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NMR STUDIES OF RATE PROCESSES AND CONFORMATIONS—XVIII

HINDERED NITROGEN INVERSION IN 5-MEMBERED HETEROCYCLIC AMINES*

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Abstract— Barriers to nitrogen inversion have been studied in a number of 5-membered cyclic amines by variable temperature NMR spectroscopy. Electronegative substituents (Cl, Br, N, O) on nitrogen lead to a marked increase in inversion barrier as compared to the parent compounds where nitrogen is only linked to carbon.

The substituent effects observed in these compounds are compared with those obtained in aziridine derivatives. It is found that the effects are much larger in the latter cases. The structural effect on substituent effects due to the 5-membered ring → 3-membered ring" structural change is estimated to be of the order of 6 kcal/mole.

Steric and solvent effects are also discussed.

Résumé— Les barrières d'inversion de l'azote dans un certain nombre d'amines cycliques à cinq chaînons ont été étudiées par RMN à différentes températures. La présence de substituants plus électronégatifs que le carbone (Cl, Br, N, O) liés directement à l'azote produit une augmentation notable de la barrière d'inversion.

Les effets de substituant obtenus pour ces composés ont été comparés à ceux observés pour des dérivés de l'aziridine; ces effets sont beaucoup plus importants dans ce dernier cas. La modification structurale "cycle à cinq chaînons → cycle à trois chaînons" donne lieu à un effet structural sur les effets de substituant, estimé à environ 6 kcal/mole.

Quelques interactions stériques et des effets de solvant sont aussi discutés.

BARRIERS to nitrogen inversion may be considered as useful probes for understanding structural effects in organic molecules. The rates of nitrogen inversion in alkylamines or in unstrained cycloalkylamines are generally high, and the observation of temperature dependent changes in the PMR spectrum is limited to low temperature, when changes are at all observable.

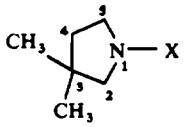
The process may be slowed down by linking electronegative heteroatoms (N,O,Cl,Br,F) to the N atom or including it into a strained cyclic system (aziridines, azetidines). When both effects are present (or two heteroatoms[2]) nitrogen inversion becomes very slow and stereoisomers arising from slowly inverting nitrogen sites may even be isolated (see Refs in [2-4]).

We present here a study of hindered nitrogen inversion in a series of tertiary pyrrolidine and Δ^3-pyrroline derivatives (I–XI) including compounds where the N atom is only linked to C atoms.* Compounds XII[6] and XIII[7a] have been included for comparison.

* Previous paper in this series: see reference 1.

† Laboratoire associé au CNRS.

* A study of N-chloropyrrolidine has been published recently. Changes in the low temperature p.m.r. spectrum of N-methyl-pyrrolidine have also been reported[5].



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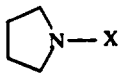
II: X = Cl
III: X = Br
IV: X = ND_2
V: X = OH



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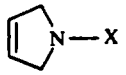
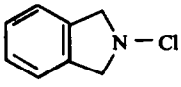
VII: X = Cl



VIII: X = CH_3
IX: X = Cl



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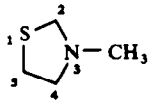

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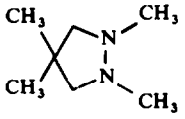

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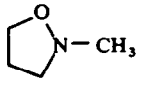
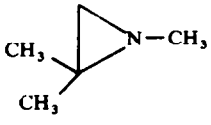


XIII



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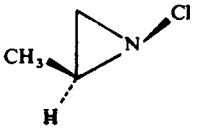

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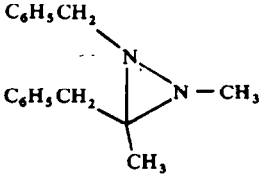
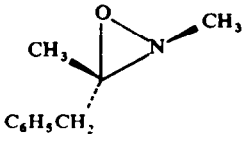


XVI



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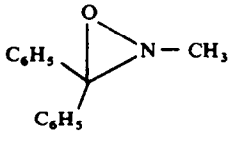
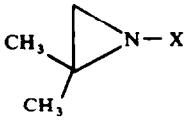


XVIII



XIX: X = NH_2
XX: X = OH

RESULTS

Preparation of the substrates. The N—Me (or N—CD_3) compounds I and XI have been obtained by reduction of the corresponding N—COOMe derivative with LAH (or LAD).

The N—Cl and N—Br compounds II, III, VII, IX, X have been obtained by direct halogenation of the corresponding secondary amines using either sodium hypochlorite or N-chloro (or N-bromo) succinimide. The N-ND_2 IV amine has been obtained by LAH reduction of the N-nitroso derivative followed by exchange with D_2O. Pyrolysis of the corresponding N-ethyl-N-oxide leads to the hydroxylamine V. (for more details see Experimental).

