

# The reaction of *o*-phenylenediamine with $\alpha,\beta$ -unsaturated carbonyl compounds

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## Abstract

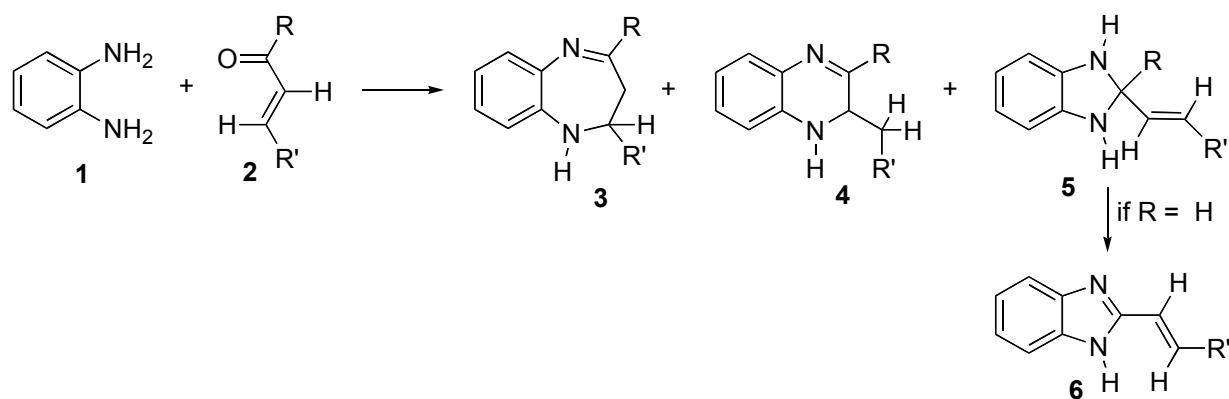
The structures of the products obtained by the reaction of *o*-phenylenediamine and two isomeric chalcones have been identified as 1,5-benzodiazepines. A <sup>1</sup>H, <sup>13</sup>C and <sup>15</sup>N NMR study in solution combined with B3LYP/6-31G\*\* calculations allowed to determine the conformations present in solution.

**Keywords:** Benzodiazepine; Karplus equation; Density functional theory calculations

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## Introduction

The reaction of binucleophiles like *o*-phenylenediamine **1** with  $\alpha,\beta$ -unsaturated carbonyl compounds **2** can afford seven- **3**, six- **4** and five-membered rings **5** (that in some cases can be oxidized to benzimidazoles **6**) (Scheme 1). Benzodiazepines **3** correspond to the attack on the CO and the terminal carbon of the olefin, quinoxalines **4** correspond to the attack on the CO and the  $\alpha$  carbon of the olefin, and the benzimidazole derivatives **5** to a double attack on the carbonyl group. *o*-Aminothiophenol has been used instead of **1**.

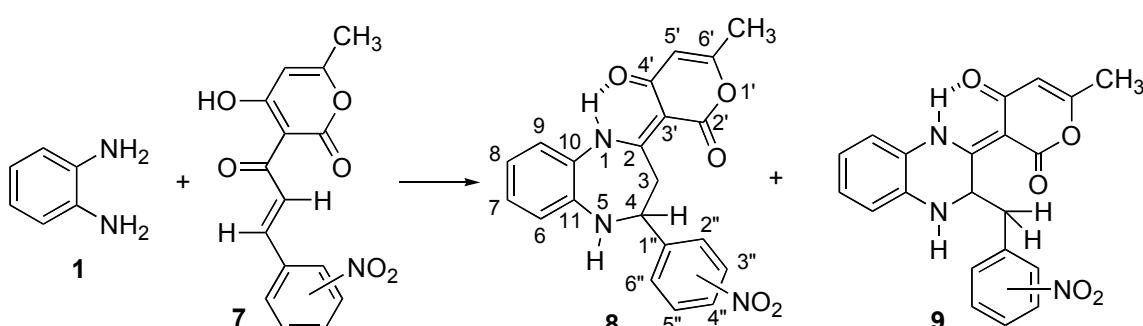
**Scheme 1**

The literature abounds in assignment errors that have been solved only recently by NMR spectroscopy and X-ray crystallography. An example of this is compounds **3** and **4**<sup>1</sup> and the corresponding sulfur derivatives of **3** and **4** (NH replaced by S).<sup>2,3</sup> Vinyl ( $R' = H$ ) and ethenyl (like styryl,  $R' = Ph$ ) benzimidazoles **6** are usually prepared using other ways.<sup>4,5</sup>

