Original Contribution

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SYNTHESIS OF AMINO DERIVATIVES OF MONOTHIO- AND DITHIO- ANALOGUES OF CYCLOHEXANESPIRO-5-HYDANTOIN

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Abstract: *This article presents methods for synthesis of 3-amino derivatives of cyclohexanespiro-5-(2-thiohydantoin) and cyclohexanespiro-5-(2,4-dithiohydantoin). It was found out that the treatment of cyclohexanespiro-5-(2-thiohydantoin) with hydrazine hydrate under different reaction conditions led to obtaining of 3-amino derivative and 2-hydrazone of the initial compound. As a result of thionation of 3-aminocyclohexanespiro-5-hydantoin with P_4S_{10} or Lawesson's reagent, the corresponding dithio-analogue was synthesized. The structures of the products obtained were verified by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data.*

Key words: *cyclohexanespiro-5-hydantoin, amino derivatives, thio-analogues, thionation*

I. Introduction

It is well known that the refluxing of cycloalkanespiro-5-hydantoins with hydrazine hydrate lead to obtaining of the relevant 3-amino derivatives [1].

Conducting the reaction between spirodithiohydantoins and hydrazine hydrate at normal conditions resulted in formation of the corresponding 4-hydrazones of the initial compounds [2].

The aim of this paper is to examine the implementation of the above said interactions on spiromonothiohydantoins, as well as to present two effective thionation techniques for obtaining of dithio-analogues of 3-aminocycloalkane-spiro-5-hydantoins.

For this purpose, studies on the treatment of cyclohexanespiro-5-(2-thiohydantoin) with hydrazine hydrate at different reaction conditions were conducted.

The thionation of 3-aminocy-clohexanespiro-5-hydantoin was performed by using P_4S_{10} and Lawesson's reagent (LR) as thionation reagents.

II. Experimental

II.1. Materials and methods

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

The cyclohexanespiro-5-hydantoin (compound **1**, Scheme 1) was synthesized *via* the Bucherer-Lieb method [3]. The cyclo-hexanespiro-5-(2,4-dithiohydantoin) (compound **2**, Scheme 1), the 4-(2-hydroxyethylimino)-cyclohexane-spiro-5-(2-thiohydantoin) (com-pound

3, Scheme 1) and the cyclohexanespiro-5-(2-thiohydantoin) (compound **4**, Scheme 1) were obtained in accordance with Marinov et al. [4]. The 3-aminocyclohexanespiro-5-hydantoin (compound **6**, Scheme 1) was synthesized in accordance with Naydenova et. al. [1]. Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide) was prepared in accordance to Ref. 5.

Melting points were determined with a digital melting point apparatus SMP 10. IR spectra were taken on spectrometer Specord – IR75 VEB Carl – Zeiss in Nujol suspension. NMR spectra were taken on a Bruker DRX-250 spectrometer, operating at 250.13 and 62.90 MHz for ^{1}H and ^{13}C, respectively, using the standard Bruker software. Chemical shifts were referenced to tetramethylsilane (TMS). Measure-ments were carried out at ambient temperature. Mass spectra were recorded using LCQ-DUO LCMS2 System Electrospray Interface on CH-5 Varian MAT spectrometer at 70 eV. The purity of the compounds was checked by thin layer chromatography on Kieselgel 60 F_{254}, 0.2 mm Merck plates, eluent systems (vol/vol ratio):

(a) chloroform : methanol = 9 : 1;
(b) ethylacetate : petroleum ether = 1 : 2;
(c) ethylacetate : petroleum ether = 1 : 5;
(d) chloroform : acetone = 9 : 1.

All known products obtained (**2**, **3**, **4**, **5** and **6**) were characterized by physicochemical parameters, IR and NMR spectral data. The results obtained from these analyses are identical with the previously published in the literature [1, 4, 6].

