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Synthesis of 3-adamantylated hydantoins and their 2-thio(seleno) analogs

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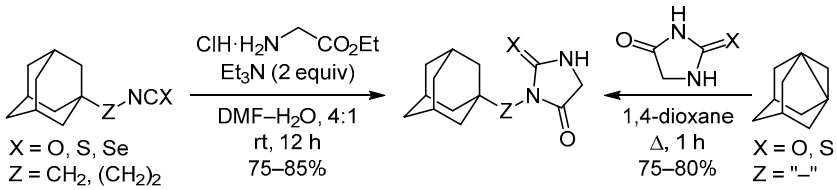


A series of 3-(adamantan-1-ylalkyl)-2-(*O*,*S*,*Se*)hydantoins were synthesized in the reaction of (adamantan-1-ylalkyl)heteroallenes with glycine ethyl ester hydrochloride under mild conditions in 75–85% yields. A method was developed for the synthesis of novel adamantan-1-ylalkyl isoselenocyanates, precursors in the synthesis of adamantylated 2-selenohydantoins. For the first time, 3-(adamantan-1-yl)-2-(*O*,*S*)hydantoins were synthesized *via* the reaction of 2-(*O*,*S*)hydantoins with 1,3-dehydroadamantane in 1,4-dioxane heated to reflux for 1 h in 75–80% yields.

Keywords: adamantane derivatives, 1,3-dehydroadamantane, hydantoin, iso(thio,seleno)cyanates, 2-selenohydantoin, 2-thiohydantoin.

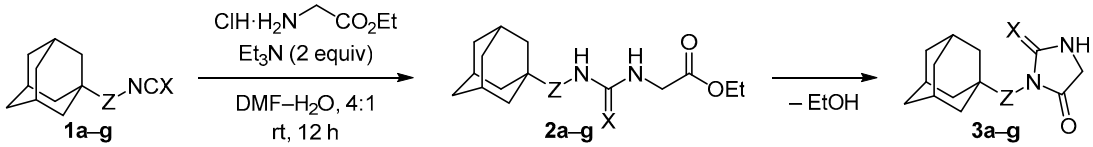
Imidazolidine-2,4-dione (hydantoin) derivatives are being studied as anti-inflammatory drugs[1] and ion channel modulators.[2] Their 2-thio analogs exhibit anticonvulsant,[3] fungicidal,[4] antiviral,[5] antimutagenic,[6] and immunomodulating[7] activity, as well as show promise for hormone-independent treatment of prostate cancer.[8] Most studies on the biological activity of 2-thiohydantoin derivatives are devoted to derivatives obtained by condensation with aldehydes.[9] Glucosidase inhibitors[10] and anticancer drug candidates[11] were found among the derivatives of 2-selenohydantoin.

The adamantane skeleton is a very attractive structural fragment in medicinal chemistry.[12] Publications on the synthesis of 1-adamantyl-containing hydantoins are limited to an example of accessing 3-(adamantan-1-yl)hydantoin *via* the reaction of adamantane with hydantoin in fuming HNO_3 in 71% yield.[13] Information on adamantane-containing 2-thiohydantoins are presented in the patent[14] in the form of a 5,5-disubstituted derivative without indicating its physicochemical or spectral characteristics, as well as a compound in which the adamantane fragment is bonded at position 3 of the PEG linker.[15] Not described in the literature but commercially available 3-[(3-chloro-1-adamantyl)methyl]-5-methylthiohydantoin is also known.[16] Data on the synthesis of 3-(adamantan-1-yl)-2-thiohydantoin and its 2-seleno analog are absent in the literature, although methods for synthesizing 3-substituted thiohydantoins have been known since the end of the 19th century.

