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Synthesis, Spectral and Single-Crystal Analyses of New Derivatives of 4-Amino-N-benzylpiperidine

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Two new compounds of thiourea derivatives of cinnamoyl and benzoylisothiocyanate with 4-amino-N-benzylpiperidine have been successfully synthesized. The new molecules, 1-(1-benzylpiperidine-4-yl)-3-benzoyl thiourea (**I**) (yield 83 %) and 1-(1-benzylpiperidine-4-yl)-3-(3-phenylacryloyl)thiourea (**II**) (yield 81%) were characterized by NMR, IR, UV, CHNS-O techniques as well as X-ray diffraction for single crystal. ^{1}H NMR spectra show chemical shift at 10.77-10.80 ppm and 8.98-8.93 ppm were assigned for both δH(N) protons. Whereas, the chemical shift for ^{13}C NMR analysis for C=O and C=S presence at δC 169-179 ppm. The significant stretching bands for ν(N-H), ν(C=S), ν(C=O) and ν(C-N) were around 3250, 800, 1650 and 1340 cm^{-1}, respectively. The important chromophore of C=O was observed with a maximum absorption at around 300 nm in the UV spectra. The structures of (**I**) and (**II**) were determined *via* X-ray diffraction analysis for single crystal. Both molecules exhibit monoclinic crystal system and adopt *trans-cis* configuration with respect to the position of the phenyl and N-benzylpiperidine groups relative to the thione S atom, across their C-N bonds. There is one intramolecular N-H···O hydrogen bonds in both molecules that lead to the formation of pseudo-six-membered, in addition to a pseudo-five-membered ring, C9–H9···S1, in (**I**) which stabilizes the molecule. In the crystal lattice, the molecules are linked by intermolecular hydrogen bonds C–H···S and C–H···O forming chain network in (**I**) and polymeric in (**II**).

Keywords: Thiourea, Benzoyl, 4-Amino-N-benzylpiperidine, X-ray crystallography.

INTRODUCTION

Thiourea derivatives obtained as aroylthiourea substituted derivatives are compounds of interest in solid-state chemistry due to their tendency to the formation of inter- and intramolecular hydrogen bonds for NH proton donor group to the carbonyl sulfur and oxygen atoms[1-3]. In addition to environmental and industrial applications, thiourea compounds are generally used in several applications for example anticancer drugs, platelet antiaggregating, antidepressants, antihyperlipidemic, antibacterial, antiparasitic, antiallergic and antiproliferative activity[4-6]. Previous studies described that thiourea compounds moieties have been extensively used as fungicides and insecticides agent[7-10]. On the other hand, thiourea compounds are suitable inclusion compounds or host materials showing various applications in the development of electronic and optoelectronic devices[11,12]. Due to atom sulfur is easily protonated in acidic solution, thiourea derivatives are effective corrosion inhibitor agents [13,14]. Thiourea ligand is not sensitive to air and moisture and heat stable thus the reaction can be carried out in ambient environments[15-17]. The literature review showed that no work has been reported on the synthesis of cinnamoyl and benzoyl thiourea with 4-amino-N-benzylpiperidine. The structural and spectral properties of 1-(1-benzylpiperidine-4-yl)-3-benzoyl thiourea (**I**) and 1-(1-benzylpiperidine-4-yl)-3-(3-phenylacryloyl)thiourea (**II**) (Fig. 1) are described in this paper.

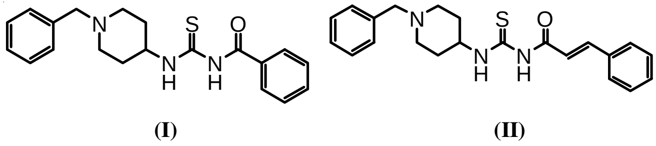

Fig. 1. Molecular structural representations of (**I**) and (**II**)

EXPERIMENTAL

Chemicals used for synthesis the new compounds were purchased from MERCK or Sigma Aldrich. NMR spectra for ^{1}H 400.11 MHz and ^{13}C 100.61 MHz were recorded using NMR Bruker Avance III 400 spectrometer in DMSO-d_6 as a solvent at room temperature in the range of 0-15 ppm and 0-200 ppm. Infrared spectra (IR) of the synthesized compounds were recorded from KBr pellets using Perkin Elmer FTIR 100 spectrophotometer in the range of 4000-400 cm^{-1}. The structures of the new compounds were solved and refined using SHELX[18]. Data collection: SMART[19]; molecular graphics: SHELXL 97[20]; cell refinement: SAINT and data reduction: structure: SHELXS 97[21] software used to prepare material for publication: SHELXTL[22] and PLATON software to calculate the hydrogen bonds[23]. The view of the molecule was obtained by using ORTEP-32 for Windows[24].

