

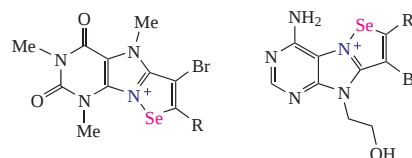
Unusual N,Se-heterocycles with cyclic Se–N⁺ bond of isoselenazolopurinium type

Pavel Arsenyan,* Jelena Vasiljeva, Anna Ivanova and Sergey Belyakov

Latvian Institute of Organic Synthesis, LV-1006, Riga, Latvia. E-mail: pavel@osi.lv

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Treatment of 8-alkynylcaffeine or -adenine derivatives with *in situ* generated SeBr₄ caused their annulation with the formation of isoselenazolium ring. The salts obtained are regarded as glutathione peroxidase mimetics.

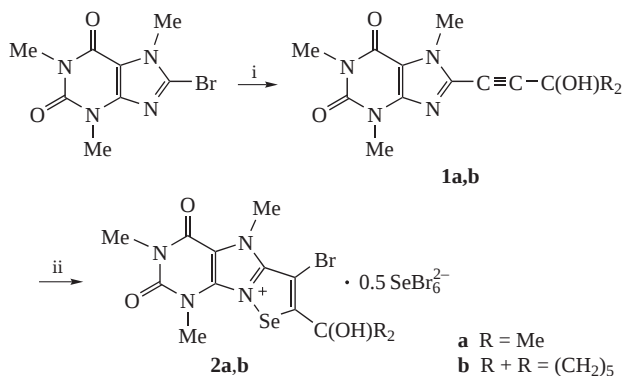


In the last decade, the synthesis of compounds containing Se–N bond has begun to play an important role in the design of potentially bioactive molecules.^{1(a)–(c)} Heterocycles with Se–N bonds, such as ebselen (2-phenyl-1,2-benzoselenazol-3-one), are clinically useful redox modulators and anti-inflammatory agents.^{1(d)–(h)} Despite extensive chemical studies and numerous applications of selenium-containing heterocycles, only a moderate number of compounds containing Se–N⁺ bond have been reported so far. Recently we described the synthesis of stable fused isoselenazolium salt systems with a Se–N⁺ bond based on cyclization of ethynyl *N*-heterocycles with selenium(II) and (IV) halides.^{2(a)} Due to the presence of this bond, such compounds exhibit the glutathione peroxidase (GPx) like activity and can serve as mild oxidants.^{2(b)} Some of selenazolium salts possess antibacterial activity. Isoselenazolium salts induce DNA double-strand breaks at moderate doses.^{2(c),(d)} Keeping in mind that modification of natural compounds could lead to even more interesting results, in continuation of our research in the field of selenium chemistry,³ here we report the method of introduction of annulated isoselenazolium ring into caffeine and adenine derivatives.

8-Ethynyl caffeines **1a,b** were chosen as model compounds for the study. The introduction of the alkynyl moiety at 8-position of caffeine was based on Sonogashira-type coupling reaction (Scheme 1).⁴ We found that the yields of the products in the palladium-catalyzed cross-coupling of terminal acetylenes HC≡CC(OH)R₂ and 8-bromocaffeine strongly depended on the

nature of the catalyst and solvent, with the 1:1 mixture of *N*-methylpyrrolidinone (NMP) and toluene as the reaction medium having provided the desired products in higher yields. Next, since reactions in aqueous solutions without an inert atmosphere are always preferable, 8-alkynylcaffeines were treated with solutions of freshly prepared aqueous selenium(IV) bromide by dissolving SeO₂ in 48% hydrobromic acid. The desired isoselenazolopurinium salts **2a,b**[†] were isolated in 38 and 58% yields, respectively. Unfortunately, these compounds were unstable on silica gel during flash chromatography. Derivatives **2a,b** were purified by crystallization from acetonitrile. Note that these compounds are the first representatives of isochalcogenazolocaffeines with isochalcogenazole cycle annulated at 7- and 8-positions of purine system.