Synthesis of 3-(adamantan-1-yl)- or 3-(adamantan-1-ylalkyl)hydantoins, 2-thio-, and 2-selenohydantoins was carried out in two stages, the reaction of (adamantan-1-yl)- or (adamantan-1-ylalkyl)heteroallenes **1a**–**g** with glycine ethyl ester hydrochloride in the presence of Et_3N, followed by cyclization of the resulting adamantyl-containing ethyl-, ethylthio-, or ethylselenoureidoacetates **2a**–**g** into the corresponding 3-(adamantan-1-ylalkyl)-2-(*O*,*S*,*Se*)hydantoins **3a**–**g**. 1-Isocyanatoadamantane (**1a**), 1-isothiocyanatoadamantane (**1b**), 1-(isocyanatomethyl)adamantane (**1c**), 1-(isothiocyanatomethyl)adamantane (**1d**), 1-(2-isothiocyanatoethyl)adamantane (**1e**), (1-isoselenocyanatomethyl)-adamantane (**1f**), and 1-(2-isoselenocyanatoethyl)-adamantane (**1g**) were chosen as the precursor heteroallenes for the synthesis (Scheme 1).

It should be noted that the literature describes a method for obtaining only 1-adamantyl isoselenocyanate from

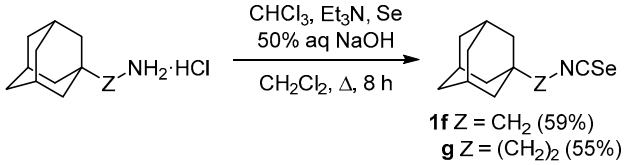
Scheme 1



3 a X = O, Z = "–" (0%); **b** X = S, Z = "–" (0%); **c** X = O, Z = CH_2 (80%); **d** X = S, Z = CH_2 (85%); **e** X = S, Z = $(CH_2)_2$ (75%); **f** X = Se, Z = CH_2 (80%); **g** X = Se, Z = $(CH_2)_2$ (80%)

1-adamantylamine,[18] whereas 1-adamantylalkyl isoselenocyanates **1f**,**g** remained unknown. They were synthesized for the first time by us from 1-aminomethyladamantane and 2-(adamantan-1-yl)ethylamine hydrochlorides, respectively, by the action of $CHCl_3$, Et_3N, 50% NaOH, and elemental selenium in CH_2Cl_2 (Scheme 2).

Scheme 2



1f Z = CH_2 (59%)
g Z = $(CH_2)_2$ (55%)

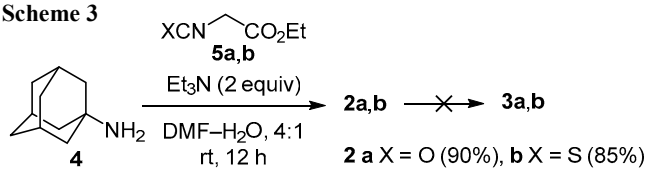
Previously, we obtained the esters of *N*-(adamantan-1-yl)ureidoacetic acids[20] and *N*-(adamantan-1-yl)-thioureidoacetic acids[21] **2a**–**e** when carrying out the reaction of ethyl 2-(isocyanato)acetate with hydrochlorides of adamantylated amines in anhydrous DMF in almost quantitative yields. At the same time, the formation of compounds **3a**–**g** was not observed. Considering that the best yields of thiohydantoins in the reaction of isothiocyanates with amines are achieved in the DMF–H_2O, 4:1 system,[22] reaction with isothiocyanates **1b**,**d**,**e** and isoselenocyanates **1f**,**g** was carried out under similar conditions in the presence of a twofold molar excess of Et_3N for 12 h. In the case of easily hydrolyzable isocyanates **1a**,**c**, the process was first carried out in anhydrous DMF; 4 h after complete conversion of the isocyanate into urea, H_2O was added, and the reaction mixture was left for another 8 h.

The subsequent cyclization of compounds **2a**–**g** depended on the nature of the bridging group Z separating the 1-adamantane substituent and the ureido group. When no bridging group was present, the cyclization of compounds **2a**–**g** to hydantoins was not observed. When alkyl bridges (Z = CH_2 and $(CH_2)_2$) were present in 3-(adamantan-1-ylalkyl)heteroallenes **1c**,**d**,**e**,**f**,**g**, cyclocondensation took place, and the rate of cyclocondensation of heteroallene with the ethylene bridge was higher.

