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Crystal Structure of an Azabicyclic Thiosemicarbazone Derivative

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The structure of 1N-nitroso-2, 6-diphenylazabicyclo[3.3.1]nonan-9-one thiosemicarbazone (NDAOT), $C_{21}H_{23}N_5OS$, F.W. = 393.506, orthorhombic, $Pna2_1$, $a = 8.426(3)\,\AA$, $b = 17.862(5)\,\AA$, $c = 13.313(4)\,\AA$, $V = 2003.6(1)\,\AA^3$, $Z = 4$, $D_{cal} = 1.304\,Mgm^{-3}$, $\mu = 0.183\,mm^{-1}$, $F(000) = 832$, $\lambda(MoK_\alpha) = 0.71073\,\AA$, final R1 and wR2 are 0.0501 and 0.1029, respectively. The cyclohexane and piperidine rings adopt chair–chair conformations. The phenyl rings are equatorially and bisectionally substituted at 2, 6-positions of the piperidine ring. The molecules are packed in the unit cell with the help of C–H···S, N–H···S, and N–H···O types of intra- and intermolecular hydrogen bondings. An intermolecular C–H···π interaction also plays a role in stabilizing the molecules in addition to van der Waals forces.

Keywords: crystal structure; conformation; cyclohexane; hydrogen bonding; NDAOT

INTRODUCTION

The relationship between metal ions and cancer is intriguing and controversial. French and Freedlander [1] suggested that one common property of some antitumour agents was their ability to function as chelating agents. Subsequently French and Blanz [2] prepared a

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number of thiosemicarbazones and found that all the tumor inhibitors were potentially capable of acting as a tridentate N-N-S type ligands.

Thiosemicarbazones (TSCs) are derivatives of carbonyl compounds, which exhibit a wide spectrum of biological activities. These include antitumor and antileukemic properties [2,3], antibacterial and antiviral activities [4,5], antimalarial activity [6], and antifertility property [7]. In general, the N, S donor ligands such as substituted thiosemicarbazones and thiosemicarbazides are attributed to their ability to form metal chelates [8,9], nonlinear optical property [10], and their reductive capacities [11].

The unsubstituted N-nitrosopiperidines are potential carcinogens and the carcinogenicity is found to be reduced when an alkyl group is substituted at the α position (C-2 and C-6). If α positions are substituted by methyl groups, they become noncarcinogens. It appears that blocking of α positions to the ring nitrogen atom by methyl groups in cyclic nitrosoamines is responsible for reducing the carcinogenic activity [12]. The phenyl rings substituted at the position of C-2 and C-6 also show significant anticancer activity. Furthermore, the size of the bicyclic ring is increased by synthetic methods to explore the highest activity.

As a part of our studies on thiosemicarbazone derivatives, we have prepared the title compound and carried out the crystal structure analysis by X-ray diffraction methods to establish the molecular structure and stereochemistry. The chemical diagram of the title compound (NDAOT) is shown in Fig. 1.

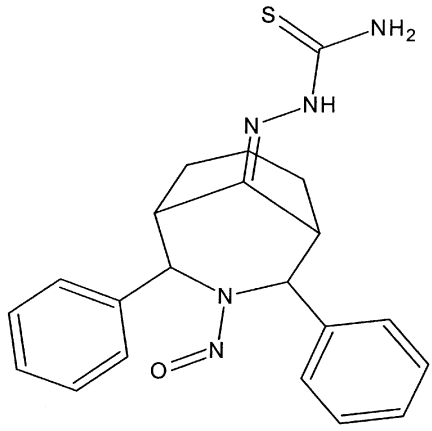


FIGURE 1 Chemical diagram of NDAOT.

X-RAY DATA COLLECTION, STRUCTURE SOLUTION, AND REFINEMENT

Data Collection

Intensity data were collected on a Siemens SMART CCD [13] area detector diffractometer using graphite monochromated MoK_α radiation ($\lambda = 0.71073$ Å) at 293(2) K for NDAOT. The entire data collection was covered over 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 10 s covered 0.3° in ω. The crystal-to-detector distance was 4 cm and the detector swing angle was –35°. Coverage of unique set was complete by more than 100%. Out of 14,963 reflections, 3942 reflections with $I \geq 2\sigma$ (I) were used for structure solution and analysis. The intensities were corrected for Lorentz and polarization effects.

