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Four cytotoxic N4-substituted thiosemicarbazones derived from 2-hydroxynaphthalene-1-carboxaldehyde

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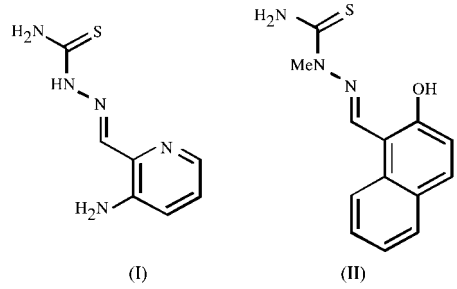
The X-ray crystal structures are reported of four novel and potentially *O*,*N*,*S*-tridentate donor ligands that demonstrate antitumour activity. These ligands are 1-[(4-methylthiosemicarbazono)methyl]-2-naphthol, $C_{13}H_{13}N_3OS$, (III), 1-[(4-ethylthiosemicarbazono)methyl]-2-naphthol, $C_{14}H_{15}N_3OS$, (IV), 1-[(4-phenylthiosemicarbazono)methyl]-2-naphthol, $C_{18}H_{15}N_3OS$, (V), and 1-[(4,4-dimethylthiosemicarbazono)methyl]-2-naphthol dimethyl sulfoxide solvate, $C_{14}H_{15}N_3OS\cdot C_2H_6OS$, (VI). These chelators are N4-substituted thiosemicarbazones, each based on the same parent aldehyde, namely 2-zhydroxynaphthalene-1-carboxaldehyde isonicotinoylhydrazone. Conformational variations within this series are discussed in relation to the optimum conformation for metal-ion binding.

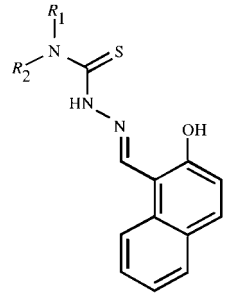
Comment

Due to its critical role in DNA synthesis and proliferation, iron is a potential target for the treatment of cancer (Richardson, 2002). To this end, the cellular antiproliferative effects of a number of iron-specific chelators and their complexes have been examined. A class of chelators with pronounced, and selective, activity against tumour cells are the thiosemicarbazones. The mechanism by which these compounds act is still not well understood, but chelation of intracellular Fe and other metal ions is believed to be important. A pertinent example is 3-aminopyridine-2-carbaldehyde thiosemicarbazone (also known as triapine), (I), which is a potent inhibitor of ribonucleotide reductase (Finch *et al.*, 1999), an enzyme which catalyzes the rate-limiting step in DNA synthesis.

Recently, we reported (Lovejoy & Richardson, 2002) the antiproliferative activity of a series of novel thiosemicarbazones based on 2-hydroxynaphthalene-1-carboxaldehyde, and found that many of them were highly active against neoplastic cellular proliferation but had much less effect on normal cells. Interestingly, structural variations at the thiosemicarbazide moiety have a marked effect on biological activity. For example, the N2-methyl-substituted thiosemicarbazone (II) exhibits poor antiproliferative activity (Lovejoy & Richardson, 2002), and we have reported the crystal structure of this compound (Lovejoy *et al.*, 2000). The absence of an ionisable H atom on N2 and the consequential lowering of Fe binding affinity were attributed to this feature.



(I) (II)



(III) R_1=Me, R_2=H
(IV) R_1=Et, R_2=H
(V) R_1=Ph, R_2=H
(VI) R_1=R_2=Me, C_2H_6OS solvate

Herein, we report the crystal structures of four N4-substituted thiosemicarbazones, (III)–(VI), each derived from the same parent aldehyde (2-hydroxynaphthalene-1-carboxaldehyde) and all displaying high antiproliferative activity (Lovejoy & Richardson, 2002). In each case, atom N2 is protonated, but the conformation of the thiosemicarbazide group varies across the series.

