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# Synthesis of the Functionally 4-Substituted 1-Methyl-3-thioxo-2,3,5,6,7,8-hexahydroisoquinolines by $S_NVin$ Reaction of 2-Acetyl-1-(*N*-morpholinyl)cyclohexene with Malonothio(dithio)amides

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**Abstract**—4-Carbamoyl(thiocarbamoyl)-3-thioxo-2,3,5,6,7,8-hexahydroisoquinolines were synthesized by the $S_NVin$ reaction of 2-acetyl-1-(*N*-morpholinyl)acetylcyclohexene with malonothio(dithio)amides. The cyclocondensation direction was confirmed with the X-ray diffraction analysis of 1-methyl-3-methylthio-5,6,7,8-tetrahydroisoquinoline-4-carboxamide.

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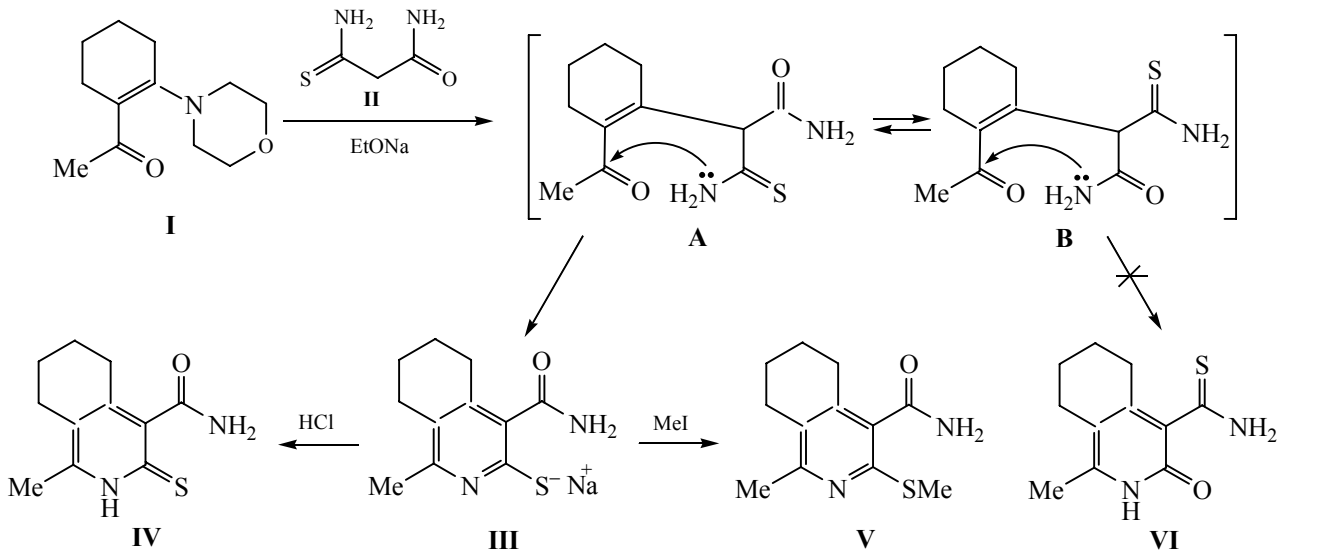
The nucleophilic vinyl substitution ($S_NVin$) of amino enones is widely used in the synthesis of biologically active nitrogen heterocycles [1–3]. Previously it has been used in the synthesis of 4-cyano-substituted 1-alkyl(phenyl)-3-oxo(thioxo, selenoxo)-5,6,7,8-tetrahydroisoquinolines [4, 5], which are promising intermediates in the search for substances with cardiac [6–9], antitumor [10] and inhibiting the HIV-1 reverse transcriptase [11] actions.

The subject of this study is the reaction of preparatively available [12] 2-acetyl-1-(*N*-morpholinyl) acetylcyclohexene **I** with malonic thio(dithio)amides in order to obtain new polyfunctional hexahydroisoquinolines. The condensation of cyclic enaminone **I** with malonothioamide **II** was found to proceed in anhydrous ethanol at 20°C in the presence of sodium ethoxide to give sodium 4-carbamoyl-1-methyl-5,6,7,8-tetrahydroisoquinoline-3-thiolate **III**. We think that the scheme of the process most likely includes the stage of nucleophilic vinyl substitution at the $C^1$ atom of alkene to form intermediate **A**, which undergoes a chemoselective cyclization into thiolate **III**. Treating of the latter with hydrochloric acid solution yields compound **IV**, which like 2-thioxo-5,6,7,8-tetrahydroquinoline [5, 13] exists mainly in the thion form.

