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Synthesis and Characterization of Various Amino Acid Derived Thiohydantoins †

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Abstract: Hydantoins and their sulfur containing analogues, thiohydantoins, are cyclic ureides that have attracted huge attention ever since their discovery. Most of them are biologically active compounds and several points of structural diversity have made them very synthetically attractive. Although substituents can be introduced to the hydantoin nucleus, most substituted hydantoins are synthesized from substrates already containing these groups, while forming the hydantoin nucleus. This is a common route to the synthesis of hydantoins and one of them is employed in this study. A series of 3-allyl-2-thiohydantoins is synthesized from various α-amino acids in a reaction with allyl isothiocyanate. The substitution of the acquired thiohydantoin depends on the structure of the starting α-amino acid. The residual group of the α-amino acid becomes the substituent at the C5-position, while N-monosubstituted amino acids give rise to a substituent in the N1-position. The reaction is carried out in a two-step process and the reaction conditions generally depend on the nature of the amino acid itself. All thiohydantoins are obtained in a good yield and fully characterized by NMR and IR spectroscopy, as well as X-ray crystallography.

Keywords: thiohydantoins; synthesis; amino acids; substitution

1. Introduction

Hydantoins represent a large group of synthetically and biologically attractive compounds [1]. Structurally, they are five-membered cyclic ureides with several points of structural diversity (Figure 1) that give them interesting physical, chemical and biological properties [2].

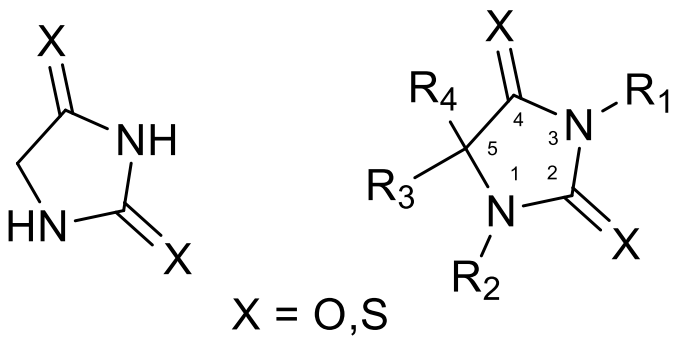


Figure 1. The structure of hydantoins and their derivatives.

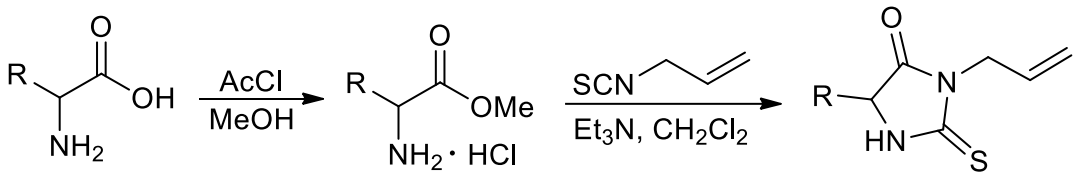
There are many synthetic routes to hydantoins. Although hydantoin derivatives can be synthesized by introducing substituents to the hydantoin nucleus, the most common route is synthesis from substrates that already contain the desired groups, while forming the hydantoin nucleus. One such route is the Bucherer–Bergs reaction, which involves aldehydes and ketones [3]. Another, perhaps more important in a physiological point of view, is the synthesis of hydantoins from amino acids, which are ever-present in the food chain and urea or thiourea [4]. This reaction is responsible for the occurrence of hydantoins in urine when protein consumption is increased. One more important route to hydantoin derivatives is the synthesis from α-amino acids and alkyl or aryl isocyanates and isothiocyanates [5]. This route is employed in this study.

Aside from them being synthetically attractive, hydantoins exhibit a wide range of biological activity [6–9]. Some of the attributed biological properties include antimicrobial, antitumor, antiandrogen, antiteratogenic, hypnotic, antiepileptic and anticonvulsant activity, wound healing, muscle relaxant, treatment of cachexia, psoriasis, chorea, anoxia, tuberculosis and some infectious diseases.

Considering the plethora of their biological activities in this paper, we present the synthesis of a series of amino acid derived 3-allyl-2-thiohydantoins.