II.2. Synthetic procedures

II.2.1. Synthesis of 3-amino-cyclohexanespiro-5-(2-thiohydantoin) (compound 5, Scheme 1)

1.00 g (0.005 mol) of cyclohexanespiro-5-(2-thiohydantoin) (compound **4**, Scheme 1) and 2 ml of 95 % hydrazine hydrate were refluxed for 4.5 hours. The reaction mixture was cooled down to room temperature and a small amount of crushed ice was added to it. The product obtained was recrystallized from ethanol.

Yield: 0.90 g (83 %);

M.p.: 239-240 ^{o}C;

$Rf_a = 0.64$; $Rf_b = 0.14$;

IR (Nujol suspension, cm^{-1}): 3347, 3167, 3080 (NH, NH_2), 1720 (C=O), 1640, 1180 (C=S);

^{1}H NMR (δ, ppm, DMSO-d_6): 1.34-1.82 (m, 10H, CH_2), 6.20 (s, 2H, NH_2), 9.60 (s, 1H, N^1-H);

^{13}C NMR (δ, ppm, DMSO-d_6): 20.2 (C^9), 24.9 (C^7), 31.2 (C^8), 53.8 (C^{10}), 60.4 (C^6), 72.3 (C^5), 167.2 (C^2), 177.1 (C^4);

MS: m/z 197, calculated for $C_8H_{13}N_3OS$ $(M)^+$ 199.

II.2.2. Synthesis of 2-hydrazone (compound 8, Scheme 1) of cyclohexanespiro-5-(2-thiohydantoin)

0.6 ml of 95 % hydrazine hydrate was added to 0.20 g (0.001 mol) cyclohexanespiro-5-(2-thiohydantoin) (compound **4**, Scheme 1). The target product crystallized after 24 hours staying at room temperature.

The compound obtained was recrystallized from ethanol.

Yield: 0.19 g (95%);

M.p.: 181-182 ^{o}C;

Rf_a = 0.86; Rf_c = 0.53;

IR (Nujol suspension, cm^{-1}): 3560, 3487, 3147, 3080 (NH, NH_2), 1731 (C=O), 1620 (C=N);

^{1}H NMR (δ, ppm, DMSO-d_6): 1.25-1.73 (m, 10H, CH_2), 10.21 (s, 1H, N^3-H), 11.43 (s, 1H, N^1-H);

^{13}C NMR (δ, ppm, DMSO-d_6): 20.4 (C^9), 24.2 (C^7), 33.5 (C^8), 60.2 (C^{10}), 65.1 (C^6), 72.2 (C^5), 178.6 (C^2), 180.7 (C^4);

MS: m/z 184, calculated for $C_8H_{14}N_4O$ $(M)^+$ 182.

II.2.3. Synthesis of 3-aminocyclohexanespiro-5-(2,4-di-thiohydantoin) (compound 7, Scheme 1)

Method a: Thionation of compound 6 with LR

A suspension of 3.66 g (0.02 mol) of 3-aminocyclohexanespiro-5-hydantoin (compound **6**, Scheme 1) and 16.18 g (0.04 mol) of LR in 40 ml toluene was refluxed for 6 hours. The solvent was decanted, then cooled down to room temperature and extracted with methylene chloride / water. The methylene chloride layer was dried over anhydrous sodium sulphate and then was evaporated to dryness. The product obtained was recrystallized from methylene chloride / petroleum ether.

Yield: 2.92 g (68 %);

M.p.: 162-163 ^{o}C;

Rf_d = 0.73; Rf_c = 0.39;

^{1}H NMR (δ, ppm, DMSO-d_6): 1.23-1.84 (m, 10H, CH_2), 7.80 (s, 2H, NH_2), 12.50 (s, 1H, N^1-H);

^{13}C NMR (δ, ppm, DMSO-d_6): 20.3-60.6 (CH_2), 72.4 (C^5), 175.4 (C^2), 206.7 (C^4);

MS: m/z 215, calculated for $C_8H_{13}N_3S_2$ $(M)^+$ 215.

