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Synthesis of 7-Acetyl-2,3,5,6,7,8-hexahydro-6-hydroxy-1,6-dimethyl-3-thioxo-8-phenyl(heteryl)isoquinoline-4-carbonitriles Based on 2,4-Diacetyl-5-hydroxy-5-methyl-3-phenyl(heteryl)cyclohexanones

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Abstract—7-Acetyl-2,3,5,6,7,8-hexahydro-6-hydroxy-1,6-dimethyl-3-thioxo-8-phenyl(heteryl)isoquinoline-4-carbonitriles were obtained by reaction of 2,4-diacetyl-5-hydroxy-5-methyl-3-phenyl(heteryl)cyclohexanones with cyanothioacetamide. Structure of 7-acetyl-5,6,7,8-tetrahydro-6-hydroxy-1,6-dimethyl-3-methylthio-8-phenylisoquinoline-4-carbonitrile was proved by X-ray diffraction method.

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Tetrahydroisoquinoline derivatives are semiproducts in the synthesis of biologically active compounds, which can be used in medicine as drugs [1, 2]. The isoquinoline frame is a basic structural component of the large number of natural alkaloids, which possess pharmacological action [3–5].

Owing to the increasing practical value of isoquinilines, the attention is concentrated on the development of the methods of their synthesis. Building up of a heterocyclic system on a carbocycle is the most common of them [6].

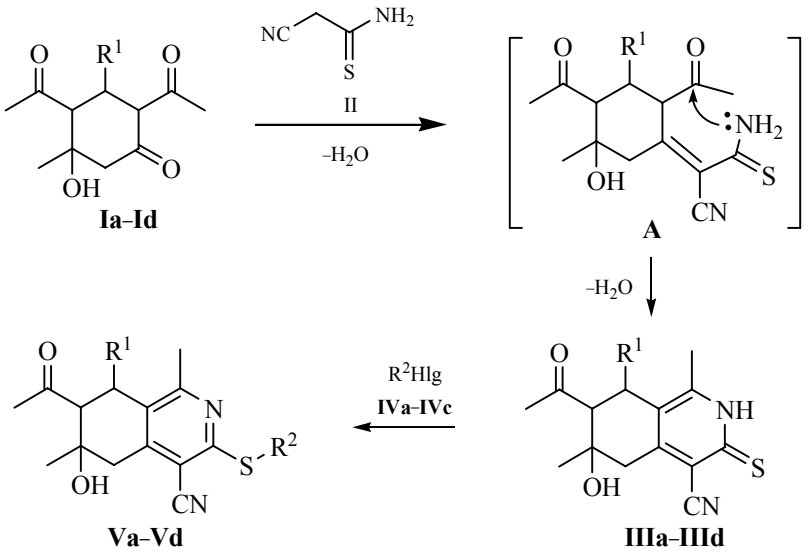
The literature analysis shows that the condensation of functionally substituted cyclohexanones with cyano (thio)acetamide proceeds ambiguously. Thus, it was reported earlier that a mixture of isoquinolines and quinolines was obtained on the basis of 2-acetylcyclohexanone derivatives [7]. At the same time Ozols et al. [8] mentioned only isoquinolinethiones as only reaction products.

To extende the studies on the nitrogen-containing fused heterocycles [9–11] in this work the reaction of 2,4-diacetyl-5-hydroxy-5-methyl-3-phenyl(heteryl)cyclohexanones **Ia–Id** with cyanothioacetamide **II** in anhydrous ethanol in the presence of morpholine was examined. This condensation was shown to occur to form evidently intermediates **A**, which underwent the intramolecular cyclization into 7-acetyl-2,3,5,6,7,8-hexahydro-6-hydroxy-1,6-dimethyl-3-thioxo-8-phenyl-(heteryl)isoquinoline-4-carbonitriles **IIIa–IIId**.

