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A Stacked Pyrazolo[3,4-*d*]pyrimidine-Based Flexible Molecule

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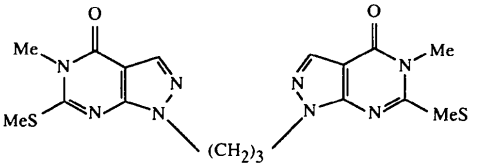
Abstract

In the crystal structure of 1,1′-(1,3-propanediyl)bis(5-methyl-6-methylthio-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]-pyrimidin-4-one), $C_{17}H_{20}N_8O_2S_2$, the pairs of pyrazolo-[3,4-*d*]pyrimidine rings of the molecules stack, due to intramolecular π–π interactions, between the heterocyclic rings.

Comment

Besides their role in DNA/RNA, non-covalent interactions between aromatic molecules are invoked to rationalize a variety of phenomena, such as the packing of aromatic molecules in crystals (Desiraju, 1995), molecular recognition (Hunter, 1994, and references therein) and asymmetric synthesis (Jones & Chapman, 1995), and also to explain the structure of many biologically relevant molecules (Saenger, 1984; Burley & Petsko, 1985; Hunter *et al.*, 1991). Use of a 'propylene linker', first documented by Brown *et al.* (1968), for the promotion of intramolecular aromatic π–π interactions (APPI) is now increasing (Leonard, 1979; Newcomb & Gellman, 1994). However, bis-thymine (Frank & Paul, 1973) and bis-theophylline (Rosen & Hybl, 1971), both containing 'propylene linkers', remain the only examples for which X-ray structure determination has shown intramolecular π–π interactions, though with extensive hydrogen bonding. In spite of considerable research activity (Shetty *et al.*, 1996, and references therein), APPI are not well understood and there is an urgent need for more simple and flexible models without too much bias for certain conformations.

Recently, we have reported (Avasthi *et al.*, 1995) the synthesis of 1,3-bis(4,6-dimethylthio-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)propane, (1), the ^{1}H NMR spectrum of which showed an unusual high-field shift for one of the methylthio groups in comparison with the corresponding signals in the ^{1}H NMR spectra of 1-alkyl-4,6-dimethylthio-1*H*-pyrazolo[3,4-*d*]pyrimidines (Garg *et al.*, 1989), indicating intramolecular APPI. Indeed, X-ray crystallographic analysis of (1) (Biswas *et al.*, 1995) showed that the structure is stabilized by intermolecular/intramolecular π–π interactions and van der Waals interactions. Since the X-ray structure analysis of (1) had shown that the overlapping area was confined to the pyrimidinyl portion of the pyrazolo[3,4-*d*]pyrimidinyl system, we decided to introduce some functionality in this portion of the molecule and study its overall effect on APPI by ^{1}H NMR and X-ray techniques. Thus, 1,1′-(1,3-propanediyl)bis(5-methyl-6-methylthio-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-one), (2), and 1-[3-(4-methoxy-6-methylthio-1*H*-pyrazolo[3,4-*d*]-pyrimidin-1-yl)propyl]-5-methyl-6-methylthio-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-one, (3), were prepared from (1) by treatment with alkali followed by methylation. Observations of significant up-field shifts of the 6-SMe and 6′-SMe protons in the ^{1}H NMR spectra of (2) and (3) in comparison with those of simpler monomeric compounds (Avasthi *et al.*, 1998) were indicative of intramolecularly stacked conformations for (2) and (3), similar to that of the starting material, (1). This prompted us to determine their crystal structures for further confirmation and comparison of the solution and solid-state conformations. The structure of (2) is reported here. The structure of (3) is of rather lower precision and only the main results are given here for comparison.



(2)

The conformation of (2) is shown in Fig. 1. The structure is folded at the centre of the bridge [C8—C9—C10 is 115.2 (2)° in (2) and 114.3 (5)° in (3)] due to intramolecular APPI between the pyrazolo[3,4-*d*]-pyrimidine rings. In both cases, the two pyrazolo[3,4-*d*]pyrimidine rings are positioned in such a way that only a part of the pyrimidinyl rings overlap (Fig. 2). The overlapping regions of the six-membered rings are separated by an average distance of 3.37 Å in (2) [3.38 Å in (3)], thus further confirming intramolecular APPI. The pyrazolo[3,4-*d*]pyrimidine rings of (2) are nearly planar [maximum deviation 0.035 (3) Å] and the angle between the least-squares planes is 12.4 (5)° [11.9° in (3)]. The molecules are packed in such a way that they stack in columns [running in the *a*-axis direction for (2)]. The approximate intermolecular spacing between the stacked heterocyclic rings is 3.4 Å for both (2) and (3), which is indicative of intermolecular stacking through APPI. Thus, the crystal structures of (2) and (3) are stabilized mainly by intermolecular/intramolecular APPI and van der Waals forces.