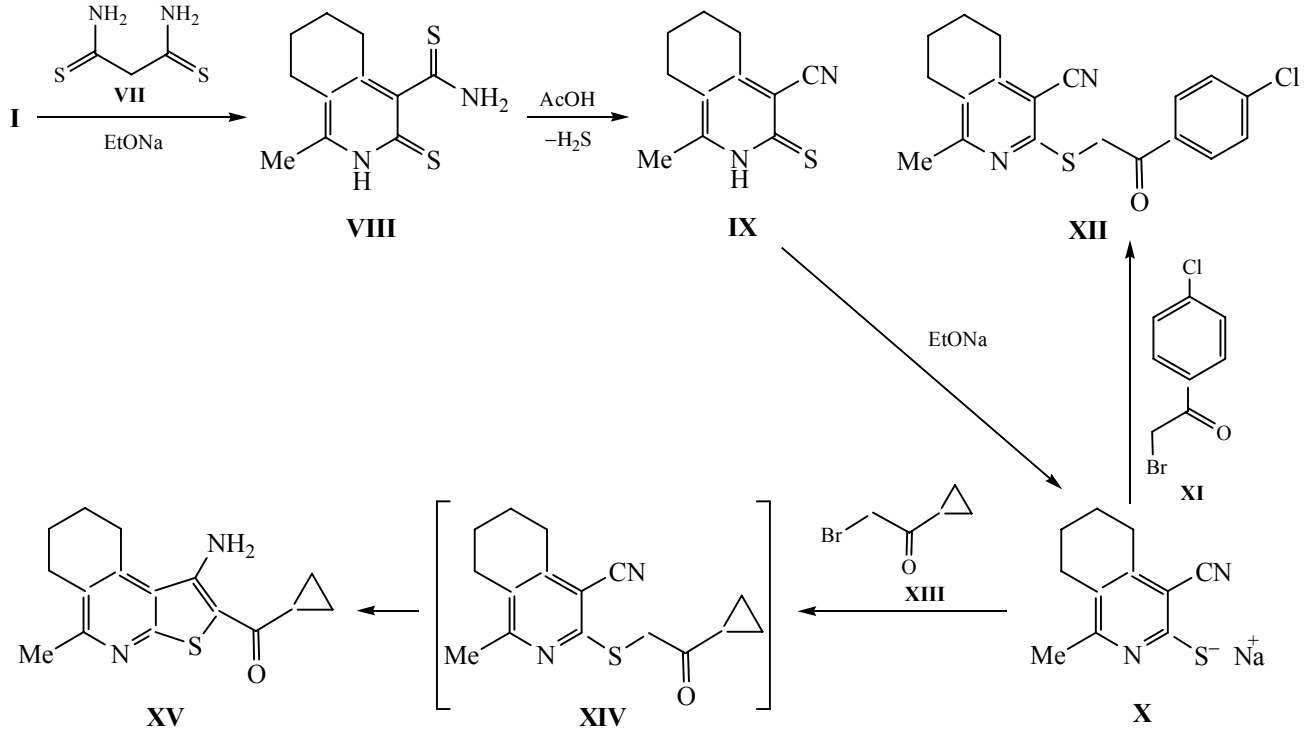
The alkylation of salt **III** with methyl iodide in DMF solution results in compound **V**. The study of the latter by the X-ray diffraction method (see the figure and the table) allowed an unequivocal establishment of the heterocyclization course of intermediate **A** to salt **III** and to exclude a possible cyclization of intermediate **B** into isoquinolin-3-one **VI**, an isomer of compound **IV**. A clear choice in favor of isomer **IV** or **VI** on the basis of IR and NMR spectra was not possible.

