Synthetic potential of substituted 7-alkylseleno-1,4-dihydro-1,6-naphthyridines*

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Acetylation, oxidation, diazotization and heterocyclization of substituted 7-alkylseleno-1,4-dihydro-1,6-naphthyridines were studied. The reactions afford new heterocyclic systems.

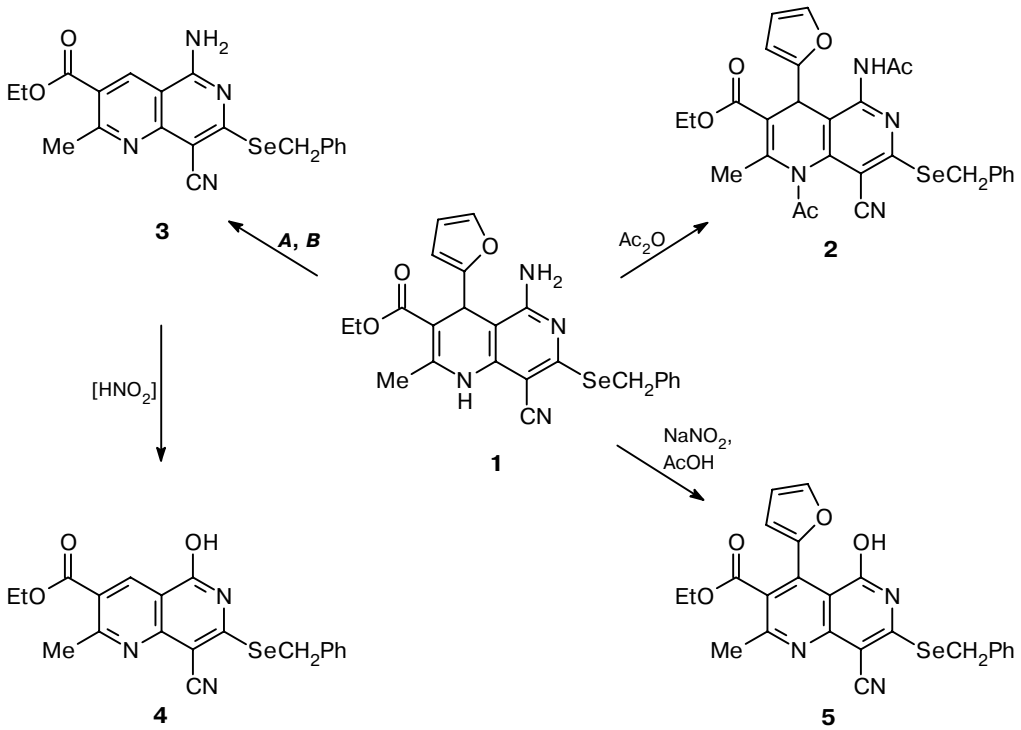
Key words: alkylseleno-1,6-naphthyridines, acetylation, oxidation, diazotization, heterocyclization, selenazolonaphthyridine.

It is known that naphthyridine derivatives[1] and organoselenium compounds[2] exhibit a broad spectrum of biological activity. This fact, with consideration of the previously developed[3,4] convenient method for the synthesis of selenium-containing 1,6-naphthyridines, makes it expedient to study the reactions of acetylation, oxidation, and iodocyclization of 7-alkylseleno-1,4-dihydro-1,6-naphthyridines for use in the synthesis of new biologically active compounds.

When refluxed in Ac_2O, naphthyridine **1** is acetylated both at the exocyclic amino group and the N atom of the dihydropyridine ring to give diacetyl derivative **2** (Scheme 1). With aminonaphthyridines as the starting reagents, this reaction has found use in the synthesis of antiinflammatory, diuretic, broncholytic, and vasodilative

* Dedicated to the memory of Professor Ya. L. Gol'dfarb on the occassion of his 100th birthday.

Scheme 1



Note. Description of methods *A* and *B* is given in the Experimental.

