

Hydrogen-bonded supramolecular structures of three related 4-(5-nitro-2-furyl)-1,4-dihydropyridines

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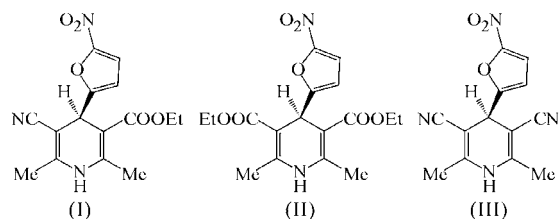
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In ethyl 5-cyano-2,6-dimethyl-4-(5-nitro-2-furyl)-1,4-dihydropyridine-3-carboxylate, $C_{15}H_{15}N_3O_5$, the molecules are linked into chains by a single $N-H\cdots O$ hydrogen bond. The molecules in diethyl 2,6-dimethyl-4-(5-nitro-2-furyl)-1,4-dihydropyridine-3,5-dicarboxylate, $C_{17}H_{20}N_2O_7$, are linked by a combination of one $N-H\cdots O$ hydrogen bond and two $C-H\cdots O$ hydrogen bonds into sheets built from equal numbers of $R_2^2(17)$ and $R_4^4(18)$ rings. In 2,6-dimethyl-4-(5-nitro-2-furyl)-1,4-dihydropyridine-3,5-dicarbonitrile, $C_{13}H_{10}N_4O_3$, the molecules are linked by a combination of a three-centre $N-H\cdots(O)_2$ hydrogen bond and two independent two-centre $C-H\cdots O$ hydrogen bonds into complex sheets containing four types of ring.

Comment

1,4-Dihydropyridine (1,4-DHP) derivatives, which are analogues of NADH coenzymes, are an important class of drugs, acting as potent blockers of calcium channels with application in the treatment of various cardiovascular diseases (Bou *et al.*, 1983; Godfraind *et al.*, 1986; Wagner *et al.*, 1988). In addition, 1,4-DHP compounds such as nifedipine, nisoldipine and nicardipine exhibit potential trypanocidal activity, inhibiting culture growth and oxygen uptake in *Trypanosoma cruzi* epimastigotes, the parasite causing Chagas' disease (Núñez-Vergara *et al.*, 1997, 1998). The drug action can be associated with the reduction of the nitro groups in these compounds. The presence of ester groups at the 3- and 5-positions in the 1,4-dihydropyridine ring is of crucial importance for the pharmaceutical effects. It has been suggested that these groups form hydrogen bonds with the receptor site (Goldmann &

Stoltefuss, 1991). Previous studies of the title compounds, namely ethyl 5-cyano-2,6-dimethyl-4-(5-nitro-2-furyl)-1,4-dihydropyridine-3-carboxylate, (I), diethyl 2,6-dimethyl-4-(5-nitro-2-furyl)-1,4-dihydropyridine-3,5-dicarboxylate, (II), and



2,6-dimethyl-4-(5-nitro-2-furyl)-1,4-dihydropyridine-3,5-dicarbonitrile, (III), have involved their NMR spectra (DaSilva *et al.*, 2005) and electroreduction of the nitro groups (Argüello *et al.*, 2005). The NMR study revealed the non-equivalence of the methylene H atoms in the ethoxycarbonyl groups, and we now report the molecular and supramolecular structures of three representative examples, *viz.* (I)–(III).

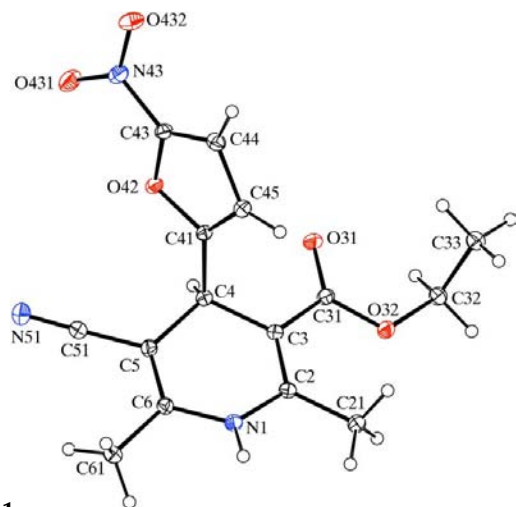


Figure 1
The *R* enantiomer of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

