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Two-dimensional NMR spectral studies of some 2,6-diarylpiperidin-4-ones

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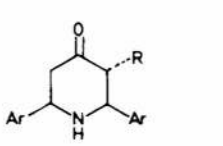
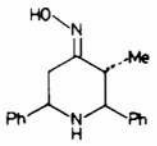
NOESY spectra have been recorded for *t*(3)-methyl-*r*(2), *c* (6)-diphenylpiperidin-4-one **1**, its oxime **2**, *t*(3)-isopropyl-*r*(2), *c*(6)-diphenylpiperidin-4-one **3**, *r*(2), *c*(6)-bis(*p*-methoxyphenyl)piperidin-4-one **4** and *r*(2),*c*(6)-bis(*o*-methoxyphenyl)piperidin-4-one **5**. For **5** ^{13}C-^{1}H HETCOR spectrum also has been recorded. In addition, proton-proton coupling constants and proton chemical shifts have been determined more precisely for **5** by recording its ^{1}H NMR spectrum at 400 MHz. The ^{13}C chemical shifts of **5** are also reported. The NOESY spectra suggest that there could be significant nOe between 1,3-diaxial protons in the chair conformation. It is confirmed that in these compounds the aromatic protons *ortho* to the piperidine ring absorb at a lower field relative to the other aromatic protons. Furthermore, these *ortho* protons have significant nOes with the adjacent axial protons, but only weak nOes with the adjacent equatorial protons. For **5**, in addition to conformation **B** with the *o*-methoxyl group *syn* to the benzylic hydrogen, conformation **C** with the *o*-methoxyl group *anti* to the benzylic hydrogen also should contribute significantly. The methoxyl group shields the *ortho* protons by magnetic anisotropic effect.

NMR spectral studies of heterocyclic compounds have helped in understanding the influence of electronic and conformational effects on chemical shifts and coupling constants. Conformational studies of heterocyclic compounds also have been made using NMR spectra[1,2]. Several NMR spectral studies[3-10] have been reported on 2,6-diarylpiperidine derivatives. In these studies information has been gained about the conformation of the piperidine ring, the orientation of an *o*-substituted phenyl group and the preferred conformation of a 3-alkyl group. In one study[10] the NOESY spectrum of *t*-(3)-isopropyl-*r*(2), *c*(6)-diphenylpiperidin-4-one has been reported, but the NOESY spectrum was not analysed in detail. It seems worthwhile to study the NOESY spectra of some more 2,6-diarylpiperidine derivatives in order to check the conclusions reached earlier. Since these compounds are known to exist largely in chair conformation **A** with equatorial orientations of the substituents[5,7,8] their NOESY spectra would furnish information regarding nOe and distance between protons. Such information is useful since nOes are being used in studying the conformations of complex molecules[11-13]. Therefore, we have recorded the NOESY spectra for piperidin-4-ones **1**, **3**, **4** and **5** and oxime **2**. In order to check the earlier ^{13}C assignments ^{13}C-^{1}H HETCOR spectrum has been recorded for **5**.



1. Ar = Ph, R = Me
3. Ar = Ph, R = i-Pr
4. Ar = p-OMe-C_6H_4, R=H
5. Ar = o-OMe-C_6H_4, R=H



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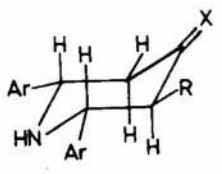


A

Results and Discussion

***t*(3)-Methyl-*r*(2), *c*(6)-diphenylpiperidin-4-one 1 and its oxime 2.** The NOESY spectra of **1** and **2** are almost similar except that the protons at C-3 and C-5 give rise to well resolved signals in the case of **2**. The NOESY spectrum of **2** is displayed in Figure 1. Among the two multiplets observed for aromatic protons the downfield peak was assigned to the *ortho*-protons (*ortho* to the piperidine ring)[8]. From Figure 1 it is seen that only the downfield protons have nOe with the benzylic protons (nOes 1 & 3). Therefore, the downfield peak should be due to the *ortho*- protons. Further, it is seen that the *ortho*-pro-

