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Four bromo-substituted pyrazoline and isoxazolinone spiro derivatives

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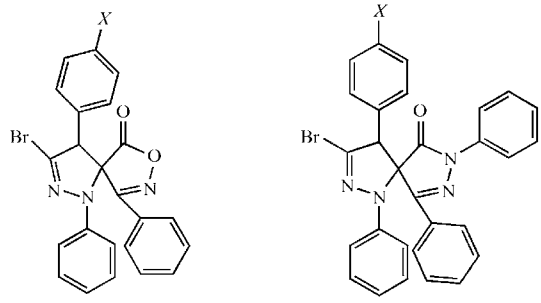
Conformational analyses and a structural comparison of the four spiro compounds 3-bromo-1,9-diphenyl-4-*p*-tolyl-7-oxa-1,2,8-triazaspiro[4.4]nona-2,8-dien-6-one, (I), $C_{24}H_{18}BrN_3O_2$, 3-bromo-4-(4-methoxyphenyl)-1,9-diphenyl-7-oxa-1,2,8-triazaspiro[4.4]nona-2,8-dien-6-one, (II), $C_{24}H_{18}BrN_3O_3$, 3-bromo-4-(4-chlorophenyl)-1,7,9-triphenyl-1,2,7,8-tetraazaspiro[4.4]-nona-2,8-dien-6-one, (III), $C_{29}H_{20}BrClN_4O$, and 3-bromo-1,7,9-triphenyl-4-*p*-tolyl-1,2,7,8-tetraazaspiro[4.4]nona-2,8-dien-6-one, (IV), $C_{30}H_{22.89}Br_{1.11}N_4O$, are presented. The molecular structures are rather similar, which is as expected since the compounds are all products of concerted 1,3-dipolar attack on (*Z*)-4-arylidene oxazolone and pyrazolone derivatives. The observed conformations tend to favour extended π conjugation of the benzene rings and other π systems, as shown by a comparison of selected geometric parameters of the four structures.

Comment

Spirans are organic compounds often present in natural products (Oh *et al.*, 2003). The creation of stereogenic quaternary C centres is a challenging task in organic chemistry, especially for spiro-centres (Hughes *et al.*, 2001). Because of their ability to generate a surrounding asymmetrical space, spirans have been exploited for asymmetric synthesis, molecular recognition and catalysis. The synthesis of biologically active heterocyclic spiro compounds (Negoro *et al.*, 1998) has mainly been addressed towards structures mimicking peptide β-turn secondary structures (Braña *et al.*, 2002). This is of particular interest when the rigidly mimicked conformation is also the bioactive one. Furthermore, the non-peptide nature of spiro compounds may prevent possible unwanted side effects (Khalil *et al.*, 1999).

The synthesis of a new dipolar intermediate, namely *C*-bromo-*N*-phenylnitrilimine, (Foti *et al.*, 1999), enabled us to obtain, by cycloaddition with selected dipolarophiles, 3-bromopyrazoles with interesting biopharmacological properties. The introduction of a Br substituent might increase the biological activity of related derivatives. In this context, we report the crystal structures of the four title bromo compounds, (I)–(IV). These spiro compounds are composed of substituted isoxazolinone or pyrazolinone rings, connected to pyrazoline rings through the asymmetric C5 spiro-centre. Beyond the spiro-centre, another asymmetric atom, C9, is present (Figs. 1–4). The conventional configuration label (Chan *et al.*, 1996) of this atom is always inverted with respect to the other asymmetric centre, C9. Therefore, the crystals of these compounds are (5*R*,9*S*)–(5*S*,9*R*) racemic mixtures, and all crystallize in centrosymmetric space groups.



