

## $A^{1,3}$ interaction and conformational preference in some *N*-acetyl-2-phenyl-*trans*-decahydroquinolin-4-ones

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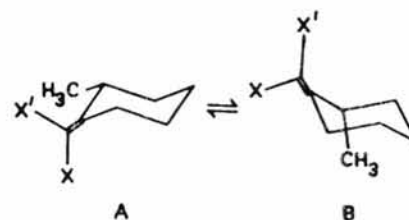
$A^{1,3}$  type strain is demonstrated directly by the nuclear magnetic resonance studies ( $^1\text{H}$  and  $^{13}\text{C}$  NMR) on the *N*-acetyl derivatives of 2-phenyl-*trans*-decahydroquinolin-4-ones **5-8**. In compounds **5-8** the bulky phenyl group is forced to assume axial orientation due to a severe  $A^{1,3}$  interaction in equatorial position. The ring torsional angles about  $\text{C}_{(2)}-\text{C}_{(3)}$  bond and Karplus constants have been determined using DAERM method. The calculated torsional angles in the *N*-acetyl derivatives are significantly higher than that in the normal chair conformation and thus confirm the nonchair (twist-boat) conformation of the heterocyclic ring with diaxial orientation of phenyl and alkyl groups in *N*-acetyl derivatives.

From a stereochemical study of the reactions of 2-alkylcyclohexane derivatives ( $A \rightleftharpoons B$ ) Johnson<sup>1</sup> concluded that there is a severe non-bonded interaction between the group X (or X') and an equatorial alkyl group. This interaction was termed  $A^{1,3}$  strain and the energy was approximated with 1,3-diaxial  $\text{CH}_3/\text{CH}_3$  interaction (3.7 kcal/mol). The presence of  $A^{1,3}$  interaction in the acyl derivatives of *cis*-2,6-dimethylpiperidine and of 2-methylpiperidine was demonstrated by NMR spectroscopy<sup>2</sup>. These two compounds are shown to adopt the alternate chair form, so that the methyl groups become axial and the strain gets relieved. The presence of partial double

bond character in amide ( $>\text{N}=\text{C}-\text{O}$ ) and

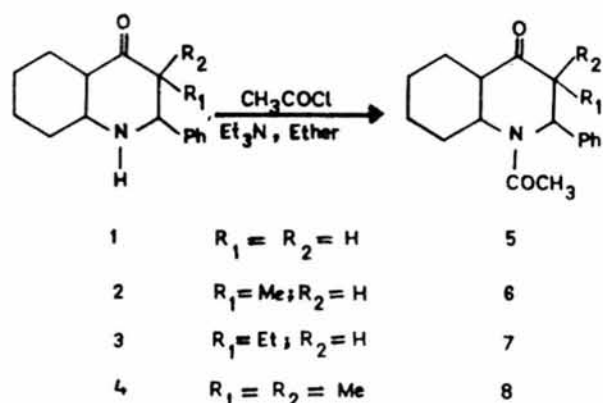
nitrosamine ( $>\text{N}=\text{N}=\text{O}$ ) due to an extensive delocalisation of the lone pair electrons of nitrogen with the hetero  $\pi$  electron system has been well documented<sup>3,4</sup>. The rotational barriers due to the partial double bond character (15-21 kcal/mol for amide and 23 kcal/mol for dimethylnitrosamine) apparently represent quantitatively the extent of delocalisation energy and also qualitatively the extent of planar configuration at  $\text{N}=\text{C}$  and  $\text{N}=\text{N}$  bonds in amide and nitrosamine.

In our earlier report, the conformational change from chair to twist-boat of the heterocyclic ring in *N*-nitroso-2-phenyl-*trans*-decahydroquinolin-4-ones is



established through NMR spectroscopy<sup>5</sup>. This conformational change is attributed to the  $A^{1,3}$  interaction between the equatorial  $\alpha$ -phenyl group and the *N*-nitroso group. In continuation of our stereochemical studies on *N*-substituted 2-phenyl-*trans*-decahydroquinolin-4-one derivatives we have synthesised four *N*-acetyl-2-phenyl-*trans*-decahydroquinolin-4-ones and analysed their conformation in the light of  $^1\text{H}$  and  $^{13}\text{C}$  NMR data. There is only one report on the stereochemistry of *N*-acyl-*trans*-decahydroquinolines<sup>6</sup>, but in these compounds there is no substituent in the 2-position to introduce  $A^{1,3}$  strain. The aim of the present communication is to demonstrate directly the presence of  $A^{1,3}$  strain by NMR spectroscopy and further to explain the conformational preference in *N*-acetyl-2-phenyl-*trans*-decahydroquinolin-4-ones.

