C26—C9—C8	123.1 (5)	O22—C22—C21	122.7 (6)
C10—C9—C8	119.8 (5)	O22—C22—C23	115.9 (5)
O10—C10—C11	119.3 (5)	C21—C22—C23	121.3 (5)
O10—C10—C9	120.2 (5)	O23—C23—C24	120.1 (6)
C11—C10—C9	120.4 (5)	O23—C23—C22	119.6 (5)
C12—C11—C10	121.2 (5)	C24—C23—C22	120.2 (6)
C12—C11—O11	122.3 (5)	O24—C24—C23	120.8 (5)
C10—C11—O11	116.6 (5)	O24—C24—C1	119.0 (5)
O12—C12—C11	115.0 (5)	C23—C24—C1	120.2 (6)
O12—C12—C13	125.1 (5)	C7—C25—C3	123.3 (5)
C11—C12—C13	119.8 (5)	C13—C26—C9	124.3 (5)
C26—C13—C12	117.2 (5)	C15—C27—C19	124.5 (5)
C26—C13—C14	122.9 (5)	C21—C28—C1	123.7 (5)

Table 4. *Hydrogen-bonding geometry (Å, °) for (II)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O4—H4···O24	0.82 (4)	2.00 (4)	2.763 (6)	155 (4)
O6—H6···O10	0.82 (3)	2.04 (2)	2.812 (6)	157 (2)
O10—H10···O6	0.82 (5)	2.28 (4)	2.812 (6)	123 (4)
O11—H11···O4*W*	0.82 (4)	1.99 (4)	2.710 (6)	145 (2)
O12—H12···O16	0.82 (2)	1.93 (2)	2.750 (5)	176 (2)
O16—H16···O17	0.82 (4)	2.26 (3)	2.701 (6)	114 (2)
O16—H16···O1S	0.82 (4)	1.94 (3)	2.708 (5)	156 (3)
O17—H17···O18	0.82 (5)	2.38 (3)	2.797 (6)	113 (3)
O18—H18···O2S	0.82 (3)	1.90 (4)	2.711 (7)	169 (3)
O22—H22···O23	0.82 (4)	2.21 (5)	2.674 (7)	116 (3)
O1S—H1S···O16	0.82 (3)	1.98 (3)	2.708 (6)	146 (3)
O1S—H1S···O17	0.82 (4)	2.31 (4)	2.955 (6)	135 (3)
O5—H5···O4*W*^{i}	0.82 (3)	2.18 (3)	2.980 (7)	167 (2)
O24—H24···O1S^{i}	0.82 (5)	1.81 (5)	2.612 (7)	166 (2)
O4*W*—H4*W*2···O5^{ii}	0.94 (4)	2.28 (5)	2.980 (7)	130 (3)
O4*W*—H4*W*1···O4^{ii}	0.97 (4)	2.12 (4)	3.077 (6)	166 (3)

Symmetry codes: (i) $x, y-1, z$; (ii) $x, 1+y, z$.

The unit-cell parameters and intensity data were recorded at 150 K on a FAST area-detector diffractometer using the routines *ENDEX*, *REFINE* and *MADONL* in the *MADNES* software (Pflugrath & Messerschmidt, 1989); detailed procedures are described by Darr *et al.* (1993). Seven CH_2 groups (C32, C34, C36, C38, C45, C47 and C49) on two of the alkyl chains in (II) were orientationally disordered; these were refined with partial site occupancies. For both compounds, all non-H atoms were anisotropic; the displacement coefficients of several atoms belonging to the solvate species [C1*S*, C2*S* and C8*S* for (I), and O3*S*, C5*S* and C6*S* for (II)] were kept approximately isotropic using the restraint parameter *ISOR* = 0.01 in *SHELXL*93 (Sheldrick, 1993). For (II), the H atoms on C39 and C50 were ignored and those on the water molecule included in positions obtained from a difference map. Other H atoms in the two compounds were included in calculated positions (riding model) with U_{iso} set at 1.2 (CH and CH_2) and 1.5 (OH and CH_3) times the U_{eq} of the parent atoms. The bond-length restraints C—C = 1.50 (1) and C—O = 1.40 (1) Å were used for the solvate ethanol molecules in (II).

