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Multicomponent Synthesis of 2-Alkylthio-6-amino-3,5-dicyano-1,4-dihydropyridine-4-spirocycloalkanes. Molecular and Crystal Structure of 6-Amino-2-(2-methylbenzylthio)-3,5-dicyano-1,4-dihydropyridine-4-spirocyclopentane

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Abstract—2-Alkylthio-6-amino-3,5-dicyano-1,4-dihydropyridine-4-spirocycloalkanes were synthesized via the reaction of cycloalkylidene malononitriles with cyanothioacetamide and alkyl halides. The structure of 6-amino-2-(2-methylbenzylthio)-3,5-dicyano-1,4-dihydropyridine-4-spirocyclopentane was determined by the X-ray diffraction analysis.

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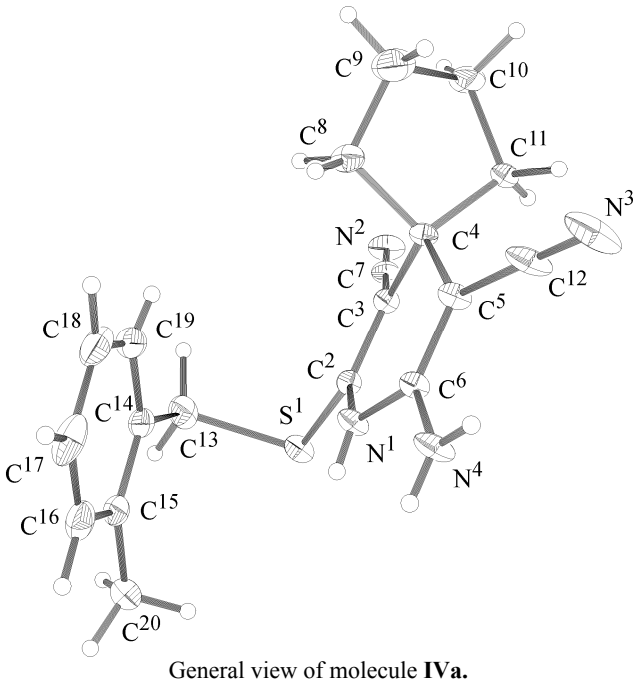
Spiro-substituted nitrogen-containing heterocycles can be used to treat certain pathologies of the central nervous system [1–3], rheumatoid arthritis, and atherosclerosis [4]. We have previously developed methods for the synthesis of functionally substituted 1,4-dihydropyridine-4-spirocycloalkanes based on the reaction of cycloalkylidene(cyano)thioacetamide with malononitrile [5] or cyanothioacetamide [6], the condensation of cyclohexylidene(cyano)thioacetamide with 1-morpholino-1-cyclopentene [7], and the reaction of cyclohexylidene(cyano)thioacetamide with Meldrum's acid [8].

In this work we developed a new method of synthesis of these compounds via a multicomponent condensation of cycloalkylidene malononitriles **I** with cyanothioacetamide **II** and alkyl halides **III** in DMF in the presence of equimolar amount of *N*-methylmorpholine. The reaction products are 2-alkylthio-6-amino-3,5-dicyano-1,4-dihydropyridine-4-spirocycloalkanes **IVa–IVe** identical to those obtained previously by the alkylation of *N*-methylmorpholinium 6-amino-3,5-dicyano-1,4-dihydropyridine-4-spirocycloalkane-2-thiolate with alkyl halides [5, 6].

The reaction scheme includes apparently the alkylation of cyanothioacetamide **II** with alkyl halides **III** to form enaminonitriles **V**. The latter are alkylated with cycloalkylidene malononitriles **I** by Stork method [9] to afford adducts **VI,** followed by the intramolecular cyclization to give iminopyridines **VII**, which are stabilized as the corresponding amino derivatives **IVa–IVe**.