Variable temperature PMR spectra. All the compounds I–XI (except VIII) display temperature dependent PMR spectra. The most pronounced effects are observed for the CH_2 groups in α position to the inverting nitrogen site. The two protons of an α-CH_2 group form an A_2 (or AA') system at room temperature and become an AB system at low temperature. Further coupling to vicinal protons leads to more complex spectral patterns. In the case of II (in $CHFCl_2$) and V different signals are also observed for the gem-dimethyl groups at low temperature. The spectrum of II at − 40° and at − 120° is shown in Fig. 1.

Free energies of activation $\Delta G_c^{\neq}$ for the observed kinetic process may be calculated for the coalescence temperature T_c using the Eyring rate equation

$$\Delta G_c^{\neq} = 4{\cdot}57\, T_c \left[9{\cdot}97 + \log \frac{T_c}{(\Delta\nu_{AB}^2 + 6J_{AB}^2)^{\frac{1}{2}}} \right]$$

with a transmission coefficient $f = 1$, and where $\Delta\nu_{AB}$ and J_{AB} are respectively the chemical shift difference and the coupling constant for the protons forming the observed AB system. The calculations are based on the parameters obtained for the CH_2 protons in position 2 for I–V and XI and in positions 2 and 5 for VI-VII-IX-X. In compounds I–V and IX–XI these protons give an AB system at low temperature and an A_2 system at room temperature (coupling with the other protons is too small to be resolved). In the case of the coalescence of the two Me singlets in II and V, the last term in the above equation becomes $\log T_c/\Delta\nu$.

Because signals are more or less overlapping and are more or less complex in the various compounds the accuracy in the determination of the parameters varies from one compound to another. Table 1 lists the main results obtained in this study: J_{AB}, $\Delta\nu_{AB}$, T_c, $\Delta G_c^{\neq}$. Results obtained for VII[5], XII[6] and XIII[7a] have also been added.

DISCUSSION

Free energies and enthalpies of activation for nitrogen inversion. In order to compare the effects of substituents on the nitrogen inversion barrier in compounds I-XIII, enthalpies and entropies of activation $\Delta H^{\neq}$ and $\Delta S^{\neq}$, are required. It is however well documented[8–10] that systematic errors and inaccuracies in the determination of exchange rates by lineshape methods lead to erroneous $\Delta H^{\neq}$ and, even much more so, $\Delta S^{\neq}$ values; values of the free energy of activation are however much more reliable. On the other hand, it is reasonable to expect that an intramolecular process like nitrogen inversion should have a small $\Delta S^{\neq}$ term (presumably of the order of 5 eu or less). Large $\Delta S^{\neq}$ values obtained at various places through the literature are probably due to systematic errors.