This study demonstrates further the utility of (2), and (3), in addition to (1), as new flexible models based on pyrazolo[3,4-*d*]pyrimidines for studying APPI.

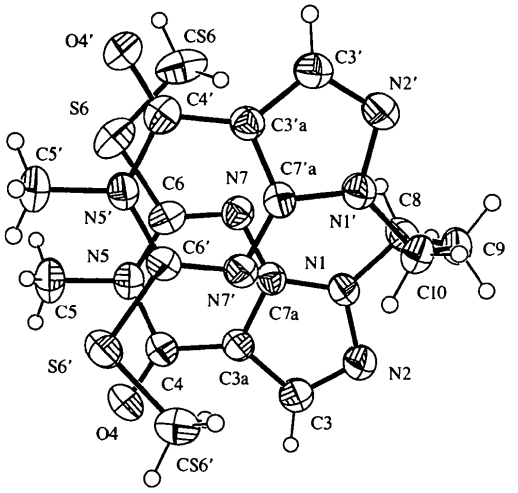


Fig. 1. The molecular structure of (2) showing the intramolecular stacking and displacement ellipsoids at 50% probability.

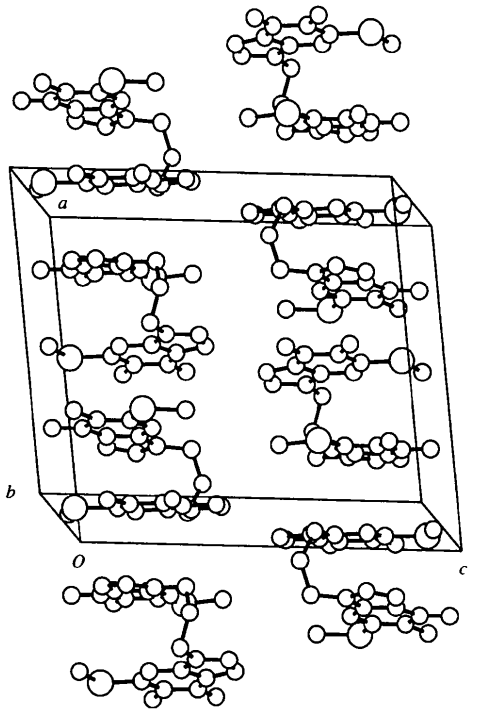


Fig. 2. The crystal packing in parallel projection.

Experimental

The syntheses of (2) and (3) were carried out by the treatment of compound (1) with aqueous alkali and subsequent methylation (Avasthi *et al.*, 1998). Diffraction-quality crystals of both compounds were obtained by slow evaporation of ethyl acetate/*n*-hexane mixtures at room temperature.

Crystal data

$C_{17}H_{20}N_8O_2S_2$
M_r = 432.53
Monoclinic
$P2_1/a$
a = 13.459 (4) Å
b = 9.2087 (15) Å
c = 15.883 (5) Å
β = 98.87 (4)°
V = 1945.1 (8) Å^3
Z = 4
D_x = 1.477 Mg m^{-3}
D_m not measured
Mo $K\alpha$ radiation
λ = 0.71073 Å
Cell parameters from 25 reflections
θ = 5.08–17.94°
μ = 0.307 mm^{-1}
T = 293 (2) K
Block
0.3 × 0.2 × 0.2 mm
Colourless

Data collection

Enraf–Nonius CAD-4 diffractometer
ω–2θ scans
Absorption correction: none
3408 measured reflections
3408 independent reflections
2041 reflections with $I > 2\sigma(I)$
θ_{max} = 24.97°
$h = -15 \rightarrow 15$
$k = 0 \rightarrow 10$
$l = 0 \rightarrow 18$
3 standard reflections
frequency: 60 min
intensity decay: <0.5%

