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Five (1*H*-pyrrol-2-yl)pyridines

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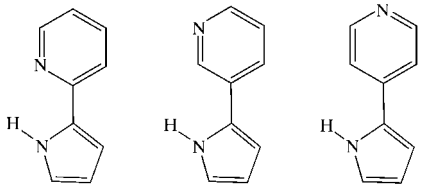
The title (1*H*-pyrrol-2-yl)pyridines, $C_9H_8N_2$, substituted at the *ortho, meta*, and *para* positions of the pyridine ring all have hydrogen-bonded arrangements with geometrically similar, nearly linear, N(pyrrole)—H···N(pyridine) hydrogen bonds of average length. The graph sets for the *ortho, meta*, and three *para* polymorphs are $R_2^2(10)$, $C(6)$, $C(7)$, $C(7)$, and $R_4^4(28)$, respectively.

Comment

Pyrroles and other simple heteroaromatic nuclei are of interest in biology and medicine, and are used widely as ligands for transition metal complexes, including porphyrins and synthetic analogs (Klappa *et al.*, 2002). Polypyrroles are of interest as conducting polymers (Wilson, 1977; de Jesus, 1996; Kanatzidis, 1990). We became interested in the (1*H*-pyrrol-2-yl)pyridines substituted in the *ortho*, (I), *meta*, (II), and *para*, (III), positions with respect to the N atom of the pyridine nucleus. We report here the crystal structures of (I), (II), and three polymorphs of (III), *viz*. (III*A*), (III*B*) and (III*C*). There are two molecules in the asymmetric unit of each of the three polymorphs of (III).



The atomic labeling and the anisotropic displacement ellipsoids for the five structures are shown as part of the packing diagrams in Figs. 1–5. The bond lengths and angles are normal, and vary slightly in the pyridine rings, depending in a reasonable way on the point of attachment of the pyrrole ring, and agreed, within experimental error, in all eight determinations of the pyrrole-ring geometry.

The rings were all planar, with dihedral angles between the rings as follows: (I) 15.5 (2)°, (II) 13.6 (2)°, (III*A*) 14.8 (2) and 13.3 (2)°, (III*B*) 12.1 (2) and 5.0 (2)°, and (III*C*) 16.8 (5)/8.3 (5) (two orientations of the disordered ring) and 0.8 (2)°. The disordered rings in (III*C*) are tilted in opposite directions to the plane of the pyrrole ring.

In all five structures, the molecules are held together by N8—H···N1 hydrogen bonds. The metrical parameters for these bonds are given in Table 1. All of the N—H···N bonds are close to linear and of average length.

In (I), there is an intramolecular N8—H···N1 contact, with N—H···N = 93°, H···N = 2.06 Å, and N···N = 2.786 (2) Å. Although the N···N distance in this contact is shorter than the intermolecular N···N distances in all of the compounds, the geometry of the arrangement, with an N—H···N angle of 93°, suggests that it is less important. The intermolecular hydrogen-bond arrangement is shown in Fig. 1. Two molecules form a dimer across a twofold axis. In graph-set notation (Etter *et al.*, 1990), this is an $R_2^2(10)$ arrangement.

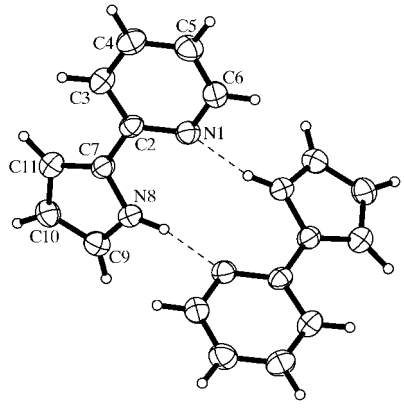


Figure 1
The intermolecular H···N contacts (dashed lines) in (I). Displacement ellipsoids are shown at the 50% probability level and H atoms are shown as small spheres of arbitrary radius.