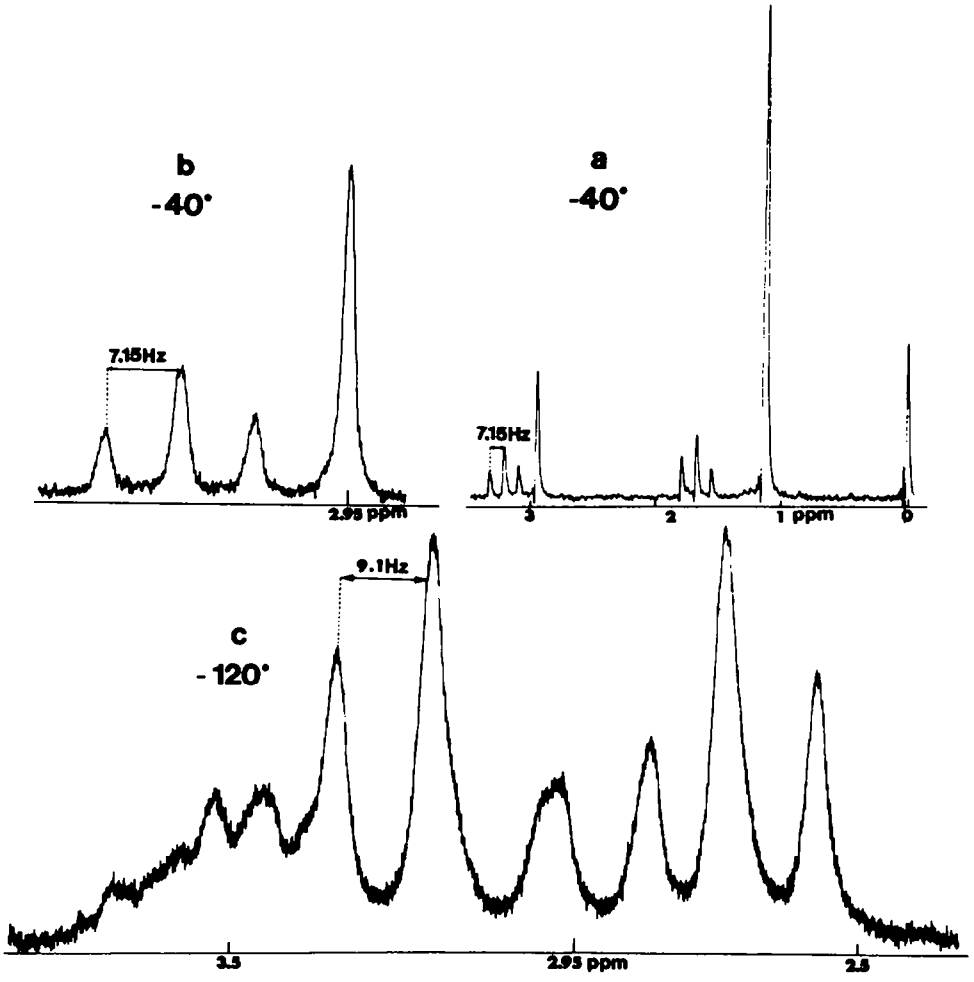


FIG. 1. 60 MHz NMR spectrum of N-Chloro-3,3-dimethyl-pyrrolidine II (in $CHFCl_2$): (a) total spectrum at $-40°$; (b) enlarged spectrum of the $CH_2(2)$ singlet and $CH_2(5)$ (triplet) protons at $-40°C$; (c) same region as in (b) but at $-120°$.

Furthermore, when observing the same process in similar compounds, one would not expect $\Delta S^{\neq}$ to vary very much from one case to another. Thus, for all cases discussed, $\Delta H^{\neq}$ values have been calculated from the available $\Delta G^{\neq}$ values (generally $\Delta G_c^{\neq}$ at coalescence temp) using values of $\pm$ 5 eu for $\Delta S^{\neq}$ (Table 1). $\Delta S^{\neq}$ values of this magnitude have been found in the racemization of optically active oxaziridines[11] (+ 5 eu; XVIII). A complete lineshape analysis of the temperature dependence of the CH_2 protons in XII leads to a $\Delta S^{\neq}$ value of $-6{\cdot}5$ eu[6]. A $\Delta S^{\neq}$ value of $+4{\cdot}2$ eu has been obtained for the epimerization of a N-methoxy-1,2-oxazolidine derivative.[2*] Although the absolute $\Delta H^{\neq}$ values obtained in this way may be in error by a few kcal/mole, the relative values from one compound to another are expected to be

* Recent accurate studies of ring inversion in cyclohexane[12] and of internal rotation processes[13] also yield small or nearly zero activation entropies.

appreciably more reliable.* When comparing two compounds we admit that it is valid to consider only the $\Delta H^{\neq}$ values calculated using the same $\Delta S^{\neq}$ ($+$ or $-$ 5 eu) for both. The difference in $\Delta H^{\neq}$ from $\Delta S^{\neq} = +5$ eu to $\Delta S^{\neq} = -5$ is of course smaller the lower the temperature at which $\Delta G_c^{\neq}$ is determined. The activation enthalpies may be considered as being equal to the potential barrier for the activation process.[4, 14]

Substituent effects on inversion barriers. Table 1 shows that the barriers to nitrogen inversion increase markedly when the nitrogen site is bonded directly to atoms more electronegative than carbon (N,O,Cl). Such barrier raising has also been observed recently in other systems, especially in 3- and 4-membered cyclic molecules (see Ref 2–5 and refs therein). It is seen that the increase Δ_1 (where Δ_1 = ($\Delta H^{\neq}$ of the compound considered)—($\Delta H^{\neq}$ of the parent compound)) of the inversion barriers within a series of structurally similar molecules is the larger for the more electronegative substituent (see Table 3; a supplementary column has been added to Table 3 for Δ_1 factors calculated from $\Delta H^{\neq}$ values obtained by taking $\Delta S^{\neq} = 0$ eu). Several steric, inductive and electrostatic effects may be invoked when one is trying to trace down the specific substituent properties which give rise to the observed barrier increase.[15] However the description of the "origin" of such substituent effects on inversion barriers depends on the theoretical language used.

Non-empirical quantum mechanical studies of nitrogen inversion in aziridine and oxaziridine[16] indicate that the N—O bond certainly plays a role in the increase of the inversion barrier. Semi-empirically, one may say that electron attraction away from the inverting site along a σ bond (i.e. a substituent with a $-$ I inductive effect) leads to an increase in the inversion barrier, in agreement with earlier expectations based on valence bond and hybridization arguments.[17]** The presence of two heteroatoms linked to nitrogen should lead to an even more important barrier increase; indeed a barrier of 29·2 kcal/mole has been found in a 5-membered cyclic amine, where nitrogen is attached to two O atoms.[2]

Explaining the origin of the effect of an heteroatom is by no means a simple and clear task. For instance the effect of an adjacent N atom is three times smaller in IV than in XII; several factors, other than those one might attribute to the N atom itself, may play a role in differentiating these two compounds (steric factors, rotation about the N–N bond . . .). Similar considerations apply to the other compounds, so that it may seem wiser in a qualitative or semi-quantitative discussion to take the substituent effects as they are without trying to relate them to a specific substituent "property".

