Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Hydrogen bonding in 2-amino-4-methoxy-6-methylpyrimidine, 2-benzylamino-4-benzyloxy-6-methylpyrimidine and 4-benzylamino-2,6-bis(benzyloxy)pyrimidine: π-stacked chains of fused $R_2^2(8)$ rings, and centrosymmetric $R_2^2(8)$ dimers

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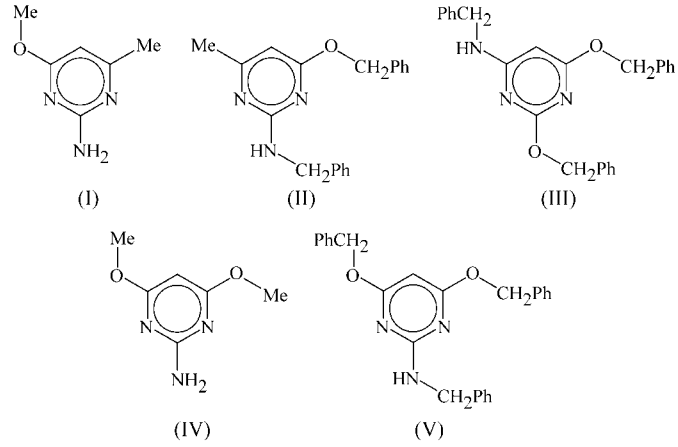
Received 31 October 2002
Accepted 6 November 2002
Online 10 December 2002

Molecules of 2-amino-4-methoxy-6-methylpyrimidine, $C_6H_9N_3O$, (I), lie on mirror planes in space group *Pnma* and are linked by two N—H···N hydrogen bonds [H···N = 2.26 and 2.34 Å, N···N = 3.136 (2) and 3.212 (2) Å, and N—H···N = 175 and 172°] into chains of edge-fused $R_2^2(8)$ rings, which themselves are linked into sheets by aromatic π–π-stacking interactions. In 2-benzylamino-4-benzyloxy-6-methylpyrimidine, $C_{19}H_{19}N_3O$, (II), and 4-benzylamino-2,6-bis(benzyloxy)-pyrimidine, $C_{25}H_{23}N_3O_2$, (III), the molecules are linked by paired N—H···N hydrogen bonds [H···N = 2.16 Å, N···N = 3.039 (2) Å and N—H···N = 165° in (II); H···N = 2.15 Å, N···N = 2.980 (2) Å and N—H···N = 176° in (III)] into centrosymmetric $R_2^2(8)$ dimers, with no direction-specific interactions between these dimeric units.

Comment

Alkoxypyrimidines are key intermediates for the synthesis of a wide range of alkoxy- and amino-substituted O^6-benzyloxy-5-nitrosopyrimidines (Marchal *et al.*, 1998, 2000; Quesada *et al.*, 2000), which are important as potential, or proven, *in vitro* inhibitors of the human DNA-repair protein O^6-alkylguanine-DNA-transferase (Chae *et al.*, 1995; Quesada *et al.*, 2002). We report here the molecular and supramolecular structures of three examples of this class, namely 2-amino-4-methoxy-6-methylpyrimidine, (I), 2-benzylamino-4-benzyloxy-6-methylpyrimidine, (II), and 4-benzylamino-2,6-bis(benzyloxy)pyrimidine, (III).



Compound (I) (Fig. 1) crystallizes in space group *Pnma* with all the non-H atoms lying on mirror planes; the plane for the reference molecule was selected as that at $y = \frac{1}{4}$. The molecules are linked by two N—H···N hydrogen bonds (Table 2) into chains of edge-fused rings, which themselves are linked into sheets by π–π-stacking interactions. The amino atom N2 in the reference molecule at (x, $\frac{1}{4}$, z) acts as hydrogen-bond donor, *via* H1 and H2, respectively, to atom N1 in the molecule at ($-\frac{1}{2} + x$, $\frac{1}{4}$, $\frac{1}{2} - z$) and atom N3 in the molecule at ($\frac{1}{2} + x$, $\frac{1}{4}$, $\frac{1}{2} - z$), and propagation of these two hydrogen bonds generates a chain of edge-fused $R_2^2(8)$ rings running parallel to the [100] direction and generated by the *a*-glide plane at $z = \frac{1}{4}$ (Fig. 2). This hydrogen-bonded substructure may alternatively be regarded as a molecular ladder, in which two $C_2^2(6)$ chains, related by the glide plane at $z = \frac{1}{4}$, act as the uprights and the C2—N2 bonds act as the rungs.

