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Crystal Structure and Conformation of a Piperidine-Containing Thiosemicarbazone Derivative

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Piperidine thiosemicarbazones have the ability to inhibit the enzyme ribonucleoside diphosphate reductase (RDR), which is essential in DNA synthesis. The present compound, t-3-methyl-r-2,c-6-diphenylpiperidin-4-one thiosemicarbazone (MDPTAN), was prepared using the Mannich reaction and crystallized with acetonitrile as solvent. The crystal data are $C_{38}H_{44}N_8S_2{\cdot}2(C_2H_3N)$; $M{\cdot}W = 759.06$, *monoclinic, space group* $P2_1/c$, $a = 16.324(4)$ Å, $b = 15.179(4)$ Å, $c = 17.650(5)$ Å, $\beta = 104.98(5)^\circ$, $V = 4225(2)$ Å^3, $Z = 4$, $D_{cal} = 1.193$ Mgm^{-3}, $\mu = 0.168\,mm^{-1}$, *and* λ (MoK_α) = 0.71073 Å. *The structure was solved by direct methods and refined to final R-values of* $R = 0.089$ *and* $wR = 0.1962$, *respectively. The piperidine rings adopt* chair *conformations. The planar phenyl rings are oriented equatorially at 2,6-positions of the piperidine ring. The N-H···N and C-H···N types of intra- and intermolecular hydrogen bondings play a major role in stabilizing the molecules in the unit cell. The molecular packing can be viewed as chain of dimers held together by two N-H···S types of intermolecular hydrogen bond networks. C-H···π weak interactions also support the packing of the molecules in addition to van der Waals forces.*

Keywords: acetonitrile(solvent); conformation; crystal structure; hydrogen bonding; MDPTAN; piperidine

INTRODUCTION

The crystal structures of tridentate (N–N–S) thiosemicarbazone (TSC) derivatives have been studied to establish the molecular geometry and

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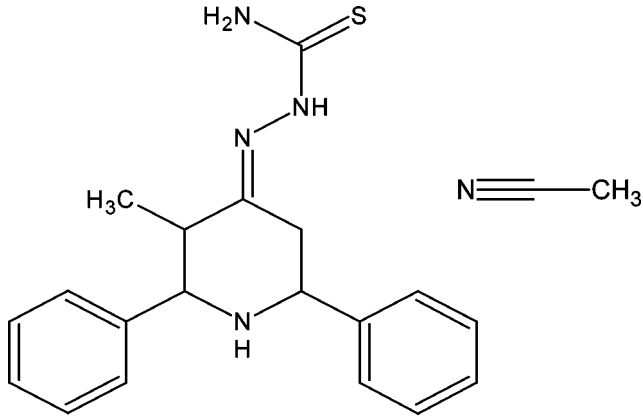


FIGURE 1 Chemical diagram of the molecule MDPTAN.

the forces involved in stabilizing the molecules, and to examine the conformational differences with the related structures to understand its biological activity.

TSC derivatives exhibit a wide range of biological activities, namely antimalarial [1], antitumor, and antileukemic properties [2,3]; antibacterial and antiviral activity [4,5]; and antifertility property [6]. In general, the tridentate N, S donor ligands of substituted TSCs and thiosemicarbazides are attributed to their ability to chelate and form metal complexes [2,7–9]. These drugs and their respective metallic complexes act either as chelating agents of the Fe atoms of the active site in the enzyme mentioned or by destroying the tyrosine radical present in a subunit of this protein, thus inhibiting the catalytic activity of the enzyme [10]. Also these derivatives possess nonlinear optical properties [11], and it has been postulated that extensive electron delocalization in the thiosemicarbazone moiety helps to exhibit second harmonic generation (SHG) efficiency [12,13].

As part of the ongoing project on TSC derivatives, the title compound was synthesized and crystallized, and the crystal structure was determined. The chemical diagram of the title compound (MDPTAN) is shown in Fig. 1.

