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# SYNTHESIS AND CONFORMATIONAL ANALYSIS OF SOME CYANOMETHYLENE DERIVATIVES OF PIPERIDINES

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Five 4-dicyanomethylene derivatives **6—10**, N-cyanoacetyl-*cis*-2,6-diphenylpiperidin-4-one **11** and 4-cyano(ethoxycarbonyl)-methylene-*cis*-2,6-bis(*o*-chlorophenyl)piperidine **12** were synthesised by condensing the appropriate piperidin-4-ones **13—17** with malononitrile/ethylcyanoacetate and their $^{1}$H and $^{13}$C NMR spectra were recorded. The $^{1}$H-$^{1}$H COSY spectrum for **6** and NOESY spectra for **8**, **10** and **11** were also recorded. Based on coupling constants and the results obtained from NOESY spectra boat conformation for **10** and epimerised chair conformations for **8** and **9** have been proposed. Other derivatives adopt normal chair conformations. Theoretical calculations and the $^{1}$H and $^{13}$C chemical shifts also support the above conformations. Mass spectra were also recorded for **6—12**.

**K e y w o r d s:** molecular conformations, saturated heterocycles, six-membered heterocycles, computations, NMR spectra, mass spectra, $A^{1,3}$ strain.

## INTRODUCTION

Cyano derivatives received considerable interest in recent years since they have been used in biological field as well as in optical fields. Considerable number of benzalmalononitrile derivatives **1** were prepared and their bacteriostatic and stimulatory activities were studied in detail by Silver *et al.* [ 1 ]. Systems containing dicyanomethylene groups especially DCM [4-dicyanomethylene-2-methyl-6-(4′-dimethylaminostyryl)-4-H-pyran] family of compounds are used as laser dyes. The biphenyl compound **2** having N,N-dimethylamino group as a donor and a cyano group as an acceptor shows lasing and Non-Linear Optical [NLO] properties [ 2 ]. A series of 4H-1,1-dioxo-4-(dicyanomethylidene)thiopyrans **3** obtained from the condensation reaction of malononitrile with 4H-1,1-dioxothiopyran-4-ones are used as electron transport materials in xerography [ 3 ]. Recently Manimekalai and Anusuya [ 4 ] reported the synthesis and spectral studies of six cyanomethylene derivatives of *cis*-2,6-diaryltetrahydrothiopyrans **4**. The study of conformations of heavily substituted ring compounds possessing $A^{1,3}$ strain is highly interesting since in these compounds conformational changes are expected to occur in order to avoid $A^{1,3}$ strain. Considerable work has been carried out on the conformational behaviour of several substituted 2,6-dialkyl- and 2,6-diarylpiperidine derivatives possessing $A^{1,3}$ strain through spectral analysis [ 5—12 ]. Therefore, there is considerable interest in the synthesis and the study of the molecular structures of cyanomethylene derivatives possessing $A^{1,3}$ strain.

The present work was undertaken to study this class of piperidine derivatives. As shown by NMR spectral studies [ 13 ], in the reaction of 2,6-diphenyl-3-alkyl-4-piperidones with malononitrile $A^{1,3}$ strain is avoided by epimerisation in the dicyanomethylene derivatives **5**. In **5** the alkyl groups at C(3) occupy axial orientations unlike the alkyl groups in the parent piperidin-4-ones. In order to obtain more information and insight into the stereodynamics of these hindered cyanomethylene derivatives, we have synthesised seven 4-cyanomethylene derivatives **6—12** with and without $A^{1,3}$ strain from their

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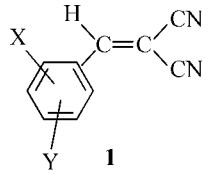
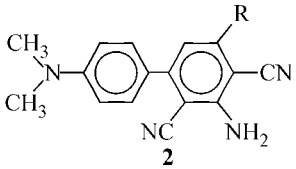


**1**



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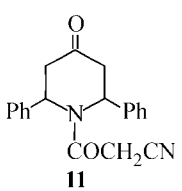

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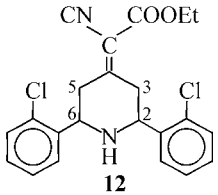
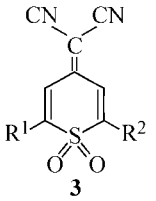


**12**



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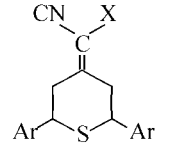
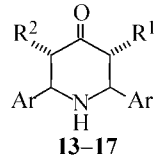
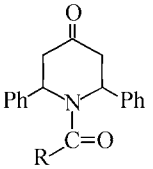


**4**; X = CN, COOEt

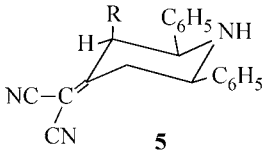


**13–17**

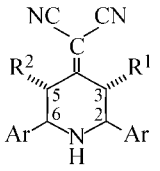
| | Ar | $R^1$ | $R^2$ |
|---|---|---|---|
| **13** | Ph | H | H |
| **14** | *o*-$ClC_6H_4$ | H | H |
| **15** | Ph | $CH_3$ | H |
| **16** | *p*-$CH_3OC_6H_4$ | $CH_3$ | H |
| **17** | Ph | $CH_3$ | $CH_3$ |



**18** R=H
**19** R=$C_6H_5$



**5**



**6–10**

| | Ar | $R^1$ | $R^2$ |
|---|---|---|---|
| **6** | Ph | H | H |
| **7** | *o*-$ClC_6H_4$ | H | H |
| **8** | Ph | $CH_3$ | H |
| **9** | *p*-$CH_3OC_6H_4$ | $CH_3$ | H |
| **10** | Ph | $CH_3$ | $CH_3$ |

respective parent piperidin-4-ones **13—17** and studied their conformational behaviour using NMR techniques. Semi empirical MO calculations were also performed to predict the favoured conformations in gaseous environment.

