Table 7. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2) *for* (4)

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
C1	0.1043 (2)	0.4572 (2)	0.61386 (6)	0.0342 (3)
C2	0.2579 (2)	0.4624 (2)	0.57131 (6)	0.0321 (3)
C3	0.4280 (2)	0.4675 (2)	0.60939 (6)	0.0336 (3)
C4	0.3585 (2)	0.4571 (2)	0.66829 (6)	0.0338 (3)
C5	0.2811 (3)	0.2640 (2)	0.67299 (7)	0.0413 (4)
C6	0.1046 (2)	0.2674 (2)	0.63845 (7)	0.0418 (4)
C7	0.1811 (2)	0.5704 (2)	0.66240 (6)	0.0356 (3)
C8	0.2174 (3)	0.7675 (2)	0.64843 (7)	0.0449 (4)
C9	0.0603 (3)	0.5665 (3)	0.71418 (8)	0.0548 (5)
C10	0.4969 (3)	0.5076 (3)	0.71197 (7)	0.0538 (5)
O11	0.58299 (14)	0.4758 (2)	0.59351 (5)	0.0515 (3)
O12	0.2617 (2)	0.31076 (14)	0.53659 (4)	0.0401 (3)
C13	0.3566 (3)	0.3644 (2)	0.48748 (7)	0.0472 (4)
C14	0.3011 (2)	0.5583 (2)	0.48052 (6)	0.0381 (3)
O15	0.2500 (2)	0.61384 (14)	0.53561 (4)	0.0404 (3)
C16	0.1360 (2)	0.5836 (3)	0.44410 (7)	0.0480 (4)
Cl17	0.19854 (7)	0.54743 (8)	0.37314 (2)	0.0592 (2)

Table 8. *Selected geometric parameters* (Å, °) *for* (4)

C2—O12	1.411 (2)	C14—O15	1.445 (2)
C2—O15	1.426 (2)	C14—C16	1.513 (2)
O12—C13	1.435 (2)	C16—Cl17	1.796 (2)
C13—C14	1.517 (2)		
O12—C2—O15	106.27 (11)	O15—C14—C13	104.07 (12)
C2—O12—C13	106.06 (12)	C16—C14—C13	113.62 (15)
O12—C13—C14	103.19 (12)	C2—O15—C14	108.56 (11)
O15—C14—C16	106.90 (13)	C14—C16—Cl17	109.30 (12)

Table 9. *Dioxolane ring torsion angles* (°), *deviation* (Å) *of flap atom from mean plane of remaining atoms, and r.m.s. deviation* (Å) *for this plane*

Results are given for both components of the disordered structure of (2).

	(1)	(2*a*)	(2*b*)	(3)	(4)
C2—O12—C13—C14	−39.4 (2)	28.5 (9)	−22.1 (6)	−34.4 (2)	−34.5 (2)
O12—C13—C14—O15	35.9 (2)	−15.0 (9)	33.3 (6)	25.0 (2)	23.8 (2)
C13—C14—O15—C2	−20.0 (2)	−4.4 (6)	−34.0 (4)	−7.1 (2)	−4.9 (2)
C14—O15—C2—O12	−3.6 (2)	23.1 (2)	23.1 (2)	−14.0 (2)	−16.3 (2)
O15—C2—O12—C13	27.6 (2)	−31.3 (5)	2.4 (5)	30.8 (2)	32.2 (2)
Flap atom	C13	O12	C14	O12	O12
Δ	0.576	0.454	0.574	0.469	0.476
r.m.s. Δ	0.016	0.019	0.010	0.032	0.022

For all compounds, data collection: *DIF*4 (Stoe & Cie, 1988); cell refinement: *DIF*4; data reduction: local programs; program(s) used to solve structure: *SHELXTL* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993); molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXL*93 and local programs.