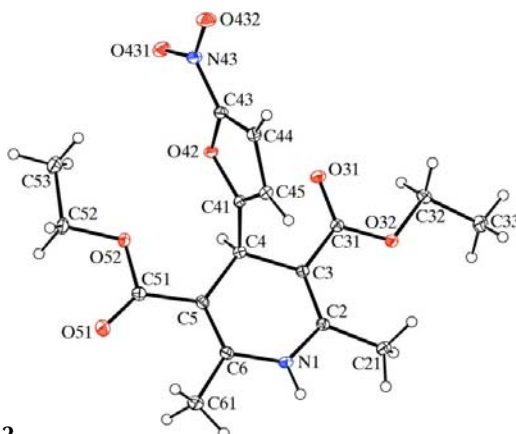


Figure 2
The molecule of (II), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

In each of compounds (I)–(III) (Figs. 1–3), the 1,4-dihydropyrimidine ring adopt a flat-boat conformation, as generally observed when this ring system carries an aryl or heteroaryl substituent at position 4 (Fossheim *et al.*, 1982; Lokaj *et al.*, 1991; Kožisek *et al.*, 1993), although an example containing a planar ring has recently been reported (Mahendra *et al.*, 2003). In each compound, the distortion of the ring from planarity is modest, with total puckering

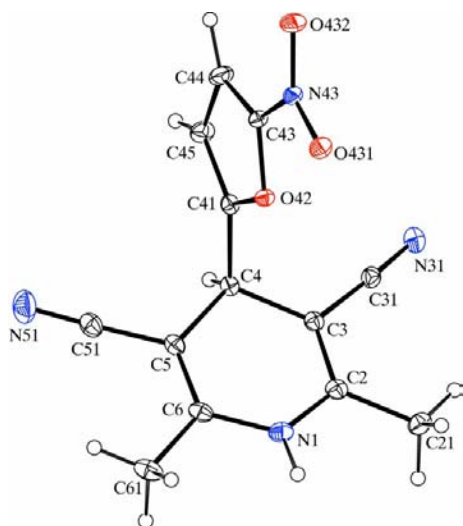


Figure 3

The molecule of (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.

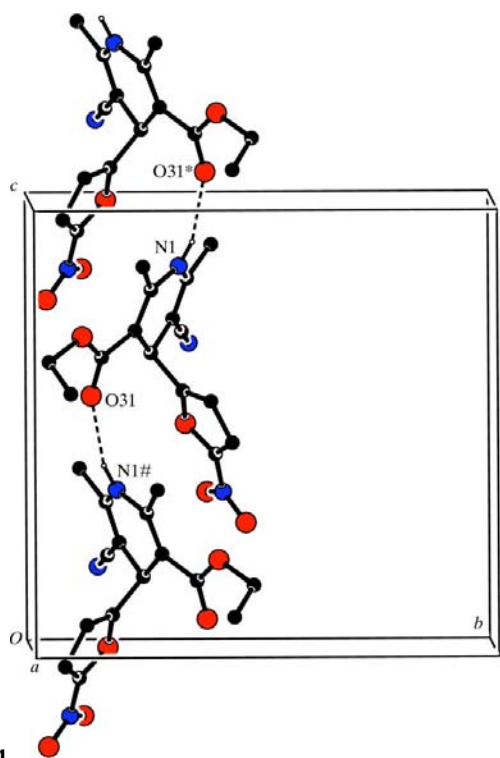


Figure 4

Part of the crystal structure of (I), showing the formation of a $C(6)$ chain along $[001]$. For the sake of clarity, H atoms bonded to C atoms have been omitted. Atoms marked with an asterisk (*) or a hash (#) are at the symmetry positions $(x, \frac{1}{2} - y, \frac{1}{2} + z)$ and $(x, \frac{1}{2} - y, -\frac{1}{2} + z)$, respectively.

amplitudes (Cremer & Pople, 1975) of only 0.190 (2), 0.105 (2) and 0.089 (2) Å for (I)–(III), respectively. In (I), atom C4 is a stereogenic centre and the selected reference molecule has the *R* configuration at this centre. However, the centrosymmetric space group accommodates equal numbers of *R* and *S* molecules.

