Short communication

Synthesis of 3',4'-Dihydro-2*H*,2'*H*,5*H*-spiro [imidazolidine-4,1'-naphthalene]-2,5-dione and its Derivatives

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Abstract

The synthesis of two novel compounds, 1-amino-3',4'-dihydro-2*H*,2'*H*,5*H*-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione and 1,3-bis(hydroxymethyl)-3',4'-dihydro-2*H*,2'*H*,5*H*-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione, was reported. The structures of the compounds were verified by ^{1}H, ^{13}C NMR and IR spectroscopy and quantum-chemical calculations at DFT level.

Keywords: tetralinspirohydantoins, imidazolidine, synthesis, DFT, GIAO, NMR.

1. Introduction

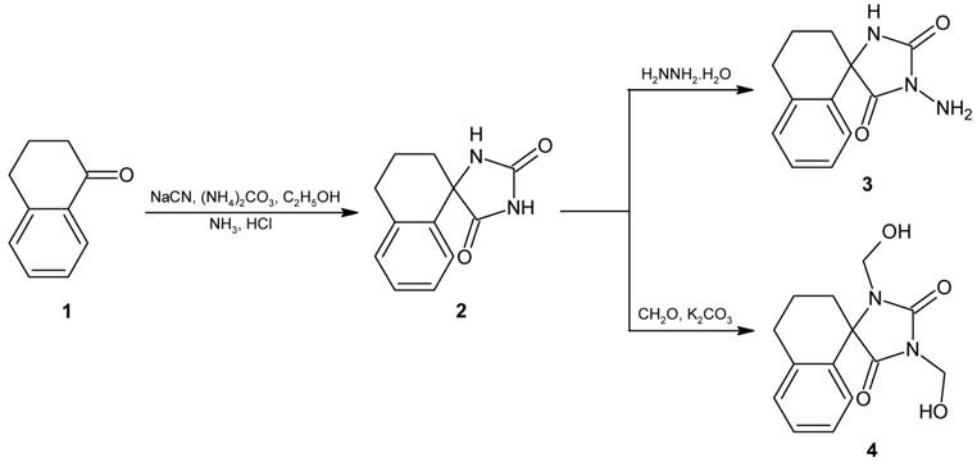
One of the most important applications of the spirohydantoins (derived from cyclic ketones fused to aromatic ring or ring system) is their ability to inhibit aldose reductase (NADPH-linked enzyme catalyzing the sorbitol formation from glucose). Several spirohydantoins, including substituted indan, tetralin, chroman and thiochroman hydantoins have been synthesized and described as inhibitors of aldose reductase isolated from calf lens.[1] Similar activity has been found for (9'-fluorene)-spiro-5-hydantoin (spiro-(fluorene-9,4'-imidazolidine)-2',5'-dione) and its derivatives[2–4] which makes them useful in the treatment of complications arising from diabetes. Some representatives of these compounds also have antitumor activity.[5,6]

Different methods for the synthesis of monothio- and dithio- analogues of cycloalkanespiro-5-hydantoins have been developed by us.[7,8]

The present paper describes the synthesis of *N*-substituted tetralinspiro-5-hydantoins. Quantum-chemical calculations at DFT level are also performed to elucidate their structure.

2. Results and Discussion

3',4'-Dihydro-2*H*,2'*H*,5*H*-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione (**2**, Scheme 1) was synthesized through a modification of the method reported by Sarges et *al*.[1] The procedure described in the present paper is based on the interaction of 3,4-dihydronaphthalen-1(2*H*)-one (**1**, Scheme 1) with NaCN, $(NH_4)_2CO_3$, 96% C_2H_5OH and 25% aqueous NH_3 in an autoclave and heating at 125 °C for 3.5 hours. The significant decrease of the reaction time (from 24 to 3.5 hours) is an advantage of this procedure.



