^{13}C NMR SPECTRAL ANALYSIS OF α-AMINONITRILES

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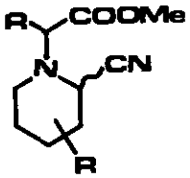
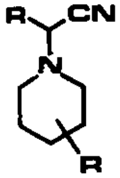
Abstract - A carbon-13 NMR spectroscopic study of α-aminonitriles derived from piperidines has been conducted. The substituent effects for cyano group in the nitrogen heterocycles is shown to obey strict regularities. The preferred conformation of a lone cyano group located to the nitrogen is found to be equatorial.

We have recently explored the preparation of the synthetically versatile iminium ion synthons, α-aminonitriles, derived from piperidinoacetic acid esters[1-4], and we have shown that both endocyclic and exocyclic nitriles of the types A and B, respectively, can be regioselectively generated from the same readily available precursors.

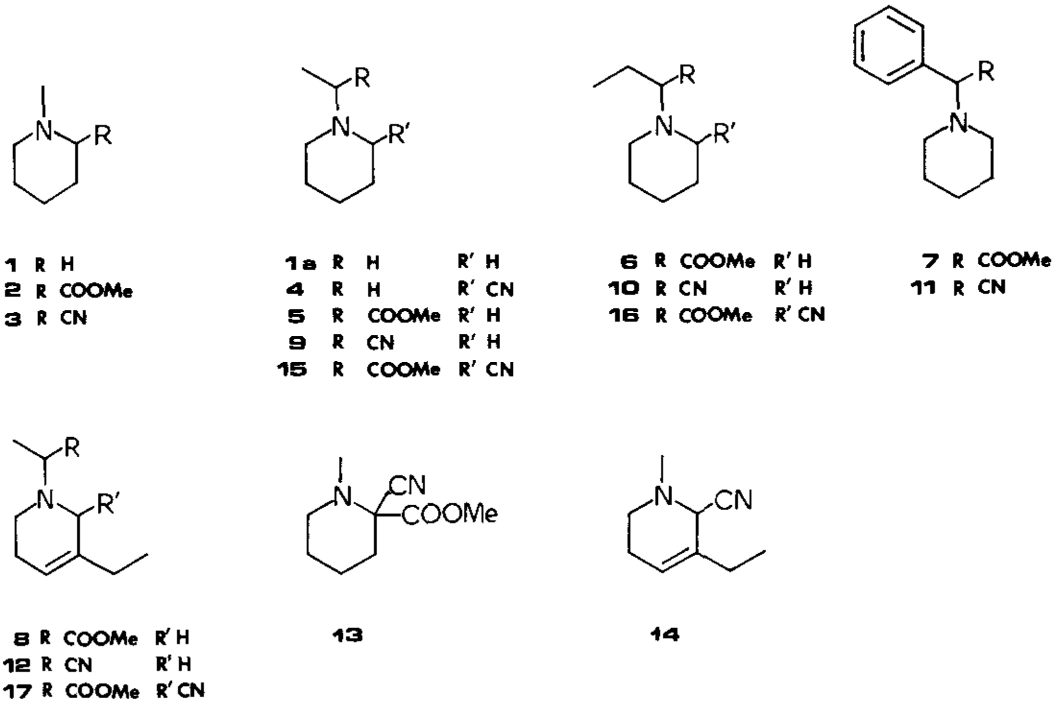


A



B

Having such an efficient synthetic method available we became interested in having at hand an accurate and rapid method for analysis of the title compounds. Furthermore, knowledge of the preferred conformations of these substituted nitrogen heterocycles would give a more profound picture of their reactions and also of the conformations of larger heterocyclic systems. With these presumptions in mind, it was evident that ^{13}C NMR spectroscopy would be the method of choice to study the questions outlined above.



1 R H
2 R COOMe
3 R CN

1a R H R' H
4 R H R' CN
5 R COOMe R' H
9 R CN R' H
15 R COOMe R' CN

6 R COOMe R' H
10 R CN R' H
16 R COOMe R' CN

7 R COOMe
11 R CN

8 R COOMe R' H
12 R CN R' H
17 R COOMe R' CN

13

14

Figure 1

The compounds studied are shown in Figure 1. Their syntheses have been reported in another paper.[3] The ^{13}C NMR spectra were recorded in $CDCl_3$ solutions on a JEOL JNM FX-60 Fourier transform spectrometer operating at 15.04 MHz. The chemical shifts are reported downfield (δ-scale) from the internal standard TMS=0.00. Other parameters have been reported in another study.[5] The assigned ^{13}C chemical shifts for compounds 1 to 14 are given in Table 1. The shift assignments are based on SFORD spectra obtained to determine the multiplicities of the peaks and on literature data[6] for simple non-cyanated piperidine derivatives. The chemical shifts for compounds 15 to 17 along with the observed δ values caused by substitution of hydrogen with cyano group at the endocyclic α position are given in Table 2.

