

Hydrogen-bonded chains in isostructural 5-methyl-2-(4-methylphenyl)-7,8-dihydro-6*H*-cyclopenta[*g*]pyrazolo[1,5-*a*]pyrimidine, 2-(4-chlorophenyl)-5-methyl-7,8-dihydro-6*H*-cyclopenta[*g*]pyrazolo[1,5-*a*]pyrimidine, and sheets of π -stacked hydrogen-bonded chains in 2-(4-methoxyphenyl)-5-methyl-7,8-dihydro-6*H*-cyclopenta[*g*]pyrazolo[1,5-*a*]pyrimidine

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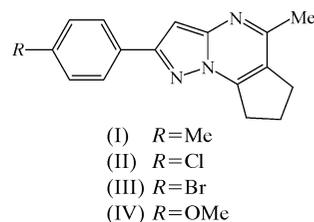
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5-Methyl-2-(4-methylphenyl)-7,8-dihydro-6*H*-cyclopenta[*g*]pyrazolo[1,5-*a*]pyrimidine, C₁₇H₁₇N₃, 2-(4-chlorophenyl)-5-methyl-7,8-dihydro-6*H*-cyclopenta[*g*]pyrazolo[1,5-*a*]pyrimidine, C₁₆H₁₄ClN₃, and 2-(4-bromophenyl)-5-methyl-7,8-dihydro-6*H*-cyclopenta[*g*]pyrazolo[1,5-*a*]pyrimidine, C₁₆H₁₄BrN₃, are isostructural; in each compound, the molecules are linked into chains by a single C—H··· π (arene) hydrogen bond. Molecules of 2-(4-methoxyphenyl)-5-methyl-7,8-dihydro-6*H*-cyclopenta[*g*]pyrazolo[1,5-*a*]pyrimidine, C₁₇H₁₇N₃O, are linked by a single C—H···N hydrogen bond into chains, which are themselves linked into sheets by a π – π stacking interaction.

Comment

Pyrazolo[1,5-*a*]pyrimidines are purine analogues which have shown useful properties as antimetabolites, and which have been of pharmaceutical interest because of their antitrypanosomal activity (Novinson *et al.*, 1976) and their anti-

schistosomal activity (Senga *et al.*, 1981). These interesting biological properties have prompted the search for new and efficient procedures of wide generality for the synthesis of pyrazolo[1,5-*a*]pyrimidine derivatives (Al-Shiekh *et al.*, 2004; Makarov *et al.*, 2005). We report here the structures of four cyclopenta[*g*]pyrazolo[1,5-*a*]pyrimidines, namely 5-methyl-2-(4-methylphenyl)-7,8-dihydro-6*H*-cyclopenta[*g*]pyrazolo[1,5-*a*]pyrimidine, (I), 2-(4-chlorophenyl)-5-methyl-7,8-dihydro-6*H*-cyclopenta[*g*]pyrazolo[1,5-*a*]pyrimidine, (II), 2-(4-bromophenyl)-5-methyl-7,8-dihydro-6*H*-cyclopenta[*g*]pyrazolo[1,5-*a*]pyrimidine, (III), and 2-(4-methoxyphenyl)-5-methyl-7,8-dihydro-6*H*-cyclopenta[*g*]pyrazolo[1,5-*a*]pyrimidine, (IV), prepared by solvent-free cyclocondensation reactions between 5-amino-1*H*-pyrazole derivatives and 2-acetylcyclopentanone, induced by microwave irradiation.



Compounds (I)–(III) form isomorphous crystals, and the compounds are isostructural. This fact is consistent with the similar steric requirements of methyl, chloro and bromo substituents, as reflected, for example, in the similar unit-cell dimensions of (I)–(III).

The corresponding bond lengths within the heterobicyclic fragments in compounds (I)–(IV) (Figs. 1–4) are very similar (Table 1), but the patterns of these bond distances show some

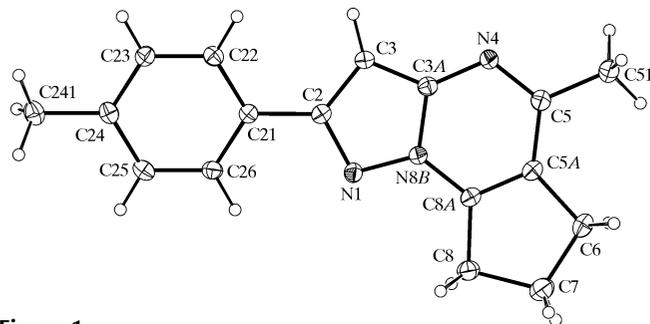


Figure 1
The molecule of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level.