Scheme 1. Synthesis of *N*-substituted tetralinspiro-5-hydantoins

The chemical structure of **2** was confirmed by ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H NMR spectrum shows two signals at 8.54 and 10.84 ppm characteristic of NH protons. The ^{13}C NMR chemical shifts analysis was facilitated by the comparison of the values obtained by the GIAO B3LYP/6-311+G(2df,p) calculations. Resonance peaks of C13 and C11 (Figure 1) appear at 156.6 and 178.1 ppm, respectively (Table 1). They are in excellent agreement with the calculated values. Substantial difference between calculated and experimental values ($\delta_{calc} - \delta_{exper} = 11$ ppm) is observed for C5.

The spirohydantoin **2** was treated with concentrated hydrazine hydrate in order to obtain the new compound **3**. The initial experiment was carried out by refluxing 10 mmol of 3',4'-dihydro-2*H*,2'*H*,5*H*-spiro[imidazolidine-

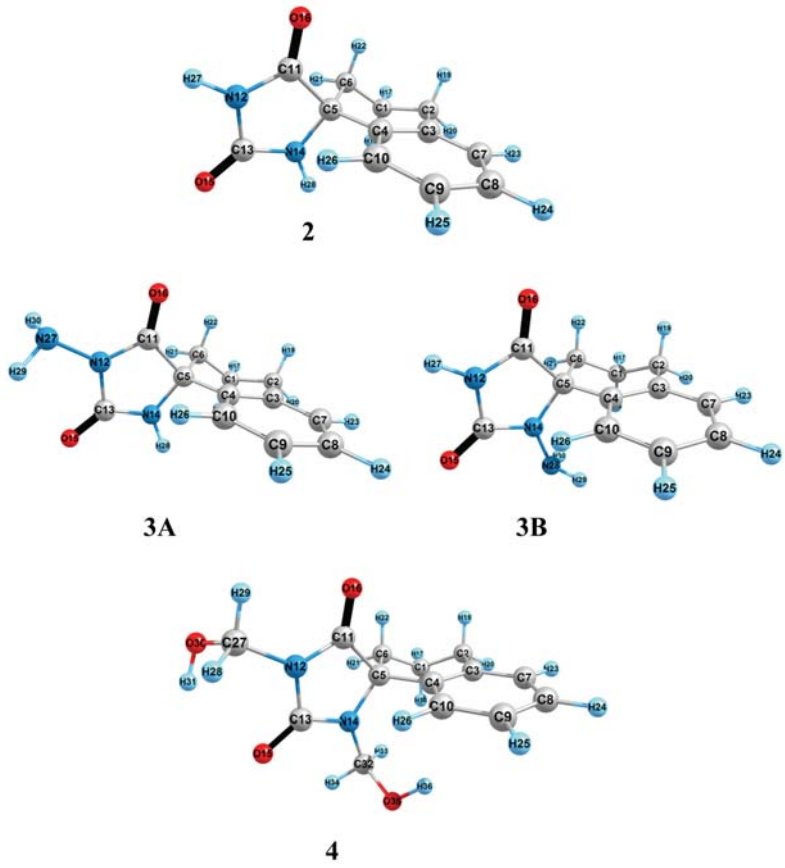


Figure 1. B3LYP/6-311+G(d,p) optimized structures of compounds **2**–**4** shown in Scheme 1.

Table 1. GIAO ^{13}C chemical shifts of **2–4** calculated at BPW91/6-311+G(2df,p) level and experimental data in DMSO-d_6. The geometry is optimized at B3LYP/6-311+G(d,p) level. For the numbering of the atoms see Figure 1.

Nuclei	2		3A		3B	4	
	calc	exptl	calc	exptl	calc	calc	exptl
C5	74.17	63.2	70.99	60.5	77.69	72.00	64.9
C11=O	179.84	178.1	177.29	179.8	176.88	178.53	174.7
C13=O	156.66	156.6	158.62	155.9	156.13	158.31	155.0
C27–OH						70.32	61.4
C32–OH						71.60	63.3

4,1'-naphthalene]-2,5-dione (**2**) with 130 mmol of hydrazine hydrate for 4.5 h. The compound **3** was obtained with 69% yield. The significantly higher yield of the product is due to the change of the reaction conditions. The interaction of 30 mmol of **2** with 260 mmol of hydrazine hydrate at reflux for 5 h led to the formation of 1-amino-3',4'-dihydro-2*H*,2'*H*,5*H*-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione (**3**, Scheme 1) with 78% yield.