Analysis of the spectra

Examination of Table 1 reveals that introduction of methoxycarbonyl group in the exocyclic α position (1a $\rightarrow$ 5) causes a high-field shift of 3ppm for the endocyclic α-carbons and leaves the other ring carbons virtually unaffected. This diamagnetic shift is due to increased γ-gauche effects exerted by the substituent (The same phenomenon can be observed between compounds 14 and 17 in Table 2). That the effect is due to steric effects and not to electronic effects, can be verified by comparing the chemical shifts of the ring carbons of 9, where the methoxycarbonyl group is replaced by nitrile, with those of 5: virtually no change can be seen between the ring carbons. The anisotropic effect should cause the ring α-carbons of 9 to experience a deshielding effect whereas in the ester 5 the effect should be of opposite sign, i.e. shielding. Inspection of the chemical shift values of the phenylglycine derivatives 7 and 11 shows that the aromatic ring has practically no effect on the piperidine ring carbon resonances. When the values of 8 are compared with those of 12, the observed chemical shift changes are not, however, large enough to give any substantial information.

Comparison of the δ values of 13 with those of 2 reveals that the addition of an extra nitrile substituent on the α-position causes, among other effects, the γ carbons (C-4 and C-6) to experience a diamagnetic shift of 3ppm. Although the shift effects of axial and equatorial methoxycarbonyl groups have previously been used successfully to distinguish between different stereostructures[7], the predominant conformation of 2 as having methoxycarbonyl group equatorial must be considered with caution.

Conformational analysis

As can be seen from Table 2, most of the signals are seen as doubled. The peaks arising from the same carbon atoms are of equal height, and very close to each other in the different isomers. As is evident from the structures of the compouns, the compounds studied are mixtures of diastereomers which naturally exhibit different spectral behaviours.

Comparison of the chemical shift values for 15 and 16 with those for 5 and 6 reveals that the mean substituent effects are those given in Table 3 where are also shown the literature data[6] for cyano-group induced substituent effects in cyclohexane derivatives in axial and equatorial cases.

TABLE 1. ^{13}C NMR data of compounds 1 - 14

C	1[a]	1a	2	3	4	5	6	7	8	9	10	11	12	13	14[b]
2	56.2	53.3	67.5	54.4	51.7	50.1	50.7	51.9	50.0	50.3	50.7	50.8	51.2	68.6	56.2
3	25.9	25.3	29.5	28.4	28.3	25.8	26.4	25.5	136.9	25.3	25.5	25.7	136.4	34.0	133.3
4	23.9	23.9	22.7	19.5	20.1	24.0	24.5	24.0	116.6	23.7	24.2	23.8	117.0	19.7	122.2
5	25.9	25.3	25.0	24.5	24.4	25.8	26.4	25.5	26.9	25.3	25.5	25.7	27.1	24.0	25.3
6	56.2	53.3	54.7	50.8	49.7	50.1	50.7	51.9	45.3	50.3	50.7	50.8	46.2	51.2	47.3
$N-CH_3$	46.4	-	44.1	44.0	-	-	-	-	-	-	-	-	-	41.4	42.3
1'	-	52.1	-	-	48.4	62.6	70.0	74.5	61.0	52.5	60.1	62.9	51.8	-	-
2'	-	11.3	-	-	11.7	14.2	22.5	-	13.9	16.8	23.8	-	16.6	-	-
3'	-	-	-	-	-	-	10.7	-	-	-	10.4	-	-	-	-
$\underline{C}OOCH_3$	-	-	173.7	-	-	172.8	172.8	171.8	172.2	-	-	-	-	168.1	-
$COO\underline{C}H_3$	-	-	51.5	-	-	50.5	50.7	51.4	50.8	-	-	-	-	53.4	-
endo-CN	-	-	-	116.0	115.7	-	-	-	-	-	-	-	-	113.4	116.1
exo -CN	-	-	-	-	-	-	-	-	-	117.2	116.9	115.5	117.0	-	-
α	-	-	-	-	-	-	-	-	25.5	-	-	-	25.3	-	26.7
β	-	-	-	-	-	-	-	-	11.2	-	-	-	11.6	-	11.8
Ar: *ipso*	-	-	-	-	-	-	-	135.8	-	-	-	134.5	-	-	-
o	-	-	-	-	-	-	-	128.4	-	-	-	128.5	-	-	-
m	-	-	-	-	-	-	-	128.0	-	-	-	128.5	-	-	-
p	-	-	-	-	-	-	-	127.7	-	-	-	127.7	-	-	-

[a] from ref. 12 [b] from ref. 13

TABLE 2 Observed ^{13}C NMR shifts for compounds **15**, **16** and **17**. The calculated $\Delta\delta$ values[a]

