Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

4,6-Dimethyl-2-[(4-phenylpiperidin-1-yl)methyl]isothiazolo[5,4-*b*]pyridin-3(2*H*)-one and 4,6-dimethyl-2-[(4-phenyl-1,2,3,6-tetrahydropyridin-1-yl)methyl]isothiazolo[5,4-*b*]pyridin-3(2*H*)-one

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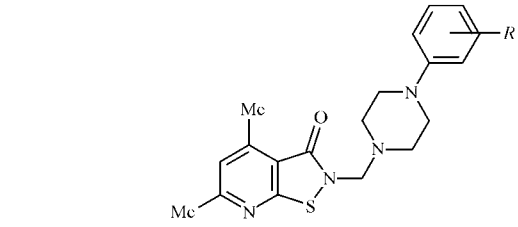
Received 18 May 2007
Accepted 25 June 2007
Online 26 July 2007

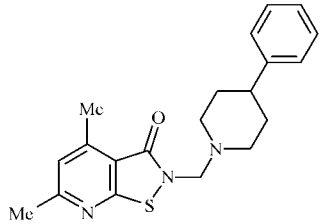
In the crystal structures of the title compounds, $C_{20}H_{23}N_3OS$, (II), and $C_{20}H_{21}N_3OS$, (III), significant differences occur in the conformation of, respectively, the phenylpiperidine and phenyltetrahydropyridine substituents at the 2-position of the isothiazolopyridine system. The piperidine ring adopts a chair conformation, while the tetrahydropyridine ring assumes a half-chair form. The phenylpiperidine and phenyltetrahydropyridine fragments exhibit different conformations resulting from the steric and conjugation effects in the phenyl ring, respectively. Theoretical calculations show that both conformations are energetically stable and correspond to a minimum of energy for the analyzed systems. The molecular packing in (II) is influenced by π–π interactions of the isothiazolopyridine systems, with a shortest centroid-to-centroid separation of 3.5843 (11) Å between pyridine rings. In the crystal structure of (III), the molecules are linked by C—H···O hydrogen bonds and C—H···π interactions.

Comment

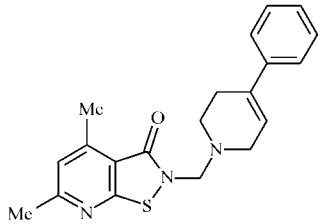
The 4-arylpiperazinyl group is known to constitute part of the pharmacophore for many pharmacologically active heterocycles (Barlocco *et al.*, 2001; Viaud *et al.*, 1995). In previous reports, we have described the syntheses of 2-[(4-arylpiperazin-1-yl)methyl]isothiazolo[5,4-*b*]pyridin-3(2*H*)-ones and detailed the evolution of their analgesic properties (Malinka *et al.*, 2001, 2005). The results of the bioanalyses showed that the unsubstituted parent compound (I*a*) was inactive in analgesic tests. A systematic modification of (I*a*) by a substitution (*R*) on the aromatic ring of the 4-phenylpiperazinyl system showed that the presence of electron-withdrawing substituents [2-Cl in (I*b*), 2-F in (I*c*), 3-CF_3 in (I*d*) and 4-NO_2 in (I*e*)] led to isothiazolopyridines active in this assay. In contrast, the use of electron-donating groups [2-OCH_3 in (I*f*) and 2-CH_3 in (I*g*)] reduced analgesic action.