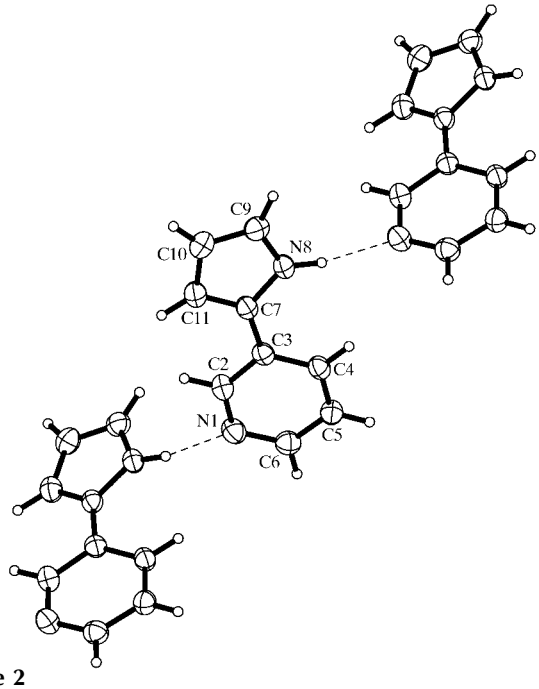


Figure 2
The intermolecular H···N contacts (dashed lines) in (II). Displacement ellipsoids are shown at the 50% probability level and H atoms are shown as small spheres of arbitrary radius.

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The hydrogen bonding in (II) is shown in Fig. 2. There are chains, with graph set $C(6)$, lying along the [101] direction, with the molecules related by the *n* glide.

The hydrogen bonding in polymorph *A* of (III) is shown in Fig. 3. There are chains, with graph set $C(7)$, parallel to the *b* axis alternating between the crystallographically independent *A* and *B* molecules. The *A* and *B* molecules are not related by any pseudosymmetry. Pairs of molecules in the chain are related by translation along *b*. Although the molecules are crystallographically independent, there is no significant difference in their hydrogen-bonding behavior.

The hydrogen bonding in polymorph *B* of (III) is shown in Fig. 4. There are chains, with graph set $C(7)$, parallel to the *c* axis alternating between the crystallographically independent *A* and *B* molecules. As in (III*A*), there is no pseudosymmetry relating the two independent molecules and no significant difference in their hydrogen-bonding behavior. Adjacent pairs of *A* and *B* molecules in the chain are related by the *c* glide.

The bonding in polymorph *C* of (III) is shown in Fig. 5. There are four-membered rings, with graph set $R_4^4(28)$, surrounding a center of symmetry, with alternating crystallographically independent *A* and *B* molecules. As a consequence of the molecular ring, the *A* and *B* molecules are related by a pseudo-fourfold symmetry axis, but this does not lead to more extended pseudosymmetry.

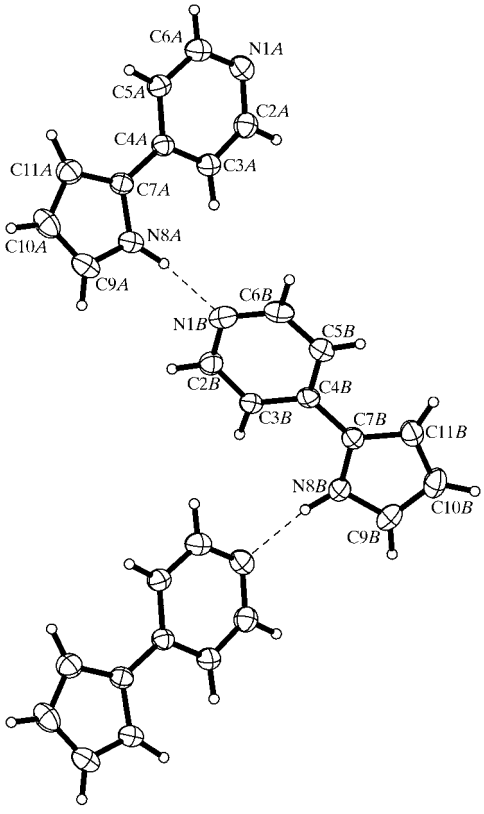


Figure 3
The intermolecular H···N contacts (dashed lines) in polymorph *A* of (III). Displacement ellipsoids are shown at the 50% probability level and H atoms are shown as small spheres of arbitrary radius.