The unambiguous structure of compound **IVa** was established by the X-ray diffraction analysis. Figure 1 shows a general view of the molecule, the bond lengths and angles are given in Tables 1 and 2.

In the investigated molecule the conformation of the hydrogenated heterocyclic ring can be described as flattened *boat.* The atoms N^1 and C^4 are displaced out of the ring plane (the plane involves the other four atoms with an accuracy of 0.003 Å) by –0.138 and –0.339 Å, respectively. The heterocycle has the same conformation in the substituted 1,4-dihydropyridine molecules [5, 10, 11], which contain bulky substituents or spirocyclohexane ring in the position 4. The cyclopentane substituent has an *envelope* conformation: the C^9 atom is displaced out of the plane of the other atoms by 0.599 Å. The dihedral angle between the plane and the *boat* bottom of the heterocycle is 94.3º. Such mutual arrangement of the rings leads to a minimum non-valence intramolecular steric contacts between the hydrogen atoms in cyclopentane moiety and cyano groups. Indeed, there is only one non-valence



General view of molecule **IVa.**

contact $H^{111}\cdots C^{12}$ (2.37 Å) in the molecule, which is less than the sum of the van der Waals radii of H and C atoms [12]. Probably, in the almost planar fragments N^4–C^6=C^5–C^{12}=N^3 of the heterocycle the conjugation leads to some shortening of the single bonds and lengthening of the double bonds in compari-son with the standard values [13] noted earlier [5]. The figure shows that the planar aryl substituent is located slightly over the heterocycle plane (torsion angles $C^3C^2S^1C^{13}$ –93.2°, $C^2S^1C^{13}C^{14}$ –54.3°, and $S^1C^{13}C^{14}C^{15}$ –73.6°.

Intermolecular hydrogen bonds N^4–$H^{42}\cdots N^3$ (–1 – *x*, 1 – *y*, –*z*) [$N^4\cdots N^3$ 3.003(6), N^4–H^{42} 0.85(4), $H^{42}\cdots N^3$ 2.20(4) Å, angle N^4–$H^{42}\cdots N^3$ 157(2)º] and N^1–$H^1\cdots N^2$ (–1 + *x*, 0.5 – *y*, –0.5 + *z*) [$N^1\cdots N^2$ 3.003(6), N^1–H^1 0.73(4), $H^1\cdots N^2$ 2.30(4) Å, angle N^1–$H^1\cdots N^2$ 162(2)°] join the molecules in the crystal into the infinite layers.

Further alkylation of compounds **IVb–IVd** with allyl bromide **IIIe** and benzyl chloride **IIIb**, respectively, in DMF in the presence of 10% aqueous solution of KOH proceeds regioselectively at the amino group and results in 6-allylamino-2-benzylthio-3,5-dicyano-1,4-dihydropyridine-4-spirocyclohexane **VIII**, 6-benzylamino-2-(4-bromophenylcarbamoyl-methylthio)-3,5-dicyano-1,4-dihydropyridine-4-spiro-cyclohexane **IX,** and 6-benzylamino-2-methylthio-3,5-dicyano-1,4-dihydropyridine-4-spirocyclohexane **X** (method *a*). Compounds **VIII–X** can be obtained in one-pot procedure by the successive treatment of the reaction mixture with the corresponding alkyl halide **IIIb–IIIe** in an alkaline medium without isolating thioethers **IV** (method *b*).

The acylation of compounds **IVb**, **IVc** with chloroacetyl chloride or acetyl bromide in the boiling toluene proceeds regioselectively exclusively at the amino group to form the corresponding *N*-acyl derivative **XI** or **XII**, respectively.