The structure of 7-acetyl-3-benzoylthio-5,6,7,8-tetrahydro-6-hydroxy-1,6-dimethyl-8-(fur-2-yl)isoquinoline-4-carbonitrile **IIIa** was confirmed by the experiment of homonuclear Overhauser effect. On selective irradiating the methyl group in the position 1 of isoquinoline, the interaction with NH-proton was observed, what is impossible in the case of quinoline formation.

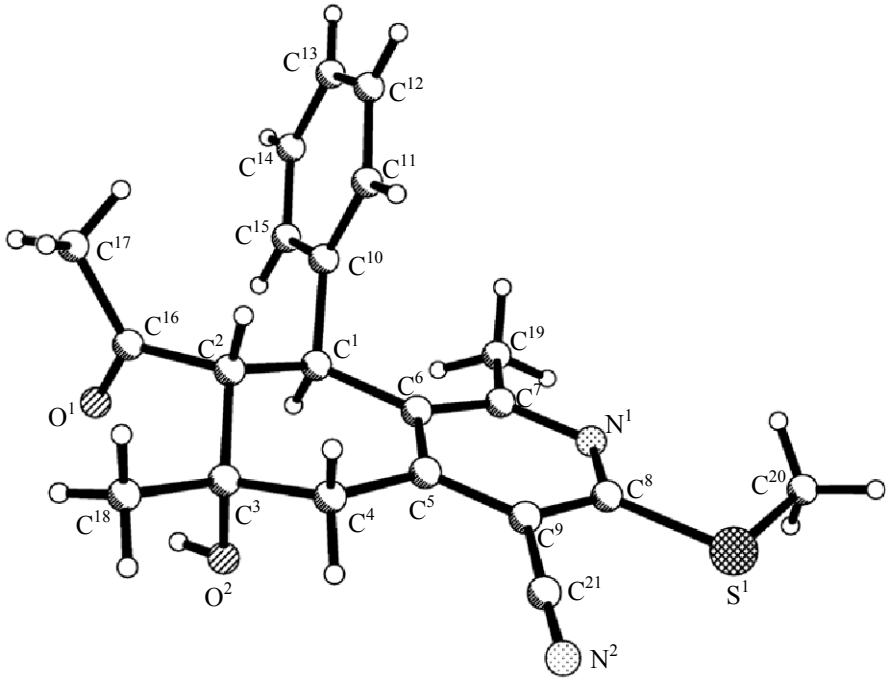
The reaction of compounds **IIIa** and **IIIb** with alkylating agents **IVa–IVc** in DMF solution in basic medium gave rise to the corresponding *S*-alkyltetrahydroisoquinolines **Va–Vd**, whose structure was confirmed by spectral studies.

For unambiguous structure determination of compound **Vd** we performed X-ray diffraction investiga-



R^1 = 3-pyridinyl (**Ia**, **IIIa**, **Va**), 2-furyl (**Ib**, **IIIb**, **Vb**, **Vc**), 5-methylfur-2-yl (**Ic**, **IIIc**), Ph (**Id**, **IIId**, **Vd**); R^2Hlg = $PhCH_2Cl$ (**IVa**), $PhC(O)CH_2Br$ (**IVb**), MeI (**IVc**); R^2 = $PhCH_2$ (**Va**), $PhC(O)CH_2$ (**Vb**), Me (**Vc**, **Vd**)

tion (see the figure, Tables 1, 2). In molecule **Vd** there are three chiral centers: atoms C^1, C^2 and C^3, which have relative configurations *S*-*R*-*S*. Cyclohexene ring is in a *semi-chair* conformation (folding parameters are [12]: *S* 0.60, Θ 34.6°, Ψ 22.1°). Phenyl, acetyl substituents, and methyl group C^{18} are equatorially oriented relative to the cycle, and hydroxy group, axially [torsion angles C^{10}–C^1–C^2–C^3 –171.82(11)°, C^{16}–C^2–C^3–C^4 –173.86(12)°, $C^{18}C^3C^2$–C^1 –174.82(12)° and $O^2C^3C^2C^1$ –50.72(14)°]. Carbonyl group is oriented to hydroxy group due to the formation of a weak intramolecular hydrogen bond O^2–$H^2\cdots O^1$ [H···O 2.23(2) Å, O–H···O 136(2)°]. In the molecule a sufficient steric repulsion between methyl C^{19} and phenyl groups is observed as evidenced by the strongly shortened intramolecular contact $C^{10}\cdots C^{19}$ 2.99 Å (sum



General view of molecule **Vd**.