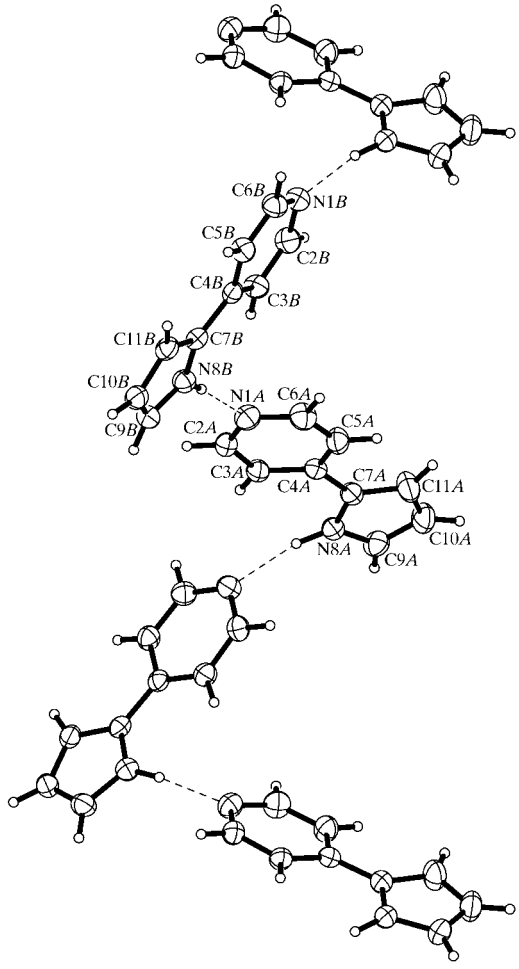


Figure 4
The intermolecular H···N contacts (dashed lines) in polymorph *B* of (III). Displacement ellipsoids are shown at the 50% probability level and H atoms are shown as small spheres of arbitrary radius.

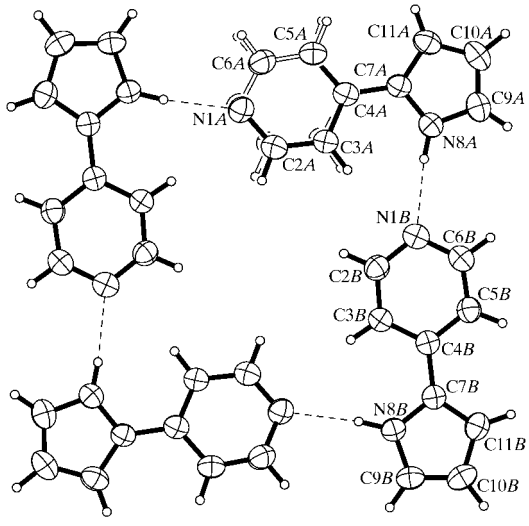
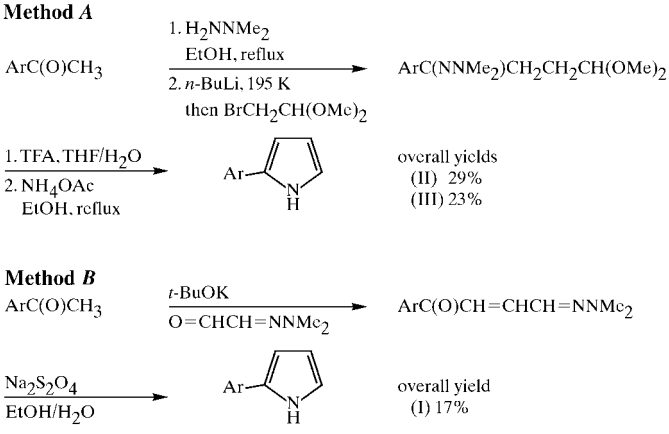


Figure 5
The intermolecular H···N contacts (dashed lines) in polymorph *C* of (III). Displacement ellipsoids are shown at the 50% probability level and H atoms are shown as small spheres of arbitrary radius. The disorder in the pyridine ring of molecule *A* is shown only in the labeled molecule.

