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^{15}N Nuclear Magnetic Resonance Studies of Azabicycles; Unusual Deshielding of Nitrogen in the 7-Azabicyclo[2.2.1]heptyl Ring System

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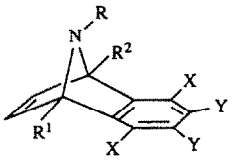
Key Words: ^{15}N Nmr spectra; bridged bicyclic amines; 7-azabenzonorbornanes/enes; tropanes/enes; homotropanes/enes; slow nitrogen inversion.

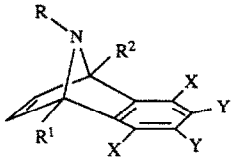
Abstract *^{15}N-enriched samples of derivatives of the 7-azabicyclo[2.2.1]heptyl system were synthesised and ^{15}N NMR spectra were recorded using ^{15}N-enriched and natural abundance samples; separate signals were observed for the two invertomers in N-methyl and N-chloro derivatives. Considerable deshielding was observed in comparison with simple amines and with 8-azabicyclo[3.2.1]octyl and 9-azabicyclo[4.2.1]nonyl analogues. Predictable changes in chemical shift resulted from substitution at nitrogen and at α-carbons; the effects of configuration at nitrogen, of unsaturation, and of substitution further from the nitrogen were also explored.*

Introduction

We have described the preparation, spectroscopy and studies of nitrogen inversion of a number of derivatives of the 1,4-dihydro-1,4-iminonaphthalene (7-azabenzonorbornadiene) ring system.[1] These 7-azabicyclo[2.2.1]heptyl derivatives show unusually slow inversion at nitrogen and we have established invertomer preferences and inversion barriers.[1] The high barrier to inversion allows a considerable measure of stereochemical control in reactions at the nitrogen atom[2] although the 'bicyclic effect'[3] which causes the high inversion barrier is not well understood.[1,4,5] Preliminary studies of the ^{15}N NMR spectra of selected 7-azabicyclo[2.2.1]heptyl derivatives[6] showed substantial downfield shifts compared with other amines, emphasising the unusual nature of the bridging nitrogen in these systems. We describe here ^{15}N NMR studies of a wider range of examples of the 1,4-dihydro-1,4-iminonaphthalene ring system **(1)** - **(11)** in which substituents are varied systematically at nitrogen, at the bridgehead carbons, and in the aryl ring. A selected group of multicyclic bridged amines **(12d)** - **(16d)** is also included in the study in order to assess any effect of proximate ethano- and etheno- bridges on the ^{15}N chemical shifts. Derivatives of the 8-azabicyclo[3.2.1]octyl (tropane) system **(17)** and **(21)**[7] and of the 9-azabicyclo[4.2.1]nonyl (homotropane) system **(18)** - **(20)** and **(22)** - **(26)**[8] have been prepared as part of other studies and ^{15}N measurements are included here for comparison.

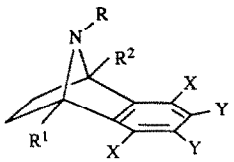


syn-

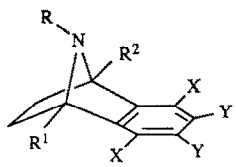


anti

R^1	R^2	X	Y	R=H	R=Me	R=Cl
H	H	Me	Me	(1a)	(4a)	
H	H	H	H	(1b)	(4b)	(5b)
H	H	OMe	H	(1c)	(4c)	(5c)
H	H	F	F	(1d)	(4d)	(5d)
Me	H	H	H	(2b)		
Me	H	OMe	H	(2c)		
Me	H	F	F	(2d)		
Me	Me	OMe	H	(3c)		

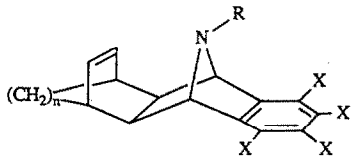


syn-

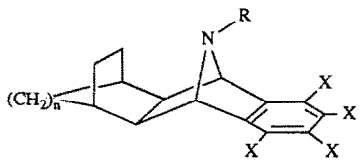


anti

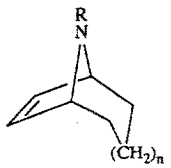
H	H	Me	Me	(6a)	(9a)	
H	H	H	H	(6b)	(9b)	(10b)
H	H	OMe	H	(6c)	(9c)	(10c)
H	H	F	F	(6d)	(9d)	(10d)
Me	H	H	H	(7b)		
Me	H	OMe	H	(7c)		
Me	H	F	F	(7d)		
Me	Me	OMe	H	(8c)		(11c)



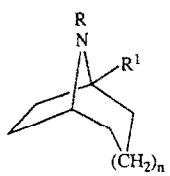
X	n	R=H	R=Me
F	1		(12d)
F	2	(13d)	(14d)
H	2	(14b)	



X	n	R=H	R=Me
F	1		(15d)
F	2		(16d)



R^1	n	R=H	R=Me	R=Bz
	1			(17)
	2	(18)	(19)	(20)



H	1			(21)
H	2	(22)	(23)	(24)
Me	2	(25)		(26)

Synthesis

Routes to the secondary amines **(1a-d)**, **(3c)**, **(6a-d)** and **(8c)** have been described earlier.[1] The 1-methyl derivatives **(2b-d)** were prepared from N-trimethylsilyl-2-methylpyrrole by addition of the appropriate benzyne; hydrogenation afforded **(7b-d)**. Preparation of the N-methyl derivatives **(4a-d)** and **(9a-d)** and the N-chloro compounds **(5b-d)**, **(10b-d)** and **(11)** followed the general methods recorded in reference 1. Samples of ^{15}N-enriched **(1a,c)** and **(6a,c)** were synthesised from ^{15}N-enriched pyrrole (ca. 2%) which was prepared, in turn, from ^{15}N-enriched (5%) ammonium sulphate. The N-methyl amines **(4a,c)** and **(9a,c)** were also prepared in enriched form, as were the N-chloro-derivatives **(5c)** and **(10c)**. The remaining measurements were made on samples containing ^{15}N at natural abundance (0.37%). The multicyclic amines **(12d)** - **(14d)** were prepared using cycloaddition reactions with cyclopentadiene and cyclohexadiene by methods similar to those described earlier;[1b] catalytic hydrogenation yielded the saturated compounds **(15d)** and **(16d)**. The facial selectivity shown in these reactions will be discussed fully elsewhere.[9] Routes to the tropanes[7] and homotropanes[8] have been published in preliminary form.

Results

Measurement of ^{15}N NMR spectra at natural abundance was relatively straightforward for secondary amines using concentrated solutions (0.4 - 0.5 g in ca. 1 cm^3 of solvent) in 10 mm NMR tubes and spectra were referenced to internal, coaxial nitromethane. Tertiary amines required significantly longer accumulation times in view of the slower relaxation.[10a] In the case of N-chloro-derivatives, the use of the shiftless relaxation agent Cr(acac)$_3$ was sometimes necessary and, even then, at least 50K scans were required in order to obtain a reasonable signal-to-noise (S/N) ratio. Long-term accumulation was also necessary when looking for signals due to minor invertomers under conditions of slow inversion. Measurements were made using ^{15}N-enriched samples whenever possible since results were obtained more easily and quickly, even at modest (2%) incorporation levels; however, in many cases this was not practical. ^{15}N NMR spectra of **(1c)**, **(4b)** and **(4c)** shown in figure 1 are illustrative. The spectrum of the secondary amine **(1c)** shows a good S/N ratio resulting from 2% enrichment, long accumulation and the presence of a hydrogen attached to the nitrogen atom (fig. 1a). The spectrum of **(4b)** (fig. 1b) illustrates the poorer S/N ratio for a tertiary amine using a sample at natural abundance but, nevertheless, allows observation of signals due to both *syn*- and *anti*-invertomers under conditions of slow inversion (-20°C). The spectrum of **(4c)** illustrates the reduction in accumulation time which becomes possible when a 2% ^{15}N-enriched sample is used under otherwise similar conditions (fig. 1c).

