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Impact on NMR spectra by *ortho* substitution of 2, 6-*bis* (polymethoxyphenyl) piperidin-4-ones

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ABSTRACT

Synthesis of new molecules with bio-potent piperidine/piperidone skeleton and their stereochemical investigation are important in the field of medicinal chemistry due to the presence of piperidine/piperidone skeleton as a building block in numerous naturally occurring alkaloids and biologically active compounds. Since the stereochemistry of any molecules plays vital role in eliciting their biological response, it is very important to ascertain the configuration and conformation of the molecules that obtained for the biological screening. Hence, it was planned to synthesis some polyfunctionalized piperidin-4-ones as new bio-active molecules to establish their stereochemistry. Particularly, the synthesis has been targeted to polyfunctionalized 2,6-*bis*(polymethoxyphenyl)piperidin-4-ones in view of the fact that the methoxy groups are responsible for various biological actions including antioxidant property. Thus, the target molecules 3,5-dimethyl-2,6-*bis*(3,4-dimethoxyphenyl)piperidin-4-one (1) and 3,5-dimethyl-2,6-*bis*(2,5-dimethoxyphenyl)piperidin-4-one (2) were achieved as single isomer by modified Mannich condensations. Identification and characterization of the synthesized molecules were made by analytical (TLC, melting point, elemental analyses) and spectral (IR and NMR) studies. The NMR spectral studies, particularly, the proton NMR spectral data were very useful to determine the configuration and conformation of the new molecules 1 and 2. Accordingly, both of them exist in chair conformation with equatorial orientations of methyl groups on the active methylene centers (C-3 and C-5) and polymethoxyphenyl groups on both sides of the secondary amine (C-2 and C-6). Another interesting observation from the proton NMR is, the *ortho* substitution on 1 (i.e., molecule 2) cause a significant deshielding on benzylic (H-2a/H-6a) and *ortho* protons, and a minor deshielding on methinic protons (H-3a/H-5a), whereas, all the above three signals appear as broad singlet due to the restricted rotation by the interaction of *ortho* methoxy groups with the methyl groups at C-3 and C-5.

KEY WORDS: Mannich reaction, Mannich base, Polymethoxyphenyl, Piperidin-4-one, Ortho effect.

1. INTRODUCTION

Nitrogen heterocycles represent a vital role in organic chemistry especially in the field of medicinal chemistry (Angle, 1995). Nitrogen heterocycle is present as part of the skeletal backbone of many therapeutic agents and naturally occurring compounds and thus exhibit interesting chemical reactions and important biological actions such as antibacterial, antifungal, antiinflammatory, antiarrhythmic, antiallergic, antiprotozoan, anticholinergic, antitumor, antituberclostic, anticonvulsant, antiviral, antimalarial, local anesthetic, antineoplastic, hypotensive, cytotoxic, muscle relaxant, analgesic, herbicidal, tyrosinase inhibitor, tranquilizer, nicotinic acetylcholine receptor, central nerves system (CNS) stimulant and CNS depressant (Baliah, 1983; Reddy, 1997; Kumar, 2009).

It is important to a chemist to understand the broad consequence of the trend in research in the modern pharmaceutical industry. The design and discovery of new drugs require a team effort, and in fact, this not only involves chemists but also researchers from a wide range of disciplines, very particularly, pharmacologists and biochemists amongst others. The major role of pharmacologists lies to design and operate model system for detecting and evaluating the activity of compounds for the control of diseases. It is a big task of finding a potent drug, which does not have side effects in some individuals. Hence, a detailed study of absorption, distribution, metabolism and excretion (ADME) of drug is an essential part of pharmacology.