Another question to be asked when studying substituent effects is the following: are there structural effects on substituent effects? and if yes, how does molecular structure affect substituent effects

In Table 2 we have collected literature data about nitrogen inversion in a relatively homogeneous series of aziridine derivatives (XIV–XVIII) and we have calculated

* Using $\Delta S^{\neq} = \pm 10$ eu rather than ± 5 eu changes $\Delta H^{\neq}$ values appreciably, but leads only to small changes (a few tenth of a kcal/mole) in the variations from one compound to another.

** It should be noted that such a formulation is purely phenomenological. Electronegativity increase may run parallel to barrier increase but cannot be considered as the *origin* of the barrier increase, which depends on all types of interactions present in the ground and transition states. (see ref. 4).

the corresponding $\Delta H^{\neq}$ values in a similar way as for compounds I–XII (Table 1) using $\Delta S^{\neq} = \pm 5$ eu (see also above).* In Table 3 we have listed the increase in barrier Δ_2 in a given compound (XV–XVII) with respect to the parent system (XIV). It is then possible to compare Δ_1 and Δ_2 for a given type of substitution in the reasonably comparable series of 5-membered (I, II, XII, XIII) and 3-membered (XIV–XVIII) ring compounds.

It is clear from the Δ_1 and Δ_2 values listed in Table 3 that the barrier increase due to a given substituent is much larger in the case of 3-membered cyclic molecules than in 5-membered ones. Furthermore the difference $\Delta\Delta = \Delta_2 - \Delta_1$ (Table 3) indicates that going from 5-membered to 3-membered cyclic structures increases the effect of a given substituent by a grossly "constant" factor of *ca* 6 ± 1 kcal/mole. Thus, the "5-membered ring → 3-membered ring" structural change leads to a *ca* + 6 kcal/mole *structural effect on substituent effects.*†

This result might indicate that there is an *accumulative* effect and perhaps even an *amplificative-accumulation* effect when several barrier increasing factors act on the same nitrogen site; the effect of the second or third structural factor being amplified by the first or the first two factors.

In the case of aziridines, the influence of electronegative substituents may then be considered as being amplified by the strain effect of the 3-membered ring (i.e. by the changes in the various electronic and nuclear interactions brought about by the 3-membered cyclic structure with respect to the 5-membered ring). Similarly, it seems possible that the very high barrier (29·2 kcal/mole; $\Delta_1 = 29{\cdot}2 - 8{\cdot}2 = 21$ kcal/mole) found for an N-methoxy-1,2-oxazolidine derivative[2] incorporates an amplification by the first O atom (as XIII; $\Delta_1 = 8{\cdot}5$ kcal/mole) of the effect of the second O atom (which would amount to: $21 - 8{\cdot}5 \sim 12{\cdot}5$ kcal/mole).‡

One may then speculate that an N-methoxyoxaziridin (or even more so trifluoroamine NF_3) should have a very high barrier to nitrogen inversion (of the order of 40–50 kcal/mole).§

Using the present results one may also try to estimate an approximate value of the inversion barrier in the recently prepared N-amino[20] or in the unknown N-hydroxy (or N-alkoxy[21]) aziridines (XIX and XX). The Δ_2 factor for these two compounds are *ca* 7 (XIX) and 11·5 (XX) kcal/mole (Table 3), leading to activation enthalpies of grossly 26–27 and 30–32 kcal/moles for XIX and XX respectively.

It may also be noted that the barriers obtained for the 5-membered N-Cl II, N-ND_2 IV, and N-OH V, compounds (Table 1) are very similar to those found for acyclic amines: N-chlorodibenzylamine ($\Delta G_c^{\neq}$ ($-75°$) = 9·7 kcal/mole),[22] N-aminodibenzylamine ($\Delta G_c^{\neq}$ ($-95°$) = 8·5 kcal/mole)[23] and N-methoxybenzylmethylamine E_a = 12·9 kcal/mole)[24]‖

* In the case where large $\Delta S^{\neq}$ values have been reported the activation parameters have been recalculated using $\Delta S^{\neq} = \pm 5$ eu. Another N-chloro-aziridine derivative has been studied recently,[18] but in this case the presence of additional steric effects is expected to lower the inversion barrier.

† One could think that the structure effect on substituent effects might be proportional to the barrier height, but the results are not accurate enough to permit such a conclusion to be drawn.

‡ Other structural features may however also contribute to this effect.[2]

§ A barrier of 56–59 kcal/mole has been estimated for NF_3.[19]

‖ In the last two cases where hindered rotation about the N—N or N—O bonds might also be operative, the results have been interpreted in terms of nitrogen inversion.