For both compounds, data collection: *MADNES*; cell refinement: *REFINE* in *MADNES*; data reduction: *ABSMAD* (Karaulov, 1991); program(s) used to solve structures: *SHELXS*86 (Sheldrick, 1990); program(s) used to refine structures: *SHELXL*93; molecular graphics: *SNOOPI* (Davies, 1983); software used to prepare material for publication: *SHELXL*93.

We thank the EPSRC and the University of Sheffield for support of this work.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: KA1222). Services for accessing these data are described at the back of the journal.

References

Adams, H., Davis, F. & Stirling, C. J. M. (1994). *J. Chem. Soc. Chem. Commun.* pp. 2527–2529.
Aoyama, Y., Yanaka, Y. & Sugahara, S. (1989). *J. Am. Chem. Soc.* **111**, 5397–5404.
Beer, P. D., Smyth, A. C., Tite, E. L. & Ibbotson, A. (1989). *J. Organomet. Chem.* **376**, C11–C14.
Cram, D. J. & Cram, J. M. (1994). In *Container Molecules and Their Guests*. Cambridge: Royal Society of Chemistry.
Darr, J. A., Drake, S. R., Hursthouse, M. B. & Malik, K. M. A. (1993). *Inorg. Chem.* **32**, 5704–5708.
Davies, K. (1983). *SNOOPI. Molecular Plotting Program*. University of Oxford, England.
Davis, F., Gerber, M., Cowlam, N. & Stirling, C. J. M. (1996). *Thin Solid Films*, **284–285**, 678–682.
Davis, F. & Stirling, C. J. M. (1995). *J. Am. Chem. Soc.* **117**, 10385–10386.
Gutsche, C. D. (1989). In *Calixarenes*. Cambridge: Royal Society of Chemistry.
Holmes, J. & Tasker, P. A. (1990). European Patent No. 440 773; *Chem. Abstr.* **114**, 188903w.
Huisman, B. H., Van-Velzen, E. U. T., Van-Veggel, F. C. J. M., Engbersen, J. F. J. & Reinhoudt, D. N. (1995). *Tetrahedron Lett.* **36**, 3273–3276.
Karaulov, A. I. (1991). *ABSMAD. Program for FAST Data Processing*. University of Wales, Cardiff, Wales.
Leigh, D., Linnane, P., Pritchard, R. G. & Jackson, G. (1994). *J. Chem. Soc. Chem. Commun.* pp. 389–390.
Pflugrath, J. W. & Messerschmidt, A. (1989). *MADNES*. Version of 11 September 1989. Distributed by Delft Instruments, Delft, The Netherlands.
Sheldrick, G. M. (1990). *Acta Cryst.* A**46**, 467–473.
Sheldrick, G. M. (1993). *SHELXL*93. *Program for the Refinement of Crystal Structures*. University of Göttingen, Germany.
Van-Velzen, E. U. T., Engbersen, J. F. J., Delange, P. J., Mahy, J. W. G. & Reinhoudt, D. N. (1995). *J. Am. Chem. Soc.* **117**, 6853–6862.

Acta Cryst. (1998). C**54**, 992–994

4,6-Dimethyl-2-(4-phenylpiperazin-1-ylmethyl)isothiazolo[5,4-*b*]pyridin-3(2*H*)-one

ZBIGNIEW KARCZMARZYK[a] AND WIESŁAW MALINKA[b]

[a]Department of Chemistry, Agricultural and Teachers' University, ul. 3 Maja 54, PL-08 110 Siedlce, Poland, and [b]Department of Chemistry of Drugs, University of Medicine, ul. Tamka 1, PL-50 137 Wrocław, Poland. E-mail: kar@wsrp.siedlce.pl

(*Received 22 October 1997; accepted 22 January 1998*)