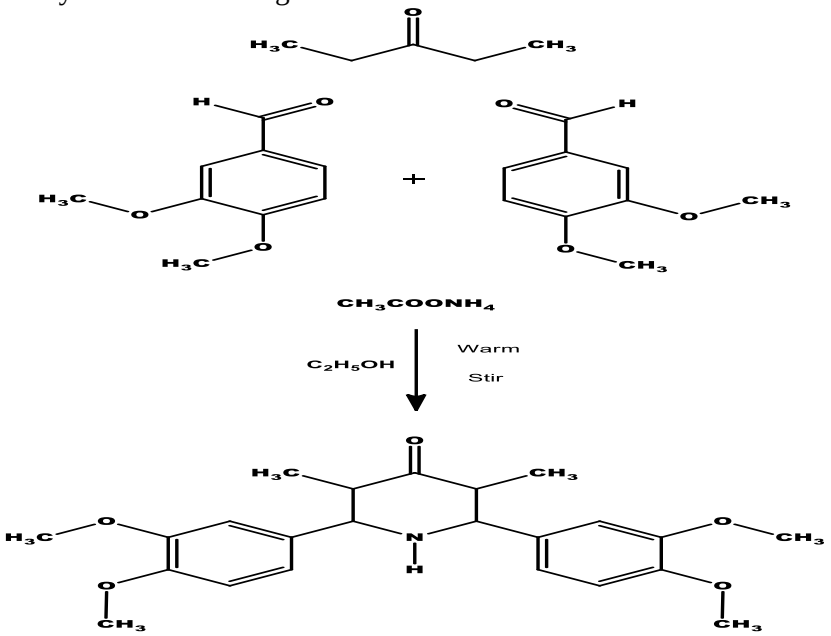
Biological actions of a compound are depends on the involved function of the structure. Minor changes may exhibit prominent implication in activity. Even a minor change such as replacement of one group for other at a specific site in the molecule may sometime completely reverse the biological action of the compound.

Since the stereochemistry of the molecules is an inevitable criterion for the biological activities, it is of importance to establish the stereochemistry of the biologically active molecules. NMR technique is a versatile tool for the structural elucidation of most of the organic compounds and useful for the conformational analysis. ^{1}H NMR and ^{13}C NMR techniques have been extensively applied in deriving stereodynamical information about a wide variety of systems. They give information about the influence of electronic and conformational effects on chemical shifts and coupling constants. Vicinal coupling constant values have been used for the conformational analysis that can give an indication of the orientation of the substituents (Caldwell, 1993; Parthiban, 2009).

Hence, the current study has been carried out to synthesis two polyfunctionalized polymethoxyphenyl piperidones, *viz.*, 3,5-Dimethyl-2,6-*bis*(3,4-dimethoxyphenyl)piperidin-4-one (1) and 3,5-Dimethyl-2,6-*bis*(2,5-dimethoxyphenyl)piperidin-4-one (2) to establish the stereochemistry of the new molecules and to explore the impact of *ortho* substitution on NMR spectra.

