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Note

Conformational analysis of some *N*-hydroxypiperidin-4-one oximes

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Analysis of the spectral data (^{1}H NMR and ^{13}C NMR) indicates that out of ten *N*-hydroxypiperidin-4-one oximes **3a-j**, the compounds **3b** and **3c** exist predominantly in chair conformation with the aryl and alkyl substituents in the equatorial positions, whereas the compounds **3d-j** exist in boat conformation. The introduction of an oxime group at C-4 causes a flattening of the ring about C(5)-C(6) bond. The NOESY spectrum (Nuclear Overhauser effect) recorded for the compound **3d** further supports the assigned boat conformation.

Keywords: ^{1}H NMR, ^{13}C NMR, NOESY, conformation and *N*-hydroxypiperidone oximes

Several 2,6-diarylpiperidin-4-ones synthesized by Noller & Baliah[1] have been subjected to various physico-chemical studies[2-5]. Aroney *et al.*[5] have analysed the ^{1}H NMR spectra of some of these compounds. K Pandiarajan *et al*.[6] have established the conformations of several piperidin-4-ones and their oximes. Some *N*-formyl-cis-2,6-diarylpiperidines[7-10] have been prepared and their preferred conformation is assigned by R Jeyaraman *et al*.[11] A detailed conformational study of some *N*-hydroxypiperidin-4-one oximes **3a-j** is reported in this paper using ^{1}H NMR and ^{13}C NMR spectroscopy. The preferred conformation of these compounds has been established using the chemical shift values and coupling constants.

Results and Discussion

In the present study, the *N*-hydroxy-3-alkyl-2,6-diphenylpiperidin-4-one oximes **3b-d**, *N*-hydroxy-2,6-diaryl-3,5-dimethylpiperidin-4-ones oximes **3e -3j** are prepared from their respective *N*-hydroxypiperidones **2a-2j** by treating with hydroxylamine hydrochloride. The *N*-hydroxpiperidones are prepared from their respective piperidones by treating with *m*-chloro-perbenzoic acid. The reaction is represented in **Scheme I**.

Coupling constants and conformation

In the case of 3-alkyl oximes **3b** and **3c** the vicinal coupling constant of **3b** is 10.91 Hz (J_{2a3a}) and 13.47 (J_{5a6a}) and for **3c** is 10.52 Hz (J_{2a3a}) and 10.72 Hz (J_{5a6a}). These values are characteristic of usual diaxial coupling and hence a chair conformation is assigned for **3b** and **3c (Figure 1)**. However for compound **3d-j** the vicinal coupling constants are markedly less and so a boat conformation is assigned.

NOESY

The NOESY spectrum is recorded for **3d** to arrive at the preferred conformation unambiguously. The four prominent NOEs show the interaction between N-OH and C=N-OH, *para* protons and H_{2a}, H_{6a}, H_{5a} and H_{5e}, and between H_{2a} and methine proton. These NOEs support the boat conformation of **3d (Figure 2)** because in other conformation these interactions are not possible. Further the NOESY spectrum of **3d** is compared[12,13] with that of **1d (Figure 3)**, **2d (Figure 4)**, and **1d$_1$ (Figure 5)**. In compound **1d** and **2d**, there is no NOE between H_{2a} and isopropyl-methine proton. This is possible only if they exist in chair conformation. In chair form the isopropyl-methine proton is far away from H_{2a}. However in **1d$_1$** there is significant NOE between the H_{2a} and isopropylmethine proton. This NOE would be possible only if **1d$_1$** adopts a boat conformation.

