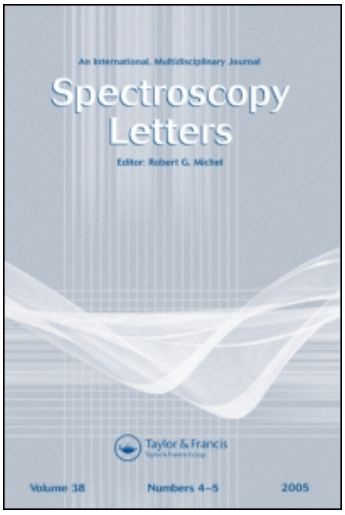

Spectroscopy Letters
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597299

NMR Studies of Drugs: Antipyrine and Analogs. II. ^{1}H and ^{13}C Chemical Shift Dispersion as Conformation Indicator for the *N*-Phenyl Ring.

Kunisi S. Venkatasubban[a]; Robert Rothchild[bc]
[a] Department of Natural Sciences, University of North Florida, Jacksonville, FL [b] Department of Science, The City University of New York, John Jay College of Criminal Justice, New York, NY [c] The Doctoral Faculty, The Graduate School and University Center, City University of New York,

To cite this Article Venkatasubban, Kunisi S. and Rothchild, Robert(1997) 'NMR Studies of Drugs: Antipyrine and Analogs. II. ^{1}H and ^{13}C Chemical Shift Dispersion as Conformation Indicator for the *N*-Phenyl Ring.', Spectroscopy Letters, 30: 8, 1685 — 1697
To link to this Article: DOI: 10.1080/00387019708006752
URL: http://dx.doi.org/10.1080/00387019708006752

SPECTROSCOPY LETTERS, 30(8), 1685-1697 (1997)

NMR STUDIES OF DRUGS: ANTIPYRINE AND ANALOGS. II. ^{1}H AND ^{13}C CHEMICAL SHIFT DISPERSION AS CONFORMATION INDICATOR FOR THE N-PHENYL RING.

Key Words: Nuclear magnetic resonance; Steric hindrance; Conformational analysis; Conjugation; 1,2-dihydro-1,5-dimethyl-2-phenyl-3H-pyrazol-3-one.

Kunisi S. Venkatasubban[a]* and Robert Rothchild[b,c]*

a) University of North Florida, Department of Natural Sciences, 4567 St. John's Bluff Road South, Jacksonville FL 32224-2645; b) The City University of New York, John Jay College of Criminal Justice, Department of Science, 445 West 59th Street, New York NY 10019-1128; c) The Doctoral Faculty, The Graduate School and University Center, City University of New York.

ABSTRACT

A potentially useful simple method is proposed to determine whether the N-phenyl rings in the analgesic drug, antipyrine (and analogs), preferentially exist in a conformation which is approximately coplanar with, or is perpendicular to, the five-membered heterocyclic rings. The method is based on the magnitude of "spectral dispersion," that is, the degree of NMR chemical shift differences for the proton and the protonated carbon signals of the N-phenyl. A narrow range of chemical shifts is considered suggestive of a preferred perpendicular conformation, which reduces mesomeric effects of conjugation and minimizes steric hindrance with nearby groups. Representative chemical shift data for model compounds are presented.

* To whom correspondence should be sent at the University of North Florida (for K.S.V.) or John Jay College (for R.R.)

INTRODUCTION

The preceding paper (1) has discussed our studies of the important analgesic drug, antipyrine, 1a, in which achiral and chiral lanthanide shift reagents (LSR) were employed in attempts to evaluate the conformation of the N-phenyl ring, i.e., to determine whether "perpendicular" or "coplanar" conformations are preferred for the N-phenyl and five-membered heterocyclic rings. Rapid phenyl rotation in antipyrine and related systems could lead to a fast exchange limit (FEL) system if the phenyl rotation rate is high relative to the timescale of the NMR LSR experiment. In evaluating NMR data for various analogs of antipyrine, we found evidence for trends in the ^{1}H and ^{13}C NMR spectra that suggest a potentially useful and simple method to distinguish preferred phenyl conformations (i.e., coplanar or perpendicular) even if phenyl rotation is fast. In particular, this method could be useful in fast phenyl rotation regimes where LSR approaches would be ambiguous. Structures of these compounds are summarized in Figure 1.