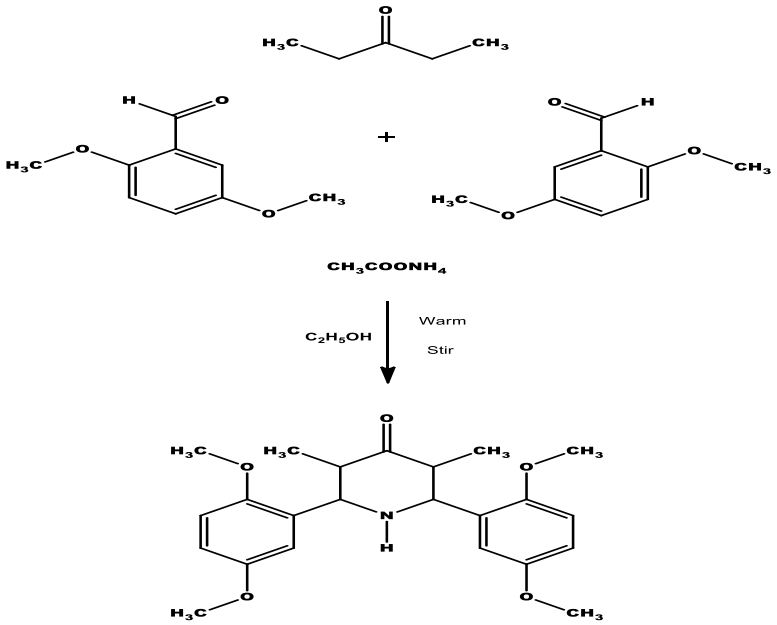
2. MATERIALS AND METHODS

Synthesis of 3,5-dimethyl-2,6-*bis*(3,4-dimethoxyphenyl)piperidin-4-one (1): The 3,5-dimethyl-2,6-*bis*(3,4-dimethoxyphenyl)piperidin-4-one was synthesized by modified Mannich condensations (Noller, 1948) in one-pot, using 3,4-dimethoxy benzaldehyde (0.2 mol), 3-pentanone (0.1 mol) and ammonium acetate (0.1 mol) in 50 ml of absolute ethanol (to this reaction mixture, a small portion of acetic acid has been added to improve the solubility of veratraldehyde in ethanol). Initially, the mixture was gently warmed on a hot plate at 318 K (45°C) with moderate stirring then, until the complete consumption of the starting materials, which was stirred at 35-40°C. After the conversion of starting materials, the crude piperidone was separated by filtration and gently washed with 5:1 mixture of cold ethanol and ether. Synthesis of this target molecule is shown in Scheme 1.



Scheme.1. Synthesis of the target compound 3,5-dimethyl-2,6-*bis*(3,4-dimethoxyphenyl)piperidin-4-one (compound 1)

Synthesis of 3,5-dimethyl-2,6-*bis*(2,5-dimethoxyphenyl) piperidin-4-one (2): The 3,5-dimethyl-2,6-*bis*(2,5-dimethoxyphenyl)piperidin-4-one was synthesized by modified Mannich condensations in one-pot, using 2,5-dimethoxybenzaldehyde (0.2 mol), 3-pentanone (0.1 mol) and ammonium acetate (0.1 mol) in 50 ml of absolute ethanol. Initially, the mixture was gently warmed on a hot plate at 318 K (45° C) with moderate stirring then, until the complete consumption of the starting materials, which was stirred at 35-40° C. At the end, the crude piperidone was separated by filtration, and gently washed with a mixture of cold ethanol and ether (5:1). Synthesis of this target molecule is represented in Scheme.2.



Scheme.2. Synthesis of the target compound 3,5-dimethyl-2,6-*bis*(2,5-dimethoxyphenyl)piperidin-4-one (compound 2)

Spectral measurements: Infra-red spectra: IR spectra were recorded in Shimadzu FT-IR spectrophotometer as neat samples and only noteworthy absorption levels (reciprocal centimeters) are listed.
NMR spectra: ^{1}H NMR, and ^{13}C NMR spectra were recorded on Varian 500 MHz NMR spectrometer.
Recording of one-dimensional NMR spectra: The ^{1}H and ^{13}C NMR spectra were measured on 0.03M and 0.05M solutions, respectively in $CDCl_3$ with TMS as internal reference in 5 mm NMR tubes on Varian 500 MHz NMR spectrometer at 294 K. The pulse conditions were as follows: ^{1}H NMR spectra: SF 499.96 MHz, AQ 2.73 s, NS 32, DS 0, SW 5998.8 Hz, pulse 4.65 µs, angle 45º, width 9.3 µs, DR 0.366 Hz, RD 5 s, RG 13, data points 16384, pre scan delay 1 s; ^{13}C NMR spectra: SF 125.52 MHz, AQ 1.25 s, NS 250, DS 4, SW 26178.01 Hz, Pulse 3.13 µs, angle 30º, width 9.4 µs, DR 0.798 Hz, RD 1 s, RG 25, data points 32768, pre scan delay 1 s.
Abbreviations: SF, spectrometer frequency; AQ, acquisition time; NS, number of transients (Number of scans); DS, dummy scans; SW, spectral width; DR, digital resolution; RD, relaxation delay; RG, receiver gain.
Elemental analysis: Satisfactory microanalyses were obtained from Heraeus Carlo Erba elemental analyzer.