The cyclohexene ring is in a *semichair* conformation with a planar $C^6$–$C^3$–$C^4$–$C^9$ fragment [torsion angle 179.17(11)°]. The atoms $C^7$ and $C^8$ are disordered over two positions, A and B, with the relative occupancy of 0.671(7):0.329(7), which corresponds to two mirror symmetrical *semichair* conformations of the ring. The atoms $C^7$ and $C^8$ deviate from the mean plane of the remaining ring atoms by 0.465(6) and –0.315(5) Å (conformation **A**), –0.440(11) and 0.367(11) Å (conformation **B**), respectively. The amide moiety is strongly turned relative to the pyridine ring plane [the $C^3C^2C^{11}O^1$ torsion angle is –71.99(16)°], which leads to the strong disturbance of the conjugation between the π-systems of the substituent and the pyridine ring. This causes the elongation of $C^2$–$C^{11}$ bond to 1.5097(15) Å as compared with an average value of 1.50 Å [15]. The $C^{10}$-methyl group lies in the ring plane and is oriented towards the $N^1$ atom [torsion angle $C^{10}S^1C^1N^1$ 4.77(11)°].



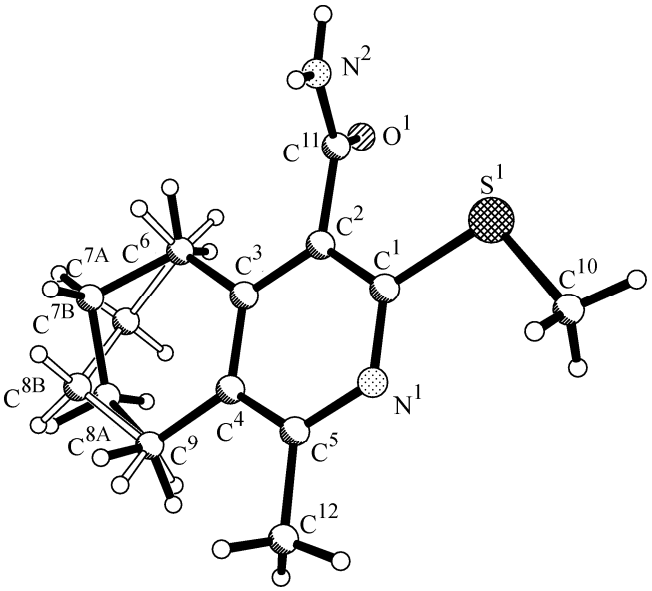

In the crystal the molecules form the centrosymmetric dimers through the hydrogen bonding between the amide groups $N^2–H^{2b}\cdots O^{1i}$ (1 – *x*, 1 – *y*, –*z*) [H···O 2.021(16) Å, N–H···O 175.5(16)°]. In the crystal is formed also a relatively weak hydrogen bond involving the pyridine nitrogen atom $N^{(2)}–H^{2a}\cdots N^{1ii}$ (–*x*, 1 – *y*, 1 – *z*) [H···N 2.335(15) Å, N–H···N 167.7(16)°].

Malonic acid dithioamide (**VII**) is found to be equally effective in the $S_NVin$ reaction with morpholinocyclohexene **I**. The use of the conditions similar to those for the CH-acid **II** allows us obtaining 1-methyl-3-thioxo-2,3,5,6,7,8-hexahydroisoquinoline-4-carbothioamide **VIII** in 69% yield omitting the intermediate thiolate isolation. Heating of compound **VII** in glacial acetic acid is accompanied with the hydrogen sulfide



elimination and transformation into the previously described 1-methyl-3-thioxo-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitrile **IX** [4]. The treatment of the latter with an alcoholic solution of sodium ethoxide leads to 1-methyl-4-cyano-5,6,7,8-tetrahydroisoquinoline-3-sodium thiolate **X** stable in the solid state. The latter is a convenient reagent for the subsequent modification that is illustrated by the example of its alkylation with α-bromoacetophenone **XI** to form thioester **XII**. In the case of α-bromomethylcyclopropylketone **XIII** corresponding thioether **XIV** cannot be isolated due to its fast intramolecular cyclization by Thorpe reaction into thieno[2,3-*c*]isoquinoline derivative **XV**.

The structure of the synthesized compounds was confirmed by the spectroscopic data. The IR spectra of key compounds **III**–**V** contain the absorption band at 1680–1702 $cm^{-1}$ belonging to C=O group of carbamoyl moiety. The IR spectra of compounds **X** and **XII** include a weak band of the C≡N group at 2214 and 2222 $cm^{-1}$, respectively.



General view of molecule **VI**.

