The reaction of *o*-phenylenediamine with α,β-unsaturated carbonyl compounds

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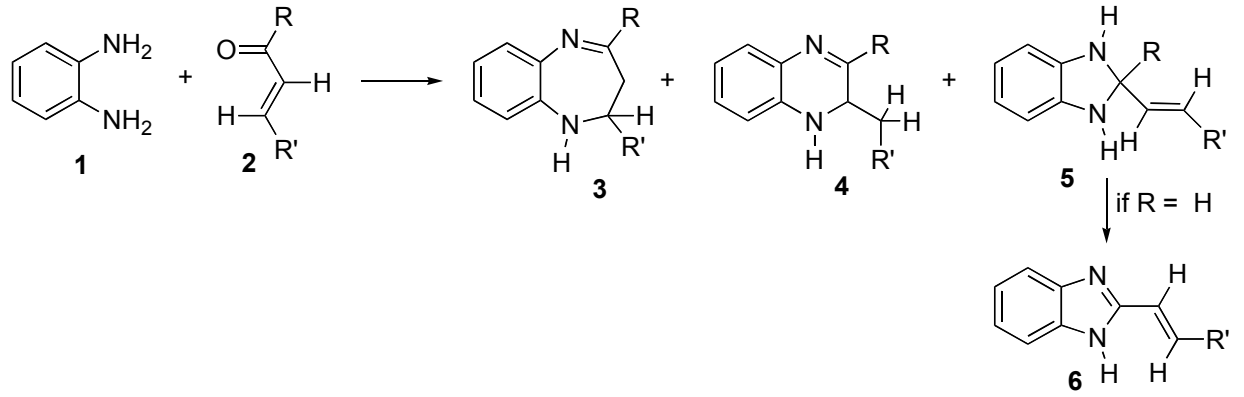
Abstract
The structures of the products obtained by the reaction of *o*-phenylenediamine and two isomeric chalcones have been identified as 1,5-benzodiazepines. A ^{1}H, ^{13}C and ^{15}N NMR study in solution combined with B3LYP/6-31G** calculations allowed to determine the conformations present in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

Keywords: Benzodiazepine; Karplus equation; Density functional theory calculations

Introduction

The reaction of binucleophiles like *o*-phenylenediamine **1** with α,β-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 α 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**.



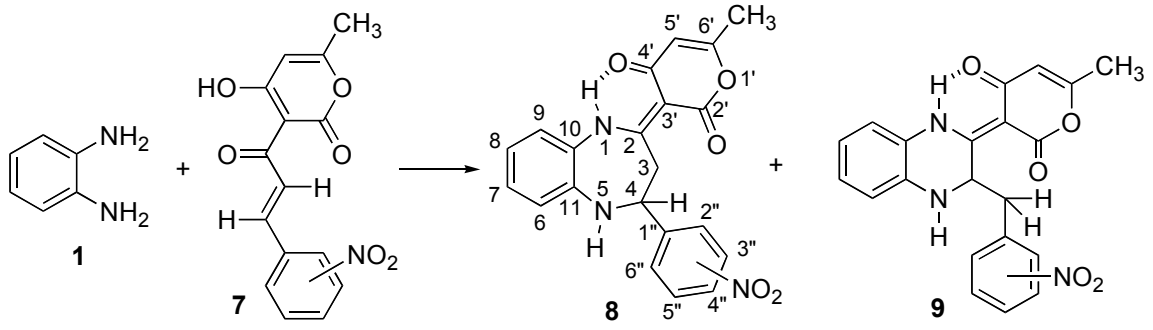
Scheme 1

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**[1] and the corresponding sulfur derivatives of **3** and **4** (NH replaced by S).[2,3] Vinyl (R' = H) and ethenyl (like styryl, R' = Ph) benzimidazoles **6** are usually prepared using other ways.[4,5]

The problem of differentiating between structures **3** and **4** has conclusively been solved by a rigorous analysis of their NMR spectral characteristics.[1,2] 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).[1]

