Chemistry of Heterocyclic Compounds, Vol. 46, No. 12, March, 2011 (Russian Original Vol. 46, No. 12, December, 2010)

SYNTHESIS OF 7-ACETYL-8-ARYL(HETARYL)- 6-HYDROXY-1,6-DIMETHYL-3-SELENOXO-2,3,5,6,7,8-HEXAHYDROISO-QUINOLINE-4-CARBONITRILES BY THE CONDENSATION OF 2,4-DIACETYL-3-ARYL(HETARYL)- 5-HYDROXY-5-METHYL-CYCLOHEXANONES WITH CYANOSELENOACETAMIDE

V. D. Dyachenko[1]* and S. M. Sukach[1]

7-Acetyl-8-aryl(hetaryl)-6-hydroxy-1,6-dimethyl-3-selenoxo-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitriles have been obtained by the condensation of 2,4-diacetyl-3-aryl(hetaryl)-5-hydroxy-5-methylcyclohexanones with cyanoselenoacetamide.

Keywords: 2,4-diacetyl-3-aryl(hetaryl)-5-hydroxy-5-methylcyclohexanones, 7-acetyl-8-aryl(hetaryl)-6-hydroxy-1,6-dimethyl-3-selenoxo-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitriles, selenoether, alkylation, condensation.

Derivatives of partially hydrogenated isoquinolines are present in nature in the form of alkaloids [1], which is a powerful stimulus for their detailed study.

Unlike the functionally substituted 3-oxo- and 3-thioxo-2,3,5,6,7,8-hexahydroisoquinolines synthesized previously [2], their 3-selenoxo analogs are unknown.

It has been shown for the first time that the previously unknown 7-acetyl-8-aryl(hetaryl)-6-hydroxy-1,6-dimethyl-3-selenoxo-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitriles **3a-e** are formed on condensing 2,4-diacetyl-3-aryl(hetaryl)-5-hydroxy-5-methylcyclohexanones **1a-e** with cyanoselenoacetamide (**2**) in absolute ethanol in the presence of triethylamine in an atmosphere of argon at 60°C. The reaction scheme probably includes a stage of forming intermediates **4** which cyclocondense intramolecularly into compounds **3a-e**.

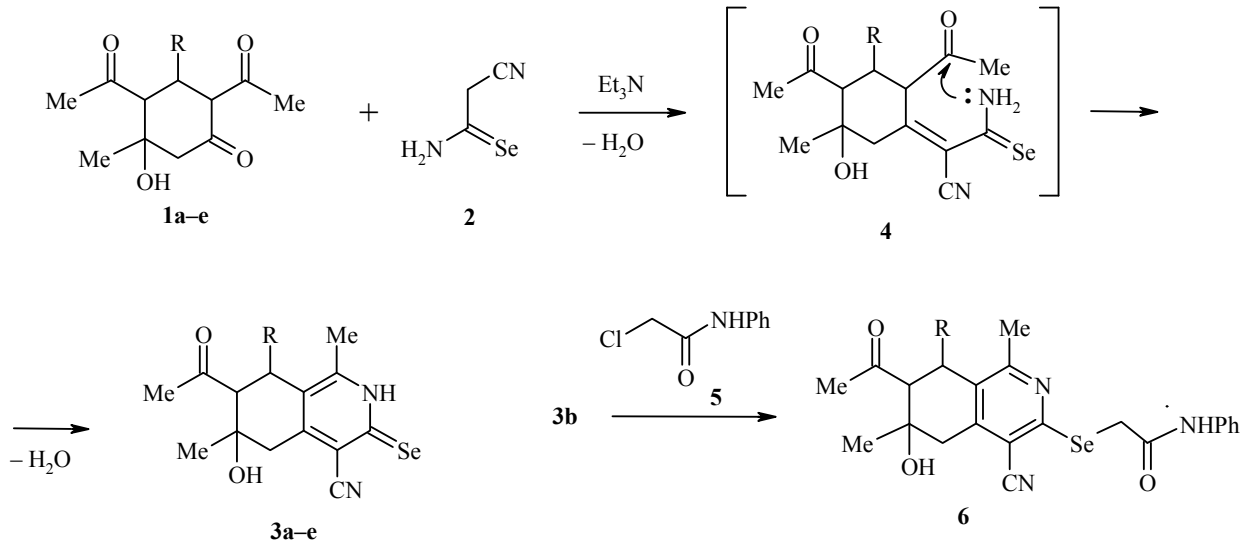
The structure of isoquinoline **3b** was confirmed by alkylation with 2-chloro-N-phenylacetamide (**5**), as a result of which 2-[7-acetyl-4-cyano-8-(fur-2-yl)-6-hydroxy-1,6-dimethyl-5,6,7,8-tetrahydroisoquinolin-3-yl-selenyl]-N-phenylacetamide (**6**) was formed. We note that the isostructural analogs of compounds **3**, the 2-selenoxo-1,2,5,6,7-hexahydroquinolines, are also alkylated by alkyl halides at the selenium atom with the formation of selenoethers [3].