The supramolecular structures of compounds (I)–(III) are all different and each is based on a different selection of hydrogen bonds. It is of interest to note the changes in the supramolecular structures which are associated with the changes in the substituents at positions 3 and 5 of the dihydropyrimidine ring.

In compound (I), the molecules are linked into simple chains by a single hydrogen bond (Table 1). Atom N1 in the molecule at (x, y, z) acts as hydrogen-bond donor to carbonyl atom O31 in the molecule at $(x, \frac{1}{2} - y, \frac{1}{2} + z)$, thereby producing a $C(6)$ (Bernstein *et al.*, 1995) chain running parallel to the $[001]$ direction and generated by the c -glide plane at $y = \frac{1}{4}$ (Fig. 4). Two such chains, running antiparallel to one another, pass through each unit cell, but there are no direction-specific interactions between adjacent chains.

The formation of the sheet structure in compound (II) can readily be analysed in terms of two one-dimensional substructures, one involving both $N-H \cdots O$ and $C-H \cdots O$ hydrogen bonds, and the other only a $C-H \cdots O$ hydrogen bond (Table 2). In the first substructure, atoms N1 and C45 in the molecule at (x, y, z) act as hydrogen-bond donors to atoms O31 and O431, respectively, in the molecule at $(x, \frac{1}{2} - y, \frac{1}{2} + z)$, so forming a chain of edge-fused $R_2^2(17)$ rings running parallel to the $[001]$ direction and generated by the c -glide plane at $y = \frac{1}{4}$ (Fig. 5). The second substructure is much simpler: atom C44 in the molecule at (x, y, z) acts as hydrogen-bond donor to ester atom O32 in the molecule at $(1 + x, y, z)$, so generating by translation a simple $C(8)$ chain running parallel to the $[100]$ direction. The combination of these two one-dimensional motifs then generates an (010) sheet consisting of alternating columns, all parallel to $[001]$, of $R_2^2(17)$ and $R_4^4(18)$ rings (Fig. 6). Two sheets of this type, related to one another by inversion, pass through each unit cell. The only direction-

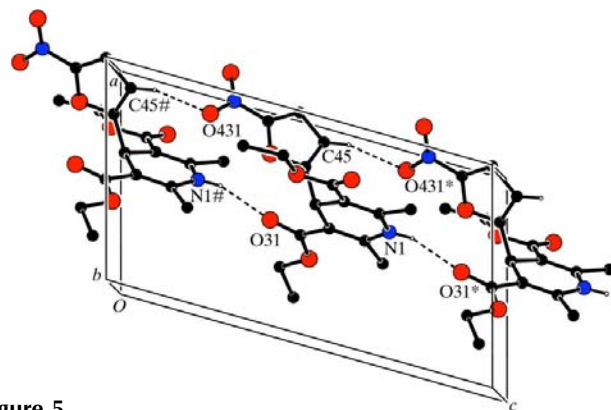


Figure 5

Part of the crystal structure of (II), showing the formation of a chain of edge-fused $R_2^2(17)$ rings along $[001]$. For the sake of clarity, H atoms not involved in the motif shown have been omitted. Atoms marked with an asterisk (*) or a hash (#) are at the symmetry positions $(x, \frac{1}{2} - y, \frac{1}{2} + z)$ and $(x, \frac{1}{2} - y, -\frac{1}{2} + z)$, respectively.

specific interaction of possible significance is a C—H··· π (furan) hydrogen bond (Table 2). Atom C52 in the molecule at (x, y, z) , which lies in the sheet generated by the glide planes at $y = \frac{1}{4}$, acts as hydrogen-bond donor to the furyl ring of the molecule at $(2 - x, 1 - y, 1 - z)$, which forms part of the sheet generated by the glide plane at $y = \frac{3}{4}$. Propagation of this interaction then links each (010) sheet to the two adjacent sheets.