Selected bond lengths and angles are shown in Tables 1, 3, 5 and 7 for compounds (III)–(VI), respectively. It can be seen that there is little variation in the bond lengths within this

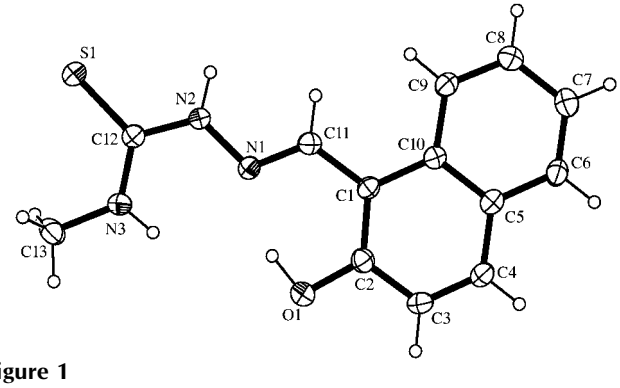


Figure 1
A view of the molecule of (III), showing the atom-numbering scheme and 30% probability displacement ellipsoids.

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series, but there are some subtle distinctions between their overall structures, as discussed below, particularly with regard to hydrogen bonding.

The structure of (III) (Fig. 1 and Table 1) reveals an almost planar molecule, with all non-H atoms within 0.04 Å of the least-squares plane and dihedral angles all within 2° of either 0 or 180°. Intramolecular hydrogen bonding is a feature of the structure. The hydroxyl group is hydrogen bonded to the adjacent imine N atom (Table 2). A weaker and more acute hydrogen bond is formed between the imine N atom and the adjacent NH group. In this conformation, the S atom is *anti* to atom N1 and is able to form a hydrogen bond with the remaining hydrazide H atom. This interaction creates a polymeric hydrogen-bonded chain, shown in the packing diagram of (III) (Fig. 2).

The *N*-ethyl analogue, (IV) (Fig. 3 and Table 3), exhibits a similar conformation and similar intramolecular hydrogen-bonding interactions to the *N*-methyl analogue, (III) (Table 4). Again, an intermolecular hydrogen bond involving the S atom is observed in (IV). In contrast with the hydrogen-bonded polymer found in (III), the intermolecular hydrogen bonds in (IV) result in C_2-symmetric dimers, as shown in Fig. 4. The molecule of (IV) is somewhat less planar than that of (III); the largest torsion angle deviation from either 0 or 180° is 7.6 (3)° for N3—C12—N2—N1, which may be attributed to the distortion resulting from the cyclic intermolecular hydrogen-bonding motif.

A similar structure is again seen in the *N*-phenyl compound, (V) (Fig. 5 and Table 5), although the phenyl ring is rotated by *ca* 37° out of the plane defined by the rest of the molecule, to minimize *ortho*-H-atom repulsions with atoms S1 and H3*A* (the H atom attached to N3). The relevant intramolecular hydrogen bonds (Table 6) are again similar in (V). Like (IV), the *N*-phenyl analogue forms C_2-symmetric hydrogen-bonded dimers (Fig. 6). The unique intermolecular interaction again involves the S atom as acceptor.

The structure of the *N*,*N*-dimethyl analogue, (VI), is unique among the compounds reported here. The potentially coordinating atoms O1, N1 and S1 are adjacent and define a *syn* conformation (Fig. 7 and Table 7). In this case, there are only two significant hydrogen bonds and both are intramolecular (Table 8), involving the hydroxyl group and the *syn* N1 and S1 atoms. The structure of (VI) also contains a molecule of dimethyl sulfoxide (DMSO), which is disordered about a pseudo-mirror plane that includes the two methyl C atoms. There are no significant intermolecular hydrogen bonds in (VI), except that between the minor (15%) DMSO contributor and the NH group.