The inability to obtain compounds **3a**,**b** from *N*-(adamantan-1-yl)ureidoacetic and *N*-(adamantan-1-yl)thioureidoacetic acid esters **2a**,**b** is probably related to the bulk of the adamantane substituent that lowers the nucleophilicity of the nitrogen atom N-1, which prevents the cyclization process from occurring. An attempt to synthesize (thio)hydantoins **3a**,**b** *via* reaction of 1-aminoadamantane **4** with heteroallenes **5a**,**b** was also unsuccessful, and the only reaction products were compounds **2a**,**b** (Scheme 3).

Experiments on cyclocondensation of (thio)ureido esters **2a**,**b** in boiling EtOH with the addition of concentrated HCl,[19] H_2SO_4,[23] or CF_3CO_2H[24] did not lead to success: the

Scheme 3



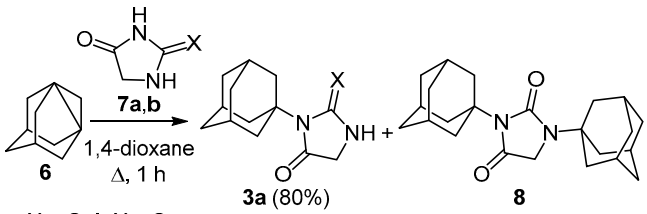
2 a X = O (90%), **b** X = S (85%)

reaction proceeded ambiguously and was accompanied by either hydrolysis of the ester group or its decarboxylation. In this regard, 1,3-dehydroadamantane (1,3-DHA) (**6**) was used to introduce the 1-adamantyl group in position 3 of hydantoin **7a** and 2-thiohydantoin **7b**, which readily reacts with NH acids, in particular with different azoles.[25] The presence of two N–H bonds in the starting 2-(*O*,*S*)-hydantoins did not exclude the formation of two isomeric products at the H–N(1) and H–N(3) bonds, respectively.

It is known that the acidity of the H–N(3) bond in compounds **7a**,**b** significantly exceeds the acidity of the H–N(1) bond. This fact is illustrated by the ^{1}H NMR spectra, in which the chemical shifts of protons of the 1-NH and 3-NH groups are respectively 7.70 and 10.62 ppm for hydantoin **7a** and 9.80 and 11.62 ppm for 2-thiohydantoin **7b**.[26] Apparently, the chemoselectivity of the reaction involving 1,3-DHA (**6**) will be determined by differences in the NH acidity of these bonds.

The reaction of 1,3-DHA (**6**) with compounds **7a**,**b** was carried out by heating under reflux in 1,4-dioxane. Chromato-mass spectrometry analysis showed that complete conversion of 1,3-DHA (**6**) is observed after 1 h with the formation of products **3a**,**b** in 80 and 75% yields, respectively. Besides, in the case of hydantoin **7a**, compound **8**, the addition product to both NH groups of the substrate 1,3-DHA (**6**), was found in the reaction mixture (with *m*/*z* 368) (Scheme 4).

Scheme 4



a X = O, **b** X = S

Thus, a preparatively convenient method for the synthesis of novel adamantan-1-ylalkyl isoselenocyanate precursors in the preparation of adamantyl-containing 2-selenohydantoins was developed as a result of the study. The reaction of (adamantan-1-ylalkyl)heteroallenes with glycine ethyl ester hydrochloride under mild conditions yields a series of 3-(adamantan-1-ylalkyl)-2-(*O*,*S*,*Se*)hydantoins, whereas 3-(adamantan-1-yl)-2-(*O*,*S*)hydantoins were first synthesized by the reaction of (thio)hydantoins with 1,3-dehydroadamantane. Hydantoin yields were 75–85%.

Experimental

^{1}H and ^{13}C NMR spectra were acquired on a Bruker DRX-500 spectrometer (500 and 126 MHz, respectively) in DMSO-d_6, with TMS as internal standard. Signals in ^{13}C NMR spectra were assigned based on literature data.[11,27] Mass spectra were recorded on an Agilent GC 5975/MSD 7820 GC-MS system with an HP-5MS (30 m) capillary quartz column, He carrier gas. Programmable column heating from 80 to 280°C, evaporator temperature 250°C. Elemental analysis was performed on a PerkinElmer Series II 2400 Elemental Analyzer.