One signal was observed for each of the secondary amines **(1a-d)**, **(2b-d)**, **(3c)**, **(6a-d)**, **(7b-d)** and **(8c)** since inversion at nitrogen is rapid; exchange of the amine proton is also likely to be rapid. In the N-methyl amines **(4a-d)** and **(9a-d)**, inversion was slower and at 253 K, two signals were seen in each case corresponding to the major and minor invertomers. The systematic observation of two invertomers in the N-methyl and N-chloro-amines using ^{1}H and/or ^{13}C NMR spectroscopy has already been described in detail.[1] Samples of the N-chloro-amines were allowed to equilibrate thermally and comparisons were therefore made with 'thermodynamic' equilibrium ratios as recorded in reference 1b. Inversion in the N-chloroamines **(5b-d)** and **(10b-d)** was sufficiently slow on the NMR time scale that the ^{15}N signals due to the major and minor invertomers were resolved at ambient temperature. However, the spectra of the more reactive amines **(5b,c)** were measured at 0°C to minimise any thermal decomposition.

Secondary 1,4-iminonaphthalenes

Chemical shift values for the secondary amines are summarised in table 1.

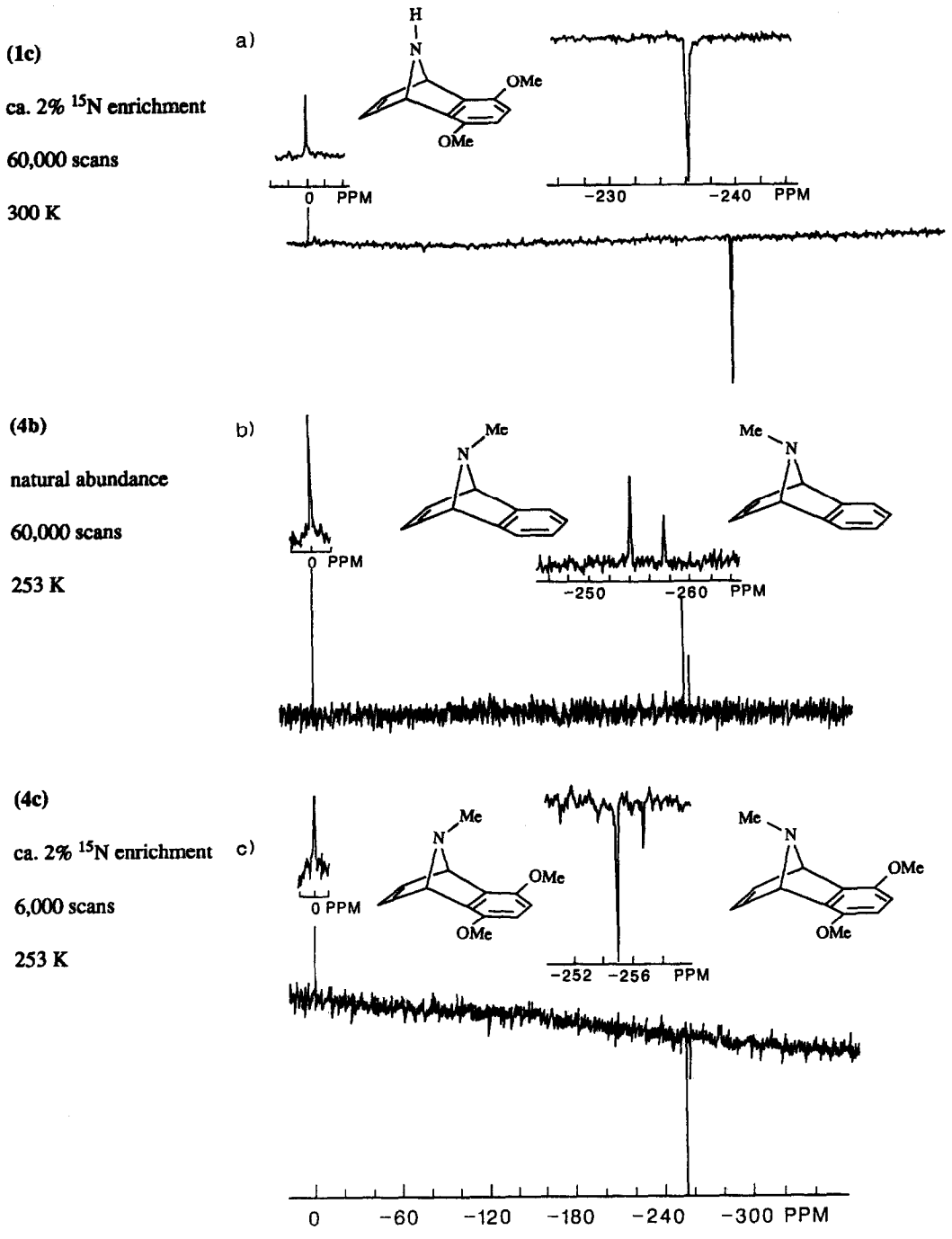
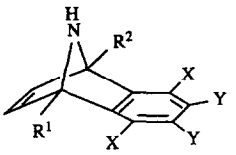
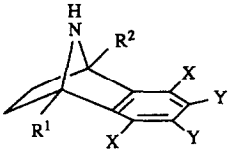


Figure 1. ^{15}N NMR Spectra. Samples in $CDCl_3$; δ values relative to $CH_3NO_2 = 0$.

Table 1. ^{15}N Chemical Shift Values for Secondary Amines

R^1	R^2	X	Y				
H	H	Me	Me	**(1a)**[b]	-244.7	**(6a)**[b,c]	-279.3
H	H	H	H	**(1b)**[d]	-239.6	**(6b)**	-277.5
H	H	OMe	H	**(1c)**[b]	-236.3	**(6c)**[b]	-276.9
H	H	F	F	**(1d)**	-241.7	**(6d)**	-280.0
Me	H	H	H	**(2b)**	-225.6	**(7b)**	-265.8
Me	H	OMe	H	**(2c)**	-226.2	**(7c)**	-265.0
Me	H	F	F	**(2d)**	-226.8	**(7d)**	-263.3
Me	Me	OMe	H	**(3c)**[e]	-214.4	**(8c)**	-251.7

a. Measurements at 300 K in $CDCl_3$ in 10 mm NMR tubes (chemical shift values in ppm relative to neat CH_3NO_2 contained in an internal, coaxial 5mm tube).
b. Sample enriched in ^{15}N (ca. 2%).
c. Measured at 263 K with added $Cr(acac)_3$.
d. Measured in CD_2Cl_2.[6a]
e. Measured in CD_2Cl_2/CH_2Cl_2.[6a]

A number of points emerge from these measurements.

a) The substantial downfield shifts in these amines become clear when comparison is made with data for other cyclic secondary amines.[10a] Thus, pyrrolidine and piperidine show signals in the range -342 to -344 ppm (relative to neat nitromethane); alkyl substituents in these rings extend the range to *ca.* -300 to -350 ppm. In contrast, strained azacycles appear at higher field and are typified by aziridine itself (*ca.* -390 ppm); this value is also lowered (to *ca.* -350 ppm) by alkyl substituents in the ring.

b) The presence of an unsaturated bridge in **(1)**, **(2)** and **(3)** leads to substantial deshielding (by 34.6 - 40.6 ppm) when comparison is made with the corresponding saturated analogues **(6)**, **(7)** and **(8)**.