The structures of (I) and (II) are very similar, as are those of (III) and (IV), as they differ only in the *para* substituent of the aromatic ring attached to C9. Since the four conformations are reasonably similar, we will discuss these two pairs together, reporting the four respective values for each mentioned geometric parameter or referring to the comparative table listed below (Table 4). The two core rings are oriented almost perpendicular to one another, with the angles between their mean planes being 89.0 (1), 88.5 (2), 87.7 (1) and 88.6 (2)°, respectively.

The isoxazolinone rings in (I) and (II), and the pyrazolinone rings in (III) and (IV), are less puckered [maximum deviations from the mean plane for atom C1 are 0.045 (4), 0.066 (6), 0.081 (4) and 0.040 (4) Å, respectively] than the corresponding pyrazoline rings, which show a slight envelope-like distortion: atom C5 is always above the mean plane, by

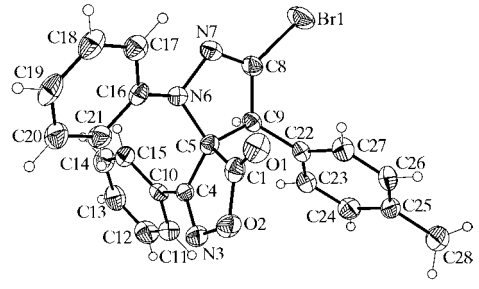


Figure 1
The (5*R*,9*S*)-isomer of (I), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 35% probability level and H atoms are shown as small spheres of arbitrary radii.

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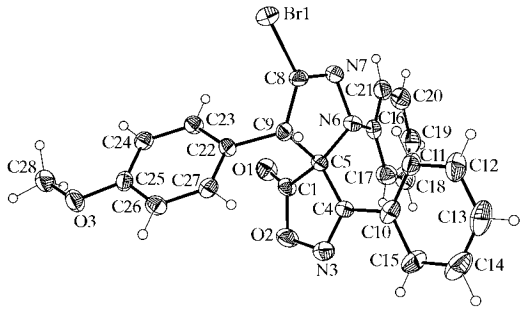

Figure 2
The (5*R*,9*S*)-isomer of (II), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 35% probability level and H atoms are shown as small spheres of arbitrary radii.

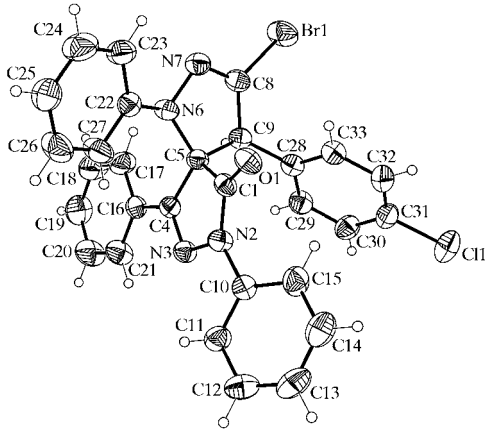

Figure 3
The (5*R*,9*S*)-isomer of (III), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 35% probability level and H atoms are shown as small spheres of arbitrary radii.

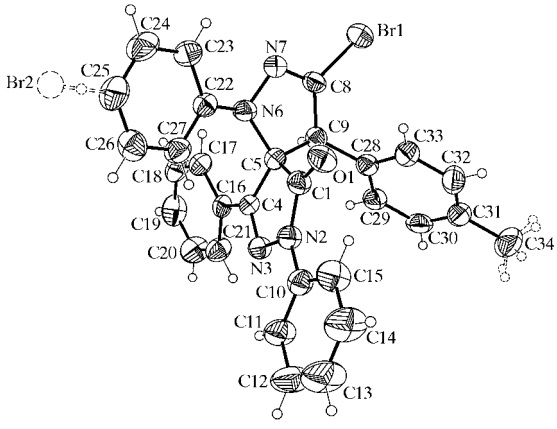

Figure 4
The (5*R*,9*S*)-isomer of (IV), showing the atom-labelling scheme. Displacement ellipsoids are drawn at the 35% probability level and H atoms are shown as small spheres of arbitrary radii. Dashed outlines indicate the disordered methyl group and Br atom.

