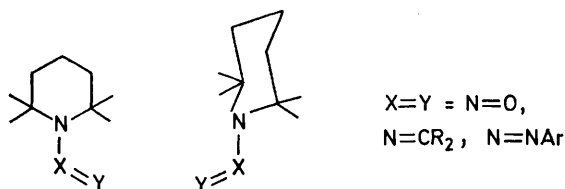


## Conformational Studies by Dynamic Nuclear Magnetic Resonance. Part 17.† Stereodynamic Processes in Hindered Piperidyl-amides and -amidines

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It has been shown that molecules containing hindered piperidyl rings can have planar or perpendicular conformations depending on the functional group attached to nitrogen. In addition, we have shown that when the group is CR=NPh (amidines) the molecule may switch from a planar to a perpendicular conformation depending on the steric hindrance generated by alkyl substituents. Also, the position of the 2,6-*cis*-methyls in the dimethylpiperidyl ring (axial or equatorial) depends on the overall molecular conformation (planar or perpendicular). Finally, in at least one case we demonstrated that the dynamic motion usually observed is rotation at the NC bond, as previously assumed, in that only at lower temperature could a second motion (ring reversal or nitrogen inversion) be detected.

In previous Parts 1-3 it has been shown that *N*-substituted piperidine derivatives may adopt the preferential ground state conformations (A) or (B) depending on the X=Y moiety linked to nitrogen. In the 'planar' conformation (A) the N-X=Y plane is coplanar with the



(A) planar

(B) perpendicular

virtual plane created by the rapid ring reversal and nitrogen inversion of the piperidyl ring (*i.e.* it is orthogonal to the symmetry plane bisecting the piperidyl ring through nitrogen and C-4), whereas in the 'perpendicular' conformation (B) the N-X=Y group lies in a plane which is perpendicular to such a dynamic plane (*i.e.* it is parallel to the symmetry plane of the piperidyl ring).

<sup>13</sup>C N.m.r. spectroscopy proves to be a valuable technique<sup>2,3</sup> for distinguishing (A) from (B), provided the spectra are taken at temperatures low enough that rotation about the N-X bond is slow on the n.m.r. time scale. In fact, in the planar conformation (A), the 2- and 6-methyls are diastereotopic and C-2 and -6, as well as C-3 and -5, are anisochronous,<sup>‡</sup> whereas in the perpendicular conformation (B), the 2- and 6-methyls remain diastereotopic but C-2 and -6 and C-3 and -5 become isochronous. While the non-equivalence of the 2- and 6-methyls in the planar conformation is evident from an inspection of structure (A), this is not straightforward in the case of the perpendicular conformation (B). Actually in the latter case, despite rapid ring reversal and nitrogen inversion, the equatorial and axial methyls never become equivalent if the group X=Y lacks a symmetry axis on the n.m.r. time scale.<sup>1</sup> This

† Part 16, L. Lunazzi, G. Panciera, and M. Guerra, *J.C.S. Perkin II*, 1980, 52.

condition is fulfilled when the N-X rotation is slower than the nuclear spin lifetime and vanishes when it is faster. It was thus shown that the ground state conformation of *N*-nitrosopiperidines<sup>1</sup> (X=Y = N=O) and piperidyltriazenes<sup>3</sup> (X=Y = N=NAr) is planar regardless of the number of methyl groups on C-2 and -6 of the piperidyl ring; that of piperidylhydrazones<sup>1,2</sup> (X=Y = N=CR<sub>2</sub>), on the other hand, is perpendicular when four methyls are present. For the 2,6-dimethyl derivatives the conformation could not be established. In order to obtain more information and give additional insight into the stereodynamics of hindered piperidine derivatives, we have tried to find a class of compounds where either conformation (A) or (B) could be observed simply by varying the extent of substitution on C-2 and -6 of the piperidyl ring and/or the steric properties of groups in its proximity.

We report here the results of our studies on 2,6-*cis*-dimethylpiperidyl- (DMP) and 2,2,6,6-tetramethylpiperidyl-amides (TMP) [X=Y = C(R)=O] and -amidines [X=Y = C(R)=NPh] and show that in the latter series of compounds there is the expected conformational change, as well as other stereodynamic phenomena.

### RESULTS AND DISCUSSION

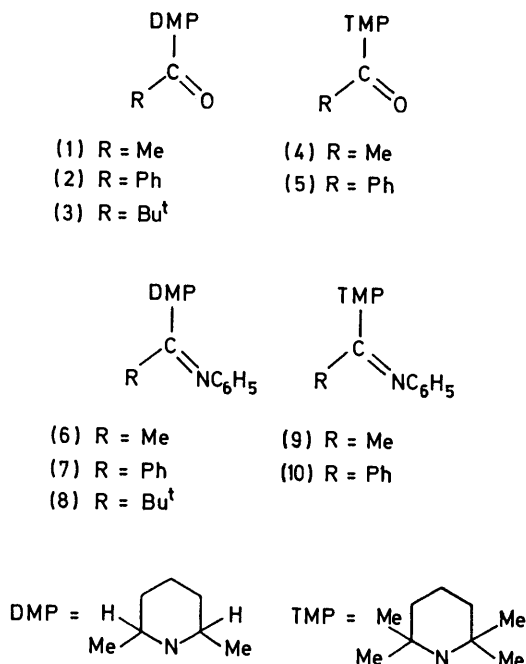
Compounds (1)–(10) selected for the present work are listed below. Since the results obtained for amides (1)–(5) and amidines (6)–(10) were quite different, they will be considered separately.