## RESULTS AND DISCUSSION

Malononitrile on condensation with *cis*-2,6-diarylpiperidin-4-ones **13** and **14**, *t*(3)-methyl-r(2),*c*(6)-diarylpiperidin-4-ones **15** and **16** and *t*(3),*t*(5)-dimethyl-r(2),*c*(6)-diphenylpiperidin-4-one **17** yielded the expected 4-dicyanomethylene derivatives **6—10**. With ethylcyanoacetate, the expected 4-cyano(ethoxycarbonyl)methylene derivative was obtained with *cis*-2,6-bis(*o*-chlorophenyl)piperidin-4-one **14** alone, while unreacted parent compounds were recovered with the other piperidin-4-ones **15—17**. However *cis*-2,6-diphenylpiperidin-4-one **13** gave a different product during the condensation reaction with ethylcyanoacetate instead of the expected 4-cyano(ethoxycarbonyl)methylene derivative. The product was identified as *N*-cyanoacetyl-*cis*-2,6-diphenylpiperidin-4-one (**11**) by spectral analysis (presence of cyano carbon signal in $^{13}C$ NMR spectrum and absence of signals for ethyl group in both $^{1}H$ and $^{13}C$ NMR spectra). This kind of reaction is probably hindered in **14** due to the presence of bulky *o*-chloro group in the phenyl ring.

The high resolution $^{1}H$ and $^{13}C$ NMR spectra were recorded for 4-dicyanomethylene-r(2),*c*(6)-diphenylpiperidine (**6**), 4-dicyanomethylene-r(2),*c*(6)-bis(*o*-chlorophenyl)piperidine (**7**), 4-dicyanomethylene-*t*(3)-methyl-r(2),*c*(6)-diphenylpiperidine (**8**), 4-dicyanomethylene-*t*(3)-methyl-r(2),*c*(6)-bis(*p*-methoxyphenyl)piperidine (**9**), 4-dicyanomethylene-*t*(3),*t*(5)-dimethyl-r(2),*c*(6)-diphenylpiperidine (**10**), N-cyanoacetyl-*cis*-2,6-diphenylpiperidin-4-one (**11**) and 4-cyano(ethoxycarbonyl)methylene-r(2),*c*(6)-bis(*o*-chlorophenyl)piperidine (**12**) in $CDCl_3$ and analysed. The physical and mass spectral data for **6—12** are given in Table 1. The signals in the $^{1}H$ NMR spectra were assigned based on their positions, integrals and multiplicities. The $^{1}H$-$^{1}H$ COSY spectrum for **6** and NOESY spectra for **8**, **10** and **11** were also recorded to confirm the assignments. The coupling constants were determined using first-order analysis and the various coupling constants and $^{1}H$ chemical shifts obtained in this manner are displayed in Tables 2 and 3, respectively, along with the data for parent compounds **13—17** [ 14, 15 ]. The assignment of the signals in the $^{13}C$ NMR spectra was done based on

Table 1

*Physical and mass spectral data for* **6—12**

| Compound | Yield (%) | m. p. (°C) | m/e |
|---|---|---|---|
| 1 | 2 | 3 | 4 |
| **6** | 80 | 145 | 298 $(M—1)^{\ddagger\bullet}$ (base peak), 258 $(M—CH_3CN)^{\ddagger\bullet}$, 250 $(M—NH_3, 3H_2, \dot{C}H)^+$, 222 $(M—Ph)^+$, 208 $(M—Ph\dot{C}H_2)^+$, 194 $(M—PhCH=NH)^{\ddagger\bullet}$, 106 $(Ph\overset{+}{C}HNH_2)$, 91 $(Ph\overset{+}{C}H_2)$, 78 $(PhH)^{\ddagger\bullet}$, 51 $(CH\equiv C—CN)^{\ddagger\bullet}$, other peaks are at 116, 129, 152, 166, 179, 235 and 274. |
| **7** | 80 | 179 | 367 $(M^{\ddagger\bullet})$, 350 $(M—NH_3)^{\ddagger\bullet}$, 332 $(M—Cl)^{\ddagger\bullet}$, 315 $[M—(CH\equiv C—CN), \dot{H}]^+$, 299 $(M—CH_2(CN)_2, H_2)$, 242 $(M—Ar\dot{C}H_2)^+$, 228 $[M—(ArCH=NH)]^{\ddagger\bullet}$, 193 (base peak), 166 $(ArCH=CHCN)^{\ddagger\bullet}$, 140 $(Ar\overset{+}{C}HNH_2)$, 125 $(ArCH_2^+)$, 112 $(Ar^+)$, 77 $(Ph^+)$, 63 $(CH_2=CH—Cl)^{\ddagger\bullet}$, 51 $(CH\equiv C—CN)^{\ddagger\bullet}$, other peaks are at 89, 178, 213, 262 and 280. |
| **8** | 70 | 155 | 313 $(M^{\ddagger\bullet})$, 299 $(M—\dot{C}H_2)^+$, 284 $(M—HCN, H_2)^{\ddagger\bullet}$, 259 $(M—2HCN)^{\ddagger\bullet}$, 248 $(M—\dot{C}H(CN)_2)^+$, 232 $[M—C_6H_6, H_2, \dot{H}]^+$, 222 $(M—Ph\dot{C}H_2)^+$, 208 $[M—(PhCH=NH)]^{\ddagger\bullet}$, 106 $(Ph\overset{+}{C}HNH_2)$ (base peak), 91 $(PhCH_2^+)$, 78 $(PhH)^{\ddagger\bullet}$, 65 $(C_5H_5^+)$, 51 $(CH\equiv C—CN)^{\ddagger\bullet}$, other peaks are at 116, 128, 143, 166, 179 and 193 |
| **9** | 70 | 162 | 373 $(M^{\ddagger\bullet})$, 356 $(M—CH_4, \dot{H})^+$, 341 $(M—CH_3OH)^{\ddagger\bullet}$, 327 $(M—CH_4, HCHO)^{\ddagger\bullet}$, 306 $(M—CH_2(CN)_2, \dot{H})^+$, 292 $(M—\dot{C}H(CN)_2, CH_4)^+$, 273 $(M—CH_2(CN_2), H_2, CH_3OH)^{\ddagger\bullet}$, 238 $[M—(ArCH=NH)]^{\ddagger\bullet}$ (base peak), 134 $(ArCH=\overset{+}{C}H)$, 106 $(Ph\overset{+}{C}HNH_2)$, 91 $(Ph\overset{+}{C}H_2)$, 77 $(Ph^+)$, 65 $(C_5H_5^+)$, other peaks are at 152, 168, 184, 194, 212, 223 and 254. |
| **]10** | 60 | 164 | 327 $(M^{\ddagger\bullet})$, 312 $(M—\dot{C}H_3)^+$, 279 $(M—NH_3, CH_4, \dot{C}H_3)^+$, 262 $(M—\dot{C}H(CN)_2)^+$, 249 $(M—C_6H_6)^{\ddagger\bullet}$, 236 $(M—Ph\dot{C}H_2)^+$, 222 $(M—(PhCH=NH))^{\ddagger\bullet}$, 106 $(Ph\overset{+}{C}HNH_2)$ (base peak), 91 $(Ph\overset{+}{C}H_2)$, 77 $(C_6H_5^+)$, 65 $(C_5H_5^+)$, 51 $(CH\equiv C—CN)^{\ddagger\bullet}$, other peaks are at 117, 133, 146, 157, 180, 194 and 207. |
| **11** | 75 | 180 | 317 $(M—1)^+$, 313 $(M—2H_2, \dot{H})^+$, 300 $(M—H_2O)^{\ddagger\bullet}$, 271 $(M—HCHO, \dot{O}H)^+$, 232 $(M—NH_2COCH_2CN, H_2)^{\ddagger\bullet}$, 223 $(M—\dot{C}_6H_5, H_2O)^+$, 202 (M—benzyne, $\dot{C}H_2CN)^+$, 195 $(Ph—CH=NCH_2Ph)^{\ddagger\bullet}$, 183 $(M—PhCH_2CH_2CHO, \dot{H})^+$, 129 $(Ph—C\equiv C—\overset{+}{C}O)$, 106 $(Ph\overset{+}{C}HNH_2)$, 91 $(Ph\overset{+}{C}H_2)$, 77 $(Ph^+)$, 51 $(CH\equiv C—CN)^{\ddagger\bullet}$, other peaks are at 279, 256, 166, 153, 115 and 57. |

