

Short Note

5'-Oxospiro-(fluorene-9,4'-imidazolidine)-2'-thione

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Abstract: The structure verification of 5'-oxospiro-(fluorene-9,4'-imidazolidine)-2'-thione by NMR is reported. Toward this aim, 2D NMR techniques including ¹H-¹H COSY, HMQC, and HMBC experiments were used to assist with the assignment of the ¹H and ¹³C chemical shifts for the corresponding structure. The mutual interpretation of the 1D and 2D NMR spectra ensured a complete and accurate ¹H and ¹³C NMR data assignment for 5'-oxospiro-(fluorene-9,4'-imidazolidine)-2'-thione.

Keywords: 5'-oxospiro-(fluorene-9,4'-imidazolidine)-2'-thione; spirohydantoin; assignment; NMR



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1. Introduction

The diverse bioactivity of spirohydantoin has a significant role in numerous practical applications. The lipase catalysis of 5,5-spirohydantoin is often responsible for the production of specific amino acids that benefit the synthesis of mGluR agonists [1,2] and phosphotyrosyl mimetics [3] as well as an increase in the drug transport efficiency through lipophilic membranes [4]. In addition, 1-substituted 5-spirohydantoin has been found to be suitable for the treatment of tropical diseases [5] whereas some cyclopropanespirohydantoin derivatives have been tested as anticonvulsant agents [6,7]. The synthesis of spirohydantoin participates in the production of the drug sorbinil, which is used to treat chronic complications of diabetes mellitus [8]. Moreover, spiro[imidazolidine-4,3'-indole]2,2',5'-(1H)-trione has been found to inhibit the function of the vanilloid receptor (VR1), which is needed in cases of pain treatment [9]. Another important property of the spirohydantoin is their complexation ability. Previously, 3-thiolanespiro-5'-hydantoin and 4-thio-1H-tetrahydropyranespiro-5'-hydantoin were used as ligands to form Pt(II) and Pt(IV) complexes [10]. Furthermore, the potential of 5'-oxospiro-(fluorene-9,4'-imidazolidine)-2'-one and 5'-oxospiro-(fluorene-9,4'-imidazolidine)-2'-thione to participate as ligands in Pt(II) [11] and Cu(II) [12] complexes has been tested. The crystal structure and bioactivity of the 2'-thio derivative has also been additionally studied [13]. However, the structure of 5'-oxospiro-(fluorene-9,4'-imidazolidine)-2'-thione was previously only supported by ¹H NMR, ¹³C NMR, ATR, and Raman data [11]. Therefore, the aim of the current work was the structure verification of 5'-oxospiro-(fluorene-9,4'-imidazolidine)-2'-thione (Figure 1) by using a combination of 1D (¹H, ¹³C, DEPT 135) and 2D NMR techniques (¹H-¹H COSY, HMQC, HMBC). Thus, a complete and accurate assignment of the ¹H and ¹³C chemical shifts were provided, increasing the degree of confidence with which the structure of 5'-oxospiro-(fluorene-9,4'-imidazolidine)-2'-thione was verified.

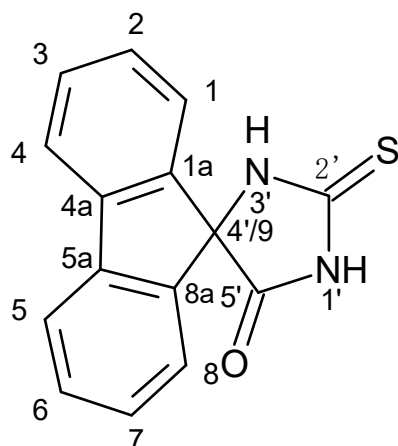


Figure 1. The structure of 5'-oxospiro-(fluorene-9,4'-imidazolidine)-2'-thione.

2. Results

The molecular formula of 5'-oxospiro-(fluorene-9,4'-imidazolidine)-2'-thione is $C_{15}H_{10}N_2OS$. There were nine signals in the ^{13}C NMR spectrum as six of them corresponded to six pairs of chemically equivalent carbons (Table 1), respectively. The two ^{13}C NMR signals with the highest chemical shifts, δ_C 183.60 ppm and δ_C 174.80 ppm, were assigned to the thiocarbonyl and carbonyl carbon atoms, $C^{2'}=S$ and $C^{5'}=O$, respectively. The signal at δ_C 74.84 ppm was for the spiro-carbon, $C-4'/9$.