**Amides.**—The <sup>13</sup>C n.m.r. spectra of amides (1)–(5) at appropriate low temperatures show diastereotopic piperidyl methyls and anisochronous piperidyl carbons, *i.e.* C-2 ≠ C-6 and C-3 ≠ C-5, thus indicating that the RCO plane is parallel, or nearly so, to the dynamically averaged plane of the piperidyl ring. Hence, amides (1)–(5) adopt the planar conformation (A) as observed for the *N*-nitroso<sup>1</sup> and triazene derivatives.<sup>3</sup> It is

‡ In order to distinguish the non-equivalence of piperidyl ring carbons in the planar conformation (which depends on being at the left- or at right-hand side of XY) from the non-equivalence of methyls in positions 2 and 6 in the perpendicular conformation (which depends on being axial or equatorial), we have labelled the first anisochronous and the second diastereotopic.

worth mentioning that for compounds (4) and (5) the  $^1\text{H}$  n.m.r. spectra (60 MHz) failed to reveal anisochronous signals.

The  $^{13}\text{C}$  n.m.r. spectra of the *N*-benzoylamide (5) at



various temperatures are shown in Figure 1. Down to  $-100^\circ\text{C}$  all the aliphatic carbons show single sharp signals, but below  $-135^\circ\text{C}$  the carbons of the four methyl groups and C-2 and -6 as well as C-3 and -5 of the

TABLE I

Free energies of activation for the rotational process of amides (1)–(5) and amidines (6)–(10) measured from C-13 spectra at 25.16 MHz. DMP = 2,6-*cis*-dimethylpiperidyl, TMP = 2,2,6,6-tetramethylpiperidyl

Compound	$\Delta G^\ddagger$ / kcal mol <sup>-1</sup>	Temp. ( $^\circ\text{C}$ )	Solvent	Conformation
(1) R = Me	$13.8 \pm 0.1$	-7 to +18	$\text{CDCl}_3$	Planar
(2) Ph	$12.1 \pm 0.1$	-30 to -17	$\text{CHF}_2\text{Cl}$	Planar
(3) Bu <sup>t</sup>	$12.3 \pm 0.1$	-34 to -18	$\text{CHF}_2\text{Cl}$	Planar
(4) Me	$6.7 \pm 0.1$	-133	$\text{CHF}_2\text{Cl}$ - $\text{CHFCl}_2$	Planar
(5) Ph	$6.7 \pm 0.1$	-133	$\text{CHF}_2\text{Cl}$ - $\text{CHFCl}_2$	Planar
(6) Me	$10.9 \pm 0.1$	-45	$\text{CS}_2$	Planar
(7) Ph	$10.4 \pm 0.1$ *	-55	$\text{CHF}_2\text{Cl}$	Planar
(8) Bu <sup>t</sup>			$\text{CHF}_2\text{Cl}$	Perpendicular
(9) Me	$8.0 \pm 0.1$	-96	$\text{CHF}_2\text{Cl}$	Perpendicular
(10) Ph	$8.9 \pm 0.1$	-78	$\text{CHF}_2\text{Cl}$	Perpendicular

\* Line-shape analysis of the 60-MHz proton spectrum between  $-72$  and  $-52^\circ$  yielded  $\Delta G^\ddagger 10.6 \pm 0.1$  kcal mol<sup>-1</sup>.

piperidyl ring give doublets, as expected for a planar conformation. From the various coalescence temperatures of different doublets, the  $\Delta G^\ddagger$  values were determined for the amides (1)–(5). The averaged values are listed in Table I. In order to test the reliability of the method employed for the evaluation of

the activation parameters in amides (1)–(5), an independent determination was carried out in one case by a total line-shape analysis of the  $^1\text{H}$  n.m.r. spectrum. It was found that the  $\Delta G^\ddagger$  value calculated in this way was equal, within the error, to that derived from the  $^{13}\text{C}$  spectrum employing the coalescence method (see footnote to Table I).

With regard to the main point of this work, piperidyl-amides turned out to be an unlucky choice since they were found to keep to a planar conformation, regardless of the increase of steric hindrance created by placing four methyl groups on C-2 and -6 of the piperidyl ring

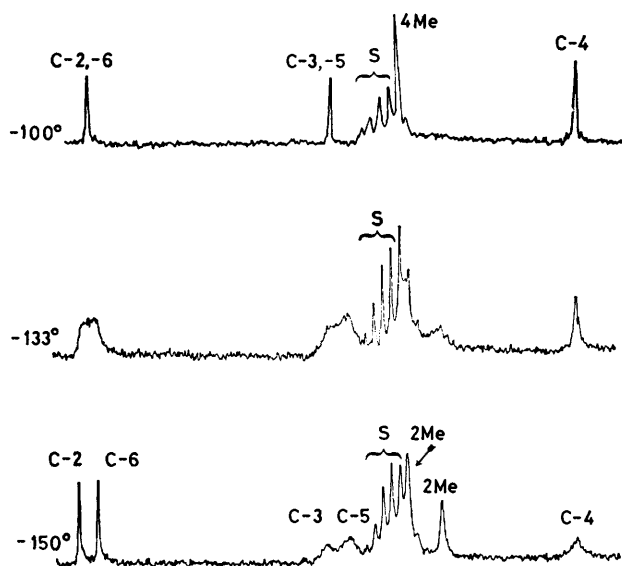


FIGURE 1 Aliphatic region of the C-13 spectrum at 25.16 MHz, of amide (5) at various temperatures. Whereas at  $-100^\circ\text{C}$  single sharp signals are observed for chemically equivalent carbons, these broaden at *ca.*  $-130^\circ$  and split into doublets at  $-150^\circ$  (with the obvious exception of C-4) as expected for planar conformations. The group of signals marked with S are those of  $[^2\text{H}_6]$ acetone used as the lock