0.197 (4), 0.094 (6), 0.142 (4) and 0.143 (4) Å, respectively. Cremer & Pople (1975) puckering parameters for the C5/N6/N7/C8/C9 ring are q_2 = 0.287 (3), 0.142 (5), 0.214 (4) and 0.239 (4) Å, respectively, and φ_2 = −5.9 (7), 5 (2), −2 (1) and −6 (1)°, respectively. This is expected because of the further chiral sp^3-hybridized endocyclic C atom present in pyrazolines.

The aromatic rings conjugated with endocyclic double bonds or sp^2-hybridized atoms tend to lie in the same plane as the attached core rings, developing extended π conjugations. On the other hand, these are partially hampered because of steric hindrance (see Table 4 for a comparison of torsion angles and angles between mean planes). These quasi-coplanar orientations of the aromatic rings are also supported by intramolecular dipolar interactions between aromatic *ortho*-H and electronegative N3, O1 and N7 atoms, which are sometimes cited as intramolecular hydrogen bonds (see Tables 1–3).

In compound (I), the packing is mainly characterized by an unusual intermolecular interaction between atom Br1 and the N3—O2 bond [Br1···O2^{i} = 3.310 (3) Å and Br1···N3^{i} = 3.377 (3) Å; symmetry code: (i) $\frac{3}{2}-x, y-\frac{1}{2}, z$], which may be interpreted as a stabilizing intermolecular combination between a Br atomic orbital and the lowest unoccupied molecular anti-bonding orbital centred on the C═N—O system of the next molecule along the crystallographic screw *b* axis (Fig. 4). Other weak dipolar interactions and a hydrogen bond (Table 1) contribute to the three-dimensional packing.

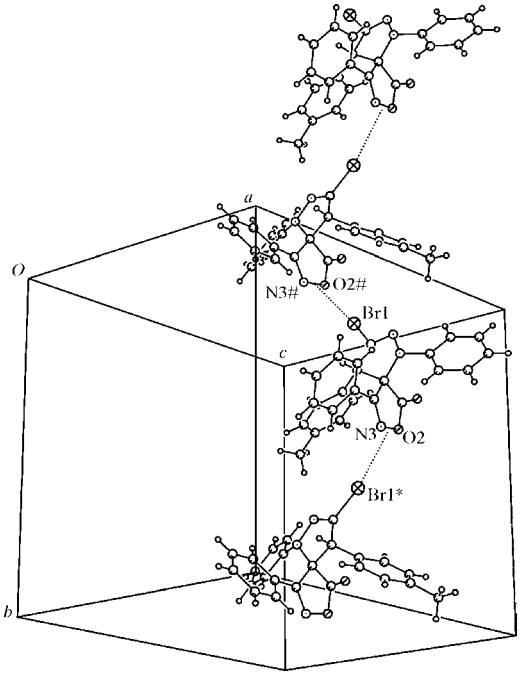

Figure 5
The crystal packing of (I), showing the intermolecular interactions between Br1 and atoms O2 and N3 of another molecule (dotted lines). Atoms marked with an asterisk (*) or hash (#) are at the symmetry positions ($\frac{3}{2}-x, y+\frac{1}{2}, z$) and ($\frac{3}{2}-x, y-\frac{1}{2}, z$), respectively.

In compound (II), the three-dimensional structure is generated by weak intermolecular dipolar interactions. As usual for these systems, there is an interaction between the carbonyl O atom and the methyl group of another molecule. Although it is too weak to be considered as a hydrogen bond [C28···O1 = 3.376 (9) Å and H28···O1 = 2.644 (5) Å, and C28—H28···O1 = 133.3 (4)°], it is doubled because it occurs between objects related by a symmetry inversion centre, thus forming dimers with an $R_2^2(22)$ first-order graph set (Fig. 5).