Bond lengths (*d*) and angles (ω) in the structure of **VI**

| Bond | *d*, Å | Angle | ω, deg |
|---|---|---|---|
| $S^1$–$C^1$ | 1.7636(12) | $C^1S^1C^{10}$ | 103.37(6) |
| $S^1$–$C^{10}$ | 1.7752(15) | $C^5N^1C^1$ | 118.31(10) |
| $O^1$–$C^{11}$ | 1.2242(15) | $N^1C^1C^2$ | 122.60(10) |
| $N^1$–$C^5$ | 1.3410(14) | $N^1C^1S^1$ | 119.27(9) |
| $N^1$–$C^1$ | 1.3431(13) | $C^2C^1S^1$ | 118.12(8) |
| $N^2$–$C^{11}$ | 1.3166(16) | $C^1C^2C^3$ | 118.89(10) |
| $N^2$–$H^{2A}$ | 0.807(15) | $C^1C^2C^{11}$ | 121.42(10) |
| $N^2$–$H^{2B}$ | 0.878(16) | $C^3C^2C^{11}$ | 119.68(10) |
| $C^1$–$C^2$ | 1.3897(16) | $C^2C^3C^4$ | 118.88(11) |
| $C^2$–$C^3$ | 1.3913(16) | $C^2C^3C^6$ | 119.81(10) |
| $C^2$–$C^{11}$ | 1.5097(15) | $C^4C^3C^6$ | 121.31(11) |
| $C^3$–$C^4$ | 1.4022(16) | $C^5C^4C^3$ | 118.06(10) |
| $C^3$–$C^6$ | 1.5083(17) | $C^5C^4C^9$ | 120.37(10) |
| $C^4$–$C^5$ | 1.3897(17) | $C^3C^4C^9$ | 121.54(11) |
| $C^4$–$C^9$ | 1.5129(16) | $N^1C^5C^4$ | 123.24(10) |
| $C^5$–$C^{12}$ | 1.5099(16) | $N^1C^5C^{12}$ | 115.70(11) |
| $C^6$–$C^{7A}$ | 1.510(3) | $C^4C^5C^{12}$ | 121.05(11) |
| $C^6$–$C^{7B}$ | 1.555(6) | $C^3C^6C^{7A}$ | 112.79(14) |
| $C^{7A}$–$C^{8A}$ | 1.510(6) | $C^3C^6C^{7B}$ | 111.0(2) |
| $C^{7B}$–$C^{8B}$ | 1.505(13) | $C^{8A}C^{7A}C^6$ | 108.9(3) |
| $C^{8A}$–$C^9$ | 1.530(4) | $C^{8B}C^{7B}C^6$ | 110.1(7) |
| $C^{8B}$–$C^9$ | 1.509(8) | $C^{7A}C^{8A}C^9$ | 111.0(3) |
| | | $C^{7B}C^{8B}C^9$ | 108.3(6) |
| | | $C^{8B}C^9C^4$ | 113.8(3) |
| | | $C^4C^9C^{8A}$ | 112.52(17) |
| | | $O^1C^{11}N^2$ | 123.39(11) |
| | | $O^1C^{11}C^2$ | 120.59(11) |
| | | $N^2C^{11}C^2$ | 115.99(11) |

A characteristic feature of the $^1H$ NMR spectra of isoquinolines **III**–**V**, **VIII,** and **X** is the presence of singlet signals of methyl groups at 2.12–2.52 ppm, as well as the typical multiplet signals of the tetramethylene protons at 1.55–2.78 ppm and low-field signals of the protons of chalcogen-containing amide group. In addition, in the spectra of isoquinoline-3-thione **IV** and **VIII** derivatives there are the signals of NH-protons of the the endocyclic thioamide fragment at 11.87 and 13.79 ppm, respectively. Comparing the $^{13}C$ NMR spectra of related compounds **IV** and **VIII** a significant effect of 4-(thio)carbamoyl substituent on the chemical shifts of the thiopyridone carbon atoms was revealed. Compound **IV** was characterized by the signals at 114.22 ($C^6$), 127.63 ($C^4$), 146.05 ($C^1$), 161.45 ($C^3$), 163.71 ($C^5$) ppm, and the compound **VIII**, by the signals at 121.19 ($C^6$), 151.70 ($C^4$), 155.77 ($C^1$), 167.30 ($C^5$), 173.95 ($C^3$) ppm.