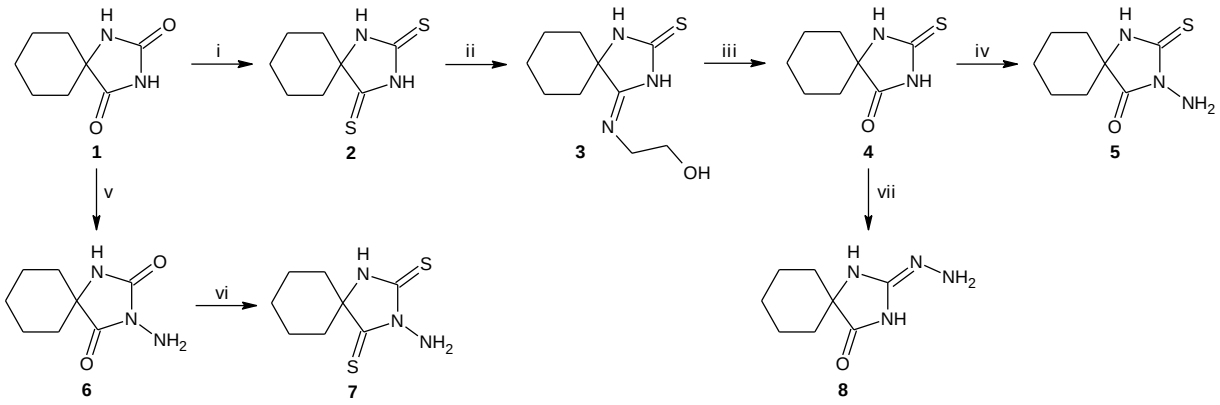
Method b: Thionation of compound 6 with P_4S_{10}

The reaction was carried out in a similar manner to the above mentioned procedure (Method a), except that in this case the reactants (mole ratio of compound **6** and P_4S_{10} = 1 : 1) were refluxed in a media of xylene for 5 hours. As a result of this interaction, product **7** was obtained with 43 % yield.

III. Results and discussion

The synthesis of the target compounds (**5**, **7** and **8**) was performed in accordance to Scheme 1.

The initial cyclohexanespiro-5-hydantoin (compound **1**, Scheme 1) was prepared *via* the Bucherer-Lieb method [3]. In this case the cyclohexanone was subjected to an interaction with sodium cyanide, ammonium carbonate and ethanol. Thus product obtained was converted to its 2-thioanalogue (compound **4**, Scheme 1) in accordance with Marinov et al. [4].