End of Table 1

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| **12** | 60 | 208 | 413 (M—1)$^{+\cdot}$, 396 (M—$NH_3$, $\dot{H}$)$^+$, 378 (M—HCl)$^{+\cdot}$, 366 (M—$CH_3CHO$, $2H_2$)$^{+\cdot}$, 341 (M—$\dot{C}OOC_2H_5$)$^+$, 316 (M—$CO_2$, $C_2H_4$, $\dot{C}N$)$^+$, 301 (M—ArH, $\dot{H}$)$^+$, 140 ($Ar\overset{+}{C}HNH_2$) (base peak), 125 ($Ar\overset{+}{C}H_2$), 77 ($Ph^+$), 75 (benzyne cation), 52 ($\overset{+}{C}H$=CHCN), other peaks are at 288, 261, 253, 240, 212, 194, 168, 163 and 102. |

comparison with suitable model compounds [ 4 ] and these assignments were further confirmed by the results obtained in the $^1H$-$^{13}C$ COSY spectra recorded for all the compounds. Table 4 reports $^{13}C$ chemical shifts of 4-cyanomethylene derivatives **6-12** and their parent piperidin-4-ones **13—17** [ 16, 17 ].

**Molecular conformations.** For compounds **6**, **7** and **12** normal chair conformation with the equatorial orientations of aryl rings at C(2) and C(6) have been proposed based on the large (≈10 Hz) and small couplings (≈2 Hz) observed about C(5)—C(6)/C(2)—C(3) bonds. The conformational behaviour of the other compounds **8—11** is somewhat more complex. It is very interesting to note that the

Table 2

*Coupling constants* (*Hz*) *for* 4-*cyanomethylene derivatives* **6—12** *and parent piperidin*-4-*ones* **13—17**

| Compound | $J_{2,3}$ | $J_{3,3}$ (gem) | $J_{5,6}$ | $J_{5,5}$ (gem) | $J_{H,CH_3}$ |
|---|---|---|---|---|---|
| **6** | 10.82 (a,a)<br>1.99 (a,e) | 14.23 | 10.82 (a,a)<br>1.99 (a,e) | 14.23 | — |
| **7** | 10.74 (a,a)<br>1.95 (a,e) | 14.17 | 10.74 (a,a)<br>1.95 (a,e) | 14.17 | — |
| **8** | 3.15 | — | 11.07 (a,a)<br>2.89 (a,e) | 14.19 | 6.88 |
| **9** | 2.93 | — | 10.74 (a,a)<br>— | 14.16 | 6.84 |
| **10** | 3.62 | — | 3.62 | — | 6.85 |
| **11** | 11.50 (*cis*)<br>4.74 (*trans*) | 17.31 | 11.50 (*cis*)<br>4.74 (*trans*) | 17.31 | — |
| **12** | 11.34 (a,a)<br>1.93 (a,e) | 13.44 | 11.55<br>a | 13.08 | — |
| **13**[b] | 9.96 (a,a)<br>4.47 (a,e) | 12.13 | 9.96 (a,a)<br>4.47 (a,e) | 12.13 | — |
| **14**[c] | 11.63 (a,a)<br>2.55 (a,e) | d | 11.63 (a,a)<br>2.55 (a,e) | d | — |
| **15**[c] | 10.36 | — | 11.85 (a,a)<br>2.83(a,e) | 13.21 | d |
| **16** | 10.50 | — | 11.97 (a,a)<br>2.73 (a,e) | 12.90 | 6.60 |
| **17** | 10.35 | — | 10.35 | — | d |

[a] Difficult to extract since doublets are observed for H(6) and $H_{5e}$; [b] taken from Ref. 14; [c] taken from Ref. 13; [d] not reported.