Structure Solution and Refinement

The structure was solved by direct methods using the program SHELXS97 [14] and refined on F^2 by full-matrix least-squares procedures using the program SHELXL97 [15]. The nonhydrogen atoms were refined anisotropically and all the hydrogen atoms were located from a difference Fourier map. The final cycle of refinement converged to $R1 = 0.0501$ and $wR2 = 0.1029$ for the observed reflections. The maximum and minimum heights in the final difference Fourier map were found to be 0.274 and $-0.135\ e{\cdot}Å^{-3}$, respectively. The geometrical calculations and the figures were done using the programs PARST [16] and ZORTEP [17]. The packing diagram of the molecule was done by using PLATON [18] graphical program. The crystal data and other relevant parameters are given in Table 1.

RESULTS AND DISCUSSION

Figure 2 shows the ZORTEP plot of the molecule NDAOT with the thermal ellipsoids drawn at 30% probability level. The thiosemicarbazone moiety of the molecule is planar and adopts an extended conformation with respect to the best plane of the piperidine ring, which is evidenced from the torsion angles. The thiosemicarbazone moiety is oriented at angles of 47.7(1) and 71.9(1)° to the piperidine and cyclohexane rings respectively. The S atom is *trans* to N10, and E configuration is stabilized by intramolecular hydrogen bonding between the N10 and the N13-HA groups [19].

TABLE 1 Crystal Data for NDAOT

Parameter	NDAOT
CCDC No	CCDC 213181
Empirical formula	$C_{21}H_{23}N_5OS$
Formula weight	393.506
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, $Pna2_1$
Unit cell dimensions	$a = 8.426(3)$ Å
	$b = 17.862(5)$ Å
	$c = 13.313(4)$ Å
Volume	2003.6(1) Å^3
Z, calculated density	4, 1.304 mg/ m^3
Absorption coefficient	0.183 mm^{-1}
F (000)	832
Crystal size	0.3 × 0.35 × 0.25 mm
Theta range for data collection	1.91 to 26.0°
Index ranges	$-10 \leq h \leq 10$
	$-20 \leq k \leq 22$
	$-16 \leq l \leq 16$
Reflections collected/unique	14963/3942 [R (int) = 0.0302]
Reflection with $1 \geq 2\sigma(I)$	3397
Completeness to theta = 26.00	100.0%
Refinement method	Full-matrix least squares of F^2
Data/restraints/parameters	3942/0/253
Goodness of fit on F^2	1.141
Final R indices [I > 2sigma(I)]	R1 = 0.0501 wR2 = 0.1029
R indices (all data)	R1 = 0.0599 wR2 = 0.1069
Largest diff. peak and hole	0.274 and −0.135 e·Å^{-3}

The bond lengths of the thiosemicarbazone moiety in comparison with literature values show extensive delocalization. Figure 3 explains the resonance structures of the thiosemicarbazone moiety.

The planar phenyl rings are substituted equatorially at the second position and bisectionally at the sixth position of the piperidine ring. The orientation angles, 62.9(1)° for the rings C16 through C21 and 55.5(1)° for the rings C22 through C27, support this conformation. Both phenyl rings are oriented at angles of 71.25(1)° and 66.63(1)° with respect to the best plane of the piperidine ring.

A study of asymmetry parameters, least-squares planes [16], and torsion angles shows that the piperidine ring adopts a *chair* conformation [$Q_T = 0.529$] and the atoms N1 and C9 deviate by –0.245 and 0.725 Å on either side of the plane of piperidine ring. The deviation of the piperidine ring from the ideal *chair* to distorted *chair* is due to

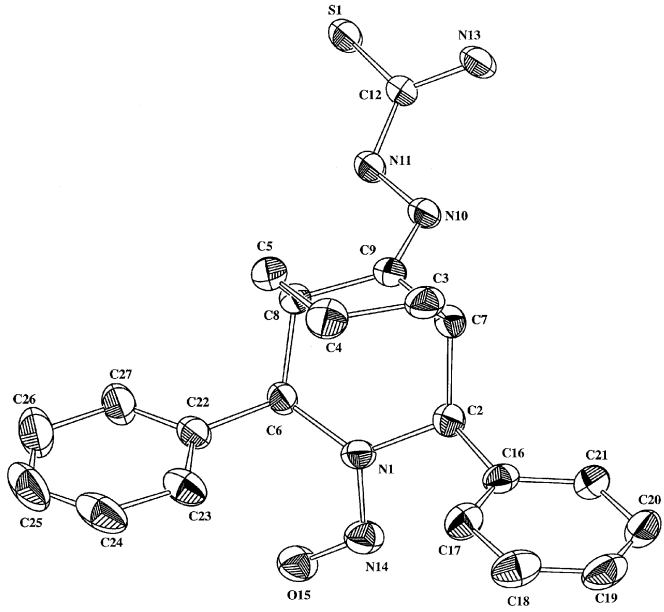


FIGURE 2 ZORTEP plot of the molecule NDAOT with 30% of probability level.