The supramolecular structure of compound (III) consists of hydrogen-bonded sheets containing four types of ring. However, as for (II), the formation of the sheet in (III) is readily analysed in terms of simpler zero- and one-dimensional substructures. The basic building block in the supramolecular structure of (III) can be regarded as a cyclic centrosymmetric dimer. Atom N1 in the molecule at (x, y, z)

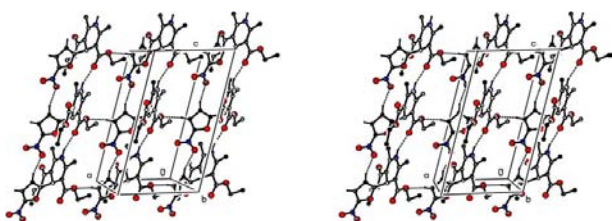


Figure 6
Stereoview of part of the crystal structure of (II), showing the formation of an (010) sheet built from $R_2^2(17)$ and $R_4^4(18)$ rings. For the sake of clarity, H atoms not involved in the motifs shown have been omitted.

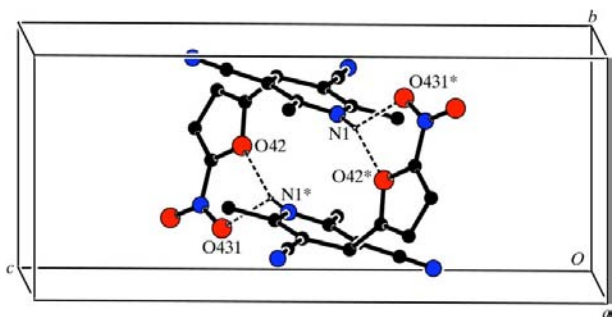


Figure 7
Part of the crystal structure of (III), showing the formation of a cyclic centrosymmetric dimer. For the sake of clarity, H atoms bonded to C atoms have been omitted. Atoms marked with an asterisk (*) are at the symmetry position $(1 - x, 1 - y, 1 - z)$.

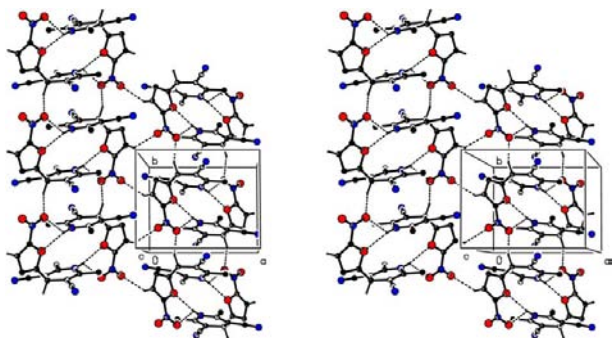


Figure 8
Stereoview of part of the crystal structure of (III), showing the formation of a (102) sheet built from $R_1^1(5)$, $R_2^2(14)$, $R_3^3(14)$ and $R_4^4(14)$ rings. For the sake of clarity, H atoms not involved in the motifs shown have been omitted.

acts as hydrogen-bond donor to both O42 and O431 in the molecule at $(1 - x, 1 - y, 1 - z)$, forming an effectively planar three-centre N—H···(O)₂ system (Table 3). The resulting dimer centred at $(\frac{1}{2}, \frac{1}{2}, \frac{1}{2})$ contains an $R_2^2(14)$ ring generated by the shorter component of the three-centre hydrogen bond and two $R_1^1(5)$ rings generated by both components (Fig. 7). Two independent C—H···O hydrogen bonds then link these dimers into sheets, and it is convenient to consider the action of each hydrogen bond in turn. Atom C4 in the molecule at (x, y, z) , part of the dimer centred at $(\frac{1}{2}, \frac{1}{2}, \frac{1}{2})$, acts as hydrogen-bond donor to atom O431 in the molecule at $(x, 1 + y, z)$, part of the dimer centred at $(\frac{1}{2}, \frac{3}{2}, \frac{1}{2})$. Propagation of this hydrogen bond by translation and inversion then generates a chain of edge-fused rings along $(\frac{1}{2}, y, \frac{1}{2})$, with $R_2^2(14)$ rings centred at $(\frac{1}{2}, n + \frac{1}{2}, \frac{1}{2})$ ($n = \text{zero or integer}$) and $R_4^4(14)$ rings centred at $(\frac{1}{2}, n, \frac{1}{2})$ ($n = \text{zero or integer}$) (Fig. 8). Finally, these chains are linked by the second C—H···O hydrogen bond. Atom C44 in the molecule at (x, y, z) , which lies in the chain of rings along $(\frac{1}{2}, y, \frac{1}{2})$, acts as hydrogen-bond donor to atom O432 in the molecule at $(-x, \frac{1}{2} + y, \frac{3}{2} - z)$, which itself lies in the chain of rings along $(-\frac{1}{2}, y, 1)$. Propagation by the space group of this hydrogen bond then links the [010] chains of rings into a (102) sheet (Fig. 8). There are no direction-specific interactions between adjacent sheets.