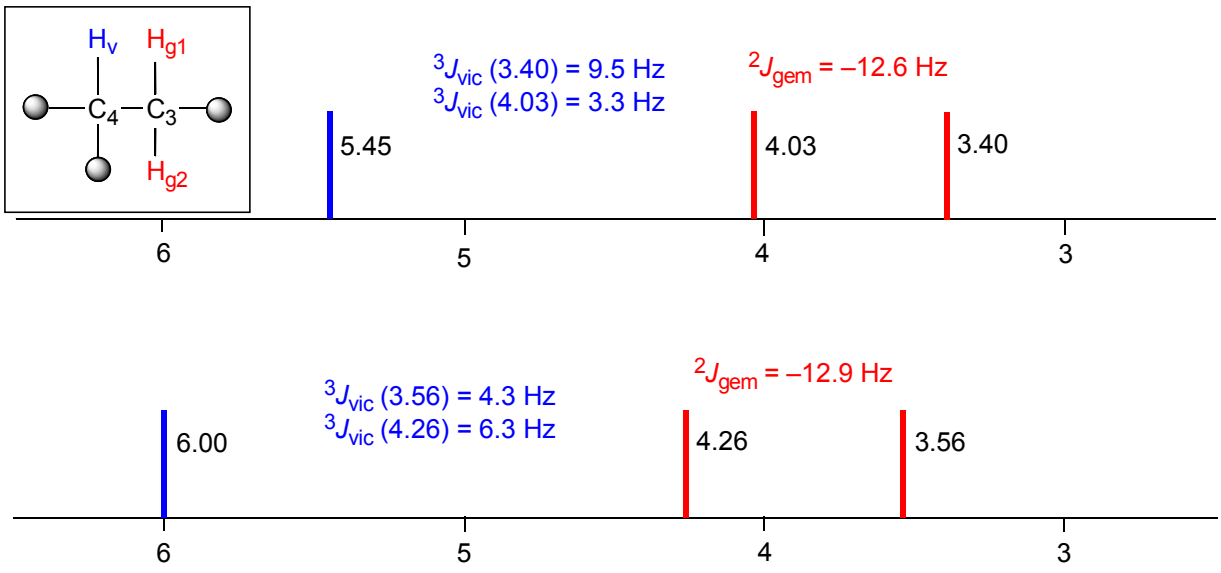


(**a**) 4-NO_2, (**b**) 2-NO_2

Scheme 2

The reaction affords in both cases only one compound. The main features of ^{1}H NMR spectra in $CDCl_3$ of the isolated compounds are reported in Figure 1.

(a) 4-NO_2 derivative



(b) 2-NO_2 derivative

Figure 1

It appears that the spectrum of the 4-NO_2 derivative is consistent with a 1,5-benzodiazepine (or thiazepine)[1,2] thus it corresponds to **8a**. However, that of the 2-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}C and ^{15}N NMR spectra of **8a** and that of the unknown 2-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[1] (similarly for benzothiazepines),[2] are much larger (see for instance N5) than those observed between the 4-NO_2 **a** and 2-NO_2 **b** derivatives. Highlighted in red are the most important differences related to the position of the nitro group which affect δC3, δC4 and the $^{1}J_{NH}$ coupling of N5.

Table 1. ^{13}C and ^{15}N chemical shifts (δ in ppm)of compounds **8a** and **8b** in $CDCl_3$

Atom	**8a**	**8b**	$\Delta\delta$ (**8a** –**8b**)	$\Delta\delta$ (**8** – **9**)[1]
N1	–219.2[a]	–218.5[c]	–0.7	8.0
C2	163.50*	162.9	0.6	---
C3	36.4	34.0	2.4	–1.1 (CH_2)
C4	67.3	63.5	3.8	14.5 (CH)
N5	–305.5[b]	–306.4[d]	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_3	19.9	19.8	0.1	0.0
C1"	151.0	137.4	---	---
C2"	126.92	(NO_2) 148.2	---	---
C3"	124.1	125.0	---	---
C4"	(NO_2) 147.6	128.8	---	---
C5"	124.1	133.0	---	---
C6"	126.92	128.2	---	---

