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ON THE REGIOSELECTIVITY OF THE REACTION OF CYANOTHIOACETAMIDE WITH 2-ACETYLCYCLO-HEXANONE, 2-ACETYLCYCLOPENTANONE, AND 2-ACETYL-1-(MORPHOLIN-4-YL)-1-CYCLOALKENES

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It has been established that the interaction of cyanothioacetamide with 2-acetylcyclohexanone, 2-acetylcyclopentanone, or their enamines (2-acetyl-1-(morpholin-4-yl)-1-cycloalkenes) contrary to the literature data have a non-regiospecific character and leads to the formation of mixtures of 3-cyano-4-methyl-5,6-tri(tetra)methylenepyridine-2(1H)-thiones and 3-cyano-6-methyl-4,5-tri(tetra)methylene-pyridine-2(1H)-thiones with a predominance of the latter.

Keywords: 2-acetylcyclohexanone, 2-acetylcyclopentanone, cyanothioacetamide, Guareschi-Thorpe reaction, regioselectivity.

One of the most convenient and efficient methods to build the pyridine ring is the interaction of 1,3-dicarbonyl compounds (β-ketoesters, β-ketoaldehydes, and 1,3-diketones) with cyanoacetic ester and ammonia (or with derivatives of cyanoacetamide), known as the Guareschi-Thorpe reaction. This approach enables the ready preparation of substituted pyridine derivatives by an alternative route in those cases when direct functionalization is hindered (see reviews [1-3]). With symmetrical 1,3-diketones, the reaction proceeds smoothly and unambiguously. However, on obtaining pyridines according to Guareschi-Thorpe protocol using unsymmetrical diketones the problem arises in connection with the possibility of forming isomers with different (4 or 6) positions of substituents in the pyridine nucleus (Scheme 1).

As follows from the literature data [1-3], the regioselectivity of the process and the ratio of 4-*R*- and 6-*R*-isomers are determined predominantly by the structure of the diketone substrate. Examples are known of both low-selectivity cyclization with formation of isomeric mixtures and of regiospecific processes leading to formation of one of the two possible isomers. The modification of the starting substrate was proposed as a possible solution of the regiocontrol problem, as in the majority of cases 1,3-diketones or β-ketoesters may be

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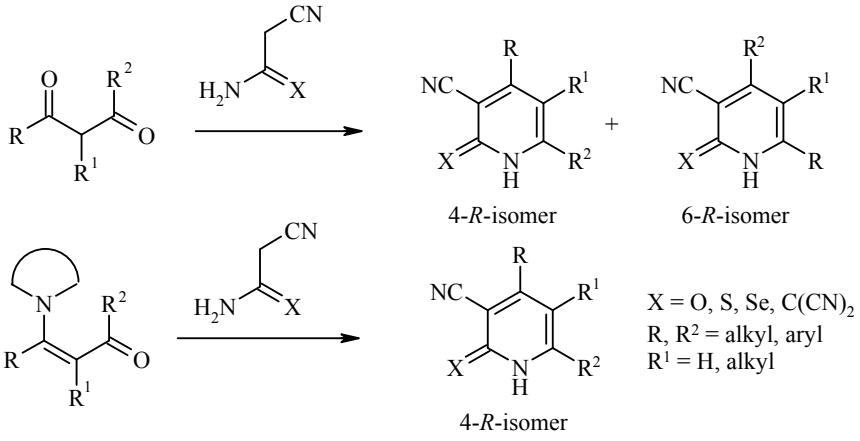
successfully replaced by the corresponding enamino ketones or enamino esters [1]. In this case the reaction may often proceed in higher yield under milder conditions and exclusively regiospecifically (Scheme 1).