[compounds (4) and (5)], or a *t*-butyl on the amide carbon [compound (3)]. However, the comparison of the rotational barrier is meaningful throughout the series (1)–(5) since  $\Delta G^\ddagger$  values refer to the same dynamic phenomenon, which involves a planar (or quasi-planar) ground-state conformation and a perpendicular transition state. For the amides (1)–(3), the larger  $\Delta G^\ddagger$  value of (1) with respect to (3) support the expectation that in planar compounds the bulkiest substituent entails the lowest rotational barrier.<sup>4</sup> In fact, it is conceivable that the increased dimensions of R destabilize the perpendicular transition state less than the planar ground state, thus resulting in a barrier lowering [ $\Delta(\Delta G^\ddagger)$  1.4 kcal mol<sup>-1</sup> between (1) and (3)]. On the other hand, the lower  $\Delta G^\ddagger$  value of (2) with respect to (1) may be due to a quite common effect in aromatic amides, *i.e.* a reduction of the N-CO double bond character because of Ph-CO conjugation.<sup>5</sup>

Compounds (4) and (5) show much lower barriers than the corresponding DMP derivatives (1) and (2), an apparent consequence of the conformation of the DMP

ring, which forces the two *cis*-methyls into an axial position<sup>6</sup> in order to avoid the steric repulsions between the coplanar R-CO moiety and the methyls in the equatorial position.<sup>7</sup> In the TMP derivatives the two additional methyls on C-2 and -6 must be equatorial, and this makes steric repulsion unavoidable if the chair conformation of the piperidyl ring has to be maintained. Consequently, the planar ground state in (4) and (5) is more destabilized than the perpendicular transition state, and  $\Delta G^\ddagger$  is lowered. However, this is not a general finding because in triazenes<sup>3</sup> and *N*-nitroso-compounds,<sup>1,3</sup> the DMP and TMP derivatives have identical rotational barriers. In these cases, the TMP ring is likely to assume a non-chair (twisted) conformation in order to avoid the aforementioned steric strain. At present we are unable to advance any reasonable explanation for the different behaviour of the amides with respect to the *N*-nitroso and triazene derivatives.

Finally, it is quite surprising that, unlike amides (1) and (2), as well as other compounds hitherto reported,<sup>5</sup> amides (4) and (5) have equal  $\Delta G^\ddagger$  values. A tentative explanation might be found in the intense crowding arising from the presence of five methyls in (4), which would twist the CH<sub>3</sub>CO plane away from perfect planarity more than the PhCO plane in (5). This twisting could then reduce the rotational barrier of (4) as much as conjugation of the phenyl ring does in the case of (5). An alternative explanation is that steric interactions in (5) cause the phenyl ring to be twisted out of the plane of the amide group, thus eliminating the conjugative effect of phenyl which is responsible for the lower barrier in aromatic amides.

**Amidines.**—The change in the spectral patterns produced by variation of the temperature of the TMP derivative (10) and its counterpart (7) indicates that the two compounds behave differently (Figure 2). For compound (10) at  $-90^\circ$  only two pairs of methyls become diastereotopic, while C-2 and -6 and C-3 and -5 remain isochronous: the perpendicular ground-state conformation (B) appears to be adopted. On the other hand, the conformation of (7) is planar since at  $-85^\circ$  all aliphatic carbons, including those of the piperidyl ring, are non-equivalent. An identical situation occurs for amidines (6) and (9) which similarly adopt the planar and perpendicular conformation, respectively. Hence the conformation of piperidylamidines depends on the extent of substitution by methyl groups on C-2 and -6 of the piperidyl ring.

We now have a class of compounds whose conformations switch from planar to perpendicular depending on the crowding of the substituted piperidyl group. If conformational control by steric interactions is a general property of amidines, one might expect to detect the same phenomenon by acting on other groups of the imino-function. This possibility has been tested by replacing methyl on the imino-carbon with *t*-butyl in the planar amidine (6), to give the amidine (8). Since in (8), at temperatures down to  $-160^\circ$ , there was no evidence for line broadening due to C-N rotation, the

C(Bu<sup>t</sup>)=NPh moiety lies in a plane perpendicular to the piperidyl ring, unlike the position of -C(Me)=NPh in (6). In fact, in a 2,6-*cis*-dimethylpiperidine derivative, namely amidine (8), the only arrangement consistent with the absence of anisochronous carbons at temperatures low enough to ensure a slow N-CN rotation is the perpendicular conformation (B).

The possibility of a planar arrangement of (8) associated with a rotational barrier too low to be detected is