(I*a*) *R*=H (I*b*) *R*=2-Cl (I*c*) *R*=2-F (I*d*) *R*=3-CF_3
(I*e*) *R*=4-NO_2 (I*f*) *R*=2-OCH_3 (I*g*) *R*=2-CH_3 (I*h*) *R*=5-Cl-2-CH_3
(I*i*) *R*=2-OC_2H_5



(II)



(III)

The X-ray crystallographic data for isothiazolopyridines (I) (Karczmarzyk & Malinka, 2005) showed that for the unsubstituted compound (I*a*) and its derivatives with electron-withdrawing substituents 3-CF_3, (I*d*), and 4-NO_2, (I*e*), a lone pair on the piperazine 4-N atom forms part of a 4-N–aromatic ring π system. The near coplanarity of the piperazine and benzene rings observed in (I*a*), (I*d*) and (I*e*) is constrained by the occurrence of this effect. In *ortho*-substituted compounds [2-Cl in (I*b*), 2-OCH_3 in (I*f*), 5-Cl-2-CH_3 in (I*h*), 2-OC_2H_5 in (I*i*) and 2-CH_3 in (I*g*)], the 4-N–Ar conjugation is very weak or not present. The nearly perpendicular orientation of the piperazine and aromatic rings within these compounds is the result of an *ortho* steric hindrance effect. X-ray data also indicated that a chair conformation of the piperazine ring might be considered as a pharmacophoric conformation for analgesic isothiazolopyridines of type (I).

To find out whether replacement of the 4-N atom of the piperazine ring by a methylene or a vinyl C atom in the inactive compound (I*a*) induces analgesic action, we prepared the analogues (II) and (III) (Figs. 1 and 2), and determined the conformation of the piperidine rings and the effect of the Ar–

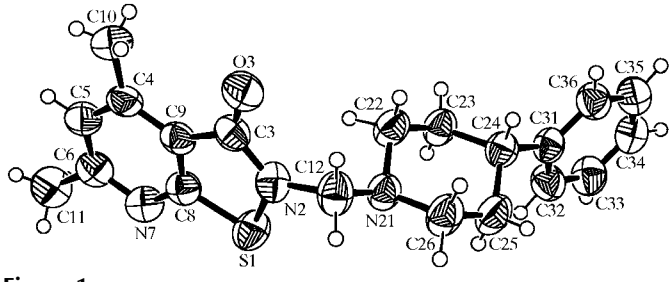


Figure 1
A view of (II), showing the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level. H atoms are represented as small spheres of arbitrary radii.

 DOI: 10.1107/S0108270107031071

piperidine conjugation for these compounds. In pharmacological investigation, compound (III), to our surprise, exhibited significant analgesic action (Malinka *et al.*, 2005). Evaluation of the analgesic activity of (II) is in progress.

The geometry (bond lengths, angles and planarity) of the isothiazolopyridine system is very similar in (II) and (III) and the related structures (I*a*), (I*b*) and (I*d*)–(I*i*). The conformation of the phenylpiperidine and phenyltetrahydropyridine substituents is described by the torsion angles S1—N2—C12—N21 of 56.69 (18) and 25.74 (16)°, N2—C12—N21—C22 of 69.03 (19) and 78.47 (16)°, and N2—C12—N21—C26 of −168.97 (16) and −157.01 (13)° for (II) and (III), respectively. Comparison of these torsion angles with those found in (I*a*) [24.5 (2), 77.9 (2) and −159.4 (2)°, respectively] shows nearly the same *cis–gauche–trans* conformation of the substituent in (I*a*) and (III) and a somewhat different *gauche–gauche–trans* conformation in (II) (Fig. 3).

The piperidine ring in (II) adopts a chair conformation, while the occurrence of the double bond in the tetrahydropyridine ring of (III) favours a half-chair conformation. The puckering parameters (Cremer & Pople, 1975) are Q = 0.581 (2) Å and θ = 179.5 (2)° for the piperidine ring, and Q = 0.515 (1) Å, θ = 128.2 (2)° and φ = −157.1 (2)° for the tetrahydropyridine ring. The bond lengths and angles in the phenylpiperidine system of (II) are normal, and the conjugation effect between the electron systems of the piperidine and benzene rings characteristic for (I*a*) does not occur. The mutual, nearly perpendicular, orientation of the piperidine and benzene rings, described by the C23—C24—C31—C32 torsion angle of −71.9 (2)°, is constrained by steric interaction of the H atoms of the methylene and methine groups. In (III), a weak conjugation of the vinyl bond C24═C25 in the tetrahydropyridine ring with the π-electron system of the benzene ring is observed. The double bond of 1.344 (2) Å is longer than expected for a Csp^2═Csp^2 bond in cyclohexene [1.326 (12) Å; Allen *et al.*, 1987], and the C25—C24—C31—C32 torsion angle of 175.07 (16)° confirms the occurrence of this conjugation, while the C24—C31 bond length of 1.489 (2) Å, comparable to an average Csp^2—C_{ar} (C═C—C_{ar}; unconjugated) single bond of 1.488 (12) Å (Allen *et al.*, 1987), is more characteristic for an unconjugated system.