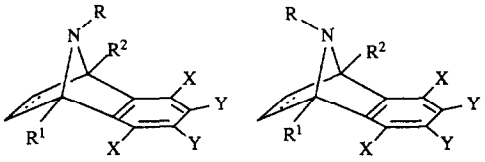
c) Variation of the substituents in the aryl ring (from tetramethyl to tetrafluoro) gives rise to relatively small shift differences.

d) The introduction of a methyl group at the bridgehead position (β- effect) brings the nitrogen resonances to lower field by 10.1 - 14.9 ppm for **(1b-d)** → **(2b-d)** and by 11.7 - 16.7 ppm for the ethano-bridged analogues **(6b-d)** → **(7b-d)**. The effect is approximately additive since the incorporation of a second bridgehead methyl in **(3c)** and **(8c)** leads to further downfield increments of 11.8 and 13.3 ppm respectively (total relative shifts of 21.9 and 25.2 ppm relative to **(1c)** and **(6c)**). These results are in accord with well-established observations in acyclic amines where deshielding of *ca.* 5 to 15 ppm per alkyl group is observed.[10a]

N-Methyl and N-Chloro- 1,4-iminonaphthalenes

Chemical shift values for the N-methyl- and N-chloro- amines are listed in table 2.

Table 2. ^{15}N Chemical Shift Values for N-Methyl- and N-Chloroamines



R	R^1	R^2	X	Y		*syn-* (major)	*anti-* (minor)	Temp. °K
Me	H	H	Me	Me	(4a)[b]	-259.3 (70%)	-260.6 (30%)	253
Me	H	H	H	H	(4b)	-254.1 (71%)	-257.5 (29%)	253
Me	H	H	OMe	H	(4c)[b]	-255.0 (80%)	-256.8 (20%)	253
Me	H	H	F	F	(4d)[d]	-255.0 (88%)	-253.7 (12%)	253
Me	H	H	Me	Me	(9a)[b]	-291.0 (95%)	-300.0 (5%)	253
Me	H	H	H	H	(9b)	-287.5 (94%)	-298.1 (6%)	258
					(9b)[c]	-288.3	-298.8	243
Me	H	H	OMe	H	(9c)[b]	-290.9 (97%)	-297.2 (3%)	253
Me	H	H	F	F	(9d)	-288.6 (98%)	e	253
Cl	H	H	H	H	(5b)	-204.7 (63%)	-200.5 (37%)	263
Cl	H	H	OMe	H	(5c)[b]	-201.9 (60%)	-204.2 (40%)	263
Cl	H	H	F	F	(5d)	-208.6 (84%)	-207.2 (16%)	300
Cl	H	H	H	H	(10b)	-226.6 (53%)	-246.3 (47%)	300
Cl	H	H	OMe	H	(10c)[b]	-227.9 (54%)	-245.4 (46%)	300
Cl	H	H	F	F	(10d)[f]	-233.7 (80%)	-256.0 (20%)	300
Cl	Me	Me	OMe	H	(11c)[f,g]	-200.1 (71%)	-218.3 (29%)	300

a. Measurements in $CDCl_3$ in 10 mm NMR tubes (chemical shift values in ppm relative to neat CH_3NO_2 contained in an internal, coaxial 5mm tube). Invertomer ratios were measured from ^1H NMR spectra.[1]
b. Sample enriched in ^{15}N (ca. 2%).
c. Values quoted by Quin et al.[6b] using a 23% ^{15}N-enriched sample. These values were recorded as 91.9 and 81.4 ppm respectively relative to liquid ammonia; liquid ammonia is -380.2 ppm from nitromethane.[10a]
d. A value of -251.5 ppm was earlier measured for (4d) at ambient temperature in CD_2Cl_2 with added $Cr(acac)_3$.[6a] The value for the corresponding N-benzyl analogue was -243.2 ppm.[6a] In both cases, these are weighted time-averages.
e. This assignment could not be made with certainty in view of the poor S/N ratio.
f. Measured with added $Cr(acac)_3$.
g. Measured in CD_2Cl_2/CH_2Cl_2.[6a]

Separate signals for the *syn-* and *anti-* invertomers are discernible under conditions of slow inversion for all these amines except (9d) where the signal due to the 2% of the *anti-* invertomer could not be assigned with certainty using a non-enriched sample. The general observations listed above for the secondary amines are echoed in these results which also provide data relating to substitution and stereochemistry at nitrogen.

a) The attachment of a methyl group to nitrogen in **(4)** and **(9)** (α- effect)[10a] leads to a consistent shielding effect. The *syn-* and *anti-* N-methyl amines are shifted upfield by between 8.6 and 20.7 ppm compared to the (rapidly inverting) secondary amines. The values for **(4)** and **(9)** cover the range -253 to -300 ppm whereas N-methylpyrrolidine and N-methylpiperidine are at approximately -340 to -344 ppm;[10a] again, strained amines such as N-methyl aziridine (-379.5 ppm) appear at much higher field.

The N-chloro amines **(5)**, **(10)** and **(11)** are at lowest field of all (approx. 24 to 52 ppm downfield of the corresponding secondary amines). Substantial deshielding of the nitrogen nucleus by chlorine has already been observed in alkyl amines.[11]

b) The presence of an unsaturated bridge in **(4a-d)** again leads to deshielding compared with the saturated compounds **(9a-d)**. The downfield increment on 'desaturation' of the 2-carbon bridge is *ca.* 31 - 36 ppm for the *syn-* invertomers and *ca.* 40 ppm for the *anti-* invertomers. The corresponding effect of unsaturation in the N-chloroamines **(5b-d)** leads to downfield shifts of *ca.* 22 - 26 ppm for the *syn-* and *ca.* 41 - 49 ppm for the *anti-* invertomers when comparison is made with **(10b-d)**. The *syn-* / *anti-* differences will be addressed later.

c) Variation of the substituents in the aryl ring makes relatively little difference to chemical shifts. The greatest differences are seen in the tetrafluorobenzo compounds but the tetrafluoro effect is variable: the tetrafluorobenzo N-chloroamines **(5d)** and **(10d)** appear upfield of the benzo and dimethoxybenzo analogues whereas the tetrafluorobenzo N-methyl compounds **(4d)** and **(9d)** tend to be closer to, or slightly downfield of, the more electron-rich aryl analogues.

d) The value for the N-chloroamine **(11c)** confirms the deshielding β-effect of methyl substituents at the bridgehead carbons, downfield increments of 27.8 (*syn-*) and 27.1 ppm (*anti-*) being observed when hydrogens at both bridgehead positions in the parent compound **(10c)** are replaced by methyl groups in **(11c)**.

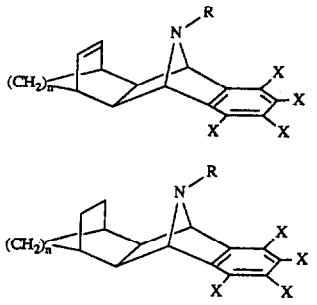
e) The results in table 2 allow some quantification of the effect of stereochemistry at nitrogen on chemical shifts in the N-methyl and N-chloro- amine families. The chemical shift differences between *syn-* and *anti-* invertomers in the 'unsaturated' compounds **(4a-d)** and **(5a-d)** is small [-3.4 to +4.2 ppm (where the - sign denotes *anti-* upfield of *syn-*)] which implies a generally equal balance between the effects of etheno and benzo bridges on the bridging nitrogen and attached substituent. In contrast, the differences between the two invertomers in the 'saturated' analogues are greater (the *anti-* consistently upfield of the *syn-*), ranging from -6.3 to -10.6 ppm for **(9a-d)**, -17.5 to -22.3 ppm for **(10a-d)** and -18.2 ppm for **(11c)** indicating a substantially different environment for the two 'faces' of the nitrogen.