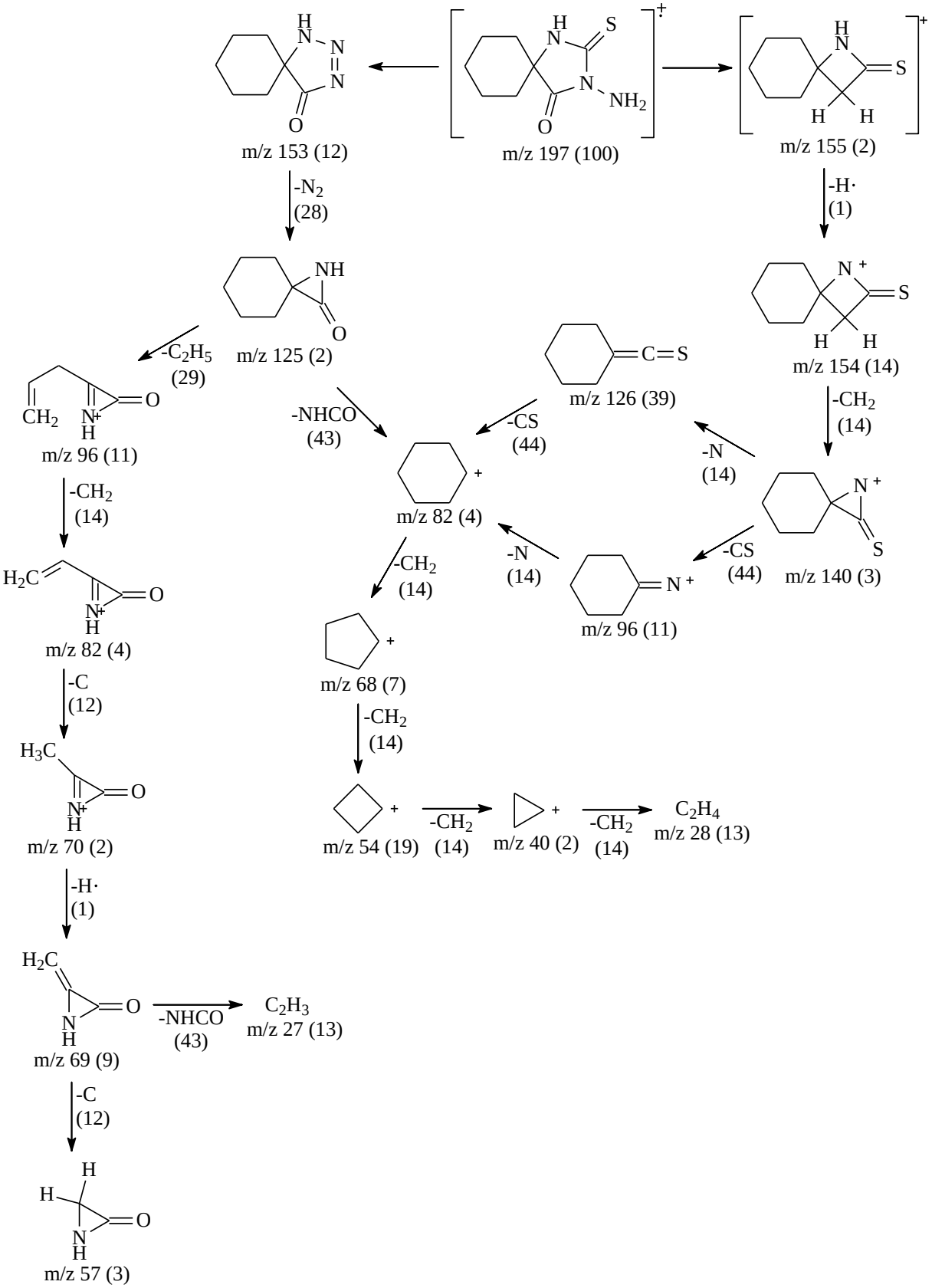


Scheme 1. *Reagents and conditions: (i) P_4S_{10} or LR, xylene or toluene, reflux [4]; (ii) 2-aminoethanol, reflux [4]; (iii) hydrochloric acid, reflux [4]; (iv) hydrazine hydrate, reflux; (v) hydrazine hydrate, reflux [1]; (vi) P_4S_{10} or LR, xylene or toluene, reflux; (vii) hydrazine hydrate, room temperature*

