Synthesis and structural investigation of some 1,4-disubstituted-2-pyrrolidinones

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Abstract

A series of 1,4-disubstituted 2-pyrrolidinones was synthesized by condensation of 1-aryl-4-hydrazinecarbonyl-2-pyrrolidinones with aromatic aldehydes, acetone, 2-butanone, and 2,4-pentane-dione. Most of the reaction products have isomers owing to the amide and azomethine structural units in their molecules. Computer molecular modeling was used to study individual features of each isomer. The structures of the synthesized compounds were unambiguously elucidated by combining IR, mass, ^{1}H, and ^{13}C NMR spectroscopy on the basis of the theoretical characteristics derived from molecular modeling. In this work the NMR spectra of the studied compounds **3**–**9** revealed a successful choice of the representative examples and good support for the explication of the peculiarities of *s-cis* and *s-trans* isomers formed in amides by the existence of *E*/*Z*- configurations in azomethine fragments using solvents of different polarity. Data for the complete NMR assignments are presented.

Keywords: 1,4-Disubstituted-2-pyrrolidinones, NMR spectra, isomerization, molecular modeling

Introduction

We continued our interest in the chemistry of N-aryl- substituted amino acids and products of their cyclization. It is important to note that the series of synthesized hydrazones examined in the present work may be obtained as *E/Z*- geometric isomers. Furthermore, the molecules of such hydrazones contain mono-substituted amide structural fragments which, depending on the circumstances, can produce various associates, possibly because the compounds prepared exist mainly as mixtures of isomers, so their detailed structural analysis is complicated.

NMR spectra appear to be especially useful for structural characterization of mixtures of stereoisomers. Elucidation of the intricate NMR spectra of these compounds was possible only through ascertaining the completeness of effects by considering the data derived from computer molecular modeling computations.

The aim of our work was the synthesis of compounds **3**–**10** and the choice of relevant approaches to the structural analysis of the synthesized products distinguished by their property to form isomers of different orientation and origination.

The compounds prepared are important reagents for the synthesis of carbohydrazides, hydrazones and heterocycles which are used for chemical and pharmacological purposes and show analgesic, antidepressive, antibacterial,[1] and anti-inflammatory [2] activities.