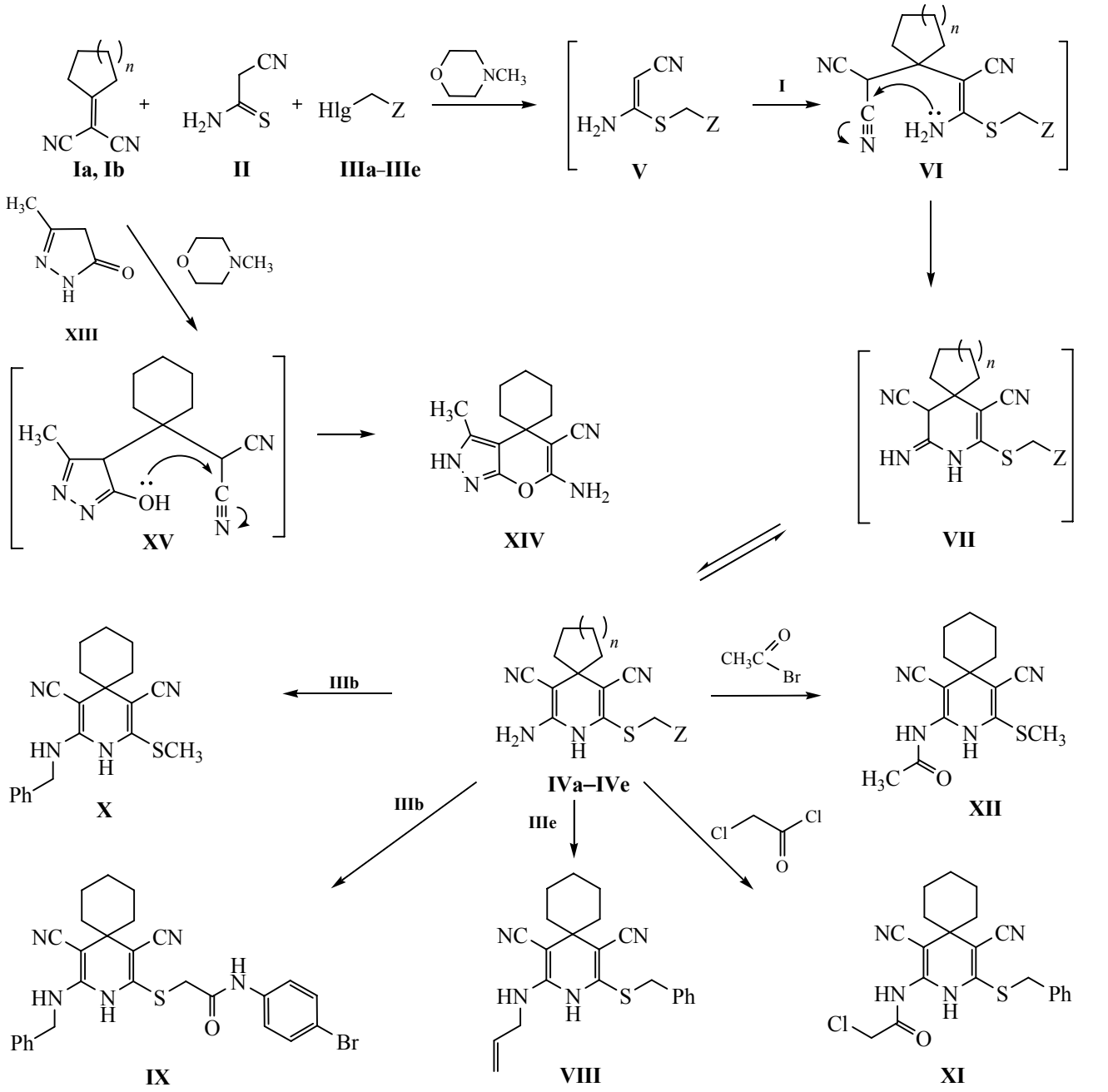
The structure of the synthesized compounds **IVa–IVe**, **VIII–X** was confirmed by the physicochemical and spectral data. A characteristic feature of the ^{1}H NMR spectra of the compounds **VIII** and **IX** is the presence of the signals of nonequivalent protons of SCH_2-group as two doublets at δ 4.08 and 4.41 ppm (^2J 14.0 Hz) (**VIII**) and at δ 3.81 and 4.18 ppm (^2J 15.5 Hz) (**IX**). The splitting of the methylene proton signals indicates the absence of free rotation of substituents at the sulfur atom.