Before discussing these results in more detail, chemical shift measurements for some other model compounds should be considered.

Multicyclic Amines (12) - (16)

The 'multicyclic' derivatives of the 1,2,3,4-tetrahydro-1,4-imino- naphthalene ring system shown in table 3 were selected in order to probe the question of through-space π-lone pair interactions in these systems.[9] It was established above that variation of substituents in the aryl ring lead to relatively small changes of chemical shift at the bridging nitrogen and this is reinforced in the multicyclic systems by comparison of **(14b)** and **(14d)** (table 3). In view of this, further measurements were made only on the tetrafluoraryl compounds **(12d-16d)**.

Table 3. ^{15}N Chemical Shift Values for Multicyclic Amines[a]



X	n	R		
F	1	Me	**(12d)**	-302.3
F	2	H	**(13d)**	-304.7
F	2	Me	**(14d)**	-301.0
H	2	H	**(14b)**	-303.0
F	1	Me	**(15d)**	-299.0
F	2	Me	**(16d)**	-299.2

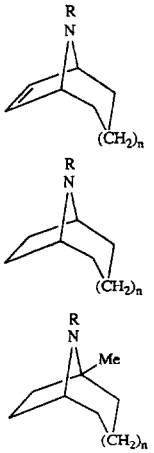
a. Measurements in $CDCl_3$ at 300 K in ppm relative to CH_3NO_2 as described in tables 1 and 2.

As expected,[1b] signals due to only one invertomer were observed in the NMR spectra. The nitrogen lone pair is clearly forced to be in close proximity to the etheno or ethano bridge which forms part of the bicyclo[2.2.1]heptene/ane portion of **(12d)** and **(15d)** respectively or the bicyclo[2.2.2]octene/ane portion of **(13d)**, **(14d)** or **(16d)**. Taking *syn*-**(9d)** as a point of reference (-288.6 ppm) for the *syn*- methyl compounds, the effect of the ethano bridge of the additional carbobicyclic unit leads to upfield shifts of 10.4 and 10.6 ppm in **(15d)** and **(16d)** respectively. The corresponding differences in **(12d)** and **(14d)** (in which the lone pair is forced to interact with the π-system of the etheno bridge) are 13.7 and 12.4 ppm respectively. Thus the 'n/π effect' here leads to an additional shielding increment which is small when compared with the shift differences encountered earlier.

Tropanes and Homotropanes (17) - (26)

Finally, table 4 summarises ^{15}N chemical shift data for higher homologues, tropanes/enes and homotropanes/enes.

Table 4. ^{15}N Chemical Shift Values for 8-Azabicyclo[3.2.1]octyl and 9-azabicyclo[4.2.1]nonyl Derivatives.[a]



n=1	R=Bz	**(17)**	-300.4
n=2	R=H[HCl]	**(18)**	-313.0
n=2	R=Me	**(19)**	-329.8
n=2	R=Bz	**(20)**	-320.6
n=1	R=Bz	**(21)**	-305.8
n=2	R=H[HCl]	**(22)**	-308.1
n=2	R=Me	**(23)**	-324.6
n=2	R=Bz	**(24)**	-314.8
n=2	R=H[HCl]	**(25)**	-299.1
n=2	R=Bz	**(26)**	-314.0

a. Spectra were measured relative to CH_3NO_2 at 300 K; tertiary amines were studied in $CDCl_3$ and secondary amines as hydrochloride salts in D_2O.

All the tertiary amines in table 4 show chemical shifts in the region -300 to -329 ppm which corresponds to the low-field end of the chemical shift range for normal tertiary amines.[10] Values of -321.1 and -342.6 ppm (relative to CH_3NO_2) have been reported for atropine and scopolamine.[12] The secondary amines in table 4 were studied as hydrochloride salts in D_2O and cover the range -299 to -313 ppm consistent with the normal range for secondary amines.

Turning to the 8-azabicyclo[3.2.1]octyl system, the saturated N-benzyl amine **(21)** appears at -305.8 ppm; the incorporation of unsaturation into the 2-carbon bridge **(17)** leads to modest deshielding of 5.4 ppm. In contrast, the corresponding effect for the higher homologues is an *upfield* shift of 4.9 ppm for the secondary amine salts **(22)** → **(18)**, 5.2 ppm for the N-methyl analogues **(23)** → **(19)**, and 5.8 ppm for the N-benzyl compounds **(24)** → **(20)**. The addition of a bridgehead methyl group in the amine hydrochloride **(25)** leads to deshielding (9.0 ppm) as in earlier examples (β- effect). However, the corresponding increment for the N-benzyl compound **(26)** is a modest 0.8 ppm.

Discussion of Results

The ^{15}N chemical shifts described for these derivatives of the 7-azabicyclo[2.2.1]heptyl system constitute the lowest field signals yet recorded for secondary and tertiary amines. These low-field signals are not the consequence of angle strain since, as established above, the aziridine nitrogen is significantly shielded relative to other cyclic amines. The downfield shifts are indicative of electron-withdrawal from nitrogen into the bicyclic framework and this is consistent with earlier observations concerning the 'bicyclic effect' and its consequences for barriers to inversion at nitrogen.[13] The 'normal' chemical shifts displayed by the higher homologues **(17)** - **(26)** (table 4) emphasise the unusual nature of the title ring system. Significant deshielding of the bridging atom has been recorded in other 7-bridged bicyclo[2.2.1]heptyl systems where the bridge is carbon,[14] oxygen,[15] phosphorus,[16] and silicon.[17]

Other effects are superimposed onto the basic 'bicyclic' effect. Firstly, the effects of substituents at nitrogen are predictable in qualitative terms. Thus, shielding by a methyl substituent at nitrogen and deshielding by an N-chloro substituent have been described above (table 2) and are well precedented in simpler systems.[10,11]

Secondly, the downfield shift resulting from methyl substitution at the 1,4- carbons (β-effect) is a substantial and consistent feature of the NH and NCl series in agreement with earlier observations.[10a]

The third major effect results from unsaturation in the 2-carbon bridges. This effect has also been seen in the bridged 6-ring systems listed above.[14-17] The observed downfield shifts have been ascribed essentially to σ-π^* interactions between the 1,7- (4,7-) bonds and the π- bonds in these rigid bicyclic frameworks. These effects are seen particularly clearly in norbornadiene[14] where the interaction of the two double bonds leads to a low-lying π^* orbital and hence a substantial electron withdrawal from C_7; the $\Delta\delta$ value (downfield shift) for the bridging carbon in going from norbornene to norbornadiene is 36.7 ppm. A similar interaction presumably explains the large downfield ^{15}N shifts observed on incorporation of unsaturation into the second C-C bridge in the secondary amines in table 1 [$\Delta\delta$ values of between 35.2 and 40.6 for **(6a-d)** → **(1a-d)**; **(7b-d)** → **(2b-d)**; **(8c)** → **(3c)**]. The effect appears to be general; it is also seen in the N-methyl systems in table 2 [$\Delta\delta$ values of between 39.4 and 40.6 for **(9a-d)** → **(4a-d)**] as well as for the N-chloro analogues [$\Delta\delta$ of 41.2 - 48.8 for **(10b-d)** → **(5b-d)**]. A downfield shift is also seen on introduction of a double bond into the 2-carbon bridge of the tropane skeleton [5.4 ppm for **(21)** → **(17)**; table 3]. The smaller shift here suggests that the effect has not been totally lost in this less rigid bicyclic framework but that it has certainly been heavily attenuated. Whilst conformational effects in the homotropanes have not been quantified, the observed chemical shift values together with the upfield shifts on incorporation of unsaturation imply that neither the 'bicyclic effect' nor the σ-π^* interaction operates to a significant extent in these higher homologues. Their behaviour appears closer to that of monocyclic systems where, for example, an upfield shift of ca. 10 ppm has been observed on incorporation of a 3,4- double bond into the piperidine ring system.[18]