Two isomers of compound **3** are possible: 1-amino-3',4'-dihydro-2*H*,2'*H*,5*H*-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione (**3A**) and 3-amino-3',4'-dihydro-2*H*,2'*H*,5*H*-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione (**3B**) (Figure 1). According to our B3LYP/6-311+G(d,p) calculations the isomer **3A** is more stable by 2.03 kcal mol^{-1} than **3B**. This result is consistent with the data obtained from ^{13}C NMR (Table 1) in DMSO-d_6. Two carbonyl signals at 178.1 and 156.6 ppm, and a signal at 63.2 ppm for the spiro carbon, which are in a better agreement with the calculated values for **3A**, indicate presence of this isomer.

1,3-Bis(hydroxymethyl)-3',4'-dihydro-2*H*,2'*H*,5*H*-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione (**4**, Scheme 1), was obtained by treatment of 3',4'-dihydro-2*H*,2'*H*,5*H*-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione (**2**) with 38% aqueous CH_2O and K_2CO_3 at normal conditions. The carbonyl signals of C13 and C11 (Figure 1) in the ^{13}C NMR spectrum of **4** appear at 155.0 and 174.7 ppm, respectively (Table 1). They are down-field shifted in comparison to respective signals for **2** while the signal at 64.9 ppm for the spiro carbon is up-field shifted. Two signals at 61.4 and 63.3 ppm are characteristic of C27 and C32 (CH_2OH) carbons. The calculated values are in good agreement with the experimental ones (Table 1).

The B3LYP/6-311+G(d,p) calculated structures of tetralinspiro-5-hydantoins **2–4** are shown in Figure 1 and the bond length values are listed in Table 2. The substitution of hydrogen atoms connected to nitrogen atoms in five-membered ring of **2** with CH_2OH groups leads to some structural changes in **4.** The C5–N14 and C13=O15 bonds lengthen by 0.007 Å and 0.006 Å, respectively, while the N12–C13 bond shortened. The structural changes in five-membered ring of **3A** are different as a result of the substitution of the hydrogen atom at N12 of **2** with an amino group. The N12–C13 and C11–N12 bonds lengthen by 0.005 Å and 0.006 Å, while the C13–N14 bond shortened by 0.004 Å.

Table 2. Selected bond lengths (in Å) for compounds **2–4** as calculated at B3LYP/6-311+G(d,p) level. For the numbering of the atoms see Figure 1.

Bond	2	3A	4
C5–N14	1.475	1.477	1.482
C13–N14	1.370	1.366	1.369
N12–C13	1.410	1.415	1.407
C11–N12	1.377	1.383	1.377
C5–C11	1.553	1.551	1.554
C11=O16	1.206	1.204	1.207
C13=O15	1.209	1.211	1.215

3. Experimental

3. 1. General

All chemicals used were purchased from Merck and Sigma-Aldrich. The melting points were determined with a digital melting point apparatus SMP 10. NMR spectra were taken on a Bruker Avance II + 600 MHz spectrometer, operating at 600.130 and 150.903 MHz for ^1H and ^{13}C, respectively, using the standard Bruker software. Chemical shifts were referenced to tetramethylsilane (TMS). Measurements were carried out at ambient temperature. The elemental analysis data were obtained with an automatic analyzer Carlo Erba 1106. The FTIR spectra were recorded with a VERTEX 70 FT-IR spectrometer (Bruker Optics). The crystals were stirred with KBr. The spectra are from 4000 cm^{-1} to 400 cm^{-1} at resolution 2 cm^{-1} with 49 scans. The purity of the compounds was checked by thin layer chromatography on Kieselgel 60 F_{254}, 0.2 mm Merck plates, eluent system (vol. ratio): benzene : ethanol = 5 : 1. Mass spectra were recorded using LCQ-DUO LCMS^2 System Electrospray Interface on CH-5 Varian MAT spectrometer at 70 eV.