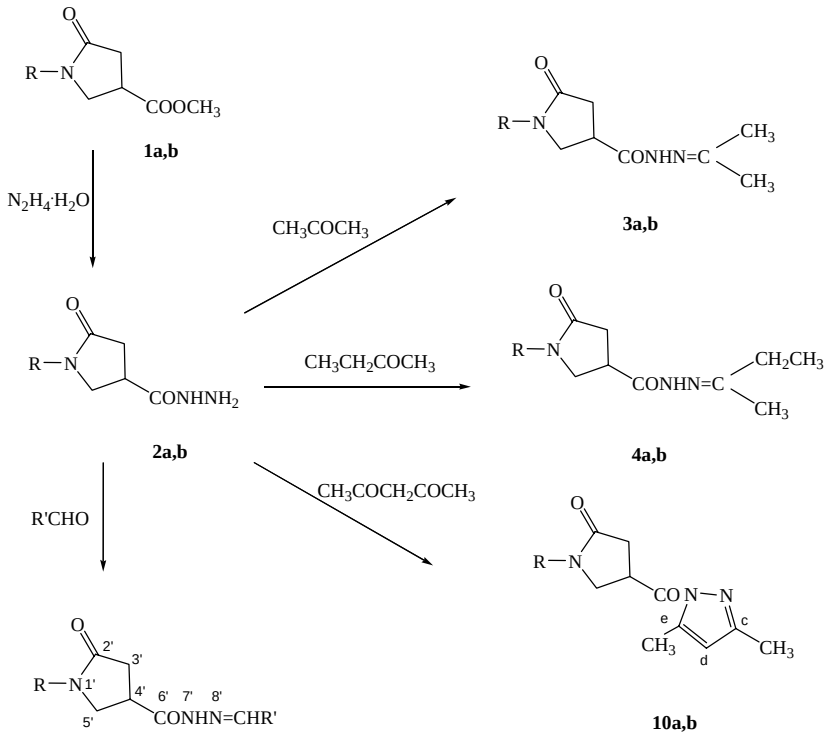
Results and Discussion

The synthesis of substituted 2-pyrrolidinones containing aromatic and carbohydrazide, hydrazone, or pyrazolylcarbonyl fragments is outlined below in Scheme 1. The corresponding carbohydrazides **2a,b** were synthesized in good yields (Table 1) by reacting methyl esters **1a,b** with hydrazine hydrate in 2-propanol under reflux. Condensation of 1-aryl-4-hydrazinecarbonyl-2-pyrrolidinones **2** with acetone gave the corresponding isopropylidenehydrazinecarbonyl-2-pyrrolidinones **3a,b** and with 2-butanone furnished methylpropylidenehydrazinecarbonyl-2-pyrrolidinones **4a,b**. The carbohydrazides **2** reacted with aromatic aldehydes in boiling 2-propanol resulting in formation of 1-aryl-4-arylidenehydrazinecarbonyl-2-pyrrolidinones **5**–**9**.
It was reported [3] that the reaction of N-substituted hydrazines with β–dicarbonyl compounds led to the pyrazole structure. 1-Aryl-4[(3,5-dimethylpyrazol-1-yl)carbonyl]-2-pyrrolidinones **10a,b** were synthesized by condensation of hydrazides **2** with 2,4-pentanedione in 2-propanol in the presence of a catalytic amount of hydrochloric acid.

The structures of the synthesized compounds **2**–**10** were investigated by IR, mass, and ^{1}H, and ^{13}C NMR spectroscopy. In the present work, the structural elucidation was mainly focused on the analysis of NMR spectra closely linked to the molecular modeling data. The assignments of NMR resonances rested on the chemical shifts,[4,5] signal intensity, multiplicities, and comparison with structurally related compounds. An APT ^{13}C NMR experiment was used to prove the interpretation of carbon resonances in some cases. The data on ^{1}H and ^{13}C NMR chemical shifts are summarized in Tables 2–5. The carbon atoms are marked arbitrarily according to the numbering given in Scheme 1.

The compounds **3**–**9** studied possess amide and azomethine groups. These structural fragments allowed the formation of isomers [6–12] notably reflected in the NMR spectra. The NMR spectra of compounds **3a**,**4a** and **8a** were recorded in $CDCl_3$ and d_6-DMSO. These solvents exhibit different polarization and electron donation properties,[13-15] and examination of the spectra of the above compounds using different solvents showed dissimilar appearances.

No CONH rotational isomers were observed in $CDCl_3$. The proton of the CONH group in ^1H NMR spectra of compound **3a** in $CDCl_3$ occurs as a broadened singlet (Fig. 1) produced by free rotation around the amide bond. Compound **4a** showed two broadened singlets with an intensity ratio 1:5 (Fig. 1) attributed to the existence of *E/Z*- stereoisomers caused by the arrangement of substituents in the azomethine group.



Scheme 1. Synthesis of 1,4-disubstituted 2-pyrrolidinones

Two sets of resonances of the two CH_3 groups in compound **3a** are caused by their different locations with respect to the nitrogen's lone pair in the azomethine group. The difference in the chemical shift of these groups in ^{13}C NMR spectra reaches 9 ppm, and in the ^1H NMR spectra –0.13 ppm. Compound **4a** bears different substituents on the azomethine group. Two sets of resonances (intensity 1:5) differing by 0.10 ppm for CH_3, 0.03 ppm for CH_2CH_3 were registered in the ^1H NMR spectra due to the non-equivalence of the substituents. The corresponding resonances in the ^{13}C NMR spectra were slight, but the existence of their traces was sufficient evidence of changes in the geometry of this compound.