In these compounds, coplanarity of the N-phenyl and the five-membered heterocyclic rings would be expected to maximize conjugation by allowing the p orbitals in the two rings to be parallel; resonance stabilization should result. However, this fully coplanar conformation would maximize steric hindrance, especially the non-bonded repulsions between the phenyl ortho protons with the carbonyl oxygen (on one side) and the N-CH_3 group (on the other side). Twisting of the N-phenyl to a perpendicular conformation would minimize steric repulsions but would sacrifice resonance stabilization. If conjugation is broken in the "perpendicular phenyl" conformation, different chemical shift values might be expected for the N-phenyl group relative to the shift values in a "coplanar phenyl" system where mesomeric effects might be significant.

EXPERIMENTAL

NMR data obtained here followed procedures described earlier (1,2), or was derived from literature values.

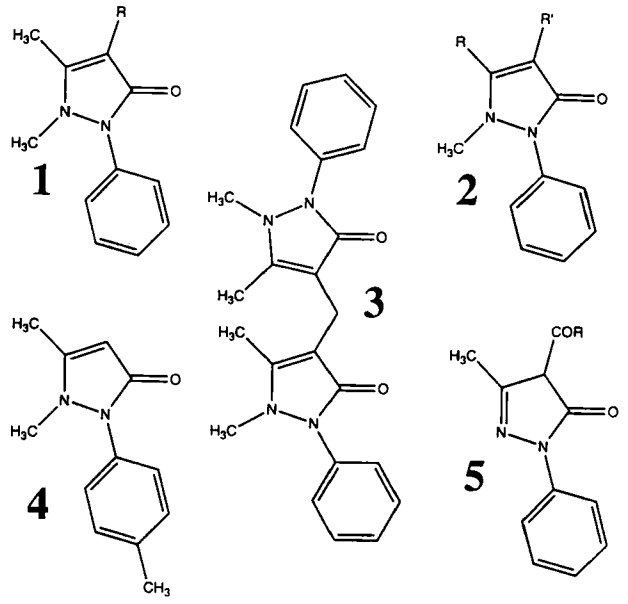

Fig. 1. Structures of compounds in Table 1. Antipyrine, 1a[R=H]; aminopropylon, 1b [R=-NHCOCH(CH_3)N(CH_3)$_2$]; 4-hydroxyantipyrine, 1c [R=OH]; ampyrone, 1d [R = NH_2]; aminopyrine, 1e [R = N(CH_3)$_2$]; 4-acetamidoantipyrine, 1f [R=-NHCOCH_3]; 4-antipyrinecarboxaldehyde, 1g [R = -CHO]; famprofazone, 2 [R= -CH_2N(CH_3)CH(CH_3)$CH_2C_6H_5$; R'= -CH(CH_3)$_2$]; 4,4'-diantipyrylmethane monohydrate, 3; 2,3-dimethyl-1-(4-methylphenyl)-3-pyrazolin-5-one, 4; 4-acetyl-2,4-dihydro-5-methyl-2-phenyl-3H-pyrazol-3-one monohydrate, 5a [R = CH_3]; 2,4-dihydro-5-methyl-2-phenyl-4-propionyl-3H-pyrazol-3-one, 5b [R = -CH_2CH_3]; 2,4-dihydro-5-methyl-2-phenyl-4-trichloroacetyl-3H-pyrazol-3-one, 5c [R = -CCl_3].

DISCUSSION

A recent extensive compilation of Fourier transform NMR data offered a relatively consistent set of 300 MHz ^{1}H and 75 MHz ^{13}C spectra which included numerous compounds to serve as antipyrine analogs and model compounds (3). These spectra, while unassigned, provided ^{1}H spectra (from which chemical shifts could be estimated to $\pm$0.02 ppm) and ^{13}C spectra (with broadband proton decoupling) which included APT parity

information. The attached proton test, APT, usually permits a clear distinction to be made between methine and methyl carbons, on the one hand, and methylenes and unprotonated carbons, on the other (3,4). For designated carbons in the N-phenyl spectral region, we could rather confidently identify the ortho (2',6'), meta (3',5'), and para (4') methine carbons without any further assignments, and without recourse to chemical shift arguments. In the ^1H NMR spectra, the N-phenyl ortho, meta and para signals were often unambiguously assignable if sufficient spectral dispersion was present, with the 2H intensity gross doublet (d) assignable to the ortho protons, the 2H gross triplet (t) to the meta protons, and the 1H gross triplet to the single para proton.