TABLE 1. SPECTRAL DATA AND ACTIVATION PARAMETERS FOR NITROGEN INVERSION IN COMPOUNDS I–XIII

Compound	Solvent	Signal observed (at T°C)	J_{AB} Hz	$\Delta\nu_{AB}$ Hz	T_c °C	ΔG_c^*	ΔH^* ($\Delta S^* = +5$eu) kcal/mole	ΔH^* ($\Delta S^* = -5$eu) kcal/mole
I	$CHFCl_2$	CH_2(2) (−130)	9·0 ± 0·5	54·3 ± 1	−117 ± 4	7·4 ± 0·3	8·2	6·6
II	$CHFCl_2$	CH_2(2) (−120)	9·1 ± 0·3	36·6 ± 0·5	−79 ± 3	9·4 ± 0·2	10·4	8·4
		CH_3 (−120)	—	2·7 ± 0·1	−97 ± 3	9·5 ± 0·2	10·4	8·6
	$CFCl_3$	CH_2(2) (−116)	8·7 ± 0·3	36·7 ± 0·5	−87 ± 3	9·0 ± 0·2	9·9	8·1
III	$CFCl_3$	CH_2(2) (−116)	6·0 ± 1	35·5 ± 1·5	−98 ± 3	8·5 ± 0·3	9·4	7·6
IV	$CHFCl_2$	CH_2(2) (−125)	8·4 ± 0·2	35·6 ± 0·5	−98 ± 3	8·5 ± 0·2	9·4	7·6
V	$CDCl_3$	CH_2(2) (−58)	9·8 ± 0·2	27·5 ± 0·4	−11 ± 3	13·0 ± 0·2	14·3	11·7
		CH_3	—	5·5 ± 0·1	−25 ± 3	13·2 ± 0·2	14·4	12·0
	D_2O	CH_2(2) (−8)	11·6 ± 0·2	32·9 ± 0·4	30 ± 5	15·0 ± 0·4	16·5	13·5
		CH_3	—	6·8 ± 0·2	+7 ± 4	14·9 ± 0·3	16·3	13·5
VI	$CHFCl_2$	CH_2(2·5) (−125)		69 ± 2	−107 ± 3	7·9 ± 0·2	8·7	7·1

VII[a]	CF_2Cl_2	CH_2(2·5)		26·3	−64°[b]	10·4	11·4	9·4
VIII	$CHFCl_2$	CH_2(2·5)						
IX	$CFCl_3$	CH_2(2·5) (−120)	14·5 ± 0·5	9·8 ± 0·7	−98 ± 5	8·5 ± 0·4	9·4	7·6
X	$CFCl_3$	CH_2(2·5) (−110)	14·6 ± 0·4	9·8 ± 0·5	−92 ± 3	8·8 ± 0·2	9·7	7·9
XI	$CHFCl_2$	CH_2(2) (−120)	9·7 ± 0·2	7·9 ± 0·5	−100 ± 3	8·6 ± 0·2	9·5	7·7
XII[c]	CH_2Cl_2	CH_2(3·5) (−68)	9·1 ± 0·1	40·7 ± 0·5	−45°	11·1 ± 0·2	12·2	10·0
XIII[d]	$CDCl_3$	CH_2(3)	—		+42°	15·6 ± 0·5	17·2	14·0

[a] See Ref 5. 100 MHz spectra with double irradiation. Complete lineshape analysis gave E_a = 13·9 kcal/mole and log A = 16·9 ($\sim\Delta S^{\ddagger}$ = 17·5 eu).

[b] No line broadening observed down to −135°.

[c] See Ref 6. Complete lineshape analysis $\Delta H^{\ddagger}$ = 9·5 kcal/mole; $\Delta S^{\ddagger}$ = −6·5 eu.

[d] See Ref 7a.

TABLE 2. ACTIVATION PARAMETERS FOR NITROGEN INVERSION IN COMPOUNDS XIV–XVII

Compound	Solvent	$\Delta G^{\ddagger}_{300}$ kcal/mole	$\Delta H^{\ddagger}$ ($\Delta S^{\ddagger} = +5$ eu) kcal/mole	$\Delta H^{\ddagger}$ ($\Delta S^{\ddagger} = -5$ eu) kcal/mole	Literature data
XIV[28]	Neat	18·5	20·0	17·0	$E_a = 24{\cdot}1$ kcal/mole $\Delta S^{\ddagger} = 17$ eu
XV[29]	CCl_4	26·0	27·5	24·5	$k(+80°) = 2{\cdot}08{\cdot}10^{-4}$ sec^{-1} $k(+110°) = 2{\cdot}5{\cdot}10^{-3}$ sec^{-1} (gives: $\Delta H^{\ddagger} = 21{\cdot}5$ kcal/mole; $\Delta S^{\ddagger} = -15$ eu)
XVI[30]	C_2Cl_4	27·5–27·0	29·0	25·5	$\Delta G^{\ddagger}(+70°) = 27{\cdot}3$ kcal/mole
XVII[31]	C_2Cl_4	33·0–32·0	34·5	30·5	$\Delta G^{\ddagger}(+115°) = 32{\cdot}5$ kcal/mole
XVIII[11]	C_2Cl_4	32·6	34·1	31·1	$\Delta H^{\ddagger} = 34{\cdot}1$ kcal/mole $\Delta S^{\ddagger} = +5$ eu

[a] Approximate value of $\Delta G^{\ddagger}$ at 300° K calculated from literature data.