Figure 1(a) shows a structure of cation of salt **2a**.[†] The torsion angle N(12)–Se(1)···O(14)–H and valence angle Se(1)···O(1)–H promote an increase in the intramolecular interaction between



Scheme 1 Reagents and conditions: i, HC≡CC(OH)R₂, [Pd], PhMe–NMP; ii, SeO₂, conc. HBr, dioxane, ~20 °C, 24 h.

[†] **Compounds 2a,b (general procedure).** Alkyne **1a,b** (1 mmol) in dioxane (10 ml) was added to a solution of selenium dioxide (0.444 g, 4 mmol) in HBr (0.45 ml), and the mixture was stirred at room temperature for 24 h. After consumption of substrate (LC-MS), ethanol (40 ml) was added and the solution was filtered through paper. The filtrate was passed through ion-exchange resin which was pre-treated with hydrochloric acid. The solvent was evaporated and the crude product was recrystallized from acetonitrile.

6-Bromo-7-(2-hydroxyprop-2-yl)-1,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-[1,2]selenazolo[2,3-*e*]purin-9-ium hexabromoselenate(IV) 2a. Yield 34%, mp 177–180 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 4.33 (s, 3H, N³Me), 3.67 (s, 3H, N³Me), 3.28 (s, 3H, N¹Me), 1.73 (s, 6H, 2Me). MS (ESI), *m/z*: 435.1. Found (%): C, 21.16; H, 2.32; N, 7.32. Calc. for C₂₆H₃₂Br₈N₈O₆Se₃·2H₂O (%): C, 20.57; H, 2.30; N, 8.00.

6-Bromo-7-(1-hydroxycyclohexyl)-1,3,5-trimethyl-2,4-dioxo-2,3,4,5-tetrahydro-1H-[1,2]selenazolo[2,3-*e*]purin-9-ium hexabromoselenate(IV) 2b. Yield 54%, mp 160–162 °C. ¹H NMR (400 MHz, DMSO-*d*₆) δ: 4.37 (s, 3H, N³Me), 3.69 (s, 3H, N³Me), 3.27 (s, 3H, N¹Me), 2.19–2.27 (m, 2H, cyclohexyl), 1.91–1.96 (d, 2H, cyclohexyl, *J* 13.3 Hz), 1.61–1.71 (m, 5H, cyclohexyl), 1.21–1.30 (m, 1H, cyclohexyl). ¹³C NMR (100.6 MHz, DMSO-*d*₆) δ: 153.8, 149.4, 107.1, 148.3, 77.8, 66.2, 33.8, 32.6, 30.3, 28.3, 23.9, 20.4. Found (%): C, 24.47; H, 2.64; N, 6.89. Calc. for C₃₂H₄₀Br₈N₈O₆Se₃·2H₂O (%): C, 23.58; H, 2.75; N, 7.04.

[†] Monocrystals grown for X-ray analyses differed in anion and solvate molecule compositions.

Crystallographic data for 2a [tetrabromoselenate(II), solvate with MeCN]. C₃₀H₃₈Br₆N₁₀O₆Se₃ (*M* = 1351.04), triclinic, space group *P* $\bar{1}$, at 163 K: *a* = 9.4447(2), *b* = 10.5194(2) and *c* = 11.0932(2) Å, α = 85.8949(9),

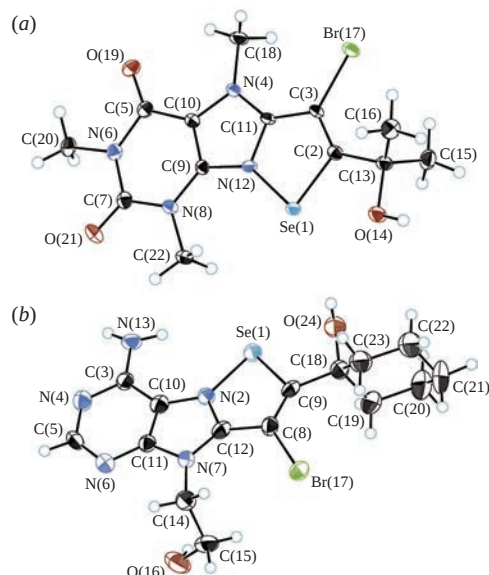


Figure 1 ORTEP diagram of cations of compounds (a) **2a** and (b) **5b** with atomic labels and thermal ellipsoids (50%).