The *N*-acetyl-2-phenyl-*trans*-decahydroquinolin-4-ones **5-8** were prepared from the corresponding 2-phenyl-*trans*-decahydroquinolin-4-ones **1-4** by reaction with acetyl chloride in ether-triethylamine



Scheme I

medium (Scheme I). The parent amines **1-4** are found to exist in twin-chair conformation. The *trans*-fusion of the two rings and the equatorial orientation of the phenyl and alkyl groups in the amines have already been confirmed through  $^1H$  and  $^{13}C$  NMR data<sup>7</sup>. The phenyl and alkyl groups in adjacent positions in diequatorial orientation represent *trans*-configuration in the parent amines. The IR spectra of the acetylated products showed two carbonyl absorptions. The high intensity peak appearing at  $1720-1700\text{ cm}^{-1}$  corresponds to the ring carbonyl group, while the peak at  $1645-1620\text{ cm}^{-1}$  is due to the amide carbonyl function.

The acetyl group in amides can adopt either a coplanar orientation or a perpendicular orientation with respect to C(2)-N-C(9) plane of the heterocyclic ring. In the  $^1H$  NMR spectra of the amides **5-8** recorded at  $23^\circ$  and  $55^\circ C$ , the signals for H(2) and H(9) protons appear broad. The observed line-broadening is an indication of a dynamic process taking place in the molecule. The most probable dynamic process is the rotation about N—CO bond<sup>8,9</sup> which arises due to conjugation of the nitrogen lone pair with CO  $\pi$  electrons of the acetyl group. Such a conjugation is possible only when the acetyl group is coplanar with the C(2)-N-C(9) plane. The IR spectra of the amides **5-8** bring support to the coplanar orientation of the acetyl group. The Bohlmann bands ( $2815-2500\text{ cm}^{-1}$ ) observed for the amines are absent in the amides. Bohlmann bands arise due to antiperiplanarity of the nitrogen  $\pi$ -electrons with  $\alpha$ -C-H bonds. Since in the amides the nitrogen  $\pi$ -electrons are not free and are involved in conjugation the Bohlman band disappears. The coplanarity of the acetyl group with the ring has also been confirmed by

the single crystal X-ray diffraction study<sup>10</sup> on *N*-acetyl-*t*(3)-ethyl-*r*(2)-phenyl-*trans*-decahydroquinolin-4-one **7**.

In the coplanar orientation of the *N*-acetyl group there will be severe  $A^{1,3}$  interaction between the acetyl group and the  $\alpha$ -phenyl group in its equatorial orientation. This interaction cannot be avoided by ring flip into the alternate chair form (when the phenyl group becomes axial), since the *trans*-decahydroquinoline molecule is rigid. The other possibility is that heterocyclic part of the molecule may change into a twist-boat form wherein the phenyl and the alkyl groups become axial and the  $A^{1,3}$  interaction is relieved. The conformational change from chair to twist-boat in the heterocyclic part of the *trans*-decahydroquinoline system is reflected in the NMR data.

Since the  $^1H$  NMR spectra of the amides **5-8** recorded at  $55^\circ C$  show broad signals for H(2) and H(9) protons, the spectra were recorded at sufficiently high temperature ( $70^\circ C$ ) to ensure the condition of rapid exchange. The proton signals in **5-8** were assigned by comparison with the signals of the parent amines **1-4**.