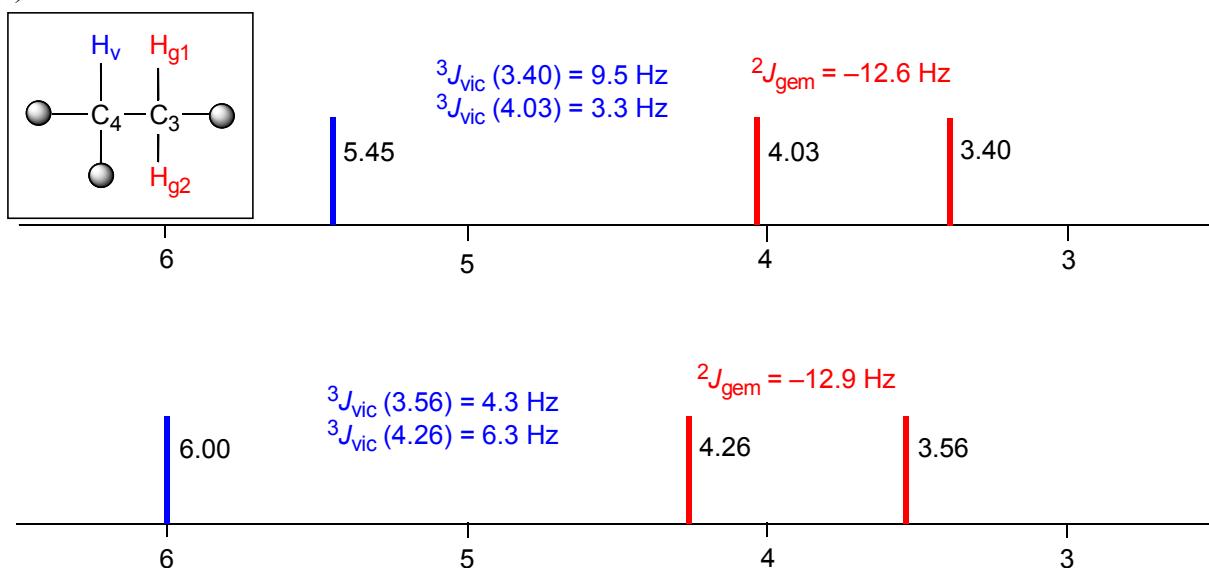
The problem of differentiating between structures **3** and **4** has conclusively been solved by a rigorous analysis of their NMR spectral characteristics.<sup>1,2</sup> However, in this report, a case that shows interesting variations in the NMR characteristics making the assignment more complicated will be described.

## Results and Discussion

The reaction of *o*-phenylenediamine **1** and chalcones **7a,b** could afford either a 1,5-benzodiazepine **8** or a 3,4-dihydroquinoxaline **9** (Scheme 2).<sup>1</sup>

(a) 4-NO<sub>2</sub>, (b) 2-NO<sub>2</sub>**Scheme 2**

The reaction affords in both cases only one compound. The main features of  $^1\text{H}$  NMR spectra in  $\text{CDCl}_3$  of the isolated compounds are reported in Figure 1.

(a) 4- $\text{NO}_2$  derivative(b) 2- $\text{NO}_2$  derivative**Figure 1**

It appears that the spectrum of the 4- $\text{NO}_2$  derivative is consistent with a 1,5-benzodiazepine (or thiazepine)<sup>1,2</sup> thus it corresponds to **8a**. However, that of the 2- $\text{NO}_2$  derivative is different, not only the chemical shifts but also the Karplus-type coupling constants are clearly different. Our first hypothesis is that in the latter case the compound could have the structure **9b**. To verify this assumption, the  $^{13}\text{C}$  and  $^{15}\text{N}$  NMR spectra of **8a** and that of the unknown 2- $\text{NO}_2$  derivative **b** have been recorded (Table 1). It is clear that the chemical shift differences  $\Delta\delta$  between benzodiazepines **8** and quinoxalines **9** reported in the literature<sup>1</sup> (similarly for benzothiazepines),<sup>2</sup> are much larger (see for instance N5) than those observed between the 4- $\text{NO}_2$  **a** and 2- $\text{NO}_2$  **b** derivatives. Highlighted in red are the most important differences related to the position of the nitro group which affect  $\delta\text{C}3$ ,  $\delta\text{C}4$  and the  $^1\text{J}_{\text{NH}}$  coupling of N5.