selenium and oxygen with Se···O distance of 2.539(3) Å. The Se(1)–C(2) covalent bond [1.869(3) Å] in cation is shorter than Se(1)–N(12) bond [1.876(3) Å]. In addition, in the crystal structure there are hydrogen bonds of OH···Br type [O···Br 3.414(3) Å, H···Br 2.51 Å, ∠O–H···Br 153°] between cation and tetrabromoselenate(II) anion, halogen bonds between anion and Br(17) atom [Br···Br distance is 3.363(2) Å] and σ -hole interactions between Se(1) atom and solvent (acetonitrile) molecule [Se···O distance is 3.183(3) Å]. Moreover, isoselenazolocaffeinium salts are the only condensed purines containing formally quaternary nitrogen atom, which forms covalent bond with endocyclic heteroatom.

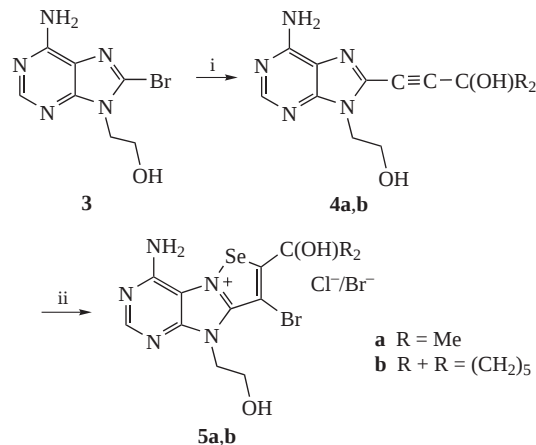
Analogous adenine salts were accessed from 8-bromo-9-(2-hydroxyethyl)adenine **3**⁵ (Scheme 2), which was converted into 8-alkynyl derivatives **4a,b**.[§] Their further cyclization with *in situ* prepared SeBr₄ gave isoselenazolocaffeinium bromides **5a,b** in 76–77% yields.[¶] The singlet signal of selenium in ⁷⁷Se NMR spectrum of salt **5a** was detected at 1105.5 ppm, which confirmed

$\beta = 84.2797(9)$ and $\gamma = 73.7263(8)^\circ$, $V = 1051.61(4)$ Å³, $Z = 1$, $d_{\text{calc}} = 2.133$ g cm^{−3}, $\mu(\text{MoK}\alpha) = 8.377$ mm^{−1}, $F(000) = 648$. Total of 8169 reflections were measured, 5395 independent reflections ($R_{\text{int}} = 0.0393$) were used in a further refinement, which converged to $wR_2 = 0.828$ and GOF = 1.068 for all independent reflections [$R_1 = 0.0319$ was calculated against F for 4794 observed reflections with $I > 2\sigma(I)$].

Crystallographic data for 5b. C₁₅H₁₉Br_{1.5}Cl_{0.5}N₅O₂Se ($M = 517.90$) are triclinic, space group $P\bar{1}$, at 293 K: $a = 6.9791(2)$, $b = 8.6795(4)$ and $c = 16.3447(6)$ Å, $\alpha = 92.639(2)$, $\beta = 94.592(2)$ and $\gamma = 108.120(2)^\circ$, $V = 935.33(6)$ Å³, $Z = 2$, $d_{\text{calc}} = 1.839$ g cm^{−3}, $\mu(\text{MoK}\alpha) = 5.302$ mm^{−1}, $F(000) = 510$. Total of 5974 reflections were measured and 4076 independent reflections ($R_{\text{int}} = 0.0371$) were used in a further refinement. The refinement converged to $wR_2 = 0.1274$ and GOF = 1.059 for all independent reflections [$R_1 = 0.0527$ was calculated against F for 3244 observed reflections with $I > 2\sigma(I)$].

