# Mannich Reaction on 2-(2-Benzofuranyl)-1*H*-indole. Determination of Structure by NMR Spectroscopic Techniques

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Analysis of the product from the Mannich reaction of 2-(2-benzofuranyl)-1*H*-indole *via* $^1$H and $^{13}$C nmr spectroscopy was performed. The studies included use of Pr(Fod)$_3$ shift reagent, proton-coupled $^{13}$C spectra, deuterium isotope induced shifts and protonation studies. It was found that the reaction occurred on the indole moiety at C-3.

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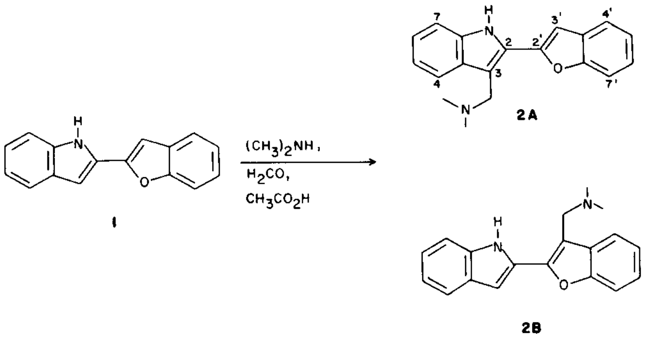
During the course of some synthetic studies we had the opportunity to perform a Mannich reaction on **1** shown below. It was not clear what the addition product was since the 60 MHz proton nmr spectrum did not reveal any signals above δ 7 other than the expected aliphatic resonance. It may be noted that the starting material did not have signals above δ 7, whereas in 2-phenylindole the H-3 signal is found at δ 6.8. Based on charge densities[1], it is expected that addition would occur on the indole ring. However, the apparent planar nature of this molecule, as indicated by $^1$H nmr, may alter this situation.

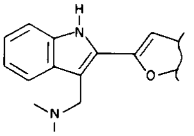


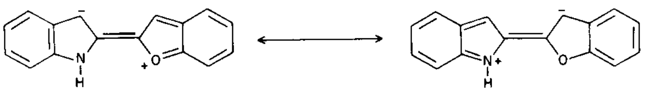
In order to determine the regiospecificity of this Mannich reaction, it was decided to use the lanthanide shift reagent Pr(Fod)$_3$ to enhance the proton nmr spectral dispersion. Upon incremental addition of Pr(Fod)$_3$ a single proton was shifted upfield from the remaining aromatic multiplets. However, it appeared slightly broadened and did not seem to reveal coupling to the indole NH group. A similar experiment was performed on 2-phenylindole and in this instance a clear doublet was observed. While this was a first indication to the nature of the addition product, it is possible that the shift reagent caused decoupling between H-3 and the NH proton due to exchange phenomena.

Carbon-13 nmr is very sensitive to minor differences in structure and it was felt that this would allow a distinction between the two possible products. In order to perform this task, it was necessary to assign the carbon-13 spectrum as completely as possible. The signal assignments were made on the basis of shift theory, multiplicities and fingerprints obtained in the $^1$H-coupled spectrum, deuterium isotope effects and comparison with structurally related materials. All assignments are summarized in Table I.

The assignments for the parent compound **1** were based upon the models, 2-phenylindole, **3** and 2-phenylbenzofuran, **4**, as well as coupling information (2,3). The two lowest field signals arise from the oxygenated carbons of the furan ring. The signal at δ 154.2 is a broad multiplet while that at δ 149.9 is a sharp doublet. These signals can then be readily assigned to C-7a′ and C-2′ respectively. The next lowest field signal can then be assigned to C-7a by analogy with the model systems. There are three remaining non-protonated aromatic signals. The chemical shift difference between these signals is small (0.6 ppm) and it was not possible to give specific assignments.

