Synthesis of (4',5'-diaza-9'-fluorene)-spiro-5-hydantoin

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Synthesis of (4',5'-diaza-9'-fluorene)-spiro-5-hydantoin: *The paper presents a method for synthesis of (4',5'-diaza-9'-fluorene)-spiro-5-hydantoin. The newly obtained compound was synthesized by a treatment of 4,5-diazafluoren-9-one with sodium cyanide, ammonium carbonate, ethanol and ammonium hydroxide at high pressure and high temperature. The structure of (4',5'-diaza-9'-fluorene)-spiro-5-hydantoin was verified by UV-Vis, IR, ^{1}H NMR and ^{13}C NMR spectroscopy.*

Key words: *Synthesis, (4',5'-Diaza-9'-fluorene)-spiro-5-hydantoin, NMR Spectroscopy.*

INTRODUCTION

Study interest in (9'-fluorene)-spiro-5-hydantoin /spiro-(fluorene-9,4'-imidazolidine)-2',5'-dione/ and its derivatives is mainly due to their biological activity. Some representatives of these compounds are known as aldose reductase inhibitors [1-6]. This fact makes them useful in the treatment of complications arising from diabetes. It is important to note that such compounds have antitumor activity [7, 8].

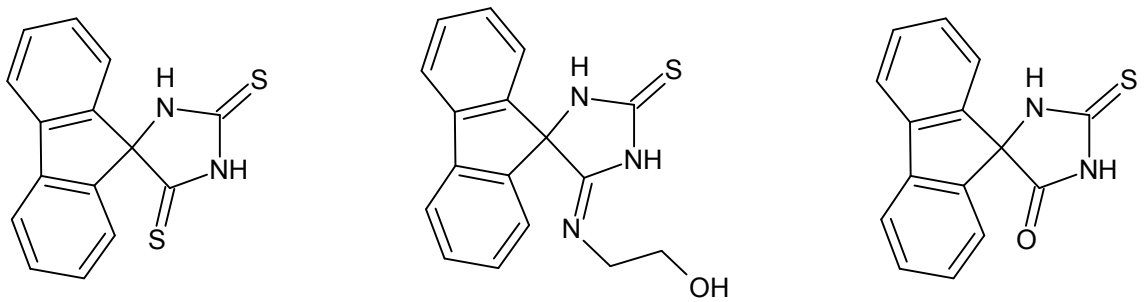
On the other hand, fluorene derivatives are compounds having luminescent and electroluminescent properties caused by the inter- and intra-molecular charge distribution. That is why, some of the organic (and polymeric) light emitting diodes (OLED) are based on fluorene-containing compounds [9-11].

4,5-diaza-fluorenes have good ability to chelate metal ions [12, 13]. It is known that such compounds can be used as fluorescent sensors for metal ions, such as Cu(II) and Ni(II) [14, 15].

Furthermore, azaspirohydantoins and their thioanalogues have been found useful in the medical treatment of disorders in mammalian central or peripheral nervous systems [16].

In previous works of ours we have described different methods for synthesis of monothio- and dithioanalogues of (9'-fluorene)-spiro-5-hydantoin and its derivatives, investigating their eventual biological activity. We have presented synthetic techniques for obtaining (9'-fluorene)-spiro-5-(2,4-dithiohydantoin) /spiro-(fluorene-9,4'-imidazolidine)-2',5'-dithione/ (figure 1a), using different thionation reagents to its dioxoanalogue [17, 18], followed by preparation of corresponding derivatives: 4-(2-hydroxyethylimino)-(9'-fluorene)-spiro-5-(2-thiohydantoin) (figure 1b) and (9'-fluorene)-spiro-5-(2-thiohydantoin) (figure 1c) [18, 19]. Moreover, the synthesis and structural characterization of Cu(II) and Ni(II) complexes of (9-fluorene)-spiro-5-dithiohydantoin have been reported [20].

The aim of this study is to present the synthesis and spectral characterization of a new compound, named (4',5'-diaza-9'-fluorene)-spiro-5-hydantoin.



a) b) c)

Figure 1

EXPERIMENTAL

Materials and methods

All chemicals used were purchased from Merck and Sigma-Aldrich.

The melting point was determined with a digital melting point apparatus SMP 10.

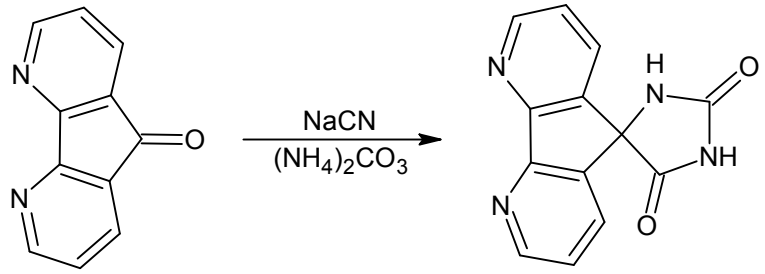
Electronic spectrum was taken on a Specord UV-Vis spectrometer.

