SYNTHESES AND CONFORMATIONAL STUDIES ON CERTAIN N-NITROSO PIPERIDIN-4-ONES

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ABSTRACT

Heterocyclic compounds gain importance owing to their pharmacological, agro-chemical 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 Gaivoronksaya, 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 Gaivoronksaya (Shintani et al., 1948). 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-aril, 2-heteroaryl piperidin-4-ones in the construction of polycyclic systems such as benzo[4]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-tetramethyl piperidin-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 tachykinin 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 ¹H NMR and ¹³C NMR spectra were recorded on a Bruker AMX 400 MHz spectrometer and 2D NMR spectra were recorded on a AV 500 MHz instrument in CDCl₃ solution with TMS as an internal standard.

2.1. Synthesis of 2,6-Bis(2-chlorophenyl)-c3,t-3-dimethylpiperidin-4-one (1)

To a solution of ammonium acetate (0.05 mole) in dry ethanol, 2-Chlorobenzaldehyde (0.1 mole) and isopropyl methyl 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 2,6-Bis(2-chlorophenyl)-c3,t-3-dimethylpiperidin-4-one was filtered and washed well with the dry alcohol. Yield : 11.5 g (75%) m.p: 148°-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 2,6-Bis(2-chlorophenyl)-t3,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 (0.05 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 2,6-Bis(2-chlorophenyl)-t3,t-5-dimethylpiperidin-4-one was separated was washed well with the dry alcohol.

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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 condenser. 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 & 13C and 2D (1H, 1H-COSY & 1H, 13C-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-dimethylpiperidin-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](image)

The structure of the compound 1 was confirmed by IR spectra, 1H, 13C 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-chlorophenyl) -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 (H₆a, H₅a, H₅e) since no coupling partner is available at C₅ for C₂ proton, the benzylic proton at C₂ appeared as a singlet at 3.79 ppm. The chemical shift value of H₂ 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 J values of 11.1 (J₆a₅a) and 5.1 Hz (J₅a₅e), is assigned to the axial proton at C₆ (H₆) and it confirmed the equatorial orientation of the chlorophenyl group at C₅. The coupling constant (J₆a₅a & J₅a₅e) data were employed to calculate the dihedral angles between the vicinal protons (H₆ & H₅a, H₆e) by DAERM. The cis (H₆-C₆-C₇-H₅e) and trans (H₆-C₆-C₇-H₅a) 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 (J₆a₅e = 14.0 Hz and J₅a₅e = 12.0 Hz) can be assigned to the axial proton of C₅ (H₅e). Similarly the signal at 2.66 ppm appeared as a double doublet with coupling constant values of 14.0 Hz (J₅a₅e) and 3.5 Hz (J₆a₅e) can be assigned to the equatorial proton at C₅ (H₅e).

The presence of NH proton at 1.75 ppm was confirmed using the D₂O exchange studies (Spectrum 3).

The 13C 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-chlorophenyl) -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 C₂ and C₅ positions (Fig. 1).

![Fig. 1](image)

The complete assignments of 1H and 13C 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).
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}$$

$\text{J}_{2a,3a}$ 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$_2$ and C$_6$ and methyl groups at C$_3$ and 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 2,6-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](image-url)

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 °C (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}$$

$\text{J}_{6a,5a}$ values of 11.5 and 3.5 Hz, ascribable to $^{3}$$

$\text{J}_{6a,5e}$, 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$_5$). Similarly, the proton H$_2$ of the AX spin system gave a doublet at 3.61 ppm with a $^{3}$$

$\text{J}_{5a,5e}$ value of 10.5 Hz, 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}$$

$\text{J}_{6a,5a}$ & $^{3}$$

$\text{J}_{6a,5e}$) data were employed to calculate the dihedral angles between the vicinal protons (H$_6$ & H$_{5a}$ H$_{5e}$) by DAERM.$^{24}$ The cis (H$_2$-C$_6$-C$_5$-H$_{5a}$) and trans (H$_2$-C$_6$-C$_5$-H$_{5e}$) 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 2,6-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).
4. SUMMARY

