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Ethyl 3-Amino-3-selenoxopropanoate as a New Reagent for the Synthesis of Selenium-Containing Heterocycles

I. V. Dyachenko and V. D. Dyachenko

Shevchenko Lugansk University, ul. Oboronnaya 2, Lugansk, 91011 Ukraine
e-mail: dyachvd@mail.ru

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Abstract—Interaction of ethyl cyanoacetate with hydrogen selenide afforded new reagent for obtaining selenium-containing heterocycles such as ethyl 3-amino-3-selenoxopropanoate. Starting from the latter substituted selenazoles and ethyl 3-selenoxo-2,3,5,6,7,8-hexahydroisiquinoline-4-carboxylates were synthesized. The structure of the obtained compounds was confirmed by IR, NMR spectroscopy and gas chromatography-mass spectrometry.

Keywords: cyanoacetic ester, selenide, ethyl 3-amino-3-selenoxopropanoate, substituted selenazoles ethyl 3-selenoxo-2,3,5,6,7,8-hexahydroisiquinoline-4-carboxylates, S_NVin reaction

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Some organoselenium derivatives show a wide range of pharmacological [1–4] and biological properties [5–7]. Synthesis of new selenium-containing reagents particularly enhances the possibilities of the preparation of previously unknown organic substances [8].

In continuation of the studies on the chemistry of selenium-containing organic compounds [9–11] we obtained ethyl 3-amino-3-selenoxopropanoate **I** by reacting ethyl cyanoacetate **II** with hydrogen selenide at 0–5°C in the presence of triethylamine. In addition, we performed some its transformations. Thus, reaction with phenacyl bromides **IIIa** and **IIIb** involving selenoamide group resulted in the formation of an expected Hantzsch selenazoles **IVa** and **IVb**. Note that previously studied reaction of cyanoacetic ester with P_2Se_5 followed by reacting the product with 4-nitrophenacylbromide afforded ethyl 2-[4-(4-nitrophenyl)selenazol-2-yl]acetate. However, in [12] the physicochemical and spectroscopic characteristics of this compound were not mentioned.

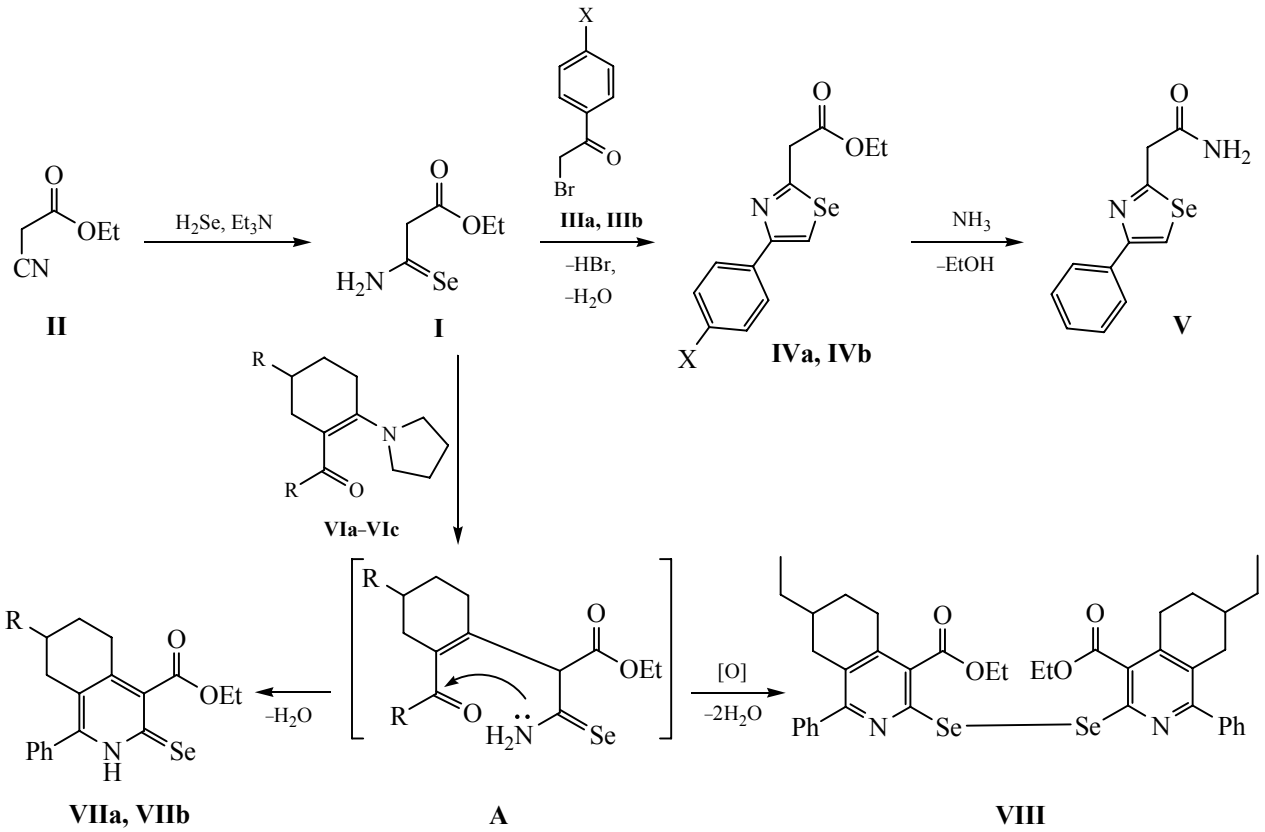
Upon heating selenazole **IVa** in ethanol solution with ammonia ammonolysis of the ester group occurred to form the corresponding 2-thiazole-2-acetamide **V**. Furthermore, compound **I** reacted as *C*-nucleophile in the reaction of vinyl nucleophilic substitution (S_NVin) [13, 14] with enaminoketones **VIa**–**VIc** in anhydrous ethanol at 20°C in the presence of sodium ethylate, leading to the formation of the substituted ethyl 3-selenoxo-2,3,5,6,7,8-hexahydroisoquinolinecarboxylates **VIIa** and **VIIb**, and diselenide