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drugs, as well as those that prevent arrhythmia and inhibit the activity of acetylcholine.[5—7]

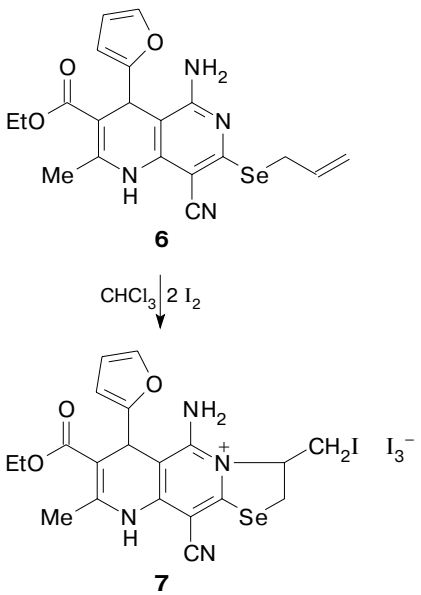
The literature data on the oxidation of 1,4-dihydro-1,6-naphthyridines are lacking, while successful diazotization of 1,6-naphthyridine derivatives was described in the only paper.[8] For this reason, we found it interesting to examine the conditions under which the functional groups of naphthyridine **1** containing labile furan and dihydropyridine fragments can be oxidized. It turned out that, when treated with a solution of $NaNO_2$ in conc. H_2SO_4 at 18—22 °C, naphthyridine **1** in AcOH undergoes aromatization with elimination of the furyl residue to give 4-unsubstituted naphthyridine **3** (method *A*, see Scheme 1). Aromatization is also effective when naphthyridine **1** is refluxed in glacial AcOH (method *B*). At the same time, an excess of $NaNO_2$ causes nitrosation of the amino group in the oxidized naphthyridine **3** with a $NaNO_2$—H_2SO_4—AcOH system (method *A*) and the formation of hydroxy derivative **4**. Refluxing of naphthyridine **1** in glacial AcOH in the presence of $NaNO_2$ brings about simultaneous acid aromatization and diazotization, yielding hydroxynaphthyridine **5**.

Thus, substituted 5-amino-1,4-dihydro-1,6-naphthyridine **1** can be oxidized selectively to a desired state by choosing an appropriate oxidative medium.

Heating of substituted allylselenonaphthyridine **6** with iodine in chloroform causes its iodocyclization into tetrahydroselenazolo[3,2-*g*][1,6]naphthyridinium triiodide **7** (Scheme 2). This reaction can be regarded as an synchronous, regio- and stereoselective, intramolecular electrophilic heterocyclization.[9,10]

The structures of the products synthesized were confirmed by elemental analysis and ^{1}H NMR and IR spectroscopy (see Experimental).

Scheme 2



Hence, 7-alkylseleno-1,4-dihydro-1,6-naphthyridines were found to be convenient reagents in the regiospecific synthesis of not easily available, including annelated, heterocycles with potential biological activity.

Experimental

Melting points were determined on a Kofler stage. IR spectra were recorded on an IKS-29 instrument (Vaseline oil). ^{1}H NMR spectra were recorded on a Bruker AM-300 instrument (300.13 MHz) in DMSO-d_6 with Me_4Si as the internal standard. Pyridine was dried according to a standard procedure.[11]

The course of the reactions was monitored and the purity of the products was checked by TLC on Silufol UV-254 plates in an acetone—heptane system (3 : 5); visualization with iodine vapors.

