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5-Amino-4-methylsulfonyl-1-phenyl-1*H*-pyrazole

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Key indicators

Single-crystal X-ray study
T = 293 K
Mean σ(C–C) = 0.003 Å
R factor = 0.038
wR factor = 0.105
Data-to-parameter ratio = 17.2

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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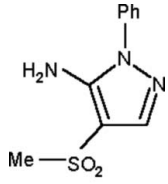
The title compound, $C_{10}H_{11}N_3O_2S$, was designed and synthesized as a potential antitumour agent and a single-crystal X-ray analysis was undertaken to determine the three-dimensional arrangement of the putative pharmacophoric groups. The central pyrazole ring is exactly planar and the 1-phenyl group has no effect on the π-electron system of the pyrazole nucleus. In contrast, the 5-amino N atom is strongly conjugated with the pyrazole ring such that the flow of the resulting negative charge is in the direction of the 4-sulfonyl O atoms. All of the potential hydrogen-bond donors and acceptors are actually involved in hydrogen bonding.

Comment

As part of our ongoing project aimed at developing new therapeutic agents, we focused our attention on derivatives of pyrazole, which are known to possess a wide spectrum of biological activities (Badiger & Adhikari, 1987; Ohki *et al.*, 2002). Recently, it has been reported that addition of essentially polar substituents, with the ability to form hydrogen bonds, to the 4- and 5-positions of 1-phenylpyrazole endows the molecule with the ability to induce apoptopic death of transformed cells, which makes it useful for treatment of cancer (Robin *et al.*, 2005). Following these reports, we synthesized a series of 4,5-disubstituted 1-phenylpyrazoles and selected the 4-methylsulfonyl-5-amino derivative, (I), for a single-crystal X-ray analysis.



(I)

The purpose of this structure determination was therefore twofold. First, we were interested in the spatial relationship between the putative pharmacophoric elements, *viz*. the phenyl ring and hydrogen-bond donors and acceptors, which is indispensable for subsequent structure–activity relationships and molecular modelling studies. Another point of interest stems from isomerism of the pyrazole derivatives (in our case, for example, four isomers are possible), which, in general, is resolvable by using empirical rules and/or NOE NMR spectroscopy (Černuchová *et al.*, 2005*a*). However, in some cases, spectroscopic methods fail to assign unequivocally the correct structure so that additional methods must be employed; thus the need to verify the most probable structure of (I) by using an X-ray analysis.

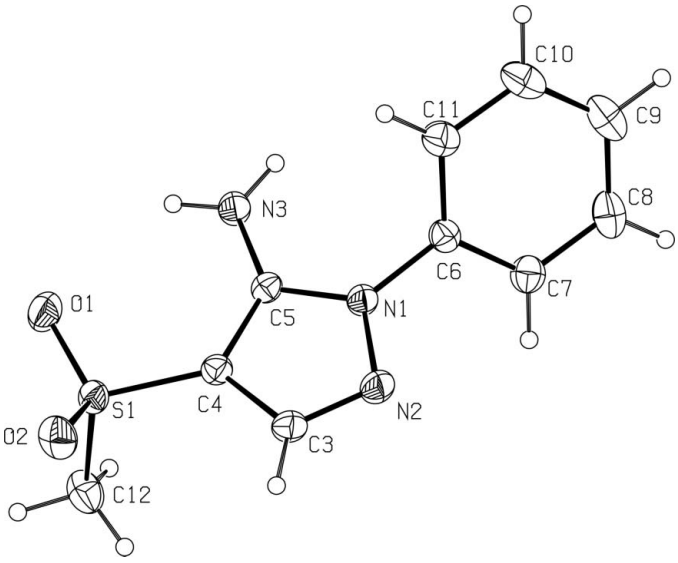


Figure 1
Displacement ellipsoid plot, at the 35% probability level, of (I), with the atom-labelling scheme. H atoms are drawn as small circles of arbitrary size.

The molecular structure and the atom-numbering scheme are shown in Fig. 1. As can be seen, the X-ray analysis confirmed the spectroscopic assignments, *viz.* the compound has the methylsulfonyl and amino groups bonded to the pyrazole nucleus at the 4- and 5-positions, respectively.

As mentioned above, the main purpose of this structure determination was to establish the relative disposition of the pharmacophoric elements (the 1-phenyl group and heteroatoms able to act as hydrogen-bond donors and acceptors), which in turn is given by the bonding and torsional characteristics of the molecule (Table 1). As expected, the pyrazole ring is planar to within the limits of experimental error [r.m.s. deviation 0.005 (3) Å]; atoms C6 and S1 are displaced from this plane by 0.051 (3) and 0.038 (3) Å, respectively, on opposite sides of the ring, while the amine atom N3 lies in the plane of the ring [deviation 0.006 (3) Å]. The 1-phenyl ring is also exactly planar [r.m.s. deviation 0.002 (3) Å] and inclined at an angle of 55.3 (1)° to the mean plane of the heterocycle. That the phenyl ring is deconjugated with the pyrazole ring is further indicated by the N1—C6 bond length of 1.434 (2) Å, which is even longer than the value of 1.425 (3) Å reported for a pure Nsp^2—Csp^2 single bond (Adler *et al.*, 1976). On the other hand, the lone-pair electrons on atom N3 are delocalized through conjugation with the aromatic C4—C5 bond, as substantiated by (i) the bond order (*ca* 1.5) of the formally single C5—N3 bond as estimated from the bond-order–bond-length curves proposed by Burke-Laing & Laing (1976), and (ii) the endocyclic C4—C5 bond distance [1.398 (2) Å], which is lengthened by *ca* 0.04 Å with respect to that found in the unsubstituted pyrazole (Berthou *et al.*, 1970). A similar effect has also been observed for 5-amino-2-pyrazolium picrate (Infantes *et al.*, 1999) and leads to accumulation of negative charge on atom C4. However, in contrast to the latter compound, in the present molecule, (I), the negative charge on C4 is most likely further transferred to the sulfonyl O atoms as shown by (i) the C4—S1 bond distance of 1.717 (2) Å, which is intermediate between a double and a single bond, assuming values of 1.61 and 1.82 Å for double S=C and single S—C bond lengths, respectively (Abrahams, 1956), and (ii) near coplanarity of the S1—O1 bond with the aminopyrazole substructure [C5—C4—S1—O1 = 11.38 (18)°]. A partial loss of the bond-order equivalency in the pyrazole ring of (I) (Table 1), not observed in pyrazole and its 5-amino analogue (Berthou *et al.*, 1970; Infantes *et al.*, 1999), might also be related to the electron-accepting effect of the methylsulfonyl group.