3. 2. Synthesis of 3',4'-Dihydro-2*H*,2'*H*,5*H*-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione (2, Scheme 1) (a modification of the method reported by Sarges et al.[1])

A suspension of 13.3 mL (14.62 g, 100 mmol) of 3,4-dihydronaphthalen-1(2*H*)-one (**1**, Scheme 1), 7.35 g (150

mmol) NaCN, 28.8 g (300 mmol) $(NH_4)_2CO_3$, 150 mL 96% C_2H_5OH and 160 mL 25% aqueous NH_3 were heated in an autoclave at 125 °C for 3.5 h. After cooling to the room temperature, the reaction mixture was poured into 750 mL of water and acidified to pH 2 with 6 N HCl. The light brown product crystallized was filtered off and washed with water until the washings attained a neutral pH. The obtained product **2** was recrystallized from tetrahydrofuran.

Yield: 18.5 g (86%); M. p. 243–244 °C (lit.[1] 240–242 °C); R_f = 0.65; Anal. calcd. for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96; found: C, 66.28; H, 5.51; N, 12.96%; IR (KBr, cm^{-1}): 3220 (N–H), 3051 (N–H), 2944 (arom.), 2869 (CH_2), 1767 (C=O), 1708 (C=O); ^{1}H NMR (δ, DMSO-d_6, ppm): 1.79–2.50 (m, 6H, aliph.), 7.05–7.24 (m, 4H, arom.), 8.54 (s, 1H, NH), 10.84 (s, 1H, NH); ^{13}C NMR (δ, DMSO-d_6, ppm): 18.5 (CH_2), 28.6 (CH_2), 33.6 (CH_2), 63.2 (spiro C-atom), 126.6 (CH, arom.), 126.7 (CH, arom.), 128.1 (CH, arom.), 129.4 (CH, arom.), 134.4 (C, arom.), 137.9 (C, arom.), 156.6 (C=O), 178.1 (C=O); ^{13}C DEPT-135 (δ, DMSO-d_6, ppm): 18.9 (CH_2), 28.9 (CH_2), 33.9 (CH_2), 127.0 (CH, arom.), 127.1 (CH, arom.), 128.5 (CH, arom.), 129.8 (CH, arom.). MS (*m/z*) 216 (M^+).

3. 3. Synthesis of 1-Amino-3',4'-dihydro-2*H*,2'*H*,5*H*-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione (3, Scheme 1)

A suspension of 6.48 g (30 mmol) 3',4'-dihydro-2*H*,2'*H*,5*H*-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione (**2**, Scheme 1) and 13.00 g (260 mmol) concentrated hydrazine hydrate was refluxed for 5 h. After cooling to the room temperature, the mixture was poured onto a small quantity of crushed ice. The colorless obtained product **3** was filtered off and recrystallized from ethyl acetate.

Yield: 5.4 g (78%); M. p. 187–188 °C; R_f = 0.54; Anal. calcd. for $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.67; N, 18.17; found: C, 62.18; H, 5.58; N, 17.98%; IR (KBr, cm^{-1}): 3406, 3343, 3230 (NH, NH_2), 3100 (arom.), 2870 (CH_2), 1779 (C=O), 1723 (C=O); ^{1}H NMR (δ, DMSO-d_6, ppm): 1.82–2.50 (m, 6H, aliph.), 7.01–7.25 (m, 4H, arom.), 4.84 (s, 2H, NH_2), 8.75 (s, 1H, NH); ^{13}C NMR (δ, DMSO-d_6, ppm): 18.4 (CH_2), 28.5 (CH_2), 33.6 (CH_2), 60.5 (spiro C-atom), 126.5 (CH, arom.), 126.9 (CH, arom.), 128.2 (CH, arom.), 129.4 (CH, arom.), 134.3 (C, arom.), 137.9 (C, arom.), 155.9 (C=O), 179.8 (C=O); ^{13}C DEPT-135 (δ, DMSO-d_6, ppm): 18.8 (CH_2), 28.9 (CH_2), 34.0 (CH_2), 126.9 (CH, arom.), 127.3 (CH, arom.), 128.5 (CH, arom.), 129.7 (CH, arom.). MS (*m/z*) 231 (M^+).

