INTRAMOLECULAR HYDROGEN BONDING IN THE NITROBENZOPYRIDINES

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Abstract : The available data on the spectroscopy of the nitrobenzopyridines are insufficient, out-dated, and modern theory is missing. A careful study of the ^{1}H-NMR spectra of these compounds revealed the existence of C–H---O–N=O hydrogen bonds, the hydrogen being at *peri* position to the nitro group. The existence of these bonds explains the down-field shifts observed in the signals of the involved protons. Spectral data from the naphthalene series and from ^{17}O-NMR measurements, both involving the nitro group/*peri*-hydrogen relation, confirmed our proposal.

Introduction

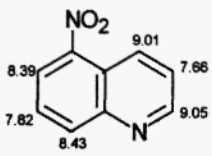
The papers related to the nitrobenzopyridines have been reviewed several times (1-8). Benzo[b]pyridine (quinoline) and benzo[c]pyridine (isoquinoline) are nitrated by means of *mixed acid* (H_2SO_4/HNO_3). However, only one acid is used first, thus giving the sulphate or the nitrate of the nitrogenous base in use. Then the salt is nitrated. Reaction occurs in the carbocyclic ring, at the α-positions, 5 and 8, and not in the β- ones, 6 and 7, (9). Almost equal quantities of 5-nitro- and 8-nitroquinoline are obtained, **1** and **2**, but in the case of isoquinoline a ratio 9 to 1 is obtained (3) for the 5-nitro and 8-nitro derivatives, **3** and **4**.

Besides direct nitration, the Skraup synthesis can be employed (10). *m*-Nitroaniline yields a mixture of 5-nitro- and 7-nitroquinoline, whereas *o*-nitroaniline and *p*-nitroaniline give a single product: 8-nitroquinoline and 6-nitroquinoline, respectively.

^{1}H-NMR Spectroscopy

A very low resolution ^{1}H-NMR spectrum of 5-nitroquinoline in acetone, at 100 MHz, has been described (11). The chemical shifts observed in $CDCl_3$ solution (100 MHz) were given afterwards (12), but the spin-spin coupling constants were not mentioned. Therefore, we determined the ^{1}H-NMR spectrum of 5-nitroquinoline, **1**, in $CDCl_3$, with higher resolution (300 MHz): 7.66 ppm (H-3), dd, $J_{3,2}$ = 4.2, $J_{3,4}$ = 9 Hz; 7.82 ppm (H-7), dd, $J_{7,6}$ = 7.8, $J_{7,8}$ = 8.4 Hz; 8.39 ppm (H-6), dd, $J_{6,7}$ = 7.8, $J_{6,8}$ = 1.2 Hz; 8.43 ppm (H-8), ddd, $J_{8,7}$ = 8.4, $J_{8,6}$ = 1.2, $J_{8,4}$ = 0.9 Hz; 9.01 ppm (H-4), ddd, $J_{4,3}$ = 8.7, $J_{4,2}$ = 1.8, $J_{4,8}$ = 0.9 Hz; 9.05 ppm (H-2), dd, $J_{2,3}$ = 4.2, $J_{2,4}$ = 1.8 Hz. Notice that H-4 and H-8 have cross-ring coupling (trans-annular coupling), resulting ABCD spin systems. The chemical shift for H-4 is 8.00 ppm in the quinoline spectrum (13), whereas in the 5-nitroquinoline spectrum the chemical shift for H-4 is 9.01 ppm. This downfield shift can be explained by hydrogen bond formation, C–H---O type, between H-4 and the nitro group, **5**. Thus, a six membered secondary ring is formed. The relative position between the nitro group and the hydrogen at C-4 is equivalent to *meta* if they were in a single ring, discarding consequently that the Δδ shift could be attributed to the mesomeric effect of the nitro group.

H-6 (*ortho*) shows a 0.96 ppm downfield Δδ, since in the quinoline spectrum H-6 appears at 7.43 ppm.



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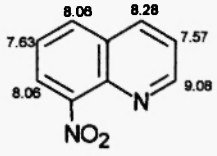

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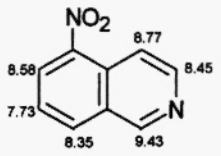

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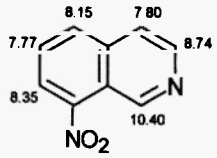

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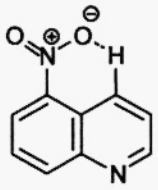

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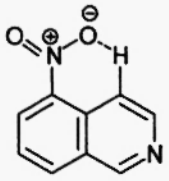

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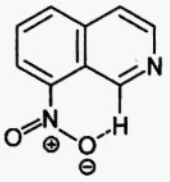