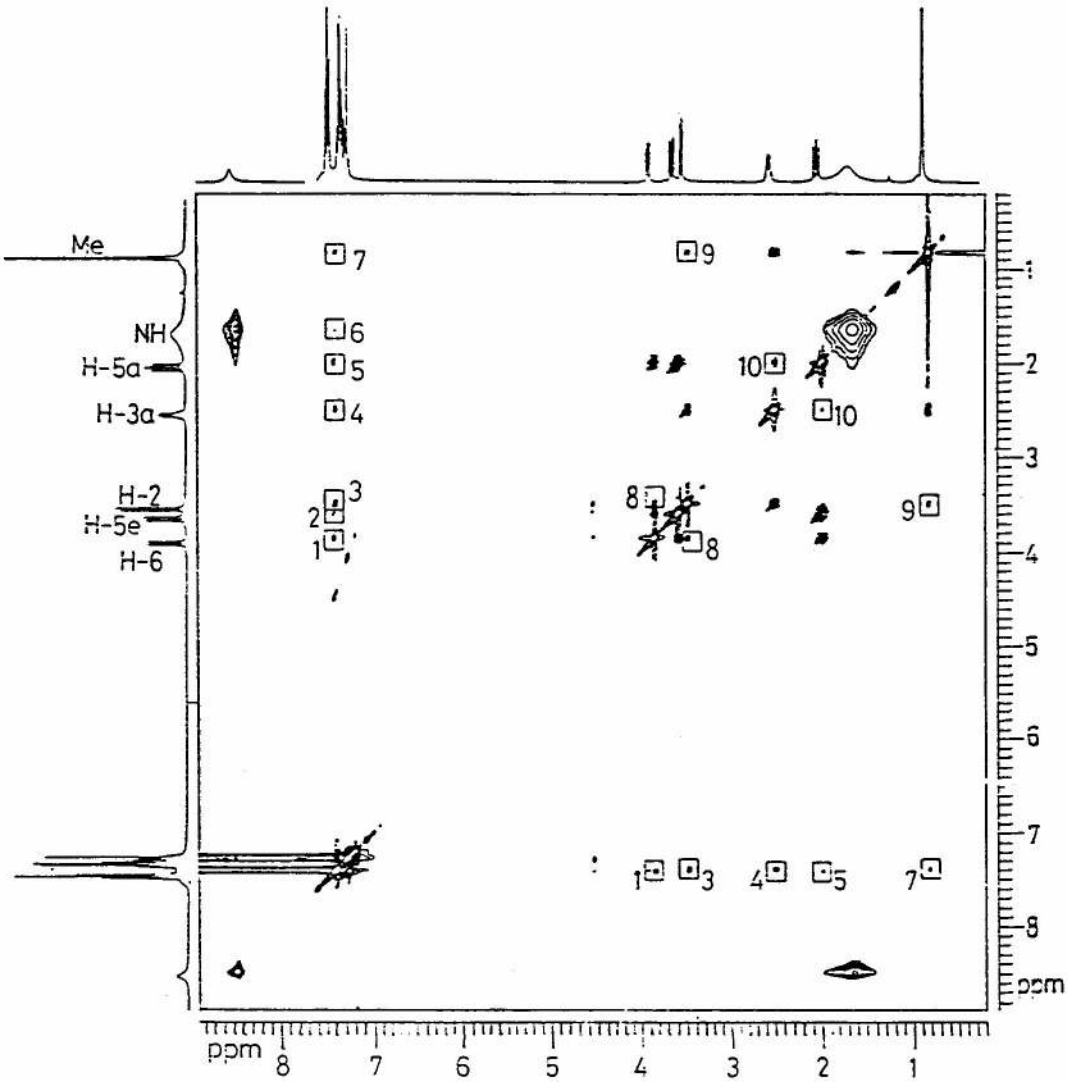


Figure 1 — NOESY spectrum of t(3)-methyl-*r*(2), *c*(6)- diphenylpiperidin-4-one oxime

tons have significant nOe with adjacent axial protons (H-3a and H-5a) (NOes 4 & 5) but have only a very small nOe with the adjacent equatorial proton (H-5e)(nOe 2). Based on the conclusions of Ouellette *et al.*[14] on the conformation of alkylbenzenes, phenyl groups in these compounds should be expected to be parallel to C(2)-H and C(6)-H bonds as shown in Figure 2. In the parallel conformation of the phenyl group shown in Figure 2 the *ortho*- hydrogen which is *anti* to the benzylic hydrogen is very near to an adjacent axial hydrogen but the equatorial hydrogen is far away from either of the *ortho*-hydrogens. Since the *ortho*-protons have a very small nOe with N-H (nOe 6) it could be inferred that N-H should be preferentially equatorial. Moreover, the *ortho*-protons have significant nOe with the protons of an

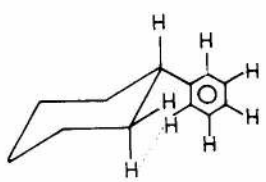


Figure 2 -- Conformation of phenyl group in piperidine derivatives

adjacent equatorial methyl group (nOe 7). From Figure 3 it can be seen that two of the methyl protons could come close to the *ortho* protons to have significant nOe with them.