## EXPERIMENTAL

The crystals of compound **IV** are triclinic, $C_{12}H_{16}N_2OS$, at 298 K *a* 7.9528(13), *b* 8.9781(14), *c* 9.1514(17) Å, α 79.179(14)°, β 68.028(16)°, γ 84.970(13)°, *V* 595.07(17) $Å^3$, *Mr* 236.33, *Z* 2; space group $P\bar{1}$, $d_{calc}$ 1.319 g $cm^{-1}$, μ(Mo$K_\alpha$) 0.253 $mm^{-1}$, *F*(000) 252. The unit cell parameters and intensities of 6315 reflections (3878 independent, $R_{int}$ 0.014) were

measured on a Xcalibur 3 automatic four-circle diffractometer (Mo$K_\alpha$, graphite monochromator, CCD detector, ω-scanning, $2\theta_{max}$ 64.8°).

The structure was solved by the direct method using SHELX-97 program package [15]. The positions of hydrogen atoms were geometrically calculated and refined by a *rider* model with $U_{iso} = nU_{eq}$ for the carrier atom ($n$ = 1.5 for $CH_3$-groups and $n$ = 1.2 for methylene groups). The structure was refined with respect to $F^2$ using full-matrix anisotropic approximation for non-hydrogen atoms to $wR_2$ 0.099 for 3878 reflections ($R_1$ 0.039 for 2474 reflections with $F > 4\sigma(F)$, $S$ 1.00). The bond lengths and angles are given in the table.

The melting points were determined on a Koeffler block. The IR spectra were recorded on a Spectrum One (Perkin Elmer) FIR-spectrometer from KBr pellets. The $^1$H and $^{13}$C NMR spectra were registered on a Bruker DR×500 spectrometer (500.068 and 125.7578 MHz, respectively) in DMSO-$d_6$ relative to internal reference TMS. The mass spectra were taken on a Crommas GC/MS-Hewlett-Packard 5890/5972 spectrometer, column HP-S MS (70 eV) in $CH_2Cl_2$ solution. The reaction progress and purity of the compounds were monitored by TLC on Silufol UV 254 plates eluting with an acetone–hexane mixture (3:5) and detecting with iodine vapor and ultraviolet irradiation.

**Sodium 4-carbamoyl-1-methyl-5,6,7,8-tetrahydroisoquinoline-3-thiolate (III)**. To a stirred mixture of 2.1 g (10 mmol) of enamino ketone **I** and 1.2 g (10 mmol) of thioamide **II** in 15 ml of anhydrous ethanol at 20°C was added sodium ethylate solution prepared from 0.23 g (10 mmol) of sodium and 5 ml of anhydrous ethanol. The mixture was stirred for 30 min and kept for 1 day. The formed precipitate was filtered off, washed with anhydrous ethanol and hexane. Yield 1.67 g (74%), yellow powder, mp 230ºC (decomp.). IR spectrum, ν, cm$^{-1}$: 3315, 3195, 1688, 1230 ($CONH_2$). $^1$H NMR spectrum, δ, ppm: 7.34 br.s (1H, $NH_2$), 7.21 br.s (1H, $NH_2$), 2.59 m (2H, $CH_2$), 2.48 m (2H, $CH_2$), 2.26 s (3H, Me), 1.68 m (4H, $2CH_2$). Mass spectrum, *m/z* ($I_{rel}$, %): 221 $[M - Na]^+$ (100). Found, %: C 53.95; H 5.28; N 11.33. $NaC_{11}H_{13}N_2OS$. Calculated, %: C 54.08; H 5.36; N 11.47.