We thank EPSRC and Shell for financial support.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: KA1114). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Acta Cryst. (1995). C**51**, 1829–1832

Bicyclic [*b*]-Heteroannulated Pyridazine Derivatives. 3. Partially Hydrogenated Triazolo[4,3-*b*]pyridazines

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(*Received* 15 *November* 1994; *accepted* 24 *February* 1995)

Abstract

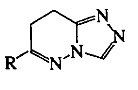
The structures of 6-benzyloxy-7,8-dihydro-8-phenyl-3-trifluoromethyl-*s*-triazolo[4,3-*b*]pyridazine, (1), and its isomer, 5-benzyl-5,6,7,8-tetrahydro-8-phenyl-3-trifluoromethyl-*s*-triazolo[4,3-*b*]pyridazin-6-one, (2), $C_{19}H_{15}F_3N_4O$, have been solved. The two molecules differ in the bonding at N5 and in the conformation of the pyridazine ring which contains this atom. This partially hydrogenated six-membered ring is puckered in both molecules, adopting a half-chair shape in (1) and a twist-boat shape in (2). In both molecules, the triazole ring and the mean plane of the pyridazine ring are not coplanar.

Comment

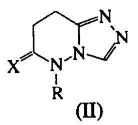
Many derivatives of bicyclic [*b*]-heteroannulated pyridazine are known as compounds of interesting biological activity. In particular, triazolo[4,3-*b*]pyridazines are classified as ligands of the benzodiazepine receptor with partial agonist activity (Lippa, Crichtett, Sano, Klepner, Greenblatt, Coupet & Beer, 1979; Albright, Moran, Wright Jr, Collins, Beer, Lippa & Greenblatt, 1981;

Doble & Martin, 1992; Borea, Gilli, Bertolasi & Ferretti, 1986) and constitute an interesting subject for studying the correlation between structure and affinity to the receptor (Karolak-Wojciechowska, Lange, Kwiatkowski, Gniewosz & Plenkiewicz, 1994). Since the structure–activity correlations can be based on structural and electronic parameters derived from a geometrical description of the molecule (Konschin, Tylli, Gynther & Rouvinen, 1989; Diaz-Arauzo, Koehler, Hagen & Cook, 1991), the three-dimensional structures and conformations of all investigated molecules have to be determined.

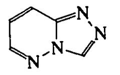
The geometry of the basic triazolo[4,3-*b*]pyridazine ring system (III), which is aromatic and therefore planar, is well known from crystallographic data (Bertolasi, Ferretti, Gilli & Borea, 1990; Boulanger, Ledent, Vercauteren, Norberg, Evrard & Durant, 1988; Golič, Leban, Stanovnik & Tišler, 1977, 1978; Boulanger, Ledent, Norberg, Vercauteren, Evrard & Durant, 1989; Larson, Yoghan Kang, Revankar & Robins, 1989), but no structures with a partially hydrogenated pyridazine ring [as in (I) and (II)] can be found in the Cambridge Structural Database (CSD; Allen, Kennard & Taylor, 1983). This prompted us to solve the structures of 6-benzyloxy-7,8-dihydro-8-phenyl-3-trifluoromethyl-*s*-triazolo[4,3-*b*]pyridazine, (1), and its 5-benzyl-6-oxo isomer, (2), which have been prepared recently by benzylation of 7,8-dihydro-8-phenyl-3-trifluoromethyl-*s*-triazolo[4,3-*b*]pyridazin-6(5*H*)-one (Lange, Karolak-Wojciechowska, Gniewosz & Plenkiewicz, 1994). Structure determination of these isomers by X-ray diffraction made it possible to establish the criteria for identifying the products of O *versus* N alkylation in the studied heterocyclic system by comparing the appropriate ^{1}H and ^{13}C NMR spectra (Lange *et al.*, 1994).