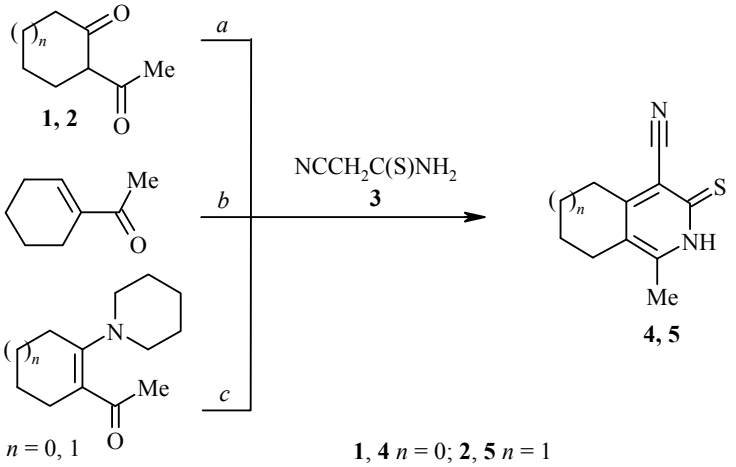
Scheme 1



It is necessary to note specifically that literature data indicate the appreciably more selective character of the Guareschi–Thorpe reaction in the case of 2-acylcycloalkanones compared with acyclic 1,3-diketones. It is postulated that the interaction of 2-acylcyclopentanones and hexanones [4-10], 2,4-diacetyl-3-aryl-5-hydroxy-5-methylcyclohexanones (β-cycloketols) [11], 2-RC(O)-5,5-dimethyltetrahydro(thio)pyran-4-ones [12, 13] with cyanoacetamide and its S- and Se-containing analogs proceeds initially as a Knoevenagel condensation exclusively at the endocyclic carbonyl group with subsequent ring closure involving the exocyclic acyl group.

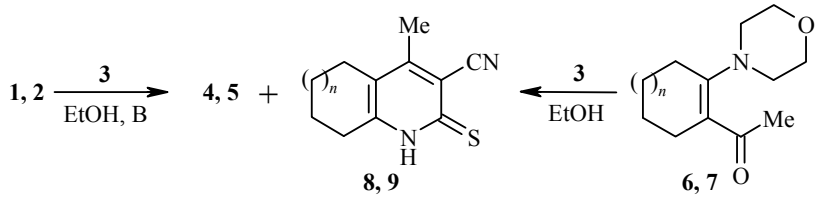
While continuing work in the area of the 3-cyanopyridine-2(1*H*)-thiones chemistry we paid attention to the reaction of 2-acetylcyclopentanone (**1**) and 2-acetylcyclohexanone (**2**) with cyanothioacetamide (**3**) [4, 5]. The products of the interaction, namely 1-methyl-3-thioxo-3,5,6,7-tetrahydro-2*H*-cyclopenta[*c*]pyridine-4-carbonitrile (**4**) and 1-methyl-3-thioxo-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (**5**) are promising for subsequent transformations into polyheterocyclic systems. Compounds **4** and **5**, apart from reaction of diketones **1, 2** with thioamide **3** (method *a*), were also obtained in reactions of thioamide **3** with 2-acetylcyclo-hexene (method *b*) [4] or 2-acetyl-1-piperidyl-1-cycloalkenes (method *c*) [4]. In all three cases the formation of only one regioisomer was postulated (Scheme 2).

Scheme 2



On reproducing the experimental procedures from [4] we have established that the interaction of thioamide **3** with diketones **1** and **2** in the presence of a base (triethylamine or morpholine), and also the condensation of thioamide **3** with enamino ketones **6** and **7** are not regiospecific and lead to the formation of mixtures of isomeric compounds **4**+**8** and **5**+**9**, respectively (Scheme 3).

Scheme 3



6, **8** *n* = 0; **7**, **9** *n* = 1; B = Et_3N, morpholine

The formation of mixtures of regioisomers **4**+**8** and **5**+**9** in the course of the reaction was confirmed by data of ^1H and ^{13}C NMR spectroscopy, and also by the results of two-dimensional ^1H–^1H COSY and ^1H–^{13}C HMBC experiments. In the ^1H NMR spectrum of a sample obtained by the interaction of 2-acetylcyclohexanone (**2**) and thioamide **3**, apart from the signals of the methyl group protons and NH of isoquinolinethione **5** at 2.35 and 13.74 ppm respectively, minor peaks were detected for the regioisomeric quinolinethione **9** at 2.32 and 13.62 ppm (ratio of isomers **5:9** was ~3:1, Fig. 1, *b*). The ^1H NMR spectrum of the product of the interaction of 2-acetylcyclopentanone (**1**) and thioamide **3** disclosed a similar picture. From the ratio of the integral intensities of the singlets of the methyl group protons (2.33 and 2.35 ppm) the ratio of the isomers **4** and **8** approached 1:1 (Fig. 1, *a*). More surprising was the fact that the same picture was observed in the ^1H NMR spectra of the reaction products of thioamide **3** with β-enamino ketones **6** and **7**. In this case the formation of mixtures of isomers may be explained by the partial hydrolysis of the latter to diketones **1** and **2** respectively under the reaction conditions given in [4] (96% EtOH, room temperature, 3 h). In the ^{13}C NMR spectra of the obtained products, a doubling of the number of signals was also observed, indicating the formation of isomeric products.