It is known from the coordination chemistry of similar thiosemicarbazones (Gyepes *et al.*, 1981; Soriano-García *et al.*, 1985; Zimmer *et al.*, 1991) that they bind as meridional *O*,*N*,*S*-

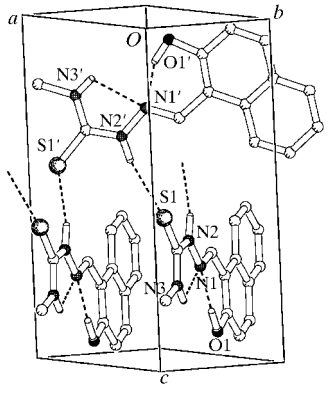

Figure 2
A diagram showing the hydrogen-bonded chain in (III) with the unit cell. H atoms on C atoms have been omitted for clarity. Primed atoms are at the symmetry position $(1 - x, y - \frac{1}{2}, 1 - z)$.

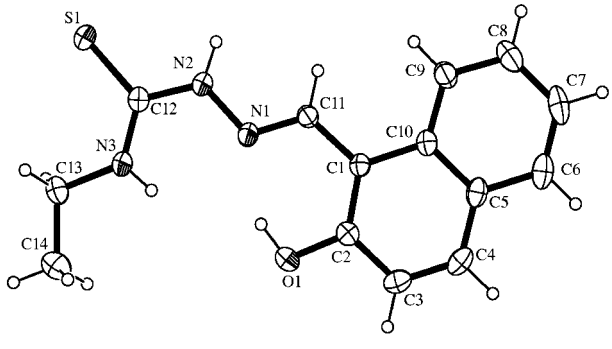

Figure 3
A view of the molecule of (IV), showing the atom-numbering scheme and 30% probability displacement ellipsoids.

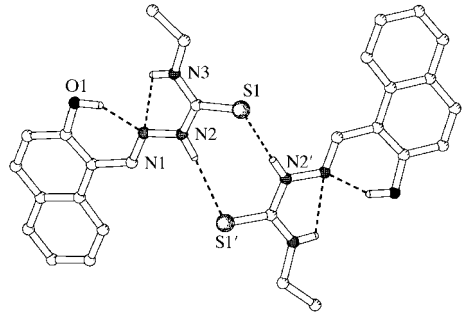

Figure 4
A diagram showing the hydrogen-bonded dimer of (IV). H atoms on C atoms have been omitted for clarity. Atoms S1′ and N2′ are at the symmetry position $(1 - x, y, \frac{3}{2} - z)$.

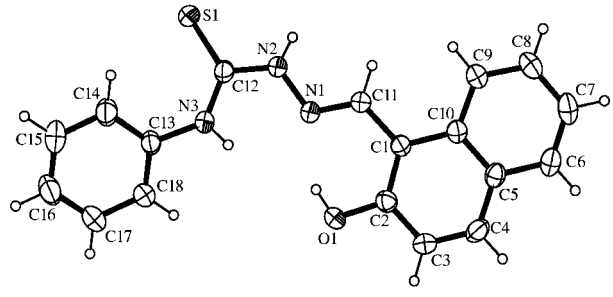

Figure 5
A view of the molecule of (V), showing the atom-numbering scheme and 30% probability displacement ellipsoids.

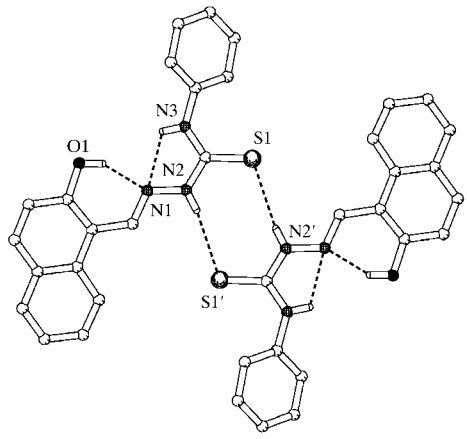

Figure 6
A diagram of the hydrogen-bonded dimer of (V). H atoms on C atoms have been omitted for clarity. Atoms S1′ and N2′ are at the symmetry position $(1-x, y, \frac{3}{2}-z)$.