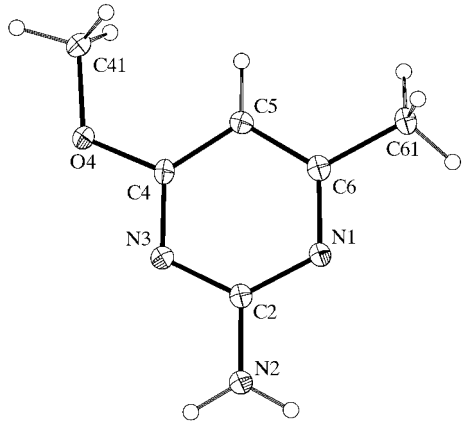


Figure 1
The molecule of compound (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level. All the non-H atoms lie on a mirror plane. For the sake of clarity, only one set of half-occupancy H-atom sites is shown for each of the methyl groups.

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 DOI: 10.1107/S0108270102020206

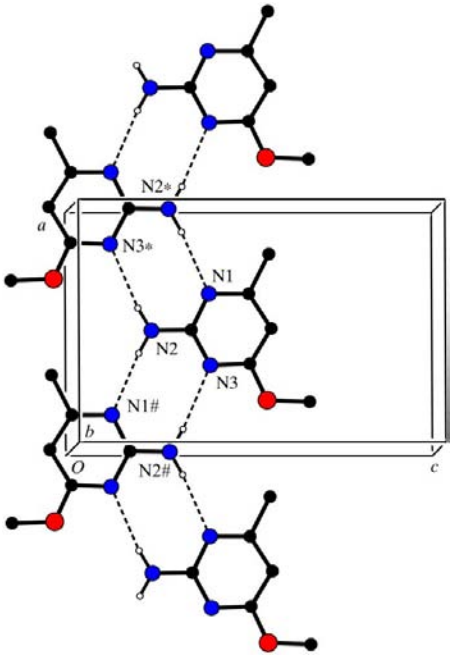

Figure 2
Part of the crystal structure of (I), showing the formation of a chain of edge-fused rings along [100]. For the sake of clarity, H atoms bonded to C atoms have been omitted. Atoms marked with an asterisk (*) or hash (#) are at the symmetry positions $(\frac{1}{2}+x, \frac{1}{4}, \frac{1}{2}-z)$ and $(-\frac{1}{2}+x, \frac{1}{4}, \frac{1}{2}-z)$, respectively.

The π–π-stacking interactions (Fig. 3) link the reference molecule at $(x, \frac{1}{4}, z)$, which forms part of the hydrogen-bonded chain along $(x, \frac{1}{4}, \frac{1}{4})$, with the two molecules at $(1-x, \frac{3}{4}, 1-z)$ and $(1-x, -\frac{1}{4}, 1-z)$, which lie, respectively, in the hydrogen-bonded chains along $(-x, \frac{3}{4}, \frac{3}{4})$ and $(-x, -\frac{1}{4}, \frac{3}{4})$. The interplanar spacing is 3.273 (2) Å, the centroid separation is 3.588 (2) Å and the centroid offset is 1.470 (2) Å. By this means, a (001) sheet is formed, centred at $z = \frac{1}{2}$ and lying in the domain $0.22 < z < 0.78$; a similar sheet, centred at $z = 0$, lies in the domain $-0.28 < z < 0.28$, but there are no direction-specific interactions between adjacent sheets.

In both (II) (Fig. 4) and (III) (Fig. 5), there is just a single N—H bond, and a single N—H···N hydrogen bond (Tables 4 and 6) leads to the formation of centrosymmetric $R_2^2(8)$ dimers centred at $(\frac{1}{2}, \frac{1}{2}, \frac{1}{2})$ (Figs. 6 and 7). In neither structure are there any other hydrogen bonds or any π–π-stacking interactions.