Table 1. Some bond lengths (*d*, Å) in molecule **IVa**

Bond	*d*	Bond	*d*
N^1–C^2	1.373(5)	C^4–C^8	1.556(5)
C^2–S^1	1.768(4)	C^4–C^{11}	1.557(5)
S^1–C^{13}	1.843(5)	C^5–C^6	1.364(5)
C^2–C^3	1.352(5)	C^5–C^{12}	1.415(5)
C^3–C^7	1.427(5)	C^{12}–N^3	1.139(6)
C^7–N^2	1.149(5)	C^6–N^4	1.349(5)
C^3–C^4	1.516(5)	C^6–N^1	1.373(5)
C^4–C^5	1.524(5)		

Table 2. Some bond angles (ω, deg) in molecule **IVa**

Angle	ω	Angle	ω
$C^2S^1C^{13}$	99.4(2)	$C^5C^4C^{11}$	112.3(3)
$C^2N^1C^6$	121.0(3)	$C^8C^4C^{11}$	102.9(3)
$C^3C^2N^1$	120.2(3)	$C^6C^5C^{12}$	116.5(3)
$C^3C^2S^1$	123.8(3)	$C^6C^5C^4$	123.2(3)
$N^1C^2S^1$	115.9(3)	$C^{12}C^5C^4$	120.2(3)
$C^2C^3C^7$	118.3(3)	$N^4C^6C^5$	125.6(3)
$C^2C^3C^4$	122.9(3)	$N^4C^6N^1$	115.2(3)
$C^7C^3C^4$	118.7(3)	$C^5C^6N^1$	119.2(3)
$C^3C^4C^5$	106.2(3)	$N^2C^7C^3$	177.1(4)
$C^3C^4C^8$	109.8(3)	$N^3C^{12}C^5$	178.7(5)
$C^5C^4C^8$	113.7(3)	$C^{14}C^{13}S^1$	113.0(3)
$C^3C^4C^{11}$	112.1(3)		



I, n = 1 (**a**), n = 2 (**b**); **III, IV**, Hgl = Br, Z = 2-$CH_3C_6H_4$, n = 1 (**a**), Hgl = Cl, Z = Ph, n = 2 (**b**), Hgl = I, Z = H, n = 2 (**c**), Hlg = Cl, Z = 4-BrC_6H_4NHCO, n = 2 (**d**), Hgl = Br, Z = $CH{=}CH_2$, n = 1 (**e**).

Introduction of 3-methylpyrazol-5-one **XIII** into the reaction with cyclohexylidene malononitrile **Ib** in ethanol in the presence of *N*-methylmorpholine led to the formation of a previously unknown 6'-amino-3'-methyl-2'*H*-spiro[cyclohexane-1,4'-pyran[2,3-*c*]pyrazolo]-5'-carbonitrile **XIV** as a result of the Michael's reaction, which proceeds with the cyclization of the corresponding adduct **XV**. Note that in the ^{1}H NMR spectrum of compound **XIV** the assignment of the NH-proton signal of pyrazole ring as belonging to the 2*H*-isomer, but not to the 1*H*-isomer, was carried out taking into account the X-ray diffraction data for 4-alkyl-substituted 2*H*-pyrazolo[2,3-*c*]pyrans [14].

