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CHEMISTRY

Synthesis of Selenium Analogs of 1-Azabicyclo[3.3.1]nonane

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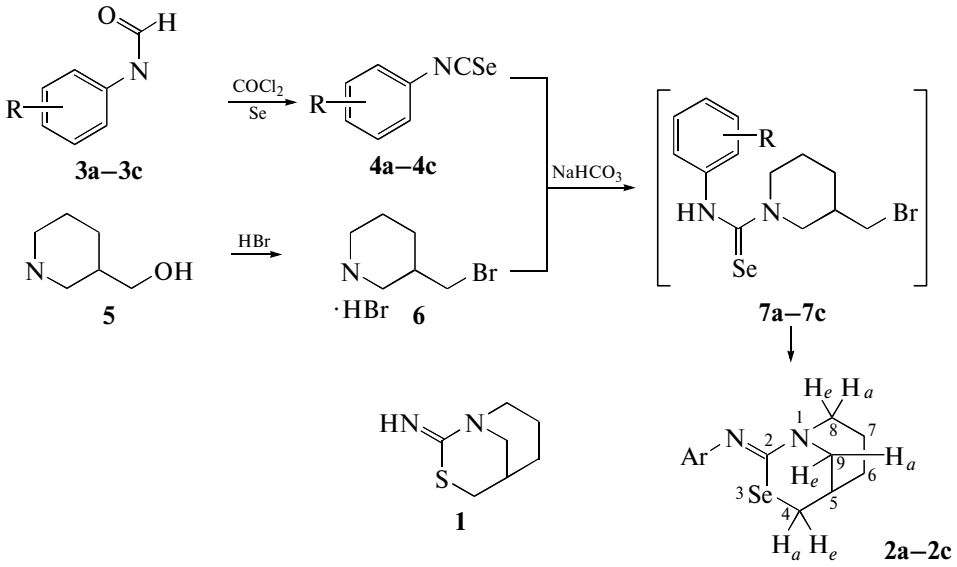
The synthesis of organoselenium compounds, especially selenium-containing heterocycles, have lately attracted considerable attention due to their chemical properties and a wide spectrum of biological activity [1]. In particular, they show antioxidant [2], anti-inflammatory [3], and antiviral [4] properties. Isoselenocyanates are efficient reagents for the preparation of selenium-containing heterocyclic compounds on account of their high reactivity, low toxicity, and relative stability [5]. For example, isoselenocyanates were used in the synthesis of selenazolidines and selenadiazines [6].

We reported recently the synthesis of bicyclic tetrahydrothiazines (**1**), which can be considered as cyclic derivatives of isothiourea [7]. This paper deals with the synthesis of previously unknown selenium-containing heterocyclic compounds.

Selenium analogs (**2a**–**2c**) of such bicyclic molecules in the series of 1-azabicyclo[3.3.1]nonane were obtained by the condensation of aryl isoselenocyanates (**4a**–**4c**) with 3-bromomethylpiperidine (**6**). Aryl isoselenocyanates (**4a**–**4c**) were prepared from the corresponding formamides (**3a**–**3c**) by refluxing in toluene with phosgene and selenium (powder) in the presence of triethylamine [8]. 3-Bromomethylpiperidine (**6**) was synthesized in quantitative yield from the corresponding alcohol (**5**) by heating at reflux with hydrobromic acid. The condensation of the initial compounds was carried out in an ethanol solution in the presence of sodium hydrogen carbonate. Resulting selenourea (**7a**–**7c**) immediately undergoes intramolecular alkylation at the selenium atom, transformation into isoselenourea, and ring closure to give a bicyclic structure of N-aryl(3-selena-1-azabicyclo[3.3.1]non-2-yliden)amine (**2a**–**2c**).



(R = H (**a**), 3'-Cl-4'-Me (**b**), 4'-F (**c**))

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The obtained bicyclic compounds (**2a**–**2c**) were found to show high inhibitory activity in the glutamate-stimulated $^{45}Ca^{2+}$ uptake by rat cerebral cortex synaptosomes, which affects pathological processes in various neurodegenerative diseases [9]. Thus, it was shown for compound **2b** that $K_{inh} = 5.6\%$ (K_{inh} is the percentage of $^{45}Ca^{2+}$ uptake by rat cerebral cortex synaptosomes relative to control, control = 100%) and $IC_{50} = 34.7$ μM are at the level of those for compounds used in the treatment of Alzheimer disease, for example Memantin ($K_{inh} = 8\%$, $IC_{50} = 22.9$ μM).