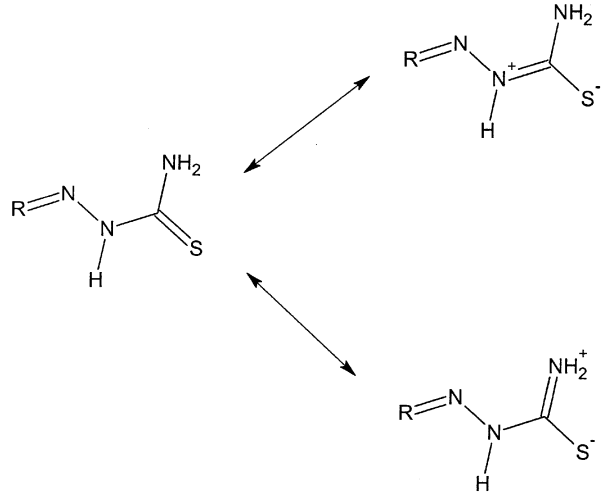


FIGURE 3 Resonance structure of thiosemicarbazone moiety.

the formation of resonance character for the nitroso group atoms substituted at N1 position of the piperidine ring.

The N-nitroso group is equatorially substituted to the best plane of the piperidine ring [68.1(1)°]. The bond lengths and bond angles reveal that the bonds N1–N14–O15 possess the partial double-bond character and planar conformation because of extensive delocalization of the lone pair of electrons of the nitrogen atom with the hetero-π electron system of the nitroso group.

The cyclohexane ring adopts a *chair* conformation [$Q_T = 0.576$], wherein the atoms C4 and C9 deviate by –0.616 and 0.701 Å from the best plane of the cyclohexane ring constituted by the C8, C3, C5, and C7 atoms. The best plane of the cyclohexane and piperidine rings orient at an angle of 64.6(1)° with each other.

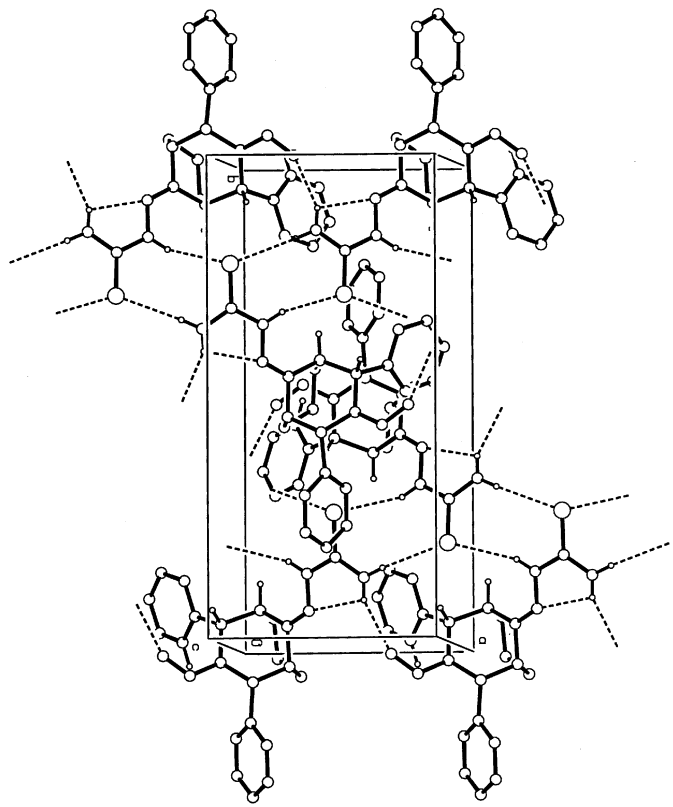


FIGURE 4 Packing diagram of the NDAOT molecules viewed down the c-axis. The dashed lines indicate the H-bonds.