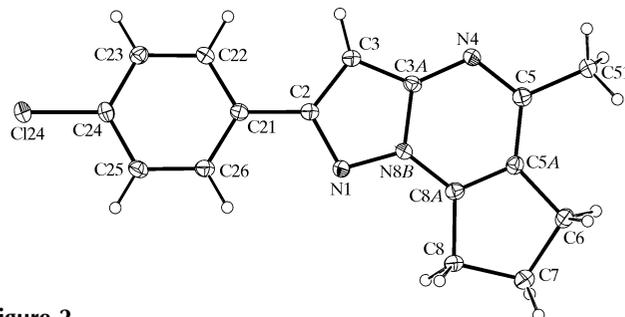


Figure 2
The molecule of (II), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level.

interesting properties. In each of (I)–(IV), the N1–C2 bond, which is formally a double bond, is not significantly shorter than the C3A–N4 and C8A–N8B bonds, both of which are formally single bonds; at the same time, the cross-ring bonds C3A–N8B are by far the longest C–N bond in any molecule. These observations, together with the clear bond fixation in the pyrimidine ring, suggest that the ten π electrons of the pyrazolopyrimidine units are not fully delocalized around the periphery, but instead adopt a more characteristic arrangement, reminiscent of that in naphthalene.

In all of these compounds, the five-membered carbocyclic ring has an envelope conformation, with the fold across the line C6··C8; the total puckering amplitude Q (Cremer & Pople, 1975) is larger in (III) [0.231 (4) Å] than in any of (I) [0.111 (3) Å], (II) [0.159 (3) Å] or (IV) [0.095 (2) Å], but in each case the ring-puckering parameter φ_2 [257.1 (14)° in (I), 255.0 (10)° in (II), 73.3 (8)° in (III) and 73.6 (8)° in (IV) for the atom sequence C5A–C6–C7–C8–C8A] is very close to the ideal value of $36n^\circ$ (Evans & Boeyens, 1989), with $n = 7$ in (I) and (II), and $n = 2$ in (III) and (IV). The 4-substituted C21–C26 aryl ring is nearly coplanar with the heterobicyclic ring system in each of (I)–(IV); thus, the dihedral angles between the aryl ring and the mean plane of the pyrazolopyrimidine ring system are 12.0 (2)° in (I), 14.5 (2)° in (II), 14.2 (2)° in (III) and 3.6 (2)° in (IV). In compound (IV), methoxy atom C241 is nearly coplanar with the aryl ring and, consistent with this, the exocyclic C–C–O angles at atom C24 show the usual deviations from 120° (Table 1).

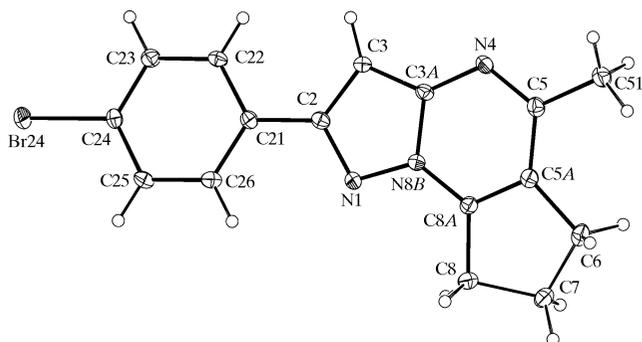


Figure 3
The molecule of (III), showing the atom-labelling scheme. For clarity, only the major orientation of the disordered CH₂ group is shown. Displacement ellipsoids are drawn at the 30% probability level.

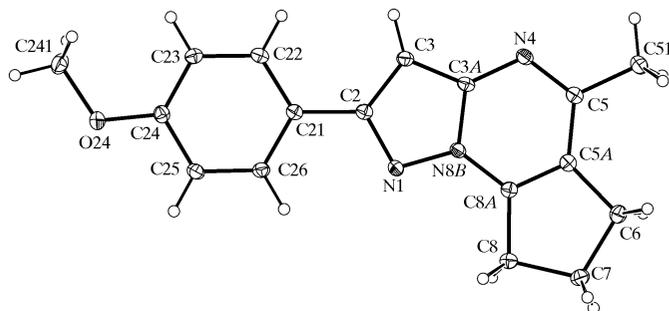


Figure 4
The molecule of (IV), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 30% probability level.