Table 3

$^1$H *chemical shifts* (ppm) *for* 4-*cyanomethylene derivatives* **6**—**12** *and parent piperidin*-4-*ones* **13**—**17**

| Compound | H(2) | H (3) | H (5) | H(6) | Alkyl protons | Other protons |
|---|---|---|---|---|---|---|
| **6** | 3.92 | 2.59 (ax)<br>3.19 (eq) | 2.59 (ax)<br>3.19 (eq) | 3.92 | — | 7.48–7.47, 7.40–7.26<br>2.20 (NH) |
| **7** | 4.43 | 2.44 (ax)<br>3.36 (eq) | 2.44 (ax)<br>3.36 (eq) | 4.43 | — | 7.79–7.77, 7.41–7.25<br>2.12 (NH) |
| **8** | 4.14 | 3.29 | 2.76 (ax)<br>3.09 (eq) | 3.92 | 1.13 | 7.55–7.54, 7.46–7.29<br>2.04 (NH) |
| **9** | 4.03 | 3.18 | 2.68 (ax)<br>2.99 (eq) | 3.81–3.78 | 1.09 ($CH_3$)<br>3.80, 3.82 ($OCH_3$) | 7.42–7.40, 7.35–7.25, 6.93–6.88<br>1.86 (NH) |
| **10** | 4.13 | 3.30 | 3.30 | 4.13 | 1.22 ($CH_3$) | 7.51–7.26<br>1.94 (NH) |
| **11** | 4.79 | 3.15 (t)<br>2.87 (c) | 3.15 (t)<br>2.87 (c) | 4.79 | — | 7.57–7.54, 7.46–7.39, 7.26–7.15<br>5.96 (CO**CH$_2$**CN) |
| **12** | 4.41 | 2.45 (ax)<br>3.39 (eq) | 2.22 (ax)<br>4.33–4.28 (eq) | 4.48 | 4.33–4.28 (COO**CH$_2$**$CH_3$)<br>1.36 ($COOCH_2$**CH$_3$**) | 7.82–7.55, 7.64–7.60, 7.48–7.22<br>1.88 (NH) |
| **13**[b] | 4.07 | 2.60 (ax)<br>2.60 (eq) | 2.60 (ax)<br>2.60 (eq) | 4.07 | — | 7.48–7.24 |
| **14**[c] | 4.62 | 2.47 (ax)<br>2.73 (eq) | 2.47 (ax)<br>2.73 (eq) | 4.62 | — | 7.83–7.80, 7.38–7.21 |
| **15**[c] | 3.63 | a | 2.74 (ax)<br>2.83 (eq) | 4.10 | 0.84[b] | 7.48–7.44, 7.39–7.24<br>2.11 (NH) |
| **16** | 3.56 | d | 2.70 (ax)<br>2.58 (eq) | 4.02 | 0.82 ($CH_3$) 3.81,3.79 ($OCH_3$) | 7.38–7.35, 6.90–6.85<br>1.93 (NH) |
| **17**[c] | 3.62 | 2.80 | 2.80 | 3.62 | 0.84[b] | 7.47–7.44, 7.41–7.25<br>1.95[b] |

[a] Not reported; [b]taken from Ref. 14; [c]taken from Ref. 13; [d]could not be determined due to overlapping with $OCH_3$ signal.

coupling constants about C(2)—C(3) bond in the 3-methyl derivatives **8** and **9** are considerably lower (≈3 Hz) when compared to their corresponding parent piperidin-4-ones **15** and **16** (≈10.0 Hz) which exist in normal chair conformation. These coupling constants cannot be accounted by normal chair conformation **CE**. Moreover in the normal chair conformation severe $A^{1,3}$ strain exists between dicyanomethylene group and equatorial methyl group at C(3) in **8** and **9**. Haller and Ludtke [ 13 ] have reported that epimerisation at C(3) takes place in the 3-methyl derivative **8** during condensation reaction of piperidin-4-one with malononitrile in order to avoid $A^{1,3}$ strain. In order to relieve $A^{1,3}$ strain, the 3-methyl derivatives **8** and **9** may adopt even boat conformations since the boat conformations have been reported in literature for some compounds [ 6—8 ]. The possible conformations for the 3-methyl derivatives **8** and **9** are shown in Scheme 1. The observed coupling constants and allylic strain ruled out the possibility of existing alternate chair conformation **CA** and the boat conformations $\mathbf{B_2}$, $\mathbf{B_3}$ and $\mathbf{B_5}$. Semi empirical calculations of some model compounds [ 10 ] shown that the boat form $\mathbf{B_4}$ with alkyl group at flagpole position is having higher energy compared with other forms and hence not favoured in the present study as well. The observed coupling constants are accounted in terms of all the remaining structures (**EC**, $\mathbf{B_1}$ and $\mathbf{B_6}$). In order to find out whether epimerisation or conformational changes occur in **8** and **9**, a NOESY spectrum has been recorded for **8**.

In the epimerised chair conformation **EC**, NOE is expected between methyl and methylene protons at C(5) having large total width [axial proton at C(5)] and weak NOE is expected between methyl

protons and the benzylic proton H(2). In the boat conformation **$B_1$**, methyl protons are however not expected to reveal NOE with methylene protons at C(5). In the boat conformation **$B_6$**, methyl protons are expected to reveal strong NOE with H(2) as well as with methylene proton at C(5) having large total width (axial like proton). In the NOESY spectrum strong NOE between methyl protons and methylene proton at C(5) was observed which ruled out the possibility of existing **8** in the boat conformation **$B_1$**. The observation of weak NOE between methyl protons and H(2) in the NOESY spectrum ruled out the boat form **$B_6$** as well. Thus, the results obtained from the NOESY spectrum of **8** are in accordance with the epimerised chair conformation **EC** only. One can also expect similar epimerised chair form **EC** for the 3-methyl-*p*-methoxy derivative **9**.