TABLE 3. STRUCTURAL EFFECTS ON NITROGEN INVERSION BARRIERS

Substituent on Nitrogen	Δ_1^a kcal/mole				Δ_2^b kcal/mole				$\Delta\Delta^c$ kcal/mole			
	Compound	$\Delta S^* =$ +5eu	0	−5eu	Compound	$\Delta S^* =$ +5eu	0	−5eu	$\Delta S^* =$ +5eu	0	−5eu	
$-CH_3$	(I)	0	0	0	(XIV)	0	0	0	0	0	0	
–Cl	(II)	2·2	2·0	1·8	(XV)	7·5	7·5	7·5	5·3	5·5	5·7	
$\geq N-R$	(XII)	4·0	3·7	3·4	(XVI)	9·0	9·0	8·5	5·0	5·3	5·1	
$\geq O$	(XIII)	8·4[d]	7·7[d]	6·9[d]	(XVII)	14·5	14·0	13·5	6·0	6·3	6·6	
$-NH_2$	(IV)	1·2	1·1	1·0	(XIX)[e]	7·2	7·1	7·0	—	—	—	
–OH	(V)	6·2	5·7	5·4	(XX)[e]	12·2	11·7	11·4	—	—	—	

[a] Change in ΔH^* with respect to the N—CH_3 compound I; $\Delta_1 = \Delta H^*(X) - 8{\cdot}2$ or $\Delta_1 = \Delta H^*(X) - 6{\cdot}6$.

[b] Change in ΔH^* with respect to the N—CH_3 compound XIV; $\Delta_2 = \Delta H^*(X) - 20{\cdot}0$ or $\Delta_2 = \Delta H^*(X) - 17{\cdot}0$.

[c] Change in ΔH^* from the five-membered ring to the three-membered ring series; $\Delta\Delta = \Delta_2 - \Delta_1$. If $\Delta S^* = \pm 10$ eu is used, the $\Delta\Delta$ values change by less than 0·5 kcal/mole.

[d] Corrected for the absence of the gem-dimethyl groups in XIII as compared to I by subtracting 0·5 kcal/mole.

[e] Obtained from $\Delta_2 = \Delta\Delta + \Delta_1$ ($\Delta\Delta \sim 6$ kcal/mole; see text).

Steric effects. It is seen that the presence of a double bond in the Δ^3-pyrrolines (VIII–IX) lowers the nitrogen inversion barrier (by *ca* 2 kcal/mole in IX) with respect to VI and VII. The same holds for the benzo derivative X (Table 1).

In addition to a possible homoconjugation of the nitrogen lone-pair with the π-system, this barrier lowering may arise from the negative strain effect due to the introduction of a double bond in the 5-membered ring: opening of the C_2-C_3-C_4 and C_3-C_4-C_5 angles from tetrahedral (in VI, VII) to 120° (in VIII–X) also tends to open the C_2—N—C_5 angle and thus to bring the stable pyramidal state nearer to the planar (C_2—N—$C_5 \sim 120°$) transition state. The gem-dimethyl group in I–II lowers the inversion barrier with respect to VI–VII by *ca* 0·5–1 kcal/mole (Table 1), presumably because of steric interaction with the substituent on nitrogen which destabilizes the pyramidal state with respect to the transition state.

The slight barrier increase (of the order of 0·5 kcal/mole; Table 1) observed for XI with respect to VI might arise from a pinching effect due to the smaller C–S–C angle (*ca* 100°–105°) as compared to the tetrahedral C–C–C angle, although several other "effects" may be operative.

Solvent effects. It may also be noted that the inversion barrier of II determined in $CHFCl_2$ is *ca* 0·5 kcal/mole higher than in $CFCl_3$. This barrier raising effect is similar to that observed for chloroform solutions as compared to more inert solvents.[25] Thus, in $CHFCl_2$, IX and X would probably have ΔG_c^* values of 9·0 and 9·3 kcal/mole respectively.

Changing from organic ($CDCl_3$) to water solutions leads generally to a marked increase in nitrogen inversion barrier.[25] This is also seen in the case of compound V; changing from $CDCl_3$ to D_2O solutions brings the coalescence temperature from $-11°$ to $+30°$, which corresponds to a barrier increase of *ca* 2 kcal/mole.* A 1·3 kcal/mole solvent effect has also been observed for XIII.[7a]

EXPERIMENTAL

M.ps were obtained on a Kofler block and are uncorrected. Elemental analyses were performed at the Strasbourg Division of the microanalytical laboratory of the Centre National de la Recherche Scientifique. NMR spectra were measured with a Varian A-60 spectrometer equipped with the variable temp accessory. The temps down to $-50°$ were measured by means of the Varian MeOH and glycol samples and shift-temp correlation charts; the temps lower than $-50°$ have been measured using a copper-constantan thermocouple inserted directly in a spinning sample tube; their absolute values are correct to within $\pm 2°$. Both techniques give the same temp within $\pm 1°$ in their common range. Spectra calibration was effected at every temp with a Hewlett-Packard 200 CD wide-range oscillator and a Hewlett-Packard 5212 A frequency counter. During the recording of the spectra a low enough radiofrequency field was used so as to avoid differential saturation effects.