There is significant nOe between the two benzylic protons (nOe 8). There is also strong nOe between H-3a and H-5a (nOe 10). This suggests that in the

chair conformation **B** of a six-membered ring there should be significant nOe between the 1,3-diaxial protons. There is also significant nOe between C(2)-H and the methyl protons (nOe 9). Further, it can also be seen from Figure 3 that the methyl proton *anti* to H-3a could have significant nOe with H- 2.

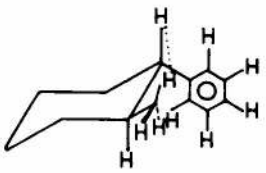
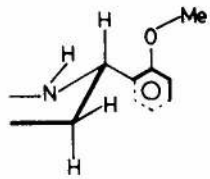


Figure 3 — Spacial disposition of the methyl protons, C(2)-phenyl protons and H-2 in **1** and **2**

***t*-(3)-Isopropyl-*r*(2), *c*(6)-diphenylpiperidin-4-one 3**. The NOESY spectrum of **3** is displayed in Figure 4. In this case the *ortho* protons of the two phenyl groups give rise to distinct peaks. The



B

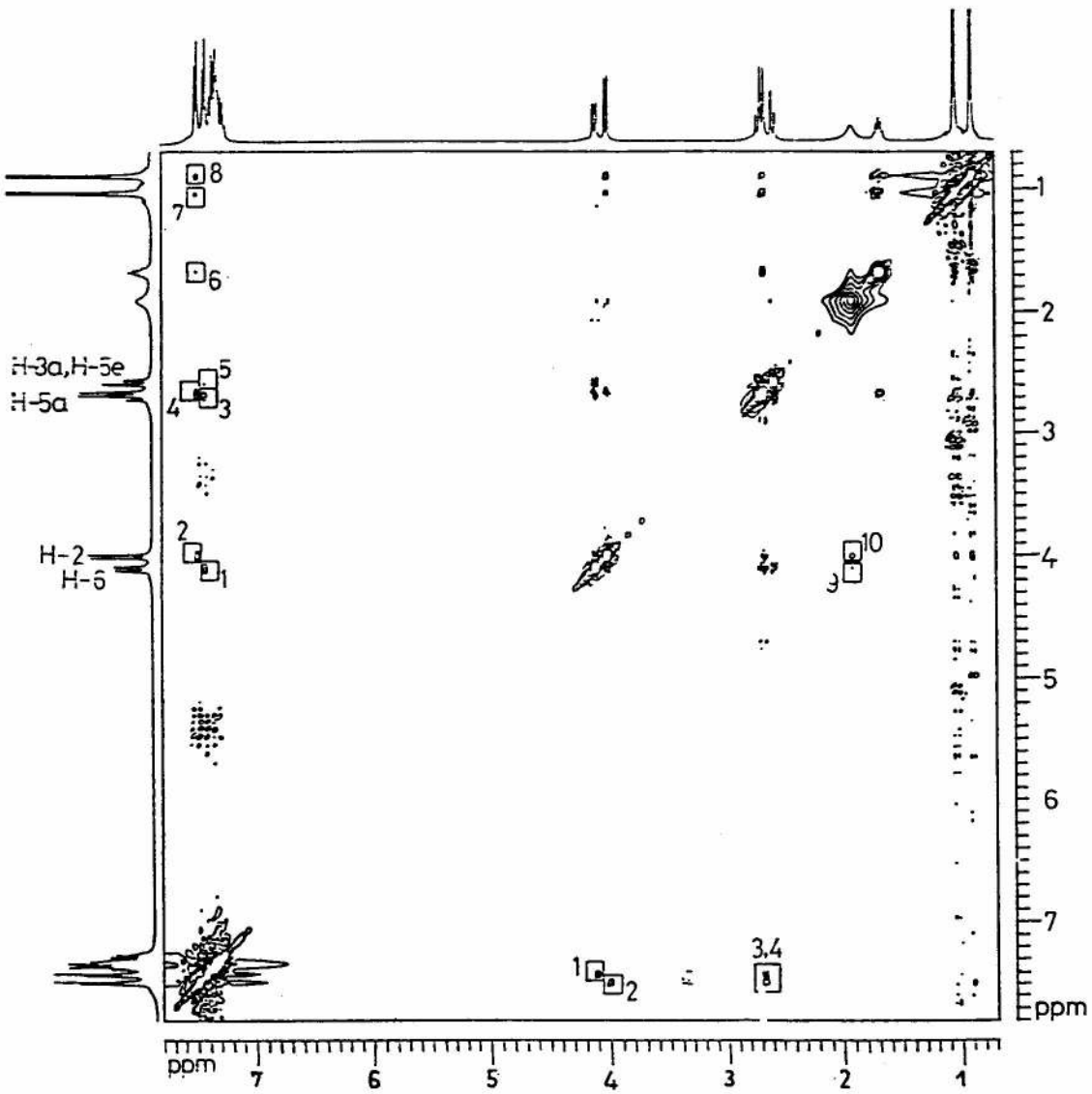


Figure 4 —NOESY spectrum of *t*(3)-isopropyl-*r*(2)-*c*(6)-diphenylpiperidin-4-one

NOESY spectrum clearly shows that the *ortho* protons of the C(2)-phenyl group appear at a lower field. H-2 has nOe with the downfield *ortho* protons (nOe 2) whereas H-6 has nOe with the upfield *ortho* protons (nOe 1). An interesting observation is that no nOe is observed between the isopropyl methine proton and H-2. This suggests that the isopropyl methine proton is not *anti* to H-3. This is in accordance with the conclusion reached based on vicinal coupling constant[10].

***r*(2), *c*(6)-Bis (*p*-methoxyphenyl)piperidine-4-one 4 and *r*(2), *c*(6)-bis (*o*-methoxyphenyl) piperidin-4-one 5**. The NOESY spectrum of **4** is displayed in Figure 5. The aromatic protons give rise to two multiplets. The upfield protons show strong nOe with the OCH_3 protons (nOe 2) whereas the downfield protons show strong nOe with the benzylic proton as well as as with the adjacent axial proton (nOes 1 and 3). Thus, the downfield peak is due to protons *ortho* to the piperidine ring.

The NOESY spectrum of **5** is displayed in Figure 6. We have recorded its ^1H NMR spectrum at 400 MHz and extracted the various coupling constants and chemical shifts more precisely. The signals could be assigned correctly using NOESY spectrum. The ^{13}C chemical shifts were assigned unambiguously using ^{13}C-^1H HETCOR specturm. The proton chemical shifts (δ, ppm) are as follows: 4.49 (H-2 and H-6), 2.67 (H_{3e} and H_{5e}), 2.57 (H_{3a} and H_{5a}) 7.58 (H-6′, H-6"), 7.27 (H-4′, H-4"), 7.00 (H-5′, H-5"),