A comparison of the cell volumes of (III*A*), (III*B*), and (III*C*) [1495.6 (7), 1513.8 (7), and 1488.0 (7) Å^3, respectively] suggests that at low temperature the (III*C*) form is the most stable and the (III*B*) form the least stable (Dunitz, 1995).

Experimental

The (1*H*-pyrrol-2-yl)pyridines (I)–(III) are well known compounds, and (I) is an inhibitor of prolyl 4-hydroxylase (Dowell *et al.*, 1993). We chose methods that were (i) inexpensive, (ii) relatively high-yielding, and (iii) easily applied to acetophenones in order to generate a large variety of 2-aryl-1*H*-pyrroles for medicinal chemistry studies. A variation of the Knorr pyrrole synthesis (see *Scheme* below, method *A*) was suitable for easy formation of (II) and (III) (Kruse *et al.*, 1987). The starting methyl ketones are, in general, inexpensive and readily available, and the intermediates require minimal purification. The synthesis of (I) was more difficult. Method *A* failed due to a very poor yield in the alkylation step and failure of the *N*,*N*-dimethylhydrazone to hydrolyze under several conditions. The problem was solved by preparing and utilizing 1-aryl-4-(*N*,*N*-dimethylhydrazono)-2-buten-1-ones (Severin *et al.*, 1975) in two steps (see *Scheme* below, method *B*). The aldol step is rapid, but the cyclization step proceeded in lower yield, due in part, at least, to loss of product (I) because of its extremely high volatility. The literature melting points follow the usual pattern for aromatic compounds, with the *para*-isomer having the highest melting point, *viz*. 447–448 K (CCl_4; Afonin *et al.*, 2000); *cf.* the *meta*-isomer melting point of 373–375 K (benzene–petroleum ether; Pictet & Crepieux, 1895) and the *ortho*-isomer melting point of 361–362 K (petroleum ether; Petrova *et al.*, 1997). The R_F values (SiO_2, 1:1 EtOAc, hexanes) among the isomers rose sharply from *para* (0.04) to *meta* (0.16) to *ortho* (0.49).



The initial attempt to grow crystals of (III) was carried out by recrystallization of a slightly impure sample (light brown in color) from methanol. The crystals were a mixture of dendrites and tear-shaped crystals. The sample was purified further; new crystals grown from acetonitrile appeared to be satisfactory for X-ray diffraction and the structure of (III*A*) was determined. It was then decided to check the unit cells of the original crystals. A needle, cut from a dendrite, had a different cell; the structure was determined as (III*B*). A tear-shaped crystal had a still different cell; the structure was determined as (III*C*). The melting point of (III*A*) was 445–447 K, in agreement with the literature value. The melting points of (III*B*) and (III*C*) were essentially the same, *viz*. 444–446 and 442–443 K, respectively, although both samples had shown some decomposition at about 430 K.

Table 1
Distances and angles (Å, °) for the N8—H···N1 contacts in the five title compounds (I)–(III*C*).

	D	*A*	*D*—H	*D*—H···*A*	H···*A*	*D*···*A*
(I)	N8	N1^{i}	0.91	163	2.06	2.949
(II)	N8	N1^{ii}	0.93	169	1.99	2.901
(III*A*)	N8*A*	N1*B*	0.97	171	1.95	2.913
(III*A*)	N8*B*	N1^{iii}	0.93	161	2.03	2.920
(III*B*)	N8*A*	N1*B*^{iv}	0.96	168	1.94	2.891
(III*B*)	N8*B*	N1*A*	0.95	167	1.99	2.920
(III*C*)	N8*A*	N1*B*	0.91	174	2.07	2.976
(III*C*)	N8*B*	N1*A*^{v}	0.95	174	2.08	3.021
(III*C*)	N8*B*	N1*A*′^{v}	0.95	169	2.02	2.956

† Note: the s.u. values are N8—H and H···N1 = 0.02 Å, N8—H···N1 = 1° and N8···N1 = 0.002–0.003 Å. Symmetry codes: (i) $1-y, 1-x, \frac{1}{2}-z$; (ii) $-\frac{1}{2}+x, \frac{1}{2}-y, -\frac{1}{2}+z$; (iii) $x, -1+y, z$; (iv) $x, \frac{1}{2}-y, -\frac{1}{2}+z$; (v) $-x, 1-y, 1-z$.