For the compounds **3e-j** also, a boat conformation **(Figure 6)** is assigned based on the following discussion. In compound **3e**, there is a distinct decrease in the vicinal coupling constant J_{5a6a}= 5.45 Hz indicating significant change in the dihedral angles due to the flattening of bonds C (5)-C(6). So a contribution of boat form causes a decrease in J_{5a6a}. The abnormal coupling constant in **3f** suggests that it exits in asymmetric non-chair conformation leading to a boat form. This helps to avoid steric interaction of the methyl group with the hydroxyl group. For

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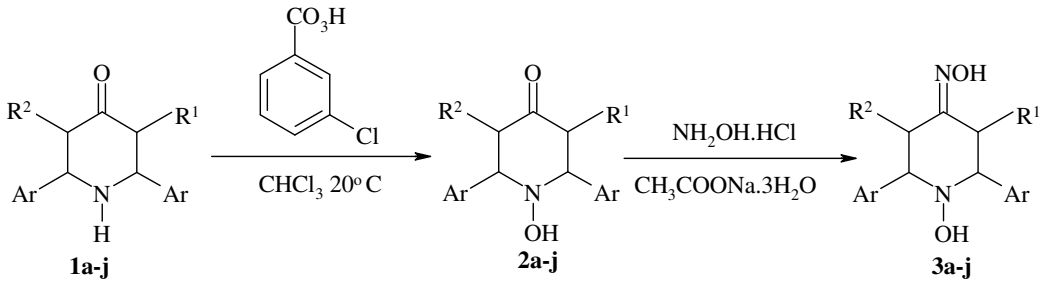
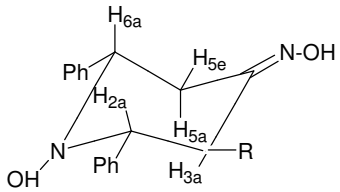


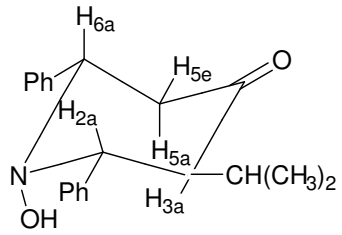
Compds	3a	3b	3c	3d	3e	3f	3g	3h	3i	3j
R^2	H	CH_3	C_2H_5	$CH(CH_3)_2$	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3
R^1	H	H	H	H	CH_3	CH_3	CH_3	CH_3	CH_3	CH_3
Ar	Ph	Ph	Ph	Ph	H	*p*-OCH_3-C_6H_4	*o*-ClC_6H_4	*m*-$NO_2C_6H_4$	*p*-ClC_6H_4	*p*-$NO_2C_6H_4$

Scheme I



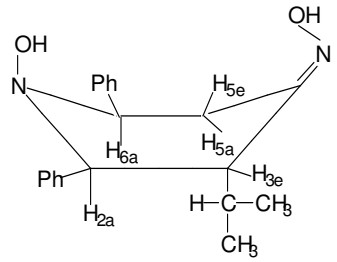
3a-c

Figure 1



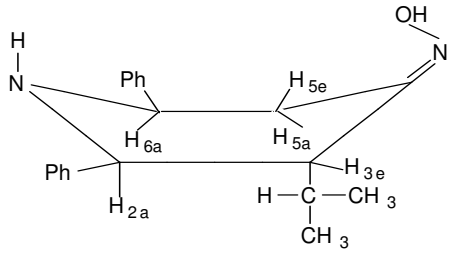
2d

Figure 4



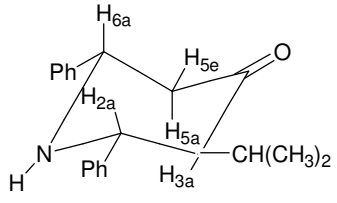
3d

Figure 2



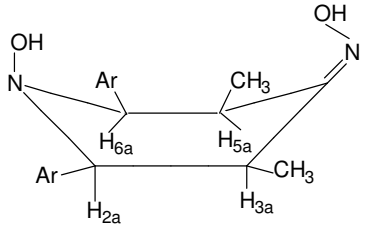
1 d 1

Figure 5



1d

Figure 3



3e-j

Figure 6

compound **3g** the coupling constant between anti α and anti β protons $J_{2a\ 3a}$ is 9.47 Hz, whereas there is a zero coupling between J_{5a6a}. So the H_{6a} appears as a singlet at δ 4.38 ppm. This shows that the C(5)-C(6) bond has almost flattened. As a result, **3g** adopts a boat conformation. In a boat conformation the N-O bond completely eclipses the α(C-H) bond and therefore the observed coupling constant will be below 4 Hz, as zero in this case. For compounds **3h** and **3i**, a boat conformation is assigned based on the above same reason. For compound **3j**, the observation of one large and one small magnitude of the vicinal coupling constant 9.46 Hz and 5.19 Hz correspond to J_{2a3a} and J_{5a6a} respectively. This decrease is attributed