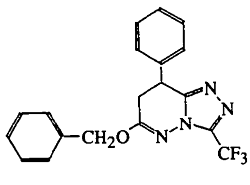
(I)



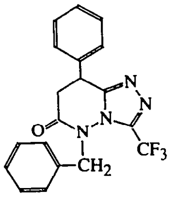
(II)



(III)

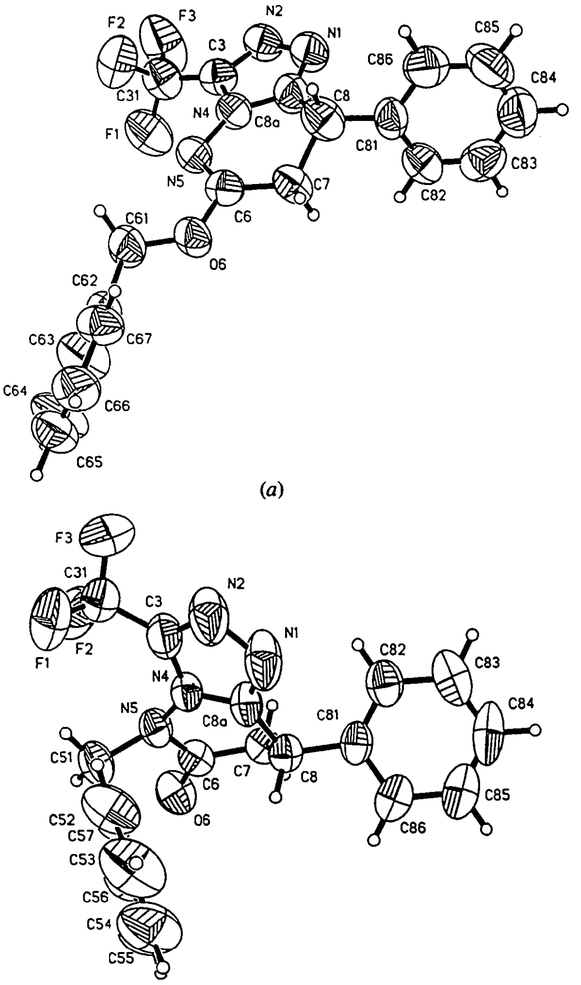


(1)



(2)

The molecules of (1) and (2) are depicted in Fig. 1. The phenyl and the five-membered triazole rings contain only conjugated π-electron bonds and are planar within experimental error. In both molecules, the geometry of the triazole rings is consistent with that of many related structures (Allen, Kennard & Taylor, 1983). The conformations of the non-planar six-membered partially hydrogenated (C7—C8) rings are significantly different. The O-alkylated compound (1) has a half-chair conformation with a twofold axis bisecting the N5—N4 and C7—C8 bonds (Fig. 1*a*), while in the N-alkylated isomer (2), the ring conformation can be described as a twist boat (Fig. 1*b*) with the best-fitted symmetry plane passing through the N4 and C7 atoms (Griffin, Duax & Weeks, 1984). The least-squares plane calculated for all six atoms of the heteroring forms a dihedral angle with the plane of the triazole moiety of 5.6 (1)° in (1) and 18.8 (2)° in (2). With the exception of N5, which is imidic in (1) and tetrahedral in (2), the atoms in the pyridazine ring have identical hybridization. In the CSD, we found only seven triazolo[4,3-*b*]pyridazines (Bertolasi *et al.*, 1990; Boulanger *et al.*, 1988, 1989; Golič *et al.*, 1977, 1978; Larson *et al.*, 1989), all with conjugated π-electron bonds in planar pyridazine and triazole rings [see (III) above]. In order to compare the conformations of the pyridazine rings, six torsion angles of each of the known seven structures were compared



(*a*)

(*b*)

Fig. 1. View of the molecules of (*a*) compound (1) and (*b*) compound (2), showing 50% probability displacement ellipsoids.

with values calculated for (1) and (2). In the planar molecules all angles are close to zero, while in (1) and (2) they are greater than 10° (Table 4). The particularly large angles, *T*1, *T*2 and *T*3 (see Table 4) are based on the sp^3 atoms C7 and C8. The remaining three angles in (1) and (2) are evidently smaller, as a result of the sp^2-hybridization of C8a and N4. The angle *T*4 of −5.9° in (1) is not significantly larger than that of the planar molecules, while in (2), *T*4 is 1.3°. The opposite signs of the *T*4 angle indicates that the atom N5, or C8, of one structure is on the opposite side of the planar triazole ring with respect to its disposition in the other structure, in accordance with the distance of the C8 atom from the triazole ring plane: −0.197 (5) in (1) and 0.208 (3) Å in (2).