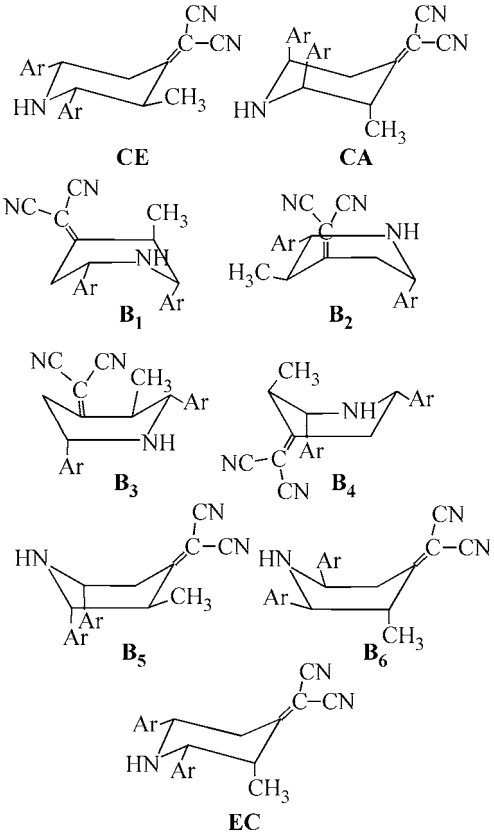
The comparison of coupling constants about C(5)—C(6)/C(2)—C(3) bond in 3,5-dimethyl derivative **10** with that of the corresponding parent piperidin-4-one **17** reveals that there is a drastic change in the coupling constant due to the conversion of >C=O to >C=C(CN)$_2$ group. The abnormal coupling constant in **10** cannot be accounted by normal chair conformation **CE**. The possible conformations for the 3,5-dimethyl derivative **10** are given in Scheme 2. The boat form **$B_1$** is equivalent to **$B_2$**, and **$B_3$** is equivalent to **$B_4$**. The observation of small coupling about C(α)—C(β) bond ruled out the possibility of existing **10** in the chair conformation **CE**. In the epimerised chair form **EC** and boat conformations **$B_1$**, **$B_2$**, **$B_3$** and **$B_4$**, two different coupling constants (≈10 and 4 Hz) are expected about C(α)—C(β) bond. The observation of only one coupling (3.62 Hz) about C(α)—C(β) bond in **10** ruled out the possibility of its existing in these conformations. Moreover, $A^{1,3}$ strain cannot be completely removed in the epimerised chair conformation **EC**. The observed coupling constant suggests that **10** should exist in boat conformation **$B_6$** only. This is further confirmed by the results obtained in the NOESY spectrum which shows strong NOE between methyl protons with benzylic and methine protons.

Table 4

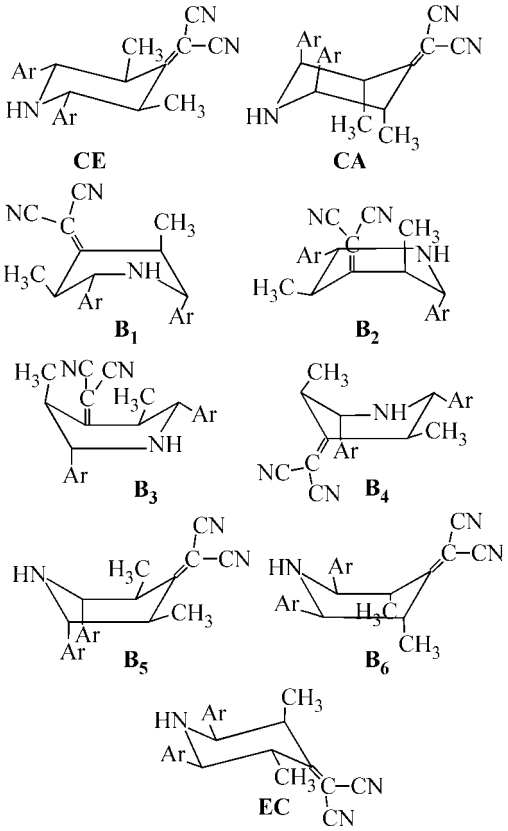
$^{13}$C *chemical shifts* (ppm) *for* 4-*cyanomethylene derivatives* **6**—**12** *and parent piperidin*-4-*ones* **13**—**17**

| Compound | C(2) | C(3) | C(4) | C(5) | C(6) | Alkylcarbons | CN | $=C^{CN}$ | Othercarbons |
|---|---|---|---|---|---|---|---|---|---|
| **6** | 62.38 | 43.30 | 180.31 | 43.30 | 62.38 | – | 111.89 | 84.26 | 142–125 (aromatic) |
| **7** | 57.51 | 40.51 | 178.35 | 40.51 | 57.51 | – | 111.11 | 84.50 | 139–127 (aromatic) |
| **8** | 64.06 | 44.38 | 186.25 | 39.66 | 62.70 | 13.88 ($CH_3$) | 111.93<br>112.14 | 83.56 | 143–127 (aromatic) |
| **9** | 62.88 | 43.90 | 186.02 | 39.10 | 61.49 | 13.16 ($CH_3$)<br>55.20 ($OCH_3$) | 111.50<br>111.31 | 82.54 | 160–113 (aromatic) |
| **10** | 63.41 | 42.85 | 191.43 | 42.85 | 63.41 | 15.98 ($CH_3$) | 112.91 | 84.0 | 140–128 |
| **11** | 54.36 | 33.66 | a | 33.66 | 54.36 | – | 114.24 | – | 142–124 (aromatic)<br>162.62 (**CO**$CH_2$CN)<br>106.56<br>(NCO**$CH_2$**CN) |
| **12** | 57.85 | 37.54 | 161.65 | 42.22 | 57.62 | 62.12 (COO**$CH_2$**$CH_3$)<br>14.13 ($COOCH_2$**$CH_3$**) | 114.99 | 104.47 | 158–127 (aromatic)<br>172.53 (**CO**OEt) |
| **13** | 61.00 | 50.20 | 207.80 | 50.20 | 61.00 | – | – | – | 143–126 |
| **14** | 56.40 | 47.80 | 207.00 | 47.80 | 56.40 | – | – | – | 140–127 |
| **15** | 68.40 | 51.60 | 209.50 | 50.90 | 61.50 | 10.10 ($CH_3$) | – | – | 143–127 |
| **16** | 67.70 | 51.70 | 209.80 | 51.00 | 60.90 | b | – | – | 113–160 |
| **17** | 68.80 | 52.00 | 211.10 | 52.00 | 68.80 | 10.50 ($CH_3$) | – | – | 142–127 |