Precursor 1-isocyanatoadamantane (**1a**), 1-aminoadamantane (**4**), ethyl isocyanatoacetate (**5a**), ethyl isothiocyanatoacetate (**5b**), glycine ethyl ester hydrochloride, hydantoin (**7a**), and 2-thiohydantoin (**7b**) supplied by Aldrich were used without purification. 1-Isothiocyanatoadamantane (**1b**),[28] 1-(isocyanatomethyl)adamantane (**1c**),[29] 1-(isothiocyanatomethyl)adamantane (**1d**),[28] 1-(2-isothiocyanatoethyl)adamantane (**1e**),[28] and 1,3-dehydroadamantane (**6**)[30] were prepared by published methods.

(1-Isoselenocyanatomethyl)adamantane (1f). Et_3N (4 ml), $CHCl_3$ (3 ml), Aliquat 336 (0.3 g), and 50% aqueous NaOH (8 ml) were added to 1-aminomethyladamantane hydrochloride (5.0 g, 25.0 mmol) in CH_2Cl_2 (20 ml). The reaction mixture was heated under reflux for 4 h, then fine elemental Se (5.0 g, 63.3 mmol) was added, and heating under reflux was continued for another 4 h. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 (30 ml) and H_2O (30 ml). Any unreacted Se was filtered, the organic layer was separated and dried over Na_2SO_4. The drying agent was filtered, and the filtrate was evaporated under reduced pressure. The product was purified by column chromatography on silica gel, eluent hexane. Yield 3.75 g (59%), light-yellow solid, mp 198–199°C. ^{1}H NMR spectrum, δ, ppm: 3.94 (2H, s, C$\underline{H_2}$NCSe); 2.01 (3H, s, H Ad); 1.73–1.61 (6H, m, H Ad); 1.50 (6H, s, H Ad). Mass spectrum, *m*/*z* (I_{rel}, %): 255 $[M]^+$ (20), 149 $[Ad–CH_2]^+$ (100), 135 $[Ad]^+$ (50). Found, %: C 56.65; H 6.70; N 5.55. $C_{12}H_{17}NSe$. Calculated, %: C 56.69; H 6.74; N 5.51.

1-(2-Isothiocyanatoethyl)adamantane (1g) was obtained in the same way as compound **1f** from 2-(adamantan-1-yl)-ethylamine (2.0 g, 11.2 mmol), $CHCl_3$ (1,5 ml), Aliquat 336 (0.15 g), elemental Se (5.0 g, 63.3 mmol), and 50% aqueous NaOH (4 ml) in CH_2Cl_2 (10 ml). Yield 1.65 g (55%), light-yellow solid, mp 78–79°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.60 (2H, t, *J* = 8.0, C$\underline{H_2}$NCSe); 1.98 (3H, s, H Ad); 1.73–1.61 (6H, m, H Ad); 1.56 (2H, t, *J* = 8.0, AdC$\underline{H_2}$); 1.49 (6H, s, H Ad). Mass spectrum, *m*/*z* (I_{rel}, %): 269 $[M+H]^+$ (40), 188 $[M–Se]^+$ (20), 163 $[Ad–CH_2–CH_2]^+$ (70), 149 $[Ad–CH_2]^+$ (3), 135 $[Ad]^+$ (100). Found, %: C 58.18; H 7.16; N 5.25. $C_{13}H_{19}NSe$. Calculated, %: C 58.21; H 7.14; N 5.22.

3-(Adamantan-1-yl)imidazolidine-2,4-dione (3a). Freshly distilled 1,3-DHA **6** (0.8 g, 6.0 mmol) was added to a solution of imidazolidine-2,4-dione (**7a**) (0.5 g, 5.0 mmol) in anhydrous 1,4-dioxane (25 ml). The reaction mixture was heated under reflux for 1 h. The solvent was removed under reduced pressure, and the product was recrystallized from $CHCl_3$. Yield 0.93 g (80%), white solid, decomposes without melting above 250°C (decomp. temp. 250°C[13]). ^{1}H NMR spectrum, δ, ppm: 9.68 (1H, s, NH); 3.96 (2H, s, NHC$\underline{H_2}$); 2.13–1.57 (15H, m, H Ad). ^{13}C NMR spectrum, δ, ppm: 170.5 (N$\underline{C}$(O)CH_2); 157.5 (N$\underline{C}$(O)NH); 45.5 (C Ad); 44.3 ($\underline{C}H_2$NH); 40.4 (3CH Ad); 35.4 ($3CH_2$ Ad); 29.5 ($3CH_2$ Ad). Mass spectrum, *m*/*z* (I_{rel}, %): 234 $[M]^+$ (42), 178 $[Ad–NH–C=O]^+$ (85), 135 $[Ad]^+$ (100). Found, %: C 66.59; H 7.79; N 12.00. $C_{13}H_{18}N_2O_2$. Calculated, %: C 66.64; H 7.74; N 11.96.

