A Carbon-13 and Nitrogen-15 NMR Study of some Nitrogen Heterocycles

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A number of phenyl-substituted nitrogen heterocycles and the corresponding 2,6-diethylphenyl derivatives were examined by ^{13}C nmr in order to verify that the heterocyclic ring system was the same in both series. The heterocyclic ring carbon shifts did not differ substantially between the phenyl and 2,6-diethylphenyl derivatives for all systems except one, where substantial differences were also seen in the ^{15}N chemical shifts. Acetylated derivatives were prepared to confirm the cyclization mode in this latter case.

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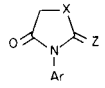
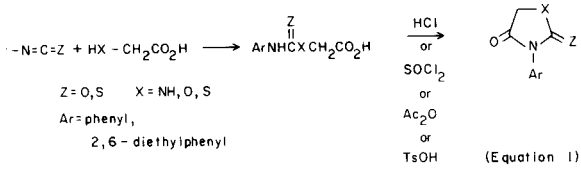
Introduction.

As part of a program to discover novel herbicides, a series of nitrogen heterocycles was chosen as a candidate for synthesis (1). The proposed compounds were of the following general structure:



Ar = phenyl, 2,6-diethylphenyl
X = NH, O, S
Z = NH, O, S

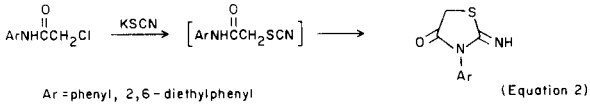
The general synthetic route which was employed for the preparation of the majority of these compounds was the cyclodehydration of the appropriate acyclic precursor (Equation 1):



Z = O, S X = NH, O, S
Ar = phenyl, 2,6-diethylphenyl

(Equation 1)

The two heterocyclic derivatives where X = S and Z = NH were prepared by cyclization of a different type of acyclic precursor (Equation 2):

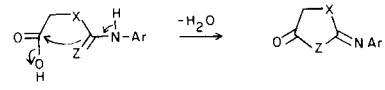


Ar = phenyl, 2,6-diethylphenyl

(Equation 2)

The synthesis of the phenyl-substituted compounds proceeded smoothly according to known procedures. The preparation of the 2,6-diethylphenyl-substituted compounds proved to be more difficult, requiring more vigorous reaction conditions and longer reaction times (1).

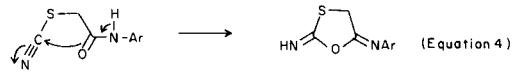
The difficulties encountered with the preparation of the 2,6-diethylphenyl series were initially ascribed to the steric hindrance caused by the two *ortho* substituents. The possibility also existed that these steric factors might have induced a different mode of cyclization of the acyclic precursors giving rise to another ring system (Equation 3):



(Equation 3)

Ar = 2,6-diethylphenyl

For the case of the acyclic precursor shown in Equation 2, the following would have resulted (Equation 4):



(Equation 4)

Ar = 2,6-diethylphenyl

During the preparation of this manuscript, a report appeared which described a similar problem of differentiating between two possible modes of cyclization in an analogous system (2). The authors chose to answer the question surrounding the identities of their reaction products by additional, less ambiguous syntheses. This report, however, describes a spectroscopic approach to this problem. In order to determine if the same mode of cyclization had occurred in the phenyl and 2,6-diethylphenyl series, ^{13}C nmr spectra were obtained. For the cases where X = NH and Z = O, ^{15}N spectra were also obtained.

EXPERIMENTAL

Proton-decoupled natural abundance ^{13}C spectra were obtained at 22.6 MHz and 35° on a Bruker WH-90 Fourier transform nmr spectrometer equipped with quadrature detection capability. All compounds were run in 10 mm O.D. tubes at an approximate concentration of 100 mg./ml. in DMSO-d_6 with internal TMS. A spectral width of 5000 Hz was digitized

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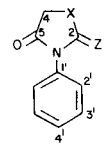
Table I