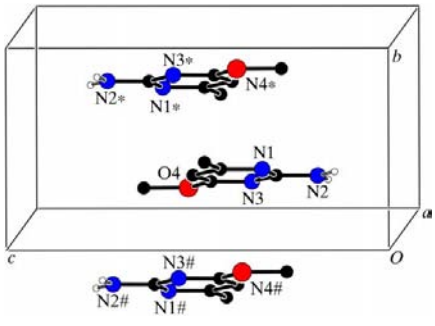

Figure 3
Part of the crystal structure of (I), showing the π–π-stacking interactions. For the sake of clarity, H atoms bonded to C atoms have been omitted. Atoms marked with an asterisk (*) or hash (#) are at the symmetry positions $(1-x, \frac{3}{4}, 1-z)$ and $(1-x, -\frac{1}{4}, 1-z)$, respectively.

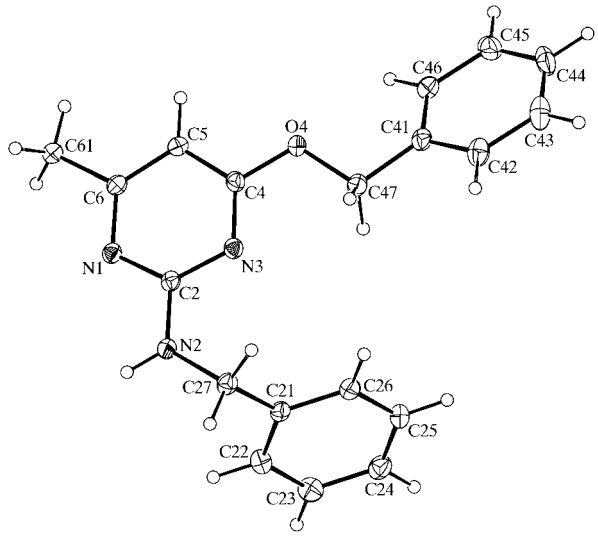

Figure 4
The molecule of compound (II), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level.

The gross supramolecular structure of (I) resembles that of the 4,6-dimethoxy analogue, (IV) (Low *et al.*, 2002), while differing from it in detail. The chains of edge-fused rings in

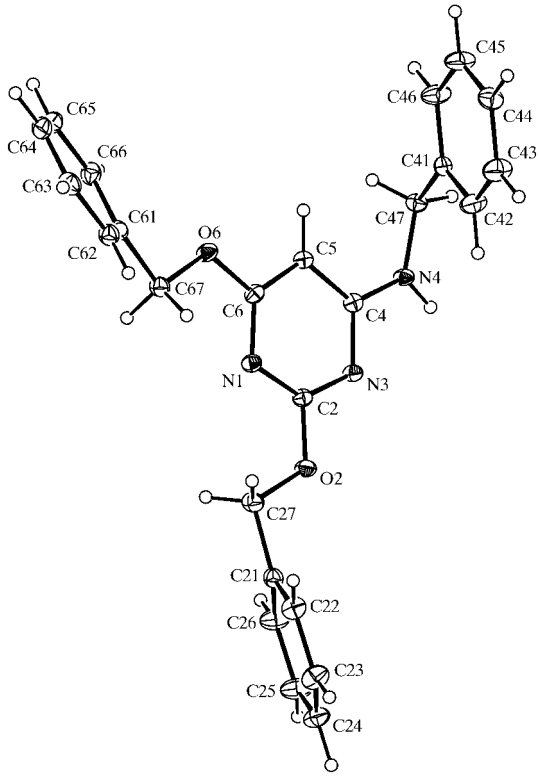

Figure 5
The molecule of compound (III), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level.

(IV) contain two different types of $R_2^2(8)$ ring, both centrosymmetric, incorporating only atoms N1 and N2 in one type of ring and only N2 and N3 in the other; by contrast, the chain in (I) contains only one type of ring, and this includes all three N atoms. Moreover, whereas in (I), the chain is generated by a glide plane, in (IV) it is generated by a combination of inversions and twofold rotations. The supramolecular structures of (I) and (IV) also differ in the effects of the π–π stacking, which gives a two-dimensional array in (I), but a three-dimensional structure in (IV). On the other hand, the centrosymmetric dimer structures found for (II) and (III) exactly mimic that observed in (V) (Low *et al.*, 2002), which is a positional isomer of (III).