[a] Not observed; [b] not reported.

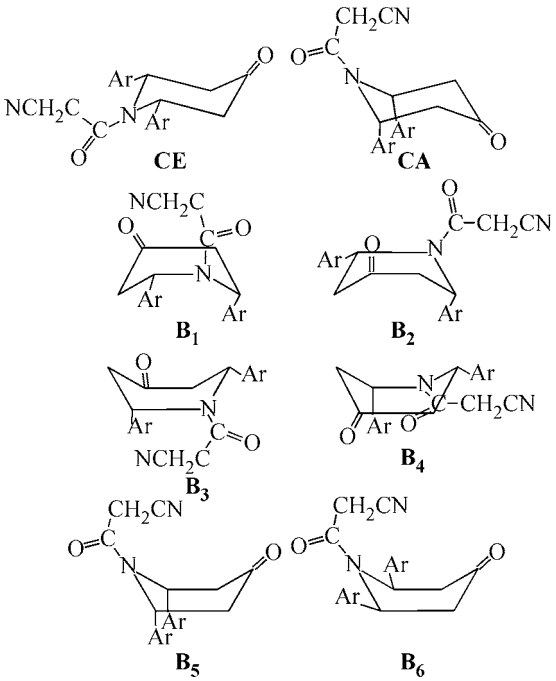



Scheme 1




Scheme 2

The comparison of the coupling constants of N-cyanoacetyl-*cis*-2,6-diphenylpiperidin- 4-one (**11**) with other derivatives **6**, **7** and **12** and its parent *cis*-2,6-diphenylpiperidin-4-one **13** reveals that $J_{gem}$ [$J_{5a,5e}/J_{3a,3e}$] is considerably higher in **11** relative to the other compounds. Similar large magnitude has been observed in the closely related N-formyl-*cis*-2,6-diphenylpiperidin-4-one (**18**) and N-benzoyl-*cis*-2,6-diphenylpiperidin-4-one (**19**) for which boat conformations have been proposed [ 10, 15 ]. The observation of one large (11.50 Hz) and one small coupling (4.74 Hz) about C(2)—C(3)/C(5)—C(6) bond is accounted by normal chair conformation **CE**. $A^{1,3}$ strain is expected to be present between cyanoacetyl group and equatorial phenyl groups at C(2) and C(6) in **CE**. If $A^{1,3}$ strain is severe, the N-cyanoacetyl derivative **11** will exist in the alternate chair form **CA** or a boat form. The possible conformations for N-cyanoacetyl derivative **11** are shown in Scheme 3.




Scheme 3

The alternate chair form **CA** is not favoured since both the couplings are expected to be around 3.0 Hz which is in contrast to the observation of one large and one small couplings about C(α)—C(β) bond. The boat forms $\mathbf{B_1}$ is equivalent to $\mathbf{B_2}$ and the boat form $\mathbf{B_3}$ is equivalent to $\mathbf{B_4}$ since they differ in the orientation of the carbonyl group of the cyanoacetyl moiety only. These boat forms are also ne-

Table 5

*Relative heat of formation* (Kcal/mol) *of various conformers of* **8**, **10** *and* **11**

| Compound | Conformations | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **EC** | **CE** | **CA** | **$B_1$** | **$B_2$** | **$B_3$** | **$B_4$** | **$B_5$** | **$B_6$** |
| **8** | 0 | 4.12 | 5.32 | 2.94 | 7.91 | 2.72 | 2.28 | 10.23 | 2.23 |
| **10** | — | 6.15 | 3.78 | 11.64 | — | — | 0.00 | 11.71 | 0 |
| **11** | — | 0 | 1.87 | 0.01 | 3.42 | 4.31 | 2.54 | 4.39 | 5.37 |

glected since the coupling constants about C(α)—C(β) bond are expected to be around 10 and 3 Hz on one side and 3.0 and 3.0 Hz on the other side. The observation of one large and one small coupling about both sides ruled out the boat forms **$B_1$**—**$B_4$**. In boat form **$B_6$** allylic strain exists similar to **CE** and hence it is expected to have higher energy compared to **CE** and hence not favoured in the present study. The observed coupling constants are in favour of boat form **$B_5$** in which the phenyl groups occupy axial like orientations.