Synthesis of (I) and (II): Benzoyl/cinnamoyl isothiocyanate was first prepared by adding an acetone solution containing ammonium thiocyanate into benzoyl/cinnamoyl chloride in acetone. The mixtures were stirred for 10 min before the precipitate was filtered and washed with cold acetone. The reaction between of benzoyl/cinnamoyl isothiocyanate and 4-amino-N-benzylpiperidine in acetone was stirred for 15 min under 70 °C with a mol ratio of 1:1. The mixture was refluxed for 3 h and filtered into a beaker containing some ice. A white precipitate was formed immediately, filtered and dried. The isolated product had a melting point of 173.5-175.2°C (Fig. 2).

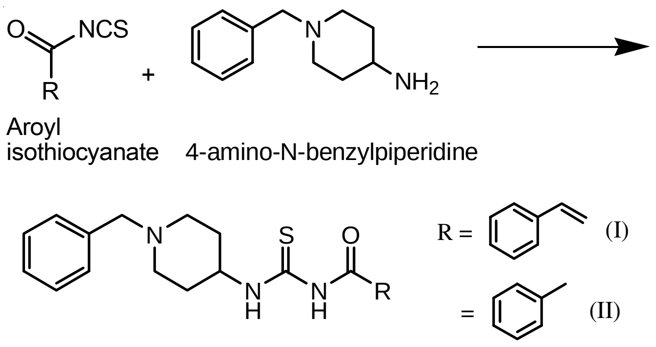

Fig. 2. Synthetic routes of (**I**) and (**II**)

RESULTS AND DISCUSSION

Ultraviolet spectra: Ultraviolet absorption for (**I**) and (**II**) show $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transition (HUMO→LUMO). The ultraviolet spectra exhibited an important bands for chromophore carbonyl (C=O) group. Both compounds show maximum absorption bands for chromophore C=O in compound (**I**) and (**II**) at 325.40 nm and 322.70 nm, respectively (Fig. 3). Table-1 shows the maximum absorption for each compounds; (**I**) and (**II**) from the UV spectra study.

Infrared spectra: The IR spectra revealed the expected frequencies of the ν(N-H), ν(C=O), ν(C-N) and ν(C=S) in both compounds. An average intensity bands presence at 3243.68 cm^{-1} (**I**) and 3178.39 cm^{-1} (**II**) which relates to stretching ν(N-H). The stretching band of ν(N-H) (**I**) has higher frequency comparing with compound (**II**) because of the position the of electron withdrawing group around NH moiety. The absorption bands nearby 1666.39 and 1681.87 cm^{-1} represent the stretching of ν(C=O) in (**I**) and (**II**), respectively and it is decreasing in frequencies compared with typical carbonyl absorption (1700 cm^{-1})[25]. This is due to conjugated resonance of phenyl group and the formation of intramolecular hydrogen bonding with N-H[26]. The stretching vibrations of ν(C-N) band are at 1338.53 cm^{-1} (**I**) and 1340.56 cm^{-1} (**II**). 907.63 cm^{-1} (**I**) and 858.94 cm^{-1} (**II**) are assigned for stretching ν(C=S) modes. From IR spectra analysis (Table-2) show that the thiourea moieties were formed for compounds (**I**) and (**II**) in good agreement with previous studies[27,28].