1-Acetyl-5-acetylamino-7-benzylseleno-8-cyano-3-ethoxycarbonyl-4-(2-furyl)-2-methyl-1,4-dihydro-1,6-naphthyridine (2). Anhydrous pyridine (1 mL) was added to a suspension of naphthyridine **1** [2] (0.60 g, 1.2 mmol) in 7 mL of Ac_2O. The reaction mixture was refluxed for 1.5 h and then cooled. The precipitate that formed was filtered off and washed with 95% EtOH. Yield 0.64 g (92%), m.p. 210—212 °C. Found (%): C, 58.40; H, 4.43; N, 9.59; Se, 13.61. $C_{28}H_{26}N_4O_5Se$. Calculated (%): C, 58.23; H, 4.54; N, 9.70; Se, 13.67. IR, ν/cm^{-1}: 3255, 3308 (NH); 2200 (C≡N); 1673, 1702, 1736 (C=O). ^{1}H NMR, δ: 1.21 (t, 3 H, C$\underline{H}_3$CH$_2$O, *J* = 8.0 Hz); 1.30 (s, 3 H, C(2)Me); 2.45, 2.50 (both s, each 3 H, 2 Ac); 4.07 (q, 2 H, CH$_3$C$\underline{H}_2$O, *J* = 8.0 Hz); 4.38, 4.41 (both d, each 1 H, SeCH$_2$, *J* = 12.4 Hz); 4.84 (s, 1 H, C(4)H); 6.02 (d, 1 H, furyl C(3)H, *J* = 3.0 Hz); 6.27 (dd, 1 H, furyl C(4)H, *J* = 3.0 Hz, *J* = 2.2 Hz); 7.13—7.38 (m, 6 H, furyl C(5)H, Ph); 9.57 (br.s, 1 H, NHCO).

5-Amino-7-benzylseleno-8-cyano-3-ethoxycarbonyl-2-methyl-1,6-naphthyridine (3). Method *A*. A solution of $NaNO_2$ (0.10 g, 1.5 mmol) in 1 mL of conc. H_2SO_4 was slowly added to a suspension of naphthyridine **1** (0.50 g, 1.0 mmol) in 5 mL of glacial AcOH, the reaction temperature being maintained within 18—22 °C. The reaction mixture was stirred for 5 min, and then pH was adjusted to pH 7 by slow addition of a saturated aqueous solution of AcONa. The precipitate that formed was filtered off and washed with water and with 95% EtOH. Yield 0.28 g (65%).

Method *B*. A suspension of naphthyridine **1** (0.50 g, 1.0 mmol) in 15 mL of glacial AcOH was refluxed for 1 h. After 24 h, the precipitate that formed was filtered off and washed with 95% EtOH. Yield 0.31 g (72%), m.p. 259—260 °C (from BuOH). Found (%): C, 56.35; H, 4.39; N, 13.26; Se, 18.72. $C_{20}H_{18}N_4O_2Se$. Calculated (%): C, 56.48; H, 4.27; N, 13.17; Se, 18.56. IR, ν/cm^{-1}: 3249, 3338, 3392 (NH$_2$); 2190 (C≡N); 1695 (C=O); 1607 (δ NH$_2$). ^{1}H NMR, δ: 1.40 (t, 3 H, C$\underline{H}_3$CH$_2$O, *J* = 7.7 Hz); 2.86 (s, 3 H, C(2)Me); 4.37 (q, 2 H, CH$_3$C$\underline{H}_2$O, *J* = 7.7 Hz); 4.58 (s, 2 H, SeCH$_2$); 7.13—7.49 (m, 5 H, Ph); 8.38 (br.s, 2 H, NH$_2$); 9.13 (s, 1 H, C(4)H).

7-Benzylseleno-8-cyano-3-ethoxycarbonyl-5-hydroxy-2-methyl-1,6-naphthyridine (4) was obtained as described in method *A* for compound **3** from naphthyridine **3** (0.70 g, 1.65 mmol) and $NaNO_2$ (0.17 g, 2.47 mmol). Yield 0.41 g (59%), m.p. 207—209 °C (from EtOH). Found (%): C, 56.14; H, 4.20; N, 9.71; Se, 18.63. $C_{20}H_{17}N_3O_3Se$. Calculated (%): C, 56.35; H, 4.02; N, 9.86; Se, 18.52. IR, ν/cm^{-1}: 3342 (OH); 2215 (C≡N); 1713 (C=O). ^{1}H NMR, δ: 1.36 (t, 3 H, C$\underline{H}_3$CH$_2$O, *J* = 7.7 Hz); 2.84 (s, 3 H, C(2)Me); 4.35 (q, 2 H, CH$_3$C$\underline{H}_2$O,

J = 7.7 Hz); 4.69 (s, 2 H, $SeCH_2$); 7.17—7.36 (m, 5 H, Ph); 8.78 (s, 1 H, C(4)H); 12.73 (br.s, 1 H, OH).