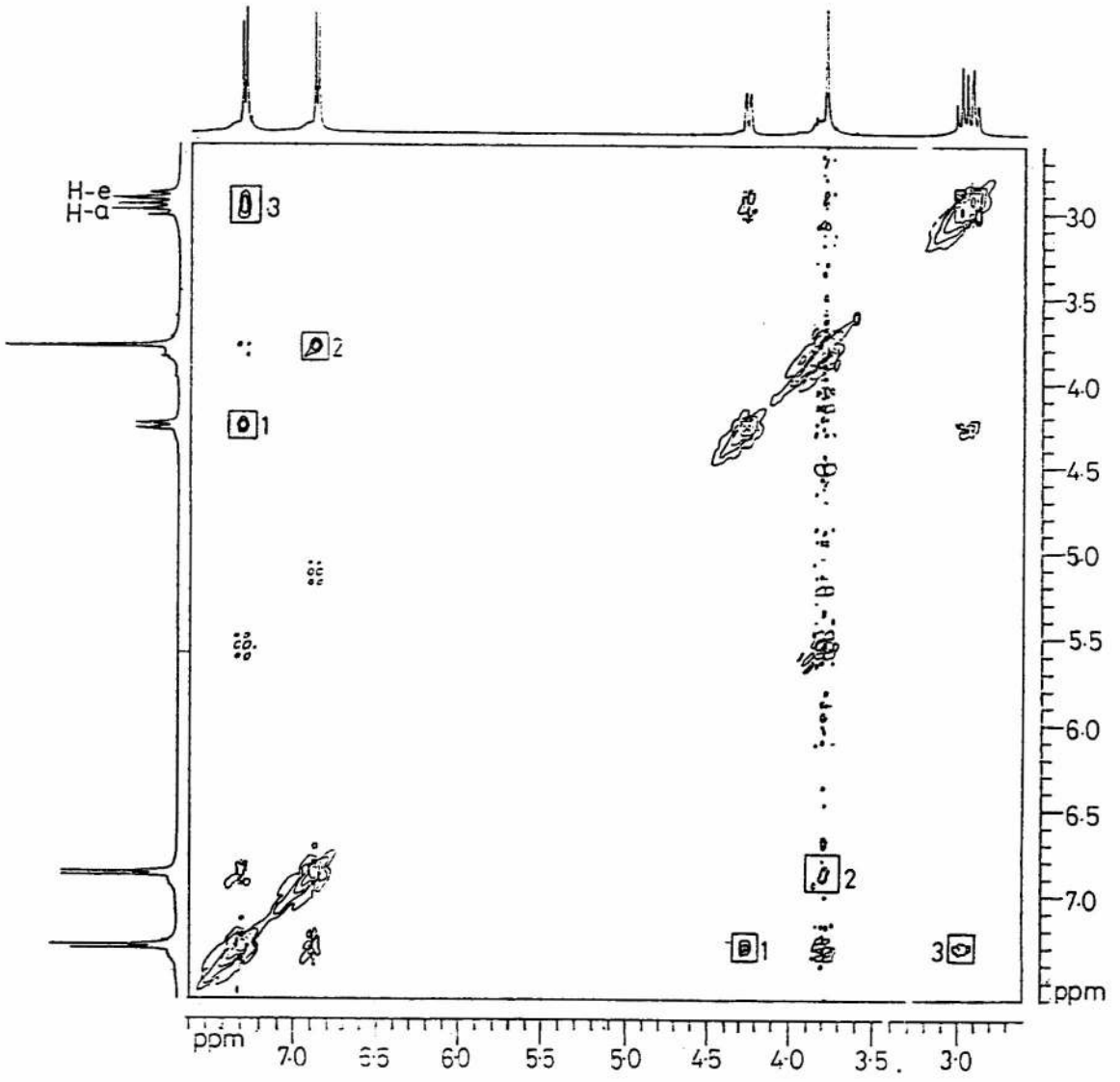


Figure 5—NOESY spectrum of *r*(2), *c*(6)-bis(*p*-methyoxyphenyl)piperidin-4-one

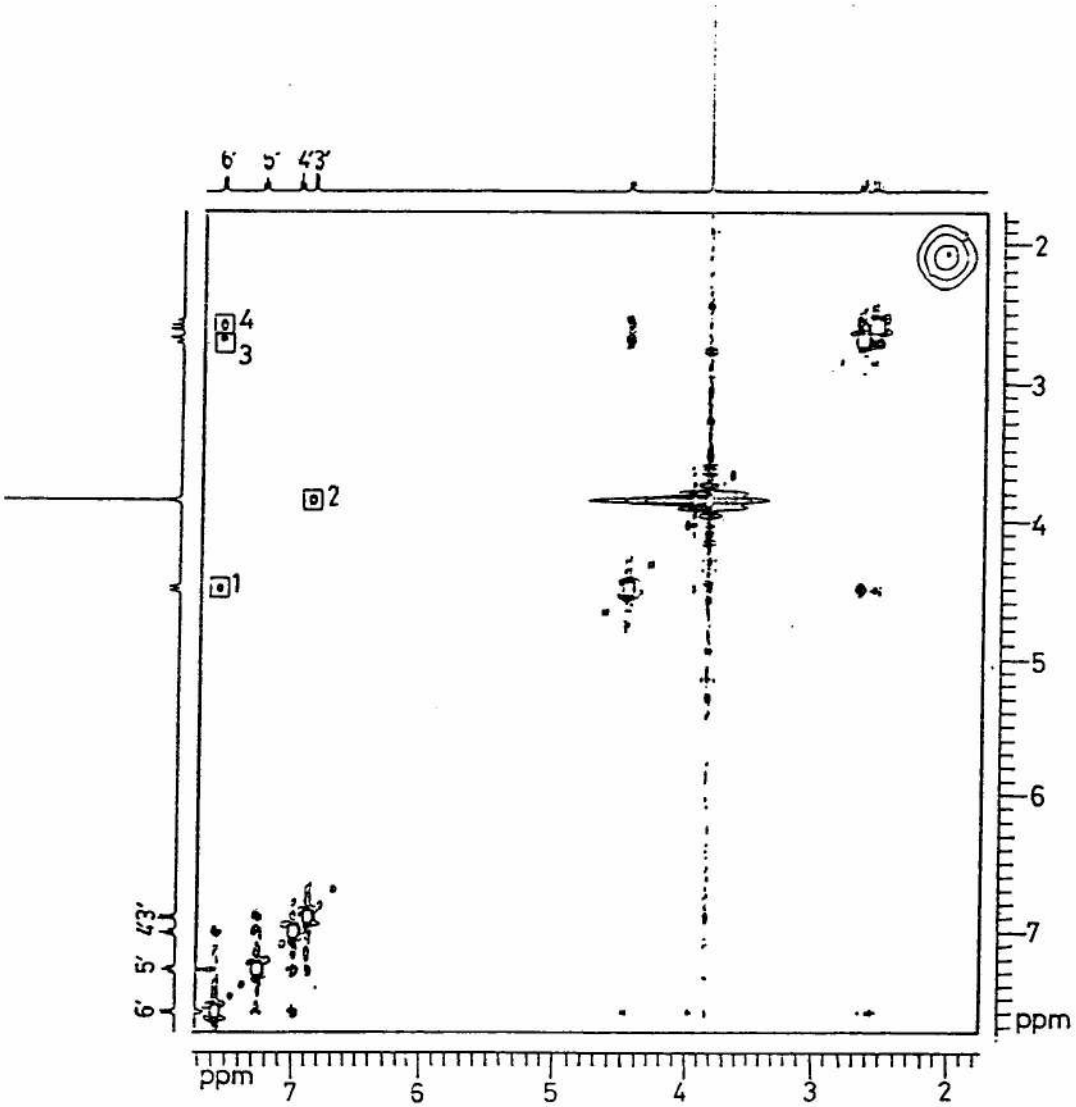
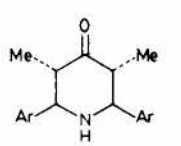


