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SYNTHESIS AND CONFORMATIONAL STUDIES ON CERTAIN *N*-NITROSO PIPERIDIN-4-ONES

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ABSTRACT

Heterocyclic compounds gain importance owing to their pharmacological, agro- hemical and in brief, biological activities. The piperidin-4-one units are present in a variety of alkaloids which are occurring naturally. They find wide applications as drugs. Further, the stereochemical studies of piperidinone chemistry are thought provoking and quiet interesting.

Keywords: *n*-nitroso piperidin-4-ones, Heterocyclic compounds, pharmacology.

1. INTRODUCTION

Piperidones are an important group of heterocyclic compounds in the field of medicinal chemistry due to their broad spectrum of biological activities. One such class of compounds containing 4-piperidones and their derivatives, whose synthesis and stereodynamics are well investigated (Prostokov and Gaivoronskaya, 1978). Many natural products and drugs contain the piperidine ring system as a structural element. Nitrogen heterocycles, in particular 4-piperidones display important biological properties such as antiviral, antitumor, analgesics and antihypertensive activities (Miyoshi *et al.,* 1995; Riley *et al.,* 1973). The importance of 4-piperidones as intermediates in the synthesis of a variety of compounds of physiological activity has been reviewed by Prostokov and Gaivoronskaya (Shintani *et al.,* 2004). The extensive studies undertaken in the past on 4-piperidones have their relation to the synthesis of drugs (Boach *et al.,* 1948)The utility of 2-aryl, 2-heteroarylpiperidin-4-ones in the construction of polycyclic systems such as benzo[*a*]quinolin-4-ones, indole alkaloids, have been disclosed by Rubiralta *et al.,* 1989 recently in a series of papers.

They have also described the importance of the introduction of bulky substituent in the nitrogen side of 4-piperidones, thereby making the ring system to adopt favorable conformation for the intramolecular ring closure leading to the construction of benzomorphon related compounds. Piperidone derivatives have also been noted to act as potential inhibitors of human placental aromatase *in vitro*. 3,5-bis(arylidine)piperidin-4-ones behave as cytotoxic and anticancer agents. 2,2,6,6-tetramethylpiperidin-4-one hydrochloride has been used as a spin trap in several EPR studies and it's hydrazones are used as antioxidants. 2-Aryl piperidin-4-ones are used as key intermediates for the synthesis of techykinin antagonists and indolizidine alkaloids (Boach *et al.,* 1948).

2. EXPERIMENTAL SECTION

Melting points of all the compounds were determined on an electrically heated block (RAAGA make) with a calibrated thermometer and are uncorrected. The IR spectra were recorded on a FTIR instrument (Perkin-Elmer). The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AMX 400 MHz spectrometer and 2D NMR spectra were recorded on a AV 500 MHz instrument in $CDCl_3$ solution with TMS as an internal standard.

2.1. Synthesis of r-2,c-6-Bis(2-chlorophenyl)-c-3,t-3-dimethylpiperidin-4-one (1)

To a solution of ammonium acetate (0.05 mole) in dry ethanol, 2-Chlorobenzaldehyde (0.1 mole) and isopropylmethyl ketone (0.05 mole) was added. The above contents were taken in a round bottom flask and fitted with a double walled condensor. It was heated for 30 minutes. Then it was kept at room temperature overnight. The formed crystals of *r*-2,*c*-6-bis(2-chlorophenyl)-*c*-3,*t*-3-dimethylpiperidin-4-one was filtered and washed well with the dry alcohol. Yield : 11.5 g (75%) m.p: 148° C-150° C & MS (m/z) : 347.31(M^+), 276.14, 252.06 (100%), 149.22, 129.28, 115.18, 69.24

2.2. Synthesis of r-2,c-6-Bis(2-chlorophenyl)-t-3,t-5-dimethylpiperidin-4-one (2)

To a solution of ammonium acetate (0.05 mole) in dry ethanol, 2-chlorobenzaldehyde (0.1 mole) and diethyl ketone (0.05mole) was added. The above contents were taken in a round bottom flask and fitted with a double walled condensor. It was heated for 30 minutes. Then it was kept at room temperature overnight. The crystals of *r*-2,*c*-6-bis(2-chlorophenyl)-*t*-3,*t*-5-dimethylpiperidin-4-one was separated was washed well with the dry alcohol.