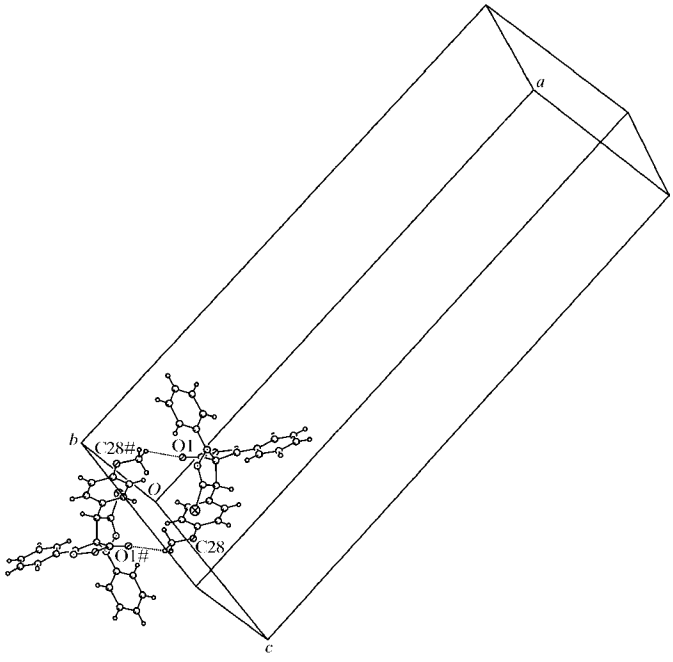

Figure 6
The crystal packing of (II), showing the weak interaction, doubled by the crystallographic inversion centre, stabilizing the dimers (dotted lines). Atoms marked with a hash (#) are generated through inversion.

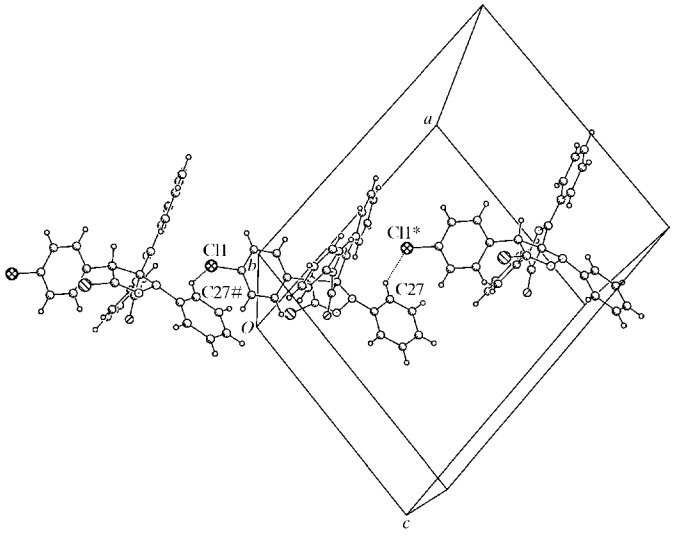

Figure 7
The crystal packing of (III), showing the formation of molecular chains along the [101] direction. Atoms marked with an asterisk (*) or hash (#) are at the symmetry positions $(x+\frac{1}{2}, \frac{3}{2}-y, z+\frac{1}{2})$ and $(x-\frac{1}{2}, \frac{3}{2}-y, z-\frac{1}{2})$, respectively.

The crystal packing of (III) is dominated by dipolar interactions. Among these, we mention the intermolecular interaction between atom H27 and the Cl atom of another molecule, which could be interpreted as a weak hydrogen-bond interaction, creating one-dimensional $C(11)$ chains along the [101] axis (Fig. 6).

The structure of (IV) presented more problems in the refinement because of the presence of small amounts (about 10–15%, varying across the several tested samples) of a side product which occupies the same crystallographic site, but bearing another Br atom substituted on the aromatic C25 atom (Fig. 3). These molecules are embedded in the lattice packing (atom Br2 interacts with the aromatic π system of other molecules). Several polar and dipolar interactions support the overall crystal packing.