IR spectrum was taken on a Bruker-113 spectrometer in KBr disc.

NMR spectra were taken on a Bruker Avance II + 600 MHz spectrometer, operating at 600.130 and 150.903 MHz for ^{1}H and ^{13}C, respectively, using the standard Bruker software. The ^{1}H-broadband-decoupled ^{13}C NMR and DEPT-135 spectra were measured to obtain differentiation between CH and quaternary carbons. Chemical shifts were referenced to tetramethylsilane (TMS). Measurements were carried out at ambient temperature.

Purity of (4',5'-diaza-9'-fluorene)-spiro-5-hydantoin was checked through thin layer chromatography on Kieselgel 60 F_{254}, 0.2 mm Merck plate, eluent system (volume ratio): chloroform : methanol : acetic acid = 9 : 2 : 1.

The target compound was synthesized in accordance to scheme 1.



1 **2**

Scheme 1

Synthesis of (4',5'-diaza-9'-fluorene)-spiro-5-hydantoin

A suspension of 2.00 g (0.011 mol) of 4,5-diazaluorene-9-one (compound 1, scheme 1), 0.81 g (0.017 mol) sodium cyanide, 3.20 g (0.033 mol) ammonium carbonate, 16.5 ml ethanol and 17.6 ml 25 % ammonium hydroxide was heated in an autoclave at 125 ^{o}C for six hours. After cooling down to room temperature, the reaction mixture was poured into water (volume ratio = 1 : 10). The mixture was acidified with 17 % hydrochloric acid to pH 6.3. After extraction with chloroform, the combined extracts were dried with anhydrous sodium sulfate. The dried extracts were evaporated to dryness. The product obtained (compound 2, scheme 1) was recristallized from tetrahydrofuran.

Yield: 0.70 g (24 %);

M. p.: 210-211 ^{o}C;

R_f = 0.69;

UV-Vis (EtOH): λ_{max} = 312, 300, 244, 204 nm;

IR (KBr, cm^{-1}): 3206 (N-H), 3136 (N-H), 3059 (arom.), 1784 (C=O), 1725 (C=O);

^{1}H ЯМР (δ, ppm, DMSO-d_6): 7.46 (dd, J = 7.6, 4.9 Hz, 1H, arom.), 8.03 (dd, J = 7.7, 1.3 Hz, 1H, arom.), 8.32 (s, 1H), 8.69 (dd, J = 4.9, 1.3 Hz, 1H, arom.), 9.95 (s,1H);

^{13}C ЯМР (δ, ppm, DMSO-d_6): 70.5 (C, spiro), 124.7 (CH, arom.), 131.8 (CH, arom.), 142.3 (C, arom.), 151.6 (CH, arom.), 152.9 (C, arom.), 156.5 (C=O), 158.0 (C=O).

RESULTS AND DISCUSSION

The target compound was synthesized by a treatment of 4,5-diazafluoren-9-one with sodium cyanide, ammonium carbonate, ethanol and ammonium hydroxide at high pressure and high temperature. Compound 2 /(4',5'-diaza-9'-fluorene)-spiro-5-hydantoin/

has the molecular formula $C_{13}H_8N_4O_2$. Its structure is given in scheme 1. The product obtained was investigated by electronic UV-Vis, IR, ^{1}H NMR and ^{13}C NMR spectroscopy. Maxima in the electronic spectrum of the (4',5'-diaza-9'-fluorene)-spiro-5-hydantoin were observed at 312, 300, 244, and 204 nm. The IR bands at 3206 cm^{-1} and 3136 cm^{-1} of (4',5'-diaza-9'-fluorene)-spiro-5-hydantoin may refer to the stretching vibrations of the two N-H groups of the hydantoin ring. In the IR spectrum of compound 2 the bands at 1784 cm^{-1} and 1725 cm^{-1} can be attributed to stretching vibrations of the two C=O groups of the hydantoin ring. The ^{13}C NMR spectrum of (4',5'-diaza-9'-fluorene)-spiro-5-hydantoin showed 8 signals. The signals with the highest chemical shifts in ^{13}C NMR spectrum, 156.5 ppm and 158.0 ppm, are assigned to the carbonyl groups of the hydantoin ring. These signals did not appear in the ^{13}C DEPT-135 spectrum. In the ^{1}H NMR spectrum of compound 2 the three signals with multiplicity doublet of doublets refer to the protons in the aromatic moiety. The singlets at 8.32 ppm and 9.95 ppm are for the protons in the hydantoin ring.

CONCLUSIONS

The application of the above mentioned experimental conditions (see the experimental part) led to successful obtaining of a new compound, (4',5'-diaza-9'-fluorene)-spiro-5-hydantoin. The product obtained was characterized by means of UV-Vis, IR, ^{1}H NMR and ^{13}C NMR spectroscopy. The data obtained from these analyses confirmed the suggested structure of the compound.

The evaluation of the biological activity of the product obtained is in progress.

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