**Table 1.**  $^{13}\text{C}$  and  $^{15}\text{N}$  chemical shifts ( $\delta$  in ppm) of compounds **8a** and **8b** in  $\text{CDCl}_3$ 

Atom	<b>8a</b>	<b>8b</b>	$\Delta\delta$ ( <b>8a</b> - <b>8b</b> )	$\Delta\delta$ ( <b>8</b> - <b>9</b> ) <sup>1</sup>
N1	-219.2 <sup>a</sup>	-218.5 <sup>c</sup>	-0.7	8.0
C2	163.50*	162.9	0.6	---
<b>C3</b>	36.4	34.0	<b>2.4</b>	-1.1 (CH <sub>2</sub> )
<b>C4</b>	67.3	63.5	<b>3.8</b>	14.5 (CH)
N5	-305.5 <sup>b</sup>	-306.4 <sup>d</sup>	0.9	21.8
C6	121.4	121.3	0.1	5.8
C7	128.8	128.6	0.2	0.3
C8	122.3	122.2	0.1	0.9
C9	125.0	124.8	0.2	5.9
C10	126.88	127.0	-0.1	1.3
C11	138.8	140.1	-1.3	4.5
C2'	171.9	172.3	-0.4	9.4
C3'	96.6	96.9	-0.3	2.4
C4'	184.7	184.7	0.0	-1.0
C5'	107.3	107.1	0.2	0.1
C6'	163.55*	163.4	0.2	-0.5
CH <sub>3</sub>	19.9	19.8	0.1	0.0
C1''	151.0	137.4	---	---
C2''	126.92	(NO <sub>2</sub> ) 148.2	---	---
C3''	124.1	125.0	---	---
C4''	(NO <sub>2</sub> ) 147.6	128.8	---	---
C5''	124.1	133.0	---	---
C6''	126.92	128.2	---	---

<sup>a</sup>  $^1J = 84.7$  Hz; <sup>b</sup>  $^1J = 82.3$  Hz; <sup>c</sup>  $^1J = 83.7$  Hz ( $\Delta J$  N1 = 1.0 Hz); <sup>d</sup>  $^1J = 78.8$  Hz ( $\Delta J$  N5 = 3.5 Hz)

Following the assignment of both **8a** and **8b** 1,5-benzodiazepines, the differences in  $^1\text{H}$  NMR data (Figure 1) are next given in Table 2. The assignments of Tables 1 and 2 are based on ( $^1\text{H}$ - $^1\text{H}$ ) gs-NOESY experiments as well as on gs-HMQC and gs-HMBC heteronuclear ( $^1\text{H}$ - $^{13}\text{C}$  and  $^1\text{H}$ - $^{15}\text{N}$ ) correlations.

**Table 2.**  $^1\text{H}$  chemical shifts ( $\delta$  in ppm) and  $^1\text{H}$ - $^1\text{H}$  coupling constants ( $J$  in Hz) of compounds **8a** and **8b** in  $\text{CDCl}_3$ 

