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Synthesis and Conformational Analysis of Some 3-Alkyl-2,6-diarylpiperidin-4-one Semicarbazones

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^{1}H NMR and ^{13}C NMR of several 3-alkyl-2,6-diarylpiperidin-4-one semicarbazones **2a$_1$**, **2b$_1$-b$_5$**, **2c$_1$-2c$_3$** and **2d$_1$** have been recorded at 400 MHz. The spectral analysis data suggested that the compounds **2a$_1$**, **2b$_1$-b$_5$**, **2c$_1$-2c$_3$** exist predominantly in chair conformation with the ary1 and alky1 substituents in the equatorial positions whereas **2d$_1$** exists in boat conformation.

Key Words: Piperidone semicarbazone, Chair conformation, Boat conformation, NMR.

INTRODUCTION

Nuclear magnetic resonance (NMR) spectroscopy is one of the most powerful techniques for structural determination of organic and inorganic compounds. Noller and Baliah[1] have synthesized 2,6-diarylpiperidine-4-ones and the compounds have been subjected to several physico-chemical studies[2-5]. Pandiarajan *et al.*[6] have recorded the ^{1}H NMR spectra of several 2,6-diarylpiperidine-4-ones with and without alkyl groups at N, C-3 and C-5 positions at 270 MHz. Analysis of the spectral data suggests that these compounds exist predominantly in chair conformation with the aryl and alkyl substituents in the equatorial positions. Introducing of an alkyl group at C-3 causes a flattening of the ring about the C(2) and C(3) bond. An axial methyl group at C-3 causes a flattening of the C(5)-C(6) bond. Presence of an *o*-chloro substituent does not seem to cause a significant change in the conformation of the ring. Rotation of the phenyl groups is fast on NMR time scale under the experimental conditions. There are reports[7] on the conformation of N-acetyl-r(2),c(6)-diphenylpiperidin-4-one semicarbazone and t(3)methyl-N-acetyl-r(2),c(6)-diphenylpiperidin-4-one semicarbazone. The compounds are found to be in chair conformation. In this paper, the synthesis and conformational analysis of some 3-alkyl-2,6-diarylpiperidin-4-one semicarbazones are reported.

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EXPERIMENTAL

The C, H, N analysis was done on a Heraeus-C, H, N rapid analyzer. ^{13}C NMR spectra were recorded on a DRX 500 and AMX 400 spectra operating at 125.7 and 100 MHz, respectively using 10 mm sample tubes. Solution for the measurement of spectra were prepared by dissolving 0.5 g of the sample in 2.5 mL of chloroform-d containing 1 % TMS and acetone. All the chemical shift values are referenced to TMS.

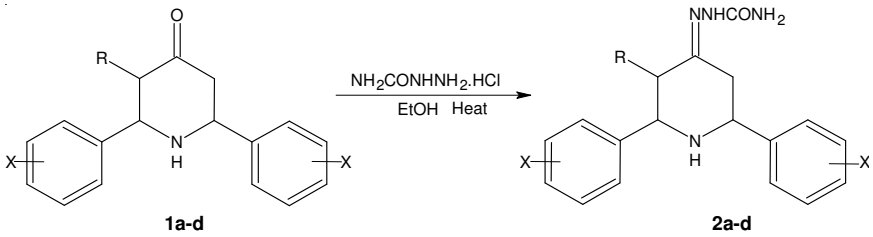
Proton NMR spectra were recorded on a DRX 500 NMR and AMX 400 NMR spectrometer operating at 500 and 400 MHz, respectively. Samples were prepared by dissolving about 10 mg of sample in 0.5 mL of acetone and chloroform-d containing 1 % TMS. All the chemical shifts are with reference to TMS.