Both molecules contain an equatorial phenyl substituent at C8. This ring is inclined to the triazole ring plane at 96.9 (1) and 46.6 (1)° in (1) and (2), respectively. The second phenyl ring, in the benzyl substituent, is inclined to the triazole ring at about 50° in both isomers (Table 2). All intermolecular contacts are longer than the sum of the van der Waals radii.

Experimental

The preparation of compounds (1) and (2) were performed according to the procedure described by Lange, Karolak-Wojciechowska, Gniewosz & Plenkiewicz (1994). Each set of crystals was grown by slow evaporation of an ethanol solution.

Compound (1)

Crystal data

$C_{19}H_{15}F_3N_4O$
$M_r = 372.35$
Monoclinic
$P2_1/c$
$a = 15.397\ (4)$ Å
$b = 9.696\ (3)$ Å
$c = 12.140\ (3)$ Å
$\beta = 104.43\ (2)°$
$V = 1755.2\ (8)$ Å^3
$Z = 4$
$D_x = 1.409$ Mg m^{-3}

Cu $K\alpha$ radiation
$\lambda = 1.54178$ Å
Cell parameters from 25 reflections
$\theta = 10–42°$
$\mu = 0.91$ mm^{-1}
$T = 293$ K
Needle
0.5 × 0.3 × 0.2 mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: none
3866 measured reflections
3490 independent reflections
1786 observed reflections $[F > 4\sigma(F)]$

$R_{\rm int} = 0.021$
$\theta_{\rm max} = 75°$
$h = 0 \rightarrow 18$
$k = 0 \rightarrow 11$
$l = -14 \rightarrow 14$
3 standard reflections monitored every 100 reflections intensity decay: 2%

Refinement

Refinement on *F*
$R = 0.073$
$wR = 0.071$
$S = 5.4$
1786 reflections
245 parameters
H-atom parameters not refined
$w = 1/\sigma^2(F)$
$(\Delta/\sigma)_{\rm max} = 0.02$

$\Delta\rho_{\rm max} = 0.619$ e Å^{-3}
$\Delta\rho_{\rm min} = -0.296$ e Å^{-3}
Extinction correction: $F_c^* = F_c(1 - gF_c^2/\sin\omega)$
Extinction coefficient: $g = 0.002$
Atomic scattering factors from *SHELXTL/PC* (Sheldrick, 1990)

Compound (2)

Crystal data

$C_{19}H_{15}F_3N_4O$
$M_r = 372.35$
Monoclinic
Cc
$a = 13.291\ (2)$ Å
$b = 16.973\ (3)$ Å
$c = 8.741\ (1)$ Å
$\beta = 114.16\ (1)°$
$V = 1799.0\ (1)$ Å^3
$Z = 4$
$D_x = 1.375$ Mg m^{-3}

Cu $K\alpha$ radiation
$\lambda = 1.54178$ Å
Cell parameters from 25 reflections
$\theta = 10–42°$
$\mu = 0.91$ mm^{-1}
$T = 293$ K
Needle
0.6 × 0.5 × 0.3 mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: none
2006 measured reflections
1935 independent reflections
1881 observed reflections $[F > 4\sigma(F)]$

$R_{\rm int} = 0.032$
$\theta_{\rm max} = 75°$
$h = 0 \rightarrow 16$
$k = 0 \rightarrow 21$
$l = -10 \rightarrow 9$
3 standard reflections monitored every 100 reflections intensity decay: 2%

Refinement

Refinement on *F*
$R = 0.053$
$wR = 0.059$
$S = 6.3$
1881 reflections
242 parameters
H-atom parameters not refined