Figure 6— NOESY spectrum of *r*(2), *c*(6)-bis(*o*-methoxyphenyl)piperidin-4-one

6.89 H-3′, H-3"). The proton coupling constants are as follows: $J_{2a,3a} = J_{5a,6a} = 11.8$ Hz, $J_{2a,3e} = J_{5a,6e} = 2.6$Hz, $J_{3a,3e} = J_{5a,5e} = -13.8$ Hz. The ^{13}C chemical shifts (δ, ppm) are as follows: 54.8 (C-2 and C-6), 45.3 (C-3 and C-5), 209.5 (C-4), 131.0 (C-1′, C-1"), 156.5 (C-2′, C-2"), 110.5 (C-3′, C-3"), 128.5 (C-4′, C-4"), 121 (C-5′, C-5"), 126.7 (C–6′, C-6") and 55.4 (methyl carbon). Though the ^{13}C chemical shifts were not reported for **5**, the chemical shifts of its 3, 5-dimethyl derivative **6**, have been reported. For four aromatic carhons (C-1′, C-2", C-3′ and C-5"), the assignments have been given based on steric and electronic effects. These assignments seem to be correct based on ^{13}C-^{1}H HETCOR spectrum of **5**. Among the four aromatic protons the upfield signal



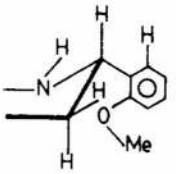
6 Ar = p-OMe-C_6H_4

was assigned to H-5′ based on the possibility that H-3′could be deshielded by the methoxyl group due to steric effect. However, the present study shows that it is incorrect.

However, C-3′absorbs at a higher field that C-5′. This suggests that in addition to steric effect magnetic anisotropic effect also may be important. Probably

this causes a shielding on H-3′. However, magnetic anisotropic effects are not important for carbons.

Moreover, in **5** the protons H-6′ and H-6″ have significant nOe with the benzylic protons (nOe 1). This suggests that conformation **C**, in which the methoxyl group is *anti* to the benzylic hydrogen, should also be populated to a significant extent. Since there is no nOe between the methoxyl protons and the benzylic protons it is obvious that O-methyl group is *anti* to the benzylic carbon. This is in accordance with conclusions reached on the preferred conformation of *o*-substituted anisoles using NMR spectra and AM1 calculations[15].



C

Experimental Section

The ketones were prepared following literature methods[16-18]. Oxime **2** was prepared following the procedure of Baliah *et al*[19].

Phase-sensitive NOESY and ^{13}C-^{1}H HETCOR spectra were recorded on a Brucker AMX-400 Spectrometer using standard experimental parameters. For NOESY spectra the mixing time was 400 ms.

Acknowledgement

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