Because the orientation of the piperidine ring in (II), the tetrahydropyridine ring in (III) and the piperazine ring in (I*a*) with respect to the benzene ring is strictly connected with the steric and conjugation effects, the energy for free rotation on the N24—C31 or C24—C31 bond, taking account of the one degree of freedom described by the C23—N(C)24—C31—C32 torsion angle (ψ), was calculated for isolated molecules of (I*a*), (II) and (III) using the AM1 semi-empirical SCF–MO method (Dewar *et al.*, 1985) implemented in the program package *WINMOPAC* (Shchepin & Litvinov, 1998). The differences in heat of formation, ΔH, of the conformations were calculated after energy minimization and optimization of all geometrical parameters for each rotation, with a 10° increment from −180 to +180° of ψ (Fig. 4). The calculation showed that the energy differences between rotamers, of

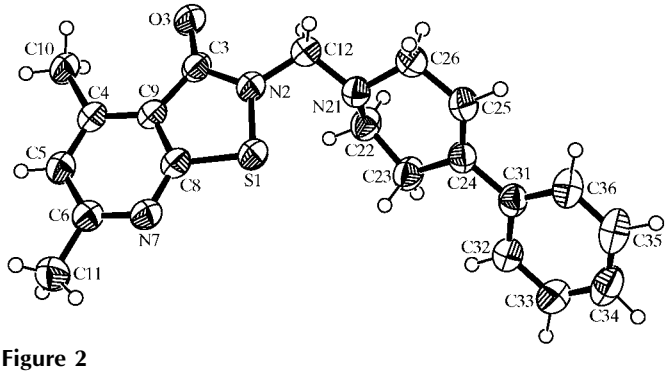


Figure 2
A view of (III), showing the atomic numbering scheme. Displacement ellipsoids are drawn at the 50% probability level. H atoms are represented as small spheres of arbitrary radii.

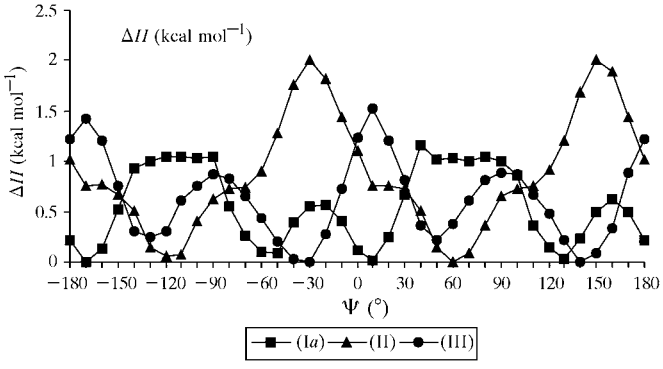


Figure 4
The energy effect upon C(N)24—C31 rotation as calculated using the AM1 semi-empirical method.

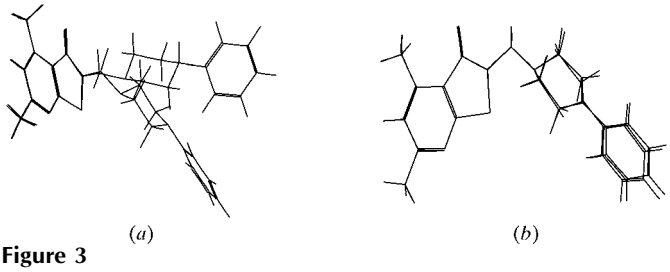


Figure 3
Overlays of (*a*) molecules (I*a*) and (II), and (*b*) molecules (I*a*) and (III) by least-squares fitting of the isothiazolopyridine ring systems [the average deviation of atoms is 0.029 and 0.004 Å for (*a*) and (*b*), respectively].