3. RESULTS AND DISCUSSION

NMR Spectroscopy: 1D NMR Spectroscopy: Nuclear Magnetic Resonance (NMR) spectroscopy is a well-established technique for providing information about structural diagnosis of organic molecule. It involves transition of nucleus from one spin state to another state with the resultant absorption of electromagnetic radiation in the radio wave frequency region by spin active nuclei when they are placed in a magnetic field. The energy associated with NMR experiments is incapable of disrupting even the weakest chemical bond in a molecule. One-dimensional NMR (1D NMR) spectrum constitutes a plot of the frequencies of the absorption peaks versus peak intensities.
Physical properties and elemental analysis of the target compounds 1 and 2: The nature and physical appearance, color, melting point, yield and elemental composition of the target piperidones 1 and 2 are presented in Table.1. The observed C, H, N and O percentages are in good agreement with the theoretical values of the compounds.

Table.1. Physical properties and elemental analysis report of compounds 1 and 2.

Physical properties	Compound 1	Compound 2
Molecular formula	$C_{23}H_{29}NO_5$	$C_{23}H_{29}NO_5$
Molecular weight	399.48	399.48
Color	White	Cream white
Physical appearance and nature	Amorphous powder	Crystalline
Melting point	140 ^{0}C	210 ^{0}C
Yield	79%	83%
Elemental composition: C	63.97 (64.02)	64.00 (64.02)
H	6.78 (6.77)	6.78 (6.77)
N	3.23 (3.25)	3.24 (3.25)
O	26.02 (25.96)	25.98 (25.96)

The values within the brackets are calculated values.

IR spectral analysis of the target compounds 1 and 2: In 3,5-dimethyl-2,6-*bis*(3,4-dimethoxyphenyl)piperidin-4-one (compound 1), the characteristic vibrational band at 1711 cm^{-1} is supported by the reported stretching frequency of the C=O group of the unsubsubstituted 2,6-diphenylpiperidin-4-one. Also the absence of the stretching frequency of the C=O group of the starting material 3,4-dimethoxy benzaldehyde (veratraldehyde) at 1683 cm^{-1} supports the complete consumption of aldehyde starting material and formation of the expected cyclic ketone. Similarly, a sharp band observed at 1707 cm^{-1} for the compound 2 instead of the sharp band at 1677 cm^{-1} for the 2,5-dimethoxybenzaldehyde.

The strong absorption band observed at about 3300 cm^{-1} in the IR spectrum is normally assigned to the N-H stretching mode of the secondary amine (Silverstein, 2002). Hence, the appeared characteristic IR band at 3323 cm^{-1} for both the target molecules 1 and 2, is assigned to the N-H stretching of the secondary amine.
Several other characteristic bands of the target compounds were also observed and thus, the formation of the target compounds 1 and 2 are confirmed by IR spectroscopy.
NMR spectral analysis of target compound 1:
^{1}H NMR: The ^{1}H NMR spectral signals are assigned based on their position, multiplicity and integral values. In general, the aromatic protons absorb in the downfield region at around 7 ppm due to magnetic anisotropic effect (ring current effect). Labelling of the target compound 1 is depicted in Figure.1 and its NMR spectral assignments are summarized in Table.2.

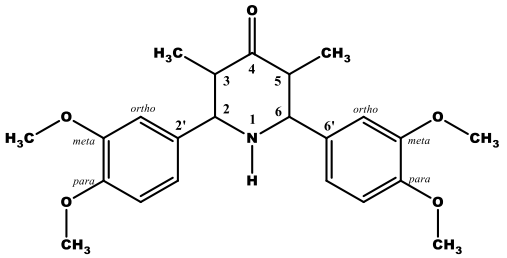


Figure.1. Numberings of the target compound 1

In the ^{1}H NMR spectrum of 3,5-dimethyl-2,6-*bis*(3,4-dimethoxyphenyl)piperidin-4-one three signals observed in the aryl region correspond to two protons integral each. They are a doublet at 7.01 ppm (J = 1.5 Hz), a doublet of doublets at 6.95 ppm (J = 8.0, 2.0 Hz) and another doublet at 6.83 ppm (J = 8.5 Hz), which are respectively assigned to *ortho'* protons (opposite to OCH_3 group), *ortho* protons (adjacent to OCH_3 group) and *meta'* protons.

The high intensity sharp singlets at 3.91 (6H) and 3.87 (6H) ppm are definitely due to the resonance of methoxy groups at *meta* and *para* positions of the phenyl groups attached to C-2 and C-4.