The  $^1H$  NMR data of the amides along with the parent amines are summarised in Table I. It can be seen from Table I that the ring protons H(2) and H(3) (heterocyclic part) in **5-8** are shifted downfield compared to the respective amines **1-4**. The deshielding observed on H(2) varies from 1.7-2.0 ppm, which is larger than that expected for equatorial proton in the chair conformation (1.39 ppm)<sup>11</sup>. The large deshielding may be due to a change in the conformation of the heterocyclic ring in the amides. Comparison of the chemical shift of benzylic proton H(2) with H(9) reveals that H(2) is deshielded to a greater extent than H(9) (1.0-1.2 ppm) indicating that H(2) lies in the plane of the N-C=O moiety. However, the deshielding observed on H(9) is close to the deshielding on H(9) axial proton (1.18 ppm) in *N*-acetyl-7-methyl-*trans*-decahydroquinoline **9**<sup>12</sup> (which is in twin-chair conformation) suggesting that the carbocyclic part of the *trans*-decahydroquinoline

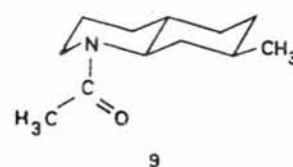
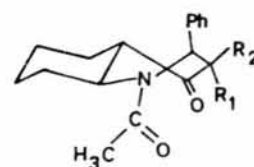
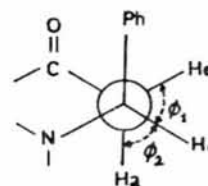


**Table I**—<sup>1</sup>H NMR data of *N*-acetyl-2-phenyl-*trans*-decahydroquinolin-4-ones **5-8** and 2-phenyl-*trans*-decahydroquinolin-4-ones **1-4** [δ ppm, *J* in Hz]

| Compd    | H-2                                        | H-3                                                                              | H-9                                    | H-10 | CH <sub>3</sub> | CH <sub>2</sub> | NH proton | Acetyl protons | Aromatic protons |
|----------|--------------------------------------------|----------------------------------------------------------------------------------|----------------------------------------|------|-----------------|-----------------|-----------|----------------|------------------|
| <b>5</b> | 5-73                                       | 3.28, 2.85<br><i>J</i> <sub>2,3</sub> =1.5, 6.4<br><i>J</i> <sub>3,3</sub> =19.1 | 3.69<br><i>J</i> <sub>9,10</sub> =11.2 | 2.05 | -               | -               | -         | 2.15           | 7.41-7.26        |
| <b>1</b> | 4.02<br><i>J</i> <sub>2,3</sub> =11.9, 3.0 | 2.60, 2.53<br><i>J</i> <sub>3,3</sub> =13.4                                      | 2.63<br><i>J</i> <sub>9,10</sub> =10.7 | 2.19 | -               | -               | 1.63      | -              | 7.41-7.26        |
| <b>6</b> | 5.50                                       | 3.38<br><i>J</i> <sub>2,3</sub> =1.5                                             | 3.65<br><i>J</i> <sub>9,10</sub> =11.2 | 2.13 | 1.19            | -               | -         | 2.17           | 7.43-7.27        |
| <b>2</b> | 3.53<br><i>J</i> <sub>2,3</sub> =10.3      | 2.65                                                                             | 2.65<br><i>J</i> <sub>9,10</sub> =11.0 | 2.28 | 0.77            | -               | 1.70      | -              | 7.39-7.26        |
| <b>7</b> | 5.53                                       | 3.12<br><i>J</i> <sub>2,3</sub> =2.0                                             | 3.62<br><i>J</i> <sub>9,10</sub> =11.2 | 2.09 | 1.02            | 1.70<br>1.50    | -         | 2.17           | 7.42-7.27        |
| <b>3</b> | 3.63<br><i>J</i> <sub>2,3</sub> =10.8      | 2.57                                                                             | 2.57<br><i>J</i> <sub>9,10</sub> =11.0 | 2.27 | 0.72            | 1.59<br>1.04    | 1.63      | -              | 7.40-7.26        |
| <b>8</b> | 5.41                                       | -                                                                                | 3.72<br><i>J</i> <sub>9,10</sub> =11.2 | 2.60 | 1.24<br>1.14    | -               | -         | 2.15           | 7.41-7.24        |
| <b>4</b> | 3.71                                       | -                                                                                | 2.52<br><i>J</i> <sub>9,10</sub> =10.5 | 2.52 | 1.10<br>0.90    | -               | 1.63      | -              | 7.45-7.24        |

system exists in the chair conformation itself in the amides as in the parent amines.