The results of ^1H–^1H COSY and ^1H–^{13}C HMBC experiments are given in Figs. 2 and 3 respectively for the products of interaction of 2-acetylcyclohexanone (**2**) and cyanothioacetamide (**3**). Thus, peaks were observed in Fig. 2 for the minor isomer **9**: 2.32/2.32 (CH_3) and 2.69/2.69 ppm (8-CH_2), and the complex nature of the multiplets at 1.71, 2.43, and 2.73 ppm was detected. Even more informative was the experiment on the heteronuclear correlation by ^1H–^{13}C nuclei through 2-3 bonds (HMBC method with detection on protons) on a sample of the mixture of compounds **5** and **9** (Fig. 3). It is evident that the singlet in the region of 2.32 ppm belongs to the methyl group of the minor quinolinethione **9**. Three cross-peaks were detected for the 4-CH_3 protons, 2.32/114.4 (4-CH_3/C-4), 2.32/121.67 (4-CH_3/C-4a), and 2.32/156.5 (4-CH_3/C-3), while for 1-CH_3 of the major isomer **5**, two correlations were detected at 2.35/121.89 (1-CH_3/C-8a) and 2.35/152.3 (1-CH_3/C-1).

A series of experiments was carried out on a study of the interaction of thioamide **3** with 2-acetylcyclohexanone (**2**). It was established that neither the yield nor the ratio of isomeric products **5** and **9** in the obtained mixture depend essentially on the reaction conditions (20°C or refluxing) and the choice of the base catalyst (triethylamine, *N*-methylmorpholine or morpholine). Thus, the reaction of thioamide **3** with diketone **2** in 96% EtOH in the presence of triethylamine (20°C, 3 day) gave a mixture of thiones **5** and **9** in a ratio of ~5:2 in an overall yield of 74% (from the integral intensity ratio of the NH and CH_3 protons peaks), while upon ten minutes refluxing in EtOH, thiones **5** and **9** were formed in a ratio of ~7:2 in an overall yield of 70%. A high resolution IR spectrum of the mixture of compounds **5** and **9** proved to be uninformative for clarifying the formation of a mixture of regioisomers because of the complete overlap of the absorption bands. For example, in place of the expected two closely located absorption bands for the stretching vibrations of the conjugated nitrile groups of each of the isomers **5** and **9** one common absorption band was detected at 2218 cm^{-1} in the spectrum.

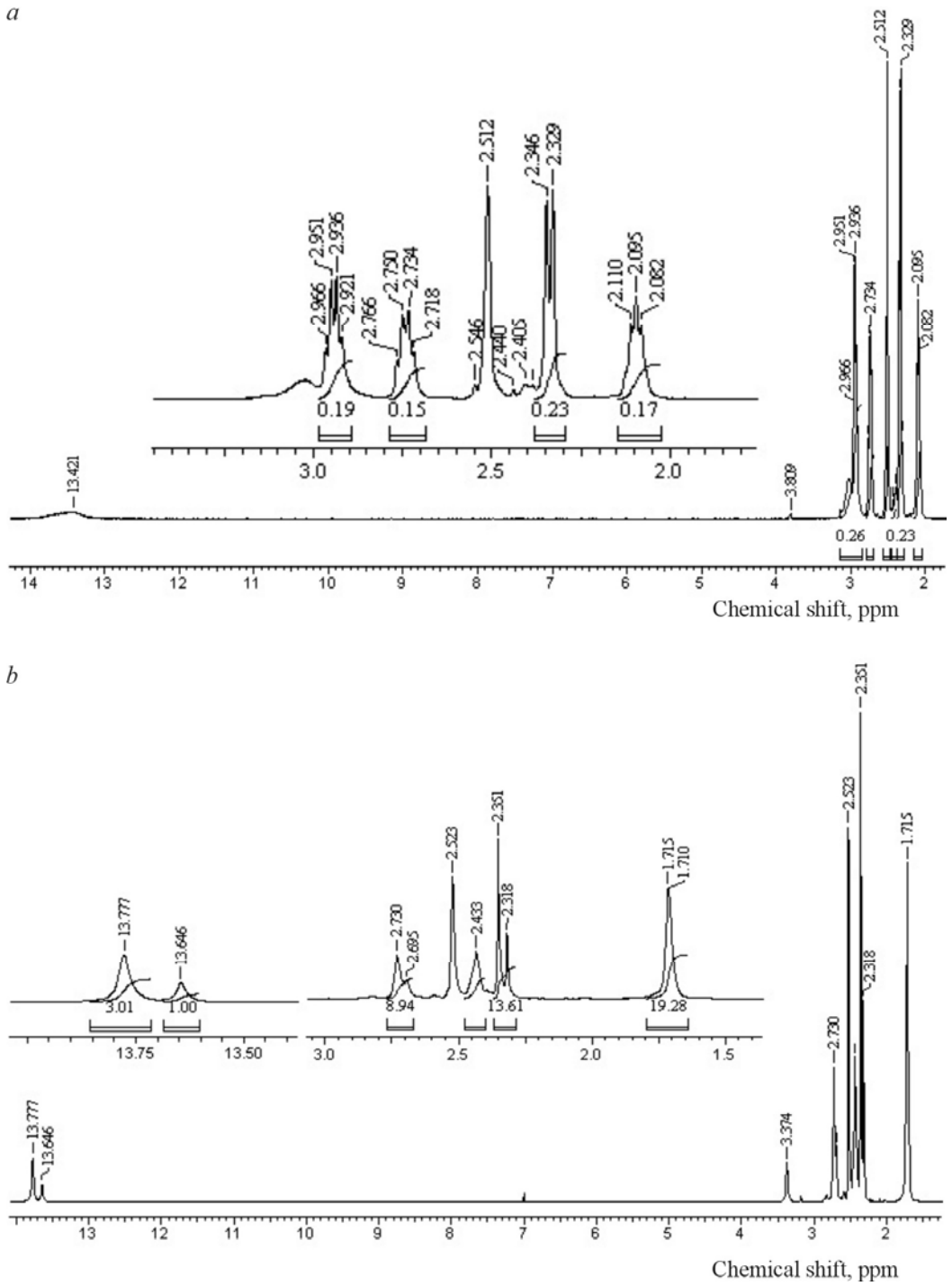
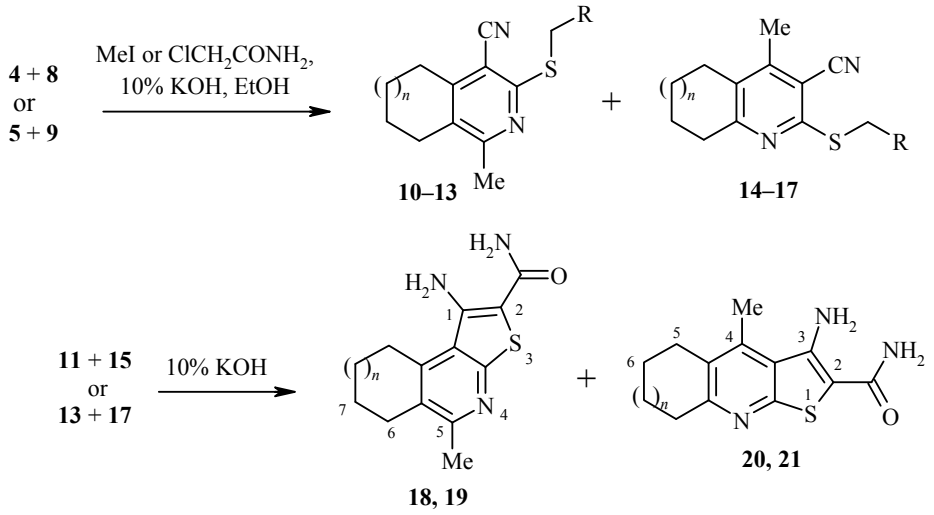