[a] ^1J = 84.7 Hz; [b] ^1J = 82.3 Hz; [c] ^1J = 83.7 Hz (ΔJ N1= 1.0 Hz); [d] ^1J = 78.8 Hz (ΔJ N5= 3.5 Hz)

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

Table 2. ^{1}H chemical shifts (δ in ppm) and ^{1}H-^{1}H coupling constants (J in Hz) of compounds **8a** and **8b** in $CDCl_3$

Atom	**8a**	**8b**
H1 (NH)	15.52 (s)	15.67 (s)
H_A	3.40 (dd), $^2J_{AM} = -12.6$	3.56 (dd), $^2J_{AM} = -12.9$
H_M	4.03 (dd), $^3J_{MX} = 3.3$	4.26 (dd), $^3J_{MX} = 6.3$
H_X	5.45 (ddd),[a] $^3J_{AX} = 9.5$	6.00 (m), $^3J_{AX} = 4.3$
H5 (NH)	4.11 (s)	4.09 (d), $^3J_{H5X} = 3.3$
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), $^4J_{H5'CH3} = 0.9$	5.69 (q), $^4J_{H5'CH3} = 0.8$
CH_3	2.14 (d)	2.06 (d)
H2"	7.61 (m)	(NO_2)
H3"	8.19 (m)	8.00 (dd), $^3J_{H3"H4"} = 8.1$, $^4J_{H3"H5"} = 1.4$
H4"	(NO_2)	7.43 (ddd), $^3J_{H4"H5"} = 7.7$, $^4J_{H4"H6"} = 1.5$
H5"	8.19 (m)	7.52 (ddd), $^3J_{H5"H6"} = 7.9$
H6"	7.61 (m)	7.83 (dd)

[a] $J = 1.7$ 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,[6] allow the inference of certain conclusions about the conformational changes introduced in the seven-membered ring by the 2-NO_2 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:

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

Using eq. [1], the compounds should have the conformation represented in Figure 3. We have assumed a perfect ethane geometry with angles of 60º and 180º. In the case of the 4-NO_2 derivative **8a**, angles of 170º and 50º (with regard to H_M a *gauche* – 10º) 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_2 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_M, the H_X atom occupies in one case a *gauche* conformation (+15º) and in the other an *anti* conformation (–15º). The average couplings would be 4.5 Hz (instead of 4.3 Hz) and 5.7 Hz (instead of 6.3 Hz).