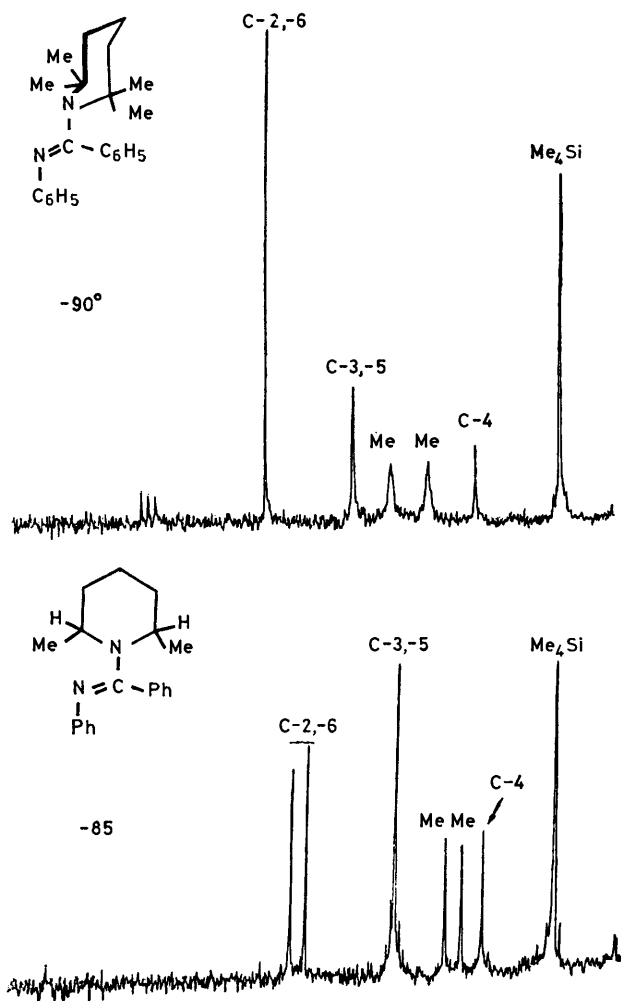


FIGURE 2 Aliphatic region of the C-13 spectra, at 25.16 MHz, of amidines (10) in CS<sub>2</sub>-CDCl<sub>3</sub> (upper) and (7) in CHF<sub>2</sub>Cl (lower) at low temperature. In the upper picture only the methyl signals are split, indicating a perpendicular conformation. In the lower spectrum both the methyl and piperidyl carbons in positions 2 and 6 are split, indicating a planar conformation. The signals of C-3 and -5 have too small a chemical-shift difference to be detected on this scale

in our opinion remote, in view of the milder conditions required to stop rotation in all the other molecules examined.

In conclusion, the conformational change in amidines is independent of the position of the bulky group attached to the amide moiety of the molecule. An interesting consequence for the stereochemistry of the piperidyl methyls can be anticipated from the perpendicular con-

TABLE 2  
 Physical or spectroscopic data for amides (1)—(5) and amidines (6)—(10)

Compound	M.p. or b.p. ( <i>p</i> /mmHg) (°C)	Crystallisation solvent <sup>a</sup>	$\nu_{\max}$ . (Nujol)/ cm <sup>-1</sup>	$\delta_{\text{H}}$ (CDCl <sub>3</sub> )	Found (Calc.) (%)		
					C	H	N
(1)	105—107 (1)		1 640	1.23 (6 H, d, 2Me), 1.66 (6 H, m, 3CH <sub>2</sub> ), 2.12 (3 H, s, 1Me), 4.4 (2 H, m, 2CH)	68.9 (69.6)	11.2 (11.0)	9.1 (9.0)
(2)	113—114 <sup>b</sup>	C <sub>6</sub> H <sub>6</sub> -LP		1.25 (6 H, d, 2Me), 1.62 (6 H, m, 3CH <sub>2</sub> ), 4.25 (2 H, m, 2CH), 7.32 (5 H, s, ArH)	77.8 (77.4)	9.1 (8.8)	6.8 (6.5)
(3)	53—55 60 (0.5) <sup>c</sup>		1 630	1.30 (9 H, s, 3Me), 1.25 (6 H, d, 2Me), 1.61 (6 H, m, 3CH <sub>2</sub> ), 4.57 (2 H, m, 2CH)	72.7 (73.2)	12.2 (11.7)	7.4 (7.1)
(4)	94—96(0.5)		1 645	1.43 (12 H, s, 4Me), 1.77 (6 H, m, 3CH <sub>2</sub> ), 2.11 (3 H s, 1Me)	72.0 (72.1)	11.4 (11.6)	7.3 (7.7)
(5)	88—89	LP	1 630	1.36 (12 H, s, 4Me), 1.77 (6 H, s, 3CH <sub>2</sub> ), 7.34 (5 H, s, ArH)	78.7 (78.3)	9.2 (9.5)	6.0 (5.7)
(6)	111—112	EtOH	1 620	1.25 (6 H, d, 2Me), 1.67 (6 H, m, DMP ring), 1.86 (3 H, s, 1Me), 6.97 (5 H, m, ArH), 4.46 (2 H, m, 2CH)	77.6 (78.2)	9.9 (9.6)	11.8 (12.2)
(7)	99—100	MeOH	1 600	1.25 (6 H, d, 2Me), 1.63 (6 H, m, DMP ring), 4.33 (2 H, m, 2CH), 6.75 (10 H, m, ArH)	81.6 (82.1)	7.9 (8.3)	9.2 (9.6)
(8)	49—51	MeOH	1 630	1.15 (6 H, d, 2Me), 1.30 (9 H, s, Bu <sup>t</sup> ), 2.66 (2 H, m, 2CH), 7.0 (5 H, m, ArH)	79.6 (79.4)	10.8 (10.4)	10.0 (10.3)
(9)	<i>d</i>		1 630	1.32 (12 H, s, 4Me), 1.54 (6 H, m, 3CH <sub>2</sub> ), 1.84 (3 H, s, 1Me), 6.97 (5 H, m, ArH)	79.4 (79.0)	10.3 (10.1)	11.4 (10.8)
(10)	114—115	EtOH	1 600	1.33 (12 H, s, 4Me), 1.70 (6 H, m, 3CH <sub>2</sub> ), 6.85 (10 H, ArH)	82.0 (81.8)	9.1 (9.2)	9.7 (9.1)

<sup>a</sup> LP = light petroleum. <sup>b</sup> Ref. 6. <sup>c</sup> Sublimed. <sup>d</sup> Oil, pure by t.l.c. (see Experimental section).