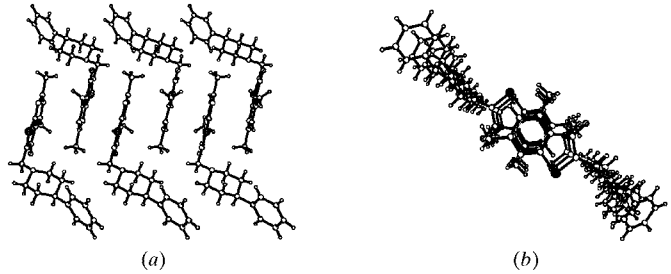


Figure 5
A view of part of the crystal structure of (II) along (*a*) [100] and (*b*) [010], showing the formation of a column of stacked pyridine rings.

about 1.0, 2.0 and 1.5 kcal mol^{-1} for (I*a*), (II) and (III), respectively, are relatively low, but certain tendencies in the energy minima distributions are visible. The conjugation of the vinyl bond in the tetrahydropyridine ring and the lone pair at the N atom of the piperazine ring with the π-electron system of the benzene ring gives the minimum of energy for ψ close to 0° in (I*a*) and −30° in (III). The lack of the mentioned conjugation in the phenylpiperidine system in (II) moves the minimum of energy to a ψ value of about 60°. The calculated conformations with minima of energy are in good agreement with those observed in the crystalline state of the investigated molecules.

There are no classical hydrogen bonds present in the crystal structure of (II). The molecular packing is influenced by the presence of weak π–π interactions (Spek, 2003). The pyridine rings of the isothiazolopyridine systems belonging to the inversion- and translation-related molecules overlap each other, forming molecular stacks in the [010] direction, with centroid-to-centroid separations of 3.5843 (11) Å between the pyridine rings at (x, y, z), and ($-x$, $-y$ + 1, $-z$ + 1), and 3.6498 (11) Å for the pyridine rings at (x, y, z) and ($-x$, $-y$ + 2, $-z$ + 1) (Fig. 5). The π–π distances are 3.405 and 3.555 Å, respectively, and are comparable to a van der Waals distance of about 3.4 Å for the overlapping π-aromatic ring systems. The packing of the molecules in the crystal structure of (III) is governed by C—H···O hydrogen bonds, linking the molecules into molecular chains parallel to the [010] direction, and C—H···π interactions (Table 1). In conclusion, (i) the small difference in rotation energy within the aryl-piperazine(piperidine) systems of isothiazolopyridines (I*a*), (II) and (III) allows the side chain to adopt any spatial shape under physiological conditions, and (ii) the analgesic activity of piperidine derivative (III) suggests that the 4-N piperazine atom of analgesic isothiazolopyridines (I) is not protonated in the bioactive form of these compounds. Therefore, an electrostatic potential on the piperazine N atoms cannot be ruled out when analyzing the biological properties of the compounds of series (I).

Experimental

Compound (III) was prepared from 2-hydroxymethyl-4,6-dimethyl-isothiazolo[5,4-*b*]pyridin-3(2*H*)-one and commercially available 4-phenyl-1,2,3,6-tetrahydropyridine according to the method described by Malinka *et al.* (2005). Compound (II) was obtained similarly. The chemical experimental data for the preparation of (II), along with its physicochemical and spectral data (^{1}H NMR), are given in supporting material, available on request. Crystals suitable for X-ray diffraction analysis were grown by slow evaporation from a hexane solution.