Despite the strong similarities between compounds (I)–(IV) in terms both of their overall constitutions and of their intramolecular geometries and conformations, the pattern of supramolecular aggregation in compound (IV) is very different from that in the isostructural trio (I)–(III), both from the point of view of the direction-specific interactions present and in terms of their overall supramolecular structures.

In each of compounds (I)–(III), the molecules are linked into chains by a single C–H·· π (arene) hydrogen bond (Table 2); atom C6 in the molecule at (x, y, z) acts as a donor, *via* atom H6A, to the pyrazole ring in the molecule at $(x, -1 + y, z)$, so generating by translation a chain running parallel to the [010] direction (Fig. 5). It should be noted that C–H··N and, in (II) and (III), C–H··halogen hydrogen bonds, as well as aromatic π – π stacking interactions, are all absent from the structures of (I)–(III).

By contrast, in compound (IV), the molecules are linked into chains by a C–H··N hydrogen bond (Table 2), and these chains are themselves linked into sheets by a π – π stacking interaction. Aryl atom C22 in the molecule at (x, y, z) acts as a hydrogen-bond donor to pyrimidine atom N4 in the molecule at $(1 - x, -\frac{1}{2} + y, \frac{1}{2} - z)$, so forming a C(7) chain running parallel to the [010] direction and generated by the 2₁ screw axis along $(\frac{1}{2}, y, \frac{1}{4})$ (Fig. 6). The π – π stacking interaction involves the fused heterocyclic rings of the molecules at (x, y, z) and $(1 - x, 2 - y, -z)$, where the interplanar spacing is

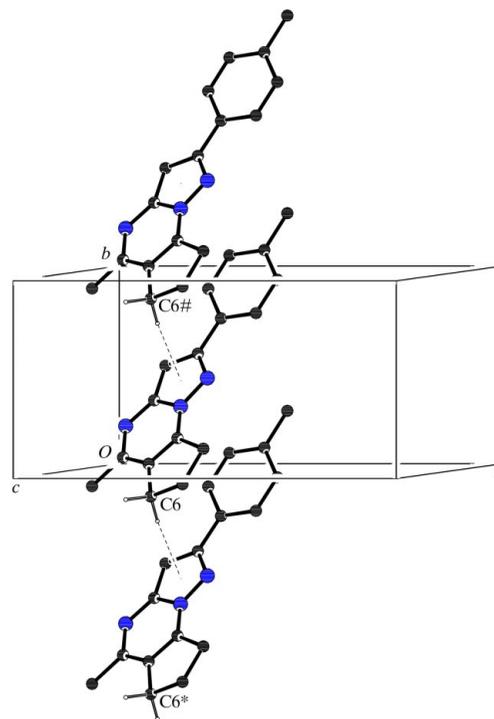


Figure 5
Part of the crystal structure of (I), showing the formation *via* C–H·· π (arene) hydrogen bonds (dashed lines) of a chain along [010]. For clarity, H atoms bonded to those C atoms that are not involved in the motif shown have been omitted. Atoms marked with an asterisk (*) or a hash (#) are at the symmetry positions $(x, -1 + y, z)$ and $(x, 1 + y, z)$, respectively. The [010] chains in (II) and (III) are essentially identical to that in (I).

3.504 (2) Å; the ring-centroid separation of the pyrazole and pyrimidine rings, respectively, is 3.577 (2) Å, corresponding to a ring-centroid offset of 0.719 (2) Å; the corresponding separation of the pyrimidine centroids is 3.799 (2) Å, with a centroid offset of 1.489 (2) Å. These two molecules lie in the $C(7)$ chains along $(\frac{1}{2}, y, \frac{1}{4})$ and $(\frac{1}{2}, y, -\frac{1}{4})$, respectively, and propagation by the space group of this stacking interaction generates a sheet lying parallel to (100) (Fig. 7).