There are two doublets observed in the upfield region at 3.54 and 0.84 ppm. Of them, the doublet at 3.54 ppm corresponds to two protons whereas the 0.84 ppm doublet corresponds to six protons. Consequently, by comparing with 3,5-dimethyl-2,6-diphenylpiperidin-4-one, 3,5-dimethyl-2,6-*bis*(3-methoxyphenyl)piperidin-4-one and 3,5-dimethyl-2,6-*bis*(4-methoxyphenyl)piperidin-4-one, the two protons doublet is assigned to the protons at C-2 and C4, which are in axial position (i.e., H-2a and H-4a, $^{3}J_{2a,3a}$ = 10.5 Hz). Hence, it is clear by the diaxial vicinal coupling constant that the protons at C-2 and C-6 are in axial position, which indicates the equatorial disposition of the polyfunctionalized phenyl groups attached to C-2 and C-4.

Table.2. ^{1}H NMR spectral assignments of 3,5-dimethyl-2,6-*bis*(3,4-dimethoxyphenyl)piperidin-4-one (compound 1) in $CDCl_3$

Chemical shift [δ (ppm)]	Proton
7.01, d, 2H, J = 1.5 Hz	*ortho'* protons (i.e., protons opposite to OCH_3 group)
6.95, dd, 2H, J = 8.0, 2.0 Hz	*ortho* protons (i.e., protons adjacent to OCH_3 group)
6.83, d, 2H, J = 8.5 Hz	*meta'* protons
3.91, s, 12H	*para*-OCH_3 protons
3.87, s, 6H	*meta*-OCH_3 protons
3.54, d, 2H, $^{3}J_{2a,3a}$ = 10.5 Hz	H-2a and H-4a (benzylic protons)
2.75, m, 2H	H-3a and H-5a (methinic protons)
2.10, s, 1H	NH
0.84, d, J = 7.0 Hz	Methyl groups at C-3 and C-5

By a close analysis of the NMR spectrum, interesting information has been arrived from the vicinal coupling constant. The doublet at 3.54 ppm is due to the splitting of the protons at C-2/C-4 by the protons at C-3/C-5, whereas, a multiplet is observed at 2.75 ppm due to the splitting of the H-3/H-5 by H-2/H-6 followed by the methyl groups at C-3/C-5. The vicinal coupling constant $^{3}J_{2a,3a}$ = 10.5 Hz clearly indicates that the doublet is due to vicinal diaxial protons. Hence, it is clear that the protons at C-2, C-3, C-4 and C-6 are in axial orientation, thus, it is clear that the methyl groups at C-3 and C-5 occupy the equatorial position. The methyl groups at C-3 and C-5 appear at 0.84 ppm (d, J = 6.5 Hz). The protons at C-3 and C-5 split the methyl signal as doublet. From the data of analogous 2,6-diarylpiperidin-4-ones, it can be witnessed that the singlet at 2.10 ppm is due to the secondary amine group (i.e., NH proton in the first position).

By summarizing the above informations, it is proposed that the synthesized new molecule 1 exists in a chair conformation with equatorial disposition of the methyl group at C-3/C-5 and 3,4-dimethoxyphenyl group at C-2/C-4.

^{13}C NMR: The ^{13}C NMR spectral assignment of 3,5-dimethyl-2,6-*bis*(3,4-dimethoxyphenyl)piperidin-4-one is presented in Table.3. There are seven resonances in the aryl region beyond the triplet centered at 77.16 ppm by the residual $CHCl_3$ of NMR solvent $CDCl_3$. (Note: the signals at 176.90 and 21.04 ppm are owing to the COOH and CH_3 of acetic acid traces, which had been used in a small portion to the reaction mixture to improve the solubility of veratraldehyde in ethanol). Among them, the most downfield signal at 211.19 ppm is designated to the carbonyl carbon (i.e., C-4). Of the remaining six signals at 149.06, 148.74, 134.29, 120.21, 110.88 and 110.46 ppm, the most downfield signals are attributed to OCH_3 bearing *ipso* carbons, while, the phenyl *ipso* carbons (C-2' and C-6') resonated at 134.29 ppm. Rest of the aryl region signals at 120.21, 110.88 and 110.46 ppm are assigned to the remaining phenyl carbons.