Compound (II)

Crystal data

$C_{20}H_{23}N_3OS$
M_r = 353.47
Monoclinic, $C2/c$
a = 29.384 (6) Å
b = 7.146 (1) Å
c = 21.750 (4) Å
β = 126.39 (3)°
V = 3676.4 (18) Å^3
Z = 8
Cu $K\alpha$ radiation
μ = 1.66 mm^{-1}
T = 293 (2) K
0.55 × 0.42 × 0.20 mm

Data collection

Bruker SMART APEX CCD diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2002)
T_{min} = 0.498, T_{max} = 0.733
19486 measured reflections
3471 independent reflections
3267 reflections with $I > 2\sigma(I)$
R_{int} = 0.020

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.046
$wR(F^2)$ = 0.207
S = 1.00
3471 reflections
229 parameters
H atoms refined by a mixture of constrained and independent refinement
$\Delta\rho_{max}$ = 0.21 e Å^{-3}
$\Delta\rho_{min}$ = −0.29 e Å^{-3}

Compound (III)

Crystal data

$C_{20}H_{21}N_3OS$
M_r = 351.46
Monoclinic, $P2_1/c$
a = 17.548 (3) Å
b = 11.007 (2) Å
c = 9.033 (2) Å
β = 93.83 (3)°
V = 1740.8 (6) Å^3
Z = 4
Cu $K\alpha$ radiation
μ = 1.75 mm^{-1}
T = 293 (2) K
0.35 × 0.13 × 0.10 mm

Data collection

Bruker SMART APEX CCD diffractometer
Absorption correction: multi-scan (*SADABS*; Sheldrick, 2002).
T_{min} = 0.635, T_{max} = 0.845
19164 measured reflections
3279 independent reflections
3192 reflections with $I > 2\sigma(I)$
R_{int} = 0.017

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.039
$wR(F^2)$ = 0.114
S = 1.05
3279 reflections
289 parameters
Only H-atom coordinates refined
$\Delta\rho_{max}$ = 0.24 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °) for (III).

CgA, *CgB* and *CgC* are the centroids of the pyridine, isothiazole and benzene rings, respectively.

D—H···A	D—H	H···A	D···A	D—H···A
C10—H103···O3^{i}	0.89 (2)	2.59 (2)	3.450 (2)	160.9 (18)
C10—H102···*CgA*^{ii}	1.01 (2)	2.783 (19)	3.4919 (19)	127.7 (15)
C22—H222···*CgB*^{iii}	1.01 (2)	2.88 (2)	3.831 (2)	155.4 (16)
C26—H261···*CgC*^{iv}	0.93 (2)	2.90 (3)	3.784 (2)	159.1 (18)

Symmetry codes: (i) $-x, y+\frac{1}{2}, -z+\frac{3}{2}$; (ii) $-x, -y+2, -z+1$; (iii) $-x+1, -y+1, -z+1$; (iv) $x, -y+\frac{1}{2}, z-\frac{3}{2}$.

All H atoms in (II) were treated as riding on their parent C atoms, with C—H distances of 0.93 (aromatic), 0.96 (CH_3), 0.97 (CH_2) and 0.98 Å (CH), and U_{iso}(H) values of 1.5U_{eq}(C). In (III), the H atoms were located in a difference Fourier map and their coordinates were refined isotropically [C—H = 0.88 (3)–1.02 (3) Å and U_{iso}(H) = 1.5U_{eq}(C)].

For both compounds, data collection: *SMART* (Bruker, 2003); cell refinement: *SAINT* (Bruker, 2003); data reduction: *SAINT*; program(s) used to solve structure: *SIR92* (Altomare *et al.*, 1993); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *ORTEP-3 for Windows* (Farrugia, 1997) and *XP* in *SHELXTL-Plus* (Sheldrick, 1989); software used to prepare material for publication: *SHELXL97* and *WinGX* (Farrugia, 1999).

The authors express their thanks to Professor J. Karolak-Wojciechowska from the Institute of General and Ecological

Chemistry, Technical University in Łódź, for her kind consent to use the *XP* program.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: TR3017). Services for accessing these data are described at the back of the journal.

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