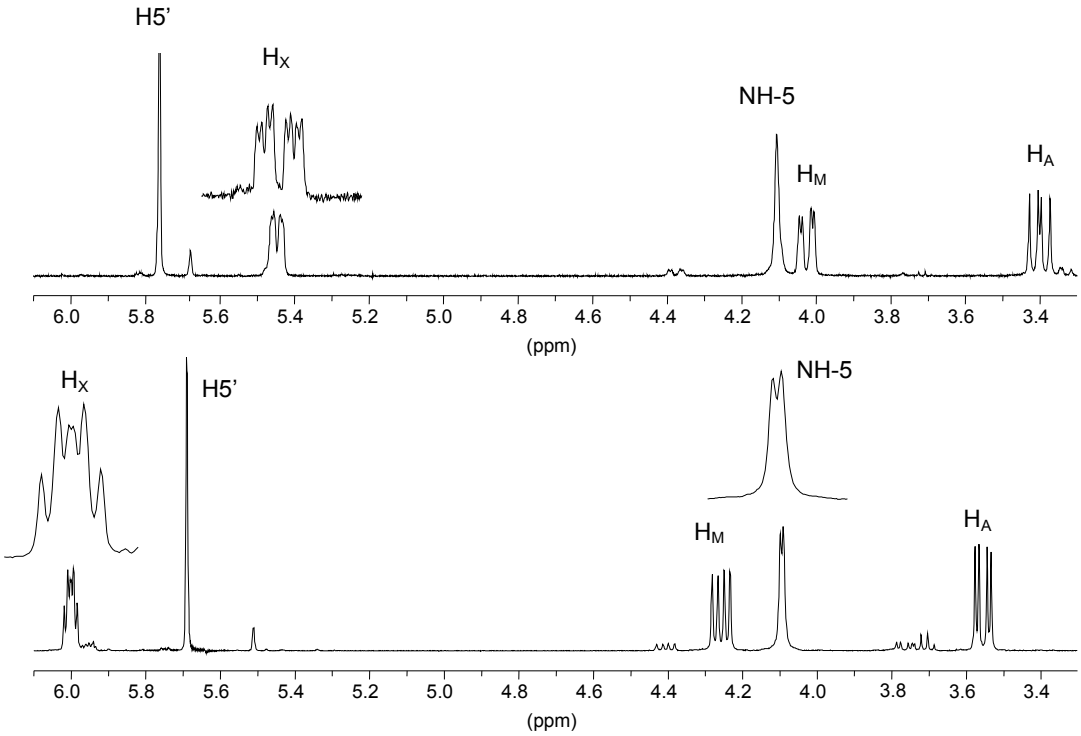


Figure 2. Experimental ^{1}H-NMR of 4-NO_2- (**8a** top) and 2-NO_2-isomers (**8b** bottom).

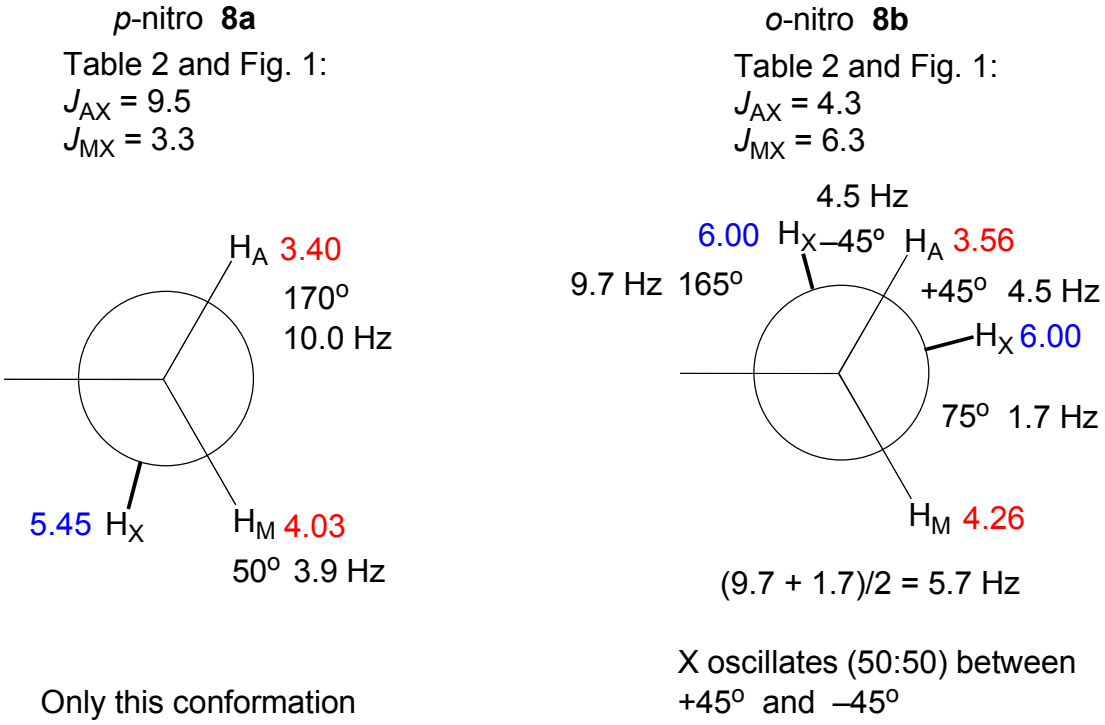


Figure 3

The validity of the conformations assigned to derivatives **8a** and **8b** were tested by carrying out Density Funtional 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_2 derivative **8a**, there are two minimum energy conformations with relative values of 0.0 and 4.7 kJ mol^{-1}, thus, we can assume that only the most stable one (Figure 4) is present in solution. This structure has HCCH dihedral angles of 179.7º and 61.4º (the C2-C3-C4-C1" angle amounts to 176.7º), close to those calculated in Figure 3 (170º and 50º, respectively).