Experimental

Products (I) and (II) were obtained from *C*-bromo-*N*-phenylnitrilimine, generated *in situ*, and (*Z*)-4-(arylmethylidene)oxazol-5-ones, as described previously by Foti *et al.* (2001). The same procedure, but using (*Z*)-4-(arylmethylidene)pyrazol-5-ones, led to the formation of (III) and (IV). After purification of the products, crystals suitable for X-ray analysis were obtained from chloroform solutions by slow evaporation.

Compound (I)

Crystal data

$C_{24}H_{18}BrN_3O_2$
M_r = 460.32
Orthorhombic, *Pbca*
a = 14.180 (2) Å
b = 16.076 (2) Å
c = 18.413 (2) Å
V = 4197.4 (9) Å^3
Z = 8
D_x = 1.457 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 30 reflections
θ = 5.3–12.5°
μ = 1.98 mm^{-1}
T = 298 (2) K
Irregular, light yellow
0.40 × 0.32 × 0.28 mm

Data collection

Bruker *P*4 diffractometer
$2\theta/\omega$ scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.414, T_{max} = 0.573
5243 measured reflections
4267 independent reflections
1805 reflections with $I > 2\sigma(I)$
R_{int} = 0.043
θ_{max} = 26.4°
$h = -1 \rightarrow 17$
$k = -1 \rightarrow 20$
$l = -1 \rightarrow 23$
3 standard reflections
every 197 reflections
intensity decay: none

Refinement

Refinement on F^2
$R(F)$ = 0.053
$wR(F^2)$ = 0.105
S = 1.00
4267 reflections
273 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0333P)^2 + 1.0734P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.003
$\Delta\rho_{max}$ = 0.26 e Å^{-3}
$\Delta\rho_{min}$ = −0.27 e Å^{-3}
Extinction correction: *SHELXL*97 (Sheldrick, 1997)
Extinction coefficient: 0.00148 (12)

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

D—H···A	D—H	H···A	D···A	D—H···A
C28—H28C···O1^{i}	0.96	2.55	3.482 (5)	163

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

Compound (II)

Crystal data

$C_{24}H_{18}BrN_3O_3$
M_r = 476.32
Monoclinic, $C2/c$
a = 35.375 (3) Å
b = 9.200 (1) Å
c = 12.807 (2) Å
β = 94.81 (1)°
V = 4153.2 (9) Å^3
Z = 8
D_x = 1.524 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 44 reflections
θ = 5.2–15.4°
μ = 2.01 mm^{-1}
T = 298 (2) K
Prismatic, yellow
0.50 × 0.23 × 0.15 mm

Data collection

Bruker $P4$ diffractometer
ω scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.388, T_{max} = 0.739
4814 measured reflections
4047 independent reflections
2153 reflections with $I > 2\sigma(I)$
R_{int} = 0.061
θ_{max} = 26°
$h = -1 \rightarrow 43$
$k = -11 \rightarrow 1$
$l = -15 \rightarrow 15$
3 standard reflections
every 197 reflections
intensity decay: none

Refinement

Refinement on F^2
$R(F)$ = 0.067
$wR(F^2)$ = 0.200
S = 1.08
4047 reflections
282 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.1P)^2$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 1.46 e Å^{-3}
$\Delta\rho_{min}$ = −0.38 e Å^{-3}

Compound (III)

Crystal data

$C_{29}H_{20}BrClN_4O$
M_r = 555.85
Monoclinic, $C2/c$
a = 16.735 (1) Å
b = 21.454 (2) Å
c = 14.254 (1) Å
β = 100.498 (6)°
V = 5032.3 (7) Å^3
Z = 8
D_x = 1.467 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 52 reflections
θ = 2.9–15.4°
μ = 1.77 mm^{-1}
T = 298 (2) K
Irregular, pale yellow
0.39 × 0.30 × 0.19 mm