Atom	<b>8a</b>	<b>8b</b>
H1 (NH)	15.52 (s)	15.67 (s)
H <sub>A</sub>	3.40 (dd), $^2J_{\text{AM}} = -12.6$	3.56 (dd), $^2J_{\text{AM}} = -12.9$
H <sub>M</sub>	4.03 (dd), $^3J_{\text{MX}} = 3.3$	4.26 (dd), $^3J_{\text{MX}} = 6.3$
H <sub>X</sub>	5.45 (ddd), <sup>a</sup> $^3J_{\text{AX}} = 9.5$	6.00 (m), $^3J_{\text{AX}} = 4.3$
H5 (NH)	4.11 (s)	4.09 (d), $^3J_{\text{H}5\text{X}} = 3.3$
H6	6.97 (d)	6.85 (d)
H7	7.25 (t)	7.19 (t)
H8	7.06 (t)	7.04 (t)
H9	7.20 (d)	7.18 (d)
H5'	5.76 (q), $^4J_{\text{H}5'\text{CH}_3} = 0.9$	5.69 (q), $^4J_{\text{H}5'\text{CH}_3} = 0.8$
CH <sub>3</sub>	2.14 (d)	2.06 (d)
H2"	7.61 (m)	(NO <sub>2</sub> )
H3"	8.19 (m)	8.00 (dd), $^3J_{\text{H}3''\text{H}4''} = 8.1$ , $^4J_{\text{H}3''\text{H}5''} = 1.4$
H4"	(NO <sub>2</sub> )	7.43 (ddd), $^3J_{\text{H}4''\text{H}5''} = 7.7$ , $^4J_{\text{H}4''\text{H}6''} = 1.5$
H5"	8.19 (m)	7.52 (ddd), $^3J_{\text{H}5''\text{H}6''} = 7.9$
H6"	7.61 (m)	7.83 (dd)

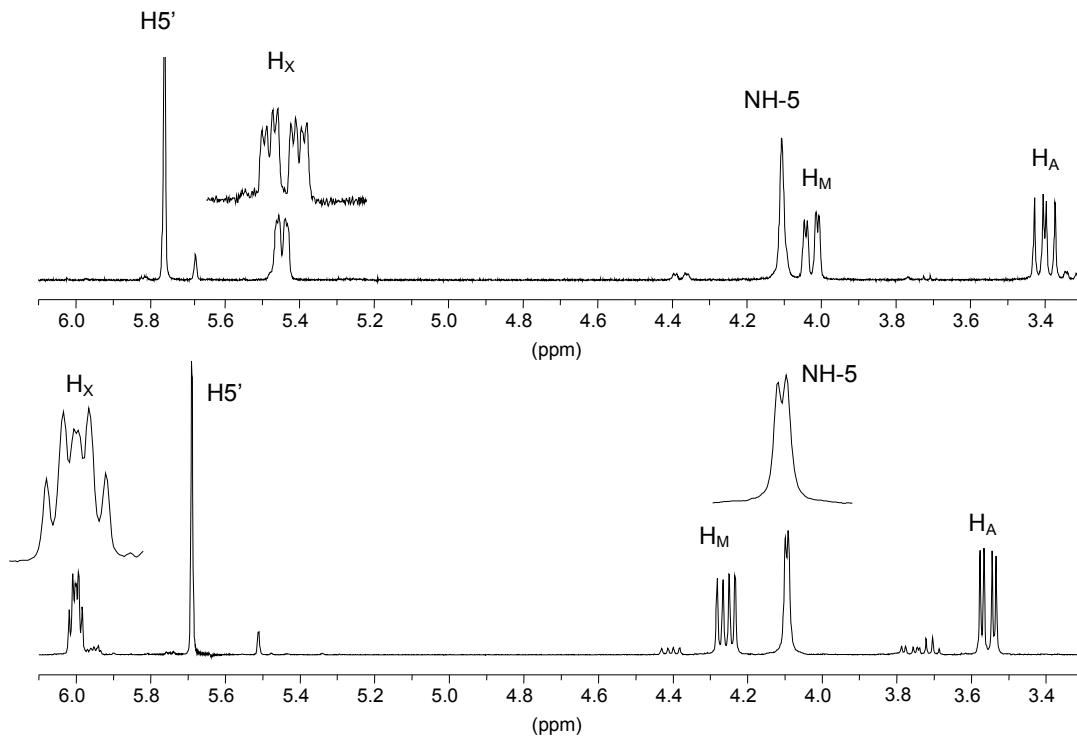
<sup>a</sup>  $J = 1.7$  Hz

The analysis of the AMX system corresponding to the protons at positions 3 and 4 leads to the couplings represented in Figure 1 (the experimental spectra are reported in Figure 2).