Carbon-13 Chemical Shifts (a) of 3-Phenyl Nitrogen Heterocycles

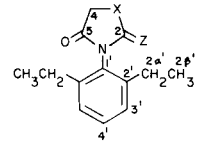


Compound	X	Z	C_2	C_4	C_5	C_1'	C_2'	C_3'	C_4'
1	NH	O	156.59	171.10	46.01	132.26	126.66	128.70	127.68
2	NH	S	183.31	171.98	49.00	133.45	128.54*	128.68*	128.35
3 (b)	$NCOCH_3$	O	153.00	168.31	47.81	131.24	127.00	128.86	128.51
4	S	O	171.80*	171.26*	34.14	133.34	127.79	129.06	128.84
5	S	S	203.48	173.90	36.92	135.47	128.57*	129.11	129.11
6	S	NH	158.43	171.37	33.55	134.91	128.49*	128.87*	128.27
7	O	O	155.10	170.39	68.36	131.32	126.44	129.00	128.60

(a) In ppm from TMS. Estimated accuracy ± 0.03 ppm. Asterisks indicate ambiguity of assignments. (b) CH_3, 24.16 ppm; acetyl CO, 167.42 ppm. The assignments of the acetyl CO and C_4 may be reversed.

Table II

Carbon-13 Chemical Shifts (a) of 3-(2,6-Diethylphenyl) Nitrogen Heterocycles



Compound	X	Z	C_2	C_4	C_5	C_1'	C_2'	C_3'	C_4'	$C_{2\alpha}'$	$C_{2\beta}'$
8	NH	O	150.69	168.38	47.58	132.40	141.03	126.09	127.60	24.22	14.40
9	NH	S	183.31	172.55	49.00	130.35	142.02	126.09	129.27	23.62	14.10
10 (b)	$NCOCH_3$	O	153.08	168.37	48.05	130.00	142.32	126.55	127.89	23.73	14.45
11	S	O	171.62*	171.48*	34.17	130.35	141.65	126.68	126.86	23.65	14.27
12	S	S	202.75	174.17	36.78	132.16	141.22	126.46	129.78	23.27	13.99
13	S	NH	157.40	171.64	33.55	132.37	141.60	126.28	129.08	23.63	14.08
14	O	O	155.10	170.93	68.95	130.19	142.10	126.82	127.57	23.73	14.48

(a) In ppm from TMS. Estimated accuracy ± 0.03 ppm. Asterisks indicate ambiguity of assignments. (b) CH_3, 24.24 ppm; acetyl CO, 168.02 ppm. The assignments of the acetyl CO and C_4 may be reversed.

Table III

Nitrogen-15 Chemical Shifts and $^1J_{NH}$ of Some Nitrogen Heterocycles (a)

Compound (b)	N_1	N_3
1	60.4 (98)	142.8
8	83.4 (92)	(c)

(a) Chemical shifts are in ppm from external aqueous $^{15}NH_4NO_3$. Positive shifts are downfield. Coupling constants, in parentheses, are in Hz. (b) Designations are as in Tables I and II. (c) Not observed.

in 8192 points with 0.5 Hz line broadening arising from exponential filtering. In general, a pulse delay of 5 seconds was used with a 53° radio-frequency pulse of 8.5 μ seconds.

Natural abundance ^{15}N nmr spectra were obtained at 9.12 MHz and 40° on the same instrument used for the ^{13}C spectra. Samples were run as saturated solutions (approximately 0.5 to 1.1*M*) in DMSO-d_6 using 15 mm tubes. A spectral width of 5000 Hz was digitized in 4096 points with 1 or 2 Hz of line broadening due to exponential filtering. A pulse delay of 10 or 20 seconds was used with a 56° pulse of 25 μ seconds. The proton-coupled spectra were obtained using a gated decoupling technique (3). The spectrum of **1** used for chemical shift measurement was obtained using standard proton decoupling. Chemical shifts were referenced to external 1*M* $^{15}NH_4NO_3$ contained in a 3 mm concentric capillary.

Results and Discussion.

In Tables I and II are the ^{13}C chemical shifts of a number of 3-aryl nitrogen heterocycles. Assignments were made on the basis of model compounds and substituent effects (4,5). With the phenyl derivatives, the two-carbon resonance furthest upfield was assigned to the *ortho* carbons (C_2'), although in several cases, the resonances for C_2' and C_3' are so close that such an assignment could not be made with confidence (5). Single-frequency off-

resonance decoupling was used to confirm the assignments of C_1' and C_4' in several cases.

The C_4 carbonyl resonances occur in the region 168.3 to 174.2 ppm. The chemical shift of C_2 varies greatly depending on the nature of X and Z. When Z = O, C_2 occurs in the 150-155 ppm region for all derivatives except when X = S, in which case the shift is about 172 ppm. When Z = S, C_2 occurs at about 183 ppm for X = NH and at about 203 ppm for X = S. When Z = NH and X = S, C_2 appears at about 158 ppm.

