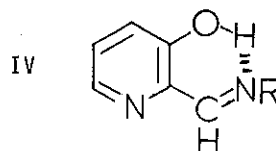
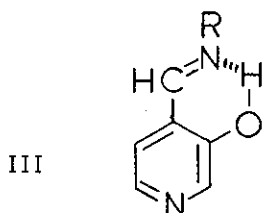
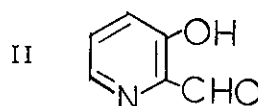
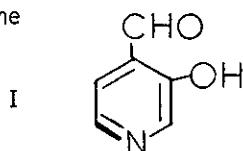


STUDIES ON THE NATURE OF VITAMIN B<sub>6</sub> INTERMEDIATESWayne P. Duncan, Charles B. Rose<sup>\*</sup>  
=====Department of Chemistry, University of Nevada, Reno, Nevada 89557 USAGerald O. Dudek  
=====Department of Chemistry, Harvard University, Cambridge, Massachusetts 02138 USA

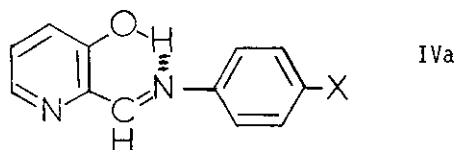
The extent of intramolecular hydrogen-bonding of Pyridoxal analogs  
can be determined by the phenoxyl H chemical shift.

In the course of our investigations on Vitamin B<sub>6</sub> (Pyridoxal) model systems our attention has been drawn to substituent effects in strongly intramolecular hydrogen-bonded species.<sup>1</sup> More specifically, we have studied the Schiff bases of ortho - hydroxy pyridine aldehydes (I and II) in which the phenolic hydrogen is strongly bridged to the azomethine nitrogen (III, IV).



Because of the similarities in substituent placement in Vitamin B<sub>6</sub> and our model compounds, we have examined the substituent effects in the following series of

compounds:



The Schiff bases were prepared by condensation of 3-hydroxypyridine-2-aldehyde with the appropriate substituted aniline in absolute ethanol (or methanol). No catalyst was required for this reaction and the resulting bright orange to yellow compounds were recrystallized from ethanol.<sup>2</sup>

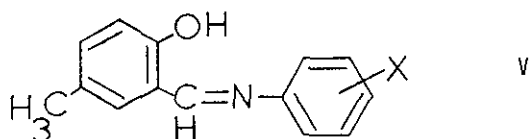
The commonly employed technique<sup>3-5</sup> of proton nmr spectroscopy was used to examine the intramolecular hydrogen bonds in this study. The chemical shift of the phenoxyl hydrogen atom were correlated with the Hammett  $\sigma$  constants.<sup>6</sup> Figure 1 is the Hammett plot for the para-substituted series (IVa). Each point represents an average of at least two determinations. The average deviation for all measurements was 0.03  $\delta$  units.<sup>7</sup> The straight line in the Hammett plot was determined by a least squares linear regression analysis<sup>8</sup> that has the form:

$$\delta = -0.858 \sigma + 13.10$$

Table I shows the deviation of the individual substituents from the straight line determined by the above method. All spectra were run on a Varian Associates A-60 spectrometer at 35°C using deuteriochloroform as solvent and tetramethylsilane as an internal reference standard. Although we have previously noted<sup>1</sup> that the chemical shift of the intramolecularly phenoxyl bonded hydrogen is not concentration dependent, all compounds studied were analyzed at a sample concentration of about 0.2 M, hence any intermolecular hydrogen-bonding effects should be constant and negligible.

As is shown by the Hammett plot, correlation between the phenoxyl hydrogen chemical shift and the para substituent's electron-attracting ability is excellent

with a correlation coefficient of 0.993. These results are similar to those of Klicnar, *et al.*<sup>9,10</sup> who used infrared and proton nmr techniques to study a series of anils that included the system V.

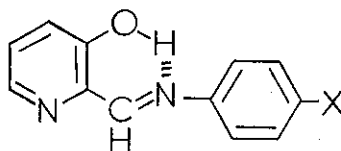


These investigators obtained a correlation for this system that can be represented by the equation:  $\delta = -1.29 \sigma^- + 9.22$ . A comparison of the results for the two systems reveals a remarkable similarity and demonstrates the dependence of the intramolecular hydrogen-bond strength upon the electronic factors within the amine moiety.