It was surprising to find the C-2 shift at approximately δ 128 since the analogous carbon in 2-phenylindole resonates at δ 138. However, it was possible to find a similar compound in the literature, shown below, to confirm this shift assignment (4). The somewhat unusual upfield shift for C-2 probably reflects strong influence of canonical forms such as shown, where C-2 is now enolic.





The planar nature of this molecule was previously suggested by the low field chemical shifts of H-3 and H-3′.

The next group of three signals are protonated and each half of the proton-coupled spectrum for these carbons appears as a sharp doublet. This coupling pattern is indicative of "*meta*" type carbons (5). By analogy with the model compounds, it was seen that C-6′ is found at lower field than C-6 and each carbon signal is still lower than C-5. The C-7 and C-7′ assignments were also based upon the model compounds. It is expected that the indole car-

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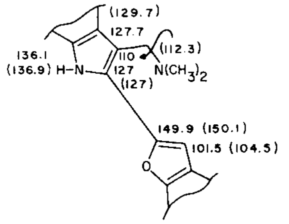
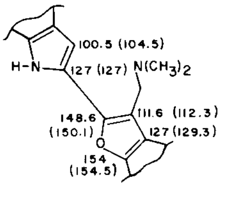
bon sould be found at higher field than the analogous benzofuran carbon. Additionally, the higher field signal appears to be more complex in it's coupling pattern and thus is designated C-7. The C-2 and C-2′ assignments are based upon similar reasoning.

The assignments for the product material follow directly from the parent compound, with only the obvious ambiguities introduced by the position of the amino function. From the proton-coupled carbon spectrum, it is quite clear that the nonprotonated $C_2'$ is a small doublet. This coupling can only arise from the proton at $C_3'$. While this observation conclusively answers the question which isomer is formed, we wanted to see if alternative methods could be used to arrive at the same result such that we could develop a methodology to look at similar types of problems.

Using the assignments for the parent compound and the fact that the $CH_2N(CH_3)_2$ moiety should affect each ring in a similar manner, *i.e.*, substituted at C-3 or C-3′, an assumption found true for simple methyl substitution (6) calculated shifts for **2A** and **2B** were derived. The values in parentheses are the actual values of the potential assignments. For example, the shift of C-3 is 100.5 + 9.6 [shift increment for $-CH_2N(CH_3)_2$] yielding $\delta$ 110.1.



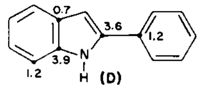
**2A**



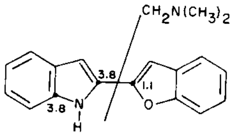
**2B**

Clearly this rather simplistic approach does not allow one to distinguish **2A** from **2B**.

Another alternate method of analysis of the problem using carbon-13 nmr is similar to that described for $^1H$ nmr, *i.e.*, identification of either C-3 or C-3′. An experiment which might help in this assignment is the deuterium isotope induced shift effect (8). Exchange of the NH proton by deuterium should cause upfield shifts in $\alpha$ and $\beta$-carbon resonances due to deuterium-induced isotope shifts; thus, in **2A** we should observe a pair of resonances for C-3 at $\delta$ 112.3 while for **2B** the upfield resonance at $\delta$ 104.5 might be a doublet. This hypothesis was checked using the model 2-phenylindole, due to the insolubility of **1**. The deuterium isotope shifts are shown below, in Hz at 25.1 MHz. While C-3 did not exhibit splitting it was substantially broadened.

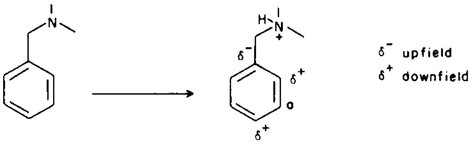


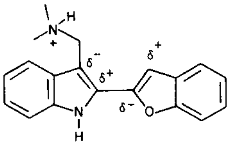
The same experiment on the product material showed the following results.



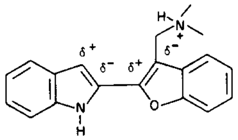
Due to overlapping signals and other factors no other deuterium isotope shifts were observed, nor was there any broadening in the highest field signal.