formation (B) in (8). It has in fact been shown that, for planar 2,6-*cis*-DMP derivatives, the two piperidyl methyls are axial<sup>3,4,6-9</sup> in order to relieve the considerable steric interactions between the X=Y group and methyls if they were equatorial. Clearly, this constraint vanishes in the perpendicular conformation (B); it may, therefore, be expected that the piperidyl methyls in amidine (8) are equatorial rather than axial as in (6). A proof of this assumption can be obtained from inspection of the room-temperature proton spectra (Table 2). The chemical shift of the CH protons of (6) is  $\delta$  4.46 whereas that of (8) is  $\delta$  2.66, a difference so large (1.8 p.p.m.) that it can only be attributed to a dramatic change in the conformation and not only to the substitution of a methyl with a *t*-butyl group. It is well known that equatorial methine protons lie at much lower field than those in the axial position. Accordingly, the CH of (6) is equatorial (hence the methyls are axial) and those of (8) axial (hence the methyls are equatorial). In addition, the multiplet for CH in (6) is unresolved due to the couplings  $J_{\text{CH,Me}}$  6.5,  $J_{2e,3e}$  *ca.*  $3 \pm 1$ , and  $J_{2e,3a}$  *ca.*  $2 \pm 1$  Hz as well as because of the long-range couplings which prevent spectral resolution. On the other hand the CH of (8) displays a sextet with a separation of 6.5 Hz which can be only interpreted by taking into account  $J_{\text{CH,Me}}$  6.5 and  $J_{2a,3a}$  12—13 Hz.

Further evidence for the ground-state stereochemistry assigned in solution to amidines (6) and (8) came from their single-crystal X-ray structures.<sup>10</sup> The molecular

\* The *Z*-configuration of amidine (8), prepared from the corresponding imidoyl chloride and DMP, is consistent with both the identical stereochemistry assigned to imidoyl chlorides<sup>11</sup> and the retention of configuration in nucleophilic substitutions on the C=N bond.<sup>12</sup> More surprising is the result for amidine (6) which, however, can be explained by considering that this compound is prepared by a sequence of reactions whose mechanism and stereochemistry are unexplored.

structures in Figure 3 show the planar conformation with axial methyls for amidine (6), and the perpendicular conformation with the equatorial methyls for compound

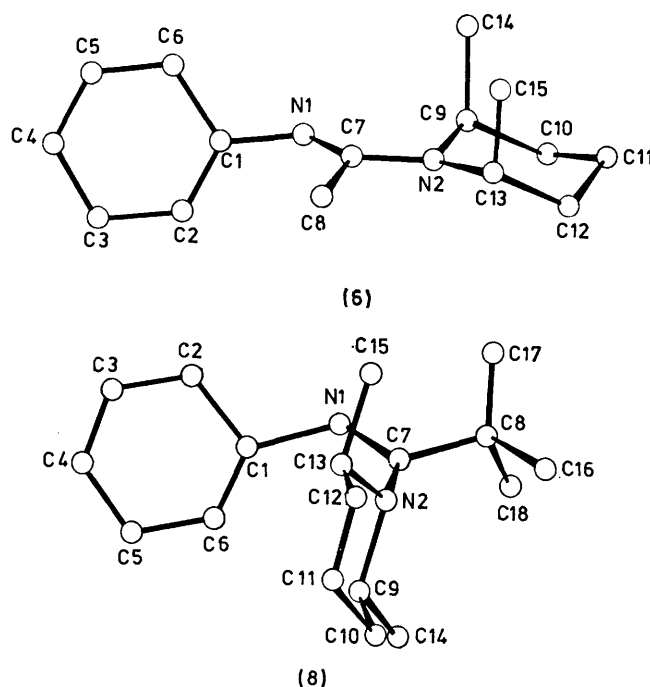


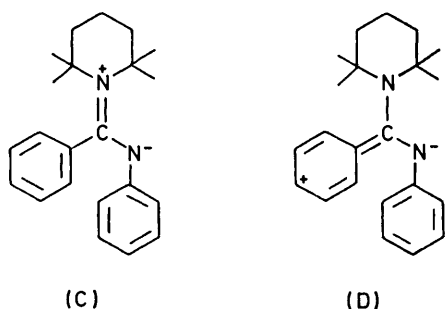
FIGURE 3 Schematic view of the X-ray structure of amidines (6) and (8)

(8). The two compounds have an additional stereochemical difference which is not apparent in solution. In amidine (6) the NPh is *trans* to the piperidyl ring (*E*-configuration) as found in triazenes,<sup>3</sup> whereas in amidine (8) it is *cis* (*Z*-configuration).\*

A comparison of  $\Delta G^\ddagger$  values for rotation about the

NC bond is meaningful only within a series of compounds having the same conformation, (A) or (B). First, it may be observed that the two planar amidines (6) and (7) have smaller rotational barriers (10.9 and 10.4 kcal mol<sup>-1</sup>) than the corresponding amides (1) and (2) (13.8 and 12.1 kcal mol<sup>-1</sup>). This indicates that the amidines have lower double-bond character than the corresponding amides. Moreover, as already pointed out for the amides, the conjugation of *C*-phenyl with C=N also reduces the double-bond character of N-C of amidine (7) with respect to (6).

The opposite trend is expected to occur for amidines (9) and (10) whose configuration is perpendicular in the ground state and planar in the transition state. This implies that the conjugative effect of phenyl with C=N operates in the transition state rather than in the ground state and reduces the contribution of structure (C) in favour of (D). Consequently, it is the transition



state which is destabilized in (10) with respect to (9) and the  $\Delta G^\ddagger$  value is increased rather than decreased, as in planar derivatives. Consistently, the rotational barrier for (10) is higher (8.9 kcal mol<sup>-1</sup>) than for (9) (8.3 kcal mol<sup>-1</sup>).