Table 1. Bond lengths (*d,* Å) in the structure **Vd**

Bond	*d*	Bond	*d*	Bond	*d*	Bond	*d*
S^1–C^8	1.7586(13)	C^1–C^{10}	1.5192(18)	C^4–C^5	1.495(2)	C^{10}–C^{11}	1.380(2)
S^1–C^{20}	1.774(2)	C^1–C^6	1.5247(17)	C^5–C^6	1.3899(18)	C^{10}–C^{15}	1.3838(18)
O^1–C^{16}	1.2023(19)	C^1–C^2	1.5437(19)	C^5–C^9	1.3985(18)	C^{11}–C^{12}	1.381(2)
O^2–C^3	1.4268(19)	C^2–C^{16}	1.5211(19)	C^6–C^7	1.3986(19)	C^{12}–C^{13}	1.366(2)
N^1–C^8	1.3223(17)	C^2–C^3	1.541(2)	C^7–C^{19}	1.4983(18)	C^{13}–C^{14}	1.361(2)
N^1–C^7	1.3429(16)	C^3–C^4	1.5090(19)	C^8–C^9	1.386(2)	C^{14}–C^{15}	1.378(2)
N^2–C^{21}	1.1321(19)	C^3–C^{18}	1.521(2)	C^9–C^{21}	1.438(2)	C^{16}–C^{17}	1.489(2)

Table 2. Bond angles (ω, deg) in the structure **Vd**

Angle	ω	Angle	ω	Angle	ω	Angle	ω
$C^8S^1C^{20}$	102.34(8)	$C^4C^3C^{18}$	110.15(13)	$N^1C^7C^6$	122.82(12)	$C^{15}C^{10}C^1$	120.26(13)
$C^3O^2H^2$	108.1(17)	$O^2C^3C^2$	110.26(12)	$N^1C^7C^{19}$	113.17(12)	$C^{10}C^{11}C^{12}$	120.22(13)
$C^8N^1C^7$	119.08(12)	$C^4C^3C^2$	107.20(12)	$C^6C^7C^{19}$	123.98(11)	$C^{13}C^{12}C^{11}$	120.49(16)
$C^{10}C^1C^6$	114.57(11)	$C^{18}C^3C^2$	112.56(13)	$N^1C^8C^9$	121.97(12)	$C^{14}C^{13}C^{12}$	119.94(15)
$C^{10}C^1C^2$	108.08(11)	$C^5C^4C^3$	113.94(11)	$N^1C^8S^1$	119.07(11)	$C^{13}C^{14}C^{15}$	120.13(15)
$C^6C^1C^2$	112.34(10)	$C^6C^5C^9$	118.28(13)	$C^9C^8S^1$	118.93(11)	$C^{14}C^{15}C^{10}$	120.75(15)
$C^{16}C^2C^3$	111.14(12)	$C^6C^5C^4$	122.64(12)	$C^8C^9C^5$	119.70(12)	$O^1C^{16}C^{17}$	121.70(15)
$C^{16}C^2C^1$	109.16(11)	$C^9C^5C^4$	119.08(12)	$C^8C^9C^{21}$	119.29(12)	$O^1C^{16}C^2$	119.77(15)
$C^3C^2C^1$	111.78(11)	$C^5C^6C^7$	117.96(11)	$C^5C^9C^{21}$	120.99(14)	$C^{17}C^{16}C^2$	118.52(15)
$O^2C^3C^4$	105.72(12)	$C^5C^6C^1$	120.82(12)	$C^{11}C^{10}C^{15}$	118.47(13)	$N^2C^{21}C^9$	177.98(19)
$O^2C^3C^{18}$	110.66(13)	$C^7C^6C^1$	121.06(11)	$C^{11}C^{10}C^1$	121.23(11)		

of van der Waals radii is 3.4(2) Å [13]), and also significant increase in the bond angle values $C^6C^1C^{10}$ 114.57(11)° and C^6–C^7–C^{19} 123.98(11)° in comparison with C^2–C^1–C^{10} 108.08(11)° and N^1–C^7–C^{19} 113.17(12)°, respectively. There is also a shortened intramolecular contact between acetyl and methyl substituents C^{18}–H^{18a}···C^{16} 2.67 Å (sum of van der Waals radii is 2.87 Å).