Preparation of 3-substituted-2,6-diarylpiperidin-4-ones: Substituted 2,6-diarylpiperidones were prepared according to the reported method[5]. Ammonium acetate (100 mmol), benzaldehyde (200 mmol) and appropriate ketone (200 mmol) were dissolved in 95 % alcohol (80 mL) and the solution was heated on a hot plate with gentle swirling until the colour of the mixture changed to orange. The mixture was cooled and poured into ether (100 mL) and concentrated hydrochloric acid (14 mL) was added. The precipitated 2,6-diarylpiperidin-4-one hydrochloride was collected by filtration and re-crystallization from ethanol-ether. The hydrochloride was dispersed in acetone and concentrated ammonia was added drop-wise until a clear solution was obtained. The clear solution was poured into cold water and the solid precipitated was collected and crystallized from ethanol. The observed melting points are in excellent agreement with those of the reported ones.

Preparation of semicarbazone: A mixture of respective 2,6-diarylpiperidin-4-one (1 g, 0.0027 mol), semicarbazide hydrochloride (0.316, 0.0027 mol) and sodium acetate (0.750 g) in ethanol (40 mL) was refluxed for 2 h on a steam bath and cooled. The separated solid was filtered, washed with water and re-crystallized from ethanol.

RESULTS AND DISCUSSION

When the 3-alkyl-2,6-diarylpiperidin-4-ones are treated with semicarbazide hydrochloride in ethanol medium for 3 h, the semicarbazones (**Scheme-I**) are formed. The compound **1** has a chair conformation[8] where as the semicarbazone **2** has either chair or boat conformation. The conformation is purely dependent of the substitution in the third position of the ring. As the size of the substitution increases the conformation changes from chair to twisted chair and then it attains boat form. The products are identified by ^{1}H, ^{13}C NMR. The preferred conformation is proposed from the analysis of the coupling constant.



Compd.	2a	2b	2c	2d
R	H	CH_3	CH_2CH_3	$(CH_3)_2CH$

Scheme-I

The ^1H chemical shift values and the coupling constants are compared[9-11] with compound **1a**. For the compound 2,6-*bis*(*o*-chlorophenyl)piperidin-4-one semicarbazone (**2a$_1$**) the absorption in the range of 2.13-2.19 ppm corresponds to H_{5a} (*syn* α) proton. The H_{3a} (*anti* α) appears in the region of 2.58-2.61 ppm. The H_{6a} proton (*syn* β) appears in the region of 4.15-4.18 ppm. The absorption in the region of 4.24-4.27 ppm is due to H_{2a} (*anti* β) proton. The NH_2, CONH and NH proton in the ring appear at 9.52, 6.25 and 2.04 ppm, respectively. The signal between 3.41-3.43 ppm is due to H_{5e}. The multiplet appears in the range of 6.47-8.23 ppm are due to the aromatic protons. The signal in the region of 2.13-2.19 ppm has a total width of 24.77 Hz. This is due to the combination of $J_{3a,3e} + J_{3a,2a}$ or $J_{5a,5e} + J_{5a,6a}$. The spacing between the two lines at 3.43 ppm is 13.91 Hz. This is the combination of $J_{5a,5e} + J_{6a,5e}$. The $J_{2a,3a}$ coupling constant value is 10.82 Hz and $J_{6a,5a}$ coupling constant value is 11.33 Hz which is characteristic of usual diaxial coupling. Hence from the above results the conformation adopted by **2a$_1$** is chair form (Fig. 1) as that of the compound **2a**.

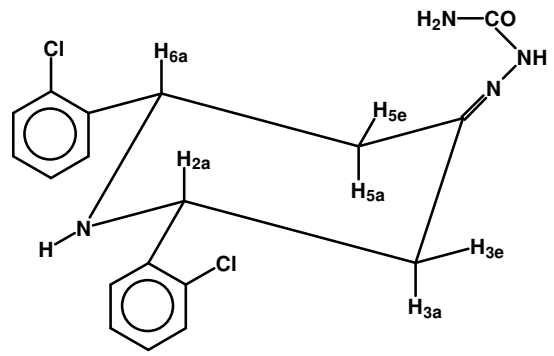
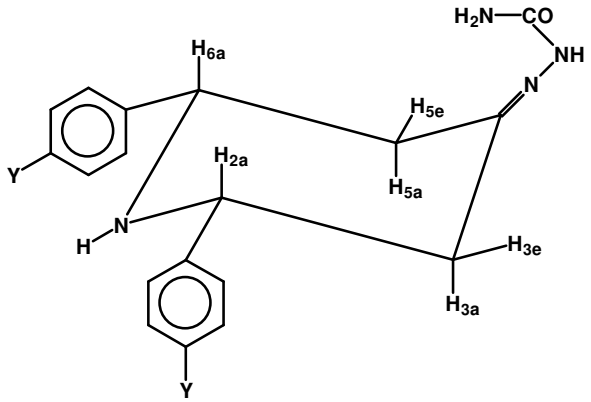