EXPERIMENTAL

Crystals of the compound **IVa** are monoclinic, at –120°C: *a* 8.344(4), *b* 18.220(7), *c* 11.282 (4) Å, β 90.90(3)°, *V* 1715(1) Å^3 , d_{calc} 1.303 g cm^{-3}, *Z* 4, space group *P*21/*n*. Cell parameters and intensities of 3184 independent reflections were measured on a four-circle automatic diffractometer Syntex P21 (λMoK_α, graphite monochromator, θ/2θ-scanning, θ_{max} 26°). The structure was solved by the direct method, which revealed all non-hydrogen atoms, and was refined in full-matrix anisotropic approximation for the non-hydrogen atoms using 2473 reflections with $I > 3\sigma$. All hydrogen atoms were identified by the difference Fourier synthesis and refined isotropically. The final values of the divergence factors: *R* 0.076, R_W 0.2139 (*S* 1.08). All calculations were performed by the program SHELXTL PLUS [15] (version PC).

The ^{1}H NMR spectra were recorded on a Gemini-200 (199.975 MHz) (**IVa–IVe**, **XI**, **XII**), Bruker AM-300 (300.13 MHz) (**XIV**), and Bruker DR-500 spectrometers (500.13 MHz) (**VIII–X**) in DMSO-d_6, internal reference TMS. The IR spectra were recorded on an IKS-40 instrument in mineral oil. The GLC spectra were recorded on instruments Grommass GC/MC-Hewlett-Packard 5890/5972 (column HP-5 MS, 70 eV) in methylene chloride solution (**VIII**, **IX**) and Kratos MS-890 (70 eV) with the direct injection of the substance into the ion source (**XIV**). The melting points were determined on a Koeffler block. The reaction progress was monitored by TLC (Silufol UV-254, acetone–hexane, 3:5, detecting with iodine vapor and UV irradiation).

General procedure for the synthesis of 2-alkylthio-6-amino-3,5-dicyano-1,4-dihydropyridine-4-spirocycloalkanes (IVa–IVe). To a stirred solution of 1 g (10 mmol) of cyanothioacetamide **II** in 15 ml of DMF were added 10 mmol of alkyl halide **III** and 1.1 ml (10 mmol) of *N*-methylmorpholine. After stirring for 5 min, to the reaction mixture was added 10 mmol of cycloalkylidene malononitrile **I.** The mixture was stirred for 1 h and then kept for 24 h at 20°C. Then the mixture was diluted with an equal volume of water. The precipitate formed was filtered off, washed with water, ethanol, and hexane. Compounds **IVa–IVd** were crystallized from EtOH. The ^{1}H NMR spectra, melting points, and chromatographic data were identical to those reported previously [5, 6]. Yields 63 (**IVa**), 74 (**IVb**), 69 (**IVc**), 79 (**IVd**) and 71% (**IVe**).

6-Allylamino-2-benzylthio-3,5-dicyano-1,4-dihydropyridine-4-spirocyclohexane (VIII). *a*. To a stirred solution of 3.4 g (10 mmol) of substituted 1,4-dihydropyridine-4-spirocyclohexane **IVb** in 15 ml of DMF was added in succession 5.6 ml (10 mmol) of 10% aqueous KOH solution and 0.85 ml (10 mmol) of allyl bromide **IIIe**. The mixture was stirred for 1 h and kept for 24 h. Then the reaction mixture was diluted with an equal volume of water. The precipitate formed was filtered off and washed with water, ethanol, and hexane. Yield 2.7 g (71%), colorless needles, mp 144–146°C (AcOH). IR spectrum, ν, cm^{-1}: 3316 (NH), 2194 (C≡N). ^{1}H NMR spectrum, δ, ppm: 1.05–1.22 m (2H, CH_2), 1.38–1.66 m (6H, $3CH_2$), 1.83–2.04 m (2H, CH_2), 2.27–2.43 m (2H, NCH_2), 4.08 d and 4.41 d (1H, SCH_2, ^2J 14.0 Hz), 5.47 d (1H, $=CH_2$, $^3J_{trans}$ 17.0 Hz), 4.41 d (1H, $=CH_2$, $^3J_{cis}$ 10.0 Hz), 5.47–5.54 m (1H, CH=), 7.19 t (2H, Ph, ^3J 7.5 Hz), 7.25 t (1H, Ph, ^3J 8.0 Hz), 7.31 d (2H, Ph, ^3J 7.5 Hz), 7.94 br.s (1H, NH), 8.8 br.s (1H, NH). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 377 (100) $[M + 1]^+$. Found, %: C 70.09; H 6.31; N 14.75. $C_{22}H_{24}N_4S$. Calculated, %: C 70.18; H 6.43; N 14.88.