to the flattening of the bonds C(5)-C(6) and in turn the dihedral angle approaches 90°. It may be proposed that a boat form contributes to a larger extent in solution. The coupling constant values of the compounds **3a-j** are furnished in **Table I**.

Chemical shifts

The oximation of ketone makes a considerable shift in proton absorptions. Due to the introduction of oxime group, the syn α and syn β hydrogens are shielded. The α and β hydrogens anti to the oxime

Table I — Coupling constant values (in Hz) of compounds **3a-j**

Compd	Coupling constants
1a$_1$	J_{2a3a}=11.49 J_{2a3e}=2.85 J_{3a3e}=13.59 J_{5a6a}=11.69 J_{5a5e}=14.02 J_{5e6a}=2.93
2a	J_{2a3a}+ J_{2a3e}=12.70 J_{3a3e}+ J_{2a3a}=27.83 J_{3a3e}=15.63
3a	J_{6a3a}+ J_{5a5e}=13.84 J_{3a3e}+ J_{3a2a}=26.80
1b$_1$	J_{2a3a}=10.10 J_{5a6a}=11.80 J_{5e6a}=2.88
1b	J_{2a3a}=10.36 J_{5a6a}=11.85 J_{6a5e}=2.83 J_{5a5e}=13.21
2b	J_{2a3a}=11.72 J_{5a36a}=13.18 J_{5e6a}=3.41 J_{5a6a}=14.61 J_{3aCH_3} = 6.84
3b	J_{2a3a}=10.91 J_{5a6a}=13.47 J_{5e6a}=3.31 J_{5e5a}=13.67 J_{3aCH_3} =6.42
1c	J_{2a3a}=10.51 J_{6a5a}=11.75 J_{6a5e}=2.83 J_{5a5e}=12.81
1c$_1$	J_{2a3a}=10.30 J_{6a5a}=11.70 J_{6a5e}=3.00 J_{3a7x}=2.70 J_{3a7y}=2.80
2c	J_{2a3a}=11.23 J_{5a6a}+ J_{6a5e}=12.69 J_{5a5e}+ J_{5a6a}=26.85 J_{5a5e}+ J_{6a5e}=13.67
3c	J_{5a6a}+ J_{5e6a}=9.34
1d	J_{2a3a}=10.51 J_{6a5a}=11.67 J_{6a5e}=3.03 J_{5a5e}=13.56
1d$_1$	J_{2a3a}=9.10 J_{6a5a}=11.20 J_{5e6a}=3.8
2d	J_{2a3a}=11.2 J_{6a5e}=3.42 J_{5a5e}=14.24
3d	J_{2a3a}=9.21 J_{5a6e}+ J_{5e6a}=13.36
1e	J_{2a3a} or J_{6a5a}=10.35
2e	J_{2a3a} or J_{6a5a}=11.72 J_{2a3a}+ J_{3aCH_3} or J_{6a5a}+ J_{5aCH_3} =17.57 J_{3aCH_3} or J_{5aCH_3} =6.84
3e	J_{2a3a}=9.35 J_{6a5a}=5.45 J_{2a3a}+ J_{3aCH_3} =16.00 J_{5aCH_3} +J_{6a5a} =12 J_{3aCH_3} =7.35 J_{5aCH_3} =7.12
2f	J_{2a3a} or J_{6a5a}=11.57 J_{3aCH_3} or J_{5aCH_3} =6.60
3f	J_{2a3a}=5.39 J_{6a5a}=8.84 J_{3aCH_3} =7.37 J_{5aCH_3} =7.38
1g$_1$	J_{2a3a} or J_{6a5a}=10.36
2g	J_{2a3a} or J_{6a5a}=11.50 J_{3aCH_3} = 6.50
3g	J_{2a3a}=9.47 J_{6a5a}=0.00 J_{3aCH_3} = 7.42 J_{5aCH_3} =7.10
2h	J_{2a3a} or J_{6a5a}=11.66 J_{3aCH_3} or J_{5aCH_3} =6.57
3h	J_{2a3a}8.30 J_{6a5a}=0.00 J_{3aCH_3} =7.39 J_{5aCH_3} =7.41
1i	J_{2a3a} or J_{6a5a}=10.36
2i	J_{2a3a} or J_{6a5a}=10.32 J_{3aCH_3} or J_{5aCH_3} = 6.59
3i	J_{2a3a}=8.50 J_{6a5a}=0.00 J_{3aCH_3} =4.64 J_{5aCH_3} = 5.44
2j	J_{2a3a} or J_{6a5a}=11.40 J_{3aCH_3} or J_{5aCH_3} =6.58
3j	J_{2a3a}=9.46 J_{6a5a}=5.19 J_{3aCH_3} =7.32 J_{5aCH_3} =7.06