It is striking that, although the substituents in the aryl rings, viz. 4-methyl in (I), 4-chloro in (II), 4-bromo in (III) and 4-methoxy in (IV), play no direct role whatever in the supramolecular aggregation, nonetheless the types of direction-specific intermolecular interaction apparent in the crystal structures of (I)–(III) are entirely different from those

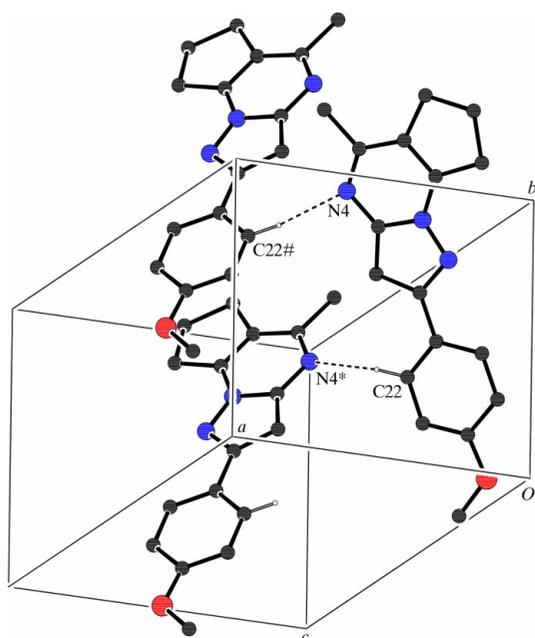


Figure 6
Part of the crystal structure of (IV), showing the formation *via* C–H...N hydrogen bonds (dashed lines) of a $C(7)$ chain along [010]. For clarity, H atoms not involved in the motif shown have been omitted. Atoms marked with an asterisk (*) or a hash (#) are at the symmetry positions $(1 - x, -\frac{1}{2} + y, \frac{1}{2} - z)$ and $(1 - x, \frac{1}{2} + y, \frac{1}{2} - z)$, respectively.

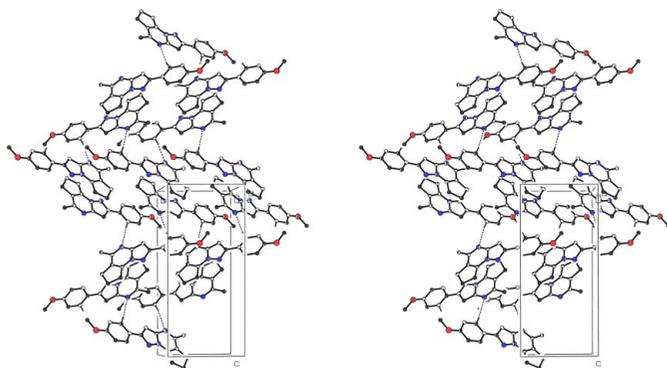


Figure 7
A stereoview of part of the crystal structure of compound (IV), showing the formation of a (100) sheet of π -stacked [010] chains. For clarity, H atoms not involved in the motif shown have been omitted.

apparent in the structure of (IV). The influence of these remote substituents on the supramolecular structures thus appears to be indirect and rather subtle, but real nonetheless; such subtle influences necessarily hinder the effective prediction of such structures.

Experimental

Equimolar mixtures of the appropriate 5-amino-3-aryl-1*H*-pyrazole (2.6 mmol) [where aryl is 4-methylphenyl for (I), 4-chlorophenyl for (II), 4-bromophenyl for (III) and 4-methoxyphenyl for (IV)] and 2-acetylcyclopentanone (2.6 mmol) were placed in open Pyrex glass vessels and irradiated in a domestic microwave oven for 1.5–2 min at 600 W. The product mixtures were extracted with ethanol and, after removal of the solvent, the resulting solids were recrystallized from dimethylformamide to give crystals of (I)–(IV) suitable for single-crystal X-ray diffraction. For (I), m.p. 512–513 K, yield 80%; MS (30 eV) m/z (%): 263 (100, M^+), 248 (4). For (II), m.p. 496–497 K, yield 83%; MS (30 eV) m/z (%): 285/283 (35/100, M^+), 268 (3), 241 (2). For (III), m.p. 496–497 K, yield 83%; MS (30 eV) m/z (%): 329/327 (97/100, M^+), 312 (3). For (IV), m.p. 497–498 K, yield 85%; MS (30 eV) m/z (%): 279 (100, M^+), 264 (27), 236 (7).