Fig. 1. ^{1}H NMR spectra of mixtures of regioisomeric compounds **4**+**8** (*a*) and **5**+**9** (*b*).

The mixtures of thiones **4**+**8** and **5**+**9** were alkylated with methyl iodide and α-chloroacetamide. In all cases products uniform in TLC were formed, which according to ^{1}H NMR spectroscopic data nevertheless were mixtures of isomeric products **10**+**14**, **11**+**15**, **12**+**16**, **13**+**17** (Scheme 4). All attempts to separate these mixtures into individual components by column chromatography or crystallization proved to be unsuccessful. The mixtures of compounds **11**+**15** and **13**+**17** on treatment with 10% KOH were cyclized according to Thorpe–Ziegler and converted into mixtures of isomeric thieno[2,3-*b*]pyridines **18**+**20** and **19**+**21**.

Scheme 4



10, **12**, **14**, **16** R = H; **11**, **13**, **15**, **17** R = $CONH_2$;
10, **11**, **14**, **15**, **18**, **20** *n* = 0; **12**, **13**, **16**, **17**, **19**, **21** *n* = 1

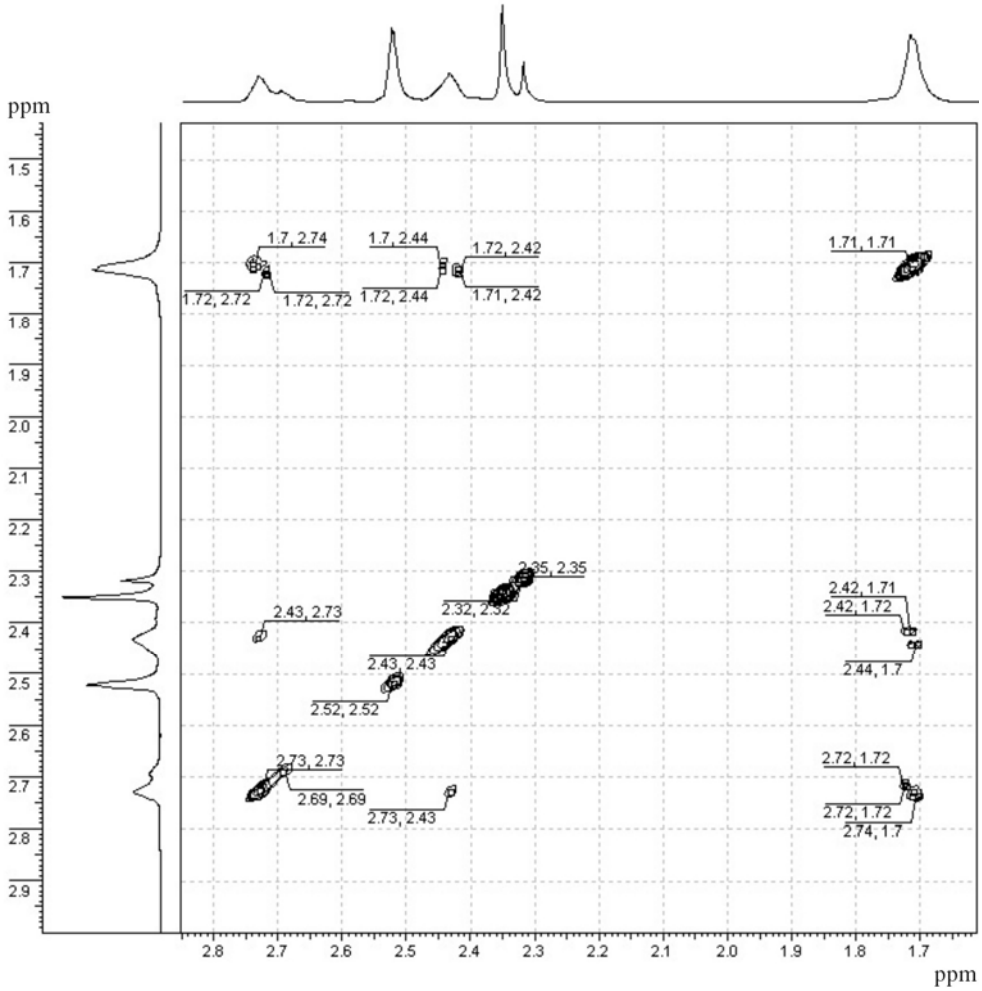


Fig. 2. 2D ^1H–^1H COSY spectrum of a mixture of isomers **5** and **9**.

An interesting special feature of the ^{1}H NMR spectra of substituted thieno[2,3-*b*]pyridines **18**+**20** and **19**+**21** was the low-field shift of the signals of the alkyl group protons located in position 4 of the pyridine ring (8-CH_2 for **18**, 9-CH_2 for **19**, 4-CH_3 for **20** and **21**) relative to the set of signals of the protons of the remaining alkyl fragments in the molecule. The protons of the methyl group of compounds **18** and **19** resonated at 2.44-2.48 ppm, while the protons of the methyl groups of isomers **20** and **21** were shifted to 2.60-2.65 ppm.