The carbon signals at 68.60 and 51.94 ppm are consigned to C-2/C-6 and C-3/C-5, respectively. These assignments have been justified by comparing the carbon resonances of analogous compounds such as 3,5-dimethyl-2,6-diphenylpiperidin-4-one, 3,5-dimethyl-2,6-*bis*(3-methoxyphenyl)piperidin-4-one and 3,5-dimethyl-2,6-*bis*(4-methoxyphenyl)piperidin-4-one. Similarly, the most upfield resonance in the ^{13}C NMR spectrum of compound 1 at 10.69 ppm is unequivocally fixed to the methyl groups (CH_3 at C-3 and C-5). The remaining two resonances at 56.01 and 55.97 ppm are designated to the OCH_3 groups at *meta* and *para* positions.

Table.3. ^{13}C NMR spectral assignments of 3,5-dimethyl-2,6-*bis*(3,4-dimethoxyphenyl)piperidin-4-one (compound 1) in $CDCl_3$

Chemical shift [δ (ppm)]	Carbon
211.19	C-4
149.06 148.74	OCH_3 bearing *ipso* carbons
134.29	Phenyl *ipso* carbons (C-2' and C-6')
120.21 110.88 110.46	Remaining phenyl carbons
68.60	C-2 and C-6
56.01 55.97	OCH_3 groups at *meta* and *para* positions
51.94	C-3 and C-5
10.69	Methyl groups at C-3 and C-5

Overall, the analysis of ^{1}H and ^{13}C NMR spectra of compound 1, along with the comparison of analogous molecules, it is clear that the target molecule exists in a chair conformation with equatorial orientation of the 3,4-dimethoxyphenyl groups at C-2/C-4 and methyl group at C-3/C-5 as depicted in Figure.2.

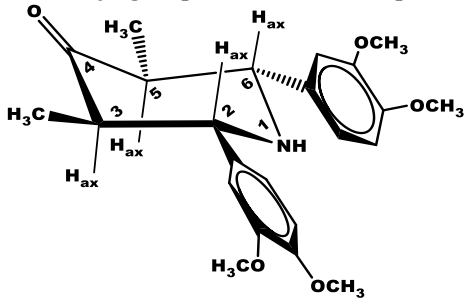


Figure.2. Chair conformation of the synthesized target compound 1 with equatorial orientations of all the alkyl and aryl substituents

Spectral analysis of target compound 2: For unambiguous comprehension of the atoms in the new molecule 2, the numberings annotated and is represented in Figure.3.

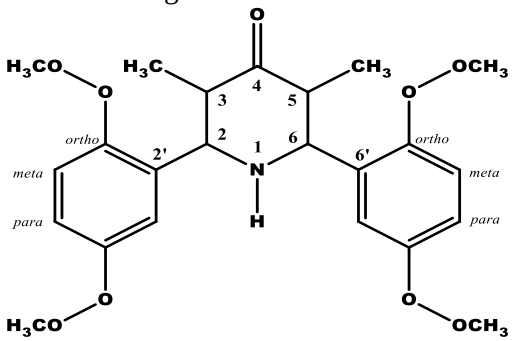


Figure.3. Numberings of the target compound 2

^{1}H NMR: The ^{1}H NMR spectral signals are assigned based on their position, multiplicity and integral values. In general, the aromatic protons absorb in the downfield region at around 7 ppm due to magnetic anisotropic effect (ring current effect).

The complete proton assignment of ^{1}H NMR spectrum of compound 2 is reproduced in Table.4. The broad singlet at 7.17 ppm that corresponds to two protons is due to the resonance of *ortho* protons of the phenyl groups at C-2 and C-6. Rest of the four phenyl protons resonance at 6.77 ppm is a multiplet, which corresponds to four protons. By the interaction of *ortho* protons and nitrogen lone pair electrons, the *ortho* protons are deshielded and their rotations are restricted in the NMR time scale and thus appear as a broad singlet at 7.17 ppm.