Yield : 12.51 g (82%) m.p. : 117° C-120° C MS (m/z): 347.14(M^+), 312.04, 252.08 (100%), 152.21, 125.16, 117.25, 73.19

2.3. Synthesis of r-2,c-6-Bis(2-chlorophenyl)-t-3-methylpiperidin-4-one (3)

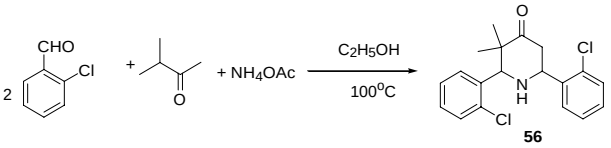
To a solution of ammonium acetate (0.05 mole) in dry ethanol 2-chlorobenzaldehyde (0.1 mole) and ethylmethyl ketone (0.05 mole) was added. The above contents were taken in a round bottom flask and fitted with a double walled condensor. It was heated for 30 minutes. Then it was kept at room temperature overnight. The crystals of r-2,c-6-bis(2-chlorophenyl)-t-3-methylpiperidin-4-one was separated out was filtered and washed well with the dry alcohol. Yield : 7.6 g (53%) m.p.: 124° C-126° C

3. RESULTS AND DISCUSSION

In the present work, *r*-2,*c*-6-bis(2-chlorophenyl)piperidin-4-ones **1 & 2** and their corresponding *N*-nitroso compounds **4 & 5** respectively, have been synthesized and their stereochemistry studied using IR spectra, ^1H & ^{13}C and 2D (^1H, ^1H–COSY & ^1H, ^{13}C-HETCOR) NMR Spectra. The NMR spectral data reveal that all the parent piperidin-4-ones **1 & 2** prefer chair conformation while the *N*-nitroso compounds **4 & 5** prefer to exist in a twist-boat conformation with coplanar orientation of *N*-N=O moiety.

3.1. r-2, c-6-bis(2-chlorophenyl)c-3, t-3-dimethyl-piperidin-4-one (1).

The piperidin-4-one **1** was synthesized by the reaction of isopropyl methyl ketone, 2-chlorobenzaldehyde and ammonium acetate in ethanol medium at 100 °C (**Scheme 11**).



Scheme 1

The structure of the compound **1** was confirmed by IR spectra, ^1H, ^{13}C NMR, 2D NMR and mass spectral data .

The IR spectrum of piperidin-4-one **1** , showed the presence of >NH (stretching band observed at 3306 cm^{-1}) and >C = O (stretching band observed at 1703 cm^{-1}) groups, which confirmed the formation of the compound **1**.

The ^1H NMR signals of the compound **1** were assigned by comparison with those of the corresponding 2,6-bis (2-clorophenyl) -3-methyl piperidin -4- one (**3**). The signal integration values were also used for the assignment.

The ^1H NMR spectrum of **1** has only ABX systems for the heterocyclic ring protons (H_{6a}, H_{5a} & H_{5e}) since no coupling partner is available at C_3 for C_2 proton, the benzylic proton at C_2 appeared as a singlet at 3.79 ppm. The chemical shift value of H_2 benzylic proton when compared to that of the 3-methyl analog **3** indicated the axial position for the proton and equatorial orientation for the chlorophenyl group. The signal at 4.59 ppm with ^3J values of 11.1 ($^3J_{6a,\ 5a}$) and 5.1 Hz ($^3J_{6a,\ 5e}$), is assigned to the axial proton at C_6 (H_6) and it confirmed the equatorial orientation of the chlorophenyl group at C_6. The coupling constant ($^3J_{6a,\ 5a}$ & $^3J_{6a,\ 5e}$) data were employed to calculate the dihedral angles between the vicinal protons (H_6 & H_{5a}, H_{5e}) by DAERM. The *cis* (H_6-C_6-C_5-H_{5e}) and trans (H_6-C_6-C_5-H_{5a}) dihedral angles of **1** were found to be **45°** & **165°** respectively. The observed vicinal coupling constants and dihedral angles confirmed that the compound **1** prefer to exist in the chair conformation. The signal at 2.75 ppm which appears as double doublet ($^2J_{5a,\ 5e}$ = 14.0 Hz and $^3J_{6a,\ 5a}$ = 12.0 Hz) can be assigned to the axial proton of C_5 (H_{5a}). Similarly the signal at 2.66 ppm appeared as a double doublet with coupling constant values of 14.0 Hz ($^2J_{5a,\ 5e}$) and 3.5 Hz ($^3J_{6a,\ 5e}$) can be assigned to the equatorial proton at C_5 (H_{5e}).