2. Results and Discussion

Eleven 2-thiohydantoin derivatives were synthesized from various α-amino acids and allyl isothiocyanate (Scheme 1) in moderate to high yields (Table 1) according to a slightly modified previously reported procedure [10]. The synthesis is carried out in a two-step process and the reaction conditions generally depend on the nature of the amino acid itself. Amino acids 1a, 1e, 1f and 1j needed higher temperature and chloroform is used instead of methylene chloride. All obtained thiohydantoins are fully characterized by NMR and IR spectroscopy, as well as X-ray crystallography (Figure 2). Thiohydantoins **3a**–**3f** are already known compounds, while **3g**–**3k** are novel.



Scheme 1. The synthesis of amino acid derived 3-allyl-2-thiohydantoins.

The reaction presented in this work represents a convenient way to synthesize various substituted 3-allyl-2-thiohydantoins, the substitution of which generally depends on the nature of the starting α-amino acid. The residual group of the α-amino acid becomes the substituent at the C5-position, while N-monosubstituted amino acids give rise to a substituent in the N1-position. As there are many substrates to choose from, including natural and unnatural α-amino acids and also various isothiocyanates, many differently substituted thiohydantoins can be obtained with different chemical and biological properties.

This is important not only for fundamental research and a better understanding of hydantoin chemistry, but also for the search for compounds with potential medicinal applications. These compounds will be subjected to extensive biological evaluation. Additionally, they are suitable for further derivatization leading to more complex compounds with possibly new chemical properties and biological activities.

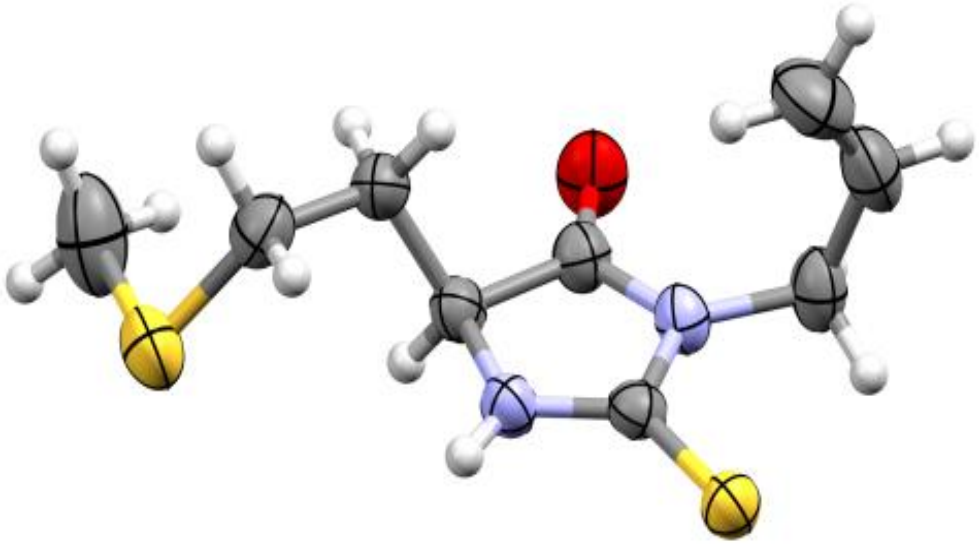
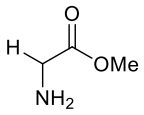
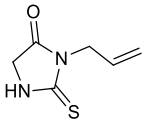
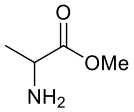
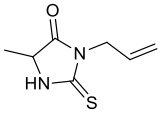
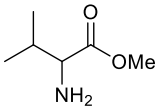
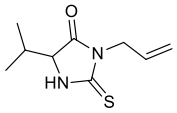
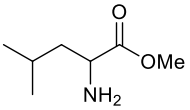
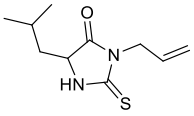
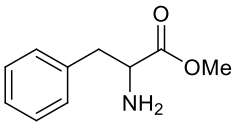
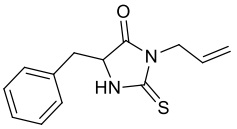
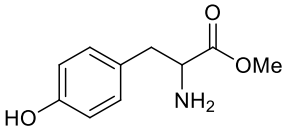
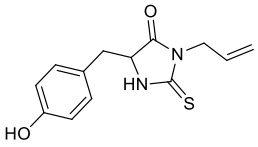
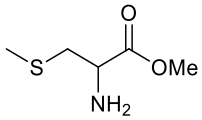
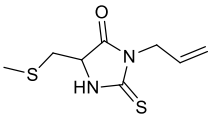
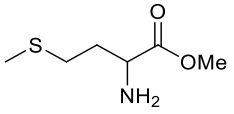
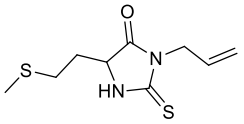
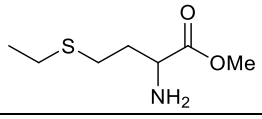
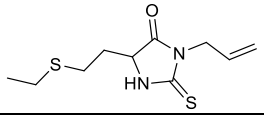
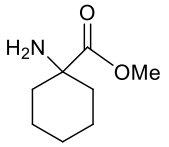
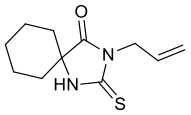
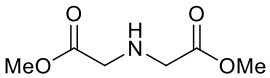
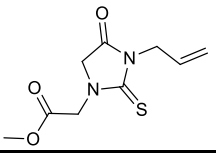