In the IR spectra of the synthesized compounds **3a-e** and **6** characteristic bands were observed for the stretching vibrations of the OH, C≡N, and C=O functional groups at 3417-3481, 2214-2224, and 1695-1721 cm^{-1} respectively.

* To whom correspondence should be addressed, e-mail: dvd_lug@online.lg.ua.

[1] Taras Shevchenko Lugansk National University, Lugansk 91011, Ukraine.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1795-1799, December, 2010. Original article submitted October 15, 2010.



1, **3 a** R = 3-Py, **b** R = 2-Fu, **c** R = 5-methylfur-2-yl,
d R = Ph, **e** R = 4-MeC_6H_4

In addition to the proton signals of substituents in the appropriate regions, characteristic of ^{1}H NMR spectra of partially hydrogenated functionally substituted isoquinolines **3a-e** and **6**, signals were present for the protons of the methylene group of the cyclohexane fragment at 2.81-3.14 and 2.92-3.61 ppm with coupling constant ^2J = 16.0-17.8 Hz.

The mass spectra of the obtained compounds **3a-e** and **6** contain low-intensity peaks for the molecular ions and high-intensity peaks for ions of the acetyl fragment, which is characteristic for acetyl-containing organic compounds [4].

EXPERIMENTAL

The IR spectra of the synthesized compounds were recorded on a Spectrum One (Perkin–Elmer) FIR spectrometer in KBr. The ^{1}H NMR spectra were recorded on a Bruker Avance 400 (400 MHz) instrument in DMSO-d_6, internal standard was TMS. The mass spectra of compounds **3a-e** and **6** were obtained on a MX-1321 (70 eV) spectrometer with direct insertion of substance into the ion source, and of compounds **1a**,**c** on a Crommas GC/MS Hewlett-Packard 5890/5972 instrument, HP-5 MS column (70 eV) in CH_2Cl_2 solution. Melting points were determined on a Kofler block. A check on the progress of reactions and the purity of the obtained compounds was effected by TLC on Silufol UV-254 plates, eluent was acetone–hexane, 3:5, developing with iodine vapor and with UV light.

2,4-Diacetyl-3-aryl(hetaryl)-5-hydroxy-5-methylcyclohexanones 1a-e were obtained by the procedure of [5].

2,4-Diacetyl-5-hydroxy-5-methyl-3-(pyrid-3-yl)cyclohexanone (1a). Yield 2.5 g (87%), white powder, mp 175°C. IR spectrum, ν, cm^{-1}: 3521 (OH), 1709 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.19 (3H, s, CH_3); 1.91 (3H, s, CH_3); 1.92 (3H, s, CH_3); 2.37, 2.92 (2H, two d, ^2J = 10.8, AB system, CH_2); 3.36 (1H, d, *J* = 10.0, H-4); 4.00 (1H, t, *J* = 9.6, H-3); 4.30 (1H, d, *J* = 8.4, H-2); 5.30 (1H, br. s, OH); 7.29-7.31 (1H, m, H-5 pyridine); 7.78 (1H, d, *J* = 6.0, H-4 pyridine); 8.38 (1H, d, *J* = 7.2, H-6 pyridine); 8.50 (1H, s, H-2 pyridine). Mass spectrum, *m/z* (I_{rel}, %): 290 $[M+H]^+$ (100). Found, %: C 66.30; H 6.57; N 4.71. $C_{16}H_{19}NO_4$. Calculated, %: C 66.42; H 6.62; N 4.84.