X-RAY DATA COLLECTION

Intensity data were collected on Siemens SMART CCD [14] area detector diffractometer using graphite monochromated MoK_α radiation ($\lambda = 0.71073$ Å) at 293(2) K. The whole data collection covered a

hemisphere of reciprocal space by a combination of three sets of exposure, each having a different Φ angle (0, 88, and 180°) for the crystal and each exposure time of 30 s covered 0.3° in ω. The crystal-to-detector distance was 4 cm and the detector swing angle was −35°. The intensity data were corrected for Lorentz and polarization effects.

STRUCTURE SOLUTION AND REFINEMENT

The structure was solved by direct methods program in SHELXS97 [15] and refined on F^2 by full-matrix least-squares procedures using SHELXL97 [16]. The nonhydrogen atoms were refined anisotropically, and the hydrogen atoms were allowed to ride over their parent atoms. The final cycle of refinement converged to R = 0.0890 and wR = 0.1962 for the observed reflections. The reliability factor is little high owing to the high mosaicity of the crystal; nevertheless, the data are good enough to establish the structure and conformation. The maximum and minimum heights in the final difference Fourier map were 0.522 and $-0.272\,e\cdot Å^{-3}$ respectively. The geometrical parameters were done using the program PARST [17], and figures were drawn using ZORTEP [18] and PLATON [19]. The crystal data and other relevant parameters are given in Table 1.

RESULTS AND DISCUSSION

The ZORTEP plot of the molecule MDPTAN is shown in Fig. 2. The asymmetric unit contains two crystallographically independent molecules (A and B). The thiosemicarbazone moieties are planar and adopt an extended conformation in both the molecules.

The S atom is *trans* to N7, and E configuration is achieved based on the intramolecular hydrogen bonding between N7 and the H atom of amine group ($N10H_2$) [20]. The bond lengths in TSC moieties C9-S1 [1.686(4), 1.679(4) Å for A and B], C9-N10 [1.287(5), 1.298(5) Å for A and B], N8-C9 [1.354(5), 1.347(5) Å for A and B] indicate the extensive delocalization of electrons in both molecules, and the resonance structures are derived (Fig. 3). The thiosemicarbazone moieties are oriented at angles 45.7(2) and 52.7(2)° to the best plane of the piperidine rings in both the molecules A and B, respectively.

The negative charge on the atom N10 increases whereas that on N7 decreases, as is commonly observed for thiosemicarbazone moieties [21,22]. Also, note that N10 may not take part either in metal complexation or in the reduction process owing to the smearing of the

TABLE 1 Crystal Data for MDPTAN

Parameter	MDPTAN
CCDC No.	CCDC 213816
Empirical formula	$C_{38}H_{44}N_8S_2{\cdot}2(C_2H_3N)$
Formula weight	759.06
Temperature	293(2) K
Wavelength (MoK_α)	0.71073 Å
Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions	a = 16.324(4) Å b = 15.179(4) Å c = 17.650(5) Å $\beta = 104.98(5)^\circ$
Volume	4225(2) $Å^3$
Z, calculated density	4, 1.193 Mgm^{-3}
Absorption coefficient	0.168 mm^{-1}
F (000)	1616
Crystal size	0.33 × 0.33 × 0.30 mm
Theta range for data collection	1.29 to 26.29°
Index ranges	$-18 \le h \le 20$ $-17 \le k \le 18$ $-21 \le l \le 21$
Reflections collected/unique/$I > 2\sigma(I)$	31710/8284/4405
Completeness to theta = 26.29	93.3%
Refinement	Full-matrix least-squares on F^2
Data/restraints/parameters	8284/0/491
Goodness of fit	1.050
Final R indices [$I > 2\sigma(I)$]	R = 0.0890 wR = 0.1962
Largest diff. peak and hole	0.522 and −0.272 e·$Å^{-3}$

electron cloud over the bond [22]. One or both these processes are thought to be responsible for the biological activity; however, the N10 atom cannot have any effect on the biological role for this compound. Also it is believed that the atoms N7 and S play key role in metal chelation and the biological activities [22].