The presence of NH proton at 1.75 ppm was confirmed using the D_2O exchange studies (**Spectrum 3**).

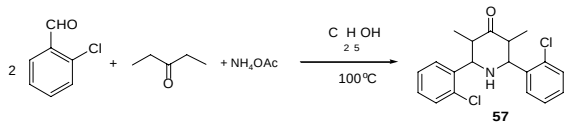
The ^{13}C NMR spectrum signals (**Spectrum 4**) of the Compound **1** were assigned on the basis of additivity and by comparison with those of the corresponding 2,6-bis (2-clorophenyl) -3-methyl piperidin -4- one(**3**).

On the basis of the above discussion, it has been concluded that *r*-2,*c*-6-bis (2-chlorophenyl) -*c*-3,*t*-3-dimethylpiperidin-4-one (**1**) prefers to adopt a chair conformation with the equatorial orientation of chlorophenyl groups at C_2 and C_6 positions (**Fig. 1**).

Fig. 1

The complete assignments of ^1H and ^{13}C NMR spectral data are presented in **Table 1 & 2**.

The piperidin-4-one **2** was synthesized by the reaction of pentan-3-one, 2-chlorobenzaldehyde and ammonium acetate in ethanol medium at 100 °C (**Scheme 2**).



Scheme 2

The structure of the compound was confirmed by IR spectra, ^{1}H, ^{13}C NMR, 2D NMR and mass spectral data.

The presence of NH stretching band (3310 cm^{-1}) and >C = O stretching band (1704 cm^{-1}) in the IR spectrum of the compound **2** indicated the formation of the compound **2**.

The compound **57** is symmetrical in nature and the assignment of ^{1}H NMR chemical shifts is very simple. The protons at C_2 and C_6 are chemically equivalent. Similarly the protons at C_3 and C_5 are also equivalent. Hence the ^{1}H NMR spectrum of **2** has only AX spin system for the heterocyclic ring protons.

The benzylic protons (H_{2a} and H_{6a}) showed a doublet at 4.38 ppm with $^{3}J_{2a, 3a}$ (= $^{3}J_{6a, 5a}$) value of 10.3 Hz, indicating that these two protons are diaxially oriented which in turn confirm the equatorial orientation of chlorophenyl groups at C_2 & C_6 and methyl groups at C_3 & C_5 respectively. The diaxial coupling constant of 10.3 Hz confirms the preference of chair conformation for the compound **2**.

On the basis of the above observations, it has been concluded that *r*-2,*c*-6-bis (2-chlorophenyl)-*t*-3,*t*-5-dimethylpiperidin-4-one (**2**), exist in chair conformation with the equatorial orientation of chlorophenyl substituent of C_2 and C_6 and methyl groups at C_3 and C_5 respectively similar to the previous compound .

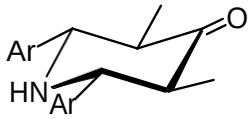
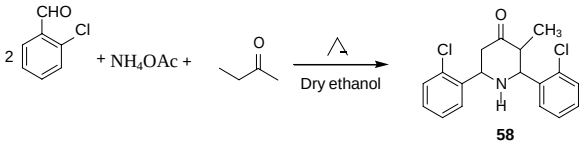


Fig. 2

The complete assignments of ^{1}H and ^{13}C NMR spectral data are presented in the **Table 3 and 4.**

3.2. r-2,c-6-Bis(2-chlorophenyl)-t-3-methylpiperidin-4-one (3)

The titled compound was synthesized by the reaction of butan-2-one,2-chlorobenzaldehyde and ammonium acetate in ethanol medium at 100 ^{o}C (**Scheme 3**).