Chemical shifts are in ppm downfield from internal TMS. Coupling constants are in Hertz (Hz). The following symbols are used for describing the NMR spectra: s: singlet; d: doublet; t: triplet; m: multiplet; b: broad.

Dimethyl-3,3-succinimide was prepared according to the literature[23] from 2,2-dimethylsuccinic acid and aqueous ammonia; m.p. 105° (lit.[32] m.p. 106°). *Dimethyl-3,3-pyrrolidine* was prepared by the general method

* When such a solvent effect is taken into account the inversion barriers measured here for I and VI agree reasonably well with those obtained by Holtzman and Saunders[26] in water solution for some 5-membered cyclic amines, using the method developed by Saunders and Yamada.[27]

of reduction of the previous imide with LAH in diethyl ether soln. The product, obtained as colourless liquid, was dried over molecular sieves and distilled, b.p. 100–105°, yield 70%; NMR spectrum ($CDCl_3$, 34°); NH, s, δ 1·97; $CH_2(2)$, s, δ 2·58; $C(CH_3)_2$, s, δ 1·05; $CH_2(4)$, t, δ 1·50, J = 7·25 Hz; $CH_2(5)$, t, δ 2·97, J = 7·25 Hz. (Found: C, 72·83; H, 13·02; N, 14·14. Calcd for $C_6H_{13}N$: C, 72·66; H, 13·21; N, 14·12%).

N-(*trideuteromethyl*)-3,3-*dimethylpyrrolidine* (I)

Compound I was obtained by LAD reduction in diethyl ether soln of the N-carbomethoxy-3,3-dimethylpyrrolidine which was prepared by treating 3,3-dimethylpyrrolidine (3 g) with methyl chloroformate (4 g) in methanolic Na_2CO_3 aq (H_2O/MeOH = 1/25; 6 g suspended Na_2CO_3). The carbomethoxy derivative was purified by distillation (b.p. 95–97°/13 mm, yield 80%), and displayed the following signals in the NMR spectrum ($CDCl_3$, 34°): $COOCH_3$, s, δ 3·66; $CH_2(2)$, d, δ 3·11; $C(CH_3)_2$, s, δ 1·06; $CH_2(4)$, t, δ 1·63, J = 7·0 Hz; $CH_2(5)$, m, δ 3·43. (Found: C, 61·14; H, 9·44; N, 9·12. Calcd for $C_8H_{15}NO_2$: C, 61·12; H, 9·62; N, 8·91%).

Compound I was then obtained by treating the carbomethoxyadduct (1·5 g) with LAD (0·4 g) in diethyl ether soln (30 ml). It was distilled from Na and stored over molecular sieves (yield 60%); NMR spectrum ($CDCl_3$, 34°): $CH_2(2)$, s, δ 2·33; $C(CH_3)_2$, s, δ 1·09; $CH_2(4)$, t, δ 1·62, J = 7·0 Hz; $CH_2(5)$, t, δ 2·62, J = 7·0 Hz.

N-*chloro*-3,3-*dimethylpyrrolidine* (II) was obtained by treating 3,3-dimethyl pyrrolidine with NaOCl according to the general method.[33] The product, obtained as a colourless liquid, was purified by distillation under reduced press and at a temp <60°; NMR spectrum ($CDCl_3$, 34°): $CH_2(2)$, s, δ 2·96; $C(CH_3)_2$, s, δ 1·13; $CH_2(4)$, t, δ 1·67, J = 7·15 Hz; $CH_2(5)$, t, δ 3·22, J = 7·15 Hz. (Found: C, 54·26; H, 9·05; N, 10·63. Calcd for $C_6H_{12}NCl$: C, 53·93; H, 9·05; N, 10·48%).

N-*Bromo*-3,3-*dimethylpyrrolidine* (III) was obtained from 3,3-dimethylpyrrolidine using N-Bromosuccinimide in abs diethyl ether and cooling to −10, −15°. The soln was filtered and the ether evaporated while cooling; then the resulting mixture was extracted with $CFCl_3$ at a temp <0°. The compound was too unstable for analysis and decomposed at temp >0°; NMR spectrum ($CFCl_3$, −40°): $CH_2(2)$, s, δ 2·90; $C(CH_3)_2$, s, δ 1·12; $CH_2(4)$, t, δ 1·54, J = 7·0 Hz; $CH_2(5)$, t, δ 3·17, J = 7·0 Hz.