Table 1 summarizes relevant ^1H and ^{13}C NMR data in $CDCl_3$. The ^1H chemical shift values for antipyrine, 1a, famprofazone, 2, and aminopropylon, 1b, that appear in Table 1 were obtained from 200 MHz spectra in our laboratories. At this field strength, the N-phenyl resonances are insufficiently resolved to allow direct chemical shift assignments. The tabulated values for antipyrine (1) and famprofazone (2) are the average of extrapolated values derived from spectra with added lanthanide shift reagents (LSR), $Eu(FOD)_3$ and $Eu(HFC)_3$. Values for aminopropylon were extrapolated from spectra with the added LSR, $Eu(FACAM)_3$. For antipyrine, the extrapolated values agreed within 0.02 ppm with values estimated directly from the 300 MHz spectra of Ref. 3. For each compound, the ^1H shifts and ^{13}C shifts are simply listed in order from higher to lower field. No attempt is made to explicitly assign and separately distinguish the ortho, meta and para carbons of the N-phenyl, since only the magnitude of the dispersion among these signals ("spectral spread") is relevant in our subsequent discussion. For the proton signals, where sufficient spectral dispersion is obtained (in the published 300 MHz spectra), the ortho, meta and para protons of the N-phenyl may be separately assigned directly. Where values were considered tentative due to overlapped multiplets in the 300 MHz ^1H spectra, this is indicated. One compound is included, 2,3-dimethyl-1-(4-

methylphenyl)-3-pyrazolin-5-one, 4, with a substituted N-aryl group, for comparison purposes; we have not attempted to determine specific chemical shifts for this p-tolyl group for the aryl carbons and protons because of the methyl substitution.

The $\Delta\delta$ values in Table 1 represent the "spectral spread," or the total dispersion in the chemical shifts for the N-phenyl protons or protonated carbons. For the protons, the $\Delta\delta$ values represent maximum shift differences between estimated centers of the ortho, meta and para multiplets, where directly observable, or differences in the extrapolated shift values for the three compounds noted above. For the carbons, the $\Delta\delta$ values reflect the spectral dispersion for the proton-bearing N-phenyl carbons (ortho, meta, para).

The compounds in which the N-phenyl is expected to be most severely hindered due to buttressing effects from both the carbonyl and the proximal N-CH_3, i.e., compounds 1,2,3, show relatively narrow spectral spread for both ^1H and ^{13}C shifts of the N-phenyl ortho, meta, and para signals. The ^1H $\Delta\delta$ ranges from ca. 0.10-0.22 ppm, and the ^{13}C $\Delta\delta$ from 2.67-6.26 ppm, with mean values of about 0.17 (for nine values) and 4.98 ppm (for seven values). We estimate the errors in determining the $\Delta\delta$ ranges as ca. 0.03 ppm for ^1H and ca. 0.2 ppm for ^{13}C.

In contrast, the three compounds 5 are antipyrine analogs in which the N-CH_3 group is not present. Hindrance of the N-phenyl in these compounds should be much less, potentially allowing for coplanarity of the N-phenyl and the five-membered heterocyclic ring to gain the stabilization of more resonance delocalization. For the three less hindered compounds, $\Delta\delta$ (^1H) is an average of 0.52 ppm (range from 0.46-0.56) and $\Delta\delta$ (^{13}C) exhibits a mean value of 8.17 ppm (range 7.63-8.49). For ^1H and ^{13}C, there is no overlap of $\Delta\delta$ values between the two groups of compounds. The $\Delta\delta$ (^1H) has a mean value about three times greater in the less hindered series than in the more hindered series, and the maximum observed $\Delta\delta$ (^1H) value in the more hindered series, i.e., 0.22 ppm, is less than half the lowest value in the less hindered series, i.e., 0.46 ppm.

Table 1. Summary of N-phenyl ^{1}H and ^{13}C NMR chemical shifts for antipyrine, analogs and model compounds (in ppm). "Spectral spread" values ($\Delta\delta$, ppm) are shown for ^{1}H and ^{13}C signals. (Data from $CDCl_3$ solution.)