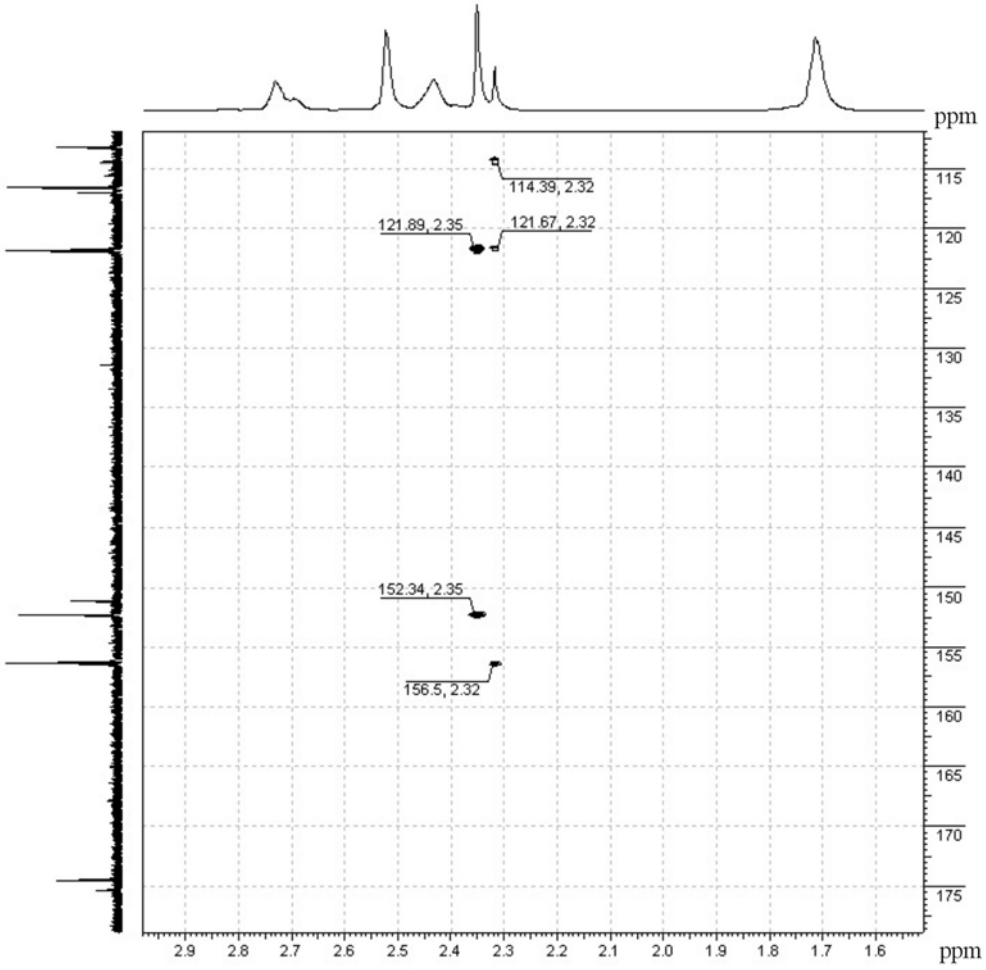


Fig. 3. ^{1}H–^{13}C HMBC (500×125 MHz, DMSO-d_6) NMR experiment for a mixture of isomers **5** and **9**.

It should be mentioned that the authors of the original work [4] were unable to observe the signals of the regioisomeric products in the ^{1}H NMR spectra obtained on an instrument with operating frequency of 90 MHz, since the chemical shifts of the signals of the isomeric compounds **4**, **5**, **8**, **9**, and their derivatives **10-21** were extremely close to overlapping. For example, a comparative analysis of the spectral data of the individual compound **13** [4], a mixture of compounds **13**+**17** obtained by us, and individual compound **17**, synthesized by alternative methods [14, 15], showed that the divergence in chemical shifts in the ^{1}H NMR spectra for the separate groups of protons did not exceed 0.03-0.05 ppm on the whole. It was also interesting to compare the ^{1}H NMR spectra of a mixture of compounds **11**+**15**, obtained on instruments with a frequency of 200 and 500 MHz. In the first case (200 MHz) the signals of the SCH_2 protons of compounds **11** and **15** form a single pseudosinglet at 3.84 ppm as a result of overlap, but in a spectrum obtained on an instrument with operating frequency 500 MHz, two peaks were detected at 3.928 ppm (minor isomer **15**) and 3.936 ppm (isomer **11**). The signals of the methyl groups protons of regioisomers in the spectrum at 500 MHz were detected as two singlets at 2.325 ppm (**11**) and

2.424 ppm (**15**), while in the spectrum obtained on a Varian Gemini 200, the singlet of the methyl protons of the minor isomer **15** at δ 2.46 ppm was partially overlapped by the proton signals of undeuterated DMSO. The latter may significantly hinder interpretation of the spectrum especially if it is considered that the chemical shifts of the signals of the remaining protons at both 200 MHz and 500 MHz coincide completely.