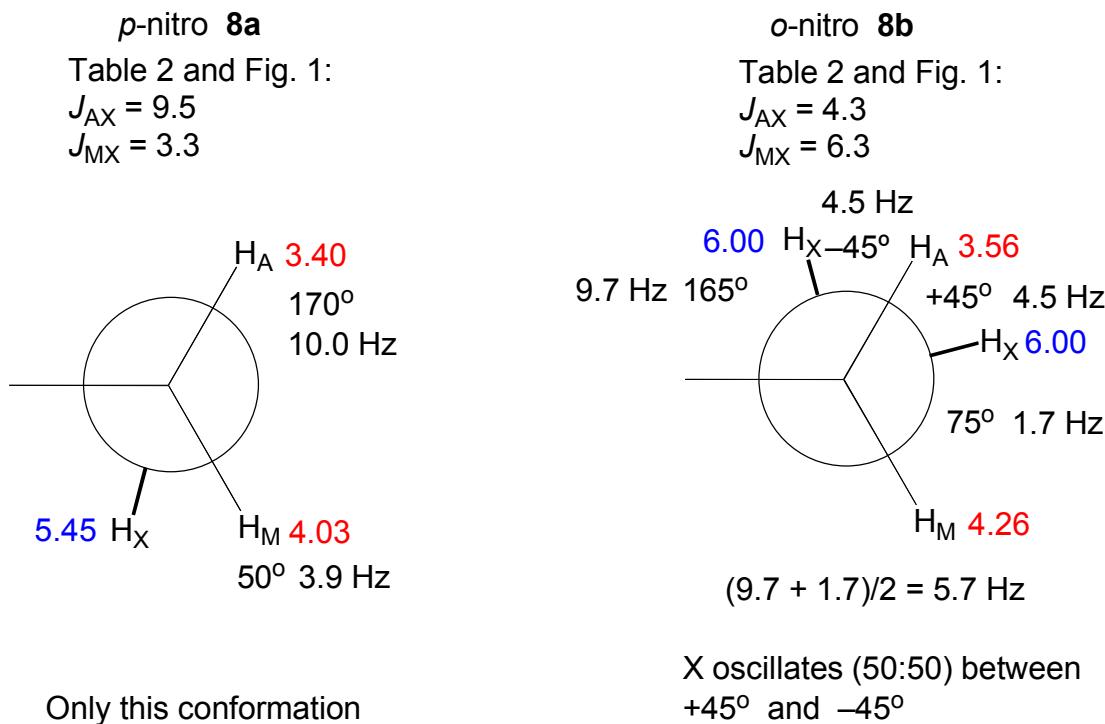
The geminal coupling constants are not useful but the two vicinal coupling constants, through the Karplus relationship,<sup>6</sup> allow the inference of certain conclusions about the conformational changes introduced in the seven-membered ring by the 2-NO<sub>2</sub> group. Since the ethane fragment belongs to a seven-membered ring and there is an N atom in one of the extremities, we have modified the original Karplus equation to fit our values:

$$^3J_{\text{HH}} \text{ (Hz)} = 7.76 \cos 2\phi - 1.10 \cos \phi + 1.40 \quad (1)$$

Using eq. [1], the compounds should have the conformation represented in Figure 3. We have assumed a perfect ethane geometry with angles of 60° and 180°. In the case of the 4-NO<sub>2</sub> derivative **8a**, angles of 170° and 50° (with regard to H<sub>M</sub> a *gauche* – 10°) led to couplings of 10.0 Hz (instead of 9.5 Hz) and 3.9 Hz (instead of 3.3 Hz). In the case of the 2-NO<sub>2</sub> derivative **8b**, there is not a single conformation that could explain the measured coupling constants. We have to assume two conformations of similar energy in rapid interconversion leading to average signals. With regard to H<sub>M</sub>, the H<sub>X</sub> atom occupies in one case a *gauche* conformation (+15°) and in the other an *anti* conformation (-15°). The average couplings would be 4.5 Hz (instead of 4.3 Hz) and 5.7 Hz (instead of 6.3 Hz).



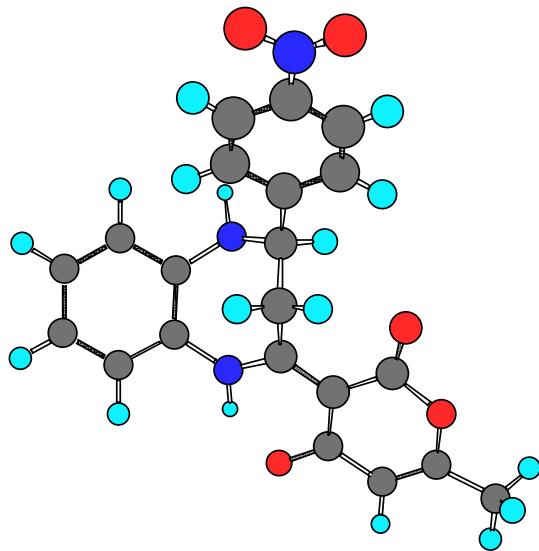
**Figure 2.** Experimental <sup>1</sup>H-NMR of 4-NO<sub>2</sub>- (**8a** top) and 2-NO<sub>2</sub>-isomers (**8b** bottom).