TABLE-1
UV ABSORPTION OF COMPOUNDS (**I**) AND (**II**)

Compound	ν(C=O) λ_{max} (nm)	ν(C=O) Transition
(**I**)	325.40	$n \rightarrow \pi^*$, $\pi \rightarrow \pi^*$
(**II**)	322.70	$n \rightarrow \pi^*$, $\pi \rightarrow \pi^*$

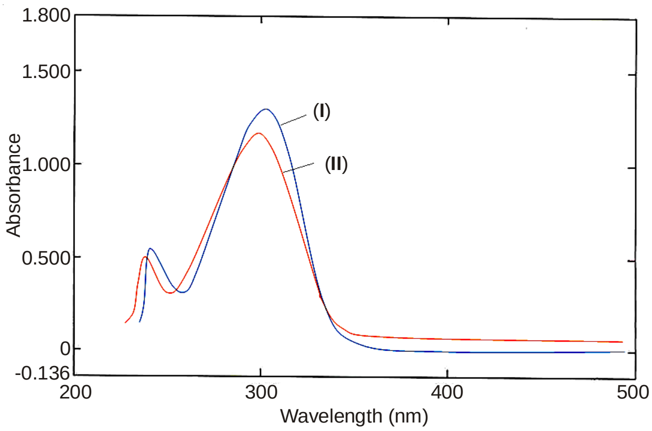

Fig. 3. UV spectra of compounds (**I**) and (**II**)

TABLE-2
IR ABSORPTION DATA FOR COMPOUNDS (**I**) AND (**II**)

Compound	Wavenumber (cm^{-1})			
	ν(N-H)	ν(C=O)	ν(C-N)	ν(C=S)
(**I**)	3243.68	1666.39	1338.53	907.63
(**II**)	3178.39	1681.87	1340.56	858.94

X-ray crystallographic studies: The new molecules were obtained as single crystals suitable for X-ray analysis (Table-3). Both (**I**) and (**II**) adopt *cis-trans* configuration with respect to position of 4-amino-N-benzylpiperidine and phenyl groups relative to the S atom, across C-N bonds (Figs. 4 and 5). The central moiety, S1/O1/N1/N2/C6/C7/C8, in compound (**I**) [maximum deviation 0.004(3) Å at atom N1] and the phenyl group (C1-C6) are planar and dihedral angle between the least planes is 35.51(18)°. The bond length of C=S group of (**I**) [1.830(4) Å] is longer than that of (**II**) [1.673(4) Å]. In compound (**II**), the dihedral angle between the central fragment, S1/O1/N1/N2/C7/C8/C9/C10/C11 [maximum deviation 0.006(3) at N1] and phenyl group (C1-C6) is 25.8(15)°. The fragment C16/C17/C18/C19/C20/C21 in (**II**) is planar with maximum deviation of 0.006(5) at C19. The C7-C8, bond length [1.315(5) Å], has a double bond character with H atoms at atoms C7 and C8 *trans* to each other.

Table-4 presented that the bond lengths and angles were in normal ranges[29] and analogous to other thiourea derivatives[30,31]. Nevertheless, C8-N1 in (**I**) is longer than C8-N2. While in (**II**), C10-N1 is longer than C10-N2. The differences are probably because of the interaction of the intramolecular hydrogen bonding[26]. C=S and C=O bond distances for both molecules show the expected double bond character.

TABLE-3
CRYSTAL DATA FOR COMPOUND (**I**) AND (**II**)

Subject	(**I**)	(**II**)
Empirical formula	$C_{20}H_{23}N_3OS$	$C_{22}H_{25}N_3OS$
Formula weight	353.47	379.51
Crystal system	Monoclinic	Monoclinic
Wavelength	0.71073 Å	
Space group	$P2_1/c$	$P2_1/c$
a (Å)	8.857(7)	31.033(3)
b (Å)	20.392(16)	5.9352(6)
c (Å)	11.953(9)	20.0798(14)
α (°)	90	90
β (°)	100.246(3)	106.066(13)
γ (°)	90	90
Volume ($Å^3$)	1881.2(6)	2075(3)
Z, calculated density (mg/m^{-3})	4, 1.248	4, 1.215
Absorption coefficient (mm^{-1})	0.184	0.172
F(000)	752	808
Crystal size (mm)	0.36×0.21×0.16	0.35×0.28×0.21
Crystal description	Block	Block
Crystal colour	Colourless	Colourless
θ Range°	1.52-26.0	2.00-24.99
Index ranges	$-16 \leq h \leq 16$ $-10 \leq k \leq 15$ $-13 \leq l \leq 13$	$-10 \leq h \leq 10$ $-24 \leq k \leq 24$ $-14 \leq l \leq 14$
Independent reflections	10024/3691 [R(int) = 0.0239]	14667/3656 [R(int) = 0.0281]
Max. and min. transmission	0.9711 and 0.9366	0.9648 and 0.9423
Procession method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	3691/0/226	3656/0/244
Goodness-of-fit on F^2	1.222	1.380
Largest diff. peak ($e.A^{-3}$)	0.226	0.193
Largest diff. hole ($e.A^{-3}$)	-0.168	-0.137
R, wR	0.0684, 0.1371	0.0840, 0.1524
R,wR (all reflection)	0.0838, 0.1437	0.0965, 0.1572