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The ^{1}H-NMR spectrum of 8-nitroquinoline, **2**, shows remarkable differences: 7.57 ppm (H-3), dd, $J_{3,4}$ = 8.4, $J_{3,2}$ = 4.2 Hz; 7.63 ppm (H-6), dd, $J_{6,5}$ = 8.1, $J_{6,7}$ = 7.5 Hz; 8.06 ppm (H-5 and H-7), d, J = 7.8 Hz (since the H-5 and H-7 doublets are superimposed, the observed J is an average of $J_{5,6}$ – 8.01 and $J_{6,7}$ = 7.5 Hz); 8.28 ppm (H-4), dd, $J_{4,3}$ = 8.4, $J_{4,2}$ = 1.8 Hz; 9.08 ppm (H-2), dd, $J_{2,3}$ = 4.5, $J_{2,4}$ = 1.8 Hz. The Δδ for the *ortho* hydrogen is 0.45 ppm since H-7 shows a δ of 8.06 ppm in **2** and 7.61 ppm in the starting quinoline. This is half the 0.96 ppm shift observed for the *ortho* hydrogen in compound **1**. This can be explained by the closeness in **2** between the nitro group and the endocyclic nitrogen, which is creating an electronic repulsion and reducing the effect of the nitro group due to rotation of this one to avoid electronic repulsion.

The ^{1}H-NMR spectra of 5-nitro- and 8-nitroisoquinoline, **3** and 4, have been reported (14,15). However, in the 5-nitroisoquinoline spectral data, there is discrepancy in the assignment of the chemical shifts for H-3 and H-4. Armarego and Batterham (14) report: 8.75 ppm (H-3) and 8.46 ppm (H-4). On the contrary, the Sadtler Collection (15) gives: 8.48 ppm (H-3) and 8.78 ppm (H-4). Discarding the tiny differences, the numbers are inverted. We propose the lower-field shift (8.78 or 8.75 ppm) corresponds to H-4, due to deshielding resulting from hydrogen bond formation, as indicated in 6. That the chemical shift for H-3 must be 8.44 or 8.46 ppm is confirmed since, in the spectrum of isoquinoline (16), a chemical shift of 8.45 ppm has been reported for H-3. The remaining data are included in formulas **3** and 4.

The downfield Δδ resulting from the negative mesomeric effect of the nitro group in the *ortho* and *para* positions are compared to the Δδ due to the postulated hydrogen bonds:

	H-6 *ortho*	H-8 *para*	H-4 *peri* H-bond		H-5 *para*	H-7 *ortho*	H-1 *peri* H-bond
5-Nitroquinoline	0.96	0.38	1.01	8-Nitroquinoline	0.38	0.45	——
5-Nitroisoquinoline	1.02	0.49	1.25	8-Nitroisoquinoline	0.44	0.85	1.25

The Δδ are higher for the *ortho* positions than for the *para*. However, there is a bigger increase in the *peri* positions, confirming our proposal of hydrogen bond formation. This occurs also in the 8-nitroisoquinoline, 7, since H-1 shows a Δδ = 1.25 ppm.

In the 1-nitronaphthalene spectrum, the signal for H-8 (*peri*) is at lowest field, the *ortho* and *para* signals show smaller shifts, in this order. These values are reported in two communications (17,18), with small variances: 8.49, 8.10 and 7.99 ppm, in the first (17), and 8.57, 8.24 and 8.13 ppm, in the second (18). These data confirm our proposition of intramolecular hydrogen bonding, and no explanation has been given before why the hydrogen at *peri* position is so shifted.

When C–H is the hydrogen donor, the resulting bond is a weak one due to the lower acidity of this hydrogen. In the thiazolic series (19,20), the $\Delta\delta$ observed are about 0.5 ppm, but in the studied nitrobenzopyridines this shift is bigger than 1 ppm. This is due to the $N^{+}–O^{-}$ dipole in the nitro group, since the negative charge favours a stronger hydrogen bond.

^{17}O-NMR studies have shown the interaction between the nitro group and a *peri*-hydrogen in bicyclic systems (21), since a downfield shift of the ^{17}O signal of the nitro group is observed ($\Delta\delta \sim 30$ ppm). This shift is expected if the nitro group is involved in hydrogen bonding. However, this was interpreted only as a variation of the torsional angle of the nitro group. In that communication the ^{1}H-NMR spectra were not determined, and so, the $\Delta\delta$ of the *peri*-hydrogens were not detected. Thus, the combined results from ^{17}O-NMR and our findings from ^{1}H-NMR, prove the existence of C–H---O–N=O hydrogen bonding in the nitrobenzopyridines, and this can be extended to the other studied compounds (21).

Experimental

The ^{1}H-NMR spectra were obtained in a Varian Inova 300 spectrometer, in $CDCl_3$ solution and TMS as internal standard, in the Unidad de Servicios de Apoyo a la Investigación (USAI).

The required nitrobenzopyridines were prepared by known methods. 5-Nitro- and 8-nitroquinoline were obtained from quinoline sulphate (22). 5-Nitro- and 8-nitroisoquinoline were prepared by the methods of Dewar and Maitlis (23).

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