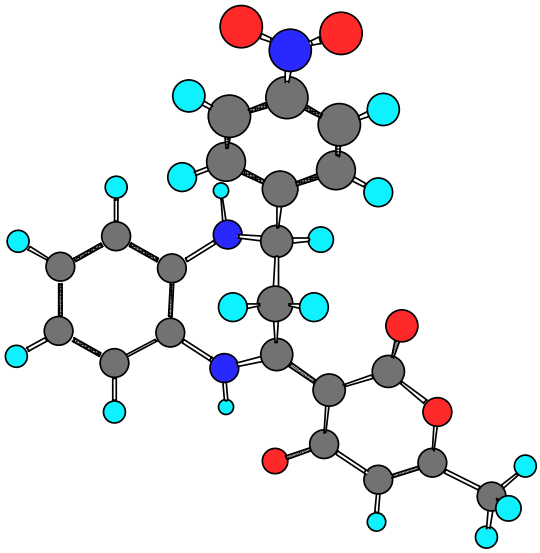


Figure 4. Minimum energy conformation of **8a.**

The 2-NO_2 derivative **8b** presents two conformations of similar energy, the **8b1** (E_{rel} = 0.0 kJ mol^{-1}) and the **8b2** (E_{rel} = 2.5 kJ mol^{-1}). The **8b1** (Figure 5) has HCCH dihedral angles of 65.4º and 52.3º (C2C3C4C1" = 71.3º) while those of **8b2** (Figure 6) are 177.1º and 56.9º (C2C3C4C1" = 176.0º). These angles can be compared with those of Figure 3: 75º and 45º for one conformation and 165º and 45º for the other.

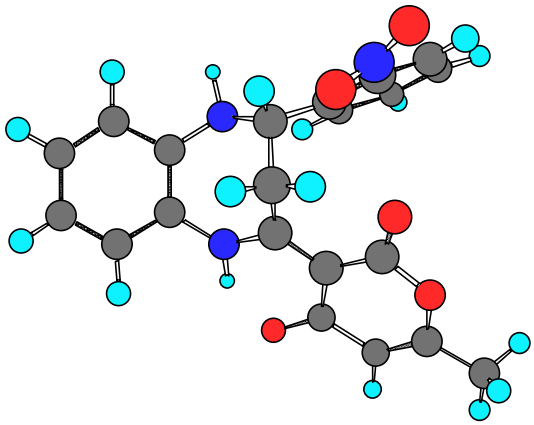


Figure 5. Minimum energy conformation of **8b1.**

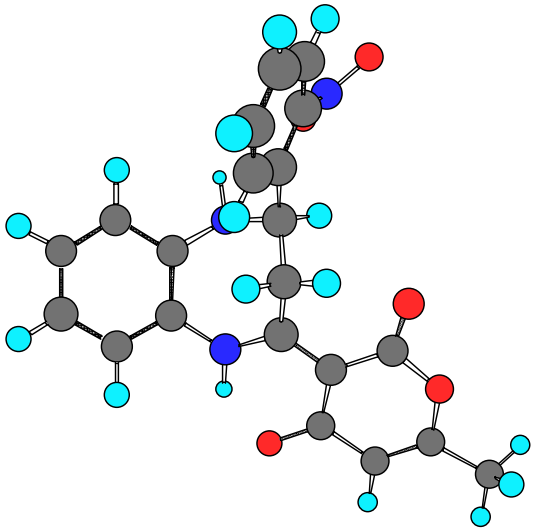


Figure 6. Minimum energy conformation of **8b2.**

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 δC3, δC4 and the $^{1}J_{NH}$ coupling of N5 are the most affected properties in Table 1. It also provides an explanation why in Figure 1, the H_X 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. ^{1}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-pyrones (chalcone analogs of DHA, **7a-b**) were prepared according to literature procedure.[7]