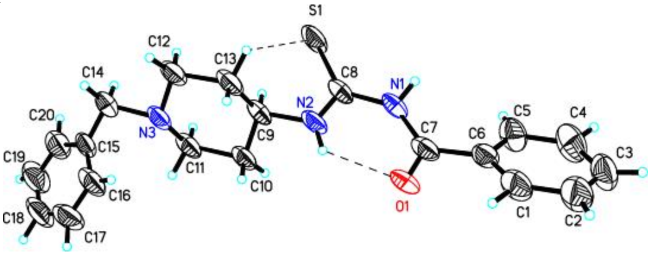

Fig. 4. Molecular structure of (**I**), (with 50 % probability displacement ellipsoids) with intramolecular hydrogen bonds

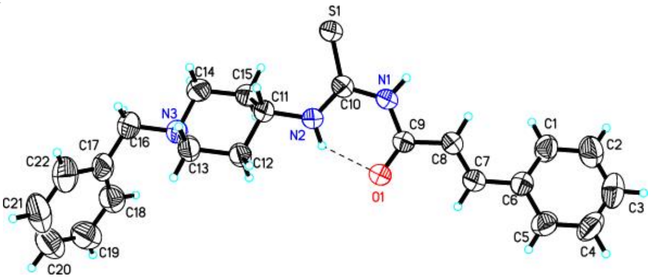

Fig. 5. Molecular structure of (**II**), (with 50 % probability displacement ellipsoids) with intramolecular hydrogen bond

TABLE-4
SELECTED BOND LENGTHS (Å) AND
ANGLES (°) FOR COMPOUNDS (**I**) AND (**II**)

Compd.	Bond	Bond distances (Å)	Distances	Angles distances (°)
(**I**)	S1-C8	1.830(4)	C7-N1-C8	144.0(0)
	O1-C7	1.029(3)	C8-N2-C9	116.0(3)
	N1-C8	1.625(5)	C11-N3-C14	108.2(3)
	N2-C8	1.098(3)	N1-C7-C6	135.7(2)
	N2-C9	1.623(4)	N1-C8-N2	117.1(3)
	N3-C12	1.319(4)	S1-C8-N1	136.83(18)
	N3-C14	1.680(5)	O1-C7-N1	115.6(3)
(**II**)	S1-C10	1.673(4)	C9-N1-C10	128.3(3)
	O1-C9	1.219(4)	C10-N2-C11	124.4(3)
	N1-C9	1.376(4)	O1-C9-N1	122.5(3)
	N1-C10	1.377(4)	S1-C10-N1	118.4(2)
	N2-C10	1.314(4)	N1-C9-C8	113.9(3)
	N3-C16	1.467(4)	N1-C10-N2	117.1(3)

There are two intramolecular hydrogen bonds in (**I**), C–H···S and N-H···O, which form two pseudo-six-membered rings, in addition to a pseudo-six-membered ring, C13–H13A···S1, in (**II**) which further stabilizes the molecule (Table-5). Compound (**I**) has shorter hydrogen bond distance of N2-H2···O1, 3.204(4) Å compare to (**II**), the distance of N2-H2···O1 is 2.645(3) Å. This difference indicates an electronic effect and steric effect of the molecules.

TABLE-5
INTRAMOLECULAR AND INTERMOLECULAR
HYDROGEN BOND DISTANCES (Å) AND
ANGLES (°) FOR COMPOUNDS (**I**) AND (**II**)

Compound	D	A	D-H	H···A	D-H···A	D-H···A
Intramolecular						
(**I**)	N2	O1	0.86	2.56	3.204(4)	133
	C13	S1	0.97	2.45	2.941(4)	111
(**II**)	N2	O1	0.86	1.96	2.645(3)	136
Intermolecular						
(**I**)	N1	S1	0.86	2.27	3.064(3)	169
	C11	O1	0.97	2.48	3.125(4)	124
(**II**)	N1	S1	0.86	2.55	3.394(4)	165
	C8	S1	0.93	2.72	3.562(5)	151
	C16	O1	0.97	2.52	3.382(5)	147

In the crystal packing of (**I**), intermolecular hydrogen bonds N1-H1A···O2 linked the molecules to form polymeric network. Whereas in (**II**), the intermolecular hydrogen bonds N1-H1A···O2 and C2-H2···O1 are forming chain network (Figs. 6 and 7).