The planar phenyl rings C11 through C16 and C17 through C22 are substituted equatorially at the 2 and 6 positions of the piperidine rings in both the molecules. The corresponding orientation angles of phenyl rings with respect to the piperidine rings are 77.4(2) and 89.6(2)° for molecule A and 80.9(2) and 79.3(2)° for molecule B. The phenyl rings are oriented at angles of 60.0(1) and 56.2(1)° to the best plane of piperidine rings A and B respectively.

A study of least-squares planes and torsion angles shows that the piperidine rings in both the molecules A and B adopt *chair* conformation ($Q_T = 0.559$ for A) and ($Q_T = 0.574$ for B) respectively

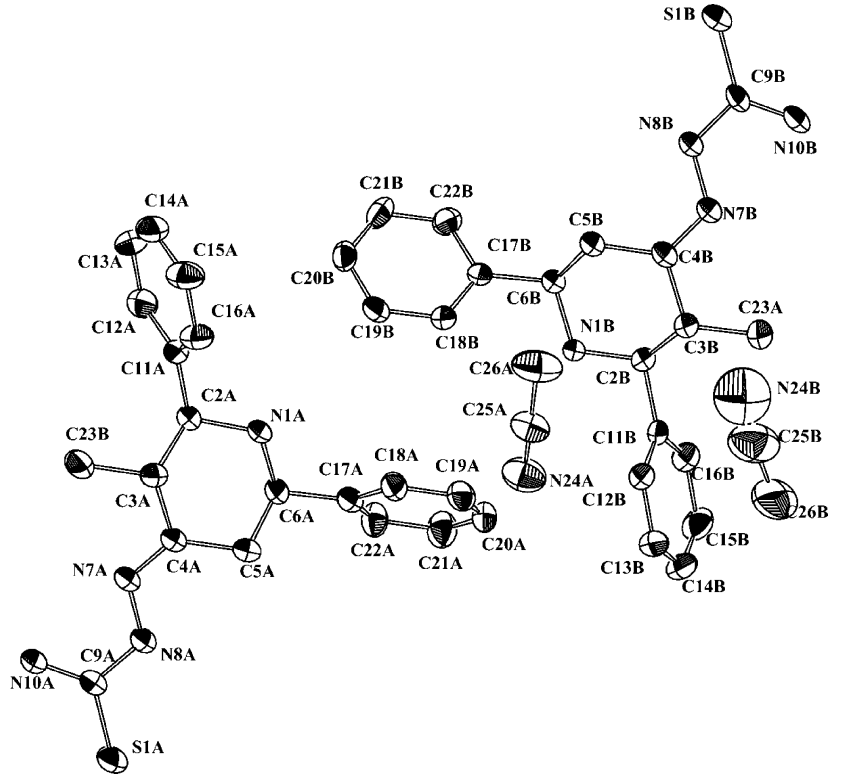


FIGURE 2 Perspective view of MDPTAN asymmetric unit is presented. The thermal ellipsoids are drawn at 30% probability.

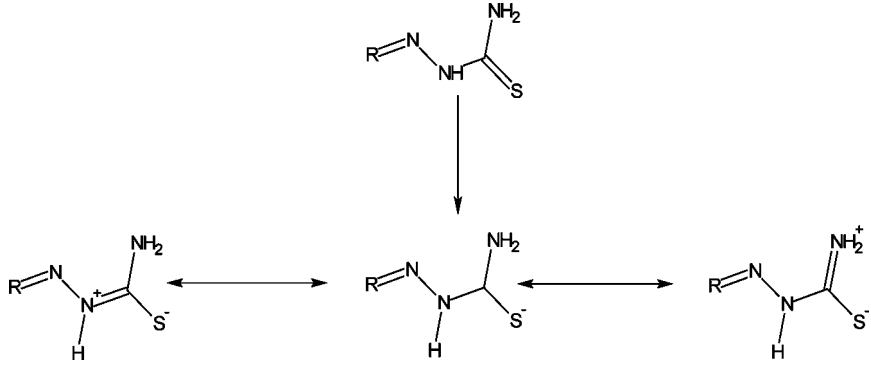


FIGURE 3 Resonance structures of thiosemicarbazone moiety.