$w = 1/[\sigma^2(F) + 0.000017F^2]$
$(\Delta/\sigma)_{\rm max} = 0.01$
$\Delta\rho_{\rm max} = 0.185$ e Å^{-3}
$\Delta\rho_{\rm min} = -0.208$ e Å^{-3}
Extinction correction: none
Atomic scattering factors from *SHELXTL/PC* (Sheldrick, 1990)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2) *for* (1)

$$U_{\rm eq} = (1/3)\Sigma_i\Sigma_jU_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	*y*	*z*	$U_{\rm eq}$
N1	0.5316 (3)	−0.1819 (4)	0.9228 (4)	0.067 (1)
N2	0.6005 (3)	−0.2393 (4)	1.0065 (4)	0.062 (1)
C3	0.6762 (3)	−0.1914 (5)	0.9942 (4)	0.051 (1)
N4	0.6613 (2)	−0.1032 (4)	0.9047 (3)	0.051 (1)
N5	0.7278 (2)	−0.0281 (4)	0.8696 (3)	0.051 (1)
C6	0.6946 (3)	0.0318 (5)	0.7754 (4)	0.048 (1)
C7	0.6005 (3)	0.0314 (5)	0.7059 (4)	0.055 (1)
C8	0.5312 (3)	0.0050 (6)	0.7714 (5)	0.075 (2)
C8a	0.5718 (3)	−0.1004 (5)	0.8630 (4)	0.061 (2)
O6	0.7496 (2)	0.1038 (3)	0.7267 (3)	0.052 (1)
C31	0.7635 (4)	−0.2249 (6)	1.0650 (5)	0.071 (2)
F1	0.8199 (2)	−0.2734 (4)	1.0091 (3)	0.110 (1)
F2	0.8052 (2)	−0.1164 (4)	1.1200 (3)	0.100 (1)
F3	0.7581 (2)	−0.3153 (4)	1.1432 (4)	0.132 (1)

C61	0.8436 (3)	0.1011 (5)	0.7844 (4)	0.064 (2)
C62	0.8941 (3)	0.1625 (6)	0.7070 (4)	0.055 (1)
C63	0.9584 (4)	0.0893 (7)	0.6753 (5)	0.093 (2)
C64	1.0068 (4)	0.1483 (8)	0.6051 (6)	0.111 (3)
C65	0.9901 (4)	0.2801 (6)	0.5677 (5)	0.080 (2)
C66	0.9251 (4)	0.3511 (5)	0.5979 (5)	0.071 (2)
C67	0.8780 (4)	0.2955 (5)	0.6679 (5)	0.067 (2)
C81	0.4399 (3)	−0.0379 (6)	0.7035 (4)	0.060 (1)
C82	0.4255 (4)	−0.1325 (5)	0.6146 (5)	0.062 (2)
C83	0.3418 (4)	−0.1652 (6)	0.5567 (5)	0.080 (2)
C84	0.2709 (4)	−0.1071 (8)	0.5818 (6)	0.097 (2)
C85	0.2815 (4)	−0.0118 (8)	0.6668 (6)	0.097 (3)
C86	0.3652 (4)	0.0251 (6)	0.7291 (5)	0.082 (2)

Table 2. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2) *for* (2)