VIII. Recently we have obtained a sulfur analog of compounds **VIIa** and **VIIb**, ethyl 3-thioxo-1-phenyl-2,3,5,6,7,8-hexahydroisoquinoline-4-carboxylate [15].

The reaction pathway is likely to include the formation of intermediate **A**, which underwent intramolecular condensation into isoquinoline **VII**. The isolation of 7-ethylisoquinolinoselenone by recrystallization from ethanol was not possible due to its rapid oxidation probably with atmospheric oxygen to form diselenide **VIII** (Scheme 1).

Spectroscopic data confirmed the structure of the synthesized compounds **I**, **IVa**, **IVb**, **V**, **VIIa**, **VIIb**, and **VIII**. For example, in the IR spectra characteristic absorption bands of the stretching vibrations of the carbonyl group at 1688–1722 cm^{-1} were observed. ^{1}H NMR spectrum of compound **I** contained the signals of amino protons as broadened singlets at 10.19 and 10.64 ppm. In the ^{1}H NMR spectrum of the substituted acetamide **V**, in addition to the signals of the aromatic protons and NH_2-group, there was the singlet of the methylene protons in the region of 3.91 ppm. ^{13}C NMR spectra of the synthesized compounds contained the signals of all the carbon atoms of the molecules.

Scheme 1.



III, IV, X = H (**a**), Br (**b**); **VI, VII**, R = H (**a**), Me (**b**), Et (**c**).

In summary, new reagent for preparing selenium-containing heterocycles, ethyl 3-amino-3-selenoxopropanoate, was synthesized by reacting ethyl cyanoacetate with hydrogen selenide.

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument from KBr pellets. ^{1}H and ^{13}C NMR spectra were registered on a Bruker DR 500 spectrometer operating at 500.13 and 125.75 MHz, respectively, internal reference TMS. Elemental analysis was performed on a EuroVector EA-3000 analyzer. GC-MS (chemical ionization) analysis was made on a Hewlett-Packard 5890/5972 Chrommass GC/MS instrument (column HP5-MS) in solutions with CF_3COOH. Melting points were determined on a Koeffler heating block. The reaction progress was monitored by TLC using Silufol UV-254 plates, eluting with acetone–hexane mixture (3 : 5) and developing with iodine vapor and UV irradiation.

Ethyl 3-amino-3-selenoxopropanoate (I). Through a mixture of 21.2 mL (0.2 mol) of cyanoacetic ester **II** and 3 drops of Et_3N cooled to 0°C H_2Se was bubbled within 3 h under argon, maintaining the reaction temperature between 0–5°C. The reaction product as an orange oil was used without further purification. Yield 31.8 g (82%). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.21 t (3H, Me, *J* 7.0 Hz), 4.00 s (2H, CH_2), 4.16 q (2H, OCH_2, *J* 7.0 Hz), 10.19 br.s (1H, NH_2), 10.64 br.s (1H, NH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 195 (82) $[M + 1]^+$. $C_5H_9NO_2Se$. *M* 194.093.

