (II) with the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

[72.30 (11)° in (I) and 66.40 (6)° in (II)] and to the C12/C11/O4 (H_3CCOH) plane [76.5 (2)° in (I) and 64.50 (8)° in (II)].

There are distinct differences in the carboxylic acid bond lengths and angles of (I) and (II). The C—O and C═O bond lengths are 1.322 (3) and 1.193 (3) Å in (I), and 1.2961 (17) and 1.2210 (18) Å in (II), respectively. The O—C—C2 and O═C—C2 angles are 109.7 (2) and 125.4 (3)° in (I), differing considerably from 113.29 (12) and 122.63 (13)° in (II). However, the O═C—O bond angles are similar, at 124.9 (3) and 124.05 (14)°, respectively. This suggests that the differences may be influenced by their different hydrogen-bonding environments (Tables 2 and 4), resulting in a twist in the COOH groups of *ca* 3°. The carboxylic group geometry in (I) is similar to that reported in a DL-phenylalanine derivative, (III) (Brady *et al.*, 1998) and in a *meta*-tyrosine derivative, (IV) (Gallagher & Murphy, 1999). The C—O and C═O bond lengths are 1.314 (2) and 1.194 (2), and 1.328 (2), 1.196 (2) Å, in (III) and (IV), respectively, with O—C═O angles of 124.00 (18) and 124.3 (3)° in (III) and (IV), respectively. The O—C—C2 and O═C—C2 angles in (III) and (IV) are intermediate between the values in (I) and (II), at 112.05 (16) and 123.95 (18)° for (III), and 110.17 (18) and 125.55 (19)° for (IV); these values for (IV) are close to those for (I) above.

The indole C═O and hydroxy Csp^3—O bond lengths of 1.232 (3) and 1.427 (3) Å, and 1.2350 (17) and 1.4187 (17) Å are similar in (I) and (II), respectively, [1.239 (2) and 1.236 (2) Å for the indole C═O bond lengths in (III) and (IV), respectively]. However, the O4—C11—C2 and C1—C2—C11 angles differ notably, with values of 110.5 (2) and 112.7 (2)° in (I), and 105.52 (11) and 110.14 (11)° in (II), and this is also indicative of dissimilar hydrogen-bonding environments. Torsion angle differences are evident, with N1—C2—C11—O4 at 78.1 (3)° in (I) and 66.92 (15)° in (II), reflecting the different participation of the alkyl OH group in hydrogen bonding in the two structures.

The hydrogen-bonding arrangements are maximized in both structures and related to those in (III) and (IV) (Brady *et al.*, 1998; Gallagher & Murphy, 1999). The hydrogen bonding in (I) and (II) is dominated by O—H···O, C—H···O and C—H···π_{arene} interactions (Tables 2 and 4, Figs. 3 and 4). The primary hydrogen bonding in (I) involves O_{acid}—H···O_{alkyl}—H···O═$C_{isoindole}$ chains [O···O 2.659 (3) and 2.718 (3) Å], similar to the primary hydrogen-bonded chain in the *meta*-tyrosine structure (Gallagher & Murphy, 1999), where the O···O distances are 2.668 (2) and 2.653 (2) Å. The O—H^{i}···O—H···O═C^{ii} chain in (I) forms a one-dimensional network in the *a* axis direction, with hydrogen-bonded rings [graph set $R_3^3(15)$] consisting of one alkyl OH and two acid OH groups as donors and an indole O═C and two alkyl OH groups as acceptors between three molecules [symmetry codes: (i) $\frac{1}{2} + x, \frac{1}{2} - y, 2 - z$; (ii) $1 + x, y, z$]. The C10—H10*A*···$O3^{ii}$ hydrogen bond [C···O 3.513 (4) Å] further generates a hydrogen-bonded ring system [graph set $R_1^2(8)$], with an alkyl OH and a Csp^3—H as donors and the indole O═C as an acceptor along the *a* axis direction [H4···$O3^{ii}$···H10*A* 66°]. The carboxylic acid O atom O2 only forms a weak C—H···O contact in (I). The C—H···π_{arene} interactions complete the intermolecular interactions, forming a three-dimensional network in the crystal structure of (I) with two (C11—H11/C12—H12*C*)···π_{indole} contacts participating in a relay of C—H···π_{arene} interactions.