Compound name	Entry number	^{1}H NMR	$\Delta\delta(^{1}H)$	^{13}C NMR	$\Delta\delta$ (^{13}C)
Antipyrine (notes 1,2)	2,1442B	7.28(m, para)		124.17	
		7.38(m, ortho)		126.46	
1a		7.45(m, meta)	0.17	129.04	4.87
Famprofazone (note 1)		7.27(m, ortho)			
		7.33(m, para)			
2		7.42(m, meta)	0.15		
Aminopropylon (note 3)		7.31(m, para)			
		7.44(m, ortho)			
1b		7.46(m, meta)	0.15		
4-Hydroxy-antipyrine	2,1443B	7.23(1H,m,para)		123.54	
		7.42(4H, approx.		126.35	
1c		singlet)	0.19	128.97	5.43
4-Amino-antipyrine	2,1443C	7.22(1H,t,para)		122.66	
		7.44(4H,m)		125.70	
(AMPYRONE)			0.22	128.92	6.26
1d					
4-Dimethylamino-		ca.7.22(1H,m,para)		123.03	
antipyrine	2,1444A	ca.7.4(4H,m)	0.18	125.75	
(AMINOPYRINE)				128.85	5.82
1e					
4-Acetamido-antipyrine	2,1445B	7.34(3H,m)		124.74	
		7.44(2H,t, meta)	0.10	127.19	
1f				129.24	4.50
4-Antipyrine-carboxaldehyde	2,1445c	7.29(2H,d, ortho)		126.99	
		7.42(1H,t, para)		129.00	
1g		7.50(2H,t, meta tentative)	0.21	129.66	2.67

Notes to Table 1: Compound names may be non-systematic names as given in The Aldrich Library of ^{13}C and ^{1}H FT NMR Spectra (Ref. 3) or The Merck Index (12th ed.) (Ref. 5). Tabulated values derived from Ref. 3 except as noted. See Results and Discussion. The "Entry Number" refers to the spectrum number in Ref. 3. The underlined number and letter (e.g., 1a) given in the "Compound Name" column refer to the specific compound structure as shown in Figure 1. Notes: (1) Extrapolated ^{1}H shift values from 200 MHz spectra with added $Eu(FOD)_3$ and $Eu(HFC)_3$. (2) The ^{1}H shift values from Ref. 3 were (ppm): 7.27 (1H,t,para); 7.36 (2H, d, ortho); 7.43 (2H, t,meta); $\Delta\delta$=0.16. (3) Extrapolated ^{1}H shift values from 200 MHz spectra with added $Eu(FACAM)_3$. Full multiplet width without LSR ca. 7.23-7.50 ppm.

Table 1 (continued)

Compound name	Entry number	^{1}H NMR	Δδ (^{1}H)	^{13}C NMR	δ(^{13}C)
4,4'-Diantipyryl-methane monohydrate 3	2,1443A	7.23(1H,t,para) 7.39(4H,m) (tentative)	0.16	123.62 125.98 128.95	5.33
2,3-Dimethyl-1-(4-methylphenyl)-3-pyrazolin-5-one 4	2,1442C	7.23(4H,s)		124.59 129.71	(5.12)
4-Acetyl-2,4-dihydro-5-methyl-2-phenyl-3H-pyrazol-3-one monohydrate 5a	2,1444B	7.27(1H,t,para) 7.42(2H,t,meta) 7.82(2H,d,ortho)	0.55	120.52 126.46 129.01	8.49
2,4-Dihydro-5-methyl-2-phenyl-4-propionyl-3H-pyrazol-3-one 5b	2,1444C	7.26(1H,t,para) 7.43(2H,t,meta) 7.82(2H,d,ortho)	0.56	120.62 126.44 129.00	8.38
2,4-Dihydro-5-methyl-2-phenyl-4-trichloroacetyl-3H-pyrazol-3-one 5c	2,1445A	7.34(1H,t,para) 7.48(2H,t,meta) 7.80(2H,d,ortho)	0.46	121.51 127.49 129.14	7.63
Acetanilide	2,1360B	7.02(1H,t,para) 7.29(2H,t,meta) 7.60(2H,d,ortho)	0.58	118.90 122.83 128.51	9.61
1-Phenyl-2-pyrrolidinone	2,1432B	7.12(1H,t,para) 7.35(2H,t,meta) 7.59(2H,d,ortho)	0.47	119.80 124.34 128.70	8.90
1-Phenyl-piperidine	2,455C	6.80(1H,t,para) 6.92(2H,d,ortho) 7.23(2H,t,meta)	0.43	116.45 119.08 128.91	12.46
Aniline	2,451A	6.62(2H,d,ortho) 6.73(1H,t,para) 7.12(2H,t,meta)	0.50	115.01 118.39 129.19	14.18
N,N-Dimethyl-aniline	2,454C	6.71(3H, approx. t, ortho, para) 7.22(2H,t,meta)	0.51	112.59 116.56 128.98	16.39