Scheme 3

The structure of the compound was confirmed by IR spectra, ^{1}H & ^{13}C NMR spectral data. In addition DEPT spectrum was also used for the assignment of ^{13}C NMR spectrum.

The ^{1}H NMR spectrum of **3** has ABX and AX spin systems for the heterocyclic ring protons. The H_{6a}, H_{5a} and H_{5e} protons which belongs to the ABX spin system and the H_{6a} and H_{5e} protons (AX spin system) showed two double doublets at 4.07 and 2.62 ppm respectively, were assigned on the basis of the magnitudes of their coupling constant (J) values. The H_{5a} of the ABX spin system was found to have been mingled with the H_{3a} (multiplet) of the AX spin system. The signal at 4.07 ppm with ^{3}J values of 11.5 and 3.5 Hz, ascribable to $^{3}J_{6a,5a}$ and $^{3}J_{6a,5e,}$ respectively, was assigned to the axial proton at C_6 (H_6) which confirmed the equatorial orientation of the chlorophenyl group at C_6. The signal at 2.62 ppm, can also be assigned to the equatorial proton at C_5 (H_{5e}). Similarly, the proton H_2 of the AX spin system gave a doublet at 3.61 ppm with a $^{3}J_{2a,3a}$ value of 10.5Hz, indicating that these two protons are diaxially oriented, which in turn confirmed the equatorial orientation of the chlorophenyl and methyl groups at C_2 and C_3, respectively. Due to the coupling with CH_3 protons, the H_{3a} proton appeared as a multiplet at 2.62 ppm. The coupling constant ($^{3}J_{6,5a}$ & $^{3}J_{6,5e}$) data were employed to calculate the dihedral angles between the vicinal protons (H_6 & H_{5a}, H_{5e}) by DAERM.[74] The *cis* (H_6-C_6-C_5-H_{5e}) and *trans* (H_6-C_6-C_5-H_{5a}) dihedral angles of **3** were found to be **54°** and **174°**, respectively. The observed vicinal coupling constants and dihedral angles are consistent with the chair conformation for **3.**

On the basis of the above discussion, it was concluded that *r*-2,*c*-6-bis(2-chlorophenyl)-*t*-3-methylpiperidin-4-one (**3**), similar to other 2,6-diphenyl piperidin-4-ones, prefers to adopt a chair conformation with the equatorial orientation of chlorophenyl substituents at C_2 & C_6 and methyl group at C_3 respectively(**Fig. 3**).

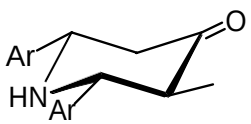


Fig. 3

The complete assignment of ^{1}H &^{13}C NMR data are presented in the **Table 5 & 6.**

4. SUMMARY

Three piperidin-4-ones *viz*. *r*-2,*c*-6-bis(2-chlorophenyl)-*c*-3,*t*-3-dimethylpiperidin-4-one **(1)**, *r*-2,*c*-6-bis(2-chlorophenyl)-*t*-3,*t*-5-dimethylpiperidin-4-one **(2)** and *r*-2,*c*-6-bis (2-chlorophenyl)-*t*-3-methylpiperidin-4-one (**3**) have been synthesized.

The preferred conformations of these compounds 1-3 have been determined using IR spectra, ^{1}H, ^{13}C, DEPT and 2D (^{1}H, ^{1}H-COSY & ^{1}H, ^{13}C-HETCOR) NMR spectra. The NMR data indicated that the parent piperidin-4-ones 56-58 adopt chair conformation.