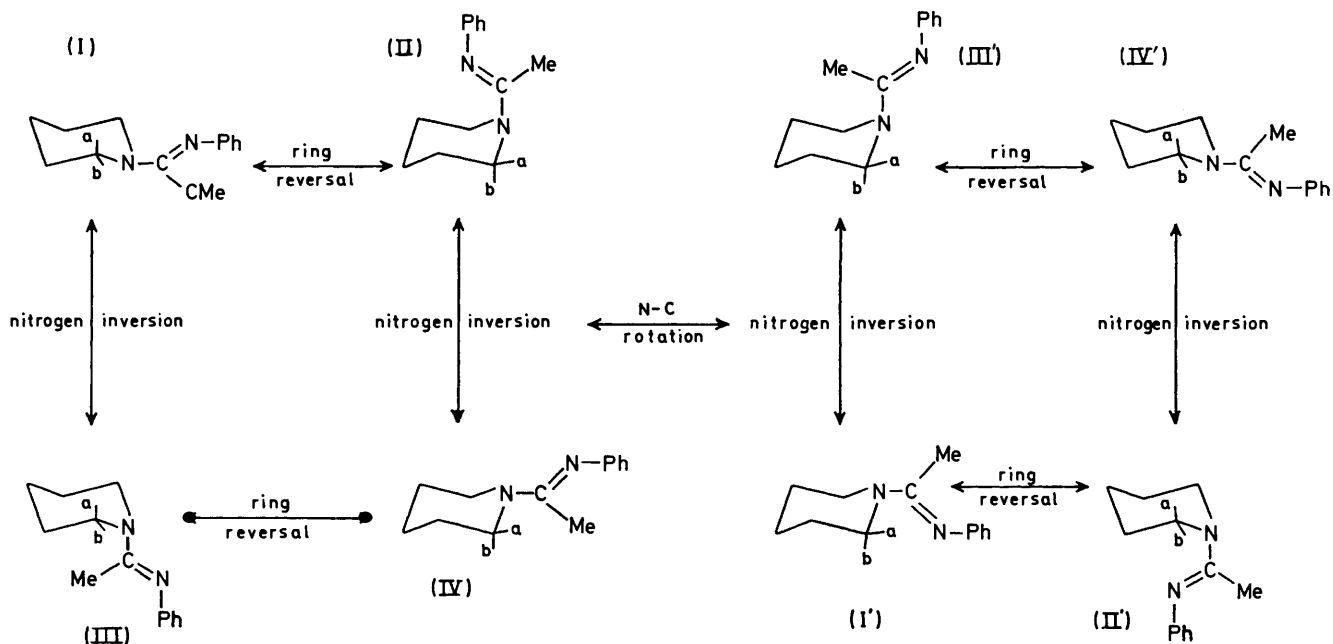
Finally, attention has to be paid to internal motions of the piperidyl ring (ring reversal and nitrogen inversion) which have so far been considered to be faster than NC rotation.

The Scheme shows that the slow NC rotation in molecules with the perpendicular conformation (B) (still with rapid motions within the ring) does not allow the equilibrium mixture of conformers (I)—(IV) to interconvert into their chemically equivalent counterparts (I')—(IV'). Since the latter conformers have the axial and equatorial methyls (indicated as a and b, respectively) interchanged with respect to the situation in (I)—(IV), two pairs of diastereotopic methyls become detectable, rather than four equivalent methyls, as in the fast rotation mode.

As (I)  $\equiv$  (I'), (II)  $\equiv$  (II') and so on, whatever the relative proportions of conformers (I)—(IV) in rapid equilibrium, the intensities of the two pairs of methyl signals are bound to be equal.

Since equal intensities for these methyl signals were observed both in the present and previous investigations,<sup>1,3</sup> it was reasonably assumed that ring reversal and nitrogen inversion were faster than rotation. There is no doubt, however, that the best proof of this assumption would be the direct observation of a second exchange process leading to unequally populated conformers at still lower temperatures. The spectral patterns of Figure 4 do show that this occurs for amidine (9). Between room temperature and  $-96^\circ$  (coalescence) only the signals of the 2- and 6-methyl groups undergo line broadening, and eventually split into a symmetrical doublet, consistent with slow rotation in a perpendicular conformer.

However, at still lower temperatures ( $-115$  to  $-125^\circ$ )



SCHEME

all the aliphatic lines of the spectrum, including the pair corresponding to the 2- and 6-methyl groups, become broad, thus indicating that a second exchange process is being observed. Finally, all the lines sharpen at  $-130^\circ$