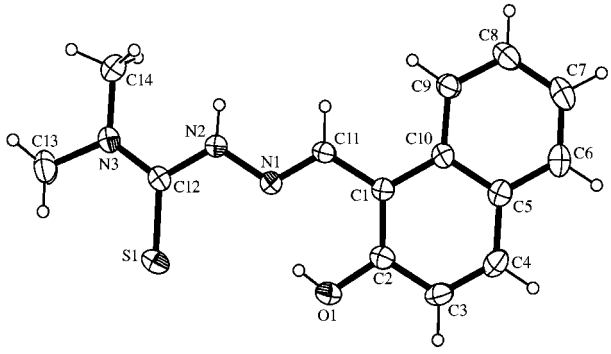

Figure 7
A view of the molecule of (VI), showing the atom-numbering scheme and 30% probability displacement ellipsoids. For clarity, the dimethyl sulfoxide solvent molecule is not shown.

chelators (in the *syn* conformation shown in the scheme above), while the terminal N3 atom does not participate in coordinate bonding. Of the four structures presented here, only (VI) is preorganized for metal binding, while the other compounds must undergo a 180° rotation of the N2—C12 bond.

In conclusion, there are two factors which result in the conformational differences between (VI) (*syn*) and the group composed of (III), (IV) and (V) (*anti*). The N3—H3*A*···N1 intramolecular hydrogen-bond interaction seen in compounds (III), (IV) and (V), albeit weak, appears to favour the *anti* conformer. In (VI), this hydrogen bond is not possible and the *anti* conformer is further destabilized by steric clashing between the *N*-methyl groups and the hydroxyl group, and the *syn* conformer ensues.

Experimental

All four compounds were prepared by Schiff base condensation of 2-hydroxynaphthalene-1-carboxaldehyde with the appropriate thiosemicarbazide in refluxing ethanol. The compounds precipitated readily from the reaction mixtures and were found to be pure by elemental analysis and NMR. Crystals of (III) were obtained from a saturated dimethylformamide solution, (IV) and (V) were crystallized from ethanol solutions, and (VI) was crystallized from a concentrated dimethyl sulfoxide solution.

Compound (III)

Crystal data

$C_{13}H_{13}N_3OS$
$M_r = 259.32$
Monoclinic, $P2_1$
$a = 9.293$ (1) Å
$b = 5.1612$ (3) Å
$c = 12.563$ (1) Å
$\beta = 91.31$ (2)°
$V = 602.40$ (9) Å^3
$Z = 2$
$D_x = 1.43$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
$\theta = 10.5$–16.0°
$\mu = 0.26$ mm^{-1}
$T = 296$ (2) K
Prism, yellow
0.50 × 0.17 × 0.10 mm

Data collection

Enraf–Nonius TurboCAD-4 diffractometer
Non-profiled $\omega/2\theta$ scans
Absorption correction: ψ scan (North *et al.*, 1968)
$T_{min} = 0.912$, $T_{max} = 0.971$
1262 measured reflections
1185 independent reflections
960 reflections with $I > 2\sigma(I)$
$R_{int} = 0.023$
$\theta_{max} = 25.0°$
$h = 0 \rightarrow 11$
$k = 0 \rightarrow 6$
$l = -14 \rightarrow 14$
3 standard reflections
frequency: 120 min
intensity decay: −2%

Refinement

Refinement on F^2
$R(F) = 0.030$
$wR(F^2) = 0.080$
$S = 1.06$
1185 reflections
176 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0508P)^2 + 0.0084P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.14$ e Å^{-3}
$\Delta\rho_{min} = -0.16$ e Å^{-3}
Absolute structure: Bernardinelli & Flack (1985)
Flack parameter = 0.01 (13)

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

C2—O1	1.356 (4)	C12—S1	1.672 (3)
C11—N1	1.288 (4)	C13—N3	1.443 (4)
C12—N3	1.333 (4)	N1—N2	1.367 (4)
C12—N2	1.355 (4)		
N1—C11—C1	122.9 (3)	C12—N2—N1	121.8 (2)
N3—C12—N2	116.4 (3)	C12—N3—C13	123.3 (3)
C11—N1—N2	115.1 (2)		

Table 2
Hydrogen-bonding and contact geometry (Å, °) for (III).