2,4-Diacetyl-5-hydroxy-5-methyl-3-(5-methylfur-2-yl)cyclohexanone (1c). Yield 3.15 g (85%), white powder, mp 125-127°C. IR spectrum, ν, cm^{-1}: 3592 (OH), 1726, 1705 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.17 (3H, s, CH_3); 2.04 (3H, s, CH_3); 2.07 (3H, s, CH_3); 2.17 (3H, s, CH_3); 2.30, 2.89 (2H, two d, ^2J = 10.8, AB system, CH_2); 3.15 (1H, d, *J* = 9.2, H-4); 3.98 (1H, d, *J* = 9.6, H-2); 4.06 (1H, t, *J* = 9.6, H-3); 5.22 (1H, br. s, OH); 5.90 (1H, d, *J* = 2.4, H-4 furan); 6.03 (1H, d, *J* = 2.4, H-3 furan). Mass spectrum, *m/z* (I_{rel}, %): 291 $[M-H]^+$ (100). Found, %: C 65.65; H 6.82. $C_{16}H_{20}O_5$. Calculated, %: C 65.74; H 6.90.

Cyanoselenoacetamide (2) was obtained by the procedure of [6].

7-Acetyl-6-hydroxy-1,6-dimethyl-8-(pyrid-3-yl)-3-selenoxo-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (3a). Cyanoselenoacetamide (**2**) (1.1 g, 7 mmol) was added to a suspension of cyclohexanone **1a** (2 g, 7 mmol) in absolute ethanol (20 ml). The reaction mixture was stirred for 15 min in an argon atmosphere, triethylamine (1 ml, 7 mmol) was then added and the mixture heated with stirring to 60°C, and then left for 24 h. The resulting solid was filtered off, and washed with ethanol. Yield 2 g (71%), yellow powder, mp 208-211°C. IR spectrum, ν, cm^{-1}: 3436 (OH), 3276 (NH), 2217 (C≡N), 1700 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.29 (3H, s, CH_3); 1.91 (3H, s, CH_3); 2.16 (3H, s, CH_3); 2.81, 2.92 (2H, two d, ^2J = 17.8, AB system, CH_2); 2.98 (1H, d, *J* = 10.5, H-7); 4.63 (1H, d, *J* = 10.5, H-8); 5.00 (1H, br. s, OH); 7.28 (1H, d, *J* = 8.1, H-4 pyridine); 7.45 (1H, m, H-5 pyridine); 8.35 (1H, d, *J* = 4.8, H-6 pyridine); 8.43 (1H, s, H-2 pyridine). The signal of the H-2 proton was not displayed, evidently as a result of rapid deuterium exchange. Mass spectrum, *m/z* (I_{rel}, %): 400 $[M]^+$ (9), 396 (18), 318 (8), 238 (20), 160 (100), 80 (35), 43 $[CH_3C{\equiv}O)^+$ (29). Found, %: C 56.91; H 4.63; N 10.45. $C_{19}H_{19}N_3O_2Se$. Calculated, %: C 57.00; H 4.78; N 10.50.

7-Acetyl-8-(fur-2-yl)-6-hydroxy-1,6-dimethyl-3-selenoxo-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (3b) was obtained analogously to compound **3a** from cyclohexanone **1b**. Yield 2.1 g (77%), yellow powder, mp 240-242°C. IR spectrum, ν, cm^{-1}: 3434 (OH), 3259 (NH), 2222 (C≡N), 1702 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz):1.26 (3H, s, CH_3); 2.10 (3H, s, CH_3); 2.18 (3H, s, CH_3); 2.86, 3, 09 (H, two d, ^2J = 17.7, AB system, CH_2); 3.03 (1H d, 7.8, H-7); 4.58 (1H, d, *J* = 7.8, H-8); 5.04 (1H, br. s, OH); 6.11 (1H, d, *J* = 3.2, H-3 furan); 6.27 (1H, dd, *J* = 4.0 and *J* = 6.0, H-4 furan); 7.50 (1H, d, *J* = 1.2, H-5 furan); 14.38 (1H, br. s, NH). Mass spectrum, *m/z* (I_{rel}, %): $[M]^+$ missing, 372 $[M+H-H_2O]^+$ (20), 371 $[M-H_2O]^+$ (11), 329 (45), 249 (14), 43 $[CH_3C{\equiv}O]^+$ (100). Found, %: C 55.49; H 4.60; N 7.08. $C_{18}H_{18}N_2O_3Se$. Calculated, %: C 55.53; H 4.66; N 7.20.