Nuclear magnetic resonance: ^1H NMR and ^{13}C NMR spectra are comparable and reliable with the structures resulted from the X-ray investigation. The two most de-shielded signals were represented NH proton at δH 9.12, δH 10.96 ppm (**I**) and δH 9.00, δH 10.97 ppm (**II**). These signals are similar to those found in the analogous molecules as reported in previous

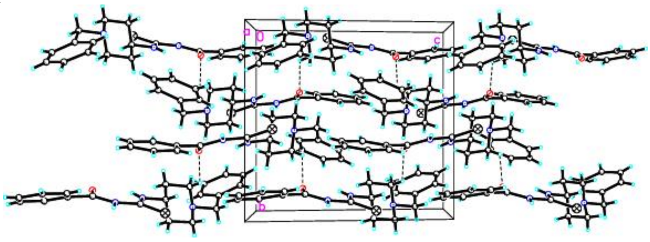

Fig. 6. Molecular packing of (**I**) viewed down the *c*-axis

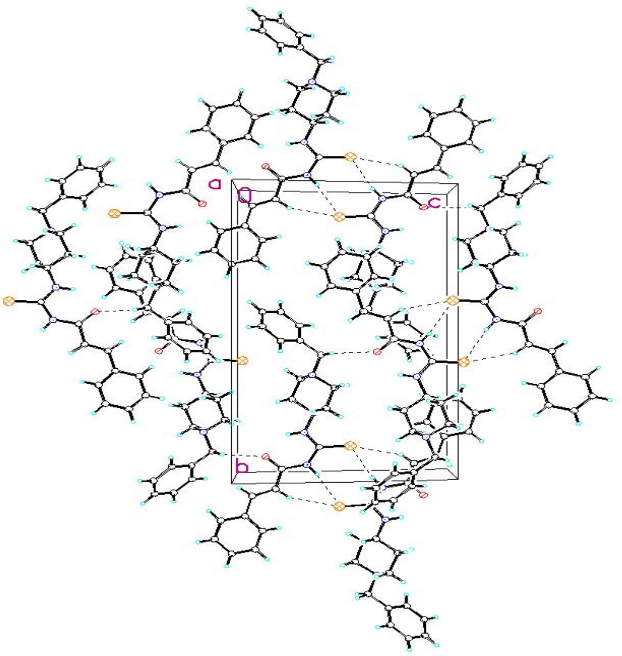

Fig. 7. Molecular packing of (**II**) viewed down the *ac* face

studies[32,33]. There are multiplet signals at δH 7.21-7.91 ppm which represent the aromatic protons of phenyl ring in (**I**) and (**II**). The ^{13}C NMR spectra exhibited a signal for C=O and C=S which was observed at δC 179.52 and 165.25 ppm for (**I**) and 179.42 and 166.48 ppm (**II**), respectively. While the aromatic carbons of the phenyl ring were around δC 128-129 ppm for both compounds. Generally, the chemical shifts of (**I**) and (**II**) show no major difference in carbon and proton NMR analysis.

Conclusion

The synthesis of two new thiourea derivatives of 4-amino-N-benzylpiperidine have been carried out and characterized by using nuclear magnetic resonance analysis (NMR), infrared (IR) and ultraviolet (UV-visible). The infrared spectra show the important stretching bands for ν(C=O), ν(N-H), ν(C=S) and ν(C-N) for (**I**) and (**II**). The UV spectra showed that there is a significant chromophores C=O which is responsible to n→π* and π→π* transition in both molecules. The structures of the new molecules were studied by single crystal X-ray diffraction analysis and exhibit monoclinic crystal systems both (**I**) and (**II**).

Supplementary data

CCDC1041584 and CCDC1041585 contain the supplementary crystallographic data for (**I**) and (**II**), respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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