It is difficult to establish any simple correlations between ^{15}N chemical shifts and changing substituents in the aryl rings. A general tendency towards reduced shielding of nitrogen in the *syn*- and *anti*- invertomers

of the tertiary amines (**4**) and (**9**) as the aryl ring becomes more electron-deficient (**a** → **d**) appears to fit with an increased effectiveness of the σ-π^*interaction referred to above as the energy of the π^* orbitals is reduced. Application of the same simple idea to the secondary amines (**1**) and (**6**) is encouraging for (**a** - **c**) but fails for the tetrafluoroaryl compounds (**1d**) and (**6d**) which are shielded. If anything, the correlation is reversed for the N-chloro amines (**5**) and (**10**).

Crystal structures of selected N-chloroamines[19] have indicated that the bicyclic skeleton alters shape substantially with changes of substituents and stereochemistry at nitrogen in order to minimise the energy of the system. Electronic changes induced by substituents in the aryl ring also influence the energy (and presumably shape) of the two invertomers. Crystal data show an increase in the CNC bond angle when the hybridisation at the 1,4- positions is altered by methyl substitution. It has been pointed out that the precise geometric relationships in simple cyclic amines can complicate attempts to achieve ^{15}N correlations.[10b] The complex mix of factors influencing the bicyclic systems appears to be quite sufficient to induce substantial but unpredictable changes in the character of the bridging nitrogen and thereby frustrate any attempts to demonstrate simple chemical shift/substituent correlations.

Despite this, it is of some interest to compare the effect of configuration at nitrogen on δ values. The values in table 2 show a generally similar magnetic environment for the nitrogen in *syn-* and *anti-* invertomers of the N-methyl amines (**4**) and also the N-chloro amines (**5**) in which both 2-carbon bridges are unsaturated. The chemical shift differences between the ^{15}N signals for each pair of invertomers are, variously, positive or negative but they remain small. In contrast, in the ethano-bridged N-methyl amines (**5**) the *anti-* invertomer shows a signal upfield of the *syn-*; the upfield position of the *anti-* signal is even more pronounced in the N-chloro amines (**10**) (17.5 - 22.3 ppm upfield of the *syn-*). 'Repulsive' n/π effects were earlier invoked in attempts to explain *syn-/anti-* preferences in derivatives of the title ring system[20] and they have also formed the basis for tentative explanations of *syn-/anti-* chemical shift differences in 7-phosphanorbornenes.[16b] All of our earlier work[1] suggests that interactions between the nitrogen lone pair and bridging π bonds are of little importance in determining relative energies of *syn-* and *anti-* invertomers (in agreement with other work[21]). We see no reason to invoke such effects as a major factor in explaining *syn-/anti-* differences here, especially when the chemical shift differences between the two invertomers are greater for the N-chloro than the N-methyl compounds despite the less diffuse lone pair in the former. We have observed earlier that the largest population differences between the two invertomers (in the ethano-bridged compounds (**9**) and (**10**)) coincide with repulsive steric interactions between the *anti-* substituent on nitrogen and the *exo-* substituents in the 2-carbon bridge. Earlier ^{15}N studies[22] in simpler cyclic systems have shown that steric compression can result in nitrogen shielding; the shielding observed in (**15d**) and (**16d**) would be consistent with such an effect. It is possible in the case of the *anti-* invertomers of the ethano-bridged amines (**9**) and (**10**) that shielding resulting from steric compression plays a major part by offsetting the deshielding induced by σ-π^* interactions, thus bringing the *anti-* signals to higher field than the *syn-*.

Experimental

Reactions were performed under dry nitrogen using solvents dried by standard methods. Magnesium sulphate was used to dry organic extracts prior to evaporation of solvent.

IR spectra were recorded in CH_2Cl_2.

^1H NMR spectra were recorded on Varian EM 390 (90 MHz), Bruker AM 300 (300 MHz) or Bruker AM 400 (400 MHz) spectrometers. Spectra were measured in $CDCl_3$ with tetramethylsilane (TMS) as reference unless indicated otherwise.

^{13}C NMR spectra were recorded on Bruker AM 300 (75 MHz) or Bruker AM 400 (100 MHz) spectrometers. Chemical shifts were measured in $CDCl_3$ solutions and are recorded in ppm relative to TMS.

^{15}N NMR spectra were recorded on a Bruker AM 300 spectrometer at 30.4 MHz. Spectra were accumulated measured using broad band proton decoupling, a pulse width of 10 μs (~22° flip angle) or 15 μs,

acquisition time of 0.639 s, a fixed delay between pulses of 0.1 s, a sweep width of 12820 Hz, and a block size of 16K zero-filled to 32K when processed, giving 0.78 Hz/point. Measurements were made in $CDCl_3$ in 10 mm tubes and chemical shifts were referenced to neat CH_3NO_2 contained in an internal, coaxial 5 mm tube. Any variations of solvent or conditions (e.g. use of $Cr(acac)_3$) are mentioned in the text. The preliminary results published earlier[6a] were recorded at the University of Warwick (using samples at natural abundance) on a Bruker WH 400 spectrometer operating at 40.55 MHz.

Temperature measurements on the NMR instruments used for the VT work were found to be accurate to within ± 1 K over the range used.

Mass spectra were measured routinely on a VG Micromass 14 spectrometer. Accurate mass measurements were obtained through the SERC service at Harwell and, more recently, Swansea.

Melting point measurements were made using a Kofler hot stage apparatus and are uncorrected.

Combustion Analyses were performed by CHN Analysis Ltd. of South Wigston, Leicester or Butterworth Laboratories Ltd., Teddington, Middlesex.

Preparative routes to samples of **(1a-d)**, **(3c)**, **(4a-d)**, **(6a-d)**, **(8c)**, and **(9a-d)** containing ^{15}N at natural abundance are described in reference 1a together with spectroscopic and other data; routes to **(5b-d)**, **(10b-d)**, **(11c)** and **(14b)** are similarly described in reference 1b. ^{15}N NMR results for the tropane and homotropane derivatives **(17)** - **(26)** have been included in table 4; the general routes to these systems have been described in preliminary form[7,8] and full details will be provided in the full papers.