Table II — ^{1}H NMR chemical shift values (in δ, ppm) of compounds **3a-j**

Compd	H_{2a}	H_{3a}	H_{3e}	H_{5a}	H_{5e}	H_{6a}	Aromatic
3a	3.86-3.77	2.23-2.16	2.58	2.23-2.16	3.55	3.86-3.77	7.62-7.37
3b	3.48	2.69-2.71	-	2.16-2.23	3.63	3.78	7.25-7.48
3c	3.77-3.79	2.50-2.61	-	2.17-2.19	3.63	2.77-3.79	7.29-7.46
3d	3.86	2.62	-	2.36-2.39	3.43	3.84-3.86	7.25-7.48
3e	3.78	3.38-3.42	-	2.80-2.83	-	3.69	7.26-7.37
3f	4.17	3.52	-	2.88	-	4.13	7.21-7.29
3g	4.55	3.48	-	2.76	-	4.38	7.22-7.43
3h	4.03	2.82-2.87	-	2.70-2.79	-	3.92	7.22-7.41
3i	3.79	2.78	-	2.64	-	3.69	7.29-7.35
3j	4.01	3.42-3.49	-	2.81-2.90	-	3.90	7.29-7.44

Table III — ^{13}C NMR chemical shift values (in δ, ppm) of compounds **3a-j**

Carbon number	**3a**	**3b**	**3c**	**3d**	**3e**	**3f**	**3g**	**3h**	**3i**	**3j**
CH_2	-	19.00	-	-	-	-	-	-	-	-
CH	-	-	28.16	-	-	-	-	-	-	-
C-2		78.40	76.60	74.55	75.56	75.52	74.56	74.92	74.86	74.72
C-3		42.00	48.50	52.66	43.02	42.19	30.16	42.11	30.90	43.94
C-4		158.00	156.39	156.27	161.95	161.90	162.12	168.01	161.07	168.82
C-5		32.30	32.50	32.36	30.93	31.10	30.89	30.62	30.90	30.93
C-6		70.14	70.10	68.98	75.56	75.62	75.50	74.52	74.86	74.10
CH_3(5)		12.00	11.43	18.08-20.80	20.73	15.71	20.50	15.52	15.59	15.54
Ipso-C-6		141.15	141.11	142.10	141.96	20.70	15.20	20.90	20.72	20.80
Ipso-C-2		142.45	142.49	142.64	143.65	141.35	141.30	141.65	141.74	141.35
Aromatic		127.00-128.40	127.00-128.51	127.00-128.50	127.38-128.47	127.25-128.40	128.32-128.90	127.39-128.04	128.61-129.41	128.33-128.85
p-OCH_3	-	-	-	-	-	55.10	-	-	-	-

group are deshielded. The signals are assigned by comparing[14] with respective ketones. For exmaple in compound **2b** the signal obtained in the region of δ 2.16-2.23 ppm corresponds to H_{5e} (syn α). The signal at δ 3.63 ppm is due to H_{5a}. The anti α hydrogen H_{3a} appears in the region of δ 2.69-2.17 ppm. The syn β hydrogen H_{6a} and anti β hydrogen H_{2a} appears at δ 3.78 and 3.48 ppm respectively. The *N*-hydroxy proton appears at δ 4.45 ppm, while the strong singlet at δ 8.32 ppm is assigned to hydrogen of oxime group. Similarly the chemical shifts are assigned to other compounds and are furnished in **Table II**. The ^{13}C NMR chemical shifts are furnished in **Table III**.