In recent work, El-Bayoumi<sup>11,12</sup> has proposed that in Schiff bases such as benzylideneanilines the two aromatic rings are non-coplanar. This is suggested by the fact that the uv spectrum of benzylideneaniline does not resemble that of the coplanar compound stilbene, but rather that of a combination of spectra of benzaldehyde and aniline. Moreover, this suggests that the non-bonded lone pair electrons of the azomethine nitrogen are in strong conjugation with the  $\pi$  electron system of the aniline ring. Therefore, the electron withdrawing ability of the substituted aniline influences the basicity of the azomethine nitrogen which, in turn, affects the strength of the intramolecular hydrogen bond. Hence, strong electron attracting groups on the aniline will reduce the electron density at the Schiff base nitrogen leading to a relatively weak hydrogen bridge. That this is indeed the case, can be seen where  $X = \text{NO}_2$  and the phenoxyl hydrogen is most strongly influenced by oxygen's electron density resulting in a chemical shift upfield relative to where  $X = \text{H}$ .<sup>7,10,13</sup>

Our data are entirely consistent with the above interpretation. Moreover, our

Table I

0.2 M in  $\text{CDCl}_3$ 

| <u>X</u>                  | <u>OH Chemical Shift (<math>\delta</math>)</u><br><u>Determination</u> |          | <u>Ave.</u> | <u>Dev.</u> | <u>Deviation from</u><br><u>straight line</u> | <u><math>\sigma^a</math></u> |
|---------------------------|------------------------------------------------------------------------|----------|-------------|-------------|-----------------------------------------------|------------------------------|
|                           | <u>1</u>                                                               | <u>2</u> |             |             |                                               |                              |
| $\text{NO}_2$             | 12.46                                                                  | 12.38    | 12.42       | 0.08        | 0.00                                          | +0.788                       |
| $\text{CO}_2\text{CH}_3$  | 12.78                                                                  | 12.78    | 12.78       | 0.00        | 0.01                                          | +0.385                       |
| Br                        | 12.84                                                                  | 12.83    | 12.84       | 0.01        | 0.06                                          | +0.232                       |
| Cl                        | 12.84                                                                  | 12.86    | 12.85       | 0.02        | 0.06                                          | +0.227                       |
| H                         | 13.16                                                                  | 13.14    | 13.15       | 0.02        | 0.05                                          | 0                            |
| $\text{CH}_3$             | 13.27                                                                  | 13.34    | 13.31       | 0.06        | 0.06                                          | -0.170                       |
| $\text{OCH}_3$            | 13.34                                                                  | 13.38    | 13.36       | 0.04        | 0.03                                          | -0.268                       |
| $\text{N}(\text{CH}_3)_2$ | 13.75                                                                  | 13.76    | 13.76       | 0.01        | 0.05                                          | -0.830                       |

average deviation = 0.03  $\delta$ <sup>a</sup> Hine, Physical Organic Chemistry, McGraw-Hill, Inc., New York, 1956, p. 87.