Compound (II) shows some interesting differences from (I). Classical COOH hydrogen bonding arises [to form dimers; graph set $R_2^2(8)$] about inversion centres as cyclical O—

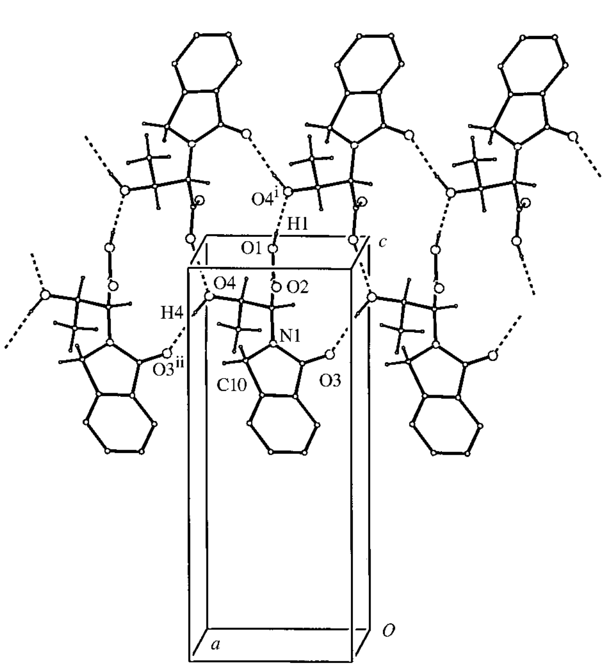


Figure 3
A view of the intermolecular interactions in (I); symmetry codes as given in Table 2.

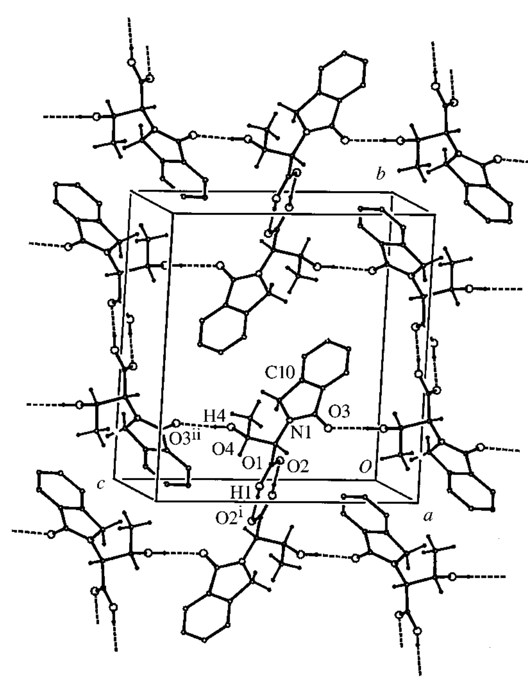


Figure 4
A view of the intermolecular interactions in (II); symmetry codes as given in Table 4.

H···O=C hydrogen bonds involving both O1 and O2 (Ferguson *et al.*, 1995). The alkyl hydroxy group O4—H···O=C3 links these dimers to form a two-dimensional network, as depicted in Fig. 4. Weaker C—H···O=C$_{indole}$ and C*sp*^{3}—H···π_{arene} interactions complete the hydrogen bonding, thus forming a three-dimensional network. The contrast in the carboxylic acid geometry between (I) and (II) can be explained by the dissimilar participation of O2 in the hydrogen bonding. The primary COOH hydrogen bonding in (II) [graph set $R_2^2(8)$] differs from that reported in the DL-phenylalanine structure (III), where pairwise intermolecular O$_{acid}$—H···O$_{indole}$ and C$_{arene}$—H···O$_{carboxylate}$ interactions form a hydrogen-bonded ring [graph set $R_2^2(9)$], and from that in the structures of (I) and DL-*meta*-tyrosine (IV), which contain O$_{acid}$—H···O—H···O=C$_{indole}$ chains.

The volumes per atom in (I) and (II) differ, with a value of 16.51 Å^3 per non-H atom for (I) and 17.04 Å^3 for (II), reflecting differing packing considerations and the extra interactions present in (I). Examination of the structures with *PLATON* (Spek, 1998) shows that there are no solvent accessible voids in either crystal lattice.

Crystal engineering studies continue to rely on stronger hydrogen bonds for the design and synthesis of three-dimensional structures (Aakeröy *et al.*, 1999). However, a thorough understanding of the control and exploitation of *X*—H···π_{arene} interactions (*X* = C, N or O) remains an elusive goal (Braga *et al.*, 1998). Theoretical calculations on C—H···π_{arene} interactions have been reported in several organic systems, including an estimation of the binding energy between the C—H donor and the aromatic π cloud (Samanta *et al.*, 1998), as well as database studies (Malone *et al.*, 1997). The role of such interactions in biological structures has also been detailed by Umezawa & Nishio (1998). However, in (I) and (II), the primary hydrogen bonding is considered prior to analysis of the weaker interactions. The stronger hydrogen bonds form a primary array which is linked into networks by the weaker interactions in both structures. Further comparative studies are in progress on related phthalimidines.