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

The preferred conformations of these compounds 1-3 have been determined using IR spectra, \(^1\text{H}, \text{\textsuperscript{13}C, DEPT and 2D (\textsuperscript{1}H, \textsuperscript{1}H-COSY & \textsuperscript{1}H, \textsuperscript{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\text{H NMR Spectrum of } r-2,c-6\text{-}\text{bis (2-chlorophenyl) -c-3, t-3 -dimethyl piperidin-}

| S. No | Chemical Shift (\(\delta\) ppm) | Assignment | Coupling Constant (Hz) |
|-------|-----------------------------|------------|------------------------|
| 1     | 7.39 – 7.20 (m, 8H)         | Aromatic   |                        |
| 2     | 4.59 (dd, 1H)               | H\(_{6a}\) | \(J_{5a,6a} = 11.1\)   |
| 3     | 3.79 (s, 1H)                | H\(_{2a}\) | \(J_{5e,6a} = 5.1\)    |
| 4     | 2.75 (dd, 1H)               | H\(_{5a}\) | \(J_{5a,5e} = 14\)     |
| 5     | 2.66 (dd, 1H)               | H\(_{5e}\) | \(J_{5a,5e} = 12\)     |
| 6     | 1.75* (s, exchangeable with D\(_2\)O) | NH | \(J_{5e,6a} = 3.5\)    |
| 7     | 1.26 (s, 3H)                | CH\(_3\) at C\(_3\) |              |
| 8     | 1.02 (s, 3H)                | CH\(_3\) at C\(_3\) |              |

* Extracted from \(^1\text{H NMR (D\(_2\)O exchanged) Spectrum}

Table 2. Assignment of \(^{13}\text{C NMR spectrum of } r-

| S. No | Chemical Shift (\(\delta\) ppm) | Assignment          |
|-------|--------------------------------|---------------------|
| 1     | 211.74                         | C\(_4\) >= 0        |
| 2     | 140.2                          | 136.9, Aromatic (ipso) |
| 3     | 134.2, 132.5                   | Carbons             |
| 4     | 130.5, 129.6, 128.7, 128.6, 127.4, 126.3 | Aromatic Carbons |
| 5     | 63.03                          | C\(_2\)              |
| 6     | 57.09                          | C\(_6\)              |
| 7     | 50.85                          | C\(_3\)              |
| 8     | 44.68                          | C\(_5\)              |
| 9     | 20.45                          | CH\(_3\) at C\(_3\) |
| 8     | 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 ($\delta$ ppm) | Assignment | Coupling Constant (Hz) |
|-------|-------------------------------|------------|------------------------|
| 1     | 7.35 – 7.19 (m, 8H)           | Aromatic protons | $J_{2a,3a} = J_{5a,6a} = 10.3$ |
| 2     | 4.38 (d, 2H)                  | $H_{2a} & H_{6a}$ |                        |
| 3     | 2.79 (bs, 2H)                 | $H_{3a} & H_{5a}$ |                        |
| 4     | 1.75(bs, exchangeable with D$_2$O) | -NH        |                        |
| 5     | 0.92 (d, 6H)                  | $-CH_3$ at C$_3$ & $J = 6.5$ |                        |

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 ($\delta$ ppm) | Assignment |
|-------|-------------------------------|------------|
| 1     | 210.14                        | C$_4$ =$\geq$ 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 ($\delta$ ppm) | Assignment | Coupling constant (Hz) |
|-------|-------------------------------|------------|------------------------|
| 1     | 7.46 to 7.26 (8H)             | Aromatic protons |                        |
| 2     | 4.07 (dd, 1H)                 | $H_{6a}$ | $J_{5a,6a} = 11.5$ |
| 3     | 3.61 (d, 1H)                  | $H_{2a}$ | $J_{5e,6a} = 3.5$ |
| 4     | 2.62 (m, 3H)                  | $H_{3a}$ & $H_{5a,5e}$ | $J_{2a,3a} = 10.5$ |
| 5     | 2.45* (s, exchangeable with D$_2$O) | NH |                        |
| 6     | 0.83 (d, 3H)                  | $CH_3$ at C$_3$ | $J = 6.5$ |

*Extracted from $^1$H NMR (D$_2$O 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 ($\delta$ ppm) | Assignment |
|-------|-------------------------------|------------|
| 1     | 208.61                        | C$_4$ =$\geq$ 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.