N-*Amino*-3,3-*dimethylpyrrolidine* (IV)

An aqueous soln of 3,3-dimethylpyrrolidine was treated with $NaNO_2$ and AcOH to produce the N-Nitroso-3,3-dimethylpyrrolidine, according to the method of Marckwald.[34] The product obtained was purified by distillation to give a yellow oil (b.p. 102–104°/13 mm, yield 70%); NMR spectrum ($CDCl_3$, 34°): $CH_2(2)$, two t, δ 3·33; δ 3·99, J = 1·2 Hz; $C(CH_3)_2$, two s, δ 1·14; δ 1·15; $CH_2(4)$, two m, centered δ 1·87; $CH_2(5)$, two m, δ 3·65; two rotamers, 38% and 62%. (Found: C, 56·42; H, 9·30; N, 21·74. Calcd for $C_6H_{12}N_2O$: C, 56·22; H, 9·44; N, 21·86%).

The N-Nitroso-3,3-dimethylpyrrolidine (3·3 g) was then reduced with LAH (1·2 g) in abs diethyl ether soln. The product obtained, N-amino-3,3-dimethylpyrrolidine distilled as a colourless liquid (b.p. 80–82°, 80 mm, yield 75%); NMR spectrum ($CDCl_3$, 34°): $N-NH_2$, b s, δ 3·12; $CH_2(2)$, s, δ 2·47; $C(CH_3)_2$, s, δ 1·09; $CH_2(4)$, t d, δ 1·59, J_1 = 7·3 Hz; J_2 = 0·8 Hz; $CH_2(5)$, t d, δ 2·75, J'_1 = 7·3 Hz; J'_2 = 0·9 Hz. (Found: C, 63·17; H, 12·30. Calcd for $C_6H_{14}N_2$: C, 63·11; H, 12·36; N, 24·53%).

The N-deutero product was obtained by treatment with D_2O, extraction with CH_2Cl_2, drying over Na_2SO_4 and molecular sieves; NMR spectrum ($CHFCl_2$, −10°): $CH_2(2)$, s, δ 2·44; $C(CH_3)_2$, s, δ 1·08; $CH_2(4)$, t, δ 1·58, J = 7·3 Hz; $CH_2(5)$, t, δ 2·71, J = 7·3 Hz.

N-*hydroxy*-3,3-*dimethylpyrrolidine* (V) was prepared according to the method described[35] for the preparation of N-hydroxypyrrolidine. N-ethyl-3,3-dimethylpyrrolidine was treated with H_2O_2 and the N-oxide obtained was pyrolized at 145–150°/15 mm. The crude product obtained was further purified by GLPC on a 3' Carbowax 20 M column (10%) on chromosorb W at 70–80°. The product collected by GLPC was redistilled and displayed the following signals in the NMR spectrum ($CDCl_3$, 34°): $CH_2(2)$, s, δ 2·8: $C(CH_3)_2$, s, δ 1·1; $CH_2(4)$, t, δ 1·63, J = 7·4 Hz; $CH_2(5)$, t, δ 3·07, J = 7·4 Hz. (Found: C, 62·88; H, 11·30; N, 12·33. Calcd for $C_6H_{13}NO$: C, 62·57; H, 11·58; N, 12·16%).

N-*methylpyrrolidine* (VI) is a commercial product and was redistilled and dried over molecular sieves before use.

N-*Chloropyrrolidine* (VII) was prepared from pyrrolidine in the same way as II.

N-*Methyl*-Δ_3-*pyrroline* (VIII) was prepared according to the literature;[36] b.p. 78–80° (lit.[37] b.p. 79–80°).

N-*chloro*-Δ_3-*pyrroline* (IX) was prepared by treating Δ_3-pyrroline (Eastman) in diethyl ether soln at −10, −15°, with N-chlorosuccinimide in the same way as described for III. The product was too unstable to be

isolated in pure form and analyzed, and was obtained as a solution in $CFCl_3$; NMR spectrum ($CFCl_3$, −40°): CH_2, s, δ 3·87; CH, s, δ 5·83.

N-*Chlorodihydroisoindole* (X)

Dihydroisoindole (isoindoline) was prepared according to the literature[38] (b.p. 100–102/15 mm (lit.[38] b.p. 115°/30 mm)). The N-chloroderivative was obtained by chlorination of the isoindoline with N-chlorosuccinimide in the same way as for IX. It was also too unstable to be isolated in pure form and analysed; NMR spectrum ($CFCl_3$, −20°): CH_2, s, δ 4·31; CH, s, δ 7·11.

3-*Methylthiazolidine* (XI). N-carbomethoxythiazolidine was prepared by reacting methyl chloroformate with thiazolidine in benzene solp in presence of triethylamine; the crude product obtained showed an NMR spectrum in agreement with the structure ($CDCl_3$, 34°): CH_2(2), s, δ 4·44; $COOCH_3$, s, δ 3·71; CH_2(4), t, δ 3·71, J = 6·2 Hz; CH_2(5), t, δ 2·97, J = 6·2 Hz) and was used without further purification. Reduction with LAH in diethylether yielded XI, b.p. 65–70°/60 mm (lit[39] b.p. 151–152°); NMR spectrum ($CDCl_3$, 34°): CH_2(2), s, δ 4·03; N—CH_3, s, δ 2·31; CH_2(4)–CH_2(5), m, δ 2·97.

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