Experimental

Compound (I) was prepared by the overnight reaction of L-threonine and *o*-phthalaldehyde in refluxing CH_3CN under N_2 (Allin *et al.*, 1996). Filtration of the hot solution and subsequent slow cooling of the filtrate allowed the isolation of colourless plates of (I) (m.p. 458–460 K, uncorrected). Spectroscopic analysis, IR (KBr, cm^{-1}): (ν_{OH}) 3256, ($\nu_{C=O}$) 1748, 1656; ^{1}H NMR (400 MHz, δ, d_6-DMSO): 1.07 (*d*, 3H, CH_3), 4.46 (*m*, 1H, CH), 4.69 (*s*, 2H, CH_2), 4.80 (*d*, 1H, CH), 5.29 (*br s*, 1H, O—H), 7.46–7.52, 7.61–7.66, 7.71–7.73 (*m*, 4H, C_6H_4). Compound (II) was prepared as detailed for (I) above, using DL-threonine as the starting material, and colourless blocks of (II) were obtained from solution (m.p. 424–427 K, uncorrected). Spectroscopic analysis, IR (KBr, cm^{-1}): (ν_{OH}) 3234, ($\nu_{C=O}$) 1759, 1644; ^{1}H NMR (400 MHz, δ, d_6-DMSO): 1.07 (*m*, 3H, CH_3), 4.45 (*m*, 1H, CH), 4.68 (*s*, 2H, CH_2), 4.73 (*d*, 1H, CH), 5.31 (*br s*, 1H, O—H), 7.48–7.52, 7.60–7.66, 7.71–7.73 (*m*, 4H, C_6H_4).

Chiral (I)

Crystal data

$C_{12}H_{13}NO_4$
M_r = 235.23
Orthorhombic, $P2_12_12_1$
a = 6.2209 (6) Å
b = 11.9726 (13) Å
c = 15.0705 (12) Å
V = 1122.5 (2) Å^3
Z = 4
D_x = 1.392 Mg m^{-3}
Mo *Kα* radiation
Cell parameters from 25 reflections
θ = 9.65–19.61°
μ = 0.105 mm^{-1}
T = 294 (1) K
Plate, colourless
0.32 × 0.14 × 0.12 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
3932 measured reflections
1967 independent reflections
1441 reflections with $I > 2\sigma(I)$
R_{int} = 0.020
θ_{max} = 25°
$h = 0 \rightarrow 7$
$k = -14 \rightarrow 14$
$l = -17 \rightarrow 17$
3 standard reflections
frequency: 120 min
intensity variation: <1%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.040
$wR(F^2)$ = 0.096
S = 1.007
1967 reflections
163 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0538P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.16 e Å^{-3}
$\Delta\rho_{min}$ = −0.15 e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.011 (3)
Absolute structure: Flack (1983)
Flack parameter not reliably determined

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

O1—C1	1.322 (3)	N1—C10	1.465 (3)
O2—C1	1.193 (3)	C1—C2	1.520 (4)
O3—C3	1.232 (3)	C2—C11	1.534 (4)
O4—C11	1.427 (3)	C3—C4	1.469 (4)
N1—C2	1.454 (3)	C9—C10	1.509 (4)
N1—C3	1.354 (3)	C11—C12	1.511 (3)
C2—N1—C3	121.6 (2)	O3—C3—N1	125.5 (2)
C2—N1—C10	125.1 (2)	O3—C3—C4	127.7 (2)
C3—N1—C10	113.0 (2)	N1—C3—C4	106.8 (2)
O1—C1—O2	124.9 (3)	C4—C9—C10	109.0 (2)
O1—C1—C2	109.7 (2)	C8—C9—C10	131.0 (3)
O2—C1—C2	125.4 (3)	N1—C10—C9	102.0 (2)
N1—C2—C1	111.4 (2)	O4—C11—C2	110.5 (2)
N1—C2—C11	114.7 (2)	O4—C11—C12	111.9 (2)
C1—C2—C11	112.7 (2)	C2—C11—C12	112.2 (2)
C3—N1—C2—C1	−104.5 (3)	N1—C2—C11—O4	78.1 (3)
O2—C1—C2—N1	0.8 (4)	C1—C2—C11—O4	−50.8 (3)

Table 2
Hydrogen-bonding geometry (Å, °) for (I).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O1—H1···O4^{i}	0.81 (4)	1.87 (4)	2.659 (3)	162 (4)
O4—H4···O3^{ii}	0.82 (4)	1.90 (4)	2.718 (3)	174 (4)
C10—H10*A*···O3^{ii}	0.97	2.57	3.513 (4)	165
C5—H5···*Cg*2^{iii}	0.93	2.80	3.512 (3)	134
C11—H11···*Cg*2^{iv}	0.98	2.77	3.573 (3)	140
C12—H12*C*···*Cg*1^{iv}	0.96	2.84	3.672 (3)	145