Figure 2. The ORTEP representation of thiohydantoin **3h**.

Table 1. The synthesis of amino acid derived 3-allyl-2-thiohydantoins.

Entry	Substrate	Product	Yield (%)
a			60
b			51
c			81
d			84
e			81
f			51
g			86
h			82
i			92

j			90
k			54

3. Experimental

3.1. General

All chemicals and reagents are commercially available and were used as received without further purification. Solvents were purified by distillation prior use. Anhydrous methanol was prepared by standard drying procedure.

Thin-layer chromatography (TLC) was performed on silica gel on A1 plates, layer thickness 0.2 mm. IR spectra were recorded on a Perkin-Elmer FT-IR spectrometer model Spectrum One. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 2000 NMR spectrometer in D_2O or $CDCl_3$ as solvents. X-ray crystallographic analysis were performed on an Oxford Diffraction Gemini S diffractometer.

3.2. General Procedure for the Preparation of the Amino Acid Methyl Esters **2a–k**

Amino acid methyl esters were prepared according to a well-known methanolic HCl method. 5 mL of methanol was added to a round bottom flask and cooled to 0 °C. Acetyl chloride (2 mL) was added slowly to the stirred solution and then stirred for another 20 min at 0 °C to generate methanolic HCl. An amino acid (5 mmol) was added in one portion and the reaction was stirred overnight at room temperature. The solvent was removed in vacuo and solid amino acid methyl ester hydrochloride (yields ranging from 88 to 96 %) was used without further purification. Successful esterification was confirmed by ^{1}H NMR spectroscopy.

3.3. General Procedure for the Preparation of the Amino Acid Derived 2-Thiohydantoins **3a–k**

A mixture of 5 mmol amino acid methyl ester hydrochloride, 5 mmol Et_3N and 15 mL of CH_2Cl_2 or $CHCl_3$ was stirred for about 20 min at room temperature until all of the ester was dissolved. Allyl isothiocyanate (5 mmol) was added dropwise and the reaction mixture was heated under reflux for 7 h. The solution was cooled at room temperature and the solvent was removed in vacuo. The residue was dissolved in CH_2Cl_2, washed with water and brine and dried over anhydrous Na_2SO_4. The solvent was once again removed in vacuo, leaving a crude solid product that was recrystallized from CH_2Cl_2/hexane.

3-allyl-2-thioxoimidazolidin-4-one (**3a**). Brownish-yellow rod-like crystals; IR (KBr) ν_{max}: 3225, 2923, 1751, 1650, 1526, 1430, 1343, 1259, 1173, 929, 697 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.17 (d, J = 1.4 Hz, 2H), 4.37 (dt, J = 1.2 and 6.0 Hz, 2H), 4.99–5.35 (m, 2H), 5.74–5.97 (m, 1H), 7.78 (bs, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 43.3, 48.5, 118.7, 130.5, 171.7, 184.7 ppm.