3-(Adamantan-1-yl)-2-thioxoimidazolidin-4-one (3b) was obtained in the same way as compound **3a** from 2-thioxoimidazolidin-4-one (**7b**) (0.58 g, 5.0 mmol) and freshly distilled 1,3-DHA (**6**) (0.8 g, 6.0 mmol). Yield 0.92 g (75%), brown solid, mp 220–222°C. ^{1}H NMR spectrum, δ, ppm: 7.40 (1H, s, NH); 2.74 (2H, s, NHC$\underline{H_2}$); 2.13–1.57 (15H, m, H Ad). ^{13}C NMR spectrum, δ, ppm: 184.8 (C=S); 171.9 (C=O); 59.3 (CH_2NH); 48.6 (C Ad); 41.4 (3CH Ad); 36.4 ($3CH_2$ Ad); 30.5 ($3CH_2$ Ad). Mass spectrum, *m*/*z* (I_{rel}, %): 250 $[M]^+$ (73), 135 $[Ad]^+$ (83), 116 $[M–Ad]^+$ (100). Found, %: C 62.42; H 7.22; N 11.24; S 12.77. $C_{13}H_{18}N_2OS$. Calculated, %: C 62.37; H 7.25; N 11.19; S 12.81.

3-[(Adamantan-1-yl)methyl]imidazolidine-2,4-dione (3c). Glycine ethyl ester hydrochloride (0.73 g, 5.23 mmol) and Et_3N (1.05 g, 10.46 mmol) were added to a solution of 1-(isocyanatomethyl)adamantane (**1c**) (1.00 g, 5.23 mmol) in anhydrous DMF (8 ml). The reaction mixture was stirred at room temperature for 4 h until full conversion of the isocyanate. Then H_2O (2 ml) was added, and stirring at room temperature was continued for additional 8 h. The solvent was removed under reduced pressure, and the product was recrystallized from EtOH. Yield 1.04 g (80%), mp 215–216°C. ^{1}H NMR spectrum, δ, ppm: 7.97 (1H, s, NH); 3.91 (2H, s, NHC$\underline{H_2}$); 3.02 (2H, s, AdCH_2); 1.90 (3H, s, H Ad); 1.67–1.44 (12H, m, H Ad). ^{13}C NMR spectrum, δ, ppm: 172.7 (C=O); 158.3 (C=O); 49.2 (AdCH_2); 45.8 (CH_2NH); 40.3 (3CH Ad); 36.3 ($3CH_2$ Ad); 34.8 (C Ad); 27.7 ($3CH_2$ Ad). Mass spectrum, *m*/*z* (I_{rel}, %): 248 $[M]^+$ (10), 135 $[Ad]^+$ (100). Found, %: C 67.75; H 8.09; N 11.32. $C_{14}H_{20}N_2O_2$. Calculated, %: C 67.72; H 8.12; N 11.28.