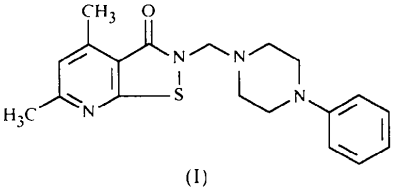
Abstract

The crystal structure of the title compound, $C_{19}H_{22}N_4OS$, is described. The isothiazolopyridine part of the molecule is planar, while the piperazine ring adopts a slightly deformed chair conformation. The structure is

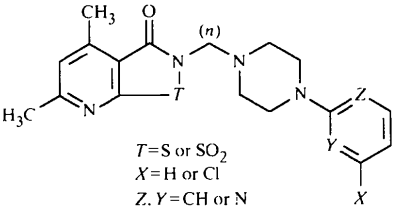
stabilized by a network of weak C—H···*X* hydrogen bonds, and the conformation of the phenylpiperazine substituent may be influenced by a C—H···S intramolecular short contact.

Comment

We report herein the results of the X-ray structure determination of the title compound, (I), as part of a larger structural and pharmacological study on a series of 2-substituted isothiazolopyridines of general structure (II). The pharmacological investigation data of the compounds of type (II) *in vivo*, by use of behavioural tests in rats and mice, suggest that the profile of biological activity is characteristic for an agonist of the receptors 5-HT-2A (Malinka, 1990, 1991; Malinka *et al.*, 1995). Particularly interesting of a number of compounds studied is the most active compound, (I). The complete crystal structure analysis of this compound was expected to yield information concerning the conformation, mutual orientation and effects of substituents on receptor affinities.



(I)



(II)

A search of the Cambridge Structural Database (1997) did not reveal any crystal structures of compounds containing the isothiazolopyridine moiety, and showed five organic structures with a 1,2-benzisothiazole part: 7-chloro-1,2-benzisothiazolin-3-one (Cavalca *et al.*, 1969), 1,2-benzisothiazolin-3-one (Cavalca *et al.*, 1970), 2-(2-hydroxy-1,1-dimethylethyl)-2,3-dihydronaphth[2,1-*d*]isothiazol-3-one (Baker *et al.*, 1995), and 2-(2-phenylethyl)-1,2-benzisothiazolin-3(2*H*)-one and 2-(4-methoxyphenyl)-1,2-benzisothiazolin-3(2*H*)-one (Kim *et al.*, 1996).

Bond lengths and angles in the isothiazolopyridine part of (I) do not differ significantly from those reported for 1,2-benzisothiazolin-3-one and 7-chloro-1,2-benzisothiazolin-3-one. In the fused ring system, the six-membered ring is planar to within 0.005 (2) Å and the five-membered ring is planar to within 0.030 (2) Å. These two rings are inclined at an angle of 2.16 (7)°. The substituents in the pyridine ring are displaced from the best pyridine plane by 0.043 (2) Å for C10 and 0.006 (4) Å for C11, while the displacement of the keto O3 atom from the best isothiazole plane is 0.084 (2) Å. The exocyclic bond angles at C3 [123.1 (2) and 128.7 (2)°] are asymmetric, and this is probably due to the C12—H122···O3 attractive interaction: H122···O3 = 2.58 (2), C12—O3 = 2.858 (3) Å and C12—H122···O3 = 94 (1)°.

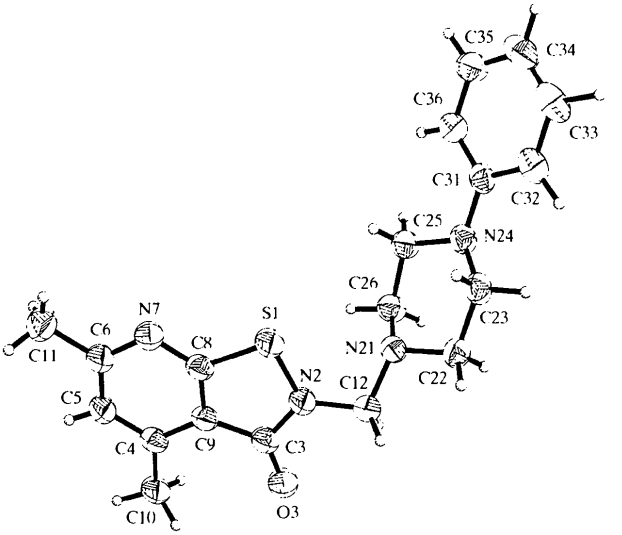


Fig. 1. *SHELXTL-Plus* (Sheldrick, 1989) plot of the title molecule, showing the atomic labelling. Non-H atoms are represented by displacement ellipsoids of 50% probability.