Data collection

Bruker $P4$ diffractometer
ω scans
Absorption correction: empirical (North *et al.*, 1968)
T_{min} = 0.577, T_{max} = 0.714
5121 measured reflections
4365 independent reflections
2467 reflections with $I > 2\sigma(I)$
R_{int} = 0.023
θ_{max} = 25°
$h = -1 \rightarrow 19$
$k = -1 \rightarrow 25$
$l = -16 \rightarrow 16$
3 standard reflections
every 197 reflections
intensity decay: none

Refinement

Refinement on F^2
$R(F)$ = 0.049
$wR(F^2)$ = 0.104
S = 1.03
4365 reflections
327 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0238P)^2 + 11.4647P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.37 e Å^{-3}
$\Delta\rho_{min}$ = −0.32 e Å^{-3}
Extinction correction: *SHELXL*97
Extinction coefficient: 0.00045 (7)

Table 2
Short intramolecular contacts (Å, °) for (III).

D—H···A	D—H	H···A	D···A	D—H···A
C15—H15···O1	0.93	2.52	3.022 (6)	114
C21—H21···N3	0.93	2.48	2.802 (6)	100
C23—H23···N7	0.93	2.43	2.756 (6)	101

Compound (IV)

Crystal data

$C_{30}H_{22.89}Br_{1.11}N_4O$
M_r = 544.11
Monoclinic, $P2_1/c$
a = 10.107 (1) Å
b = 13.578 (3) Å
c = 19.146 (3) Å
β = 98.50 (1)°
V = 2598.6 (8) Å^3
Z = 4
D_x = 1.391 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 25 reflections
θ = 4.4–16.0°
μ = 1.78 mm^{-1}
T = 298 (2) K
Prismatic, colourless
0.36 × 0.34 × 0.18 mm

Data collection

Bruker $P4$ diffractometer
ω scans
Absorption correction: ψ scan (North *et al.*, 1968)
T_{min} = 0.459, T_{max} = 0.726
5812 measured reflections
4510 independent reflections
2455 reflections with $I > 2\sigma(I)$
R_{int} = 0.037
θ_{max} = 25°
$h = -1 \rightarrow 12$
$k = -16 \rightarrow 1$
$l = -22 \rightarrow 22$
3 standard reflections
every 197 reflections
intensity decay: none

Refinement

Refinement on F^2
$R(F)$ = 0.057
$wR(F^2)$ = 0.149
S = 1.02
4510 reflections
335 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.0641P)^2 + 0.8649P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.36 e Å^{-3}
$\Delta\rho_{min}$ = −0.45 e Å^{-3}

Table 3
Short intramolecular contacts (Å, °) for (IV).

D—H···A	D—H	H···A	D···A	D—H···A
C15—H15···O1	0.93	2.35	2.967 (7)	124
C11—H11···N3	0.93	2.39	2.742 (7)	102

The X-ray diffraction analyses gave an orthorhombic crystal system for (I), and monoclinic systems for (II), (III) and (IV). These space groups were hypothesized to be centrosymmetric during the data-reduction procedure and finally confirmed by the subsequent analyses. All H atoms were treated as riding, with alkyl C—H distances of 0.98 Å, methyl C—H distances of 0.96 Å and aromatic C—H distances of 0.93 Å, and with U_{iso}(H) = 1.2U_{eq}(C). All data were measured at 298 (2) K. For disordered methyl groups, a special *SHELXL*97 (Sheldrick, 1997) instruction, defining six sites with fractional occupancy factors (AFIX 127), was applied. Intensities, which in some cases were calculated by profile fitting (Lehman & Larsen, 1974), were corrected for absorption using the ψ-scan procedure (North *et al.*, 1968). During the refinement of the structure of (IV), we observed a consistent electron density (3.5 e Å^{-3}) 1.7 Å from atom C25. It is known that, during the reaction, atom C25

Table 4
Comparison of selected distances, torsion angles and angles between mean planes (Å, °) for (I), (II), (III) and (IV).