3-allyl-5-methyl-2-thioxoimidazolidin-4-one (**3b**). Yellowish needle crystals; IR (KBr) ν_{max}: 3170, 3012, 2920, 1743, 1647, 1538, 1429, 1346, 1263, 1171, 927, 636 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.49 (d, J = 6.8 Hz, 3H), 4.21 (q, J = 6.8 Hz, 1H), 4.43 (dt, J = 1.2 and 6.0 Hz, 2H), 5.19–5.32 (m, 2H), 5.76–5.98 (m, 1H), 7.22 (bs, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 11.0, 43.3, 55.0, 118.5, 130.6, 174.1, 183.5 ppm.

3-allyl-5-isopropyl-2-thioxoimidazolidin-4-one (**3c**). Yellowish needle crystals; IR (KBr) ν_{max}: 3292, 3093, 2963, 1725, 1648, 1512, 1428, 1355, 1254, 1171, 929, 664 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.94 (d, J = 6.8 Hz, 3H), 1.08 (d, J = 6.8 Hz, 3H), 2.19–2.38 (m, 1H), 4.00 (dd, J = 1.4 and 2.0 Hz, 1H), 4.42 (d, J = 5.6

Hz, 2H), 5.18–5.32 (m, 2H), 5.73–5.96 (m, 1H), 7.61 (bs, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.3, 18.8, 30.9, 43.1, 64.6, 118.5, 130.6, 173.1, 184.0 ppm.

3-allyl-5-isobutyl-2-thioxoimidazolidin-4-one (**3d**). White tiny needle crystals; IR (KBr) ν_{max}: 3181, 3006, 2956, 1754, 1650, 1534, 1433, 1346, 1253, 1175, 926, 656 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.98 (d, J = 6.0 Hz, 3H), 1.52–1.90 (m, 3H), 4.14 (dd, J = 2.6 and 9.6 Hz, 1H), 4.42 (dd, J = 1.2 and 5.6 Hz, 2H), 5.19–5.30 (m, 2H), 5.75–5.97 (m, 1H), 7.78 (bs, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.5, 23.0, 25.2, 40.4, 43.2, 58.0, 118.4, 130.5, 174.0, 183.5 ppm.

3-allyl-5-benzyl-2-thioxoimidazolidin-4-one (**3e**). White tiny needle crystals; IR (KBr) ν_{max}: 3205, 3033, 2920, 1749, 1647, 1524, 1428, 1344, 1250, 1175, 931, 732, 651 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.89 (dd, J = 9.0 and 14.0 Hz, 1H), 3.33 (dd, J = 3.6 and 14.0 Hz, 1H), 4.31 (d, J = 3.8 Hz, 1H), 4.36 (dd, J = 1.6 and 5.6 Hz, 2H), 5.01–5.19 (m, 2H), 5.61–5.82 (m, 1H), 7.18–7.40 (m, 6H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 37.6, 43.2, 60.4, 118.4, 127.7, 129.1, 130.4, 134.6, 172.7, 183.5 ppm.

3-allyl-5-(*4-hydroxybenzyl*)*-2-thioxoimidazolidin-4-one* (***3f***). Yellow tiny crystals; IR (KBr) ν_{max}: 3258, 3013, 2925, 1726, 1650, 1528, 1437, 1263, 1171, 960, 653 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.84 (dd, J = 8.6 and 14.0 Hz, 1H), 3.23 (dd, J = 3.6 and 14.0 Hz, 1H), 4.28 (ddd, J = 0.8, 3.8 and 8.6 Hz, 1H), 4.34 (dt, J = 4.0 and 5.4 Hz, 2H), 5.0 (bs, 1H), 5.00–5.19 (m, 2H), 5.63–5.82 (m, 1H), 6.78 (d, J = 6.4 Hz, 2H), 7.07 (d, J = 6.4 Hz, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 38.7, 43.2, 60.6, 115.9, 118.3, 126.5, 130.4, 155.2, 172.7, 183.5 ppm.