C	**15**	$\Delta\delta$[a]	**16**	$\Delta\delta$[a]	**17**	$\Delta\delta$[a]
2	50.2	+0.1	50.5	-0.2	52.2	+2.2
	49.8	-0.3	49.4	-1.3	51.6	+1.6
3	29.4	+3.6	29.8	+3.3	132.3	-4.6
	28.8	+3.0	29.4	+3.0	-	-
4	20.3	-3.7	20.6	-3.9	121.6	+5.0
	20.0	-4.0	20.2	-4.3	-	-
5	24.7	-1.1	24.8	-1.6	24.6	-2.3
	-	-	-	-	25.6	-1.3
6	45.5	-4.6	44.2	-6.5	41.0	-4.3
	46.0	-4.1	46.9	-3.8	42.7	-2.6
1'	60.6	-2.0	66.9	-3.1	59.0	-2.0
	61.5	-1.1	68.1	-1.9	60.2	-0.8
2'	14.2	0	21.4	-0.9	13.8	-0.1
	14.9	+0.9	22.3	-0.2	15.2	+1.3
3'	-	-	9.5	-1.2	-	-
	-	-	9.7	-1.0	-	-
$\underline{C}OOCH_3$	171.9	-0.9	170.9	-1.9	171.6	-0.6
	172.4	-0.4	171.3	-1.5	172.3	+0.1
$COO\underline{C}H_3$	51.0	+0.5	51.6	+0.9	50.7	-0.1
CN	117.1	-	117.0	-	116.6	-
	116.2	-	116.4	-	115.4	-
α	-	-	-	-	24.6	-0.9
β	-	-	-	-	10.8	-0.4

[a] The $\Delta\delta$ values were calculated according to the following formula :

For **15**: $\Delta\delta_k = \delta_k(\mathbf{15}) - \delta_k(\mathbf{5})$

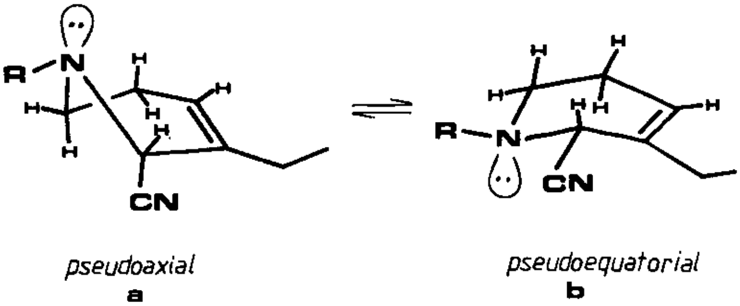
Similarly, the chemical shift values of **16** and **6**, and **17** and **8** were compared in pairs.

TABLE 3. Observed and literature[6] substituent increments for cyano group.

	ax	obs	eq
α	0	-0.4	+1
β	-1	+3.2	+3
γ^{CCC}	-5	-4.2	-2
γ^{CNC}	-5	-4.5	-2
δ	-1	-1.3	-2

The above data suggest that the cyano substituent is equatorially posed. The clearest support is expressed by the β-effect, which is distinctively positive (+3.2ppm). Interestingly, one can also notice that the γ-effects over C-C-C and C-N-C are of the same sign but unequal in magnitude. It is therefore tempting to assume that the effect of the nitrogen heteroatom is to enchance the substituent effect, especially to the γ-carbon, most plausibly through the assistance of the lone-pair electrons.

Analysis of the ^{13}C spectrum of the 2-cyano-1,2,5,6-tetrahydropyridine <u>17</u> is not quite straightforward: It is safe to assume that the alkyl substituent on the heterocyclic nitrogen will predominately exist equatorially.[11] On the other hand, the ring itself will adopt a half-chair conformation assumed to be the more stable ones[11]. The cyano group can adopt either pseudoaxial or pseudoequatorial position as depicted below:



In the case <u>a</u> where the cyano group is pseudoaxial, the transannular diaxial strain energy between the cyano group and the axial H-6_{ax} can be taken as 0.15 kcal/mol[8], or probably somewhat larger. The interaction $A^{(1,2)}$ strain[9,10] between the ethyl side chain and the equatorial hydrogen can be estimated as 0.25 kcal/mol[10]. On the other hand, in the conformer <u>b</u> with the cyano group equatorial, the $A^{(1,2)}$ strain can be regarded as negligible owing to the small radius of the cylindrically symmetric π-cloud of the cyano group. The pseudoaxial isomer would be higher by approximately 0.5 kcal/mol in energy, the pseudoequatorial isomer b being thus favored in a ratio of at least approximately 3:1, in conformity with the proposal of Johnson[10] for small groups involved in $A^{(1,2)}$ strained systems.

Since the compound exists in a uniform conformation regarding the cyano group, we can take advantage of the small (ca. -3.5ppm) γ-substituent effect over C-N-C and the positive α-effect as manifestations of pseudoequatorial position of the cyano group.

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