In the crystal intermolecular C–H···O hydrogen bonds C^{20}–H^{20A}···$O^{1'}$ [–*x*, –*y*, 1 – *z*] (H···O 2.46 Å, C–H···O 161°) and C^{20}–H^{20C}···$O^{2'}$ [–1 + *x, y, z*] (H···O 2.37 Å, C–H···O 163°), are observed, which connect the molecules into zigzag chains along *a* axis of the crystal.

EXPERIMENTAL

The IR spectra were recorded on a FTIR-spectrometer Spectrum One (Perkin Elmer) in mineral oil. The ^{1}H NMR spectra were registered on a Bruker Avance 400 instrument in DMSO-d_6 relative to internal TMS. The mass spectra were taken on a spectrometers MKh-1321 (70 eV) using direct admission of the substance into the ion source (compounds **IIId**, **Va**, **Vb**) and Crommas GC/MS–Hewlett-Packard 5890/5972, column HP-5 MS (70 eV) in CH_2Cl_2 (**Ia**, **Id**, **IIIa–IIIc**, **Vc**, **Vd**). Melting points were determined on a Koeffler apparatus. The reaction progress and purity of the compounds obtained were monitored with TLC using Silufol UV-254 plates and a mixture

acetone-hexane (3:5) as eluent, detecting with iodine vapor and UV irradiation.

X-Ray diffraction analysis of compound **Vd** was performed on a Xcalibur-3 four-circle diffractometer (MoK_α radiation, CCD-detector, graphite monochromator, ω-scanning, $2\theta_{max}$ = 55°). The unit cell parameters at 298K are as follows: *a* 8.3439(5) Å, *b* 10.2553(7) Å, *c* 11.9030[6] Å, α 99.223(5)°, β 108.308(5)°, γ 91.365(5)°, *V* 951.48[10] Å^3, *M* 366.47, *Z* 2, space group $P\bar{1}$, d_{calc} 1.28 g cm^{-3}, μ(MoK_α) 0.19 mm^{-1}, *F* (000) 388. Intensities of 8342 reflections were measured (4318 independent, R_{int} 0.016).

The structure was solved by the direct method by means of SHELXTL program package [14]. Hydrogen atoms positions were geometrically revealed and refined in a *rider*-model with $U_{iso} = nU_{equiv}$ (n = 1.5 for methyl groups and n = 1.2 for the other hydrogen atoms), except for hydroxy hydrogen atom, which was isotropically refined. The structure was refined by full-matrix least-squares procedure on F^2 in anisotropic approximation for nonhydrogen atoms to wR_2 0.105 by 4318 reflections [R_1 0.038 by 2733 reflections with $F > 4\sigma(F)$, S 1.00]. bonds lengths and bond angles are given in Tables 1 and 2, respectively. The main crystallographic data were deposited into the Cambridge Crystallographic Data Center (CCDC 753449).

2,4-Diacetyl-5-hydroxy-5-methyl-3-phenyl(heteryl)-cyclohexanones (Ia–Id) were obtained by the known procedure [15].