Table.4. ^{1}H NMR spectral assignments of compound 2 in $CDCl_3$

Chemical shift [δ (ppm)]	**Proton**
7.17, br s, 2H	*ortho* protons of the phenyl groups at C-2 and C-6
6.77, m, 4H	*meta* and *para* protons of the phenyl groups at C-2 and C-6
4.18, br s, 2H	H-2a and H-4a (benzylic protons)
3.82, 3.76, 12H	OCH_3 protons
2.77, br s, 2H	H-3a and H-5a (methinic protons)
1.96, br s, 1H	NH
0.85, d, J = 6.0 Hz, 6H	Methyl groups at C-3 and C-5

Another three broad singlets appear in the upfield region of 4.18, 2.77 and 1.96 ppm. Of them, the first two signals correspond to two protons each while the last one at 1.95 ppm corresponds to one proton, which is assigned to NH by comparing with analogous compounds. The 2.77 ppm broad singlet is due to H-3a and H-5a (methinic protons) since it is appeared similar to that of compound 1 at 2.75 ppm while the H-2a and H-4a (benzylic protons) are deshielded largely to 0.64 ppm and appeared at 4.18 ppm as a broad singlet instead of a fine doublet (3.54, d, 2H, $^{3}J_{2a,3a}$ = 10.5 Hz) at compound 1. The singlets at 3.82 and 3.76 ppm are assigned to the OCH_3 protons. The six protons integral doublet at 0.85 ppm (J = 6.0 Hz, 6H) is designated to the methyl protons at C-3 and C-5.

Interestingly, the benzylic protons (H2a/H-6a) are highly deshielded by 0.64 ppm compared to its counterpart H2a/H-6a of compound 1 and the *ortho* protons are deshielded about 0.40 ppm of its rest of the phenyl protons. Since the magnitudes of deshielding are large, it is not feasible by the electronic effect of the *ortho* substitution. It is mainly by the orientation of the *ortho* substituent. In order to avoid the dipole-dipole interaction between the C-O and C-N bonds, the (C-O bond of the) OCH_3 substituent prefers to be *syn* to the benzylic proton as shown in Figure.4. As a consequence, the *ortho* protons of the phenyl groups are also deshielded by the nitrogen lone pair. Hence, it is very clear that the non-bonded interactions between the benzylic protons and C-O of the OCH_3 groups directly deshield the benzylic protons to significantly a large extent, whereas, the *ortho* protons are only deshielded by the nitrogen lone pair. The non-bonded interactions cause the restricted rotation of the phenyl groups and thus broadening of the signals occurred.

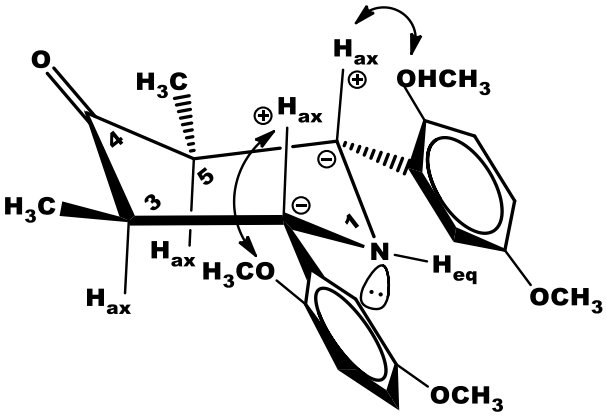


Figure.4. Interactions between the benzylic (H2a/H-6a) protons and *ortho* substituents. Also it explains the deshielding of *ortho* protons by the interaction with nitrogen lone pair

^{13}C NMR: The complete carbon resonance assignment of ^{13}C NMR spectrum of compound 2 is reproduced in Table.5.

Table.5. ^{13}C NMR spectral assignments of compound 2 in $CDCl_3$

Chemical shift [δ (ppm)]	Carbon
212.04	C-4
153.76 151.39 114.76 112.51 111.71	Phenyl carbons
59.43	C-2 and C-6
56.06 55.73	OCH_3 groups
52.01	C-3 and C-5
10.52	Methyl groups at C-3 and C-5

In the ^{13}C NMR spectrum of 2, there are six resonances in the aryl region beyond the residual solvent signal of the NMR solvent $CDCl_3$. The carbon resonance at 212.04 ppm is unambiguously assigned to the carbonyl carbon, and the remaining resonances at 153.76, 151.39, 114.76, 112.51 and 111.71 ppm are designated to the phenyl carbons.