Ethyl 2-(4-phenyl-1,3-selenazol-2-yl)acetate (IVa). A mixture of 1.9 g (10 mmol) of selenoamide **I** and 2.0 g (10 mmol) of phenacyl bromide **IIIa** in 15 mL of DMF was stirred for 2 h under argon at 20°C, then diluted with an equal volume of water. The resulting precipitate was filtered off, washed with water, ethanol and hexane. Yield 1.5 g (72%), brown crystals, mp 173–175°C (EtOH). IR spectrum, ν, cm^{-1}: 1707 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.32 t (3H, Me, *J* 6.8 Hz), 4.25 q (2H, OCH_2, *J* 6.8 Hz), 4.33 s (2H, CH_2), 7.25–7.51 m (5H, Ph), 8.95 s (1H, H^5, selenazole). Mass spectrum, *m*/*z* (I_{rel}, %): 295 (100) $[M + 1]^+$. Found, %: C 52.96; H 4.30; N 4.62.

$C_{13}H_{13}NO_2Se$. Calculated, %: C 53.07; H 4.45; N 4.76. *M* 294.215.

Ethyl 2-[4-(4-bromophenyl)-1,3-selenazol-2-yl]-acetate (IVb) was obtained similarly from 2.8 g (10 mmol) of *p*-bromophenacyl bromide **IIIb**. Yield 2.8 g (76%), brown powder, mp 85–86°C (EtOH). IR spectrum, ν, cm^{-1}: 1722 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.24 t (3H, Me, *J* 7.0 Hz), 4.19 q (2H, OCH_2, *J* 7.0 Hz), 4.22 s (2H, CH_2), 7.61 d (2H, H_{Ar}, *J* 8.3 Hz), 7.89 d (2H, H_{Ar}, *J* 8.3 Hz), 8.67 s (1H, H^5, selenazole). Mass spectrum, *m*/*z* (I_{rel}, %): 375 (100) $[M + 1]^+$. Found, %: C 41.78; H 3.15; N 3.66. $C_{13}H_{12}BrNO_2Se$. Calculated, %: C 41.85; H 3.24; N 3.75. *M* 373.111.

2-(4-Phenyl-1,3-seleazol-2-yl)acetamide (V). A mixture of 2.9 g (10 mmol) of ester **IVa**, 0.74 mL (10 mmol) of 25% aqueous ammonia, and 25 ml of ethanol was heated at reflux and filtered. The precipitate was washed with ethanol and hexane. Yield 2.0 g (74%), yellow needle crystals, mp 186–187°C (*i*-PrOH). IR spectrum, ν, cm^{-1}: 3377, 3293, 3236 (NH_2), 1688 (CONH). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 3.91 s (2H, CH_2), 7.30 t (2H, Ph, *J* 7.5 Hz), 7.32–7.46 m (2H, H_{Ar}, NH_2), 7.82 br.s (1H, NH_2), 7.92 d (2H, Ph, *J* 7.8 Hz), 8.48 s (1H, H^5, selenazole). ^{13}C NMR spectrum, δ_C, ppm: 42.54 (CH_2), 121.03 (C^4, Ph), 126.53 (C^3, C^5, Ph), 127.92 (C^1, Ph), 129.16 (C^2, C^6, Ph), 135.73 (C^5, selenazole), 153.77 (C^4, selenazole), 170.58 (C^2, selenazole), 170.74 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 266 (100) $[M + 1]^+$. Found, %: C 49.70; H 3.66; N 10.47. $C_{11}H_{10}N_2OSe$. Calculated, %: C 49.82; H 3.80; N 10.56. *M* 265.175.

Substituted ethyl 3-selenoxo-1-phenyl-2,3,5,6,7,8-hexahydroisoquinoline-4-carboxylates (VIIa, VIIb) and diselenide (VIII). A solution of 0.23 g (10 mmol) of Na in 15 mL of anhydrous ethanol was added to a stirred mixture of 10 mmol of the corresponding enaminoketone **IVa**–**IVc** and 2.5 g (12.9 mmol) of CH-acid **I** in 25 mL of anhydrous ethanol at 20°C under argon. The reaction mixture was stirred for 1 h and kept for 48 h. Next, the mixture was acidified with 10% aqueous hydrogen chloride to pH 5 and kept for 3 days. The formed precipitate was filtered off and washed with water, ethanol and hexane.