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1*A*···N1	0.95 (5)	1.75 (5)	2.641 (3)	155 (5)
N3—H3*A*···N1	0.85 (4)	2.29 (4)	2.671 (4)	107 (3)
N2—H2*A*···S1^{i}	0.92 (3)	2.60 (3)	3.467 (3)	158 (2)

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

Compound (IV)

Crystal data

$C_{14}H_{15}N_3OS$
M_r = 273.35
Monoclinic, $C2/c$
a = 26.608 (8) Å
b = 7.0551 (6) Å
c = 18.918 (5) Å
β = 129.710 (10)°
V = 2732.0 (11) Å^3
Z = 8
D_x = 1.329 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 21 reflections
θ = 11.0–14.0°
μ = 0.23 mm^{-1}
T = 296 (2) K
Prism, yellow
0.5 × 0.5 × 0.5 mm

Data collection

Enraf–Nonius TurboCAD-4 diffractometer
Non-profiled ω scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.698, T_{max} = 0.883
2466 measured reflections
2410 independent reflections
1847 reflections with $I > 2\sigma(I)$
R_{int} = 0.039
θ_{max} = 25.0°
$h = 0 \rightarrow 31$
$k = 0 \rightarrow 8$
$l = -22 \rightarrow 17$
3 standard reflections
frequency: 120 min
intensity decay: −1%

Refinement

Refinement on F^2
$R(F)$ = 0.040
$wR(F^2)$ = 0.122
S = 1.04
2410 reflections
184 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0694P)^2 + 1.4628P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.20 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}

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

C2—O1	1.351 (2)	C12—S1	1.683 (2)
C11—N1	1.285 (2)	C13—N3	1.455 (3)
C12—N3	1.323 (3)	N1—N2	1.373 (2)
C12—N2	1.353 (2)		
N1—C11—C1	121.79 (17)	C12—N2—N1	120.32 (17)
N3—C12—N2	117.07 (18)	C12—N3—C13	124.81 (19)
C11—N1—N2	116.94 (16)		

Table 4
Hydrogen-bonding and contact geometry (Å, °) for (IV).

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1A···N1	0.89 (3)	1.80 (3)	2.605 (2)	151 (3)
N3—H3A···N1	0.79 (3)	2.27 (3)	2.653 (2)	110 (2)
N2—H2A···S1^{i}	0.91 (3)	2.50 (3)	3.409 (2)	176 (2)

Symmetry code: (i) $1-x, y, \frac{3}{2}-z$.

Compound (V)

Crystal data

$C_{18}H_{15}N_3OS$
M_r = 321.39
Monoclinic, $C2/c$
a = 19.243 (4) Å
b = 6.7948 (6) Å
c = 24.471 (6) Å
β = 95.480 (10)°
V = 3185.0 (11) Å^3
Z = 8
D_x = 1.34 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 9.7–14.3°
μ = 0.21 mm^{-1}
T = 296 (2) K
Prism, yellow
0.5 × 0.4 × 0.3 mm

Data collection

Enraf–Nonius TurboCAD-4 diffractometer
Non-profiled $\omega/2\theta$ scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.911, T_{max} = 0.936
2834 measured reflections
2747 independent reflections
1425 reflections with $I > 2\sigma(I)$
R_{int} = 0.014
θ_{max} = 25.0°
$h = 0 \rightarrow 22$
$k = 0 \rightarrow 8$
$l = -29 \rightarrow 28$
3 standard reflections
frequency: 120 min
intensity decay: −5%

Refinement

Refinement on F^2
$R(F)$ = 0.040
$wR(F^2)$ = 0.126
S = 1.00
2747 reflections
220 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.0576P)^2 + 0.9608P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.16 e Å^{-3}
$\Delta\rho_{min}$ = −0.25 e Å^{-3}

Table 5
Selected geometric parameters (Å, °) for (V).