Table 1. 1H and ^{13}C NMR spectral data and $^1H-^1H$ COSY and HMBC correlations for 5'-oxospiro-(fluorene-9,4'-imidazolidine)-2'-thione [600.130 MHz (1H) and 150.903 MHz (^{13}C)]^a.

Atom	δ (^{13}C), ppm	DEPT	δ (1H), ppm	Multiplicity (J, Hz)	$^1H-^1H$ COSY ^b	HMBC ^b
3' (NH)			10.64	s	1'	2', 5', 4'/9
2' (C=S)	183.60	C				
1' (NH)			12.39	s	3'	2', 5', 4'/9
5' (C=O)	174.80	C				
4'/9	74.84	C				
1/8	123.76	CH	7.42 ^c	m	2	2,3,4a,4'/9, 5' ^e
1a/8a	141.40	C				
2/7	128.64	CH	7.39 ^c	m	1, 3	1, 1a, 3, 4, 4'/9
3/6	130.27	CH	7.52	m	2, 4	1, 2, 4, 4a, 4'/9 ^e
4/5	121.07	CH	7.93	d (7.6)	3	1, 2, 3, 4'/9 ^d , 1a
4a/5a	140.79	C				

^a In DMSO- d_6 solution. All of these assignments were in agreement with the COSY, HMQC, and HMBC spectra.

^b For brevity, these correlations are given only in one of the benzene rings. ^c Data from HMQC. ^d These correlations are weak. ^e These correlations are extremely weak.

The 1H NMR spectrum showed two singlets at δ_H 12.39 ppm and δ_H 10.64 ppm that were assigned to the NH protons. The fact that there were no HMQC correlations for the signals at δ_H 12.39 ppm and δ_H 10.64 ppm indicated that there were protons that were not bonded to carbons. The proton in the $N^{1'}H$ group was located between the thiocarbonyl and carbonyl groups, $C^{2'}=S$ and $C^{5'}=O$, therefore, it would be more strongly deshielded by their magnetic anisotropy [14–16]. Consequently, the singlet at δ_H 12.39 ppm was assigned to the $N^{1'}H$ proton while the signal at δ_H 10.64 ppm was for the $N^{3'}H$ proton. There were three HMBC correlations for each of the imido ($N^{1'}H$) and amide ($N^{3'}H$) protons (δ_H 10.64 ppm– δ_C 174.80 ppm), (δ_H 10.64 ppm– δ_C 183.60 ppm), (δ_H 10.64 ppm– δ_C 74.84 ppm) for the $N^{3'}H$ proton, and (δ_H 12.39 ppm– δ_C 174.80 ppm), (δ_H 12.39 ppm– δ_C 183.60 ppm), (δ_H 12.39 ppm– δ_C 74.84 ppm) for the $N^{1'}H$ proton. Additionally, one COSY correlation was found between the NH protons.

HMBC correlations of the H-1/8, H-2/7, H-3/6, and H-4/5 protons with the spiro-carbon, C-4'/9, were found. In this case, the strongest HMBC correlation included the chemical shift of the H-1/8 protons, ($\delta_{\text{H}} 7.42 \text{ ppm}-\delta_{\text{C}} 74.84 \text{ ppm}$), which were only three bonds away from C-4'/9. Additionally, there was an extremely weak HMBC correlation ($\delta_{\text{H}} 7.42 \text{ ppm}-\delta_{\text{C}} 174.80$) indicating the 4-bond coupling of H-1/8 with the carbonyl carbon, C-5'. The other protons H-2/7, H-3/6, and H-4/5 were at a greater bond distance from C-5', thus, it was very unlikely to find such an HMBC correlation for them.