**Figure 3**

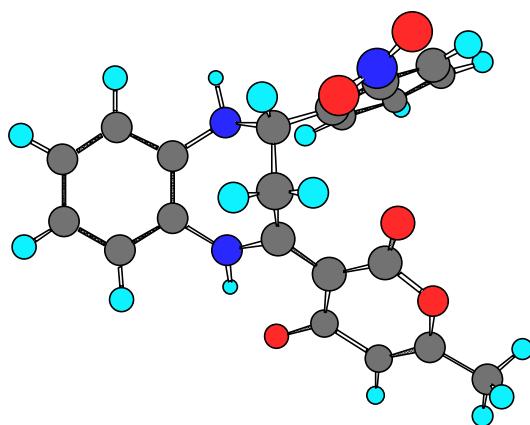
The validity of the conformations assigned to derivatives **8a** and **8b** were tested by carrying out Density Functional Theory (DFT) calculations at the B3LYP/6-31G\*\* level (see experimental part) corresponding to the seven-membered ring inversion that, due to the 10,11-fused phenyl ring and the exocyclic double bond on C2, are described as affecting essentially C3 which can be up or down (methylene flip).

In the case of the 4-NO<sub>2</sub> derivative **8a**, there are two minimum energy conformations with relative values of 0.0 and 4.7 kJ mol<sup>-1</sup>, thus, we can assume that only the most stable one (Figure 4) is present in solution. This structure has HCCH dihedral angles of 179.7° and 61.4° (the C2-C3-C4-C1" angle amounts to 176.7°), close to those calculated in Figure 3 (170° and 50°, respectively).

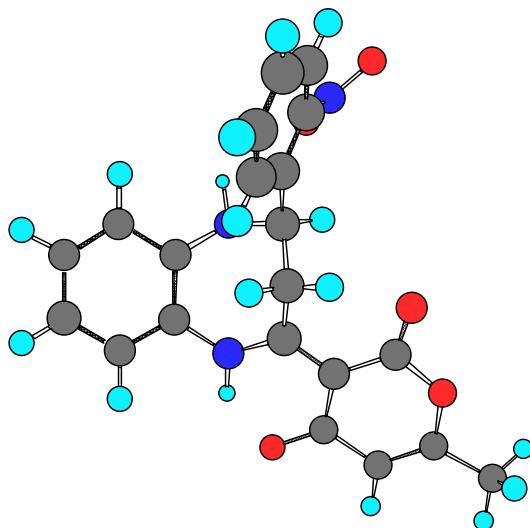


**Figure 4.** Minimum energy conformation of **8a**.

The 2-NO<sub>2</sub> derivative **8b** presents two conformations of similar energy, the **8b1** ( $E_{\text{rel}} = 0.0$  kJ mol<sup>-1</sup>) and the **8b2** ( $E_{\text{rel}} = 2.5$  kJ mol<sup>-1</sup>). The **8b1** (Figure 5) has HCCH dihedral angles of 65.4° and 52.3° ( $\text{C}2\text{C}3\text{C}4\text{C}1'' = 71.3^\circ$ ) while those of **8b2** (Figure 6) are 177.1° and 56.9° ( $\text{C}2\text{C}3\text{C}4\text{C}1'' = 176.0^\circ$ ). These angles can be compared with those of Figure 3: 75° and 45° for one conformation and 165° and 45° for the other.



**Figure 5.** Minimum energy conformation of **8b1**.



**Figure 6.** Minimum energy conformation of **8b2**.

Other relevant features of these conformations are in **8b1** the proximity of the nitro group to H4 and to one of the H3 protons; on the other hand, in conformation **8b2** the nitro group is close to H4 and to the N5–H5. A mixture of both conformations can explain why  $\delta_{C3}$ ,  $\delta_{C4}$  and the  $^1J_{NH}$  coupling of N5 are the most affected properties in Table 1. It also provides an explanation why in Figure 1, the H<sub>x</sub> proton in **8b** is deshielded compared with that in **8a** (Table 2).