	(I)	(II)	(III)	(IV)
Br1—C8	1.864 (4)	1.873 (6)	1.870 (4)	1.878 (5)
O1—C1	1.189 (5)	1.181 (7)	1.201 (4)	1.198 (5)
N3—O2/N2†	1.454 (4)	1.451 (7)	1.408 (4)	1.397 (5)
N3—C4	1.286 (4)	1.275 (7)	1.288 (5)	1.298 (6)
C4—C10/C16	1.455 (5)	1.483 (8)	1.467 (5)	1.450 (6)
N6—N7	1.418 (4)	1.412 (7)	1.406 (4)	1.398 (5)
N6—C16/C22	1.422 (5)	1.420 (8)	1.428 (6)	1.404 (6)
N7—C8	1.273 (5)	1.272 (8)	1.272 (5)	1.257 (6)
N3—C4—C10/C16—C15/C21	146.3 (4)	8.4 (9)	1.8 (6)	−16.5 (7)
C5—C4—C10/C16—C15/C21	−43.2 (6)	−173.2 (6)	175.2 (4)	156.2 (5)
N3—C4—C10/C16—C11/C21	−32.6 (6)	−171.9 (6)	−177.2 (4)	163.2 (5)
C5—C4—C10/C16—C11/C21	138.0 (4)	6.5 (9)	−3.8 (7)	−24.1 (7)
N7—N6—C16/C22—C21/C23	175.0 (3)	9.8 (8)	6.6 (6)	16.4 (7)
C5—N6—C16/C22—C21/C23	−51.4 (5)	149.6 (6)	145.7 (4)	159.7 (4)
N7—N6—C16/C22—C17/C27	−2.2 (5)	−173.1 (5)	−175.6 (4)	−168.2 (4)
C5—N6—C16/C22—C17/C27	131.4 (4)	−33.3 (8)	−36.5 (6)	−24.9 (7)
O2/N2—N3—C4—C5	4.5 (5)	7.1 (7)	5.1 (5)	5.0 (5)
O2/N3—N3—C4—C10/C16	176.3 (3)	−174.3 (5)	179.5 (3)	178.9 (4)
Pyrazolone–N3Ph			23.8 (2)	5.2 (2)
Isox[pyr]azolone–C4Ph	36.9 (1)	9.2 (2)	0.9 (2)	19.7 (2)
Pyrazoline–N6Ph	27.7 (1)	24.2 (2)	20.4 (2)	9.9 (2)

† For pairs of atom labels, the first label applies to compounds (I) and (II), while the second label applies to compounds (III) and (IV).

could be brominated, leading to a known side product. Thus, despite the relatively short distance, the model was refined by optimizing the occupancy factor of a Br atom partially replacing atom H25. Although the resulting C—Br distance of 1.707 (8) Å is more reminiscent of a C—Cl distance, the mass spectrum of (IV) clearly showed the presence of the second Br substituent and unambiguously ruled out the presence of chlorine. In the final refinement, the occupancy factor of atom Br2 was found to be 0.11 and was fixed in order to reduce the number of parameters, so that in the solid state there are 11% of dibrominated molecules.

For all four compounds, data collection: *XSCANS* (Siemens, 1989); cell refinement: *XSCANS*; data reduction: *XPREPW* (Bruker, 1997); program(s) used to solve structure: *SIR*97 (Altomare *et al.*, 1994); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *XPW* (Bruker, 1997); software used to prepare material for publication: *PARST*97 (Nardelli, 1995) and *WinGX-PC* (Version 1.6.4.05; Farrugia, 1999).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GD1337). Services for accessing these data are described at the back of the journal.

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