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker CXP-200 spectrometer (Germany), chemical shifts are given on the δ scale using Me_4Si as a reference. Melting points were determined with the use of a Boetius hot-stage apparatus and they were uncorrected. Solutions were concentrated by rotary evaporation in a vacuum of a water-jet pump.

Synthesis of *N*-aryl(3-selena-1-azabicyclo[3.3.1]non-2-yliden)amines (2a–2c) (general procedure).

Aryl isoselenocyanate **4a**–**4c** (0.01 mol) and 3-bromomethylpiperidine **6** (2.56 g, 0.01 mol) were dissolved in 30 mL of methanol. A solution of sodium hydrogen carbonate (1.85 g, 0.022 mol) in a minimal amount of water was added dropwise to the resultant solution and the mixture was stirred at ambient temperature for 1 h. The reaction mixture was diluted with water (20 mL), the methanol was evaporated, and the residue was extracted with chloroform (3 × 10 mL). The combined organic extracts were dried with sodium sulfate. The drying agent was removed by filtration, the filtrate was concentrated to give N-aryl(3-selena-1-azabicyclo[3.3.1]non-2-yliden)amine (**2a**–**2c**).

***N*-Phenyl(3-selena-1-azabicyclo[3.3.1]non-2-yliden)amine 2a.** Colorless crystals, mp 90–92°C, yield 95.2%.

^{1}H NMR ($CDCl_3$), δ, ppm): 7.35 (m, 2H, H_{arom}), 7.12 (tt, 1H, *J* 1.3, 7.3 Hz, H_{arom}), 6.88 (m, 2H, H_{arom}), 4.28 (dm, 1H, *J* 13.3 Hz, C(9)H_e), 3.69 (dq, 1H, *J* 2.1, 13.7 Hz, C(8)H_e), 3.26 (m, 3H, C(4)H_e, C(8)H_a, C(9)H_a), 2.87 (ddd, 1H, *J* 0.5, 3.0, 11.6 Hz, C(4)H_a), 2.33 (dd, 1H, *J* 2.8, 10.9 Hz, C(5)H), 1.82 (m, 3H, C(6)H_e, C(7)H_2), 1.51 (m, 1H, C(6)H_a).

***N*-(3'-Chloro-4'-methylphenyl)(3-selena-1-azabicyclo[3.3.1]non-2-yliden)amine 2b.** Brown oil, yield 88.4%.

^{1}H NMR ($CDCl_3$, δ, ppm): 7.14 (d, 1H, *J* 8.0 Hz, H_{arom}), 6.80 (d, 1H, J 2.0 Hz, H_{arom}), 6.64 (dd, 1H, *J* 2.0, 8.0 Hz, H_{arom}), 4.21 (dm, 1H, *J* 12.2 Hz, C(9)H_e), 3.63 (dq, 1H, *J* 1.9, 13.7 Hz, C(8)H_e), 3.21 (m, 3H, C(4)H_e, C(8)H_a, C(9)H_a), 2.84 (dd, 1H, *J* 2.8, 11.6 Hz, C(4)H_a), 2.33 (s, 3H, CH_3), 2.30 (dd, 1H, *J* 2.8, 10.9 Hz, C(5)H), 1.81 (m, 3H, C(6)H_e, C(7)H_2), 1.47 (m, 1H, C(6)H_a).

***N*-(4-Fluorophenyl)(3-selena-1-azabicyclo[3.3.1]non-2-yliden)amine 2c.** Colorless crystals, mp 106–108°C, yield 93.5%.

^{1}H NMR ($CDCl_3$, δ, ppm): 7.03 (m, 2H, H_{arom}), 6.82 (m, 2H, H_{arom}), 4.25 (dd, 1H, *J* 2.3, 12.8 Hz, C(9)H_e), 3.67 (dd, 1H, *J* 2.2, 13.7 Hz, C(8)H_e), 3.26 (m, 3H, C(4)H_e, C(8)H_a, C(9)H_a), 2.88 (dd, 1H, *J* 2.7, 11.5 Hz, C(4)H_a), 2.33 (dd, 1H, *J* 2.8, 10.8 Hz, C(5)H), 1.89 (m, 3H, C(6)H_e, C(7)H_2), 1.51 (m, 1H, C(6)H_a).

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