3-[(Adamantan-1-yl)methyl]-2-thioxoimidazolidin-4-one (3d). 1-(Isothiocyanatomethyl)adamantane (**1d**) (1.00 g, 4.83 mmol) was dissolved in DMF (8 ml), and glycine ethyl ester hydrochloride (0.67 g, 4.83 mmol), Et_3N (0.97 g, 9.66 mmol), and H_2O (2 ml) were added. The reaction mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure, and the product was recrystallized from EtOH. Yield 1.08 g (85%), light-yellow solid, mp >150°C (subl.). ^{1}H NMR spectrum, δ, ppm: 7.36 (1H, s, NH); 4.13 (2H, s, NHCH_2); 3.42 (2H, s, AdCH_2); 1.90–1.46 (15H, m, H Ad). ^{13}C NMR spectrum, δ, ppm: 185.1 (C=S); 171.8 (C=O); 56.4 (AdCH_2); 48.1 (CH_2NH); 40.9 (3CH Ad); 36.4 ($3CH_2$ Ad); 27.9 (C Ad); 27.8 ($3CH_2$ Ad). Mass spectrum, *m*/*z* (I_{rel}, %): 264 $[M]^+$ (75), 231$[M–S]^+$ (15), 207 $[Ad–NCS]^+$ (14), 191 $[Ad–NCO]^+$ (3), 135 $[Ad]^+$ (100). Found, %: C 63.57; H 7.60; N 10.55; S 12.15. $C_{14}H_{20}N_2OS$. Calculated, %: C 63.60; H 7.63; N 10.60; S 12.13.

3-[2-(Adamantan-1-yl)ethyl]-2-thioxoimidazolidin-4-one (3e) was obtained in the same way as compound **3c** from 1-(2-isothiocyanatoethyl)adamantane (**1e**) (1.00 g, 4.52 mmol), glycine ethyl ester hydrochloride (0.63 g, 4.52 mmol), and

Et_3N (0.92 g, 9.04 mmol). Yield 0.94 g (75%), light-yellow solid, mp 180–18°C. ^{1}H NMR spectrum, δ, ppm: 10.10 (1H, s, NH); 4.09 (2H, s, $NHC\underline{H}_2$); 3.69–3.64 (2H, m, NCH_2); 1.92 (3H, s, H Ad); 1.68–1.48 (12H, m, H Ad); 1.31–1.26 (2H, m, $AdCH_2$). ^{13}C NMR spectrum, δ, ppm: 183.1 (C=S); 172.4 (C=O); 76.6 ($NH\underline{C}H_2CH_2$); 41.5 (3C, Ad); 40.9 (NCH_2); 36.4 (3CH Ad); 35.2 ($NHCH_2\underline{C}H_2$); 31.4 (C Ad); 27.8 ($3CH_2$ Ad). Mass spectrum, *m*/*z* (I_{rel}, %): 278 $[M]^+$ (4), 245 $[M–S]^+$ (100), 143 [M–Ad] (15), 135 $[Ad]^+$ (12), 117 $[M–AdCH_2CH_2]$ (35). Found, %: C 64.68; H 7.99; N 10.02; S 11.48. $C_{15}H_{22}N_2OS$. Calculated, %: C 64.71; H 7.97; N 10.06; S 11.52.

3-[2-(Adamantan-1-yl)ethyl]-2-selenoxoimidazolidin-4-one (3g) was obtained in the same way as compound **3c** from 1-(2-isoselenocyanatoethyl)adamantane (**1g**) (0.50 g, 1.86 mmol), glycine ethyl ester hydrochloride (0.26 g, 1.86 mmol), and Et_3N (0.38 g, 3.72 mmol). Yield 0.48 g (80%), light-brown solid, decomp. temp. 130°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.94 (1H, s, NH); 3.87 (2H, s, $NHC\underline{H}_2$); 3.15 (2H, s, $AdCH_2C\underline{H}_2$); 1.93–1.47 (15H, m, H Ad); 1.20 (2H, д, *J* = 7.7, $AdC\underline{H}_2CH_2$). ^{13}C NMR spectrum, δ, ppm: 171.8 (C=O); 142.5 (C=Se); 44.3 ($AdCH_2\underline{C}H_2$); 42.0 (CH_2NH); 41.6 (3CH Ad); 36.5 ($3CH_2$ Ad); 34.3 ($Ad\underline{C}H_2CH_2$); 31.5 (C Ad); 28.0 ($3CH_2$ Ad). Mass spectrum, *m*/*z* (I_{rel}, %): 326 $[M]^+$ (11), 245 $[M–Se]^+$ (14), 205 $[AdCH_2CH_2NCO]^+$ (32), 135 (100). Found, %: C 55.42; H 6.79; N 8.65. $C_{15}H_{22}N_2OSe$. Calculated, %: C 55.38; H 6.82; N 8.61.

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