Experimental Section

Preparation of *N*-hydroxy-3-alkyl-2,6-diphenyl-piperidin-4-one oximes 3a-d and *N*-hydroxy-2,6,-diaryl-3,5-dimethylpiperidin-4-oximes 3e-j

The compounds **3a-f** were prepared by following the procedure of Baliah *et al.*[1]. The respective *N*-hydroxy-3-alkyl-2,6-diphenylpiperidin-4-ones or *N*-hydroxy-2,6-diaryl-3,5-dimethylpiperidin-4-ones (0.05 mole) and sodium acetate trihydrate (0.15 mole) were dissolved in boiling ethanol and hydroxylamine hydrochloride (0.06 mole) was added. The mixture was heated under reflux for 15 min and poured into water. The separated solid was filtered off and recrystallised from ethanol. The physical data of the compounds **3a-j** are given in **Table IV**.

Preparation of 3-alkyl-2,6-diphenylpiperidin-4-ones 2a-d and *N*-hydroxy-2,6-diaryl-3, 5-dimethyl-piperidin-4-one 2e-j

The respective piperidones **1a-j** and *m*-chloro-perbenzoic acid (1:1 w/w) were mixed in 20 mL of chloroform at 0°C. The mixture was extracted with

Table IV— The physical data of the compounds **3a-j**

Compds	m.p (°C)	Yield (%)	Mol. Formula	Found (Calcd) % C	H	N
3a	140	60	$C_{17}H_{18}N_2O_2$	72.05 (72.34	6.25 6.38	9.90 9.93)
3b	165	82	$C_{18}H_{20}N_2O_2$	73.15 (72.97	6.66 6.75	9.67 9.46)
3c	145	84	$C_{19}H_{22}N_2O_2$	73.42 (73.55	7.25 7.10)	9.01 9.03)
3d	148	78	$C_{21}H_{26}N_2O_2$	73.69 (74.55	7.19 7.69	9.00 8.28)
3e	142	60	$C_{19}H_{22}N_2O_2$	74.35 (73.55	7.08 7.10	9.06 9.03)
3f	165	85	$C_{19}H_{26}N_2O_2$	69.07 (68.11	7.05 7.03	7.33 7.57)
3g	149	70	$C_{19}H_{20}N_2Cl_2$	60.11 (60.16	5.30 5.28	8.36 7.38)
3h	167	66	$C_{19}H_{20}N_4O_6$	57.19 (57.00	5.45 5.00	14.19 14.00)
3i	153	73	$C_{19}H_{20}N_2O_2Cl_2$	61.33 (60.16	5.39 5.28	8.14 8.44)
3j	172	58	$C_{19}H_{20}N_4O_6$	57.36 (57.00	5.54 5.00	14.76 14.00)

chloroform and washed with 10% sodium bicarbonate solution. The chloroform layer was dried with anhydrous sodium sulphate and evaporated. The separated solid was subjected to column chromatography. The column was packed with silica gel (100-200 mesh) in hexane. The eluting slovent is benzene - petroleum ether (4:1 v/v).

Instrumentation

Proton NMR spectra were recorded on a Brucker AMZ-400 spectrometer operating at 400 MHz. Samples were prepared by dissolving about 10 mg of sample in 0.5 mL of chloroform-*d*, containing 1% TMS. ^{13}C NMR spectra were recorded on a Brucker AMX-400 spectrometer operating at 400 MHz and 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. All chemical shifts are in reference to TMS.

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