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij}a_i^*a_j^*\mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	U_{eq}
N1	0.8751 (4)	−0.0170 (2)	0.4482 (6)	0.095 (1)
N2	0.9868 (5)	−0.0197 (3)	0.4888 (8)	0.109 (1)
C3	1.0124 (4)	0.0432 (3)	0.4272 (8)	0.079 (1)
N4	0.9210	0.0899 (2)	0.3550	0.057 (1)
N5	0.9124 (4)	0.1645 (2)	0.2834 (5)	0.060 (1)
C6	0.8064 (4)	0.1820 (2)	0.1616 (5)	0.059 (1)
C7	0.7227 (4)	0.1175 (2)	0.1183 (5)	0.057 (1)
C8	0.7230 (4)	0.0789 (2)	0.2779 (5)	0.055 (1)
C8a	0.8387 (4)	0.0493 (2)	0.3705 (6)	0.061 (1)
O6	0.7864 (4)	0.2477 (2)	0.1059 (5)	0.082 (1)
C31	1.1255 (5)	0.0585 (3)	0.4423 (9)	0.092 (1)
F1	1.1877 (3)	0.0897 (2)	0.5920 (6)	0.118 (1)
F2	1.1296 (3)	0.1103 (2)	0.3315 (6)	0.113 (1)
F3	1.1741 (4)	−0.0060 (3)	0.4244 (8)	0.156 (2)
C51	0.9733 (5)	0.2278 (2)	0.4016 (7)	0.071 (1)
C52	0.9251 (5)	0.2425 (2)	0.5304 (7)	0.072 (1)
C53	0.8402 (6)	0.2951 (3)	0.4948 (8)	0.095 (1)
C54	0.7894 (7)	0.3070 (4)	0.6067 (4)	0.116 (2)
C55	0.8264 (8)	0.2664 (5)	0.7500 (4)	0.125 (3)
C56	0.9086 (9)	0.2142 (4)	0.7896 (9)	0.121 (2)
C57	0.9632 (6)	0.2013 (3)	0.6783 (7)	0.100 (2)
C81	0.6349 (4)	0.0158 (2)	0.2337 (6)	0.061 (1)
C82	0.6477 (4)	−0.0581 (3)	0.1821 (6)	0.072 (1)
C83	0.5607 (6)	−0.1118 (3)	0.1358 (7)	0.092 (1)
C84	0.4627 (5)	−0.0895 (4)	0.1429 (8)	0.104 (2)
C85	0.4507 (5)	−0.0177 (4)	0.1931 (9)	0.101 (2)
C86	0.5361 (4)	0.0367 (3)	0.2403 (7)	0.081 (1)

Table 3. *Selected geometric parameters* (Å, °) *for compounds* (1) *and* (2)

(1)		(2)	
N4—N5	1.412 (5)	N4—N5	1.396 (5)
N5—C6	1.274 (6)	N5—C6	1.407 (6)
C6—O6	1.348 (6)	C6—O6	1.202 (5)
O6—C61	1.448 (5)	N5—C51	1.481 (5)
C61—C62	1.490 (8)	C51—C52	1.527 (10)
N4—N5—C6	110.4 (4)	N4—N5—C6	113.8 (4)
N5—C6—C7	128.8 (4)	N5—C6—C7	116.6 (4)
N5—C6—O6	118.5 (4)	N5—C6—O6	119.3 (4)
C7—C6—O6	112.7 (4)	C7—C6—O6	124.0 (4)

Table 4. *Dihedral angles between mean planes and torsion angles in the pyridazine ring* (°) *for* (1) *and* (2)

Plane *A*: triazole ring. Plane *B*: pyridazine ring. Plane *C*: phenyl ring at C8. Plane *D*: phenyl ring at C61 in (1) or C51 in (2). Torsion angles: *T*1 = N5—C6—C7—C8, *T*2 = C6—C7—C8—C8a, *T*3 = C7—C8—C8a—N4, *T*4 = C8—C8a—N4—N5, *T*5 = C8a—N4—N5—C6 and *T*6 = N4—N5—C6—C7.

	(1)	(2)
A/*B*	5.6 (1)	18.8
A/*C*	96.9 (1)	46.6 (1)
A/*D*	50.3 (1)	50.6 (2)
*T*1	25.4	47.4
*T*2	−36.8	−58.4
*T*3	29.5	31.6
*T*4	−5.9	11.3
*T*5	−11.3	−27.4
*T*6	0.8	−4.4

The structures were refined by full-matrix least squares. The positions of all the H atoms were found from a difference map and refined using a riding model with fixed isotropic displacement parameters ($1.5U_{eq}$ of the parent C atom).

Structure solution: *SHELXTL/PC* (Sheldrick, 1990). Structure refinement: *SHELXTL/PC*. Molecular graphics: *SHELXTL/PC*. Preparation of material for publication: *CSU*88 (Vicković, 1988).

A major part of this research was carried out under grant No. 4 4404 91 02 from the Committee for Scientific Research, Poland. This financial support is gratefully acknowledged.

Lists of structure factors, anisotropic displacement parameters and H-atom coordinates have been deposited with the IUCr (Reference: KA1108). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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