Finally, it was decided to measure the protonation shifts for the product. The assignments of the carbon-13 spectrum was done in an analogous manner to that for the parent compound **1** as previously described. The chemical shift increments upon protonation are given in Table II. The direction of the chemical shift increments are predicted below using the model shown (9) as well as expected $\pi$-bond polarization effects (10).





**2A**



**2B**

The $\pi$-bond polarization effect predicts the same result on either $C_3$ or $C_3'$ in products **2A** and **2B**, respectively; however, the direction of the protonation shift for $C_2$ and $C_2'$ are different. Although the data in Table II indicates a small incremental shift for $C_2$ and $C_2'$, the shifts are in the right direction for product **2A**.

In conclusion, we have found that this type of chemical selectivity problem can be addressed in many ways with the observation of long range proton-carbon coupling constants being the most readily interpreted method. In the absence of being able to observe such coupling because of spectral complexity, protonation induced shifts appear to be a viable alternate method for structure assignment.

## EXPERIMENTAL

Melting points were obtained on a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared (ir) spectra were obtained on either a Perkin Elmer 257 or 457 spectrophotometer. Proton nuclear magnetic resonance ($^1H$ nmr) spectra were recorded on Varian T-60 or EM-360 spectrometers. Chemical shifts are reported as $\delta$ values in parts per million relative to tetramethylsilane (TMS) as an internal standard.

Natural-abundance $^{13}C$-nmr spectra were obtained at 25.2 MHz on a

Table I

$^{13}$C-Chemical Shift Values for **1** and **2** and Model Systems, in ppm from TMS

| Carbon | **1** | **2** | **3** (2) | **4** (3) | **5** (a) |
|---|---|---|---|---|---|
| 2 | 128.6 (b) | 127.0 | 138.4 | 130.4 | 123.9 |
| 3 | 100.5 | 112.3 | 99.5 | 124.8 | 112.2 |
| 3a | 128.8 (b) | 129.7 (b) | 129.5 | | 127.8 |
| 4 | 120.7 | 120.0 (c) | 120.3 | 128.7 | 119.0 |
| 5 | 122.7 | 123.5 | 122.5 | 128.4 | 121.6 |
| 6 | 119.9 | 121.8 | 120.9 | | 119.2 |
| 7 | 111.0 | 111.7 | 112.1 | | 111.1 |
| 7a | 137.3 | 136.9 | 137.9 | | 136.2 |
| 2′ | 149.9 | 150.1 | 132.9 | 155.8 | |
| 3′ | 101.7 | 104.5 | 125.7 | 106.5 | |
| 3a′ | 128.2 | 129.3 (b) | — | 129.2 | |
| 4′ | 121.2 | 120.3 (c) | 129.8 | 120.8 | |
| 5′ | 123.5 | 124.1 | 128.3 | 122.8 | |
| 6′ | 124.6 | 125.3 | | 124.2 | |
| 7′ | 111.6 | 112.3 | | 111.1 | |
| 7a′ | 154.2 | 154.5 | | 154.8 | |

(a) *N,N*-Dimethyl-1*H*-indole-3-methanamine. (b) Items in the same column may be interchanged. (c) Items in the same column may be interchanged.

Table II

$^{13}$C-Protonation Shifts for **2**

| Carbon | Protonated | Non-Protonated | $\Delta\delta$ |
|---|---|---|---|
| 2 | 128.7 (a) | 127.0 | 1.7 |
| 3 | 103.1 | 112.3 | −9.2 |
| 3a | 129.6 (a) | 129.7 (a) | −0.1 |
| 4 | 119.5 | 120.0 | −0.5 |
| 5 | 125.0 | 123.5 | 2.5 |
| 6 | 122.2 | 121.8 | 0.4 |
| 7 | 112.7 | 111.7 | 1.0 |
| 7a | 137.3 | 136.9 | 0.4 |
| 2′ | 149.2 | 150.1 | −0.9 |
| 3′ | 105.0 | 104.5 | 0.5 |
| 3a′ | 125.0 | 129.3 (a) | −4.3 |
| 4′ | 121.6 | 120.3 | 1.3 |
| 5′ | 124.5 | 124.1 | 0.4 |
| 6′ | 124.5 | 125.3 | −0.8 |
| 7′ | 112.3 | 112.3 | 0.0 |
| 7a | 155.1 | 154.5 | 0.6 |

(a) Items in same column may be interchanged.