7-Acetyl-6-hydroxy-1,6-dimethyl-8-(5-methylfur-2-yl)-3-selenoxo-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (3c) was obtained analogously to compound **3a** from cyclohexanone **1c**. Yield 1.9 g (67%), yellow powder, mp 207°C. IR spectrum, ν, cm^{-1}: 3429 (OH), 3272 (NH), 2222 (C≡N), 1702, 1695 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.30 (3H, s, CH_3); 2.12 (3H, s, CH_3); 2.25 (3H, s, CH_3); 2.34 (3H, s, CH_3); 2.91 (1H, d, *J* = 7.8, H-7); 3.14, 3.61 (2H, two d, ^2J = 16.0, AB system, CH_2); 4.69 (1H, br. s, OH); 4.74 (1H, d, *J* = 7.8, H-8); 5.92 (2H, d, *J* = 9.2, H-3 furan and H-4 furan); 7.67 (1H, br. s, NH). Mass spectrum, *m/z* (I_{rel}, %): $[M]^+$ missing, 385 $[M - H_2O]^+$ (2), 370 $[M-H_2O-CH_3]^+$ (9), 328 (25), 285 (20), 222 (17), 160 (50), 80 (74), 43 $[CH_3C{\equiv}O]^+$ (100). Found, %: C 56.52; H 4.91; N 6.80. $C_{19}H_{20}N_2O_3Se$. Calculated, %: C 56.58; H 5.00; N 6.95.

7-Acetyl-6-hydroxy-1,6-dimethyl-8-phenyl-3-selenoxo-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (3d) was obtained analogously to compound **3a** from cyclohexanone **1d**. Yield 2.1 g (75%), yellow powder, mp 215°C. IR spectrum, ν, cm^{-1}: 3422 (OH), 3280 (NH), 2221 (C≡N), 1700 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.25 (3H, s, CH_3); 1.91 (3H, s, CH_3); 2.07 (3H, s, CH_3); 2.82 (1H, d, *J* = 14.6, H-5); 2.91 (1H, d, *J* = 10.8, H-7); signal of the second proton of the 5-CH_2 group is masked by the signal of the water protons, 4.36 (1H, d, *J* = 10.8, H-8); 4.80 (1H, br. s, OH); 7.05 (2H, d, *J* = 7.0, C_6H_5); 7.22-7.28 (3H, m, C_6H_5); 14.22 (1H, br. s, NH). Mass spectrum, *m/z* (I_{rel}, %): 399 $[M]^+$ (12), 381 $[M-H_2O]^+$ (26), 339 (73), 259 (20), 160 (10), 77 $[C_6H_5]^+$ (8), 43 $[CH_3C{\equiv}O]^+$ (100). Found, % : C 60.00; H 4.91; N 6.95. $C_{20}H_{20}N_2O_2Se$. Calculated, %: C 60.15; H 5.05; N 7.01.

7-Acetyl-6-hydroxy-1,6-dimethyl-3-selenoxo-8-*p*-tolyl-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (3e) was obtained analogously to compound **3a** from cyclohexanone **1e**. Yield 2.2 g (76%), yellow powder, mp 245-247°C. IR spectrum, ν, cm^{-1}: 3417 (OH), 3263 (NH), 2224 (C≡N), 1701 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.26 (3H, s, CH_3); 1.95 (3H, s, CH_3); 2.12 (3H, s, CH_3); 2.26 (3H, s, CH_3); 2.85, 3.22 (2H, two d, ^2J = 17.76, AB system, CH_2); 2.89 (1H, d, *J* = 10.36, H-7); 4.32 (1H, d, *J* = 10.4, H-8); 4.98 (1H, br. s, OH); 6.99 (2H, d, *J* = 8.0, C_6H_4); 7.09 (2H, d, 8.0, C_6H_4); 14.27 (1H, br. s, NH). Mass spectrum, *m/z* (I_{rel}, %): 413 $[M]^+$ (10), 395 $[M-H_2O]^+$ (22), 352 $[M-H_2O-CH_3C{\equiv}O]^+$ (100), 337 (19), 273 (17), 183 (8), 105 (6), 43 $[CH_3C{\equiv}O]^+$ (99). Found, %: C 60.95; H 5.31, N 6.72. $C_{21}H_{22}N_2O_2Se$. Calculated, %: C 61.02; H 5.36; N 6.78.