Comparisons of NMR data for other "less hindered" N-phenyl compound analogs, where the 2p orbital on the nitrogen is expected to be near-parallel with the p orbitals of the phenyl, were also considered. Though these compounds are no longer as closely analogous to antipyrine as compounds 1-5, we were nevertheless interested in examining effects of the "coplanar" systems upon the N-phenyl chemical shifts. The Table 1 entry for acetanilide shows a $\Delta\delta$ (^{1}H) value fully consistent with the values seen for the less hindered compounds, 5, supporting "coplanarity" of the N-phenyl in this group. The relative chemical shifts for the ortho, meta and para protons is also consistent for all four compounds. Since secondary amides are usually considered to favor an anti conformation of the HNCO moiety, the phenyl and the carbonyl oxygen would presumably be syn in acetanilide as in all of the amide compounds in Table 1. In particular, this conformation has been reported to predominate for acetanilide to the extent of 99.9% (in pyridine) and >99% (in $CDCl_3$ at -20°) (6). The slightly higher field positions for the N-phenyl protons of acetanilide may reflect more overall mesomeric electron release from the nitrogen to the aromatic ring. In compounds 5, somewhat less shielding of the N-phenyl protons may be due to the influence of the N=C group. Similar arguments apply to $\Delta\delta$ (^{13}C) for acetanilide and compounds 5. (We have interpreted the published spectra for compounds 5 as consistent with a single enol structure, presumably resulting from enolization toward the acyl [rather than the amide] carbonyl, to give essentially one isomer, stabilized by intramolecular H-bonding. This conclusion is based on numbers of ^{13}C signals and APT parity results for 5a,b,c and the presence of low field ^{1}H signals for 5a,c.)

The Table 1 entries for 1-phenyl-2-pyrrolidinone also show ^{1}H and ^{13}C $\Delta\delta$ values fully consistent with the "less hindered" series; the lactam structure of this compound unambiguously defines a syn orientation of the N-phenyl and carbonyl groups. N-Phenylpiperidine represents a tertiary amine in which ring coplanarity is expected since major steric hindrance is absent.

Although it differs significantly from all the previous entries in the Table by not being an amide, it has a ^1H $\Delta\delta$ value quite within the range of the (presumed) coplanar amides. Its ^{13}C $\Delta\delta$ is relatively large. The average ^1H and ^{13}C chemical shift values for 1-phenylpiperidine suggest somewhat greater shielding (because of higher field shift values) than for the amides, consistent with greater mesomeric electron release to the N-phenyl from the amine versus the amides. This also seems evident for the last two entries in Table 1, aniline and N,N-dimethylaniline. Both of these compounds would be considered relatively unhindered "coplanar" systems. Despite rather dramatic structural differences between these two compounds (which do not have a carbonyl on nitrogen) and the other entries of Table 1, the same generalization is seen to apply; the two anilines both exhibit much larger $\Delta\delta$ values for ^1H and ^{13}C than the more hindered compounds 1-4. This might suggest a certain robustness in the applicability of these general observations.

A higher field NMR spectrometer would be especially desirable to measure ^1H $\Delta\delta$ for these N-phenyl compounds, in order to achieve a near first order spectrum of the aryl protons with freedom from accidental overlaps. This would avoid the need for the more laborious estimation of the N-phenyl proton shifts derived from LSR-shifted spectra by extrapolation to zero for the [LSR]/[substrate] molar ratio.

The method suggested here for judging planar versus perpendicular N-phenyl conformation in the numerous medicinal compounds related to antipyrine by use of a "spectral spread" measurement would seem to offer major advantages to the LSR-based technique detailed in the preceding accompanying paper (1). We had first explored the use of an achiral LSR, $Eu(FOD)_3$, with the achiral substrate, antipyrine, 1a. If we had seen two different signals for the ortho protons, this would have suggested an SEL coplanar system. If the N-phenyl of 1a was in an orthogonal conformation and SEL regime, the use of chiral LSR, e.g., $Eu(HFC)_3$, might have rendered the ortho positions anisochronous. (These positions are enantiotopic by

internal comparison but become diastereotopic in a chiral environment, as in a bound complex with chiral LSR.) Separated ortho signals with added chiral LSR, but not with achiral LSR, would be consistent with the SEL orthogonal system. However, there are at least three severe limitations on the LSR-based analysis. Chiral LSRs sometimes, but not always, elicit enantiomeric shift differences from nuclei that are enantiotopic by internal comparison (7). Lanthanide-induced line broadening can make clear assignments impossible (7,8). Rapid N-phenyl rotation on the timescale of the NMR LSR experiment can result in an FEL system in which the ortho signals would give a single resonance for either coplanar or perpendicular N-phenyl conformations.