Fig. 1. 2a$_1$ 2,6-*bis*(*o*-chlorophenyl)piperidin-4-one semicarbazone

The ^{13}C chemical shift values and the coupling constants are compared[9] with compound **2a**. The C-5 (*syn* α) appears at 42.78 ppm. The absorption at 58.03 ppm is due to C-6 (*syn* β). The signal at 52.60 ppm is assigned to C-3 (*anti* α) while the absorption at 66.81 ppm is due to C-2 carbon (*anti* β). The C-4 carbon appears at 149.79 ppm. The signal between 133-134 ppm is due to the *ipso* carbons. The aromatic carbons appear in the range of 125.75-126.96 ppm. The C=O carbon appears at 162.21 ppm. The chemical shifts of C-2, C-6 and C-3, C-5 carbons are compared for the compound **2a** and **2a$_1$**. There is no appreciable change in the chemcal shifts. Hence, the chair conformation (Fig. 1) is assigned to compound **2a$_1$**. Similarly the chair conformation (Fig. 2) is assigned for the compounds **2b$_1$-b$_5$** and **2c$_1$-2c$_3$** (Fig. 3) based on ^1H NMR data (Table-1), coupling constant values (Table-2) and ^{13}C NMR data (Table-3).



2b$_1$ 3-Methyl-2,6-*bis*(*p*-chlorophenyl)piperidin-4-one semicarbazone
2b$_2$ 3-Methyl-2,6-*bis*(*o*-chlorophenyl)piperidin-4-one semicarbazone
2b$_3$ 3-Methyl-2,6-*bis*(*p*-methoxyphenyl)piperidin-4-one semicarbazone
2b$_4$ 3-Methyl-2,6-*bis*(*m*-nitrophenyl)piperidin-4-one semicarbazone
2b$_5$ 3-Methyl-2,6-*bis*(*p*-methylphenyl)piperidin-4-one semicarbazone

Fig. 2

TABLE-1
COUPLING CONSTANT VALUES (δ ppm)

	2b	**2b$_1$**	**2b$_2$**	**2b$_3$**	**2b$_4$**	**2b$_5$**	**2c**	**2c$_1$**	**2c$_2$**	**2c$_3$**
$J_{2a,3a}$	10.30	12.51	9.95	10.00	10.20	9.87	10.30	10.25	10.29	10.23
$J_{5a,6a}$	11.85	10.13	10.42	11.51	14.55	10.46	11.85	14.25	12.72	12.65
$J_{5e,6a}$	2.83	–	–	–	–	2.29	2.83	–	–	–
$J_{5a,5e}$	13.28	10.13	13.84	13.64	11.26	13.53	13.28	13.68	12.16	11.12
$J_{CH_3,3a}$	6.52	6.47	6.48	6.35	6.49	6.56	6.52	–	–	–