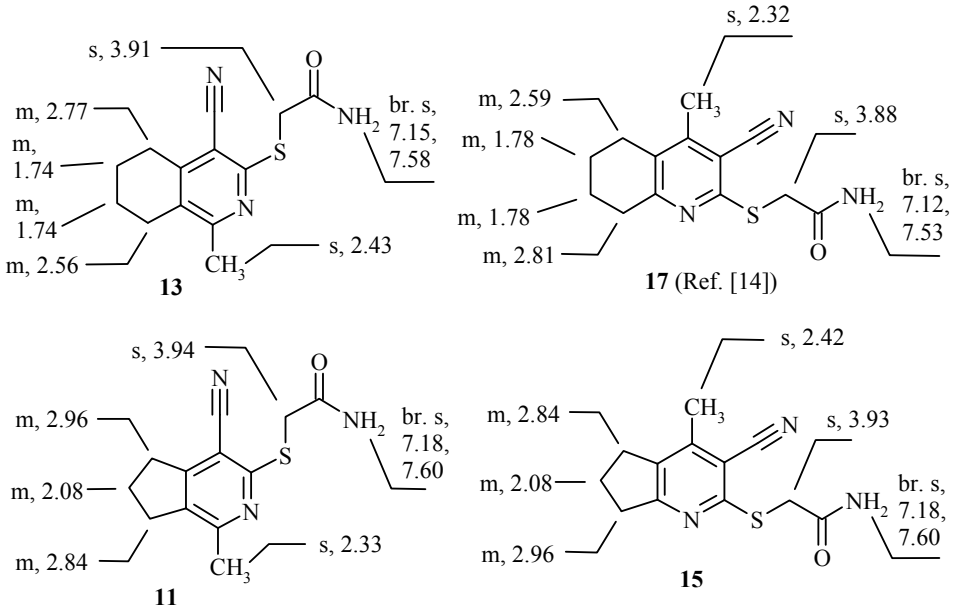


Fig. 4. Multiplicity and chemical shifts of signals (δ, ppm) in the ^{1}H NMR spectra of compounds **13** and **17**, **11** and **15**.

In summary, based on the analysis of the correlation NMR spectra, we have shown that the interaction of cyanothioacetamide with 2-acetylcyclopentanone, 2-acetylcyclohexanone, and their enamines (2-acetyl-1-(morpholin-4-yl)-1-cycloalkenes) proceeds with a low regioselectivity and leads to the formation of mixtures of 3-cyano-4-methyl-5,6-tri(tetra)methylenepyridine-2(1*H*)-thiones and 3-cyano-6-methyl-4,5-tri(tetra)-methylenepyridine-2(1*H*)-thiones with a predominance of the latter. Alkylation of the products gave a mixture of *S*-alkyl derivatives which was not separated successfully by crystallization or column chromatography.

EXPERIMENTAL

The IR spectra were recorded on a Thermo Nicolet Avatar 370 DTGS Fourier spectrophotometer in KBr (compounds **5** and **9**) and also on an IKS-29 spectrophotometer in nujol (remaining compounds). The ^{1}H and ^{13}C NMR spectra, two-dimensional ^{1}H–^{1}H COSY, and ^{1}H–^{13}C HMBC spectra were recorded on a Bruker DRX-500 instrument in DMSO-d_6 (at 500 and 125 MHz, respectively) and also on a Varian Gemini 200 (^{1}H NMR, 200 MHz) spectrometer in DMSO-d_6, internal standard was TMS. Elemental analysis was carried out on a Perkin–Elmer CHN Analyzer. Monitoring the homogeneity of substances was effected by TLC on Silufol UV-254 plates, eluent was acetone–hexane, 1:1, development with iodine vapor, UV detector. Melting points of substances were determined on a Kofler stage and are not corrected.

Diketones **1, 2** and enamines **6, 7** were obtained by the general procedure of Stork [16].

Cyanothioacetamide (3) was obtained by the procedure of Brunskill [17] modified in the following manner. Malononitrile (100 g, 1.51 mol) and EtOH (100 ml) were placed in an Erlenmeyer flask of volume 0.5 l and stirred at room temperature until dissolution of the malononitrile. Tertiary amine (Et_3N or *N*-methyl-

morpholine, 1.0-1.5 ml) was added, the flask was closed with a rubber stopper with two glass tubes, one of which must be immersed in the malononitrile solution, and a strong current of H_2S was passed through. After a short induction period, an exothermic reaction began accompanied by strong absorption of hydrogen sulfide by the reaction mass. It is important to maintain the temperature within the range 15-20°C (cooling with ice or snow), not permitting crystallization of malononitrile and heating the reaction mixture above room temperature. After approximately 30-40 min cyanothioacetamide (**3**) began to crystallize. Subsequently the reaction mixture must be stirred or periodically shaken to avoid clogging of the gas supply tube. To obtain a good yield, it was necessary to pass hydrogen sulfide through the solution for not less than 6-8 h when cooling with ice-water. At the end of the process the reaction mixture was strongly cooled (ice+NaCl), cyanothioacetamide (**3**) was filtered off, washed many times with cold EtOH until a colorless filtrate was obtained, then with cold Et_2O, and petroleum ether. Cyanothioacetamide (**3**) was obtained (130-135 g, 86-89%), as sandy-yellow needle-like crystals; mp 117-120°C (mp 121°C (EtOH) [17]). The product was suitable for further conversion without additional purification. Cyanothioacetamide (**3**) must be stored in refrigerator at 0 to +4°C. IR spectrum, ν, cm^{-1}: 3360, 3270, 3140 (NH_2), 2258 (C≡N). ^{1}H NMR spectrum, δ, ppm: 3.99 (2H, s, CH_2); 9.49 (1H, br. s) and 9.84 (1H, br. s, C(S)NH_2).