2-[7-Acetyl-4-cyano-8-(fur-2-yl)-6-hydroxy-1,6-dimethyl-5,6,7,8-tetrahydroisoquinolin-3-ylselenyl]-N-phenylacetamide (6). 2-Chloro-N-phenylacetamide (**5**) (0.24 g, 1.3 mmol) was added in a stream of argon to a solution of compound **3b** (0.5 g, 1.3 mmol) in DMF (5 ml) followed by 10% aqueous KOH solution (0.71 ml, 13 mmol). The mixture was stirred for 30 min at 50°C and then left. After 48 h the solid, which had formed was filtered off, and washed with ethanol. Yield 0.45 g (67%), yellow powder; mp 195°C. IR spectrum, ν, cm^{-1}: 3481 (OH), 3335 (NH), 2214 (C≡N), 1721 (C=O), 1669 (CONH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.26 (3H, s, CH_3); 2.11 (3H, s, CH_3); 2.19 (3H, s, CH_3); 2.83, 3.12 (2H, two d, ^2J = 17.2, AB system, CH_2); 3.03 (1H, d, *J* = 9.2, H-7); 4.13 (2H, s, $SeCH_2$); 4.69 (1H, d, *J* = 9.2, H-8); 5.01 (1H, br. s, OH); 6.10 (1H, d, *J* = 2.8, H-3 furan); 6.34 (1H, dd, *J* = 2.4 and *J* = 1.1, H-4 furan); 7.01 (1H, t, *J* = 7.2, C_6H_5); 7.29 (2H, t, *J* = 7.6, C_6H_5); 7.49-7.54 (3H, m, H-5 furan and C_6H_5); 10.26 (1H, br. s, NH). Mass spectrum, *m/z* (I_{rel}, %): 523 $[M+H]^+$ (6), 413 (11), 341 (13), 327 (9), 248 (6), 207 (8), 93 $[C_6H_5NH]^+$, 43 $[CH_3C{\equiv}O]^+$ (100). Found, %: C 59.60; H 4.79; N 7.98. $C_{26}H_{25}N_3O_4Se$. Calculated, %: C 59.77; H 4.82; N 8.04.

REFERENCES

1. V. G. Kartsev, in: V. G. Kartsev and G. A. Tolstikov (editors), *Nitrogen Heterocycles and Alkaloids*, [in Russian], Vol. 1 Interbioscreen Ltd, Moscow (2001), p. 97.
2. A. I. Ozols, Yu. E. Pelcher, Z. A. Kalme, Yu. Yu. Popelis, I. V. Turovskis, and G. Ya. Duburs, *Khim. Geterotsikl. Soedin.*, 59 (1996). [*Chem. Heterocycl. Comp.*, **32**, 52 (1996)].
3. V. D. Dyachenko and V. P. Litvinov, *Khim. Geterotsikl. Soedin.*, 1384 (1997). [*Chem. Heterocycl. Comp.*, **33**, 1203 (1997).
4. Yu. A. Pentin and L. V. Vilkov, *Physical Methods of Investigation in Chemistry* [Russian translation], Mir, Moscow (2003), p. 46.
5. A. P. Kriven'ko and V. V. Sorokin, *Substituted Cyclohexanolones; Training Manual* [in Russian], Izd. Sarat. Univ., Saratov (1999), p. 38.
6. V. P. Litvinov, V. Yu. Mortikov, Yu. A. Sharanin, and A. M. Shestopalov, *Synthesis*, 98 (1985).