2,4-Diacetyl-5-hydroxy-5-methyl-3-(pyridin-3-yl)-cyclohexanone (Ia). Yield 2.5 g (87%), white powder, mp 175°C. IR spectrum, ν, cm^{-1}: 3421 (OH), 1709 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.19 s (3H, Me), 1.91 s (3H, Me), 1.92 s (3H, Me), 2.37 d (1H, C^{4}H, *J* 10.8 Hz), 2.33–3.36 m (2H, C^{6}H$_2$), 3.97–4.02 m (1H, C^{3}H), 4.18 d (1H, C^{2}H, *J* 9.6 Hz), 5.30 s (1H, OH), 7.29–7.31 m (1H, C^{5}H$_{pyridine}$), 7.79 d (1H, C^{4}H$_{pyridine}$, *J* 6.0 Hz), 8.37–8.40 m (1H, C^{6}H$_{pyridine}$), 8.50 s (1H, C^{2}H$_{pyridine}$). Mass spectrum, *m/z* (I_{rel}, %): 290 (100) [M + 1]$^+$. Found, %: C 66.40; H 6.67; N 4.81. $C_{19}H_{19}N_3O_2S$. Calculated, %: C 66.42; H 6.62; N 4.84.

2,4-Diacetyl-5-hydroxy-5-methyl-3-(5-methylfur-2-yl)cyclohexanone (Ic). Yield 3.15 g (85%), white powder, mp 125–127°C. IR spectrum, ν, cm^{-1}: 3430 (OH), 1704 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.17 s (3H, Me), 2.04 s (3H, Me), 2.07 s (3H, Me), 2.17 s (3H, Me), 2.31 d (1H, C^{4}H, *J* 10.8 Hz), 2.89 d (1H, C^{2}H, *J* 10.8 Hz), 3.15 d (1H, C^{6}H$_2$, ^2J 9.2 Hz), 3.99 d (1H, C^{6}H$_2$, *J* 9.6 Hz), 4.04–4.09 m (1H, C^{3}H), 5.22 s (1H, OH), 5.90 s (1H, C^{3}H$_{furan}$), 6.03 d (1H, C^{4}H$_{furan}$, *J* 2.4 Hz). Mass spectrum, *m/z* (I_{rel}, %): 291 (100) [M – 1]$^+$. Found, %: C 65.77; H 6.99. $C_{19}H_{20}N_2O_3S$. Calculated, %: C 65.74; H 6.90.

7-Acetyl-2,3,5,6,7,8-hexahydro-6-hydroxy-1,6-dimethyl-8-(pyridin-3-yl)-3-thioxoisoqui-noline-4-carbonitrile (IIIa). To a suspension of 2 g (7 mmol) of cyclohexanone **Ia** in 20 ml of anhydrous ethanol was added 0.7 (7 mmol) of cyanothioacetamide **II**. The reaction mixture was stirred for 15 min, and then 0.61 ml (7 mmol) of morpholine was added. The mixture was heated to 60°C under stirring and cooled to 15°C. After 24 h the formed precipitate was filtered off and washed with ethanol. Yield 2.1 g (85%), yellow powder, mp 244–246°C. IR spectrum, ν, cm^{-1}: 3420 (OH), 3280 (NH), 2226 (C≡N), 1700 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.25 s (3H, Me), 1.86 s (3H, Me), 2.13 s (3H, Me), 2.85–2.90 m (2H, C^{5}H and C^{7}H), 3.22 d (1H, C^{5}H, ^2J 17.6 Hz), 4.49 d (1H, C^{8}H, *J* 10.4 Hz), 5.05 br.s (1H, OH), 7.27–7.29 m (1H, C^{5}H$_{pyridine}$), 7.53 d (1H, C^{4}H$_{pyridine}$, *J* 7.4 Hz), 8.37–8.41 m (2H, C^{2}H$_{pyridine}$ and C^{6}H$_{pyridine}$), 13.80 br.s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 354 (98) [M + 1]$^+$. Found, %: C 64.43; H 5.37; N 11.78. $C_{19}H_{19}N_3O_2S$. Calculated, %: C 64.57; H 5.42; N 11.89.