Compound (I)

Crystal data

$C_9H_8N_2$
M_r = 144.17
Tetragonal, $P4_32_12$
a = 8.123 (2) Å
c = 23.502 (6) Å
V = 1550.7 (7) Å^3
Z = 8
D_x = 1.235 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 3961 reflections
θ = 2.6–26.4°
μ = 0.08 mm^{-1}
T = 173 (2) K
Prism, colorless
0.50 × 0.20 × 0.20 mm

Data collection

Siemens SMART area-detector diffractometer
ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996; Blessing, 1995)
T_{min} = 0.97, T_{max} = 0.99
18 079 measured reflections
1115 independent reflections
1052 reflections with $I > 2\sigma(I)$
R_{int} = 0.048
θ_{max} = 27.5°
$h = -10 \rightarrow 10$
$k = -10 \rightarrow 10$
$l = -30 \rightarrow 30$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.044
$wR(F^2)$ = 0.100
S = 1.16
1115 reflections
104 parameters
H atoms: see below
$w = 1/[\sigma^2(F_o^2) + (0.044P)^2 + 0.304P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.006
$\Delta\rho_{max}$ = 0.13 e Å^{-3}
$\Delta\rho_{min}$ = −0.16 e Å^{-3}

Compound (II)

Crystal data

$C_9H_8N_2$
M_r = 144.17
Monoclinic, $P2_1/n$
a = 5.3537 (13) Å
b = 11.654 (3) Å
c = 11.990 (3) Å
β = 98.10 (1)°
V = 740.6 (3) Å^3
Z = 4
D_x = 1.293 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 2058 reflections
θ = 2.4–27.0°
μ = 0.08 mm^{-1}
T = 174 (2) K
Needle, colorless
0.35 × 0.15 × 0.05 mm

Data collection

Siemens SMART area-detector diffractometer
ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996; Blessing, 1995)
T_{min} = 0.97, T_{max} = 0.99
4676 measured reflections
1681 independent reflections
1232 reflections with $I > 2\sigma(I)$
R_{int} = 0.030
θ_{max} = 27.5°
$h = -6 \rightarrow 6$
$k = -11 \rightarrow 15$
$l = -15 \rightarrow 14$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.044$
$wR(F^2) = 0.114$
$S = 1.02$
1681 reflections
105 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.058P)^2 + 0.116P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.19$ e Å^{-3}
$\Delta\rho_{min} = -0.17$ e Å^{-3}
Extinction correction: *SHELXTL*
Extinction coefficient: 0.022 (6)

Compound (III*A*)

Crystal data

$C_9H_8N_2$
$M_r = 144.17$
Monoclinic, $P2_1/n$
$a = 7.402$ (2) Å
$b = 11.480$ (3) Å
$c = 17.705$ (4) Å
$\beta = 96.23$ (1)°
$V = 1495.6$ (7) Å^3
$Z = 8$
$D_x = 1.281$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 2036 reflections
$\theta = 2.9$–25.4°
$\mu = 0.08$ mm^{-1}
$T = 173$ (2) K
Needle, colorless
0.50 × 0.10 × 0.06 mm

Data collection

Siemens SMART area-detector diffractometer
ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996; Blessing, 1995)
$T_{min} = 0.97$, $T_{max} = 0.99$
9224 measured reflections
3412 independent reflections
1933 reflections with $I > 2\sigma(I)$
$R_{int} = 0.052$
$\theta_{max} = 27.5°$
$h = -9 \rightarrow 9$
$k = -14 \rightarrow 14$
$l = -14 \rightarrow 22$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.047$
$wR(F^2) = 0.118$
$S = 0.92$
3412 reflections
208 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.058P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.22$ e Å^{-3}
$\Delta\rho_{min} = -0.21$ e Å^{-3}
Extinction correction: *SHELXTL*
Extinction coefficient: 0.0061 (13)

Compound (III*B*)