3-allyl-5-((*methylthio*)*methyl*)*-2-thioxoimidazolidin-4-one* (**3g**). Light orange needle crystals; IR (KBr) ν_{max}: 3182, 3087, 2915, 1743, 1648, 1526, 1427, 1343, 1254, 1175, 921, 639 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.19 (s, 3H), 2.73 (dd, J = 9.4 and 14.0 Hz, 1H), 3.11 (dd, J = 3.6 and 14.0 Hz, 1H), 4.29 (dd, J = 3.4 and 8.2 Hz, 1H), 4.23 (d, J = 5.4 Hz, 2H), 5.19–5.34 (m, 2H), 5.75–5.98 (m, 1H), 7.41 (bs, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.2, 35.8, 43.4, 58.5, 118.6, 130.4, 172.2, 183.7 ppm.

3-allyl-5-((*methylthio*)*ethyl*)*-2-thioxoimidazolidin-4-one* (**3h**). Light orange needle crystals; IR (KBr) ν_{max}: 3169, 3002, 2921, 1741, 1646, 1531, 1432, 1346, 1255, 1165, 923, 650 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.01 (septet, J = 6.8 Hz, 1H), 2.12 (s, 3H), 2.18–2.34 (m, 1H), 2.68 (t, J = 7.4 Hz, 2H), 4.28 (ddd, J = 1.2, 4.2 and 7.4 Hz, 1H), 4.43 (d, J = 6.0 Hz, 2H), 5.18–5.31 (m, 2H), 5.76–5.97 (m, 1H), 7.81 (bs, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 15.3, 30.3, 30.4, 43.3, 58.5, 118.6, 130.5, 173.4, 183.6 ppm.

3-allyl-5-((*ethylthio*)*ethyl*)*-2-thioxoimidazolidin-4-one* (**3i**). Yellowish needle crystals; IR (KBr) ν_{max}: 3310, 3085, 2924, 1724, 1648, 1510, 1432, 1354, 1254, 1191, 930, 625 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 3H), 2.00 (septet, J = 6.4 Hz, 1H), 2.19–2.36 (m, 1H), 2.60 (q, J = 7.2 Hz, 2H), 2.71 (t, J = 6.8 Hz, 2H), 4.32 (dd, J = 4.8 and 8.2 Hz, 1H), 4.42 (d, J = 5.6 Hz, 2H), 5.19–5.30 (m, 2H), 5.76–5.94 (m, 1H), 8.22 (bs, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.5, 25.8, 27.9, 38.8, 43.2, 58.5, 118.5, 130.5, 173.5, 183.4 ppm.

3-allyl-2-thioxo-1,3-diazaspiro[4,5]decan-4-one (**3j**). Brownish orange four-sided platy crystals; IR (KBr) ν_{max}: 3271, 3180, 2939, 1745, 1716, 1651, 1508, 1427, 1215, 1099, 930, 642 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.12–1.98 (m, 10H), 4.42 (dt, J = 1.6 and 4.0 Hz, 2H), 5.15–5.26 (m, 2H), 5.78–5.95 (m, 1H), 8.71 (bs, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.6, 24.4, 33.0, 43.0, 64.3, 117.9, 130.7, 176.4, 182.0 ppm.

Methyl 2-(*3-allyl-4-oxo-2-thioxoimidazolidin-1-yl*) *acetate* (**3k**). Yellow tiny crystals; IR (KBr) ν_{max}: 3271, 3079, 2955, 1751, 1646, 1493, 1352, 1233, 1164, 940, 645 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.80 (s, 3H), 4.18 (s, 2H), 4.46 (d, J = 7.6 Hz, 2H), 4.62 (s, 2H), 5.17–5.33 (m, 2H), 5.75–5.98 (m, 1H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ, 44.4, 47.4, 52.4, 52.6, 118.5, 130.5, 167.9, 169.8, 184.1 ppm.

4. Conclusions

A series of eleven amino acid derived 3-allyl-2-thiohydantoins has been synthesized in good yields, five of which are novel. A convenient method for synthesis of various 2-thiohydantoin derivatives is described. An extensive biological evaluation will be done on the synthesized compounds. Additionally, since these compounds have functional groups in the side chains, further derivatization will be performed. As hydantoins represent a large group of biologically active and

attractive compounds, some of which are already in use as drugs, this work will serve as a useful footnote in the search for more biologically active and potentially applicable compounds.

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