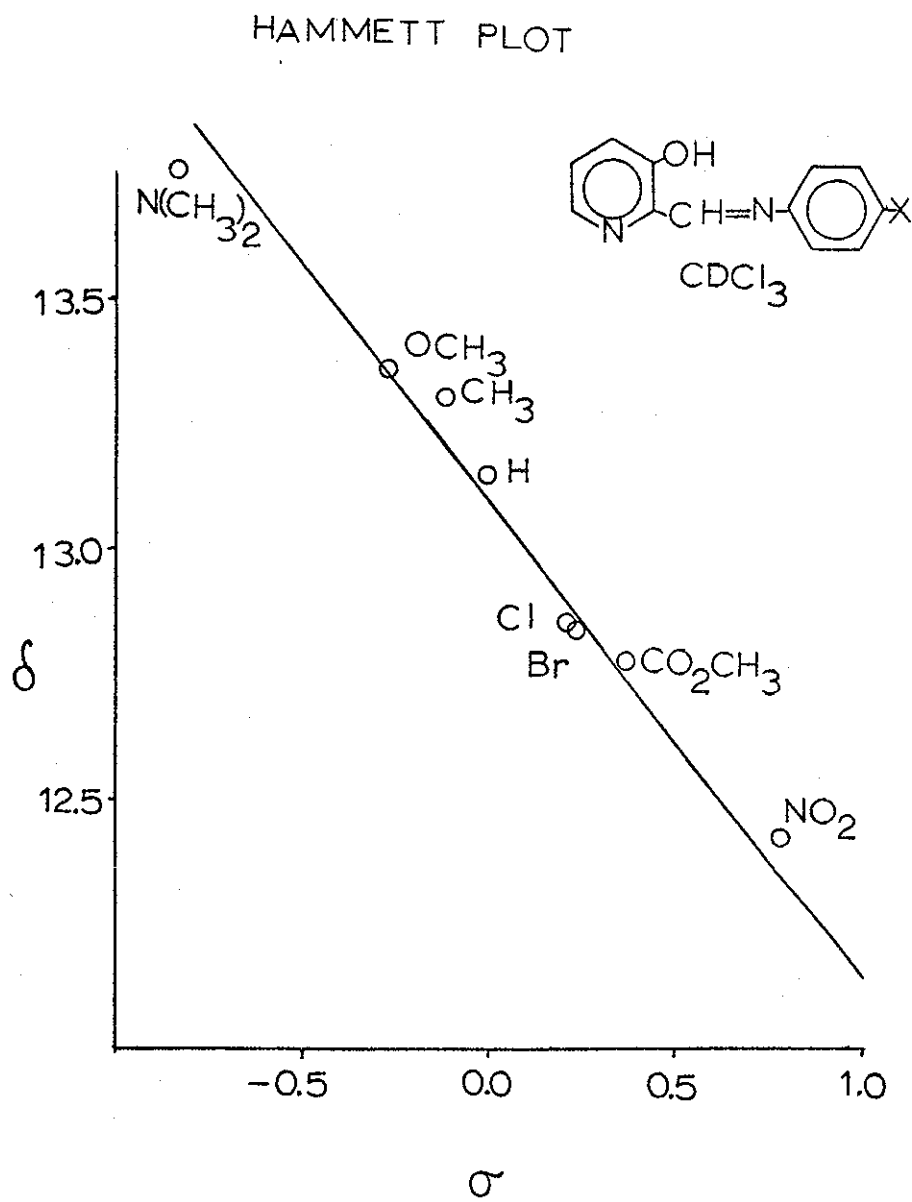


Figure 1

results are an interesting and forceful demonstration of the striking sensitivity of the chemical shift of the phenoxyl proton in the para substituted aniline Schiff bases of these vitamin B<sub>6</sub> analogs.

#### REFERENCES

- 1 Presented in part at the 26th Annual Northwest Regional Meeting of the American Chemical Society, Bozeman, Montana, June 1971.
- 2 Satisfactory elemental analyses and spectral data were obtained for all compounds reported herein.
- 3 G. O. Dudek and E. P. Dudek, Chem. Commun., 1965, 464.
- 4 G. O. Dudek and E. P. Dudek, J. Am. Chem. Soc., 1966, 88, 2407.
- 5 G. O. Dudek and E. P. Dudek, J. Chem. Soc. (B), 1971, 1356.
- 6 D. H. McDaniel and H. C. Brown, J. Org. Chem., 1958, 23, 420.
- 7 See Table I.
- 8 R. G. D. Steel and J. H. Torrie, 'Principles and Procedures of Statistics', McGraw and Hill, New York, 1960.
- 9 J. Klicnar, F. Kristek, V. Bekarec, and M. Vecera, Czech. Chem. Comm., 1969, 34, 553.
- 10 V. Bekarec, J. Klicnar, F. Kristek and M. Vecera, ibid., 1968, 33, 994.
- 11 M. A. El-Bayoumi, M. El-Aasser and F. Abdel-Halim, J. Amer. Chem. Soc., 1971, 93, 586.
- 12 M. El-Aasser, F. Abdel-Halim and M. A. El-Bayoumi, ibid., 1971, 93, 590.
13. L. K. Dyal, Australian J. Chem., 1964, 17, 419.

Received, 16th July, 1977