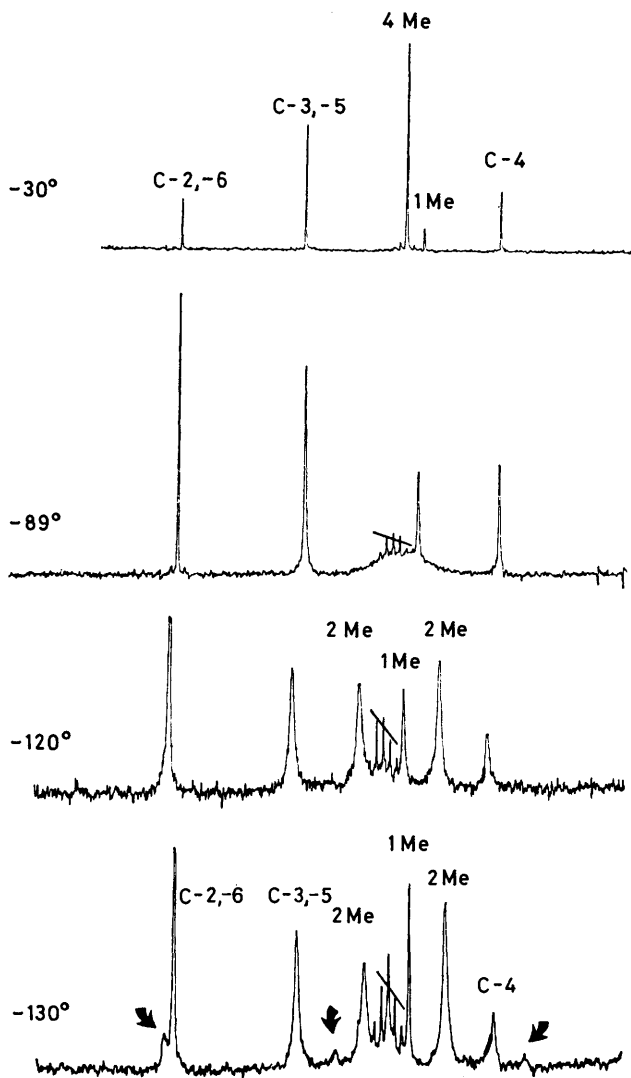


FIGURE 4 C-13 Spectra of the aliphatic region of amidines (9) at various temperatures in  $\text{CHF}_2\text{Cl}-\text{CHFCl}_2$ . At  $-30^\circ$  single signals are still observed for chemically equivalent carbons. The four methyls in positions 2 and 6 broaden ( $-89^\circ$ ) and split into a near symmetrical doublet at  $-120^\circ$ , indicating a perpendicular conformation since the C-2 and -6 and C-3 and -5 signals are still singlets. At  $-130^\circ$  additional signals (indicated by three arrows) of a second conformer are also observed. The signals are obscured by a signal from the  $[\text{2H}_6]$ acetone used as the lock

revealing additional signals of a second conformer, with an intensity ratio of *ca.* 1 : 10. This is clearly visible for C-2 and -6 and C-4.

It is difficult to decide which motion has been 'frozen' in addition to rotation. However, since in piperidine itself nitrogen inversion has a lower barrier than ring reversal,<sup>13</sup> we might assume for the sake of discussion, that nitrogen inversion is the only fast motion still experienced by amidine (9) at  $-130^\circ$ .

According to the Scheme we should therefore have a mixture of conformers (I) and (III) in rapid equilibrium and of (II) and (IV) as well as their chemically equivalent counterparts (I') and (III') and (II') and (IV'), also in rapid equilibrium. This explains why signals of different intensities are now detectable: the mixture (I)—(III) has obviously a different stability from (II)—(IV). The same argument, with the proper changes, would apply if nitrogen inversion is considered slower than ring reversal.

This finding indicates that the energies measured for the motional averaging observed in these molecules have been correctly attributed to a restricted rotation. Nonetheless in some cases, particularly for TMP derivatives like (9), there is still some doubt whether  $\Delta G^\ddagger$  refers to ring reversal rather than rotation.

Additional investigations are in progress to obtain further insight on the overall stereodynamics of this class of compounds.

#### EXPERIMENTAL

M.p.s and b.p.s are uncorrected. 2,6-*cis*-Dimethyl- and 2,2,6,6-tetramethyl-piperidine were commercially available and were distilled prior to their use.

*Amides* (1)—(5).—These compounds were prepared from equimolar amounts (*ca.* 0.1 mol) of acetyl or benzoyl chloride, the appropriate piperidine, and triethylamine in anhydrous benzene (50 ml). Whereas the formation of (1) was completed within a few minutes at room temperature, the other compounds required several hours reflux (24—70 h). The reactions were monitored by t.l.c. [silica; benzene-ethyl ether (4 : 1)]. The precipitated ammonium salt was filtered, the solvent was washed with 2N-HCl and with water, and then removed at low pressure. The residue was crystallized or distilled (Table 2). Yields were 60—80%. All compounds were characterized by i.r., n.m.r., and mass spectra ( $M^+$  and  $\text{RCO}^+$  fragments) (see Table 2).

*Amidines* (7), (8), and (10).—These compounds were prepared by reflux for 1 h of *N*-phenylbenzimidoyl chloride<sup>11</sup> and *N*-phenyl-2,2-dimethylpropanimidoyl chloride (0.06 mol) with the appropriate piperidine (0.06 mol) in dry pyridine (10 ml). After cooling and addition of 50 ml of water, the mixture was extracted with  $\text{CHCl}_3$ . The solvent was dried ( $\text{Na}_2\text{SO}_4$ ), evaporated under reduced pressure, and the residue was chromatographed [ $\text{Al}_2\text{O}_3$ ; benzene-light petroleum (1 : 12.5)]. Yields were *ca.* 70%. In addition to the characteristics listed in Table 2 the mass spectra showed  $M^+$  and ( $M - \text{DMP}$ ) or ( $M - \text{TMP}$ ) fragments.

*Acetamidine* (6).—Phosphorus oxychloride (8.7 g, 0.06 mol) in dry benzene (20 ml) was added dropwise with stirring to a solution of (1) (8.8 g, 0.06 mol) in the same solvent (20 ml), at such a rate to keep the temperature at 20—25°. The mixture, after standing overnight, had separated into two phases. Aniline (5.2 g, 0.06 mol) in benzene (20 ml) was added dropwise with vigorous stirring and the resulting mixture was heated at 65—70° for 10 h. The hydrochloride of the amidine, which separated as a yellow oil, was poured into water (150 ml) and the resulting solution was treated with 2N-NaOH until it became basic to litmus. The mixture was extracted with benzene, dried ( $\text{Na}_2\text{SO}_4$ ), distilled under reduced pressure, and the oily