The orientation of the phenylpiperazine substituent in relation to the fused bicyclic system is described by the torsion angles S1—N2—C12—N21 and N2—C12—N21—C22 of −24.5 (2) and 159.4 (2)°, respectively. The piperazine ring adopts a slightly deformed chair conformation with puckering parameters of Q = 0.559 (2) Å and θ = 160.4 (2)° (Cremer & Pople, 1975). This deformation is caused by the flatness of the pyramidal configuration of N24; this atom is displaced from the equatorial plane of the piperazine ring by 0.467 (2) Å, while N21 is displaced by 0.749 (2) Å on the opposite side. The N24—C31 bond length of 1.403 (2) Å, and the sum of the bond angles around N24 of 347.5 (2)°, show that the lone pair at N24 is partially conjugated with the π system of the phenyl ring. The phenyl ring is planar; its least-squares plane is inclined by 17.92 (6) and 48.68 (5)° with respect to the planes of the piperazine and isothiazolopyridine rings, respectively.

The molecular packing in the crystal is influenced by the presence of weak C—H···*X* hydrogen bonds. Although these contacts fall slightly outside the range

reported for similar contacts (Taylor & Kennard, 1982), they possess reasonable geometry for this type of interaction. There is also a short intramolecular contact between H261 (at C26) and S1 with H···S 2.88 (2) Å, shorter than the sum of the van der Waals radii [1.20 and 1.80 Å for H and S atoms, respectively (Taylor & Kennard, 1982)].

Experimental

4,6-Dimethyl-2-(4-phenylpiperazin-1-ylmethyl)isothiazolo[5,4-*b*]pyridin-3(2*H*)-one was prepared according to the method of Malinka & Rutkowska (1996). Crystals suitable for X-ray diffraction analysis were grown by slow evaporation of an ethanol solution.

Crystal data

$C_{19}H_{22}N_4OS$
M_r = 354.47
Monoclinic
$P2_1/c$
a = 17.435 (1) Å
b = 10.926 (1) Å
c = 9.089 (2) Å
β = 93.01 (1)°
V = 1729.0 (4) Å^3
Z = 4
D_x = 1.362 Mg m^{-3}
D_m not measured

Cu $K\alpha$ radiation
λ = 1.54178 Å
Cell parameters from 25 reflections
θ = 10–50°
μ = 1.779 mm^{-1}
T = 293 (2) K
Prism
0.40 × 0.20 × 0.20 mm
Colourless

Data collection

Kuma KM-4 four-circle diffractometer
$\omega/2\theta$ scans
Absorption correction: none
3866 measured reflections
3402 independent reflections
2653 reflections with $I > 2\sigma(I)$

R_{int} = 0.035
θ_{max} = 80.34°
h = −22 → 22
k = −13 → 0
l = −11 → 11
2 standard reflections
every 100 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.041
$wR(F^2)$ = 0.129
S = 1.085
3402 reflections
315 parameters
H atoms: see text
$w = 1/[\sigma^2(F_o^2) + (0.0875P)^2 + 0.1604P]$ where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max}$ = −0.001
$\Delta\rho_{max}$ = 0.298 e Å^{-3}
$\Delta\rho_{min}$ = −0.482 e Å^{-3}
Extinction correction: *SHELXL*93
Extinction coefficient: 0.0020 (4)
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °)*