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.040
$wR(F^2)$ = 0.121
S = 0.956
3407 reflections
266 parameters
H atoms riding
$w = 1/[\sigma^2(F_o^2) + 20 + (0.0627P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.004
$\Delta\rho_{max}$ = 0.204 e Å^{-3}
$\Delta\rho_{min}$ = −0.283 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected torsion angles (°)*

C7'a—N1'—C10—C9	125.0 (3)	C7a—N1—C8—C9	122.0 (3)
N2'—N1'—C10—C9	−55.3 (3)	N2—N1—C8—C9	−57.6 (3)
C8—C9—C10—N1'	−50.5 (3)	C10—C9—C8—N1	−51.9 (3)

Data collection: *CAD-4-MACH/PC* (Enraf–Nonius, 1993). Cell refinement: *CAD-4-MACH/PC*. Data reduction: *NRC-VAX* (Gabe *et al.*, 1989). Program(s) used to solve structure: *SHELXS86* (Sheldrick, 1990). Program(s) used to refine structure: *SHELXL93* (Sheldrick, 1993). Molecular graphics: *ORTEP* (Johnson, 1965) and *PLUTO* (Motherwell & Clegg, 1978). Software used to prepare material for publication: *SHELXL93*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: CF1197). Services for accessing these data are described at the back of the journal.

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4-Benzyl-2,9-bis(phenylsulfonyl)-1,2,3,4-tetrahydro-9*H*-β-carboline

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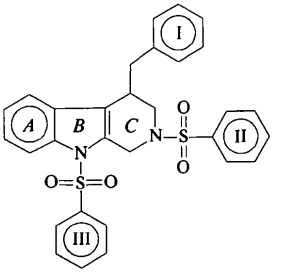
Abstract

In the title compound, $C_{30}H_{26}N_2O_4S_2$, the six-membered aromatic and five-membered heterocyclic rings are planar, and the six-membered heterocyclic ring is in a half-chair conformation. The phenylsulfonyl group attached to the N atom of the five-membered ring is almost perpendicular to the β-carboline moiety. The phenylsulfonyl groups attached to N2 and N1 are in equatorial positions. The molecules are stabilized by weak inter- and intramolecular hydrogen bonds.

Comment

The tetrahydro-β-carboline moiety occurs in many indole alkaloids and the assignment of stereochemistry to these systems is often crucial in the structure elucidation of natural products of this type (Everett *et al.*, 1990). Some β-carboline (9*H*-pyrido[3,4-*b*]indole) derivatives have been shown to be antagonists of benzodiazepines (Oakley & Jones, 1980) and have aroused considerable interest in neuropharmacology (Braestrup *et al.*, 1980; Ninan *et al.*, 1982). The structural studies of some β-carboline derivatives have been instrumental in the development of the inverse agonist/agonist pharmacophore of the benzodiazepine receptor (BzR) site. The BzR is located in the GABA receptor ion channel and plays an important role in the molecular mechanisms controlling anxiety, convulsions, memory learning and sleep in animals (Cox & Cook, 1995).

A *ZORTEP* diagram (Zsolnai, 1997) of the title molecule, (1), with the atomic numbering scheme is shown in Fig. 1. The geometries around the S atoms



(1)

(S1 and S2) are distorted from ideal tetrahedral, with the largest deviations in the O—S—O [O2—S1—O1 119.9 (3) and O4—S2—O3 120.8 (3)°] and O—S—N angles [O2—S1—N1 106.3 (2), O1—S1—N1 106.9 (3), O4—S2—N2 106.3 (2) and O3—S2—N2 107.4 (3)°], but the geometries do conform to the non-tetrahedral arrangement commonly observed in dibenzenesulfonamides (Cotton & Stokely, 1970). The values of the C—N distances in ring *C* [N2—C8 1.476 (7) and N2—C7 1.489 (7) Å] are larger than those in ring *B* [N1—C5 1.438 (7) and N1—C6 1.438 (6) Å]. The S—N bond distances [S1—N1 1.670 (5) and S2—N2 1.638 (4) Å] lie in the range 1.63–1.69 Å given by Kálmán *et al.* (1981). The average S—O, S—C and S—N distances of 1.435, 1.772 and 1.654 Å, respectively, are comparable with those found in *N*-phenylsulfonamides (Gomes *et al.*, 1993).