TABLE 3

<sup>13</sup>C Chemical shifts (25.16 MHz, p.p.m. from tetramethylsilane) of amides (1)–(5)

Compound (1)	Solvent	Temperature (°C)	Temperature					Other
			C-2, -6	C-3, -5	2,5-Me	C4		
(1)	CDCl <sub>3</sub>	+50	45.3	30.0	20.5	13.2	20.9 (MeCO)	
		-30	47.6, 42.5	29.5, 28.9	20.6, 19.5	12.7	21.4 (MeCO)	
(2)	CHF <sub>2</sub> Cl	-17	48.5	31.2	21.6	14.9		
		-120	50.8 <sub>6</sub> , 45.4	30.5 <sub>5</sub> , 30.3	22.0 <sub>6</sub> , 20.9			
(3)	CHF <sub>2</sub> Cl	0	47.7	31.1	22.05	15.25	40.7 (CMe <sub>3</sub> ), 29.4 <sub>5</sub> (3Me)	
		-40	48.6 <sub>6</sub> , 46.3	31.1, 30.7	22.8, 21.0	14.9	40.6 (CMe <sub>3</sub> ), 29.25 (3Me)	
(4)	CHF <sub>2</sub> Cl-CHFCI <sub>2</sub>	-30	56.7	36.7	29.75	14.6	28.6 (MeCO)	
		-150	58.3, 56.2	37.0, 35.1	a	14.8	29.1 <sub>5</sub> (MeCO)	
(5)	CHF <sub>2</sub> Cl-CHFCI <sub>2</sub>	-100	57.6	34.2	30.5	14.8		
		-150	58.7, 57.0	35.9, 35.2	29.8, 16.8	14.7		

<sup>a</sup> Obscured by the signal of CH<sub>3</sub>CO and by the [<sup>2</sup>H<sub>6</sub>]acetone used as the lock.

residue was chromatographed [Al<sub>2</sub>O<sub>3</sub>; diethyl ether–light petroleum (1 : 2.5)] (Table 2). The mass spectrum showed peaks at *m/e* 230 (*M*<sup>+</sup>), 215 (*M* – CH<sub>3</sub>), 139 (*M* – NPh), and 118 (*M* – DMP).

*Acetamide* (9).—A solution of Ph<sub>3</sub>P (7.9 g, 0.03 mol) in

Table 3 for amides (1)–(5) and Table 4 for amidines (6)–(10). The assignments were made by off-resonance experiments: no assignment was attempted for the 2- and 6-methyl groups and for C-2 *versus* C-6 and C-3 *versus* C-6, when they gave separate lines at low temperature.

TABLE 4

<sup>13</sup>C Chemical shifts (25.16 MHz, p.p.m. from tetramethylsilane) of amidines (6)–(10)

Compound	Solvent	Temperature (°C)	Temperature				Other
			C-2, -6	C-3, -5	2,6-Me <sub>2</sub>	C-4	
(6)	CS <sub>2</sub>	-10	45.7	30.7 <sub>5</sub>	20.1	14.7	14.2 (CH <sub>3</sub> C=N)
		-90	47.0, 43.7	30.6, 30.1 <sub>5</sub>	21.3, 18.6	14.5	14.3 (CH <sub>3</sub> C=N)
(7)	CHF <sub>2</sub> Cl	0	48.7	31.5	20.6	15.4	
		-95	49.7, 47.0	32.0, 31.9	21.7, 18.8	14.9	
(8)	CHF <sub>2</sub> Cl	-90	57.3	35.3	22.9	25.4	41 (CMe <sub>3</sub> ), 31 (3Me)
		-30	56.7	42.1	30.2	19.1	28.1 (CH <sub>3</sub> C=N)
(9)	CHF <sub>2</sub> Cl-CHFCI <sub>2</sub>	-120	55.6	41.4	33.6, 24.1 <sub>5</sub>	18.6	28.4 (CH <sub>3</sub> C=N)
		+25	55.8	40.3	29.9	17.6	
(10)	CS <sub>2</sub> -CDCl <sub>3</sub>	-90	55.6	39.7	32.5, 26.0	17.4	

benzene (30 ml) was added dropwise, with stirring, to *N*-chloroacetanilide (5.0 g, 0.03 mol) in the same solvent (30 ml). Meanwhile the temperature was kept at *ca.* 20° by means of an ice-bath. The mixture was then heated at 50° for 15 min and the solvent evaporated under reduced pressure. The residue was distilled (1 mmHg) and the fraction boiling in the range 40–65° (*N*-phenylacetimidoyl chloride) was collected directly in a benzene solution (10 ml) of TMP (5 ml), cooled at -10°. The reaction was monitored by the formation of a precipitate of ammonium salt. The mixture was treated with water (50 ml), extracted with CH<sub>2</sub>Cl<sub>2</sub>, and, after evaporation of the solvent, the residue was chromatographed [Al<sub>2</sub>O<sub>3</sub>; benzene–light petroleum (1 : 4)]. The amidine was a dense oil, pure by t.l.c., whose mass spectrum showed peaks at *m/e* 258 (*M*<sup>+</sup>), 243 (*M* – CH<sub>3</sub>), and 118 (*M* – TMP).

*Spectral Determinations*.—The n.m.r. spectra were recorded on a Varian XL-100 instrument, operating at 25.16 MHz for C-13 in the Fourier-transform mode. A few hundred transients were collected for each spectrum and the temperature was measured by inserting a thermocouple in a dummy tube before or after each scan. When gaseous solvents were required, they were condensed into the n.m.r. tubes connected to a vacuum line and sealed. Some deuteriated acetone was added for locking purposes and its multiplet becomes visible below -100°. The C-13 chemical shifts in p.p.m. from tetramethylsilane are reported in

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