1-Methyl-1,4-dihydro-1,4-iminonaphthalene (2b)

1-Methyl-5,8-dimethoxy-1,4-dihydro-1,4-iminonaphthalene (2c)

1-Methyl-5,6,7,8-tetrafluoro-1,4-dihydro-1,4-iminonaphthalene (2d)

In a typical procedure, **(2d)** was prepared by dropwise addition of a solution of n-butyllithium (2.2M in hexane; 8.5 ml) over a period of 10 min to a stirred solution of pentafluorobenzene (3.0 g; 17.9 mmol) in dry diethyl ether (50 ml) at -78°C under nitrogen. A solution of 1-trimethylsilyl-2-methylpyrrole (2.80 g; 18.3 mmol)[see below] in dry diethyl ether (20 ml) was subsequently added over a period of 10 min. The stirred reaction mixture was allowed to warm to room temperature overnight and was then poured into water (100 ml). The product was extracted into diethyl ether (2 x 100 ml) and the combined organic extracts were washed with cold 2M HCl (2 x 100 ml). The acidic extracts were combined, cooled, and basified carefully with 2M aqueous NaOH. The basic solution was extracted with dichloromethane (3 x 100 ml) and the combined organic layers were dried before evaporation under reduced pressure to yield a dark oil. The product was purified by flash chromatography over silica using a 70:30 mixture of diethyl ether:petroleum ether (b.p. 40-60°C) to yield **(2d)** (1.34 g; 32%) as a pale yellow oil. I.R. ν_{max} (CH_2Cl_2) 3260w, 3015w, 2975w, 2935w, 1485brs, 1390m, 1355m, 1290w, 1255m, 1190m, 1120m, 1105s, 1040s, 1030s, 985m, 935m, 910m, 880m, 850s, 830s, 820w cm^{-1}; ^{1}H NMR δ 7.01 (dd, 1H, J=5.3, 2.4 Hz, H_2), 6.81 (d, 1H, J=5.3 Hz, H_3), 5.20 (dd, 1H, J=2.4 Hz, J_{HF}=2.0 Hz, H_4)[23], 2.92 (brs, NH), 1.98 (d, 3H, $J_{Me,F}$=2.0 Hz, Me); ^{13}C NMR δ 147.5 (=CH), 144.9 (=CH), 74.4 (C-CH_3), 63.3 (CH), 16.5 (CH_3) [signals due to the aryl carbons were complicated by CF coupling]; ^{m}/z 229(50%) M^+, 228(50), 203(100), 202(80), 201(14), 200(10), 188(18), 187(28), 175(11), 151(22); observed accurate ^{m}/z 229.0503, calculated for $C_{11}H_7NF_4$ 229.0514.

The amine **(2b)** was prepared using a similar method to that described above from benzyne [generated *in situ* from 2-bromofluorobenzene (3.95 g; 22.6 mmol), n-butyllithium (2.5M in hexane; 9 ml)] and 1-trimethylsilyl-2-methylpyrrole (3.15 g; 20.5 mmol) to afford the product **(2b)** as a yellow oil (1.73 g; 56%). I.R. ν_{max} (CH_2Cl_2) 3020w, 2960w, 2915w, 2865w, 1600w, 1480w, 1445w, 1380m, 1350s, 1200m, 1150m, 1125w, 1090w, 1055s, 1030m, 1005m, 960m, 930w, 920w, 865s, 845s cm^{-1}; ^{1}H NMR δ 6.80-7.29 (m, 5H, aryl + H_3), 6.63 (d, 1H, J=6.0 Hz, H_2), 4.79 (d, 1H, J=3.0 Hz, H_4), 3.02 (brs, NH), 1.76 (s, 3H, Me); ^{13}C NMR δ 152.4 (aryl C), 151.6 (aryl C), 147.1 (=CH), 145.1 (=CH), 124.6 (aryl CH), 124.4 (aryl CH), 120.5 (aryl CH), 119.0 (aryl CH), 72.7 (C-CH_3), 65.6 (CH), 15.2 (CH_3); ^{m}/z 157(100%) M^+, 156(93), 131(25), 130(25), 129(24), 128(26), 127(14), 116(26), 115(21); observed accurate ^{m}/z 157.0891, calculated for $C_{11}H_{11}N$ 157.0892.

The amine (**2c**) was prepared similarly from dimethoxybenzyne [generated *in situ* from 1-chloro-2,5-dimethoxybenzene (7.10 g; 41.1 mmol) and n-butyllithium (1.6M in hexane, 26 ml)] and 1-trimethylsilyl-2-methylpyrrole (5.24 g; 34.2 mmol) to give a dark oil. Purification by flash chromatography on silica using a 99:1 mixture of diethyl ether:triethylamine) gave (**2c**) as yellow crystals, m.p. 56 - 57 °C (4.89 g; 66%). I.R. ν_{max} (CH_2Cl_2) 2960m, 2950w, 2915m, 2815m, 1490s, 1465m, 1435m, 1350m, 1240m, 1210m, 1180m, 1145m, 1075s, 1045s, 975w, 940m, 850m, 840m, 790m cm^{-1}; ^1H NMR δ 7.00 (dd, 1H, J=5.3, 2.4 Hz, H_3), 6.80 (d, 1H, J=5.3 Hz, H_2), 6.49 (s, 2H, aryl), 5.08 (d, 1H, J=2.4 Hz, H_4), 3.76 (s, 3H, OMe), 3.37 (s, 3H, OMe), 2.69 (brs, NH), 1.96 (s, 3H, Me); ^{13}C NMR δ 149.1 (aryl C), 147.9 (=CH), 147.6 (aryl C), 145.1 (=CH), 142.1 (aryl C), 140.9 (aryl C), 111.2 (aryl CH), 110.8 aryl (CH), 75.0 (C-CH_3), 62.9 (CH), 56.0 (OCH_3), 55.8 (OCH_3), 17.5 (CH_3); $^m/z$ 217(100%) M^+, 203(15), 202(87), 201(15), 188(12), 187(61), 186(14), 174(11), 159(15), 130(14); observed accurate $^m/z$ 217.1092, calculated for $C_{13}H_{15}NO_2$ 217.1091.

1-Trimethylsilyl-2-methylpyrrole

Potassium metal (5.70 g;0.15 mmol) was added in small pieces over a period of 15 min to a stirred solution of 2-methylpyrrole[24] (10.4 g; 0.13 mmol) in dry diethyl ether (45 ml) and dry benzene (20 ml) under nitrogen. The reaction mixture was stirred for 1 h and then heated at reflux for a further 5 h. The potassio-pyrrole slurry thus formed was cooled to 0°C and trimethylsilyl chloride (20 ml; 0.16 mmol) was added dropwise over 15 min. The reaction mixture was heated at reflux for 10 h and then filtered. After evaporation of the solvent under reduced pressure, fractional distillation of the residue afforded 1-trimethylsilyl-2-methylpyrrole (11.41 g; 58%) as a colourless oil b.p. 58 - 61°C (30 mm Hg). ^1H NMR δ 6.43 (m, 1H), 5.98 (m, 1H), 5.81 (m, 1H), 2.16 (s, 3H), 0.30 (s, 9H); observed accurate $^m/z$ 153.0967, calculated for $C_8H_{15}NSi$ 153.0974.

1-Methyl-1,2,3,4-tetrahydro-1,4-iminonaphthalene (7b)

1-Methyl-5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-iminonaphthalene (7c)

1-Methyl-5,6,7,8-tetrafluoro-1,2,3,4-tetrahydro-1,4-iminonaphthalene (7d)

Typically, a solution of (**2d**) (0.20 g; 0.87 mmol) in dry methanol (10 ml) was hydrogenated at atmospheric pressure in the presence of 5% Pd/C for 5h. The reaction mixture was filtered through celite and the solvent was removed under reduced pressure to yield (**2d**) as a colourless oil (0.19 g; 95%). I.R. ν_{max} (CH_2Cl_2) 2950m, 1710w, 1665w, 1490s, 1390m, 1365m, 1215w, 1180w, 1115m, 1065m, 1040m, 990m, 945w, 920w, 885w, 870m, 830m cm^{-1}; ^1H NMR δ 4.78(dd, 1H, J=4.5, J_{HF}=2.1 Hz, H_4), 2.36 (brs, NH), 2.14-2.27 (m, 1H, $H_{2/3}$exo), 1.88 (d, 3H, $J_{Me,F}$=1.1 Hz, Me), 1.76-1.85 (m, 1H, $H_{2/3}$exo), 1.28-1.47 (m, 2H, $H_{2,3}$endo); ^{13}C NMR δ 68.7 (C-CH_3), 58.1 (CH), 32.7 (CH_2), 28.5 (CH_2), 18.2 (CH_3) [signals due to the aryl carbons were complicated by CF coupling]; $^m/z$ 231(5%) M^+, 229(7), 204(11), 203(100), 202(66), 189(6), 187(7), 175(8); observed accurate $^m/z$ (M^+ - C_2H_4) 203.0352, calculated for $C_9H_5NF_4$ 203.0358.