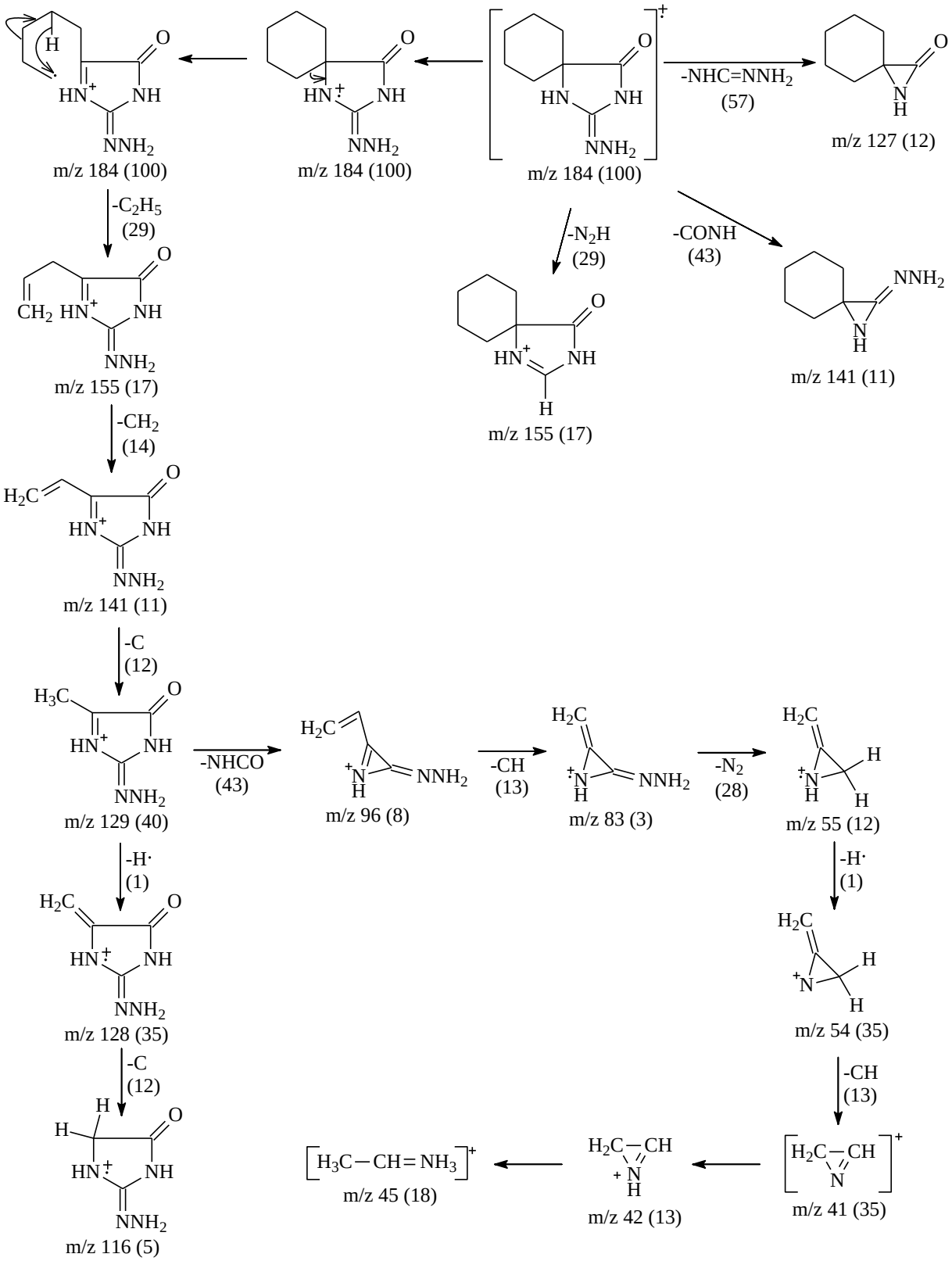
The method of obtaining of cyclohexanespiro-5-(2-thiohydantoin) (compound **4**, Scheme 1) is based on the interaction of cyclohexanespiro-5-(2,4-dithiohydantoin) (compound **2**, Scheme 1) with 2-aminoethanol, followed by a hydrolysis of the 4-(2-hydroxyethylimino)- derivative obtained (compound **3**, Scheme 1) with hydrochloric acid [4].

The interaction of cyclohexanespiro-5-(2-thiohydantoin) (**4**) with hydrazine hydrate was examined at different reaction conditions. First, compound **4** was refluxed with 50 % hydrazine hydrate for an hour and a half. As a result of this interaction the relevant 3-amino derivative (**5**) was obtained with 59 % yield. When the treatment of compound **4** was done with 95 % hydrazine hydrate at refluxing for 4.5 hours, the yield of product **5** increased to 83 %. The structure of compound **5** was confirmed by IR, NMR and mass spectral data (see the experimental part). The fragmentation of 3-aminocyclo-hexanespiro-5-(2-thiohydantoin) [also named as 3-amino-2-thioxo-1,3-diazaspiro[4.5]decan-4-one] (compound **5)** is presented in Scheme 2. Unlike the above-mentioned case, conducting the interaction between compound **4** and 95 % hydrazine hydrate at normal conditions led to obtaining the corresponding 2-hydrazone [also named as 2-hydrazinylidene-1,3-diazaspiro[4.5]decan-4-one] (compound **8**). The structure of compound **8** was confirmed by IR, NMR and mass spectral data (see the experimental part). Its fragmentation is shown in Scheme 3.