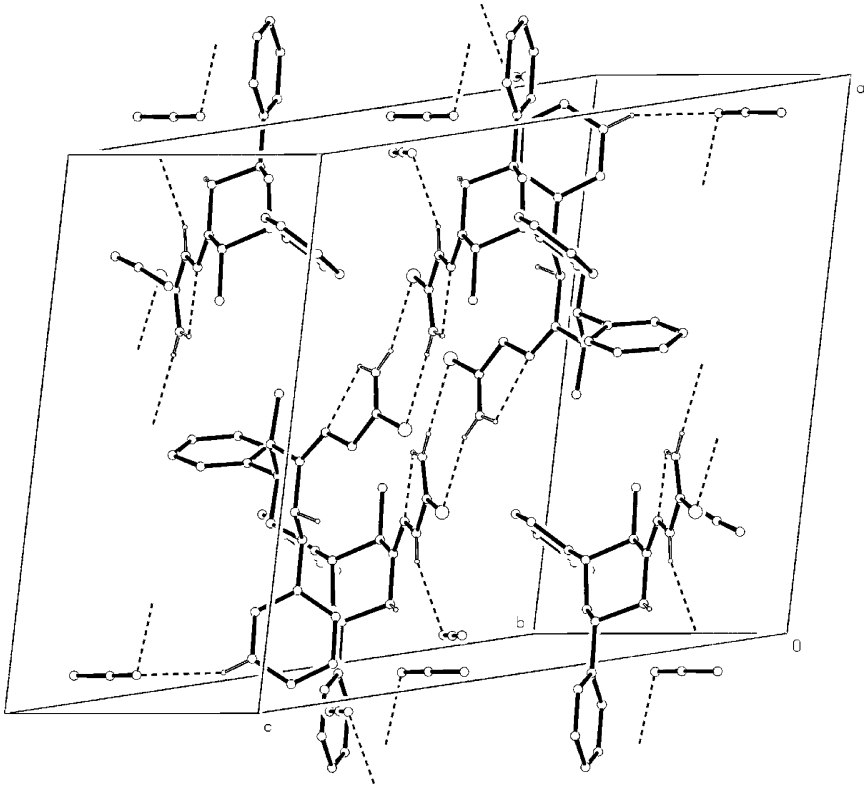


FIGURE 4 Diagram to show the packing of MDPTAN molecules. The dashed lines indicate hydrogen bonds.

[17,23]. The atoms N1 and C4 of piperidine rings deviate by 0.660 and −0.586 Å for molecule A and 0.680 and −0.605 Å for molecule B on either side of the best plane of piperidine rings.

The packing of the molecules is shown in Fig. 4. One of the intramolecular N-H···N hydrogen bonds stabilizes the planar configuration of TSC. The C-H···N, N-H···N and N-H···S types of intra- and intermolecular interactions leads to multichannel networking in the unit cell. The pairs of intermolecular N-H···S hydrogen bonds across the center of inversion result in the formation of dimer molecules [24]. The solvent molecules (actonitrile) also play a key role in packing molecules through hydrogen bonding. In addition to van der Waals forces, four C-H···π intermolecular interactions also help in the packing of molecules in the crystal [25]. The details are given in Table 2.