Experimental

Samples of compounds (I)–(III) were prepared according to published procedures (Hafiz *et al.*, 1999; DaSilva *et al.*, 2005; Argüello *et al.*, 2005). Crystals suitable for single-crystal X-ray diffraction were grown by slow evaporation of solutions in ethanol. Attempts to cut small fragments from the rather large blocks of compound (III) led to shattering of the crystals.

Compound (I)

Crystal data

$C_{15}H_{15}N_3O_5$
 $M_r = 317.30$
 Monoclinic, $P2_1/c$
 $a = 8.0214$ (3) Å
 $b = 13.7477$ (4) Å
 $c = 13.2847$ (4) Å
 $\beta = 95.3019$ (17)°
 $V = 1458.71$ (8) Å³
 $Z = 4$

$D_x = 1.445$ Mg m⁻³
 Mo $K\alpha$ radiation
 Cell parameters from 3361 reflections
 $\theta = 3.0$ – 27.6 °
 $\mu = 0.11$ mm⁻¹
 $T = 120$ (2) K
 Block, brown
 $0.14 \times 0.12 \times 0.08$ mm

Data collection

Nonius KappaCCD area-detector diffractometer
 φ and ω scans
 Absorption correction: multi-scan (SADABS; Sheldrick, 2003)
 $T_{\min} = 0.979$, $T_{\max} = 0.991$
 17958 measured reflections

3361 independent reflections
 2614 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.054$
 $\theta_{\max} = 27.6$ °
 $h = -10 \rightarrow 10$
 $k = -17 \rightarrow 17$
 $l = -17 \rightarrow 16$

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.048$
 $wR(F^2) = 0.132$
 $S = 1.06$
 3361 reflections
 211 parameters
 H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0641P)^2 + 0.6243P]$
 where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\max} < 0.001$
 $\Delta\rho_{\max} = 0.34$ e Å⁻³
 $\Delta\rho_{\min} = -0.40$ e Å⁻³

Table 1
Hydrogen-bond geometry (Å, °) for (I).

D—H...A	D—H	H...A	D...A	D—H...A
N1—H1...O31 ⁱ	0.88	2.12	2.953 (2)	157

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

Compound (II)

Crystal data

C₁₇H₂₀N₂O₇
M_r = 364.35
 Monoclinic, *P*₂₁/*c*
a = 8.0511 (2) Å
b = 15.173 (4) Å
c = 14.470 (4) Å
 β = 105.760 (2)°
V = 1701.2 (7) Å³
Z = 4
D_x = 1.423 Mg m⁻³

Mo *K*α radiation
 Cell parameters from 3898 reflections
 θ = 2.9–27.5°
 μ = 0.11 mm⁻¹
T = 120 (2) K
 Plate, yellow
 0.26 × 0.22 × 0.06 mm

Data collection

Nonius KappaCCD area-detector diffractometer
 φ and ω scans
 Absorption correction: multi-scan (SADABS; Sheldrick, 2003)
T_{min} = 0.969, *T_{max}* = 0.993
 17840 measured reflections
 3898 independent reflections

3073 reflections with *I* > 2σ(*I*)
R_{int} = 0.047
 θ_{\max} = 27.5°
h = -10 → 7
k = -19 → 19
l = -18 → 18