The spectra of compounds **3a,b** and **4a,b** in d_6-DMSO were found to be more complicated. Taking into account that dimethyl sulfoxide, as a polar solvent with donor sites, is capable of

forming hydrogen bonds, it can be assumed that some stabilization of the structural fragment CONH has happened. Consequently, the appearance of competitive intermolecular hydrogen bonds between substance–substance, substance–solvent, and internal hydrogen bonds caused the existence of quite stable *E/Z*- rotamers (describing the arrangement of substituents in terms of a single bond N-C in amides, the rotamers can be termed as *s-cis/s-trans* rotamers).[16-18]

The best way to prove the existence of isomers determined by the CONH conformation was the detection of ^{1}H NMR resonances in the low-field region. The two sets of resonances observed in the NMR spectra of compounds **3a** (Fig. 1) and **3b** in d_6-DMSO proved the hindered rotation in the CONH group. Moreover, the existence of rotamers owing to the CONH group and of the stereoisomers due to the azomethine group was observed in compounds **4a** (Figure 1) and **4b**. A stronger-field side signal was related to the resonance of the isomer with the Z structure.[4,5]

The arrangement of all possible separate isomers of compounds **3a,b**–**9a,b** was studied by computer molecular modeling using MM2 molecular mechanics and AM1, PM3 semi-empirical quantum mechanical methods.[19] Optimized to a minimum of total steric energy the models of the molecules of the compounds studied revealed their compactly folded spatial view. Computational methods in this work were used to perform a more specialized function such as a search of conformation. The possibility of formation of *E/Z*- rotation isomers in the amide fragment evaluated by studies of the rotation barrier allowed us to estimate the energetically favored and disfavored transition states of the rotamer.[19–21] The values of rotation barriers of the optimized models of the different isomers of compounds **3a** (*E*, *Z*), **4a** (*ZZ*, *EZ*, *ZE*, *EE*) and **8a** (*ZZ*, *EZ*) varied between 7–10 kcal/mol. It was noticed that the rotation barrier of *Z*- isomers in all these compounds was lower–varying between 7–8 kcal/mol. The existence of the *ZE*- and *EE*-stereoisomers was ruled out for **8a** because of the higher values of the rotation barriers (36.3 kcal/mol and 14.4 kcal/mol).

The data obtained by modeling reflected structural characteristics analogous to the ^{1}H NMR spectral findings. The total steric energy obtained for compound **3a** was almost equal (–0.4 kcal/mol) for *E/Z*- isomers, in the case of compound **3b** it reached – 4.5 kcal/mol for E/Z isomers. The values of total steric energies of the four possible isomers (Figure 1): E_{ZZ} = 0.7 kcal/mol (δ_{NH} = 10.21 ppm), E_{ZE} = 1.7 kcal/mol (δ_{NH} = 10.27 ppm), E_{EZ} = 0.4 kcal/mol (δ_{NH} = 10.35 ppm), E_{EE} = 0.6 kcal/mol (δ_{NH} = 10.43 ppm) of the model of compound **4a,** was followed by the changes of intensities of corresponding resonances of the NH group.

The compounds **5**–**8** are aryl-, and compound **9** carbazolyl- monosubstituted hydrazones. This type of hydrazones mostly exists as the *E*- geometric isomer.[22–24] The molecular modeling data discussed above clearly indicate the formation of Z- isomers of compounds **5–9**. The ^{1}H NMR spectra of these compounds present a broadened singlet in $CDCl_3$, and two resonances (intensity 3:5) for the CONH group proton in d_6-DMSO (Figure 1).

The compounds **10a,b** are pyrazole derivatives. Characteristic resonances found at 152 ppm, 143 ppm and 111 ppm are assigned to the carbons of the pyrazole ring. The signal at 6.25 ppm in ^{1}H NMR spectra fitted to the proton of CH= fragment in the pyrazole ring.[25-28]

The ^{1}H NMR multiplets of the pyrrolidinone ring of compounds **3–9** are intricate and difficult to resolve.[29–31] The integral intensity is not distributed evenly in accordance to the number of protons of $COCH_2$, CH and NCH_2 fragments. A comparison of chemical shifts of pyrrolidone ring carbons of **a**, **b** type compounds studied indicates that the C-5' atom is deshielded by about 2 ppm and the C-2', C-3' atoms are a little more shielded in the **b** series. The experimental and theoretical investigations of the structure of the analyzed compounds **3–9** by NMR spectroscopy revealed that the pyrrolidone ring should be influenced by the arrangement of amide rotamers, the formation of associates due to hydrogen bonds, the location of the substituents in the 1N- aryl, and the nature of substituents in the azomethine group. The origination of an extended π-system between the 1N-aryl fragment and N(1')-C(2') bond in the pyrrolidinone ring was observed during the structure optimization using computer molecular modeling methods. The RMS deviation from the plane computed for the optimized models of the studied compounds showed more twisting of the pyrrolidone plane for the **b**- type compounds in comparison with the **a** type (for **3a** *E/Z* – 0.02 Å, for **3b** *E/Z* – 0.12 Å). Presumably, the circumstances mentioned above specifically affect the pyrrolidinone ring, inducing the unexpected behavior of structural changes observed in the NMR spectra.