TABLE-2

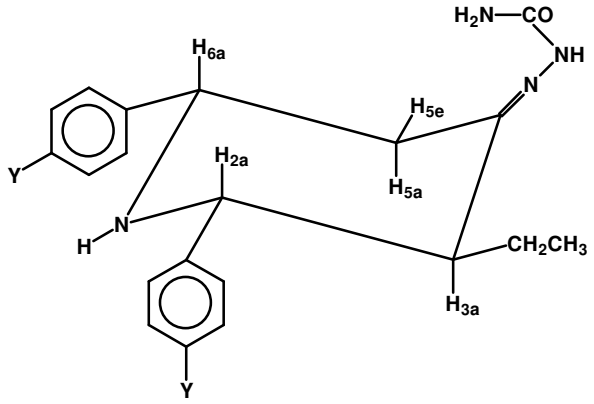
^{1}H NMR CHEMICAL SHIFTS (δ ppm)

Proton	2b	$2b_1$	$2b_2$	$2b_3$	$2b_4$	$2b_5$	2c	$2c_1$	$2c_2$	$2c_3$
H_{2a}	3.63	3.42-3.45	4.39-4.42	3.94-3.96	3.91-3.94	3.59-3.62	3.73	3.82-3.84	4.47-4.74	4.07-4.09
H_{3a}	2.55-2.75	2.62-2.66	2.65-2.97	2.80-2.99	2.77-2.79	2.59-2.61	2.59	2.52-2.79	2.64-2.77	2.70-2.74
H_{5a}	2.74	2.18-2.19	2.22-2.35	2.19-2.22	2.18-2.19	2.22-2.31	2.79	2.19-2.30	2.22-2.30	2.34-2.41
H_{5e}	2.83	3.69-3.71	3.46-3.49	3.58-3.61	3.53-3.56	3.33-3.36	2.61	3.41-3.45	3.47-3.50	3.58-3.62
H_{6a}	4.10	4.09-4.12	4.49-4.52	4.34-4.36	4.03-4.05	3.99-4.01	4.01	4.09-4.11	4.47-4.74	4.34-4.37
NH_2	–	8.95	8.66	9.09	9.01	8.79	–	9.09	8.81	9.24
CONH	–	6.10	6.06	6.17	6.12	6.06	–	6.13	6.09	6.13
-NH-	1.90	2.18	2.14	2.18	2.22	2.18	1.96	2.04	2.18	2.18
CH_3	0.80	0.99-1.01	1.08-1.10	1.05-1.06	0.91-0.93	0.98-1.00	0.70	0.95-0.98	0.98-1.00	0.98-1.02
Aromatic	7.20-7.60	7.48-7.73	7.12-8.04	7.80-8.61	7.90-8.95	7.01-7.60	7.20-7.42	7.49-7.89	7.41-8.49	7.78-8.68
					2.32(CH_3)	3.91(OCH_3)	1.35-1.41(CH_2)	1.81-1.85(CH_2)	1.95-2.02(CH_2)	1.33-1.38(CH_2)
							1.02-1.19(CH_2)	1.32-1.42(CH_2)	1.33-1.38(CH_2)	1.85-1.93(CH_2)

TABLE-3

^{13}C NMR CHEMICAL SHIFTS (δ ppm)

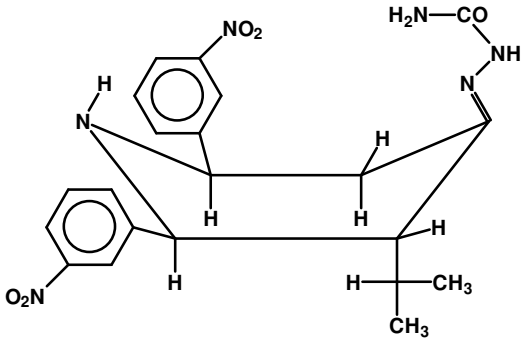
Carbon	2b	$2b_1$	$2b_2$	$2b_3$	$2b_4$	$2b_5$	2c	$2c_1$	$2c_2$	$2c_3$
C-2	68.5	62.36	62.48	62.62	61.80	64.57	66.7	61.59	60.32	64.71
C-3	51.6	52.68	52.30	52.60	52.65	53.70	58.9	45.57	45.48	49.14
C-4	209.5	156.60	156.70	156.18	156.82	154.93	209.1	148.49	147.02	156.25
C-5	50.9	49.85	49.78	48.72	49.12	49.78	51.6	49.31	32.17	33.81
C-6	51.5	58.67	56.90	50.75	56.33	58.36	61.8	55.61	56.31	57.62
CH_3	10.1	9.82	9.72	11.39	9.66	9.56	12.2	9.95	9.91	9.48
Ipso-1	141.8	139.12	141.10	141.23	138.23	138.22	142.7	140.95	138.90	144.35
Ipso-2	142.7	139.03	138.20	138.04	136.65	137.22	141.8	140.11	138.53	143.48
C=O	–	162.10	162.39	162.78	162.33	162.98	–	162.81	162.23	162.25
Aromatic carbons	126.5-128.6	125.88-131.92	124.85-130.60	124.73-129.00	126.11-128.48	124.60-130.32	126.5-128.8	126.30-130.61	124.74-133.95	127.63-132.88
					52.78(CH_3)	18.43(OCH_3)	17.3(CH_2)	16.89(CH_2)	17.00(CH_2)	16.89(CH_2)