**1-Methyl-3-thioxo-2,3,5,6,7,8-hexahydroisoquinoline-4-carboxamide (IV)**. A stirred suspension of 2.44 g (10 mmol) of thiolate **III** in 20 ml of ethanol was diluted with 10% hydrochloric acid till pH 5 and kept for 48 h. The formed precipitate was filtered off, washed with water, ethanol, and hexane. Yield 1.71 g (77%), yellow powder, mp 245–248ºC (AcOH). IR spectrum, ν, cm$^{-1}$: 3300, 3176, 1702, 1649, 1287 (NH, $CONH_2$), 1230 (C=S). $^1$H NMR spectrum, δ, ppm: 11.87 br.s (1H, NH), 7.27 br.s (2H, $NH_2$), 2.59 t (2H, $CH_2$, $J$ 5.13 Hz), 2.45 t (2H, $CH_2$, $J$ 5.22 Hz), 2.28 s (3H, Me), 1.55–1.69 m (4H, $2CH_2$). $^{13}$C NMR spectrum, $\delta_C$, ppm: 20.76 ($CH_3$), 21.81 ($CH_2$), 22.75 ($CH_2$), 25.13 ($CH_2$), 25.31 ($CH_2$), 114.22 ($C^6$), 127.63 ($C^4$), 146.05 ($C^1$), 161.45 ($C^3$), 163.71 ($C^5$), 164.81 [C(O)$NH_2$]. Mass spectrum, *m/z* ($I_{rel}$, %): 221 $[M - 1]^+$ (100). Found, %: C 59.35; H 6.28; N 12.51. $C_{11}H_{14}N_2OS$. Calculated, %: C 59.43; H 6.35; N 12.60.

**1-Methyl-3-methylthio-5,6,7,8-tetrahydroisoquinoline-4-carboxamide (V)**. A mixture of 2.44 g (10 mmol) of thiolate **III** and 0.62 ml (10 mmol) of methyl iodide in 15 ml of DMF was stirred for 3 h, then kept for 1 day and diluted with the equal volume of water under stirring. The formed precipitate was filtered off, washed with water, ethanol, and hexane. Yield 1.82 g (77%), colorless crystals, mp 235–238ºC (AcOH). IR spectrum, ν, cm$^{-1}$: 3336, 3125, 1680, 1247 (CONH). $^1$H NMR spectrum, δ, ppm: 7.66 br. S (1H, $NH_2$), 7.49 br.s (1H, $NH_2$), 2.78 t (2H, $CH_2$, $J$ 5.11 Hz), 2.67 t (2H, $CH_2$, $J$ 5.19 Hz), 2.52 s (3H, SMe), 2.40 s (3H, Me), 1.82 m (2H, $CH_2$), 1.64 m (2H, $CH_2$). $^{13}$C NMR spectrum, $\delta_C$, ppm: 12.58 ($SCH_3$), 21.32 ($CH_3$), 21.84 ($CH_2$), 22.00 ($CH_2$), 25.01 ($CH_2$), 25.94 ($CH_2$), 125.97 ($C^4$), 130.20 ($C^6$), 141.79 ($C^5$), 148.83 ($C^3$), 155.41 ($C^1$), 168.08 [C(O)$NH_2$]. Mass spectrum, *m/z* ($I_{rel}$, %): 237 $[M + 1]^+$ (100). Found, %: C 60.83; H 6.74; N 11.78. $C_{12}H_{16}N_2OS$. Calculated, %: C 60.99; H 6.82; N 11.85.

**1-Methyl-3-thioxo-2,3,5,6,7,8-hexahydroisoquinoline-4-carbothioamide (VIII)** was prepared similarly from 1.34 g (10 mmol) of malonic acid dithioamide. The formed precipitate was washed with water and dried. Yield 1.64 g (69%), brown powder, mp 250–253ºC. IR spectrum, ν, cm$^{-1}$: 3314, 3182, 1695 (NH, $NH_2C$=S), 1210 (C=S). $^1$H NMR spectrum, δ, ppm: 13.79 br.s (1H, NH), 9.63 br.s (1H, $NH_2$), 9.33 br.s (1H, $NH_2$), 2.73 m (2H, $CH_2$), 2.42 m (2H, $CH_2$), 2.34 s (3H, Me), 1.56–1.64 m (4H, $2CH_2$). $^{13}$C NMR spectrum, $\delta_C$, ppm: 16.61 ($CH_3$), 20.65 ($CH_2$), 21.06 ($CH_2$), 23.55 ($CH_2$), 28.70 ($CH_2$), 121.19 ($C^6$), 151.70 ($C^4$), 155.77 ($C^1$), 167.30 ($C^5$), 173.95 ($C^3$), 176.16 [C(S)$NH_2$]. Mass spectrum, *m/z* ($I_{rel}$, %): 205 $[M - H_2S + 1]^+$ (100). Found, %: C 55.39; H 5.88; N 11.66. $C_{11}H_{14}N_2S_2$. Calculated, %: C 55.43; H 5.92; N 11.75.