In addition to the changes in chemical shifts due to *N*-acetylation, there occurs drastic change in the coupling constants also. In *N*-acetyl-2-phenyl-*trans*-decahydroquinolin-4-one **5** the observed *vicinal* coupling constant *J*<sub>2,3</sub> values are 6.4 and 1.5 Hz and are considerably lower than the *J*<sub>2,3</sub> values (11.9 and 3.0 Hz) of 2-phenyl-*trans*-decahydroquinolin-4-one **1**. The *geminal* coupling constant (*J*<sub>3a,3e</sub>) increases in **5** (19.1 Hz). Similarly, the observed *J*<sub>2,3</sub> values for *N*-acetyl-*t*(3)-methyl-*r*(2)-phenyl-*trans*-decahydroquinolin-4-one (1.5 Hz) and *N*-acetyl-*t*(3)-ethyl-*r*(2)-phenyl-*trans*-decahydroquinolin-4-one (2.0 Hz) are very much lower than that of the corresponding parent amines **2** and **3** (10.5 Hz). The lower values indicate that the torsional angle between the *trans*-protons (*φ trans*) decreased from 180° to a greater extent in the amides. This clearly reveals that the conformation of the heterocyclic ring is modified and is no longer in the chair conformation in the amides. The preference for a nonchair conformation is presumably due to A<sup>1,3</sup> strain between the acetyl group and the α-phenyl group in the chair conformation. A twist-boat conformation with diaxial orientation of the phenyl and alkyl groups appears more probable for the heterocyclic ring in **5-8** (Figure 1). In contrast, the carbocyclic part is found to exist in the chair form with coupling constants *J*<sub>9a,8a</sub>, *J*<sub>10a,5a</sub>=10-12 Hz; *J*<sub>9a,8e</sub>, *J*<sub>10a,5e</sub>=2.9-3.6 Hz, which are characteristic of normal chair form.

**Figure 1****Figure 2**

Assuming a twist-boat conformation for the heterocyclic part, the dihedral angles between C(2)-H and C(3)-H bonds in the amides **5**, **6** and **7** are calculated by DAERM method (dihedral angle estimation by ratio method)<sup>13</sup>. Equations 1 and 2 relate coupling constants with dihedral angles and Karplus constant.

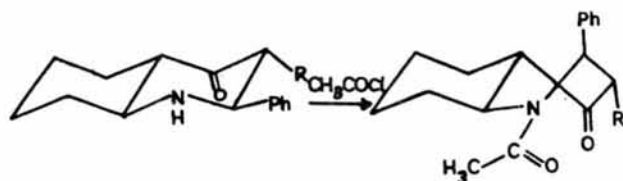
$$J_1 = K_1 \cos^2 \theta_1 - 0.3 \quad \dots (1)$$

$$J_2 = K_2 \cos^2 \theta_2 - 0.3 \quad \dots (2)$$

In the twist-boat form of the amides, both the dihedral angles ( $\theta_1$  and  $\theta_2$ ) are expected to be <90° (Figure 2). Hence, equation 3 obtained from 1 and 2 where  $K_1 = K_2$  and  $\theta_1 + \theta_2 = 120^\circ$  (in a regular tetrahedral system) is used for the calculations.

$$\frac{J_1 + 0.3}{J_2 + 0.3} = \frac{\cos^2 \theta_1}{\cos^2 \theta_1 (120 - \theta_1)} \quad \dots (3)$$

In *N*-acetyl-2-phenyl-*trans*-decahydroquinolin-4-one **5** the dihedral angle associated with the coupling constants 6.5 Hz ( $J_1$ ) and 1.5 Hz ( $J_2$ ) as per equation 3 are calculated to be 41.5° and 78.5°, respectively. The value of Karplus constant is estimated to be 11.86. Since only one coupling constant is possible ( $J_2$ ) for the amides **6** and **7**, the Karplus constant cannot be calculated. Instead the Karplus constant is taken as 11.86, from the previous calculation for compound **5**. Using this value the dihedral angles about the C(2)-C(3) bond in amides **6** and **7** are calculated to be 64.40° and 69.4° using equation 2. The DAERM calculated value 69.4° for **7** is close to the observed dihedral angle 73.3° H(2)-C(2)-C(3)-H(3) in the twist-boat form derived from X-ray analysis<sup>10</sup> of **7**. The calculated torsional angles in the amides **5-7** are significantly higher than that in the normal chair conformation (~60°) and thus confirm the twist-boat conformation of the heterocyclic ring in amides **5-8**.