Experimental Section

General Procedures. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Inova 300 MHz spectrometer operating in the Fourier transform mode with TMS as internal standard. Melting points were determined on an automatic APA1 melting point apparatus and are uncorrected. The IR spectra were determined in potassium bromide pellets on a Perkin–Elmer FT-IR system spectrum GX spectrometer. Mass spectral data were obtained using a Waters (Micromass) ZQ 2000 Spectrometer. The physical properties, analytical data and yields of the prepared compounds are given in Table 1.

The molecular modeling of the studied compounds was carried out using Chem 3D Ultra 9.0.[19] The rotational barrier of the isomers was obtained on the basis of the corresponding molecular model with minimized steric energy. The bond of interest – (C6')–(N7') was selected and allowed to rotate (Dihedral driver from the Calculations menu). The dihedral angle was rotated in 5 degrees increments through 360 degrees for a total of 72 conformations to produce the graph. The steric energy was minimized for each point.

1-Aryl-4-hydrazinecarbonyl-2-pyrrolidinones (2a,b). A solution of 0.2 mol of the corresponding ester **1a,b**, 29.8 g (0.6 mol) of hydrazine hydrate, and 30 ml of 2-propanol was heated under reflux for 1 h. The mixture was cooled, the precipitate filtered, then washed with 2-propanol and diethyl ether.

1-Aryl-4-izopropylidenehydrazinecarbonyl-2-pyrrolidinones (3a,b). A solution of 2.0 g (7.5 mmol) of the corresponding hydrazides **2a,b** and 30 ml of acetone was refluxed for 3 h. The reaction mixture was cooled, the precipitate filtered, and washed with diethyl ether.

1-Aryl-4-methylpropylidenehydrazinecarbonyl-2-pyrrolidinones (4a,b). A solution of 2.0 g (7.5 mmol) of the corresponding hydrazides **2a,b** and 30 ml of 2-butanone was refluxed for 3 h. The reaction mixture was cooled and the precipitate filtered off and washed with diethyl ether.

1-Aryl-4-arylidenehydrazinecarbonyl-2-pyrrolidinones (5–9a,b). A solution of hydrazide **2a,b** (2.0g, 7.5 mmol), 11.25 mmol of the corresponding aldehyde, and 30 ml of ethanol were refluxed for 3 h. The reaction mixture was cooled, the precipitate filtered, then washed with ethanol and diethyl ether.

1-Aryl-4-[(3, 5–dimethylpyrazole-1-yl)carbonyl]-2-pyrrolidinones (10a,b). A solution of 2.0 g (7.5 mmol) of the corresponding hydrazides **2a,b**, 2.25 g (22.5 mmol) of 2,4-pentanedione, and 30 ml of 2-propanol was refluxed for 3 h with a catalytic amount of hydrochloric acid. The solvent was evaporated in vacuum, then the product was precipitated from water, filtered, and washed with water.

Supplementary Information Available

Table 1. Characteristic data of compounds **2–10**
Table 2. ^{13}C NMR chemical shifts of compounds **2a,b, 3a,b, 3a***
Table 3. ^{13}C NMR chemical shifts of compounds **4a*, 4a,b**
Table 4. ^{13}C NMR chemical shifts of compounds **6a, 7b, 10a,b, 8a***
Table 5. Mass, IR and ^{1}H NMR spectroscopic data of compounds **2-10**
Figure 1. ^{1}H NMR spectral region of NH resonances of compounds **3a**, **4a** and **8a**

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