Compound (I)

Crystal data

$C_{17}H_{17}N_3$
 $M_r = 263.34$
Monoclinic, $P2_1/c$
 $a = 13.2882$ (7) Å
 $b = 6.8383$ (4) Å
 $c = 15.1947$ (8) Å
 $\beta = 104.018$ (3)°
 $V = 1339.60$ (13) Å³
 $Z = 4$

$D_x = 1.306$ Mg m⁻³
Mo $K\alpha$ radiation
Cell parameters from 3076 reflections
 $\theta = 3.2$ – 27.5°
 $\mu = 0.08$ mm⁻¹
 $T = 120$ (2) K
Needle, colourless
 $0.52 \times 0.08 \times 0.04$ mm

Data collection

Nonius KappaCCD diffractometer
 φ and ω scans
Absorption correction: multi-scan
(SADABS; Sheldrick, 2003)
 $T_{min} = 0.955$, $T_{max} = 0.997$
13947 measured reflections
3076 independent reflections

1640 reflections with $I > 2\sigma(I)$
 $R_{int} = 0.085$
 $\theta_{max} = 27.5^\circ$
 $h = -17 \rightarrow 16$
 $k = -8 \rightarrow 8$
 $l = -19 \rightarrow 19$

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.064$
 $wR(F^2) = 0.175$
 $S = 1.01$
3076 reflections
183 parameters
H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0891P)^2 + 0.0582P]$
where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{max} < 0.001$
 $\Delta\rho_{max} = 0.35$ e Å⁻³
 $\Delta\rho_{min} = -0.29$ e Å⁻³

Compound (II)

Crystal data

$C_{16}H_{14}ClN_3$
 $M_r = 283.75$
Monoclinic, $P2_1/c$
 $a = 13.6800$ (11) Å
 $b = 6.6669$ (6) Å
 $c = 15.2010$ (16) Å
 $\beta = 106.980$ (6)°
 $V = 1325.9$ (2) Å³
 $Z = 4$

$D_x = 1.421$ Mg m⁻³
Mo $K\alpha$ radiation
Cell parameters from 3040 reflections
 $\theta = 3.4$ – 27.6°
 $\mu = 0.28$ mm⁻¹
 $T = 120$ (2) K
Plate, colourless
 $0.34 \times 0.18 \times 0.03$ mm

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

	(I)	(II)	(III)	(IV)
N1–C2	1.348 (3)	1.349 (2)	1.351 (3)	1.3522 (16)
C2–C3	1.400 (3)	1.407 (3)	1.408 (4)	1.4047 (18)
C3–C3A	1.380 (3)	1.380 (3)	1.381 (4)	1.3858 (18)
C3A–N4	1.356 (3)	1.358 (3)	1.361 (3)	1.3622 (16)
N4–C5	1.333 (3)	1.328 (3)	1.335 (3)	1.3255 (17)
C5–C5A	1.418 (3)	1.419 (3)	1.417 (4)	1.4202 (18)
C5A–C8A	1.358 (3)	1.360 (3)	1.362 (4)	1.3614 (18)
C8A–N8B	1.354 (3)	1.345 (3)	1.353 (3)	1.3587 (16)
N8B–N1	1.357 (3)	1.355 (3)	1.355 (3)	1.3592 (14)
C3A–N8B	1.403 (3)	1.401 (3)	1.395 (3)	1.3928 (15)
C23–C24–O24				124.80 (12)
C25–C24–O24				115.26 (11)
C24–O24–C241				117.88 (10)
N1–C2–C21–C22	–168.1 (2)	–166.2 (2)	–166.4 (2)	176.30 (11)
C23–C24–O24–C241				3.40 (18)

Data collection

Nonius KappaCCD diffractometer
 φ and ω scans
 Absorption correction: multi-scan
 (SADABS; Sheldrick, 2003)
 $T_{\min} = 0.922$, $T_{\max} = 0.992$
 14750 measured reflections
 3040 independent reflections

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.056$
 $wR(F^2) = 0.141$
 $S = 1.03$
 3040 reflections
 182 parameters
 H-atom parameters constrained

Compound (III)**Crystal data**

$C_{16}H_{14}BrN_3$
 $M_r = 328.21$
 Monoclinic, $P2_1/c$
 $a = 13.5387$ (6) Å
 $b = 6.8551$ (2) Å
 $c = 15.2767$ (7) Å
 $\beta = 105.708$ (2)°
 $V = 1364.87$ (10) Å³
 $Z = 4$

Data collection

Nonius KappaCCD diffractometer
 φ and ω scans
 Absorption correction: multi-scan
 (SADABS; Sheldrick, 2003)
 $T_{\min} = 0.242$, $T_{\max} = 0.942$
 18357 measured reflections
 3125 independent reflections

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.037$
 $wR(F^2) = 0.096$
 $S = 1.05$
 3125 reflections
 186 parameters
 H-atom parameters constrained

Table 2

Hydrogen bonds and short intramolecular contacts (Å, °) for compounds (I)–(IV).