2c₁ 3-Ethyl-2,6-*bis*(*p*-chlorophenyl)piperidin-4-one semicarbazone
2c₂ 3-Ethyl-2,6-*bis*(*o*-chlorophenyl)piperidin-4-one semicarbazone
2c₃ 3-Ethyl-2,6-*bis*(*m*-nitrophenyl)piperidin-4-one semicarbazone

Fig. 3

However for the compound 3-isopropyl-2,6-*bis*(*m*-nitrophenyl)piperidin-4-one semicarbazone (**3d₁**), the $J_{2a,3a}$ coupling constant is found to be 8.77 Hz. The spacing between the two lines at 3.40 ppm is 14.83 Hz. This is the combination of $J_{5e,5a}$ and $J_{5e,6a}$ and the signal in the region of 2.51-2.57 ppm has a total width of 14.79 Hz. This is due to $J_{5a,6a} + J_{5a,5e}$. The coupling constant value of $J_{5e,6a}$ is found to be 3.4 Hz. The decrease in coupling constant value is attributed to the flattening of C-2 and C-3 bond. So the compound **3d** exists in a boat form (Fig. 4). The chemical shift values of **3d₁** are compared[9] with 3d. The absorption at 3.40 ppm corresponds to H_{5e} (*syn* α). The signal in the region of 2.51-2.57 ppm is assigned to H_{5a}. The *anti* α hydrogen H_{3a} appears at 2.79 ppm. The *syn* β hydrogen (H_{6a}) appears in the range of 4.50-4.46 ppm and the *anti* β hydrogen (H_{2a}) appears at 4.50-4.46 ppm. The NH_2, CONH and NH proton in the ring appear at 8.89, 6.04 and 2.18 ppm, respectively. The methylene proton appears in the region of 2.11-2.22 ppm. The methyl protons appear at 1.27 and 1.06 ppm. The aromatic protons appear in the region of 7.20-8.89 ppm. The ^{13}C chemical shift values of **3d₁** are compared[9] with 3d. The C-5 (*syn* α) appears at 33.63 ppm. The signal at 47.47 ppm is assigned to C-3 carbon (*anti* β). The absorption at 61.47 ppm is due to (*anti* α) C-2 carbon. The C-6 (*syn* β) carbon appears at 56.01 ppm. The absorption at 155.83 ppm is assigned to C-4 carbon. The methyl carbon appears at 11.46 and 10.94 ppm. The methylene carbon appears at 18.38 ppm. The absorption at 144.57 and 139.75 ppm is due to *ipso* carbons. γ-Effect operates on *ipso* carbon. The keto carbon appears at 162.52 ppm. The aromatic carbons appear in the region of 127.61-130.44 ppm. It is found that the *syn* α and *syn* β carbons are shielded. *anti* α and *anti* β are also shielded.



2d$_1$ 3-Isopropyl-2,6-*bis*(*m*-nitrophenyl)piperidin-4-one semicarbazone

Fig. 4

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