Crystal data

$C_9H_8N_2$
$M_r = 144.17$
Monoclinic, $P2_1/c$
$a = 15.139$ (4) Å
$b = 5.4945$ (14) Å
$c = 18.736$ (5) Å
$\beta = 103.76$ (1)°
$V = 1513.8$ (7) Å^3
$Z = 8$
$D_x = 1.265$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 2651 reflections
$\theta = 2.2$–25.8°
$\mu = 0.08$ mm^{-1}
$T = 173$ (2) K
Needle, pale yellow
0.50 × 0.05 × 0.05 mm

Data collection

Siemens SMART area-detector diffractometer
ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996; Blessing, 1995)
$T_{min} = 0.98$, $T_{max} = 1.00$
14 309 measured reflections
3452 independent reflections
2385 reflections with $I > 2\sigma(I)$
$R_{int} = 0.049$
$\theta_{max} = 27.5°$
$h = -19 \rightarrow 19$
$k = -7 \rightarrow 7$
$l = -24 \rightarrow 24$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.047$
$wR(F^2) = 0.098$
$S = 1.03$
3452 reflections
207 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.039P)^2 + 0.333P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.004$
$\Delta\rho_{max} = 0.21$ e Å^{-3}
$\Delta\rho_{min} = -0.17$ e Å^{-3}

Compound (III*C*)

Crystal data

$C_9H_8N_2$
$M_r = 144.17$
Monoclinic, $P2_1/c$
$a = 5.1519$ (13) Å
$b = 19.739$ (5) Å
$c = 14.694$ (4) Å
$\beta = 95.26$ (1)°
$V = 1488.0$ (7) Å^3
$Z = 8$
$D_x = 1.287$ Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 2761 reflections
$\theta = 2.8$–26.2°
$\mu = 0.08$ mm^{-1}
$T = 173$ (2) K
Irregular, pale yellow
0.45 × 0.15 × 0.05 mm

Data collection

Siemens SMART area-detector diffractometer
ω scans
Absorption correction: multi-scan (*SADABS*; Sheldrick, 1996; Blessing, 1995)
$T_{min} = 0.98$, $T_{max} = 1.00$
8607 measured reflections
2920 independent reflections
1985 reflections with $I > 2\sigma(I)$
$R_{int} = 0.042$
$\theta_{max} = 26.0°$
$h = -6 \rightarrow 6$
$k = -21 \rightarrow 24$
$l = -18 \rightarrow 14$

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.058$
$wR(F^2) = 0.111$
$S = 1.09$
2920 reflections
227 parameters
H atoms treated by a mixture of independent and constrained refinement
$w = 1/[\sigma^2(F_o^2) + (0.034P)^2 + 0.258P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.002$
$\Delta\rho_{max} = 0.15$ e Å^{-3}
$\Delta\rho_{min} = -0.12$ e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.0059 (13)

In all of the determinations, the H atoms were placed in idealized positions with respect to the attached atoms, except for those on the pyrrole N atoms, which were refined with isotropic displacement parameters. The *ortho* compound, (I), occurred in a non-centrosymmetric space group. However, with no atoms heavier than nitrogen in the structure, the absolute configuration could not be determined. The Friedel pairs were averaged for the final refinement. Disorder was found for the pyridine rings of molecule *A* in the (III*C*) polymorph; refinement using an ordered model with large anisotropic displacement parameters increased *R* from 0.057 to 0.061. The disorder parameter 0.475 (7) for the lesser component is not convincingly different from complete disorder. An intermolecular contact distance of 3.116 Å between atoms C2*A*′ and C5*A*′ in the next molecule along the *a* direction suggests that the two orientations probably alternate in adjacent molecules in this direction but are random between molecules in other directions.

For all compounds, data collection: *SMART* (Siemens, 1995); cell refinement: *SAINT* (Siemens, 1995); data reduction: *SAINT*; program(s) used to solve structure: *SHELXTL* (Sheldrick, 1994); program(s) used to refine structure: *SHELXTL*; molecular graphics:

SHELXTL; software used to prepare material for publication: *SHELXTL*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: KB1000). Services for accessing these data are described at the back of the journal.

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