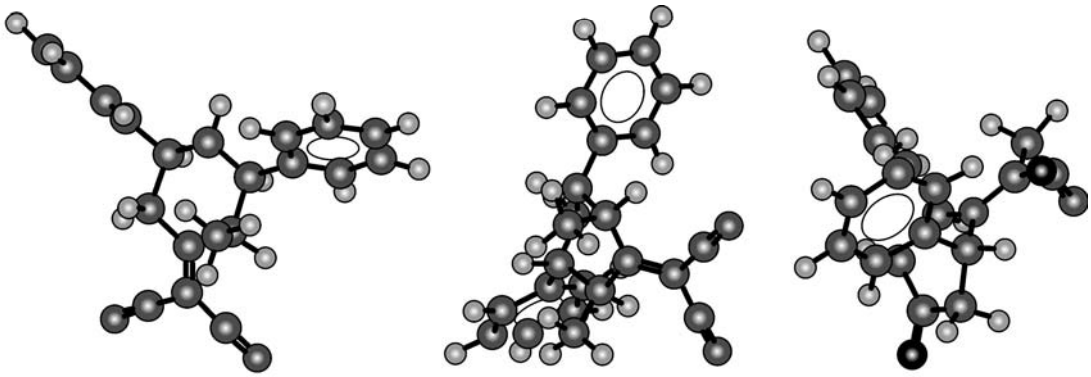
In order to confirm the favoured conformation, NOESY spectrum was recorded in which the methylene protons of cyanoacetyl group reveal weak NOE with the benzylic proton signal at 4.79 ppm alone. Both in the normal chair conformations **CE** and in boat conformation **$B_5$** NOE is expected between methylene protons of $COCH_2CN$ group and H(2)/H(6) since the distance between them less than 3 Å. Thus, from the observed NOE boat conformation **$B_5$** cannot be differentiated from normal chair conformation **CE**.

In order to know the favoured conformation, semi empirical MO calculations were performed for all the conformers shown in Scheme 3 for **11**. To confirm the structures for the 3-methyl-dicyanomethylene derivative **8** and 3,5-dimethyl-dicyanomethylene derivative **10**, theoretical calculations were also performed for all the conformers given in Schemes 1 and 2 using AM1 Hamiltonion available in Argus lab [ 18, 19 ] (version 4.0). Table 5 lists the relative heat of formations (Kcal/mol) calculated in this manner for **8**, **10** and **11**. Calculations indicate **CE** as the favoured conformation for N-cyanoacetyl derivative **11**. Probably $A^{1,3}$ strain is not so severe in N-cyanoacetyl derivative when compared to other strains present in the boat forms and axial-axial interaction present in the alternate chair conformation.

For **8** and **10** the conformations with equatorial phenyl substituents (**CE** and **$B_6$**) are energetically far away from other conformers showing that significant $A^{1,3}$ strain drives the molecules to prefer forms other than **CE**. Among the possible conformations for the 3-methyl-dicyanomethylene derivative **8** the **EC** form was found to be the most favoured conformation. Other conformations are found to have slightly larger heats of formation. This conformation is found to be retained in solution which is revealed from the NMR data. For the 3,5-dimethyl-dicyanomethylene derivative [ 10 ] the coupling constants predict **$B_6$** conformation. The theoretical calculations also indicate the same conformation. Surprisingly, the conformation **$B_4$** is also found to have the same heat of formation as that of **$B_6$** and the optimized structures **$B_4$** and **$B_6$** are almost similar. The optimized structures of **8**, **10** and **11** are given in Figure.

**Analysis of chemical shifts.** Comparison of the $^1H$ chemical shifts of 4-dicyanomethylene derivatives **6** and **7** with those of the corresponding parent piperidin-4-ones **13** and **14** reveals that equatorial methylene protons at C(5) ($H_{5e}$) and C(3) ($H_{3e}$) are deshielded by 0.59 and 0.63 ppm in **6** and **7**, respectively, due to the replacement of >C=O by $>C=C(CN)_2$ group. This is probably due to the steric interaction between cyano group and the nearby equatorial hydrogens, the interaction polarising C(5)—H and C(3)—H bonds. The equatorial hydrogens at C(5)/C(3) attain a slight positive charge and the corresponding carbons attain a slight negative charge. Indeed, in $^{13}C$ spectra (Table 4) shielding is observed on C(3) and C(5) in **6** and **7** due to the replacement of >C=O by $>C=C(CN)_2$ group.

It is also seen from Table 4 that the replacement of >C=O group by $>C=C(CN)_2$ group deshields C(2) and C(6) carbons but shields C(3), C(4) and C(5) carbons in **6** and **7**. It has been previously reported that a decrease in the electronegativity is expected to shield α carbons and deshield β carbons [ 20 ].



**8** **10** **11**

The optimized structures of **8**, **10** and **11**

The lower electronegativity of >C=C(CN)$_2$ compared to >C=O group is responsible for the downfield resonances of C(2) and C(6) carbons and upfield resonances of C(3), C(4) and C(5) carbons in **6** and **7** compared to **13** and **14**. The comparison of chemical shifts of **7** with those of **12** reveals that the replacement of one of the cyano groups by ethoxycarbonyl group deshields the nearby *syn* equatorial proton $H_{3e}$ and shields *syn* axial proton $H_{3a}$ alone. Such replacement shields C(3) carbon as well. This is probably due to the greater steric interaction between COOEt group and the *syn* equatorial hydrogen at C(3) compared to the interaction between CN group and *syn* equatorial hydrogen at C(5).

The epimerised chair conformations of 3-methyl derivatives **8** and **9** are also supported by $^1$H and $^{13}$C chemical shifts. In six membered ring compounds the introduction of an equatorial substituent is expected to shield the nearby axial proton by 0.3 ppm [ 21 ]. The comparison of the chemical shift of H(2) in 3-methyl derivative **8** with that in **6** reveals that the presence of a methyl group at C(3) deshields the nearby benzylic proton H(2) by 0.22 ppm. The deshielding magnitude suggests that the methyl group at C(3) should adopt other than equatorial position thus supporting its axial orientation and epimerised chair conformation **EC** for **8**. The replacement of >C=O group by >C=C(CN)$_2$ group deshields the benzylic protons by +0.51 ppm in **8** and 0.47 ppm in **9** which is in contrast to the shielding magnitude observed on these protons in **6** (–0.15 ppm) and **7** (–0.19 ppm) which exist in normal chair conformation. This also suggests that the conformations of **8** and **9** should be different from those of the corresponding parent piperidones **15** and **16**.