Refinement

Refinement on *F*²
R [*F*² > 2σ(*F*²)] = 0.047
wR (*F*²) = 0.128
S = 1.06
 3898 reflections
 239 parameters
 H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0587P)^2 + 0.8476P]$
 where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\max} = 0.001$
 $\Delta\rho_{\max} = 0.42 \text{ e } \text{Å}^{-3}$
 $\Delta\rho_{\min} = -0.37 \text{ e } \text{Å}^{-3}$

Table 2
Hydrogen-bond geometry (Å, °) for (II).

C_g is the centroid of the C41/O42/C43/C44/C45 ring.

D—H...A	D—H	H...A	D...A	D—H...A
N1—H1...O31 ⁱ	0.86	2.18	2.986 (2)	157
C44—H44...O32 ⁱⁱ	0.95	2.38	3.330 (2)	174
C45—H45...O431 ⁱ	0.95	2.45	3.369 (2)	163
C52—H52A...C _g ^{iv}	0.99	2.68	3.473 (2)	134

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

Compound (III)

Crystal data

C₁₅H₁₀N₄O₃
M_r = 270.25
 Monoclinic, *P*₂₁/*c*
a = 9.5651 (3) Å
b = 7.5735 (2) Å
c = 17.6385 (5) Å
 β = 96.2570 (13)°
V = 1270.14 (6) Å³
Z = 4
D_x = 1.413 Mg m⁻³

Mo *K*α radiation
 Cell parameters from 2907 reflections
 θ = 2.9–27.5°
 μ = 0.10 mm⁻¹
T = 120 (2) K
 Block, colourless
 0.90 × 0.34 × 0.22 mm

Data collection

Nonius KappaCCD area-detector diffractometer
 φ and ω scans
 Absorption correction: multi-scan (SADABS; Sheldrick, 2003)
T_{min} = 0.906, *T_{max}* = 0.977
 16132 measured reflections

2907 independent reflections
 2333 reflections with *I* > 2σ(*I*)
R_{int} = 0.035
 θ_{\max} = 27.5°
h = -12 → 12
k = -9 → 9
l = -22 → 22

Refinement

Refinement on *F*²
R [*F*² > 2σ(*F*²)] = 0.039
wR (*F*²) = 0.105
S = 1.05
 2907 reflections
 183 parameters
 H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0487P)^2 + 0.4785P]$
 where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{\max} < 0.001$
 $\Delta\rho_{\max} = 0.23 \text{ e } \text{Å}^{-3}$
 $\Delta\rho_{\min} = -0.28 \text{ e } \text{Å}^{-3}$

Table 3
Hydrogen-bond geometry (Å, °) for (III).

D—H...A	D—H	H...A	D...A	D—H...A
N1—H1...O42 ⁱ	0.88	2.35	3.2019 (15)	162
N1—H1...O431 ⁱ	0.88	2.32	2.9390 (16)	128
C4—H4...O431 ⁱⁱ	1.00	2.47	3.3262 (16)	143
C44—H44...O432 ⁱⁱⁱ	0.95	2.32	3.0446 (18)	132

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

For each of compounds (I), (II) and (III), the space group *P*₂₁/*c* was uniquely assigned from the systematic absences. All H atoms were located in difference maps and then treated as riding atoms, with C—H = 0.95 (aromatic), 0.98 (CH₃), 0.99 (CH₂) or 1.00 Å (aliphatic CH) and N—H = 0.88 Å, and with *U*_{iso}(H) = 1.2*U*_{eq}(C,N) or 1.5*U*_{eq}(methyl C).

For all three compounds, data collection: COLLECT (Nonius, 1999); cell refinement: DENZO (Otwinowski & Minor, 1997) and COLLECT; data reduction: DENZO and COLLECT; program(s) used to solve structure: OSCAIL (McArdle, 2003) and SHELXS97 (Sheldrick, 1997); program(s) used to refine structure: OSCAIL and SHELXL97 (Sheldrick, 1997); 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: SK1887). Services for accessing these data are described at the back of the journal.

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