6-Benzylamino-2-(4-bromophenylcarbomoylmethylthio)-3,5-dicyano-1,4-dihydropyridine-4-spirocyclohexane (IX) was obtained similarly from thioether **IVd** and benzyl chloride **IIIb**. Yield 4.17 g (76%), yellow powder, mp 140–142°C (AcOH). IR spectrum, ν, cm^{-1}: 3328 (NH), 2184 (C≡N), 1670 (CONH). ^{1}H NMR spectrum, δ, ppm: 1.02–1.12 m (4H, $2CH_2$), 1.63–1.84 m (4H, $2CH_2$), 2.13–2.25 m (2H, CH_2), 2.91 d and 3.02 d (1H, NCH_2, ^2J 14.1 Hz), 3.81 d and 4.18 d (1H, SCH_2, ^2J 13.5 Hz), 7.03 t (2H, Ph, ^3J 7.0 Hz), 7.11 t (1H, Ph, ^3J 6.5 Hz), 7.19 d (2H, Ph, ^3J 7.0 Hz), 7.48 d and 7.58 d (2H, C_6H_4, ^3J 8.0 Hz), 7.99 br.s (1H, NH), 8.46 br.s (1H, NH), 10.19 br.s (1H, NHCO). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 549 (100) $[M + 1]^+$. Found, %: C 58.97; H 4.68; N 12.71. $C_{27}H_{26}BrN_5OS$. Calculated, %: C 59.12; H 4.78; N 12.77.

6-Benzylamino-2-methylthio-3,5-dicyano-1,4-dihydropyridine-4-spirocyclohexane (X) was obtained similarly from thioether **IVc** and benzyl chloride **III**. Yield 2.35 g (67%), yellow crystals, mp 227–228°C (EtOH). IR spectrum, ν, cm^{-1}: 3322 (NH), 2199 (C≡N). ^{1}H NMR spectrum, δ, ppm: 1.14–1.38 m (3H, cyclohexane), 1.51–1.73 m (5H, cyclohexane), 1.99–2.17 m (2H, cyclohexane), 2.45 s (3H, CH_3), 2.84 d and 3.04 d (1H, NCH_2, ^2J 16.0 Hz), 7.12 d (2H, Ph, ^3J 8.0 Hz), 7.29–7.33 m (3H, Ph), 7.38 br.s (1H, NH), 8.45 br.s (1H, NH). Found, %: C 68.44; H 6.29; N 15.80. $C_{20}H_{22}N_4S$. Calculated, %: C 68.54; H 6.35; N 15.99.

Synthesis of compound VIII. *b*. To a stirred solution of 1 g (10 mmol) of cyanothioacetamide **II** in 15 ml of DMF was added 1.15 ml (10 mmol) of benzyl chloride **IIIb** and 1.1 ml (10 mmol) of *N*-methylmorpholine. The reaction mixture was stirred for 5 min. Then 1.5 g (10 mmol) of cyclohexylidene malononitrile **Ib** was added, and the mixture was stirred for 1 h and kept for 24 h at 20°C. Then to the stirred mixture was added 5.6 ml (10 mmol) of 10% aqueous KOH solution and 0.85 ml (10 mmol) of allyl bromide **IIIe**. The reaction mixture was stirred for 1 h and kept for 24 h. Then the mixture was diluted with an equal volume of water. The precipitate formed was filtered off and washed with water, ethanol, and hexane. Yield 2.9 g (77%).