The signals at 59.43 and 52.01 ppm are allocated to the carbon resonances of C-2/C-6 and C-3/C-5, respectively by comparing analogous molecules. Similarly, the 10.52 ppm carbon resonance is assigned to the methyl groups at C-3 and C-5. The intensed carbon resonances at 56.06 and 55.73 ppm are assigned to the OCH_3 groups.

A careful comparison of Table.3 and Table.5, provides some information about the effect of an introduction to *ortho* position of the phenyl groups at C-2 and C-4. In this case, the benzylic carbons are shielded significantly while no noteworthy changes in the methinic carbons. In compound 2, the C-2 and C-4 shielded by 9.17 ppm owing to the interactions between the *ortho* substituent and benzylic protons, their C-H bonds polarized and as a consequence, those protons acquired partial positive charge and the carbons acquired partial negative charge and thus shielded (Figure.4).

Based on proton and carbon NMR spectral studies of compound 2 along with the comparison of analogous molecules, it is suggested that the target molecule 2 adopts a chair conformation with equatorial orientation of the methyl groups at C-3 and C-5, and the aryl groups (i.e., 2,5-dimethoxyphenyl) at C-2 and C-4 as well (Figure.4).

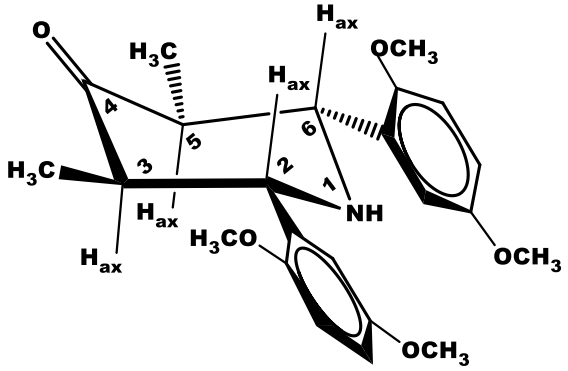


Figure.5. Stereochemistry of the synthesized compound 2 with equatorial orientations of all the alkyl and aryl substituents

4. SUMMARY AND CONCLUSIONS

Based on the biological importance of piperidine/piperidone heterocycles, some functionalized piperidin-4-ones such as 3,5-dimethyl-2,6-*bis*(3,4-dimethoxyphenyl)piperidin-4-one (compound 1) and 3,5-dimethyl-2,6-*bis*(2,5-dimethoxyphenyl)piperidin-4-one (compound 2) were synthesized by adopting the Mannich condensation using 1:2:1 ratio of 3-pentanone, appropriated benzaldehyde and ammonium acetate in warm ethanol with necessary modifications to improve the yield and reduce the work-up procedure. Accordingly, both relations afforded a satisfactory good yield.

The preliminarily identification of the synthesized target molecules were carried out by their physical appearance, elemental analysis and IR data. Further, the molecules were characterized by ^{1}H and ^{13}C NMR techniques, to explore their configuration and conformation, unambiguously. Both molecules were obtained as single isomer with good yield even though a number of stereomers are possible for both molecules. Both the target molecules 1 and 2 exist in chair conformation with equatorial disposition of the methyl groups at C-3/C-5, and the highly functionalized phenyl groups at C-2/C-6.

Interesting information obtained from the NMR data is, the benzylic protons (H2a/H-6a) of 2 are highly deshielded by 0.64 ppm compared to the H2a/H-6a of 1 Similarly, the *ortho* protons of 2 are deshielded about 0.40 ppm than its remaining phenyl protons. Since the magnitudes of deshielding are large, it is not feasible by the electronic effect of the *ortho* substitution alone, necessarily which is due to the orientation of the *ortho* substituent, in order to avoid the dipole-dipole interaction between the C-O and C-N bonds. The C-O bond of the OCH_3 substituent prefers to be *syn* to the benzylic protons.

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