Besides the geometry of the pharmacophoric groups, the ability of the potential hydrogen-bond donors and acceptors ($N3H_2$, N2, O1 and O2) to form actual hydrogen bonds is also of biological significance. As shown in Table 2, all potential hydrogen-bond donors and acceptors are involved in hydrogen bonding, which results in the formation of one intramolecular and two intermolecular hydrogen bonds. The latter two hydrogen bonds play a dominant role in the packing of the molecules in the crystal structure.

Experimental

The synthetic procedure of (I) will be described in detail elsewhere (Černuchová *et al.*, 2005*b*). In short, to phenylhydrazine (2.5 mmol) was added 3-ethoxy-2-methylsulfonylacrylonitrile (2.5 mmol) and the mixture was stirred for 10 min at room temperature. Ethanol (10 ml) was then added and the solution refluxed for 30 min. The crude product was separated by column chromatography after the solvent was evaporated (hexane/AcOEt, 7:3). The product was purified by recrystallization from the same solvent to give (I) (86% yield, m.p. 406–408 K).

Crystal data

$C_{10}H_{11}N_3O_2S$
M_r = 237.28
Monoclinic, $P2_1/n$
a = 8.083 (2) Å
b = 12.274 (3) Å
c = 11.040 (3) Å
β = 95.20 (3)°
V = 1090.8 (5) Å^3
Z = 4
D_x = 1.445 Mg m^{-3}
Mo $K\alpha$ radiation
Cell parameters from 20 reflections
θ = 7–20°
μ = 0.28 mm^{-1}
T = 293 (2) K
Prism, colourless
0.30 × 0.20 × 0.15 mm

Data collection

Siemens $P4$ diffractometer
$\omega/2\theta$ scans
Absorption correction: none
3298 measured reflections
2504 independent reflections
2080 reflections with $I > 2\sigma(I)$
R_{int} = 0.039
θ_{max} = 27.5°
$h = -1 \rightarrow 10$
$k = -1 \rightarrow 15$
$l = -14 \rightarrow 14$
3 standard reflections
every 97 reflections
intensity decay: 2%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.038
$wR(F^2)$ = 0.106
S = 1.04
2504 reflections
146 parameters
H-atom parameters constrained
$w = 1/[\sigma^2(F_o^2) + (0.051P)^2 + 0.3P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.25 e Å^{-3}
$\Delta\rho_{min}$ = −0.27 e Å^{-3}

Table 1
Selected geometric parameters (Å, °).

N1—C5	1.357 (2)	C4—C5	1.398 (2)
N1—N2	1.388 (2)	C4—S1	1.717 (2)
N1—C6	1.434 (2)	C5—N3	1.350 (2)
N2—C3	1.307 (2)	S1—O1	1.4314 (14)
C3—C4	1.408 (2)	S1—O2	1.4368 (14)
C5—N1—N2	112.47 (13)	C3—C4—S1	127.17 (13)
C5—N1—C6	128.59 (14)	N3—C5—N1	123.17 (15)
N2—N1—C6	118.93 (13)	N3—C5—C4	131.53 (15)
C3—N2—N1	104.39 (13)	O1—S1—O2	118.04 (9)
N2—C3—C4	112.46 (15)	O1—S1—C4	107.80 (8)
C5—C4—C3	105.36 (14)	O2—S1—C4	109.12 (8)
C5—C4—S1	127.45 (12)		
N2—N1—C6—C7	−54.8 (2)	C5—C4—S1—O1	11.38 (18)

Table 2
Hydrogen-bond geometry (Å, °).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N3—H3*A*···O2^{i}	0.86	2.27	3.036 (2)	148
N3—H3*B*···O1	0.86	2.38	2.968 (2)	126
N3—H3*B*···N2^{ii}	0.86	2.44	3.234 (2)	154

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

H atoms were refined with fixed geometry (C–H distance ranging from 0.93 to 0.96), riding on their carrier atoms, with U_{iso}(H) set to 1.2 (1.5 for the methyl H atoms) times U_{eq} of the parent atom.

Data collection: *XSCANS* (Siemens, 1991); cell refinement: *XSCANS*; data reduction: *XSCANS*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *PLATON* (Spek, 2003); software used to prepare material for publication: *SHELXL97*.

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