## Experimental Section

**General Procedures.** Melting points were determined in open capillaries and are uncorrected. <sup>1</sup>H NMR spectra for analytical purpose were recorded on a Bruker 300 MHz instrument using

TMS as an internal standard. IR spectra were recorded on a Buck Scientific IR M-500 spectrophotometer. Elemental analyses were carried out in a Perkin Elmer-2400 instrument and mass spectra were recorded on Kratos MS-50 mass spectrometer. Most of the common chemicals such as dehydroacetic acid (DHA), aldehydes, and *o*-phenylenediamine, were obtained from commercial suppliers. 3-Cinnamoyl-4-hydroxy-6-methyl-2-pyrone (chalcone analogs of DHA, **7a-b**) were prepared according to literature procedure.<sup>7</sup>

### General method

To a solution of **7a** (0.602 g, 2 mmol) in ethanol (30 ml) a few drops of piperidine and *o*-phenylenediamine (0.21 g, 2 mmol) were added. The mixture was heated under reflux for 3-4 h and then AcOH (1 ml) was added. Refluxing was continued for another 3-4 h. About half of the solvent was distilled off under reduced pressure and the oily residue was allowed to stand at room temperature overnight. The crystalline solid product **8a** thus separated was filtered, washed with cold aqueous ethanol (2-3 ml, 50: 50 by v/v) and dried.

Compound **8b** was prepared similarly starting from **7b**.

**6-Methyl-3-(4-(4-nitrophenyl)-4,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-2(3*H*)-ylidene)-3*H*-pyran-2,4-dione (**8a**).** Mp. 152-153 °C, yield 76%. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz, δ): 2.14 (s, 3H, CH<sub>3</sub>), 3.40 (dd, H<sub>A</sub>, *J* = 12.6, 9.5 Hz, CH<sub>2</sub>), 4.11 (s, H<sub>5</sub>, NH), 4.03 (dd, H<sub>M</sub>, *J* = 12.6, 3.3 Hz, CH<sub>2</sub>), 5.45 (dd, H<sub>X</sub>, *J* = 9.5, 3.3 Hz, PhCH), 5.76 (q, H<sub>5'</sub>), 6.97 (d, H<sub>6</sub>), 7.25 (t, H<sub>7</sub>), 7.06 (t, H<sub>8</sub>), 7.20 (d, H<sub>9</sub>), 7.61 (m, H<sub>2''</sub>), 8.19 (m, H<sub>3''</sub>), 8.19 (m, H<sub>5''</sub>), 7.61 (m, H<sub>6''</sub>), 15.52 (s, H<sub>1</sub>, NH). IR (ν<sub>max</sub>, KBr): 3399, 1705, 1644 cm<sup>-1</sup> (C=O). Mass (m/z): 396. Elemental Analysis: Found C, 63.48; H, 4.25; N, 10.50; C<sub>21</sub>H<sub>17</sub>N<sub>3</sub>O<sub>5</sub> requires: C, 63.47; H, 4.28; N, 10.57.

**6-Methyl-3-(4-(2-nitrophenyl)-4,5-dihydro-1*H*-benzo[*b*][1,4]diazepin-2(3*H*)-ylidene)-3*H*-pyran-2,4-dione (**8b**).** Mp. 208-209 °C, yield 72%. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz, δ): 2.06 (d, 3H, CH<sub>3</sub>), 3.56 (dd, H<sub>A</sub>, *J* = 12.9, 4.3 Hz, CH<sub>2</sub>), 4.09 (d, H<sub>5</sub>, NH), 4.26 (dd, H<sub>M</sub>, *J* = 12.9, 6.3 Hz, CH<sub>2</sub>), 6.00 (dd, H<sub>X</sub>, *J* = 6.3, 4.3 Hz, PhCH), 5.69 (q, H<sub>5'</sub>), 6.85 (d, H<sub>6</sub>), 7.19 (t, H<sub>7</sub>), 7.04 (t, H<sub>8</sub>), 7.18 (d, H<sub>9</sub>), 8.00 (dd, H<sub>3''</sub>, *J* = 8.1, 1.4 Hz), 7.43 (ddd, H<sub>4''</sub>, *J* = 7.7, 1.5 Hz), 7.52 (ddd, H<sub>5''</sub>, *J* = 7.9 Hz), 7.83 (dd, H<sub>6''</sub>), 15.67 (s, H<sub>1</sub>, NH). IR (ν<sub>max</sub>, KBr): 3399, 1708, 1642 cm<sup>-1</sup> (C=O). Mass (m/z): 396. Elemental Analysis: Found C, 63.42; H, 4.27; N, 10.59; C<sub>21</sub>H<sub>17</sub>N<sub>3</sub>O<sub>5</sub> requires: C, 63.47; H, 4.28; N, 10.57.