Hydrogenation of a solution of (**2b**) (0.53 g; 3.37 mmol) in dry methanol (30 ml) as described above gave (**7b**) as a yellow oil (0.54 g; 99%). I.R. ν_{max} (CH_2Cl_2) 3020w, 2955s, 2875m, 1450s, 1380m, 1350w, 1335w, 1195w, 1170w, 1135w, 1115w, 1065w, 1035w, 1000m, 970w, 945m, 905w, 870m, 855m, 815m cm^{-1}; ^1H NMR δ 6.98-7.32 (m, 4H, aryl), 4.42 (d, 1H, J=4.5 Hz, H_4), 3.71 (brs, NH), 2.05-2.49 (m, 2H, $H_{2,3}$exo), 1.70 (s, 3H, Me), 1.14-1.35 (m, 2H, $H_{2,3}$endo); ^{13}C NMR δ 149.8 (aryl C), 148.5 (aryl C), 125.9 (aryl CH), 125.7 (aryl CH), 119.0 (aryl CH), 117.6 (aryl CH), 67.1 (C-CH_3), 60.6 (CH), 32.8 (CH_2), 29.0 (CH_2), 17.2 (CH_3); $^m/z$ 159(3%) M^+, 142(6), 141(5), 132(11), 131(100), 130(47), 117(9), 115(8); observed accurate $^m/z$ (M^+ - C_2H_4) 131.0736, calculated for C_9H_9N 131.0735.

Hydrogenation of a solution of (**2c**) (0.53 g; 2.44 mmol) in methanol (20 ml) as described above gave (**7c**) as a pale yellow oil (0.53 g; 99%). ^1H NMR δ 6.60 (s, 2H, aryl), 4.62 (d, 1H, J=4.5 Hz, H_4), 3.78 (s, 3H, OMe), 3.76 (s, 3H, OMe), 2.13-2.18 (m, 1H, $H_{2/3}$exo + brs, NH), 1.85 (s, 3H, Me), 1.70-1.78 (m, 1H, $H_{2/3}$exo), 1.27-1.41 (m, 2H, $H_{2,3}$endo); ^{13}C NMR δ 147.9 (aryl C), 146.5 (aryl C), 139.2 (aryl C), 138.2 (aryl C), 110.5 (aryl CH), 110.1 (aryl CH), 68.2 (C-CH_3), 57.6 (CH), 56.0 (OCH_3), 55.9 (OCH_3), 33.0 (CH_2), 28.8

(CH_2), 19.3 (CH_3); ^{m}/z 219(6%) M^+, 192(12), 191(100), 187(13), 177(12), 176(94), 161(17); observed accurate ^{m}/z 219.1258, calculated for $C_{13}H_{17}NO_2$ 219.1259.

^{15}N-Enriched Pyrrole[25]

A solution of barium hydroxide (125 g; 0.39 mol) in water (600 ml) was placed in a 2l r.b. flask fitted with a dropping funnel and a still-head and condenser for distillation. The receiving flask contained mucic acid (80 g; 0.38 mol) and was fitted with two dry-ice condensers in series to prevent any loss of ammonia. Ammonium sulphate (5% ^{15}N-enriched; 50 g; 0.37 mol) in water (150 ml) was added gradually from the dropping funnel and the liberated ammonia distilled over. The distillation flask was heated towards the end of the reaction to ensure that all the ammonia was driven over into the mucic acid. On completion of the distillation, the mixture in the receiving flask was thoroughly mixed, stirred to a smooth paste, and the water was distilled off. The ammonium mucate was dried and powdered, mixed with glycerol (100 ml) and left to stand overnight. Careful distillation over a free flame was continued until the distillate no longer showed oily droplets when treated with aqueous sodium hydroxide. The distillate was redistilled and the aqueous layer in the receiving flask was separated and returned to the distillation flask. Water (300 ml) was added and the distillation was repeated. This distillate was redistilled a second time. Finally, the various distillates were combined and redistilled. The fraction which boiled between 127 - 131°C was collected, dried over magnesium sulphate, and filtered to give pyrrole as a yellow oil (8.7 g, 40%; lit.[25] 37-40%). The ^{1}H NMR spectrum matched that of a standard sample exactly. The 5%-enriched pyrrole was diluted with natural-abundance pyrrole to produce a larger quantity of material at a level of 2% ^{15}N-enrichment.

^{15}N-Enriched N-Trimethylsilylpyrrole was prepared from enriched (2% ^{15}N) pyrrole and hexamethyldisilazane by the method of Fessenden and Crowe[26] in 56% yield, b.p. 71-78°C (60 mm Hg) [lit.[26] 150-151°C at atmospheric pressure]. ^{1}H NMR δ 6.70 (m, 2H), 6.25 (m, 2H), 0.35 (s, 9H).

^{15}N-Enriched 5,6,7,8-Tetramethyl-1,4-dihydro-1,4-iminonaphthalene (1a) was prepared using the method described in reference 1a [for compound (7a)] but using 2%-enriched N-trimethylsilylpyrrole (12.5 g; 0.045 mmol). The sample obtained after extraction of the reaction mixture with diethyl ether followed by drying and evaporation (4.4 g; 26%) was judged by NMR spectroscopy to be of satisfactory purity. ^{1}H NMR δ 6.96 (m, 2H), 5.06 (m, 2H), 3.00 (brs, NH), 2.20 (s, 6H), 2.10 (s, 6H).

^{15}N-Enriched 5,8-Dimethoxy-1,4-dihydro-1,4-iminonaphthalene (1c) was prepared as described in reference 1a [compound (7c)] using 2%-enriched N-trimethylsilylpyrrole (10.3 g; 0.074 mmol), 1-chloro-2,5-dimethoxybenzene (10.4 g; 0.074 mmol) and n-butyllithium (2.5M; 29.5 ml) in dry diethyl ether (160 ml). The product was purified by column chromatography on silica using a mixture of 2:1 diethyl ether: petrol(b.p. 40-60°C) saturated with ammonia to give 1.8 g of crystalline material, m.p. 81 - 82°C, which matched an authentic, natural-abundance sample in all respects.

^{15}N-Enriched 5,6,7,8-Tetramethyl-1,2,3,4-tetrahydro-1,4-iminonaphthalene (6a) and **5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-iminonaphthalene (6c)** were prepared by hydrogenation of amines **(1a)** and **(1c)** respectively in absolute ethanol over 10% Pd/C at atmospheric pressure as described in reference 1a [for compounds (8a) and (8c)]. Yields were essentially quantitative and ^{1}H NMR spectra were identical to those for non-enriched, authentic samples.

^{15}N-Enriched N-Methyl-5,6,7,8-tetramethyl-1,4-dihydro-1,4-iminonaphthalene (4a) and **N-Methyl-5,8-dimethoxy-1,4-dihydro-1,4-iminonaphthalene (4c)** were prepared from the corresponding 2%-enriched secondary amines **(1a)** and **(1c)** using the method described in reference 1a [for compounds (9a) and (9c)]. ^{1}H NMR spectra matched those of authentic, non-enriched compounds.

^{15}N-Enriched N-Methyl-5,6,7,8-Tetramethyl-1,2,3,4-tetrahydro-1,4-iminonaphthalene (9a) and **N-Methyl-5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-iminonaphthalene (9c)** were prepared by hydrogenation of **(4a)** and **(4c)** respectively using the method described in reference 1a for compounds (10a) and (10c). ^{1}H NMR spectra matched those of authentic, non-enriched compounds.