The virtues of the NMR "spectral spread" method proposed here may be twofold. Firstly, it represents a technique for judging the N-phenyl conformation in solution. Secondly, we can consider an "intrinsically shorter experimental timescale" for these simple chemical shift measurements than for LSR-derived experiments. [In the LSR experiments, chemical exchange occurs between free unbound substrate and the bound complex. Large chemical shift differences, $\Delta\nu$, ca. 5-10 ppm for protons near the LSR binding site, e.g., the ortho protons, are not unusual for LSRs such as $Eu(FOD)_3$ or $Eu(HFC)_3$. On a 7 Tesla NMR, this corresponds to a $\Delta\nu$ of 1500-3000 Hz. Very rapid N-phenyl rotation would then be required to give a single set of sharply averaged resonances of the FEL regime. If the rapid rotation does not obtain, severe line broadening of intermediate exchange rates can result. In contrast, the simple chemical shift measurement without LSR involves much smaller $\Delta\nu$. Chemical shift differences for N-phenyl protons for coplanar versus perpendicular conformations may amount to only ca. 0.3 ppm, for a $\Delta\nu$ of 100 Hz or less (at 7 Tesla). This is much more likely to lead to sharp lines for the FEL regime than in the LSR experiment, since the N-phenyl can rotate much more slowly and still give FEL spectra. With observation of the sharp resonances of an FEL system,

experimental measurement becomes much easier for the "spectral spread" approach (9).]

CONCLUSIONS

We have presented here selected ^{1}H and ^{13}C NMR data for the N-phenyl moiety of antipyrine and numerous analogs and model compounds. The chemical shifts for the ortho, meta and para protons and carbons of this group appear to fall into two distinct ranges depending on whether the N-phenyl is: (a) very hindered, by being flanked by proximal syn carbonyl and N-methyl groups (as in antipyrine and the analogs 1-4), or (b) less hindered, with crowding only by a syn carbonyl but not by a vicinal N-methyl group (as in compounds 5 and the model acetanilide). The "spectral spread" separating the ^{1}H signals, $\Delta\delta$, was ca. 0.10-0.22 ppm (mean value 0.17 ppm, N=9) and for the ^{13}C signals was ca. 2.67-6.26 ppm (mean = 4.98 ppm, N=7) for the set of more hindered compounds. For the less hindered compounds, 5, the "spectral spread," $\Delta\delta$, was ca. 0.46-0.56 ppm (mean = 0.52 ppm, N=3) for protons and 7.63-8.49 ppm (mean 8.17 ppm, N=3) for the carbon shifts. The model acetanilide, with a relatively unhindered N-phenyl (similar to 5), showed $\Delta\delta$ values of 0.58 and 9.61 ppm for ^{1}H and ^{13}C, respectively, clearly comparable to 5. We believe that these larger "spectral spreads," $\Delta\delta$, seen in the less hindered compounds, are consistent with a preferred conformation in which the N-phenyl is roughly coplanar with the N-CO moiety in acetanilide and 5. Coplanarity would allow substantial resonance (mesomeric) effects which cause significant chemical shift differences at the ortho, meta, and para positions of the N-phenyl. In contrast, the smaller ranges for $\Delta\delta$ of ^{1}H and ^{13}C seen in 1-4 could imply substantially less mesomeric effects upon N-phenyl chemical shifts, which might result from a preferred conformation in which the N-phenyl is orthogonal to the heterocyclic ring. Thus, a simple evaluation of the $\Delta\delta$ magnitudes for ^{1}H and ^{13}C NMR chemical shifts may offer a direct indication of N-phenyl conformation in this series.

ACKNOWLEDGMENTS

Partial support has been provided by the U.S. Education Department Minority Science Improvement Program, National Science Foundation Instrumentation and Laboratory Improvement Program (USE9152822 and DUE9750675), The Forty-Five Foundation, and the Professional Staff Congress - City University of New York Research Award Program (to R.R.). Additional support was provided by the Petroleum Research Fund of the American Chemical Society and the Research Foundation (to K.S.V.) and by the University of North Florida for purchase of the Bruker 200 MHz NMR spectrometer.

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Date Received:May 27, 1997
Date Accepted:July 8, 1997