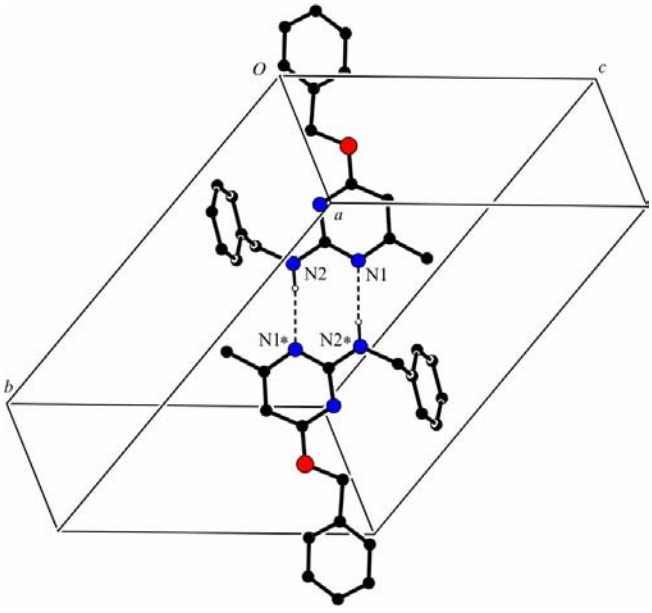

Figure 6
Part of the crystal structure of (II), showing the formation of a centrosymmetric $R_2^2(8)$ dimer. For the sake of clarity, H atoms bonded to C atoms have been omitted. Atoms marked with an asterisk are at the symmetry position $(1-x, 1-y, 1-z)$.

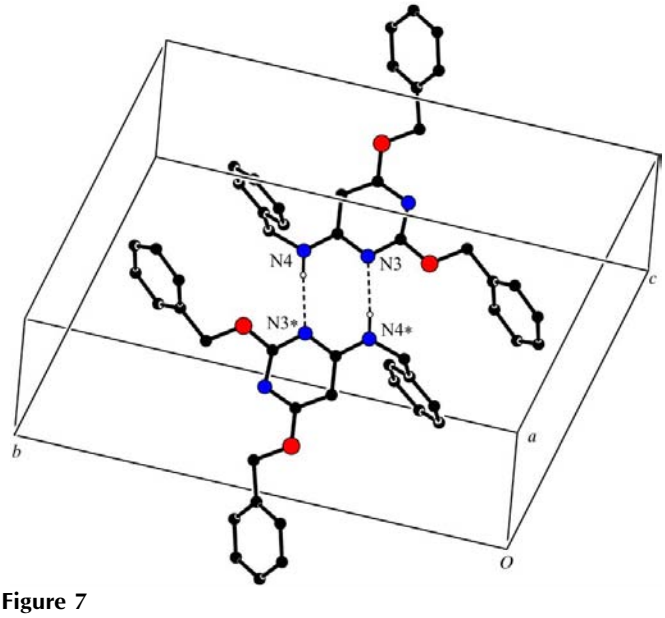

Figure 7
Part of the crystal structure of (III), showing the formation of a centrosymmetric $R_2^2(8)$ dimer. For the sake of clarity, H atoms bonded to C atoms have been omitted. Atoms marked with an asterisk are at the symmetry position $(1-x, 1-y, 1-z)$.

In all three title compounds, (I)–(III), the intramolecular distances show no evidence of significant bond fixation involving the pyrimidine rings (Tables 1, 3 and 5); in this respect, the molecular–electronic structure of (I) is markedly different from those in a large number of analogous pyrimidines carrying a 5-nitroso substituent, where highly polarized structures are the norm (Low *et al.*, 2000; Low, Cannon *et al.*, 2001; Low, Moreno *et al.*, 2001; Quesada *et al.*, 2002).

The non-H atoms in (I) are strictly coplanar and the methoxy-group conformation is such that the methyl C atom is directed away from the amino group [*cf.* compound (IV) (Low *et al.*, 2002), shown in *Scheme* above]. In both (II) and (III), the methylene C atoms of the benzyl substituents are all close to the planes of the adjacent pyrimidine rings, but the phenyl groups are twisted well out of these planes (Tables 3 and 5). We note the general similarity between the conformations of (II) and (III), and the fact that the overall conformations of the isomeric compounds (III) and (V) are unchanged by the positional exchange of the benzylamino and benzyloxy substituents. The subtle factors underpinning the preferred conformations is systems such as (I)–(V) await investigation.