The measurements were performed on a Bruker-Nonius KappaCCD diffractometer with graphite-monochromated MoK α radiation ($\lambda = 0.71073$ Å). The structure was solved by direct methods, and the non-hydrogen atoms were located from the trial structure and then refined anisotropically with SHELXL using a full-matrix least-squares procedure based on F^2 . The hydrogen atoms were located from differential Fourier synthesis and also from geometrically calculated positions and refined using riding model.

CCDC 1041474 and 1860964 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via <http://www.ccdc.cam.ac.uk>.



Scheme 2 Reagents and conditions: i, HC≡CC(OH)R₂, (Ph₃P)₂PdCl₂, CuI, DMF, Et₃N, ~20 °C, 18 h; ii, SeO₂, conc. HBr, dioxane, ~20 °C, 24 h, then ion-exchange (Cl[−]) resin.

the formation of Se–N⁺ bond. For comparison, ⁷⁷Se in ebselen (Se–N) resonates at 959 ppm.⁵ Note that adenine derivatives were more stable in physiological media compared with caffeine salts.

[§] 4-[9-(2-Hydroxyethyl)adenin-8-yl]-2-methylbut-3-yn-2-ol **4a**. 2-Methylbut-3-yn-2-ol (630 mg, 7.75 mmol), (Ph₃P)₂PdCl₂ (95.3 mg, 0.136 mmol) and CuI (15.8 mg, 0.129 mmol) were dissolved in dry DMF (15 ml) in round bottom flask under argon atmosphere at ~20 °C, then Et₃N (5 ml) was added. The solution was degassed by flushing argon for 20 min. Then 8-bromo-9-(2-hydroxyethyl)adenine **3** (500 mg, 1.94 mmol) dissolved in DMF (5 ml) was added to the stirred reaction mixture. After 48 h, DMF was distilled off *in vacuo*. The residue was washed with diethyl ether (35 ml). The product was filtered off and recrystallized from acetonitrile. Light yellow solid (335 mg, 66%) was obtained, mp > 200 °C (decomp.). ¹H NMR (400 MHz, DMSO-*d*₆) δ : 8.15 (s, 1H), 7.35 (s, 2H), 5.75 (s, 1H), 4.94 (t, 1H, J 5.7 Hz), 4.21 (t, 2H, J 5.9 Hz), 3.77 (q, 2H, J 5.8 Hz), 1.51 (s, 6H).

1-[2-[6-Amino-9-(2-hydroxyethyl)-9H-purin-8-yl]ethynyl]cyclohexan-1-ol **4b**. Compound **4b** was prepared similarly. Yield 64%. ¹H NMR (400 MHz, DMSO-*d*₆) δ : 8.15 (s, 1H), 7.36 (br. s, 2H), 4.94 (t, 1H, J 5.7 Hz), 4.23 (t, 2H, J 5.7 Hz), 3.77 (q, 2H, J 5.7 Hz), 1.98–1.84 (m, 2H), 1.76–1.39 (m, 7H), 1.36–1.20 (m, 1H).