As in the <sup>1</sup>H NMR spectra, the carbon signals of the amides **5-8** also appear broad in the <sup>13</sup>C NMR spectra recorded at 23° and 55°C. The spectral data obtained at 70°C under condition of rapid exchange are used for the conformational study. The <sup>13</sup>C chemical shifts were assigned from the multiplicities of signals in the off-resonance decoupled spectra and also by comparing the data with those of the parent amines.

In *N*-acetyl-*t*(3)-ethyl-*r*(2)-phenyl-*trans*-decahydroquinolin-4-one **7** two downfield signals (58.8 and 58.1 ppm) are very close to each other. Both the signals appear as doublets in the off-resonance spectrum. To identify the carbons responsible for these signals, 2D <sup>1</sup>H-<sup>13</sup>C HETCOR spectrum was recorded for this compound. Among the two signals the downfield one (58.8 ppm) correlates with H(2) signal at 5.63 ppm in the <sup>1</sup>H NMR spectrum, and hence this is from C(2).

Table II reports the <sup>13</sup>C chemical shifts of the amides **5-8** and the corresponding parent amines **1-4**. The data in Table II indicate that in the amides the heterocyclic ring carbons are shielded. The C(2) carbons are more shielded (5.0-7.6 ppm) than the C(9) carbons (2.5-4.3 ppm). The higher shielding observed on C(2) relative to C(9) is due to the coplanarity of the benzylic hydrogen at C(2) with the amide moiety. Such coplanar orientation deshields the

Table II—<sup>13</sup>C NMR chemical shifts (ppm) of *N*-acetyl-2-phenyl-*trans*-decahydroquinolin-4-ones **5-8** and 2-phenyl-*trans*-decahydroquinolin-4-ones<sup>7</sup> **1-4**

| Compd    | C-2  | C-3  | C-4   | C-8  | C-9  | C-10 | Other carbons           | Acetyl carbonyl carbon | Acetyl methyl carbon | CH <sub>3</sub>   | CH <sub>2</sub> | Aromatic carbons                                       |
|----------|------|------|-------|------|------|------|-------------------------|------------------------|----------------------|-------------------|-----------------|--------------------------------------------------------|
| <b>5</b> | 54.2 | 42.9 | 206.3 | 35.2 | 59.2 | 51.3 | 26.4, 26.0, 25.9        | 170.8                  | 22.7                 | -                 | -               | 142.4, 129.7, 129.4, 128.9, 128.7, 128.4, 128.0, 126.8 |
| <b>1</b> | 61.8 | 50.6 | 209.7 | 33.9 | 61.7 | 55.4 | 25.0, 24.6, 23.4        | -                      | -                    | -                 | -               | 142.6, 128.7, 127.8, 126.5                             |
| <b>6</b> | 60.8 | 46.5 | 209.4 | 35.1 | 58.8 | 50.8 | 26.6, 25.9, 25.9        | 171.6                  | 22.5                 | 16.9              | -               | 142.7, 129.7, 128.9, 128.7, 128.5, 128.1, 126.9        |
| <b>2</b> | 69.2 | 51.5 | 211.1 | 33.9 | 62.1 | 55.6 | 25.0, 24.5, 23.6        | -                      | -                    | 10.4              | -               | 141.9, 128.6, 127.9, 127.6                             |
| <b>7</b> | 58.8 | 54.0 | 208.6 | 35.2 | 58.1 | 50.9 | 26.5, 26.0 <sup>a</sup> | 171.5                  | 24.6                 | 12.8              | 22.5            | 143.0, 130.3, 129.7, 128.9, 128.7, 128.5, 128.1, 126.9 |
| <b>3</b> | 67.7 | 58.5 | 210.7 | 33.9 | 62.4 | 56.2 | 25.0, 24.6, 23.6        | -                      | -                    | 12.3              | 18.1            | 141.8, 128.6, 127.9, 127.4                             |
| <b>8</b> | 65.2 | 51.5 | 211.0 | 35.6 | 59.0 | 49.7 | 27.8, 27.4, 26.5        | 171.5                  | 23.6 <sup>b</sup>    | 26.0 <sup>b</sup> | -               | 141.8, 129.9, 129.0, 128.9, 128.7, 129.5, 128.0        |
| <b>4</b> | 70.2 | 49.8 | 214.3 | 34.0 | 62.1 | 51.2 | 25.1, 24.5, 23.9        | -                      | -                    | 20.9, 20.4        | -               | 139.5, 128.6, 127.2, 127.6                             |