Experimental

A sample of compound (I) was purchased from Aldrich and converted to (II) (m.p. 475 K) using the transalkoxylation and *N*-benzylation methodology previously described by Low *et al.* (2002). Compound (III) (m.p. 408 K) was likewise prepared from 4-amino-2-methylthio-6-methoxypyrimidine (Pfleiderer & Liedek, 1958). ^{1}H NMR (DMSO-d_6, p.p.m), for (II): δ 2.15 (*s*, 3H, CH_3), 4.47 (*d*, 2H, N–CH_2, J = 6.31 Hz), 5.28 (*s*, 2H, O–CH_2), 5.93 (*s*, 1H, C5–H), 7.26 (*m*, 10H, 2 × Ph), 7.55 (*br s*, 1H, NH, exchanges with D_2O); for (III): δ 4.42 (*d*, 2H, NH–CH_2, J = 5.28 Hz), 5.32 (*s*, 2H, O–CH_2), 5.33 (*s*, 2H, O–CH_2), 5.41 (*s*, 1H, C5–H), 5.43 (*br s*, 1H, NH exchanges with D_2O), 7.29 (*m*, 15H, 3 × Ph). Crystals suitable for single-crystal X-ray diffraction were grown by slow evaporation of solutions in ethyl acetate [for (I)], ethanol [for (II)] and *n*-butanol [for (III)].

Compound (I)

Crystal data

$C_6H_9N_3O$
M_r = 139.16
Orthorhombic, *Pnma*
a = 8.1442 (17) Å
b = 6.5456 (11) Å
c = 12.285 (2) Å
V = 654.9 (2) Å^3
Z = 4
D_x = 1.411 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 797 reflections
θ = 3.0–27.4°
μ = 0.10 mm^{-1}
T = 120 (2) K
Plate, colourless
0.25 × 0.20 × 0.02 mm

Data collection

Nonius KappaCCD diffractometer
φ scans and ω scans with κ offsets
7372 measured reflections
797 independent reflections
468 reflections with $I > 2\sigma(I)$
R_{int} = 0.099
θ_{max} = 27.4°
$h = -10 \rightarrow 10$
$k = -8 \rightarrow 8$
$l = -10 \rightarrow 15$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.050$
$wR(F^2) = 0.136$
$S = 0.98$
797 reflections
61 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0795P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.32$ e Å^{-3}
$\Delta\rho_{min} = -0.24$ e Å^{-3}

Table 1
Selected interatomic distances (Å) for (I).

N1—C2	1.354 (2)	C4—C5	1.388 (3)
C2—N3	1.346 (2)	C5—C6	1.382 (3)
N3—C4	1.327 (3)	C6—N1	1.338 (3)

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

D—H···A	D—H	H···A	D···A	D—H···A
N2—H1···N1^{i}	0.88	2.26	3.136 (2)	175
N2—H2···N3^{ii}	0.88	2.34	3.212 (2)	172

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

Compound (II)

Crystal data

$C_{19}H_{19}N_3O$
$M_r = 305.38$
Monoclinic, $P2_1/c$
$a = 5.8932$ (2) Å
$b = 18.2849$ (7) Å
$c = 15.1175$ (7) Å
$\beta = 98.704$ (2)°
$V = 1610.25$ (11) Å^3
$Z = 4$
$D_x = 1.260$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 3667 reflections
$\theta = 2.9$–27.5°
$\mu = 0.08$ mm^{-1}
$T = 120$ (2) K
Needle, colourless
0.26 × 0.18 × 0.10 mm

Data collection

Nonius KappaCCD diffractometer
φ scans, and ω scans with κ offsets
Absorption correction: multi-scan (*DENZO–SMN*; Otwinowski & Minor, 1997)
$T_{min} = 0.970$, $T_{max} = 0.992$
12 340 measured reflections
3667 independent reflections
2371 reflections with $I > 2\sigma(I)$
$R_{int} = 0.093$
$\theta_{max} = 27.5°$
$h = -7 \rightarrow 7$
$k = -23 \rightarrow 21$
$l = -19 \rightarrow 19$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.050$
$wR(F^2) = 0.125$
$S = 1.00$
3667 reflections
209 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0662P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.21$ e Å^{-3}
$\Delta\rho_{min} = -0.28$ e Å^{-3}

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

N1—C2	1.3447 (19)	C2—N2	1.3501 (19)
C2—N3	1.3493 (18)	N2—C27	1.450 (2)
N3—C4	1.3223 (19)	C4—O4	1.3505 (18)
C4—C5	1.384 (2)	O4—C47	1.4398 (19)
C5—C6	1.377 (2)	C6—C61	1.494 (2)
C6—N1	1.3486 (19)		
N1—C2—N2—C27	179.97 (12)	N3—C4—O4—C47	3.38 (19)
C2—N2—C27—C21	−80.49 (17)	C4—O4—C47—C41	172.35 (12)
N2—C27—C21—C22	−60.71 (18)	O4—C47—C41—C42	154.41 (13)

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

D—H···A	D—H	H···A	D···A	D—H···A
N2—H2···N1^{i}	0.88	2.16	3.039 (2)	176

Symmetry code: (i) $1-x, 1-y, 1-z$.