Ethyl 3-selenoxo-1-phenyl-2,3,5,6,7,8-hexahydroisoquinoline-4-carboxylate (VIIa). Yield 2.8 g (78%), yellow powder, mp 179–181°C(EtOH). IR spectrum, ν, cm^{-1}: 3405 (NH), 1703 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.34 t (3H, Me, *J* 6.8 Hz), 1.52–1.63 m (2H, CH_2), 1.66–1.79 m (2H, CH_2), 2.69 t (2H, CH_2, *J* 6.4 Hz), 2.92 t (2H, CH_2, *J* 6.6 Hz), 4.38 q (2H, OCH_2, *J* 6.8 Hz), 7.26–7.48 m (5H, Ph). The NH proton signal was not observed apparently due to a rapid deuterium exchange. ^{13}C NMR spectrum, δ_C, ppm: 14.51, 21.86, 22.17, 27.82, 27.84, 62.30, 127.11, 128.34 (C^3, C^5, Ph), 128.90 (C^4, Ph), 129.14 (C^1, Ph), 129.43 (C^2, C^6, Ph), 139.34, 148.13, 151.92, 159.46, 167.41 (C=O). Mass spectrum, *m*/*z* (I_{rel}, %): 361 (100) $[M + 1]^+$. Found, %: C 59.88; H 5.19; N 3.76. $C_{18}H_{19}NO_2Se$. Calculated, %: C 60.00; H 5.32; N 3.89. *M* 360.318.

Ethyl 7-methyl-1-phenyl-3-selenoxo-2,3,5,6,7,8-hexahydroisoquinoline-4-carboxylate (VIIb). Yield 2.66 g (71%), yellow powder, mp 229–231°C (EtOH). IR spectrum, ν, cm^{-1}: 3422 (NH), 1710 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 0.93 d (3H, Me, *J* 5.9 Hz), 1.33 t (3H, $\underline{Me}CH_2O$, *J* 6.9 Hz), 1.52–1.64 m (1H, H^7), 1.76–1.88 m (1H, H, cyclohexane), 2.27–2.34 m (2H, CH_2), 2.54–2.71 m (2H, CH_2), 2.76–2.83 m (1H, H, cyclohexane), 4.37 q (2H, OCH_2, *J* 6.9 Hz), 7.26–7.58 m (5H, Ph). The NH proton signal was not observed apparently due to a rapid deuterium exchange. Mass spectrum, *m*/*z* (I_{rel}, %): 375 (100) $[M + 1]^+$. Found, %: C 60.85; H 5.52; N 3.60. $C_{19}H_{21}NO_2Se$. Calculated, %: C 60.96; H 5.65; N 3.74. *M* 374.345.

Diethyl 3,3'-diselandiylbis(1-phenyl-7-ethyl-5,6,7,8-tetrahydroisoquinoline-4-carboxylate) (VIII). Yield 2.6 g (67%), mp 169–171°C (EtOH). IR spectrum, ν, cm^{-1}: 3401 (NH), 1702 (C=O). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 0.82 d (6H, 2Me, *J* 6.4 Hz), 1.23–1.48 m (14H, H, cyclohexane), 1.88–1.99 m (2H, CH_2, cyclohexane), 2.28–2.46 m (2H, CH_2, cyclohexane), 2.55–2.68 m (2H, CH_2, cyclohexane), 2.78–3.15 m (4H, CH_2, cyclohexane), 4.39 q (4H, $Me\underline{CH_2}O$, *J* 6.1 Hz), 7.26–7.49 m (10H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 11.59, 14.51, 27.45, 27.55, 27.67, 27.90, 28.49, 28.64, 34.83, 35.00, 62.29, 127.14, 128.33, 128.90, 129.41, 139.33, 148.31, 153.14, 159.47, 167.44, 193.14. Mass spectrum, *m*/*z* (I_{rel}, %): 775 (100) $[M + 1]^+$. Found, %: C 61.89; H 5.64; N 3.55. $C_{40}H_{44}N_2O_4Se_2$. Calculated, %: C 62.01; H 5.73; N 3.62. *M* 774.723.

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