<sup>a</sup> Intense peak appears due to overlapping of two carbon signals

<sup>b</sup> Values having the same superscript may be interchanged

concerned hydrogen. If the hydrogen attached to a carbon is deshielded by some mechanism, the carbon will experience shielding. The coplanarity of the benzylic hydrogen and the amide group is possible only in the twist-boat form of the heterocyclic ring in which phenyl group occupies axial orientation and benzylic hydrogen is equatorial. Similar large shielding is observed on C(2) (8.2 ppm) relative to C(9) (0.5 ppm) in *N*-acetyl-7-methyl-*trans*-decahydro-quanoline **9** also. It is interesting to note that C(2) resonates almost at the same field (58.8 ppm) as that of C(9) (58.1 ppm) in *N*-acetyl-*l*-(3)-ethyl-*r*-(2)-phenyl-*trans*-decahydroquinolin-4 one **7**. This may be due to a compensation of the shielding effect of acetyl group by the deshielding  $\beta$ -effect of ethyl group in the axial orientation of the twist-boat form. The  $^1\text{H}$ ,  $^{13}\text{C}$  NMR data and the estimated dihedral angles confirm the twist-boat conformation of the heterocyclic ring in the amides **5-8**.

### Experimental Section

The method of Lynch and Cole<sup>14</sup> was followed to prepare the amides **5-8**. To the ketones **1-4** (2.5-2.8 g, 0.1 mole) dissolved in dry ether (95 mL) was added triethylamine (1.5 mL) followed by acetyl chloride (1 mL) in dry ether (95 mL). The mixture was stirred for 45 min at room temperature. The reaction was monitored by TLC [silica,  $\text{CHCl}_3$ -EtOAc (19:1)]. The reaction mixture was poured into ice-cold water, extracted four times with ether (100 mL) and the extract washed with water several times. The ether layer was dried over anhydrous sodium sulphate. After removal of ether, the crude product was recrystallized twice from pet. ether (60-80°C) provided pure **5**, **6**, **7** and **8** with melting points 121-122°, 139-140°, 127-128° and 135-136°C, respectively. These compounds were characterized by their elemental analyses.

**5**: Anal. Calcd for  $\text{C}_{17}\text{H}_{21}\text{NO}_2$ : C, 75.3; H, 7.7; N, 5.2%. Found: C, 74.9; H, 7.4; N, 4.9%.

**6**: Anal. Calcd for  $\text{C}_{18}\text{H}_{23}\text{NO}_2$ : C, 75.8; H, 8.1; N, 4.9%. Found: C, 75.4; H, 7.7; N, 4.8%.

**7**: Anal. Calcd for  $\text{C}_{19}\text{H}_{25}\text{NO}_2$ : C, 76.3; H, 8.4; N, 4.7%. Found: C, 76.1; H, 8.1; N, 4.5%.

**8**: Anal. Calcd for  $\text{C}_{19}\text{H}_{25}\text{NO}_2$ : C, 76.3; H, 8.4; N, 4.7%. Found: C, 76.2; H, 7.9; N, 4.4%.

The  $^1\text{H}$  NMR spectra were recorded for 0.3M DMSO- $d_6$  solution at 70°C on a Jeol GSX-400 FT NMR spectrometer at 270 MHz using TMS as internal standard.  $^{13}\text{C}$  NMR spectra were recorded ( $\text{C}_6\text{D}_6$ ) at 70°C on a Bruker AMX-400 FT NMR spectrometer at 100 MHz with full proton decoupling (TMS was used as internal standard). 2D  $^1\text{H}$ - $^{13}\text{C}$  HETCOR spectrum was obtained on a Jeol GSX-400 FT NMR spectrometer using the following parameters: number of scans 64, number of data points 2048, acquisition time 0.066 sec., relaxation delay 1 sec. and spectral width 4571 Hz in  $F_1$  and 15576 Hz in  $F_2$ .

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