7-Benzylseleno-8-cyano-3-ethoxycarbonyl-4-(2-furyl)-5-hydroxy-2-methyl-1,6-naphthyridine (5). $NaNO_2$ (0.21 g, 3.0 mmol) was added within 5 min to a suspension of naphthyridine **1** (1.00 g, 2.0 mmol) in 20 mL of boiling AcOH, so that gas evolution was kept uniform. The reaction mixture was refluxed for 0.5 h and then cooled. The precipitate that formed was filtered off and washed with 95% EtOH. Yield 0.63 g (63%), m.p. 224—226 °C (from BuOH). Found (%): C, 58.69; H, 3.96; N, 8.35; Se, 15.92. $C_{24}H_{19}N_3O_4Se$. Calculated (%): C, 58.54; H, 3.89; N, 8.53; Se, 16.04. IR, ν/cm^{-1}: 3328 (OH); 2210 (C≡N); 1693 (C=O). ^1H NMR, δ: 1.15 (t, 3 H, $C\underline{H}_3CH_2O$, J = 7.5 Hz); 2.63 (s, 3 H, C(2)Me); 4.13 (q, 2 H, $CH_3C\underline{H}_2O$, J = 7.5 Hz); 4.62 (s, 2 H, $SeCH_2$); 6.48 (d, 1 H, furyl C(3)H, J = 3.1 Hz); 6.53 (dd, 1 H, furyl C(4)H, J = 3.1 Hz, J = 2.2 Hz); 7.17—7.41 (m, 5 H, Ph); 7.68 (d, 1 H, furyl C(5)H, J = 2.2 Hz); 12.36 (br.s, 1 H, OH).

5-Amino-10-cyano-7-ethoxycarbonyl-6-(2-furyl)-3-iodomethyl-8-methyl-2,3,6,9-tetrahydroselenazolo[3,2-*g*][1,6]naphthyridinium triiodide (7). A solution of I_2 (0.29 g, 1.13 mmol) in 15 mL of $CHCl_3$ was added with stirring to a suspension of naphthyridine **6** (0.25 g, 0.56 mmol) in 15 mL of $CHCl_3$. The reaction mixture was heated to boiling and filtered hot. After 24 h, the precipitate that formed was filtered off and washed with $CHCl_3$. Yield 0.25 g (47%), m.p. 138 °C. Found (%): C, 25.37; H, 2.31; N, 5.76; Se, 8.13. $C_{20}H_{20}I_4N_4O_3Se$. Calculated (%): C, 25.26; H, 2.12; N, 5.89; Se, 8.30. IR, ν/cm^{-1}: 3260—3405 (NH, NH_2); 2227 (C≡N); 1711 (C=O); 1638 (δ NH_2). ^1H NMR, δ: 1.28 (t, 3 H, $C\underline{H}_3CH_2O$, J = 7.9 Hz); 2.43 (s, 3 H, C(8)Me); 3.41—3.67 (m, 2 H, CH_2I); 3.76—4.24 (m, 4 H, $CH_3C\underline{H}_2O$, $SeCH_2$); 5.35 (s, 1 H, C(6)H); 5.69 (s, 1 H, C(3)H); 6.23 (d, 1 H, furyl C(3)H, J = 3.2 Hz); 6.28 (dd, 1 H, furyl C(4)H, J = 3.2 Hz, J = 2.1 Hz); 7.39 (d, 1 H, furyl C(5)H, J = 2.1 Hz); 8.70 (br.s, 2 H, NH_2); 9.76 (s, 1 H, NH).

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