As expected, the position of C_5 is a sensitive function of X and depends only slightly on Z. When X = NH or $NCOCH_3$, C_5 resonates between 46 and 49 ppm. When X = S, C_5 occurs in the range 33 to 37 ppm. The highest shift value for C_5 (69 ppm) occurs when X = O.

The chemical shifts of the heterocyclic ring carbons of the 2,6-diethylphenyl derivatives are in close agreement with the corresponding values of the phenyl compounds, except for structures **1** and **8**. The very close agreement of the heterocyclic ring carbon chemical shifts in the last six pairs of compounds is strong evidence that, in each case, the same mode of cyclization occurred. In the pair **1** and **8**, the differences for a given carbon are substantially larger than for the same carbon in any of the other pairs of compounds. However, the difference between **1** and **8** is not so large as to preclude the same heterocyclic ring structure for these two compounds.

In order to shed additional light on this problem, natural abundance ^{15}N nmr spectra were obtained for **1** and **8**. The chemical shifts listed in Table III are in the ranges expected, based on comparison with the spectra of model compounds (6,7). The data are not consistent with the alternative ring structure, since the C=N-Ar nitrogen would be expected to occur at somewhat lower field (8). However, a large difference still occurs between **1** and **8** for the ^{15}N shifts of N_1.

In order to resolve the existing ambiguity, two additional compounds were prepared. The N-acetyl derivatives **3** and **10** were synthesized from the open chain precursors, and by the ^{13}C nmr criterion, have the same heterocyclic ring. Compounds **1** and **8**, when acetylated, gave derivatives whose ^{13}C spectra were identical to those of **3** and **10**, respectively. Therefore, unless some rearrangement occurred during acetylation of **1** and **8**, which is unlikely, these compounds do indeed possess the same heterocyclic ring.

It is difficult to explain the ^{13}C and ^{15}N shift differences of the heterocyclic ring atoms in **1** and **8**. While the presence of *ortho* substituents is expected to affect the average dihedral angles between the two rings, this same factor is operative in the other pair of compounds as well. If the *ortho* ethyl groups were significantly affecting the conformation of the heterocyclic ring, larger changes might be expected in other cases, particularly where Z is sulfur, a larger atom than oxygen. It is possible that the solvation of the heterocyclic ring is affected by the presence of the ethyl substituents. However, larger shift differences in the other pairs would also be expected.

One possibility that has been investigated is a difference in the degree of enolization between **1** and **8**. These two derivatives are the only ones reported in this study which possess a proton capable of enolization with the C_2 carbonyl moiety. If the proton exchange rate is fast, and the two tautomers exist to largely different extents in the two componds, the ^{13}C and ^{15}N data could be rationalized.

Measurement of $^1J_{NH}$, the one bond nitrogen-hydrogen coupling, should provide evidence for the existence of different equilibria between rapidly exchanging tautomers in the two cases **1** and **8**. Previous studies have correlated the value of $^1J_{NH}$ with degree of enolization of some Schiff bases derived from β-diketones and related compounds (9-11). As the equilibrium is shifted to the enolic tautomer, $^1J_{NH}$ is reduced.

In Table III are the measurements of $^1J_{NH}$ for **1** and **8** in DMSO-d_6 at 40°. A reduction of $^1J_{NH}$ from 98 to 92 Hz is seen upon going from **1** to **8**, indicating that a slight shift in the tautomeric equilibrium might have occurred. However, this difference does not appear to be sufficient to account for the 6 ppm difference in the chemical shift of C_2 between **1** and **8**. If it is assumed that **1** is 100% keto form, then **8** exists in DMSO-d_6 as a 94:6 mixture of the keto:enol forms as indicated by the reduction of $^1J_{NH}$ (9-11). On this basis, the predicted chemical shift for C_2 in the pure enolic form is about 57 ppm, a value which is totally unrealistic for this sp^2 hybridized carbon.

Finally, there exists the possibility that a transannular interaction between N_1 and C_4 could account for the shift difference observed in **1** and **8**. However, a similar shift difference would also be expected in the corresponding 2-thio derivatives, **2** and **9**. Furthermore, a recent report claims that transannular interactions between electron-donating groups and electron-withdrawing groups have been demonstrated for eight-, nine- and ten-membered rings. No transannular interactions have been shown to exist in smaller or larger rings (12).

For now, the differences in the spectra of **1** and **8** must remain unexplained.

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