Due to the fact that the H-3/6 protons were farther from the spiro-carbon, C-4'/9, than the other protons, H-1/8, H-2/7, and H-4/5, the weakest HMBC correlation ($\delta_{\text{H}} 7.52 \text{ ppm}-\delta_{\text{C}} 74.84 \text{ ppm}$) was most probably a result of the coupling of H-3/6 with C-4'/9. The HMBC correlation ($\delta_{\text{H}} 7.39 \text{ ppm}-\delta_{\text{C}} 74.84 \text{ ppm}$) indicated that $\delta_{\text{H}} 7.39 \text{ ppm}$ corresponded to the H-2/7 protons that were closer to C-4'/9 than H-3/6. Thus, the weak HMBC correlation ($\delta_{\text{H}} 7.93 \text{ ppm}-\delta_{\text{C}} 74.84 \text{ ppm}$) indicated the 4-bond coupling of the H-4/5 protons with C-4'/9. The HMQC spectrum showed four correlations—($\delta_{\text{H}} 7.42 \text{ ppm}-\delta_{\text{C}} 123.76 \text{ ppm}$), ($\delta_{\text{H}} 7.39 \text{ ppm}-\delta_{\text{C}} 128.64 \text{ ppm}$), ($\delta_{\text{H}} 7.52 \text{ ppm}-\delta_{\text{C}} 130.27 \text{ ppm}$) and ($\delta_{\text{H}} 7.93 \text{ ppm}-\delta_{\text{C}} 121.07 \text{ ppm}$)—thus, the signals at 121.07 ppm, 123.76 ppm, 128.64 ppm, and 130.27 ppm were assigned to the carbons C-4/5, C-1/8, C-2/7, and C-3/6, respectively. In support of these assignments, there were only four signals in the DEPT 135 spectrum that could be found correspondingly at 121.07 ppm, 123.76 ppm, 128.64 ppm, and 130.27 ppm. There were two COSY correlations found for each of the proton pairs, H-2/7 and H-3/6, indicating the vicinal coupling ($^3J_{\text{HH}}$) with their respective neighboring protons in each benzene ring.

The chemical shifts of the quaternary carbons, C-1a/8a and C-4a/5a, were determined following the fact that the meta (vicinal) coupling ($^2J_{\text{CH}}$) in benzene rings is usually resolved [14, page 27]. The lack of HMQC correlations involving the signals at $\delta_{\text{C}} 140.79 \text{ ppm}$ and $\delta_{\text{C}} 141.40 \text{ ppm}$ as well as the fact that there were no signals at $\delta_{\text{C}} 140.79 \text{ ppm}$ and $\delta_{\text{C}} 141.40 \text{ ppm}$ in the DEPT 135 spectrum indicated that these shifts probably correspond to quaternary carbons. Based on the following HMBC correlations—($\delta_{\text{H}} 7.42 \text{ ppm}-\delta_{\text{C}} 140.79 \text{ ppm}$), ($\delta_{\text{H}} 7.52-\delta_{\text{C}} 140.79 \text{ ppm}$), ($\delta_{\text{H}} 7.39 \text{ ppm}-\delta_{\text{C}} 141.40 \text{ ppm}$) and ($\delta_{\text{H}} 7.93 \text{ ppm}-\delta_{\text{C}} 141.40 \text{ ppm}$)—the chemical shifts $\delta_{\text{C}} 140.79 \text{ ppm}$ and $\delta_{\text{C}} 141.40 \text{ ppm}$ were assigned correspondingly to the signals of C-4a/5a and C-1a/8a, respectively.