### NMR spectroscopy<sup>8</sup>

Solution NMR spectra were recorded on a Bruker DRX 400 (9.4 Tesla, 400.13 MHz for <sup>1</sup>H, 100.62 MHz for <sup>13</sup>C and 40.56 MHz for <sup>15</sup>N) spectrometer with a 5-mm inverse-detection H-X probe equipped with a z-gradient coil, at 300 K. Chemical shifts (δ in ppm) are given from internal solvent, CDCl<sub>3</sub> 7.26 for <sup>1</sup>H and 77.0 for <sup>13</sup>C, and for <sup>15</sup>N NMR nitromethane (0.00) was used as external standard. Coupling constants (*J* in Hz) are accurate to ± 0.2 Hz for <sup>1</sup>H. Typical parameters for <sup>1</sup>H NMR were spectral width 8000 Hz and pulse width 7.5 μs at an attenuation level of 0 dB. Typical parameters for <sup>13</sup>C NMR were spectral width 21 kHz, pulse width 10.6 μs at an attenuation level of -6 dB and relaxation delay 2 s; WALTZ-16 was used for broadband proton decoupling; the FIDS were multiplied by an exponential weighting (lb = 2 Hz) before Fourier transformation.

Selected parameters for ( $^1\text{H}$ - $^1\text{H}$ ) gs-NOESY were spectral width 8000 Hz, the acquisition data size was 1024 points and 16 transient was accumulated per increment, with a 1 s relaxation delay, 850 ms for the mixing time, for a total of 256 experiments, data processing using zero filling in the *F1* domain and shifted sine-bell apodization of factor 0 in both dimensions.

2D ( $^1\text{H}$ - $^{13}\text{C}$ ) gs-HMQC, ( $^1\text{H}$ - $^{13}\text{C}$ ) gs-HMBC and ( $^1\text{H}$ - $^{15}\text{N}$ ) gs-HMBC, were acquired and processed using standard Bruker NMR software and in non-phase-sensitive mode. Gradient selection was achieved through a 5% sine truncated shaped pulse gradient of 1 ms.

Selected parameters for ( $^1\text{H}$ - $^{13}\text{C}$ ) gs-HMQC and gs-HMBC spectra were spectral width 3000 (gs-HMQC) or 8000 (gs-HMBC) Hz for  $^1\text{H}$  and 12.0 kHz for  $^{13}\text{C}$ , 1024 x 256 data set, number of scans 2 (gs-HMQC) or 4 (gs-HMBC) and relaxation delay 1s. The FIDs were processed using zero filling in the *F1* domain and a sine-bell window function in both dimensions was applied prior to Fourier transformation. In the gs-HMQC experiments GARP modulation of  $^{13}\text{C}$  was used for decoupling.

Selected parameters for ( $^1\text{H}$ - $^{15}\text{N}$ ) gs-HMBC spectra were spectral width 8000 Hz for  $^1\text{H}$  and 12.5 kHz for  $^{15}\text{N}$ , 1024 x 256 data set, number of scans 4, relaxation delay 1s, 40 ms delay for the evolution of the  $^{15}\text{N}$ - $^1\text{H}$  long-range coupling. The FIDs were processed using zero filling in the *F1* domain and a sine-bell window function in both dimensions was applied prior to Fourier transformation.

**Density funtional theory (DFT) calculations.** The optimization of the structures of all compounds discussed in this paper was carried out at the hybrid B3LYP/6-31G\*\* level<sup>9,10</sup> with basis sets of Gaussian type functions using Spartan '02 for Windows.<sup>11</sup>

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