Compound (III)

Crystal data

$C_{25}H_{23}N_3O_2$
$M_r = 397.46$
Monoclinic, $P2_1/c$
$a = 5.6056$ (2) Å
$b = 18.2446$ (5) Å
$c = 20.6480$ (8) Å
$\beta = 100.965$ (1)°
$V = 2073.16$ (12) Å^3
$Z = 4$
$D_x = 1.273$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 4691 reflections
$\theta = 3.0$–27.5°
$\mu = 0.08$ mm^{-1}
$T = 120$ (2) K
Block, colourless
0.50 × 0.30 × 0.15 mm

Data collection

Nonius KappaCCD diffractometer
φ scans, and ω scans with κ offsets
Absorption correction: multi-scan (*DENZO–SMN*; Otwinowski & Minor, 1997)
$T_{min} = 0.950$, $T_{max} = 0.987$
16 019 measured reflections
4691 independent reflections
2822 reflections with $I > 2\sigma(I)$
$R_{int} = 0.076$
$\theta_{max} = 27.5°$
$h = -7 \rightarrow 6$
$k = -23 \rightarrow 18$
$l = -26 \rightarrow 26$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.054$
$wR(F^2) = 0.131$
$S = 0.96$
4691 reflections
271 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0684P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max} = 0.23$ e Å^{-3}
$\Delta\rho_{min} = -0.31$ e Å^{-3}

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

N1—C2	1.335 (2)	C2—O2	1.352 (2)
C2—N3	1.316 (2)	O2—C27	1.441 (2)
N3—C4	1.353 (2)	C4—N4	1.345 (2)
C4—C5	1.400 (2)	N4—C47	1.445 (2)
C5—C6	1.374 (2)	C6—O6	1.357 (2)
C6—N1	1.336 (2)	O6—C67	1.442 (2)
N1—C2—O2—C27	−1.4 (2)	N4—C47—C41—C42	−20.0 (2)
C2—O2—C27—C21	174.90 (15)	N1—C6—O6—C67	−3.6 (2)
O2—C27—C21—C22	−114.06 (18)	C6—O6—C67—C61	−172.75 (14)
C5—C4—N4—C47	−7.3 (2)	O6—C67—C61—C62	136.29 (16)
C4—N4—C47—C41	−65.7 (2)		

Table 6
Hydrogen-bonding geometry (Å, °) for (III).

D—H···A	D—H	H···A	D···A	D—H···A
N4—H4···N3^{i}	0.88	2.15	2.980 (2)	157

Symmetry code: (i) $1-x, 1-y, 1-z$.

For compound (I), the systematic absences permitted *Pnma* (= *Pnam*) and $Pna2_1$ as possible space groups; *Pnma* was selected and confirmed by the analysis. For both (II) and (III), space group $P2_1/c$ was uniquely assigned from the systematic absences. All H atoms

were treated as riding, with C—H distances of 0.95 (aromatic), 0.98 (CH_3) or 0.99 Å (CH_2), and N—H distances of 0.88 Å. The methyl groups in (I) were both modelled using six half-occupancy H-atom sites offset from one another by 60°.

For all compounds, data collection: *KappaCCD Server Software* (Nonius, 1997); cell refinement: *DENZO–SMN* (Otwinowski & Minor, 1997); data reduction: *DENZO–SMN*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2002); software used to prepare material for publication: *SHELXL*97 and *PRPKAPPA* (Ferguson, 1999).

X-ray data were collected at the EPSRC X-ray Crystallographic Service, University of Southampton, England; the authors thank the staff for all their help and advice. JNL thanks NCR Self-Service, Dundee, for grants which have provided computing facilities for this work.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: NA1584). Services for accessing these data are described at the back of the journal.

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