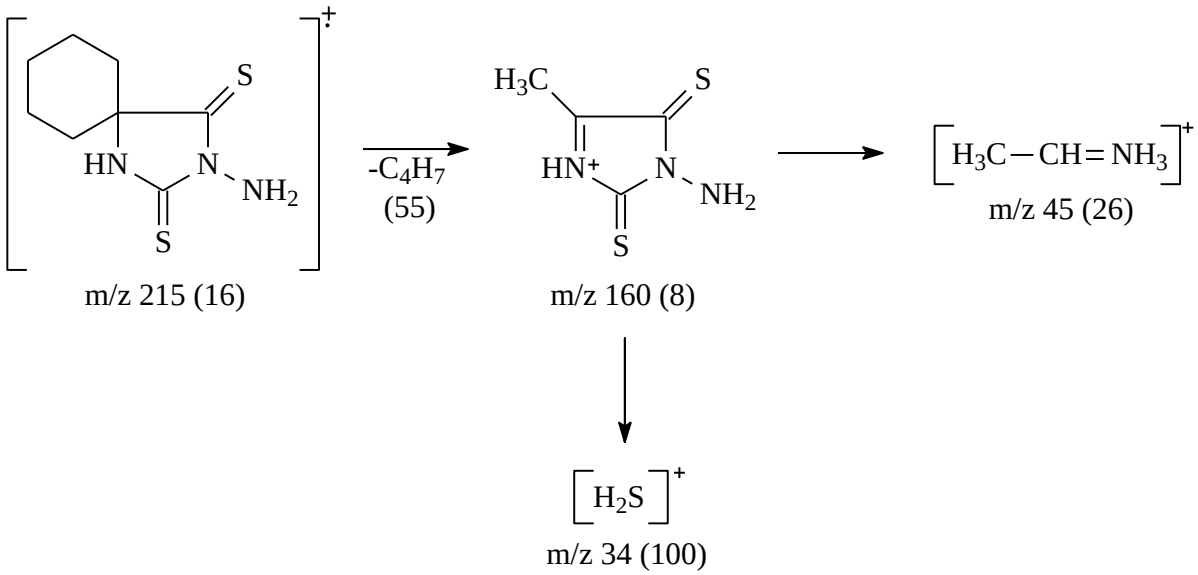
As already mentioned, one of the tasks of this study is the obtaining of 3-aminocyclohexane-spiro-5-(2,4-dithiohydantoin). For this purpose, at first 3-aminocyclohexanespiro-5-hydantoin (compound **6**, Scheme 1) was prepared. The synthesis was carried out in accordance with Naydenova et al. [1].



Scheme 2. *Fragmentation of compound* ***5***



Scheme 3. *Fragmentation of compound* ***8***



Scheme 4. *Fragmentation of compound **7***

Compound **6** was converted to its dithioanalogue 3-aminocyclohexanespiro-5-(2,4-dithiohydantoin) (compound **7**, Scheme 1) by applying two different pathways. When LR was used as thionation reagent (see Method a, experimental part), product **7** was prepared with 68 % yield. The thionation of compound **6** with P_4S_{10} (see Method b, experimental part) led to obtaining of product **7** with 43 % yield.

The spectral data of 3-aminocyclohexanespiro-5-(2,4-dithiohydantoin) [also named as 3-amino-1,3-diazaspiro[4.5]decane-2,4-dithi-one] (compound **7**) are listed in the experimental part. Its fragmentation is presented in Scheme 4.

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