3. 4. Synthesis of 1,3-Bis(hydroxymethyl)-3',4'-dihydro-2*H*,2'*H*,5*H*-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione (4, Scheme 1)

A suspension of 8.23 g (38 mmol) 3',4'-dihydro-2*H*,2'*H*,5*H*-spiro[imidazolidine-4,1'-naphthalene]-2,5-dione (**2**, Scheme 1), 45 mL 38% aqueous CH_2O and 530 mg (3.8 mmol) K_2CO_3 was stirred for 24 h at room temperature. The obtained product **4** was filtered off and recrystallized from chloroform-petroleum ether mixture.

Yield: 8.1 g (77%); M. p. 140–141 °C; R_f = 0.58; Anal. calcd. for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14; found: C, 60.67; H, 5.71; N, 10.05%; IR (KBr, cm^{-1}): 3451 (OH), 3050 (arom.), 2942–2912 (CH_2) 1768 (C=O), 1683 (C=O); ^{1}H NMR (δ, DMSO-d_6, ppm): 1.89–2.83 (m, 6H, aliph.), 3.99–5.05 (m, 4H, CH_2OH), 6.06–6.08 (s, 1H, OH), 6.46–6.48 (s, 1H, OH), 6.87–7.27 (m, 4H, arom.); ^{13}C NMR (δ, DMSO-d_6, ppm): 18.6 (CH_2), 28.5 (CH_2), 32.2 (CH_2), 61.4 (CH_2OH), 63.3 (CH_2OH), 64.9 (spiro C-atom), 126.3 (CH, arom.), 126.8 (CH, arom.), 128.5 (CH, arom.), 129.8 (CH, arom.), 131.5 (C, arom.), 139.6 (C, arom.) 155.0 (C=O), 174.7 (C=O); ^{13}C DEPT-135 (δ, DMSO-d_6, ppm): 18.9 (CH_2), 28.8 (CH_2), 32.5 (CH_2), 61.7 (CH_2OH), 63.7 (CH_2OH), 126.6 (CH, arom.), 127.0 (CH, arom.), 128.7 (CH, arom.), 129.8 (CH, arom.). MS (*m/z*) 276 (M^+).

3. 5. Quantum-chemical Calculations

The calculations were carried out using the quantum chemical package GAMESS.[9] The geometries of the compounds (Scheme 1) were located at DFT level using the hybrid B3LYP functional which combines the three-parameter exchange functional of Becke[10] with the LYP correlation one[11] and 6-311+G(d,p) basis set, without symmetry constraints by the gradient procedure. The default gradient convergence threshold (1×10^{-4} Hartree $Bohr^{-1}$) was used. Frequency calculations at the same level of theory were carried out to determine whether the optimized structures are local minima on the potential energy surface.

The NMR chemical shieldings of the compounds were calculated at BPW91/6-311+G(2df,p) level using the GIAO approach[12,13] and B3LYP/6-311+G(d,p) optimized geometry. BPW91 uses the Becke[9] exchange functional and Perdew and Wang's[14] gradient-corrected correlation functional. Solvent effect of dimethylsulfoxide (DMSO) was accounted by using the self-consisted reaction field (SCRF) method with the conductor polarizable continuum model (CPCM) formalism.[15] In this model, the solvent is approximated as a structureless polarizable continuum characterized by its macroscopic dielectric permittivity, å. In order to compare the experimental data to the calculated values, absolute shieldings for carbon atoms were transformed to chemical shifts using the reference compound tetramethylsilane, $Si(CH_3)_4$: $\delta = \delta_{calc}(ref) - \delta_{calc}$. Both $\delta_{calc}(ref)$ and δ_{calc} were evaluated at the same computational level. All NMR calculations were carried out using the Gaussian 09 package.[16]

4. References

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Povzetek

Poročamo o sintezi dveh novih spojin, 1-amino-3',4'-dihidro-2*H*,2'*H*,5*H*-spiro[imidazolidin-4,1'-naftalen]-2,5-diona in 1,3-bis(hidroksimetil)-3',4'-dihidro-2*H*,2'*H*,5*H*-spiro[imidazolidin-4,1'-naftalen]-2,5-diona. Strukturo spojin smo dokazali z ^{1}H in ^{13}C NMR ter IR spektroskopijo in kvantnokemijskimi izračuni na nivoju DFT.