7-Acetyl-2,3,5,6,7,8-hexahydro-6-hydroxy-1,6-dimethyl-3-thioxo-8-(fur-2-yl)isoquinoline-4-carbonitrile (IIIb) was obtained similarly from cyclohexanone **Ib**. Yield 1.2 g (97%), yellow powder, mp 261°C. IR spectrum, ν, cm^{-1}: 3427 (OH), 3270 (NH), 2222 (C≡N), 1701 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.32 s (3H, Me), 2.13 s (3H, Me), 2.17 s (3H, Me), 2.88 s (2H, C^{5}H$_2$), 3.08 d (1H, C^{7}H, *J* 8.04 Hz), 4.51 d (1H, C^{8}H, *J* 8.04 Hz), 4.89 br.s (1H, OH), 6.04 d (1H, C^{3}H$_{furan}$, *J* 3.15 Hz), 6,27 d.d (1H, C^{4}H$_{furan}$, *J* 3.06, 1.88 Hz), 7.37 s (1H, C^{5}H$_{furan}$), 13.74 br.s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 343 (100) [M + 1]$^+$. Found, %: C 63.07; H 5.21; N 8.11. $C_{18}H_{18}N_2O_3S$. Calculated, %: C 63.14; H 5.30; N 8.18.

7-Acetyl-2,3,5,6,7,8-hexahydro-6-hydroxy-1,6-dimethyl-8-(5-methylfur-2-yl)-3-thioxoisoquinoline-4-carbonitrile (IIIc) was obtained similarly from cyclohexanone **Ic**. Yield 3.15 g (88%), yellow powder, mp 220°C. IR spectrum, ν, cm^{-1}: 3437 (OH), 3270 (NH), 2217 (C≡N), 1704 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.06 s (3H, Me), 1.29 s (3H, Me), 2.14 s (3H, Me), 2.17 s (3H, Me), 2.83 d (1H, C^{5}H, ^2J 16.0 Hz), 3.01–3.08 m (2H, C^{5}H and C^{7}H), 4.51 d (1H, C^{8}H, *J* 8.04 Hz), 5.05 br.s (1H, OH), 5.96 d (2H, C^{3}H$_{furan}$ and C^{4}H$_{furan}$,

J 16.00 Hz), 13.86 br.s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 357 (100) $[M + 1]^+$. Found, %: C 64.03; H 5.51; N 7.83. $C_{19}H_{20}N_2O_3S$. Calculated, %: C 64.02; H 5.66; N 7.86.

7-Acetyl-2,3,5,6,7,8-hexahydro-6-hydroxy-1,6-dimethyl-3-thioxo-8-phenylisoquinoline-4-carbonitrile (IIId) was obtained similarly from cyclohexanone **Id**. Yield 0.57 g (88%), yellow powder, mp 266–268°C (published data [8] 269–270°C). Mass spectrum, *m/z* (I_{rel}, %): 352 (2) $[M]^+$, 334 (5.9) $[M - H_2O]^+$, 291 (100), 251 (4.1), 215 (10), 128 (3.1), 77 (6.6) $[Ph]^+$, 43 (84.7).

7-Acetyl-3-benzylthio-5,6,7,8-tetrahydro-6-hydroxy-1,6-dimethyl-8-(pyridin-3-yl)isoquinoline-4-carbonitrile (Va). To a solution of 0.5 g (1.4 mmol) of compound **IIIa** in 5 ml of DMF was added 0.16 ml (1.4 mmol) of benzyl chloride **IVa**, and then 0.78 ml (14 mmol) of 10% KOH solution. This mixture was stirred at heating to 50°C for 30 min. After 48 h the formed precipitate was filtered off and washed with ethanol. Yield 0.51 g (81%), grey powder, mp 240°C (MeOH). IR spectrum, ν, cm^{-1}: 3435 (OH), 2214 (C≡N), 1709 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.00 s (3H, Me), 1.95 s (3H, Me), 1.97 s (3H, Me), 2.88 d (1H, C^5H, ^2J 16.88 Hz), 3.28–3.30 m (2H, C^5H and C^7H), 4.39–4.50 m (3H, C^8H and SCH_2), 5.44 br.s (1H, OH), 7.20–7.30 m (4H, H_{Ar}), 7.38–7.43 m (3H, H_{Ar}), 8.26 d (1H, $C^2H_{pyridine}$, *J* 1.78 Hz), 8.42 d (1H, $C^6H_{pyridine}$, *J* 3.66 Hz). Mass spectrum, *m/z* (I_{rel}, %): 443 (29.2) $[M]^+$, 400 (21.7), 350 (2.8), 305 (3.6), 220 (1.4), 206 (1.5), 140 (2.0), 91 (100) $[PhCH_2]^+$, 43 (59.8). Found, %: C 70.29; H 5.61; N 9.36. $C_{26}H_{25}N_3O_2S$. Calculated, %: C 70.40; H 5.68; N 9.47.