**1-Methyl-3-thioxo-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (IX)**. A suspension of 2.38 g (10 mmol) of compound **VIII** in 20 ml of glacial acetic acid was heated to the boiling. After 1 day, the precipitate was filtered off, washed with glacial acetic acid and diethyl ether. Yield 1.71 g (84%), yellow powder, mp 290–292ºC (292–294°C [4]). $^{13}$C NMR spectrum, $\delta_C$, ppm: 16.64, 20.62, 21.03, 23.55, 28.70, 112.69, 115.98, 121.25, 151.73, 155.76, 173.89. Mass spectrum, *m*/*z* ($I_{rel}$, %): 205 $[M + 1]^+$ (100).

**Sodium 1-methyl-4-cyano-5,6,7,8-tetrahydroisoquinoline-3-thiolate (X)**. To a stirred suspension of 2.04 g (10 mmol) of compound **IX** in 25 ml of anhydrous ethanol was added sodium ethylate, prepared from 0.23 g (10 mmol) of sodium and 5 ml of anhydrous ethanol. The reaction mixture was stirred for 10 min, the precipitate was filtered off and washed with anhydrous diethyl ether. Yield 2.06 g (94%), yellow powder, mp 215ºC (decomp.). IR spectrum, ν, cm$^{-1}$: 2214 (C≡N). $^1$H NMR spectrum, δ, ppm: 2.71 m (2H, $CH_2$), 2.42 m (2H, $CH_2$), 2.32 s (3H, Me), 1.61–1.73 m (4H, 2 $CH_2$). Mass spectrum, *m*/*z* ($I_{rel}$, %): 203 $[M - Na - 1]^+$ (100). Found, %: C 58.25; H 4.88; N 12.23. $NaC_{11}H_{11}N_2S$. Calculated, %: C 58.39; H 4.90; N 12.38.

**1-Methyl-3-[2-(4-chlorophenyl)-2-oxoethylthio]-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (XII)** was prepared similarly to compound **V** from 2.5 g (10 mmol) of thiolate **X** and 2.33 g (10 mmol) of α-bromoacetophenone **XI**. Yield 2.78 g (78%), colorless crystals, mp 130–132ºC (AcOH). IR spectrum, ν, cm$^{-1}$: 1704 (C=O), 2222 (C≡N). $^1$H NMR spectrum, δ, ppm: 8.08 d (2H, $H_{Ar}$, *J* 8.56 Hz), 7.61 d (2H, $H_{Ar}$, *J* 8.56 Hz), 4.78 s (2H, $SCH_2$), 2.78 m (2H, $CH_2$), 2.49 m (2H, $CH_2$), 2.12 s (3H, Me), 1.59–1.73 m (4H, 2 $CH_2$). Mass spectrum, *m*/*z* ($I_{rel}$, %): 357 $[M + 1]^+$ (100). Found, %: C 63.88; H 4.71; N 7.82. $C_{19}H_{17}ClN_2OS$. Calculated, %: C 63.95; H 4.80; N 7.85.

**(1-Amino-5-methyl-6,7,8,9-tetrahydrothieno[2,3-*c*]isoquinolin-2-yl)(cyclopropyl)methanone (XV)** was prepared similarly to compound **V** from 2.5 g (10 mmol) of thiolate **X** and 1.63 g (10 mmol) of α-bromoketone **XIII**. Yield 2.14 g (75%), yellow powder, mp 195–197ºC (AcOH). There is fluorescence under UV irradiation. IR spectrum, ν, cm$^{-1}$: 3392, 3318, 3295 ($NH_2$), 1648 [δ($NH_2$)], 1712 (C=O). $^1$H NMR spectrum, δ, ppm: 7.65 br.s (2H, $NH_2$), 3.20 m (2H, $CH_2$), 2.62 m (2H, $CH_2$) 2.45 s (3H, Me), 2.11 m (1H, CHC=O), 0.96–1.11 m (4H, 2$CH_2$). Mass spectrum, *m*/*z* ($I_{rel}$, %): 287 $[M + 1]^+$ (100). Found, %: C 67.01; H 6.25; N 9.66. $C_{16}H_{18}N_2OS$. Calculated, %: C 67.10; H 6.33; N 9.78.

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