C_g is the centroid of the N1/C2/C3/C3A/N8B ring.

Compound	$D-H \cdots A$	$D-H$	$H \cdots A$	$D \cdots A$	$D-H \cdots A$
(I)	$C6-H6A \cdots C_g^i$	0.99	2.94	3.902 (3)	163
(II)	$C6-H6A \cdots C_g^i$	0.99	2.87	3.820 (3)	160
(III)	$C6-H6A \cdots C_g^i$	0.99	2.99	3.942 (3)	161
(IV)	$C22-H22 \cdots N4^{ii}$	0.95	2.54	3.436 (2)	156

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

Compound (IV)**Crystal data**

$C_{17}H_{17}N_3O$
 $M_r = 279.34$
 Monoclinic, $P2_1/c$
 $a = 9.4691$ (3) Å
 $b = 8.1711$ (2) Å
 $c = 18.0278$ (6) Å
 $\beta = 95.3430$ (14)°
 $V = 1388.80$ (7) Å³
 $Z = 4$

$D_x = 1.336$ Mg m⁻³

Mo $K\alpha$ radiation

Cell parameters from 3192

reflections

$\theta = 3.0$ – 27.5 °

$\mu = 0.09$ mm⁻¹

$T = 120$ (2) K

Block, colourless

$0.40 \times 0.38 \times 0.30$ mm

Data collection

Nonius KappaCCD diffractometer
 φ and ω scans
 Absorption correction: multi-scan
 (SADABS; Sheldrick, 2003)
 $T_{\min} = 0.956$, $T_{\max} = 0.975$
 16180 measured reflections
 3192 independent reflections

2520 reflections with $I > 2\sigma(I)$

$R_{\text{int}} = 0.033$

$\theta_{\text{max}} = 27.5$ °

$h = -12 \rightarrow 12$

$k = -9 \rightarrow 10$

$l = -18 \rightarrow 23$

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.042$
 $wR(F^2) = 0.126$
 $S = 1.06$
 3192 reflections
 193 parameters
 H-atom parameters constrained

$w = 1/[\sigma^2(F_o^2) + (0.0744P)^2$

$+ 0.2357P]$

where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{\text{max}} < 0.001$

$\Delta\rho_{\text{max}} = 0.28$ e Å⁻³

$\Delta\rho_{\text{min}} = -0.25$ e Å⁻³

Extinction correction: SHELXL97

Extinction coefficient: 0.028 (5)

For each of (I)–(IV), the space group $P2_1/c$ was uniquely assigned from the systematic absences. All H atoms were located from difference maps in fully ordered sites; they were then treated as riding atoms, with C–H distances of 0.95 (aromatic), 0.98 (methyl) or 0.99 Å (CH₂), and with $U_{\text{iso}}(\text{H})$ values of 1.2 $U_{\text{eq}}(\text{C})$, or 1.5 $U_{\text{eq}}(\text{C})$ for the methyl groups. For compounds (I) and (II), although not for (IV), the displacement parameters for atom C7 were somewhat higher than those of neighbouring C atoms, and were consistent with an enhanced vibrational amplitude approximately normal to the C6–C8 plane and tangential to the envelope fold. For compound (III), it was necessary to model this atom and its associated H atoms over two sets of sites, with refined occupancies of 0.853 (17) and 0.147 (17). The crystals of compound (III) are very fragile, and attempts to cut small fragments from larger crystals always resulted in shattering.

For all compounds, data collection: COLLECT (Hooft, 1999); cell refinement: DENZO (Otwinowski & Minor, 1997) and COLLECT; data reduction: DENZO and COLLECT; program(s) used to solve structure: WinGX (Farrugia, 1999) and SIR92 (Altomare *et al.*, 1993) for (I), (II) and (III), and OSCAIL (McArdle, 2003) and SHELXS97 (Sheldrick, 1997) for (IV); 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: SK1849). Services for accessing these data are described at the back of the journal.

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