7-Acetyl-3-benzoylthio-5,6,7,8-tetrahydro-6-hydroxy-1,6-dimethyl-8-(fur-2-yl)isoquinoline-4-carbonitrile (Vb) was obtained similarly from isoquinoline **IIIb** and phenacylbromide **IVb**. Yield 0.3 g (44%), yellow powder, mp 262–265°C (DMF). IR spectrum, ν, cm^{-1}: 3446 (OH), 2219 (C≡N), 1704 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.32 s (3H, Me), 2.15 s (3H, Me), 2.24 s (3H, Me), 3.01 d (1H, C^7H, *J* 9.93 Hz), 3.30 d (1H, C^5H, ^2J 17.92 Hz), 3.52 d (1H, C^5H, ^2J 17.42 Hz), 4.79 d (1H, C^8H, *J* 9.89 Hz), 4.91 br.s (1H, OH), 6.06 d (1H, C^3H_{furan}, *J* 2.77 Hz), 6.35 s (1H, C^4H_{furan}), 7.49–7.58 m (4H, H_{Ar}), 7.74 d (2H, H_{Ar}, *J* 7.17 Hz), 8.15 s (2H, SCH_2). Mass spectrum, *m/z* (I_{rel}, %): 460 (32.8) $[M]^+$, 442 (26.6), 399 (59.7), 385 (23), 331 (5.8), 307 (6.8), 251 (2.9), 153 (2.5), 105 (100), 77 (63.5), 43 (55.6). Found, %: C 67.72; H 5.15; N 6.01. $C_{26}H_{24}N_2O_4S$. Calculated, %: C 67.81; H 5.25; N 6.08.

7-Acetyl-5,6,7,8-tetrahydro-6-hydroxy-1,6-dimethyl-3-methylthio-8-(fur-2-yl)isoquinoline-4-carbonitrile (Vc) was obtained similarly from isoquinoline **IIIb** and methyl iodide **IVc**. Yield 0.4 g (75%), white powder, mp 160°C. IR spectrum, ν, cm^{-1}: 3478 (OH), 2220 (C≡N), 1706 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.26 s (3H, Me), 2.14 s (3H, Me), 2.20 s (3H, Me), 2.56 s (3H, Me), 2.82 d (1H, C^5H, ^2J 17.27 Hz), 3.03–3.12 m (2H, C^5H and C^7H), 4.70 d (1H, C^8H, *J* 9.25 Hz), 5.00 br.s (1H, OH), 6.10 d (1H, C^3H_{furan}, *J* 3.14 Hz), 6,35 d. d (1H, C^4H_{furan}, *J* 2.95 Hz, *J* 1.90 Hz), 7.51 s (1H, C^5H_{furan}). Mass spectrum, *m/z* (I_{rel}, %): 357 (100) $[M + 1]^+$. Found, %: C 63.94; H 5.52; N 7.76. $C_{19}H_{20}N_2O_3S$. Calculated, %: C 64.02; H 5.66; N 7.86.

7-Acetyl-5,6,7,8-tetrahydro-6-hydroxy-1,6-dimethyl-3-methylthio-8-phenylisoquinoline-4-carbonitrile (Vd) was obtained similarly from isoquinoline **IIId** and methyl iodide **IVc**. Yield 1.2 g (73%), colorless crystals, mp 198°C (published data [8] 200–201°C). Mass spectrum, *m/z* (I_{rel}, %): 367 (100) $[M + 1]^+$.

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