^{15}N-Enriched N-Chloro-5,8-dimethoxy-1,4-dihydro-1,4-iminonaphthalene (5c) and **N-Chloro-5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-iminonaphthalene (10c)** were prepared using sodium hypochlorite as described in reference 1b. The N-chloro-compounds were allowed to equilibrate thermally (invert) and the resultant dark oils were then stored at 0°C to minimise decomposition. The ^{1}H NMR spectra of the samples were in agreement with those described in reference 1b.

Diels-Alder addition of cyclopentadiene to (4d).

To the amine **(4d)** (1.0 g; 4.36 mmol) was added an excess of freshly distilled cyclopentadiene (1.43 g; 21.8 mmol). The mixture was stirred and heated in a sealed tube at 170°C for 16 h. The tube was allowed to cool, opened, and the contents dissolved in dichloromethane (40 ml). The amine product was extracted into aqueous acid (2M HCl) and the extracts were washed further with dichloromethane. The aqueous layer was basified with 2M NaOH and the product extracted into dichloromethane (3 x 20 ml). The combined extracts were dried and the solvent removed under vacuum. The product was washed through a short silica column using petrol (b.p. 40-60°C). Recrystallisation from acetone/diethyl ether (1:1) gave colourless crystals of **(12d)** (0.3 g; 23%), m.p. 112 - 115°C. Found: C, 65.21; H, 4.54; N, 4.72%. $C_{16}H_{13}NF_4$ requires C, 65.08; H, 4.43; N, 4.74%. ^{1}H NMR δ 6.00 (*t*, 2H), 4.11 (*t*, 2H), 2.84 (*t*, 2H), 2.18 (*t*, 2H), 1.81 (s, 3H), 1.72 (dt J=8 Hz, 1H), 1.48 (brd J=8 Hz, 1H) [Signals shown: *t* appeared as 2nd-order pseudo-triplets, J=1.5-2.0 Hz, but full analysis was not possible]. ^{13}C NMR δ 142.2 (complex aryl, $^1J_{CF}$≈250 Hz), 137.3 (complex aryl, $^1J_{CF}$≈250 Hz), 134.3 (=CH), 129.3 (complex aryl), 67.2 (CH), 53.1 (CH_2), 48.5 (CH), 44.4 (CH), 34.5 (CH_3). ^{m}/z 295 (M^+) 203, 188, 95; observed accurate ^{m}/z 295.0984, calculated for $C_{16}H_{13}NF_4$ 295.0984. Detailed evidence for the stereostructure shown will be given elsewhere.[9]

Diels-Alder addition of cyclohexadiene to (1d).

The amine **(1d)** (0.5 g; 2.32 mmol) and cyclohexadiene (0.93 g; 11.62 mmol) were heated in a sealed tube at 155°C for 15 h. The product was isolated as described above for **(12d)**. Chromatography over silica using petrol (b.p. 40-60°C) gave a crystalline sample of **(13d)** (0.34 g; 50%), m.p. 116 - 118°C. ^{1}H NMR δ 6.35 (dd J=4.8, 3.5 Hz, 2H), 4.56 (brs, 2H), 3.35 (brs, NH), 2.86 (brs, 2H,), 1.87 (brs, 2H), 1.45 and 1.18 (AA'BB' J_{gem}=7.3 Hz, 4H); ^{13}C NMR δ 139.5 (complex aryl, $^1J_{CF}$≈250 Hz), 139.0 (complex aryl, $^1J_{CF}$≈250 Hz), 134.2 (=CH), 129.3 (complex aryl), 63.3 (CH), 45.6 (CH), 33.6 (CH), 25.6 (CH_2). ^{m}/z 295(2%) M^+, 190(13), 189(100), 162(8). Detailed evidence for the stereostructure shown will be given elsewhere.[9]

Diels-Alder addition of cyclohexadiene to (4d)

The amine **(4d)** 1.5 g; 6.55 mmol) and cyclohexadiene (2.62 g; 32.0 mmol) were heated in a sealed tube overnight as described above. Following the standard work-up described for compound **(12d)**, the product was chromatographed on silica using petrol (b.p. 40-60°C) to give colourless crystals of **(14d)**, (0.31 g; 15%), m.p. 121 - 123°C. ^{1}H NMR δ 6.18 (dd J=4.8, 3.6 Hz, 2H,), 4.18 (brs, 2H), 2.72 (brs, 2H), 1.86 (s, 3H), 1.74 (brs, 2H), 1.36, 1.16 (AA'BB' J_{gem}=7.2 Hz, 4H); ^{13}C NMR δ 142.5 (complex aryl, $^1J_{CF}$≈250 Hz), 139.0 (complex aryl, $^1J_{CF}$≈250 Hz), 132.0 (=CH), 128.3 (complex aryl), 70.0 (CH), 46.9 (CH), 34.9 (CH_3), 33.2 (CH), 25.7 (CH_2). ^{m}/z 309(10%) M^+, 216(8), 204(10), 203(100), 200(8), 188(4); observed accurate ^{m}/z 309.1140, calculated for $C_{17}H_{15}NF_4$ 309.1141. Detailed evidence for the stereostructure shown will be given elsewhere.[9]

Hydrogenation of (12d)

The amine **(12d)** (0.146 g; 0.49 mmol) was dissolved in diethyl ether (25 ml) and hydrogenated over a 10% Pd/C catalyst using a balloon of hydrogen for 5 h. The catalyst was removed by filtration and the

sample was concentrated under vacuum and recrystallised from diethyl ether/acetone (1:1) to give colourless crystals of **(15d)** (0.123 g; 84%), m.p. 85 - 87°C. ^{1}H NMR δ 4.13 (brs, 2H), 2.29 (brs, 2H,), 2.02 (s, 3H), 1.81 (brd, J≈7.5 Hz, 2H), 1.77 (brs, 2H), 1.36 (brs, 2H), 1.29 (brd, J≈7.5 Hz, 2H). ^{13}C NMR: δ 129.2 (C, complex) [other aryl signals were complex due to CF coupling], 66.1 (CH), 47.7 (CH), 43.4 (CH_2), 39.2 (CH), 35.0 (CH_3), 25.0 (CH_2). ^{m}/z 297(8%) M^+, 216(4), 204(10), 203(100), 200(16); observed accurate ^{m}/z 297.1141, calculated for $C_{16}H_{15}NF_4$ 297.1140.

Hydrogenation of (14d)

The amine **(14d)** was hydrogenated as described above for the conversion of **(12d)** into **(15d)**. The product **(16d)** had m.p. 110 - 112°C. ^{1}H NMR δ 4.21 (t, J≈1.5 Hz, 2H), 2.03 (s, 3H), 1.97 (brd, J≈8 Hz, 2H), 1.77 (brs, 2H), 1.56 (m, 2H), 1.53 (s, 2H), 1.38 (brd, J≈7.5 Hz, 2H), 1.30 (brd, J≈7.5 Hz, 2H). ^{13}C NMR δ 142.8 (complex aryl, $^{1}J_{CF}$≈250 Hz), 138.9 (complex aryl, $^{1}J_{CF}$≈250 Hz), 127.9 (C), 69.0 (CH), 42.8 (CH), 35.0 (CH_3), 27.9 (CH), 27.0 (CH_2), 22.7 (CH_2). ^{m}/z 311(2%) M^+, 216(1), 204(8), 203(100), 188(2); observed accurate ^{m}/z 311.1297, calculated for $C_{17}H_{17}NF_4$ 311.1297.

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