Varian XL-100-12 spectrometer system, equipped with a 620/L 16K computer, in the Fourier transform mode with full proton decoupling. Proton coupled spectra were measured in the gated decoupling mode. General spectral and instrumental parameters were internal deuterium lock to the solvent; spectral width of 5000 Hz, a pulse width of 25 $\mu$seconds (45°), normal pulse amplifier, and a pulse repetition time of 1.8 seconds. All samples were run in dimethylsulfoxide-$d_6$ solutions in a 10 mm tube. All chemical shifts are referenced to the center peak of the multiplet $\delta$ 39.7. Deuterium isotope shift experiments were performed in a manner similar to that described by Pfeffer (8). To each part of the coaxial tube was added water or deuterium oxide and the spectra were measured at a spectral width of 1200 Hz yielding data point resolution of 0.3 Hz. Protonation of **2** was performed by addition of *ca.* 1 equivalent of trifluoroacetic acid to the dimethylsulfoxide solution.

Mass spectra were collected on a LKB-9000 Mass Spectrometer using EI.

Analytical thin-layer chromatography (tlc) was conducted on 40 mm × 80 mm precoated tlc plates, silica gel with fluorescent indicators, layer thickness 0.25 mm, manufactured by Macherey Nagel, Duren, W. Germany.

All solvents were dried over 3A° Linde molecular sieves. Compound **1** was prepared as described in reference 11. Zinc chloride was freshly prepared by fusing under vacuum, cooling, and grinding immediately prior to use. All reactants and solvents were reagent grade, and aside from drying, were used as received.

2-(2-Benzofuranyl)-*N,N*-dimethyl-1*H*-indole-3-methanamine (**2**).

To a solution of 3.16 g. (0.039 mole) of 37% formaldehyde (Baker), 4.4 g. (0.039 mole) 40% aqueous dimethylamine (Aldrich) in 50 ml. of glacial acetic acid (MCB) cooled to 0-10° was added dropwise a solution of 8.29 g. (0.356 mole) of **1** in 17 ml. of glacial acetic acid and 42 ml. of para-dioxane (MCB). When the addition was complete, the reaction was permitted to come to room temperature and stir for 2 hours. After reaction was complete, as determined by tlc, the mixture was poured onto 500 ml. of ice/water and filtered through celite. The filtrate was cooled and made basic by the dropwise addition of 50% potassium hydroxide solution. When the solution registered basic to *p*H paper (*p*H > 11) the suspension was filtered, and a pure white solid was collected. This was washed with distilled water and dried at 60° for 100 hours under reduced pressure, m.p. 114-116°, Rf 0.375 (10% ethyl acetate-methylene chloride with 0.14 ml. of concentrated aqueous ammonium hydroxide added); ir (chloroform): 3490 cm$^{-1}$ (NH); $^1$H nmr (deuteriochloroform): 60 MHz, $\delta$ 2.3 (6H, s, $CH_3$), 3.8 (2H, s, $CH_2$), 7.0-8.0 (9H, m, Ar.H), 8.8 (1H, b, NH); ms: m/e 290 ($M^+$), 246 (M-44).

*Anal.* Calcd. for $C_{19}H_{18}N_2O$: C, 77.6; H, 6.3; N, 9.6; O, 5.5. Found: C, 77.4; H, 6.0; N, 9.2.

## REFERENCES AND NOTES

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