3. Materials and Methods

All chemicals used were purchased from Merck (Darmstadt, Germany) and Sigma-Aldrich (Burlington, MA, USA). A Koffler apparatus was used to determine the melting point of the compound. Thin layer chromatography was performed on Kieselgel 60 F₂₅₄, 0.2 mm Merck plates, utilizing the following eluent systems (vol/vol ratio): (a) chloroform:acetone = 9:1 and (b) ethylacetate:petroleum ether = 1:5, in order to determine the purity of the compound. The synthesis of 5'-oxospiro-(fluorene-9,4'-imidazolidine)-2'-thione was based on the one-hour reflux of a mixture containing 0.70 g (0.0023 mol) of 4-(2-hydroxyethylimino)-(9'-fluorene)-spiro-5-(2-thiohydantoin) and 8 mL 20% hydrochloric acid. The product was cooled and after 24 h, it was filtered off and recrystallized from hot water. Yield: 0.5 g (83%); m. p. 302–303 °C; $R_{\text{fa}} = 0.63$; $R_{\text{fb}} = 0.11$. A VERTEX 70 spectrometer (Bruker Optics, Billerica, MA, USA) was used to measure the ATR spectrum of 5'-oxospiro-(fluorene-9,4'-imidazolidine)-2'-thione in the range from 4000 to 600 cm^{-1} at a resolution of 2 cm^{-1} with 25 scans. MIRacle™ with one-reflection ZnSe element (Pike) was utilized as an ATR accessory while the stirred crystals were pressed by an anvil to the reflection element. RAM II (Bruker Optics) with a focused laser beam of 500 mW power of Nd:YAG laser (1064 nm) was applied to register the Raman spectrum of the compound (the stirred crystals were placed in an aluminum disc) in the range from 4000 to 100 cm^{-1} at a resolution of 2 cm^{-1} with 25 scans. ATR (ν_{max} , cm^{-1}): 3244 (sh., ν_{NH}), 3153 (ν_{NH}), 3091 (ν_{CH}), 2909, 1751, 1729 (ν_{CO}), 1606, 1530, 1503, 1475, 1449, 1401, 1374, 1288, 1249 (ν_{CS}), 1191, 1167, 1150, 1110, 1072, 1006, 944, 923, 879, 866, 793, 775, 756, 740, 733, 724, 711, 675, 657, 636, 625, 619. Raman (ν_{max} , cm^{-1}): 3067 (ν_{CH}), 3050 (ν_{CH}), 1728 (ν_{CO}), 1624, 1607, 1486,

1448, 1359, 1296, 1233 (ν_{CS}), 1211, 1157, 1151, 1113, 1074, 1022, 1006, 942, 786, 760, 743, 726, 675, 624, 537, 515, 475, 418, 362, 296, 271, 254, 165, 115. A Bruker Avance II + 600 MHz NMR spectrometer working with a frequencies of 600.130 MHz (^1H) and 150.903 MHz (^{13}C) was utilized to register the ^1H , ^{13}C , and 2D NMR spectra of 5'-oxospiro-(fluorene-9,4'-imidazolidine)-2'-thione. TMS and DMSO- d_6 were used as the internal standard and solvent, respectively. All NMR measurements were conducted at ambient temperature (293.0 K). Chemical shifts were expressed in ppm and coupling constants (J) in Hertz. 1D and 2D NMR spectra were recorded using the standard Bruker pulse programs.

4. Conclusions

The structure of 5'-oxospiro-(fluorene-9,4'-imidazolidine)-2'-thione was completely verified by using a set of 1D and 2D NMR experiments. The interpretation of the ^1H - ^1H COSY, HMQC, and HMBC spectra assisted with the assignment of the ^1H and ^{13}C chemical shifts, which additionally enhanced the reliability of the performed structure verification.

Supplementary Materials: Figure S1: ^1H NMR. Spectrometer frequency is 600.13 MHz. DMSO- d_6 is the used solvent; Figure S2: ^{13}C NMR. Spectrometer frequency is 150.90 MHz. DMSO- d_6 is the used solvent; Figure S3: DEPT 135. Spectrometer frequency is 150.90 MHz. DMSO- d_6 is the used solvent; Figure S4: HMQC. The horizontal and vertical traces show ^1H NMR and DEPT 135 spectra, respectively. Spectrometer frequencies for ^1H NMR and DEPT 135 spectra are correspondingly 600.13 MHz and 150.90 MHz. DMSO- d_6 is the used solvent; Figure S5: ^1H - ^1H COSY. The horizontal and vertical traces show the ^1H NMR spectrum, respectively. Spectrometer frequency for ^1H NMR is correspondingly 600.13 MHz. DMSO- d_6 is the used solvent; Figure S6: Expansion of ^1H - ^1H COSY spectrum, showing the ^1H - ^1H COSY correlations of the protons H-1/8, H-2/7, H-3/6 and H-4/5; Figure S7: HMBC spectrum. The horizontal and vertical traces show ^1H and ^{13}C NMR spectra, respectively. Spectrometer frequencies for ^1H and ^{13}C NMR are correspondingly 600.13 MHz and 150.90 MHz. DMSO- d_6 is the used solvent; Figure S8: Expansion of the HMBC spectrum, showing the HMBC correlations of both NH protons; Figure S9: Expansion of the HMBC spectrum, showing the HMBC correlations of the protons H-1/8, H-2/7, H-3/6 and H-4/5; Figure S10: ATR; Figure S11: Raman.

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