[¶] 4-Amino-8-bromo-9-(2-hydroxyethyl)-7-(2-hydroxyprop-2-yl)-9H-[1,2]selenazolo[3,2-*f*]purin-5-ium bromide/chloride **5a**. Selenium(IV) oxide (170 mg, 3.92 mmol) was dissolved in 48% HBr (1.5 ml) and stirred at room temperature for 15 min. A solution of compound **6** (100 mg, 0.383 mmol) in dioxane (12 ml) was added dropwise at 2–4 °C. Then the mixture was stirred at ~20 °C for 24 h. The reaction was quenched with ethyl acetate (50 ml) and washed with sodium bicarbonate solution (20 ml). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (2 × 30 ml). The combined organic phases were washed with brine (40 ml), and then dried with anhydrous sodium sulfate. Evaporation of the solvent left the crude product, which was purified by column chromatography over silica gel (light petroleum–ethyl acetate, 8:2). The bromide anion was partly replaced with chloride one by anion-exchange resin (HCl), producing salt **5a** (126 mg, 76%). ¹H NMR (400 MHz, DMSO-*d*₆) δ : 8.45 (s, 1H, C²H), 8.30 (br. s, 2H, NH₂), 4.79 (t, 2H, CH₂N, J 5.6 Hz), 3.83 (t, 2H, CH₂OH, J 5.6 Hz), 1.75 (s, 6H, 2Me). ¹³C NMR (101 MHz, DMSO-*d*₆) δ : 180.7, 155.2, 150.9, 150.8, 150.4, 111.0, 83.1, 75.4, 59.3, 45.7, 26.5. ⁷⁷Se NMR (DMSO-*d*₆) δ : 1105.5. MS (ESI), m/z : 420.1.

4-Amino-8-bromo-7-(1-hydroxycyclohexyl)-9-(2-hydroxyethyl)-9H-[1,2]selenazolo[3,2-*f*]purin-5-ium bromide/chloride **5b**. Salt **5b** was prepared analogously. Yield 77%, mp 188–194 °C (decomp.). ¹H NMR (400 MHz, DMSO-*d*₆) δ : 9.00 (br. s, 1H, OH), 8.45 (s, 1H, C²H), 8.25 (br. s, 2H, NH₂), 4.79 (t, 2H, CH₂N, J 5.6 Hz), 3.83 (t, 2H, CH₂OH, J 5.6 Hz), 2.33–2.24 (m, 2H, cyclohexyl), 1.94–1.91 (m, 2H, cyclohexyl), 1.75–1.65 (m, 5H, cyclohexyl), 1.35–1.22 (m, 1H, cyclohexyl). ¹³C NMR (101 MHz, DMSO-*d*₆) δ : 181.3, 155.2, 150.9, 150.8, 150.6, 111.1, 82.9, 77.4, 59.3, 45.8, 32.8, 24.1, 20.6. MS (ESI), m/z : 459.9.

After treatment with ion-exchange resin, crystals of salt **5b** comprising cation as a solid solution of bromide and chloride were grown;[‡] therefore, a structure disorder occurs. Occupation *g*-factors for both anions are 0.5. Figure 1(b) shows a perspective view of compound **5b** cation. The Se–N⁺ and Se–C bond lengths are 1.874(4) and 1.870(5) Å, respectively, the N–Se–C valence angle is 84.6(2)°. Hydroxyethyl moiety of the cation is characterized by *gauche*-conformation with the torsion angle N(7)–C(14)–C(15)–O(16) being –70.2(6)°. Cyclohexane cycle acquires *chair*-conformation, but amino group enjoys a trigonal planar configuration. The crystal structure of **5b** is stabilized by intermolecular hydrogen bonds. Bromide and chloride anions are involved in H-bonds with hydroxy group of neighbor cation [for bromide O(16)⋯Br 3.213(6) Å, O(24)⋯Br 3.158(6) Å; for chloride, O(16)⋯Cl 3.013(7) Å, O(24)⋯Cl 3.163(7) Å]. Oxygen atom O(16) also is acceptor of NH⋯O type intermolecular H-bond with amino group; the length of this bond is 2.859(6) Å. The amino group is involved in an NH⋯N type H-bond with nitrogen atom N(4), the length of this bond being 2.969(6) Å. In the crystal structure by means of this bond two cations are associated in centrosymmetric dimers. Furthermore, there are bonds between bromine atom Br(17) and halogen anion with lengths 3.172(5) Å (for Br⋯Br bond) and 3.169(6) Å (for Br⋯Cl bond).

In summary, first examples of modified isoselenazolocaffeinium(adeninium) salts were obtained in acceptable yields under mild reaction conditions, from 8-alkynylpurine derivatives. Experiments on estimating the scope of this transformation and testing antiproliferative activity of cyclic Se–N⁺ bond containing condensed xanthines are underway.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2019.01.033.

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