C2—O1	1.351 (3)	C12—S1	1.668 (2)
C12—N3	1.332 (3)	C13—N3	1.430 (3)
C12—N2	1.348 (3)	N1—N2	1.372 (3)
N1—C11—C1	122.9 (2)	C12—N2—N1	122.3 (2)
N3—C12—N2	115.2 (2)	C12—N3—C13	131.1 (2)
C11—N1—N2	116.0 (2)		

Table 6
Hydrogen-bonding and contact geometry (Å, °) for (V).

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1A···N1	0.83 (4)	1.86 (4)	2.620 (3)	150 (3)
N3—H3A···N1	0.81 (3)	2.20 (3)	2.653 (3)	116 (3)
N2—H2A···S1^{i}	0.82 (3)	2.62 (3)	3.425 (3)	171 (3)

Symmetry code: (i) $\frac{3}{2}-x, \frac{1}{2}-y, -z$.

Compound (VI)

Crystal data

$C_{14}H_{15}N_3OS{\cdot}C_2H_6OS$
M_r = 351.48
Monoclinic, $P2_1/n$
a = 12.012 (2) Å
b = 7.8776 (9) Å
c = 18.631 (3) Å
β = 95.780 (10)°
V = 1754.0 (5) Å^3
Z = 4
D_x = 1.331 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 11.3–14.0°
μ = 0.32 mm^{-1}
T = 296 (2) K
Prism, yellow
0.5 × 0.4 × 0.4 mm

Data collection

Enraf–Nonius TurboCAD-4 diffractometer
Non-profiled $\omega/2\theta$ scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.854, T_{max} = 0.881
3226 measured reflections
3069 independent reflections
1929 reflections with $I > 2\sigma(I)$
R_{int} = 0.011
θ_{max} = 25.0°
$h = 0 \rightarrow 14$
$k = 0 \rightarrow 9$
$l = -22 \rightarrow 22$
3 standard reflections
frequency: 120 min
intensity decay: 5%

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0571P)^2 + 0.6902P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R(F) = 0.040$	$(\Delta/\sigma)_{max} < 0.001$
$wR(F^2) = 0.120$	$\Delta\rho_{max} = 0.20$ e Å^{-3}
$S = 1.02$	$\Delta\rho_{min} = -0.26$ e Å^{-3}
3069 reflections	
227 parameters	
H atoms treated by a mixture of independent and constrained refinement	

Table 7
Selected geometric parameters (Å, °) for (VI).

C2—O1	1.354 (3)	C12—S1	1.680 (3)
C11—N1	1.278 (3)	C13—N3	1.463 (3)
C12—N2	1.366 (3)	N1—N2	1.371 (3)
C12—N3	1.334 (3)		
N1—C11—C1	119.9 (2)	C12—N2—N1	118.2 (2)
N3—C12—N2	114.9 (2)	C12—N3—C13	121.3 (2)
C11—N1—N2	118.2 (2)		

Table 8
Hydrogen-bonding geometry (Å, °) for (VI).

D—H···A	D—H	H···A	D···A	D—H···A
O1—H1*A*···N1	0.79 (3)	1.88 (3)	2.560 (3)	145 (3)
O1—H1*A*···S1	0.79 (3)	3.02 (3)	3.705 (2)	147 (3)

In each structure, the H atoms attached to N and O atoms were located from difference maps and refined without any constraints on their positional or isotropic displacement parameters. All H atoms attached to C atoms were included at estimated positions and restrained using a riding model. 14 Friedel pairs were measured for the structure of (III) and the resulting Flack value (Bernardinelli & Flack, 1985) is 0.01 (13).

For all four compounds, data collection: *CAD*-4 *EXPRESS* (Enraf–Nonius, 1994); cell refinement: *CAD*-4 *EXPRESS*; data reduction: *XCAD*4 (Harms & Wocadlo, 1995); program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1985); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*-3 *for Windows* (Farrugia, 1997) and *PLUTON* (Spek, 1990); software used to prepare material for publication: *WinGX* (Farrugia, 1999).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: GG1180). Services for accessing these data are described at the back of the journal.

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