

Short Note

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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 was reported. For the aim, 2D NMR techniques including ¹H-¹H COSY, HMQC and HMBC experiments were used to assist 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 an 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; spirohydantoins; assignment; NMR

1. Introduction

The diverse bioactivity of spirohydantoins has a significant role in numerous practical applications. The lipase catalysis of 5,5-spirohydantoins 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 the increase of the drug transport efficiency through lipophilic membranes [4]. In addition, 1-substituted 5-spirohydantoins were found suitable for the treatment of tropical diseases [5] whereas some cyclopropanespirohydantoin derivatives were tested as anticonvulsant agents [6,7]. The synthesis of spirohydantoins participate in the production of the drug sorbinil used for treating chronic complications of diabetes mellitus [8]. Moreover, spiro[imidazolidine-4,3'-indole]2,2',5'-(1H)-trione was found to inhibit the function of the vanilloid receptor (VR1) which is needed in cases of a pain treatment [9]. Another important property of the spirohydantoins 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 was tested. The crystal structure and bioactivity of the 2'-thio derivative was additionally studied [13]. However, the structure of 5'-oxospiro-(fluorene-9,4'-imidazolidine)-2'-thione was previously supported only 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 an accurate assignment of the ¹H and ¹³C chemical shifts was provided, increasing the degree of confidence with which the structure of 5'-oxospiro-(fluorene-9,4'-imidazolidine)-2'-thione was verified.

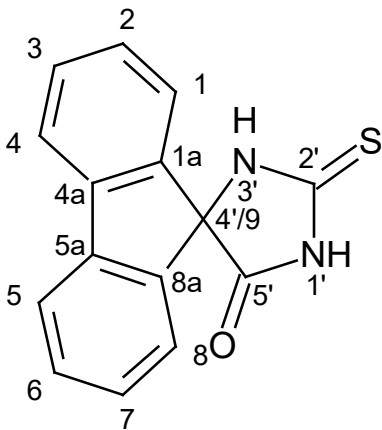


Figure 1. The structure of 5'-oxospiro-(fluorene-9,4'-imidazolidine)-2'-thione.

2. Results

The molecular formula of 5'-oxospiro-(fluorene-9,4'-imidazolidine)-2'-thione is C₁₅H₁₀N₂OS. There were 9 signals in the ¹³C NMR spectrum as 6 of them corresponded to magnetically equivalent carbons (Table 1). The two ¹³C 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, C2'=S and C5'=O. The signal at δ_c 74.84 ppm was for the spiro-carbon, C-4'/9.

Table 1. ¹H and ¹³C 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 (¹³C)]^a.

Atom	δ (¹³ C), ppm	DEPT	δ (¹ H), ppm	Multiplicity Hz)	(J, ¹ H– ¹ H 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-d₆ solution. All these assignments were in agreement with 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 not any 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 N¹H group is located between the thiocarbonyl and carbonyl groups, C2'=S and C5'=O,

therefore, it would be more strongly deshielded by their magnetic anisotropy [[14], page 58][15,16]. Consequently, the singlet at δ_{H} 12.39 ppm was assigned to the N^1H proton while the signal at δ_{H} 10.64 ppm was for the N^3H proton. There were three HMBC correlations for each of the amino 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^3H 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^1H 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, (δ_{H} 7.42 ppm – δ_{C} 74.84 ppm), which are only 3 bonds away from C-4'/9. Additionally, there was an extremely weak HMBC correlation (δ_{H} 7.42 ppm – δ_{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 are at a greater bond distance from C-5', thus, it is very unlikely to find such HMBC correlation for them.

Due to the fact that the H-3/6 protons are 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 (δ_{H} 7.52 ppm – δ_{C} 74.84 ppm) was most probably a result from the coupling of H-3/6 with C-4'/9. The HMBC correlation (δ_{H} 7.39 ppm – δ_{C} 74.84 ppm) indicated that δ_{H} 7.39 ppm corresponded to the H-2/7 protons which were closer to C-4'/9 than H-3/6. Thus, the weak HMBC correlation, (δ_{H} 7.93 ppm – δ_{C} 74.84 ppm), indicated the 4-bond coupling of the H-4/5 protons with C-4'/9. The HMQC spectrum showed 4 correlations – (δ_{H} 7.42 ppm – δ_{C} 123.76 ppm), (δ_{H} 7.39 ppm – δ_{C} 128.64 ppm), (δ_{H} 7.52 ppm – δ_{C} 130.27 ppm) and (δ_{H} 7.93 ppm – δ_{C} 121.07 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 can 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 ($^3J_{\text{CH}}$) in benzene rings is usually resolved [[14], page 27]. The lack of HMQC correlations involving the signals at δ_{C} 140.79 ppm and δ_{C} 141.40 ppm, as well as the fact that there were not any signals at δ_{C} 140.79 ppm and δ_{C} 141.40 ppm in the DEPT 135 spectrum indicated that these shifts probably correspond to quaternary carbons. Based on the following HMBC correlations - (δ_{H} 7.42 ppm – δ_{C} 140.79 ppm), (δ_{H} 7.52 – δ_{C} 140.79 ppm), (δ_{H} 7.39 ppm – δ_{C} 141.40 ppm) and (δ_{H} 7.93 ppm – δ_{C} 141.40 ppm), the chemical shifts δ_{C} 140.79 ppm and δ_{C} 141.40 ppm were assigned correspondingly to the signals of C-4a/5a and C-1a/8a.

3. Materials and Methods

All chemicals used were purchased from Merck and Sigma-Aldrich. A Koffler apparatus was used to determine the melting point of the compound. A 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, (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 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 hours, it was filtered off and recrystallized from hot water. Yield: 0.5 g (83 %); m. p. 302-303 °C; R_{fA} = 0.63; R_{fB} = 0.11. VERTEX 70 spectrometer (Bruker Optics) was used for measuring 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 a 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 for registering the Raman spectrum of the compound (the stirred crystals placed in aluminium 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 ($\nu_{\max}$, 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 for registering 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 internal standard and solvent, respectively. All NMR measurements were conducted at ambient temperature (293.0 K). Chemical shifts are 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 the assignment of the ^1H and ^{13}C chemical shifts which additionally enhanced the reliability of the performed structure verification.

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Conflicts of Interest: The authors declare no conflicts of interest.

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