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

Racemic (II)

Crystal data

$C_{12}H_{13}NO_4$
$M_r = 235.23$
Monoclinic, $P2_1/n$
$a = 5.9772$ (7) Å
$b = 14.3906$ (12) Å
$c = 13.4926$ (16) Å
$\beta = 93.131$ (7)°
$V = 1158.8$ (2) Å^3
$Z = 4$
$D_x = 1.348$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
$\theta = 9.65$–18.34°
$\mu = 0.102$ mm^{-1}
$T = 294$ (1) K
Block, colourless
0.39 × 0.35 × 0.21 mm

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
2242 measured reflections
2155 independent reflections
1623 reflections with $I > 2\sigma(I)$
$R_{int} = 0.008$
$\theta_{max} = 25.5°$
$h = -7 \rightarrow 7$
$k = 0 \rightarrow 17$
$l = 0 \rightarrow 16$
3 standard reflections
frequency: 120 min
intensity variation: <0.5%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.034$
$wR(F^2) = 0.086$
$S = 1.045$
2155 reflections
158 parameters
H atoms constrained
$w = 1/[\sigma^2(F_o^2) + (0.0378P)^2 + 0.2183P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.16$ e Å^{-3}
$\Delta\rho_{min} = -0.12$ e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.044 (3)

Table 3
Selected geometric parameters (Å, °) for (II).

O1—C1	1.2961 (17)	N1—C10	1.4669 (18)
O2—C1	1.2210 (18)	C1—C2	1.514 (2)
O3—C3	1.2350 (17)	C2—C11	1.535 (2)
O4—C11	1.4187 (17)	C3—C4	1.473 (2)
N1—C2	1.4481 (18)	C9—C10	1.495 (2)
N1—C3	1.3552 (17)	C11—C12	1.508 (2)
C2—N1—C3	122.08 (12)	O3—C3—N1	124.45 (14)
C2—N1—C10	125.06 (11)	O3—C3—C4	128.80 (13)
C3—N1—C10	112.83 (12)	N1—C3—C4	106.75 (12)
O1—C1—O2	124.05 (14)	C4—C9—C10	109.57 (12)
O1—C1—C2	113.29 (12)	C8—C9—C10	129.88 (14)
O2—C1—C2	122.63 (13)	N1—C10—C9	102.16 (11)
N1—C2—C1	111.67 (11)	O4—C11—C2	105.52 (11)
N1—C2—C11	113.71 (12)	O4—C11—C12	112.15 (13)
C1—C2—C11	110.14 (11)	C2—C11—C12	112.84 (12)
C3—N1—C2—C1	−112.29 (14)	N1—C2—C11—O4	66.92 (15)
O1—C1—C2—N1	178.16 (13)	C1—C2—C11—O4	−59.28 (15)

Table 4
Hydrogen-bonding geometry (Å, °) for (II).

D—H$\cdots A$	D—H	H$\cdots A$	$D\cdots A$	D—H$\cdots A$
O1—H1$\cdots$O2^{i}	0.82	1.82	2.6355 (16)	175
O4—H4$\cdots$O3^{ii}	0.82	1.94	2.7423 (15)	166
C10—H10$B\cdots$O3^{iii}	0.97	2.48	3.3140 (17)	144
C11—H11$\cdots Cg2^{iv}$	0.98	2.70	3.6440 (16)	161

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

For both forms, all H atoms bound to C were treated as riding, with the *SHELXL*97 (Sheldrick, 1997) defaults for C—H distances and with $U_{iso}(H) = 1.5U_{eq}(C)$ for methyl H atoms and $1.2U_{eq}(C)$ for others. For (I), H(—O) atoms were refined with isotropic displacement parameters, while for (II), H(—O) atoms were located from difference Fourier maps in the penultimate stages of refinement and subsequently treated as rigid rotating groups with $U_{iso}(H) = 1.5U_{eq}(O)$.

For both compounds, data collection: *CAD*-4-*PC Software* (Enraf–Nonius, 1992); cell refinement: *CAD*-4-*PC Software*; data reduction: *NRCVAX*96 (Gabe *et al.*, 1989); program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *NRCVAX*96 and *SHELXL*97; molecular graphics: *ORTEP*III (Burnett & Johnson, 1996), *ORTEX* (McArdle, 1995) and *PLATON* (Spek, 1998); software used to prepare material for publication: *NRCVAX*96, *SHELXL*97 and *PREP*8 (Ferguson, 1998).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: BM1380). Services for accessing these data are described at the back of the journal.

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