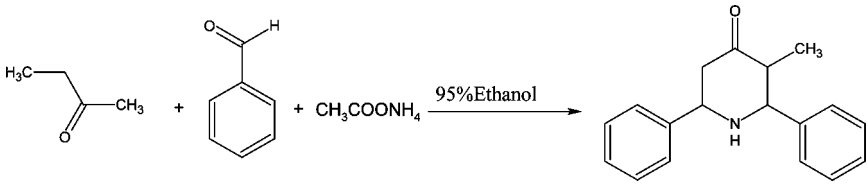
TABLE 2 Geometry (Å, °) of Various Interactions in the Structure

D-H···A	D-H	D···A	H···A	D-H···A
N10A-H10A···N7A^{i}	0.860(4)	2.589(6)	2.218(4)	105.8(3)
C19A-H19A···N24A^{i}	0.930(6)	3.420(9)	2.554(6)	155.2(4)
N10B-H10C···N7B^{i}	0.860(4)	2.581(5)	2.206(4)	106.1(3)
C12B-H12B···N24A^{i}	0.930(4)	3.531(7)	2.715(5)	146.9(3)
C5A-H5A1···N24B^{ii}	0.970(5)	3.785(2)	2.846(2)	163.3(4)
N10A-H10B···S1B^{iii}	0.860(4)	3.316(5)	2.483(2)	163.3(3)
C15A-H15A···N7A^{iv}	0.930(7)	3.454(7)	2.744(4)	133.9(4)
C15A-H15A···N10A^{iv}	0.930(7)	3.604(8)	2.937(4)	129.8(4)
C5B-H5B1···N24A^{v}	0.970(4)	3.585(8)	2.673(6)	156.8(3)
N8B-H8B···N24A^{v}	0.860(4)	3.313(7)	2.488(6)	161.0(3)
N10B-H10D···S1A^{vi}	0.860(4)	3.342(5)	2.494(2)	168.5(3)
C22B-H22B-Cg3^{i}	0.930	3.819	2.945	157.3
C13B-H13B-Cg4^{vii}	0.930	3.748	2.867	158.7
C20A-H20A-Cg2^{viii}	0.930	3.813	2.964	152.5
C20B-H20B-Cg1^{viii}	0.930	3.778	2.912	155.6

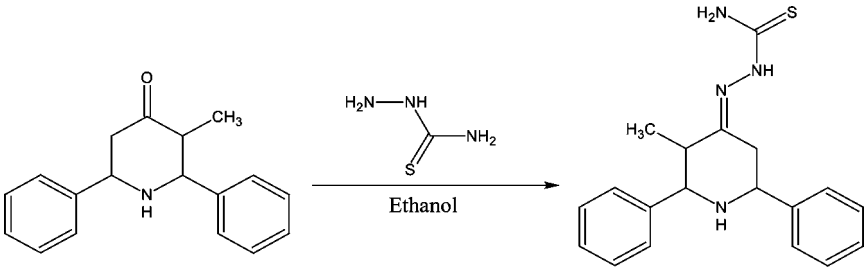
Notes: Equivalent positions: (i) x, y, z; (ii) $-x, +y+1/2, -z+1/2$; (iii) $x-1, +y+1, +z$; (iv) $-x-1, +y-1/2, -z+1/2$; (v) $-x, +y-1/2, -z+1/2$; (vi) $x+1, +y-1, +z$; (vii) $2-x, -1/2+y, 3/2-z$; (viii) $2-x, -y, 1-z$. Cg1 = C11A through C16A; Cg2 = C11B through C16B; Cg3 = C17A through C22A; Cg4 = C17B through C22B. Cg's are the centroid of the phenyl ring.

Preparation of MDPTAN

The title compound was prepared according to the Mannich condensation reaction in which benzaldehyde, ammonium acetate, and ethyl methyl ketone in the ratio of [2:1:1] in 95% ethanol was refluxed for 1 h and then kept overnight [26]. The reaction product t-3-methyl-r-2, c-6-diphenyl-piperidine-4-one obtained was recrystallized in ethanol.



This product was treated with equimolar quantity of thiosemicarbazide in the presence of a small amount of conc. HCl in ethanol on a water bath and refluxed for 2 h. The product was separated out and dried. Colorless crystals were grown by slow evaporation using acetonitrile



SCHEME 1

as solvent. Good quality crystals were chosen for structural studies. The scheme of preparation of the title compound is shown in Scheme 1.