S1—N2	1.709 (2)	C4—C5	1.382 (3)
S1—C8	1.741 (2)	C4—C9	1.402 (2)
N2—C3	1.371 (2)	C4—C10	1.498 (2)
N7—C8	1.335 (2)	C5—C6	1.401 (3)
N7—C6	1.338 (3)	C6—C11	1.499 (3)
O3—C3	1.226 (2)	C8—C9	1.392 (2)
C3—C9	1.468 (3)		
N2—S1—C8	89.23 (8)	C4—C5—C6	121.5 (2)
C3—N2—C12	123.6 (2)	N7—C6—C5	122.8 (2)
C3—N2—S1	117.30 (13)	N7—C6—C11	116.4 (2)
C12—N2—S1	118.93 (13)	C5—C6—C11	120.8 (2)
C8—N7—C6	115.3 (2)	N7—C8—C9	126.2 (2)
O3—C3—N2	123.1 (2)	N7—C8—S1	120.85 (13)
O3—C3—C9	128.7 (2)	C9—C8—S1	112.92 (14)
N2—C3—C9	108.2 (2)	C8—C9—C4	118.2 (2)
C5—C4—C9	116.0 (2)	C8—C9—C3	112.2 (2)
C5—C4—C10	121.2 (2)	C4—C9—C3	129.6 (2)
C9—C4—C10	122.8 (2)		

Table 2. *Hydrogen-bonding geometry (Å, °)*

D—H···A	D—H	H···A	D···A	D—H···A
C10—H103···O3^i	0.96 (4)	2.48 (4)	3.420 (3)	164 (3)
C34—H341···N7^{ii}	0.94 (4)	2.62 (4)	3.495 (3)	156 (3)

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

The structure was solved by direct methods using *SHELXS*86 (Sheldrick, 1990) and refined by full-matrix least squares with *SHELXL*93 (Sheldrick, 1993). All H atoms were located from difference Fourier maps and refined with isotropic displacement parameters. Molecular graphics were prepared using *XP* in *SHELXTL-Plus* (Sheldrick, 1989), the geometrical calculations were performed using *PARST* (Nardelli, 1983) and material for publication was produced using *SHELXL*93.

Data collection: Kuma KM-4 software. Cell refinement: Kuma KM-4 software. Data reduction: Kuma KM-4 software.

The authors wish to express their thanks to Professor J. Karolak-Wojciechowska from the Institute of General and Ecological Chemistry, Technical University in Łódź, Poland, for carrying out the single-crystal measurements, and for her kind consent to use the *XP* program for creating drafts.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: NA1333). Services for accessing these data are described at the back of the journal.

References

Baker, R. W., Hockless, D. C. R., Pocock, G. R., Sargent, M. V., Skelton, B. W., Sobolev, B. W., Twiss, E. & White, A. H. (1995). *J. Chem. Soc. Perkin Trans.* 1, pp. 2615–2629.
Cambridge Structural Database (1997). Version 5.13. Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, England.
Cavalca, L., Gaetani, A., Mangia, A. & Pelizzi, G. (1970). *Gazz. Chem. Ital.* **100**, 629–638.
Cavalca, L., Gasparri, G. F., Mangia, A. & Pelizzi, G. (1969). *Acta Cryst.* B**25**, 2349–2354.
Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.
Kim, W., Dannaldson, J. & Gates, K. S. (1996). *Tetrahedron Lett.* **37**, 5337–5340.
Malinka, W. (1990). *Acta Pol. Pharm. Drug Res.* **47**, 51–56.
Malinka, W. (1991). *Acta Pol. Pharm. Drug Res.* **48**, 19–23.
Malinka, W. & Rutkowska, M. (1996). Polish Patent Application No. P-314025.
Malinka, W., Sicklucka-Dziuba, M., Rajtar, G., Morawska, D. & Kleinrok, Z. (1995). *Il Farmaco*, **50**, 769–778.
Nardelli, M. (1983). *Comput. Chem.* **7**, 95–98.
Sheldrick, G. M. (1989). *SHELXTL-Plus*. Release 4.0. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.
Sheldrick, G. M. (1990). *Acta Cryst.* A**46**, 467–473.
Sheldrick, G. M. (1993). *SHELXL*93. *Program for the Refinement of Crystal Structures*. University of Göttingen, Germany.
Taylor, R. & Kennard, O. (1982). *J. Am. Chem. Soc.* **104**, 5063–5070.