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Table 1. Assignment of ^{1}H NMR Spectrum of *r*-2,*c*- 6- bis (2-chlorophenyl) -*c*-3, *t*-3 -dimethyl piperidin-

S. No	Chemical Shift (δ ppm)	Assignment	Coupling Constant (Hz)
1	7.39 – 7.20 (m, 8H)	Aromatic protons	
2	4.59 (dd, 1H)	H_{6a}	$J_{5a, 6a}$ = 11.1 $J_{5e, 6a}$ = 5.1
3	3.79 (s, 1H)	H_{2a}	
4	2.75 (dd, 1H)	H_{5a}	$J_{5a, 5e}$ = 14 $J_{5a, 6a}$ = 12
5	2.66 (dd, 1H)	H_{5e}	$J_{5a, 5e}$ = 14 $J_{5e, 6a}$ = 3.5
6	1.75* (s, exchangeable with D_2O)	NH	
7	1.26 (s, 3H)	CH_3 at C_3	
8	1.02 (s, 3H)	CH_3 at C_3	

* Extracted from ^{1}H NMR (D_2O exchanged) Spectrum

Table 2. Assignment of ^{13}C NMR spectrum of *r*-

S. No	Chemical Shift (δ ppm)	Assignment
1	211.74	C_4 >= O
2	140.2, 136.9, 134.2,132.5	Aromatic (*ipso*) Carbons
3	130.5, 129.6, 128.7, 128.6,127.4,126.3	Aromatic Carbons
4	63.03	C_2
5	57.09	C_6
6	50.85	C_3
7	44.68	C_5
8	20.45	CH_3 at C_3
9	20.02	CH_3 at C_3

Table 3. Assignment of ^{1}H NMR Spectrum of *r*-2,*c*-6-bis(2-chlorophenyl) *t*-3,*t*-5-dimethylpiperidin-4-one (2)

S. No	Chemical Shift (δ ppm)	Assignment	Coupling Constant (Hz)
1	7.35 – 7.19 (m, 8H)	Aromatic protons	
2	4.38 (d, 2H)	H_{2a} & H_{6a}	$J_{2a, 3a} = J_{5a, 6a}$ = 10.3
3	2.79 (bs, 2H)	H_{3a} & H_{5a}	
4	1.75(bs, exchangeable with D_2O)	-NH	
5	0.92 (d, 6H)	-CH$_3$ at C_3 & C_5	J = 6.5

Table 4. Assignment of ^{13}C NMR Spectrum of *r*-2,*c*-6-bis(2-chlorophenyl) *t*-3,*t*-5-dimethylpiperidin-4-one (2)

S. No	Chemical Shift (δ ppm)	Assignment
1	210.14	C_4 >= O
2	139.1, 133.9	Aromatic (*ipso*) Carbons
3	129.4, 128.7,127.3	Aromatic Carbons
4	62.49	C_2 & C_6
5	51.98	C_3 & C_5
6	9.93	CH_3 at C_3 & C_5

Table 5. Assignment of ^{1}H NMR spectrum of *r-2 c*-6-bis(2-chlorophenyl)- *t-3*- ethylpiperidin-4-one (3)

S. No	Chemical shift (δ ppm)	Assignment	Coupling constant (Hz)
1	7.46 to 7.26 (8H)	Aromatic protons	
2	4.07 (dd, 1H)	H_{6a}	$J_{5a, 6a}$ = 11.5 $J_{5e, 6a}$ = 3.5
3	3.61 (d, 1H)	H_{2a}	$J_{2a, 3a}$=10.5
4	2.62 (m, 3H)	H_{3a} & $H_{5a,5e}$	
5	2.45* (s, exchangeable with D_2O)	NH	
6	0.83 (d, 3H)	CH_3 at C_3	J = 6.5

*Extracted from ^{1}H NMR (D_2O exchanged) spectrum.

Table 6. Assignment of ^{13}C NMR spectrum of *r-2,c*-6-bis(2-chlorophenyl)- *t-3*-methylpiperidin-4-one (3)

S. No	Chemical shift (δ ppm)	Assignment
1	208.61	C_4 >=O
2	141.08, 140.22, 133.60, 133.02	Aromatic (*ipso*) carbons
3	131.5, 129.0, 128.9, 128.8, 127.8	Aromatic carbons
4	67.69	-C_2
5	60.89	-C_6
6	51.63	-C_3
7	50.81*	-C_5
8	10.06	-CH_3 at C_3

*Extracted from DEPT spectrum.