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REFERENCES

[1] Klayman, D. L., Scovill, J. P., Bartosevich, J. F., & Mason, C. J. (1979). *J. Med. Chem.*, *22*, 1367.
[2] French, F. A. & Blanz, E. J. Jr. (1966). *J. Med. Chem.*, *9*, 585.
[3] Agarwal, K. C., Cushley, R. J., McMurray, W. J., & Sartorelli, A. C. (1970). *J. Med. Chem.*, *13*, 431.
[4] Nandi, A. K., Chaudhuri, S., Mazumdar, S. K., & Ghosh, S. (1984). *J. Chem. Soc. Perkin Trans.*, *2*, 1729.
[5] Nandi, A. K., Sheldrick, W. S., & Ghosh, S. (1986). *Acta Cryst.*, *C42*, 1570.
[6] Nagarajan, K., Talwalker, P. K., Kulkarni, C. L., Venkateswaralu, A., Prabhu, S. S., & Nayak, G. V. (1984). *Indian J. Chem.*, *23B*, 1243.
[7] French, F. A. & Freedlander, B. L. (1958). *Cancer Res.*, *18*, 1290.
[8] Sorkin, E., Roth, W., & Erlenmeyer, H. (1952). *Helv. Chim. Acta.*, *35*, 1736.
[9] Cymerman, J. C., Willis, D., Rubbo, S. D., & Edgar, J. (1955). *Nature (London)*, *176*, 34.
[10] Thelander, L. & Graslund, A. (1983). *J. Biol. Chem.*, *258*, 4063.
[11] Tian, Y.-P., Duan, C.-Y., Lu, Z.-L., You, X.-Z., Fun, H.-K., & Kandasamy, S. (1996). *Polyhedron*, *15*, 2263.
[12] Tian, Y.-P., Duan, C.-Y., Chao, C.-Y., You, X.-Z., Zhang, Z.-Y., & Mak. T. C. W. (1997). *Inorg. Chem.*, *36*, 1247.
[13] Liu, Z.-H., Duan. C.-Y., Hu, J., & You, X.-Z. (1999). *Inorg. Chem.*, *38*, 1719.
[14] Siemens. (2000). *SMART and SAINT*. Siemens Analytical X-ray Instruments Inc.: Madison, Wisconsin.

[15] Sheldrick, G. M. (1997). *SHELXS97: Program for the crystal structure solution*, University of Göttingen: Göttingen, Germany.
[16] Sheldrick, G. M. (1997). *SHELXL97: Program for the crystal structure refinement*, University of Göttingen: Göttingen, Germany.
[17] Nardelli, M. (1995). *J. Appl. Cryst.*, *28*, 659.
[18] Zsolnai, L. (1998). *ZORTEP: An interactive graphics crystal structure illustrations*, University of Heidelberg: Heidelberg, Germany.
[19] Spek, A. L. (2003). *J. Appl. Cryst.*, *36*, 7.
[20] Casas, J. S., Castineiras, A., Lobana, T. S., Sanchez, A., Sordo, J., & Garcia-Tasende, M. S. (2001). *J. Chem. Cryst.*, *31*, 329.
[21] Chattopadhyay, D., Mazumdar, S. K., Banerjee, T., Ghosh, S., & Mak, T. C. W. (1988). *Acta Cryst.*, *C44*, 1025.
[22] Campbell, M. J. M. (1975). *Coord. Chem. Rev.*, *15*, 279.
[23] Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.*, *97*, 1354.
[24] Palenik, G. J., Rendle, D. F., & Carter, W. S. (1974). *Acta. Crsyt.*, *B30*, 2390.
[25] Desiraju, G. R. (1989). Crystal engineering—the design of organic solids. In: *Material Science Monographs, No. 54*, Desiraju, G. R. (Ed.), Elsvier Science: New York.
[26] Noller, C. R. & Baliah, V. (1948). *J. Am. Chem. Soc.*, *70*, 3853.