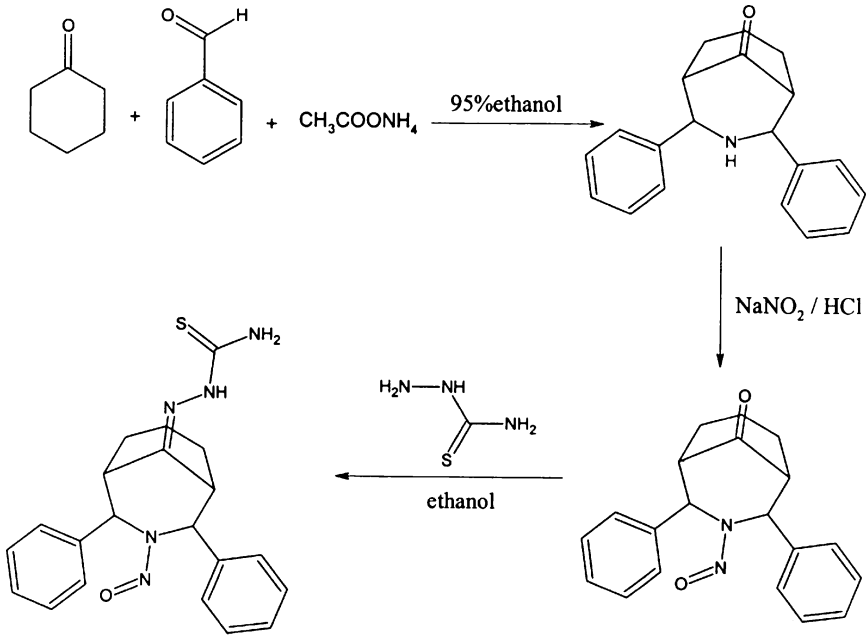
TABLE 2 Hydrogen-Bonding Geometry (Å, °)

D–H···A	d(D–H)	d(D···A)	d(H···A)	<(D–H···A)
N13–H13 A···N 10^{i}	0.860(3)	2.585(3)	2.218(2)	105.57(2)
C6–H6···S1^{ii}	0.980(3)	3.664(3)	2.817(1)	145.10(2)
N11–H11···S1^{ii}	0.860(2)	3.426(3)	2.738(1)	138.04(2)
N13–H13A···O15^{iii}	0.860(3)	3.083(3)	2.287(2)	153.77(2)
N13–H13B···S1^{iv}	0.860(2)	3.391(3)	2.580(1)	157.53(2)
C21–H21···Cg^{v}	0.930	4.144	3.218	173.9

Note: Equivalent positions: (i) x, y, z; (ii) x – 1/2, –y+1/2, +z; (iii) x +1, +y, +z; (iv) x +1/2, –y +1/2, +z; (v) –x, –y, 1/2 +z.

C_g = C22 through C27 and is the centroid of the phenyl ring.

The packing of the molecules viewed down the c axis is shown in Fig. 4. An N–H···N intramolecular hydrogen bond forms a closed five-membered ring containing the atoms N10, N11, C12, N13, and H13A. The N–H···S intermolecular hydrogen bonds across the center of inversion results in the formation of a network of dimeric structures [20]. An intermolecular C–H···π interaction plays a role



SCHEME 1

in stabilizing the molecules [21] in addition to van der Waals forces. A number of C–H···S, N–H···O, and N–H···S types of intermolecular hydrogen bond show the multichannel networking in the unit cell. The details are given in Table 2.

Preparation of NDAOT

The title compound was prepared by a Mannich condensation reaction using 2 mol of benzaldehyde, 1 mol of ammonium acetate, and 1 mol of cyclohexanone [2:1:1] and was heated on a hot plate up to the boiling range [22,23]. The reacting product 2,6-diphenylazabicyclo[3.3.1] nonan-9-one was obtained.

This product was treated with $NaNO_2$/HCl/80% ethanol and maintained at 80°C for 4 h with vigorous stirring. The resulting N-nitroso product was treated with equimolar quantity of thiosemicarbazide in the presence of a small amount of conc. HCl in methanol on a water bath and refluxed for 2 h. The product was separated out and dried using fused $CaCl_2$. Orange crystals were grown by the slow-evaporation method using methanol. The schematic preparation of the title compound is shown in Scheme 1.

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