Synthesis of compound **IX** by the method *b* is similar using the appropriate alkyl halides **IIIb** and **IIId**. Yield 4.6 g (84%).

Synthesis of compound **X** by the method *b* is similar using the appropriate alkyl halides **IIIb** and **IIIc**. Yield 2.4 g (69%).

***N*-(2-Benzylthio-3,5-dicyano-1,4-dihydropyridine-4-spirocyclohexan-6-yl)-2-chloroacetamide (XI)**. A mixture of 3.4 g (10 mmol) of compound **IVb** and 0.8 ml (10 mmol) of chloroacetyl chloride in 20 ml of toluene was refluxed for 1 h and kept for 24 h. The formed colorless crystals were filtered off and washed with hexane. Yield 2.8 g (68%), mp 121–122°C. IR spectrum, ν, cm^{-1}: 3312 (NH), 2195 (C≡N), 1671 (CONH). ^{1}H NMR spectrum, δ, ppm: 1.12–1.92 m (10H, $5CH_2$), 4.19 s (2H, SCH_2), 4.22 s (2H, $ClCH_2$), 7.14–7.43 m (5H, Ph), 10.5 br.s (1H, NH), 10.56 br.s (1H, NHCO). Found, %: C 60.95; H 5.02; N 13.44. $C_{21}H_{21}ClN_4OS$. Calculated, %: C 61.08; H 5.13; N 13.57.

***N*-(2-Methylthio-3,5-dicyano-1,4-dihydropyridine-4-spirocyclohexan-6-yl)acetamide (XII)** was obtained similarly from thioether **IVc** and acetyl bromide. Yield 2.2 g (73%), colorless crystals, mp 159–161°C. IR spectrum, ν, cm^{-1}: 3334 (NH), 2288 (C≡N), 1677 (CONH). ^{1}H NMR spectrum, δ, ppm: 1.22–1.79 m (10H, $5CH_2$), 2.05 s (3H, CH_3CO), 2.48 s (3H, SCH_3), 10.18 br.s (1H, NH), 10.34 br.s (1H, NHCO). Found, %: C 59.42; H 5.89; N 18.41. $C_{15}H_{18}N_4OS$. Calculated, %: C 59.58; H 6.00; N 18.53.

6'-Amino-3'-methylthio-2'*H*-spiro[cyclohexane-1,4'-pyrano[2,3-*c*]pyrazol]-5'-carbonitrile (XIV). To a stirred solution of 1.5 g (10 mmol) of cyclohexylidene malononitrile **Ib** in 15 ml of ethanol was added 0.98 g (10 mmol) of 3-methylpyrazol-5-one **XII** and 3 drops of *N*-methylmorpholine. The reaction mixture was stirred for 1 h and kept for 24 h. The precipitate formed was filtered off and washed with ethanol and hexane. Yield 1.7 g (69%), colorless crystals, mp 135–137°C (EtOH). IR spectrum, ν, cm^{-1}: 3280, 3349, 3412 (NH), 2188 (C≡N), 1648 (δNH_2). ^{1}H NMR spectrum, δ, ppm: 1.15–2.14 m (10H, $5CH_2$), 2.31 s (3H, CH_3), 6.34 br.s (2H, NH_2), 11.88 br.s (1H, NH). Mass spectrum (EI, 70 eV), *m*/*z* (I_{rel}, %): 245 (6) $[M + 1]^+$, 244 (25) $[M]^+$, 215 (9), 201 (100) $[M - H_2O - HCN]^+$, 188 (29), 146 (11), 123 (8), 111 (15), 91 (9), 78 (13), 66 (14), 55 (24), 39 (40). Found, %: C 63.81; H 6.48; N 22.87. $C_{13}H_{16}N_4O$. Calculated, %: C 63.92; H 6.60; N 22.93.

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