The comparison of the chemical shifts of C(2) and C(4) carbons in the 3-methyl derivative **8** with those of **6** (Table 4) reveals that C(2) is deshielded to a lesser extent (+1.68 ppm) than C(4) (+5.94 ppm) due to the presence of methyl group at C(3) in **8**. This is in contrast to the deshielding magnitude observed in the parent 3-methylpiperidin-4-one **15** [+5.94 ppm C(2); +1.70 ppm C(4)] due to the presence of methyl group at C(3). Moreover C(5) carbon resonates considerably at lower frequency in 3-methyl derivative **8** compared to **6** that is the introduction of methyl group at C(3) shields γ carbon (–3.64 ppm) considerably. This is also in contrast to the slight deshielding magnitude observed on C(5) in the corresponding parent 3-methylpiperidin-4-one **15** (+0.20 ppm) due to the presence of methyl group at C(3). All these observations suggest that the orientation of methyl group at C(3) in **8** should be different from that in **15** thus supporting epimerised chair conformation **EC** for **8** in which methyl group occupies axial orientation.

It is also seen from Table 4 that the replacement of >C=O group by >C=C(CN)$_2$ shields all ring carbons except C(6) and methyl carbons in 3-methyl derivatives **8** and **9**. If the conformations of **8** and **9** are similar to that of **6** (normal chair conformation), then one can expect both C(2) and C(6) carbons to be deshielded due to the replacement of >C=O group by >C=C(CN)$_2$ group. However C(2) carbons are shielded in **8** (–4.34 ppm) and **9** (–4.82 ppm). Moreover the shielding magnitude observed on C(5) in **8** (–11.24 ppm) and **9** (–11.98 ppm) are considerably greater than that observed in **6** (–6.9 ppm). All these findings are in agreement with a different conformation for 3-methyl derivatives **8** and **9** that is the epimerised chair conformation **EC**.

In 3,5-dimethyl derivative **10** a considerable deshielding magnitude also has been observed on the benzylic protons H(2) and H(6) due to the presence of methyl groups at C(3) and C(5). Methine protons H(3) and H(5) also resonate considerably at higher frequency in **10** (3.30 ppm) compared to $H_{5a}/H_{3a}$ in **6** (2.59 ppm). The magnitude of deshielding observed in **10** cannot be accounted by equatorial orientations of methyl groups at C(3) and C(5). Moreover replacement of >C=O group by >C=C(CN)$_2$ group deshields benzylic protons by + 0.51 ppm in **10** which is in contrast to the shielding magnitude observed on these protons in **6** (–0.15 ppm). These findings suggest that the configuration of methyl groups at C(3) and C(5) in **10** must be different from that of equatorial orientation.

Generally the introduction of methyl group in the equatorial position in six-membered ring is expected to deshield the methyl bearing carbon [ 22 ]. The comparison of the chemical shifts of C(3) in **10** (42.85 ppm) with that of **6** (43.30 ppm) reveals that the introduction of methyl groups at C(3) and C(5) shields methyl bearing carbon (–0.45 ppm). This suggests that the conformation of 3,5-dimethyl derivative **10** should be different from that of normal chair conformation. The conformation of **10** is also different from that of 3-methyl derivative **8** based on the observation that methyl carbons in **10** absorb at higher frequency (15.98 ppm) compared to that in **8** (13.88 ppm). Thus these findings are in line with a boat conformation $\mathbf{B_6}$ for **10** in which methyl groups are in axial like orientations.

The benzylic protons H(2) and H(6) resonate considerably at higher frequency in N-cyanoacetyl derivative **11** (+0.72 ppm) compared to its corresponding parent piperidin-4-one **13**. The replacement of —NH by —NCOCH$_2$CN group deshields both the methylene protons at C(5)/C(3). Moreover all the heterocyclic ring carbons are shielded due to this conversion.

## EXPERIMENTAL

**Synthesis of 4-cyanomethylene derivatives 6—12.** The parent piperidin-4-ones **13—17** were prepared following the procedure adopted by Baliah and Noller [ 23 ] and were recrystallised twice from benzene. These piperidin-4-ones were condensed with malononitrile under microwave conditions according to the procedure reported by Balalaie and Nemati [ 24 ]. The 4-dicyanomethylene derivatives **6—10** obtained were recrystallised from ethanol.

4-Cyano(ethoxycarbonyl)methylene-*cis*-2,6-bis(*o*-chlorophenyl)piperidine (**12**) was prepared from *cis*-2,6-bis(*o*-chlorophenyl)piperidin-4-one (**14**) according to the general procedure reported in literature [ 25 ]. The product obtained was recrystallised from ethanol.

*cis*-2,6-Diphenylpiperidin-4-one (**13**), when condensed with ethylcyanoacetate by adopting the same procedure mentioned as above [ 23 ], gave N-cyanoacetyl-*cis*-2,6-diphenylpiperidin-4-one (**11**) only instead of the expected cyanoacetic ester derivative. The product was crystallised from ethanol.

**Recording of spectra.** $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AMX-400 NMR spectrometer operating at 400 and 100.6 MHz for $^1$H and $^{13}$C, respectively. The $^1$H-2D phase sensitive NOESY, $^1$H-$^1$H COSY and $^1$H-$^1$C COSY spectra were recorded on a Bruker DRX 500 NMR spectrometer using standard parameters. Solutions were prepared by dissolving 10 mg ($^1$H) and 50 mg ($^{13}$C) of the compound in 0.5 ml of $CDCl_3$. All NMR measurements were made with 5 mm NMR tubes. The number of data points was either 32 K or 64 K.

Mass spectra were recorded using Finnigan Mat 8230 mass spectrometer with a sensitivity of 0.3 ng at 70 eV with a direct inlet system and the inlet temperature was maintained at 100 °C.

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