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%. ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 2.14 (s, 3H, CH_3), 3.40 (dd, H_A, J = 12.6, 9.5 Hz, CH_2), 4.11 (s, H5, NH), 4.03 (dd, H_M, J = 12.6, 3.3 Hz, CH_2), 5.45 (dd, H_X, J = 9.5, 3.3 Hz, PhCH), 5.76 (q, H5′), 6.97 (d, H6), 7.25 (t, H7), 7.06 (t, H8), 7.20 (d, H9), 7.61 (m, H2″), 8.19 (m, H3″), 8.19 (m, H5″), 7.61 (m, H6″), 15.52 (s, H1, NH). IR (ν_{max}, KBr): 3399, 1705, 1644 cm^{-1} (C=O). Mass (m/z): 396. Elemental Analysis: Found C, 63.48; H, 4.25; N, 10.50; $C_{21}H_{17}N_3O_5$ 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%. ^{1}H NMR ($CDCl_3$, 300 MHz, δ): 2.06 (d, 3H, CH_3), 3.56 (dd, H_A, J = 12.9, 4.3 Hz, CH_2), 4.09 (d, H5, NH), 4.26 (dd, H_M, J = 12.9, 6.3 Hz, CH_2), 6.00 (dd, H_X, J = 6.3, 4.3 Hz, PhCH), 5.69 (q, H5′), 6.85 (d, H6), 7.19 (t, H7), 7.04 (t, H8), 7.18 (d, H9), 8.00 (dd, H3″, J = 8.1, 1.4 Hz), 7.43 (ddd, H4″, J = 7.7, 1.5 Hz), 7.52 (ddd, H5″, J = 7.9 Hz), 7.83 (dd, H6″), 15.67 (s, H1, NH). IR (ν_{max}, KBr): 3399, 1708, 1642 cm^{-1} (C=O). Mass (m/z): 396. Elemental Analysis: Found C, 63.42; H, 4.27; N, 10.59; $C_{21}H_{17}N_3O_5$ requires: C, 63.47; H, 4.28; N, 10.57.

NMR spectroscopy[8]

Solution NMR spectra were recorded on a Bruker DRX 400 (9.4 Tesla, 400.13 MHz for ^{1}H, 100.62 MHz for ^{13}C and 40.56 MHz for ^{15}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, $CDCl_3$ 7.26 for ^{1}H and 77.0 for ^{13}C, and for ^{15}N NMR nitromethane (0.00) was used as external standard. Coupling constants (J in Hz) are accurate to ± 0.2 Hz for ^{1}H. Typical parameters for ^{1}H NMR were spectral width 8000 Hz and pulse width 7.5 μs at an attenuation level of 0 dB. Typical parameters for ^{13}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}H-^{1}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 *F*1 domain and shifted sine-bell apodization of factor 0 in both dimensions.
2D (^{1}H-^{13}C) gs-HMQC, (^{1}H-^{13}C) gs-HMBC and (^{1}H-^{15}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}H-^{13}C) gs-HMQC and gs-HMBC spectra were spectral width 3000 (gs-HMQC) or 8000 (gs-HMBC) Hz for ^{1}H and 12.0 kHz for ^{13}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 *F*1 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}C was used for decoupling.
Selected parameters for (^{1}H-^{15}N) gs-HMBC spectra were spectral width 8000 Hz for ^{1}H and 12.5 kHz for ^{15}N, 1024 x 256 data set, number of scans 4, relaxation delay 1s, 40 ms delay for the evolution of the ^{15}N-^{1}H long-range coupling. The FIDs were processed using zero filling in the *F*1 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[9,10] with basis sets of Gaussian type functions using Spartan '02 for Windows.[11]

Acknowledgements

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