Interaction of cyanothioacetamide (3) with 1,3-diketones 1, 2 was carried out according to a modified procedure [4]. A mixture of the corresponding freshly distilled diketone **1** or **2** (0.2 mol), cyanothioacetamide (**3**) (20 g, 0.2 mol), and base (morpholine, *N*-methylmorpholine, or triethylamine, 3 ml) in EtOH (50-70 ml) was stirred with heating (40-50°C) for 5-7 h, and stored at room temperature for 24 h. Glacial acetic acid (15 ml) was added to the mixture, the solid was filtered off, and washed with EtOH. Analytically pure samples were obtained by refluxing in AcOH. Mixtures of thiones **4**+**8** (64%) and **5**+**9** (69%) were obtained.

1-Methyl-3-thioxo-3,5,6,7-tetrahydro-2*H*-cyclopenta[*c*]pyridine-4-carbonitrile (4) and 4-Methyl-2-thioxo-2,5,6,7-tetrahydro-1*H*-cyclopenta[*b*]pyridine-3-carbonitrile (8) (ratio ~1:1). Yield 64%. Finely crystalline powder of sandy color; sublimes >250°C, mp 293-296°C (mp 259-260°C (AcOH) [4]). IR spectrum, ν, cm^{-1}: 2220 (C≡N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.10 (4H, m, 6-CH_2 **4**, 6-CH_2 **8**); 2.35 and 2.33 (6H, two s, $2CH_3$); 2.74 (4H, m, 7-CH_2 **4**, 5-CH_2 **8**); 2.94 (4H, m, 5-CH_2 **4**, 7-CH_2 **8**); 13.42 (2H, br. s, 2NH). ^{13}C NMR spectrum, δ, ppm: 19.2 and 17.5 (C-6 **4** and **8**); 22.1 and 24.1 (CH_3 **4** and **8**); 28.7; 29.3; 31.8; 33.7 (C-5,7 **4** and **8**); 109.7; 113.8; 116.7; 117.1; 128.2; 129.1; 148.7; 153.9; 157.8; 164.5; 176.7 (C=S). Found, %: C 63.47; H 5.29; N 14.80. $C_{10}H_{10}N_2S$. Calculated, %: C 63.13; H 5.30; N 14.72.

1-Methyl-3-thioxo-2,3,5,6,7,8-hexahydroisoquinoline-4-carbonitrile (5) and 4-Methyl-2-thioxo-1,2,5,6,7,8-hexahydroquinoline-3-carbonitrile (9) (ratio ~3:1). Yield 69%. Finely crystalline yellow powder, chromatographically homogeneous (R_f = 0.50, acetone–hexane, 1:1), starting to decompose at T >280°C, mp >300°C (mp 292-294°C [4], 328-330°C [5]). IR spectrum, ν, cm^{-1}: 2218 (C≡N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.71 (8H, m, 6,7-$(CH_2)_2$ **5** and **9**); 2.32 and 2.35 (6H, two s, $2CH_3$); 2.43 (4H, m, 8-CH_2 **5** and 5-CH_2 **9**); 2.73 (4H, m, 5-CH_2 **5** and 8-CH_2 **9**); 13.65 (1H, br. s, NH **9**); 13.78 (1H, br. s, NH **5**). ^{13}C NMR spectrum, δ, ppm: 17.3; 18.9; 20.8; 21.2; 21.7; 24.2; 27.6; 29.3 ($(CH_2)_4$ and CH_3 of both isomers); 113.3 (C-4a **5**); 114.4 (C-4 **9**); 116.6 (C≡N **5**); 117.0 (C≡N **9**); 121.7 (C-4a **9**); 121.9 (C-8a **5**); 151.2 (C-8a **9**); 152.3 (C-1 **5**); 156.4 (C-4 **5**); 156.5 (C-3 **9**); 174.5 (C=S **5**); 175.3 (C=S **9**). Found, %: C 64.89; H 5.90; N 13.80. $C_{11}H_{12}N_2S$. Calculated, %: C 64.67; H 5.92; N 13.71.

Interaction of Cyanothioacetamide (3) with 2-Acetylcyclohexanone (2) at Room Temperature. Diketone **2** (1.7 ml, 11.8 mmol), cyanothioacetamide (**3**) (1.0 g, 10 mmol), and Et_3N (0.2 ml, 1.44 mmol) were dissolved with stirring in 96% EtOH (15 ml) at 20°C. After 20-30 min, a solid product began to precipitate. The reaction mixture was left for 3 days, AcOH (1-2 ml) was added, the solid was filtered off, and washed with EtOH. A mixture of compounds **5**+**9** was obtained in 74% yield. According to the data of ^{1}H NMR spectroscopy, compounds **5** and **8** were formed in a ratio of ~5:2.

Interaction of Cyanothioacetamide (3) with 2-Acetylcyclohexanone (2) on Refluxing. A mixture of diketone (**2**) (1.7 ml, 11.80 mmol), cyanothioacetamide (**3**) (1.0 g, 10 mmol), and Et_3N (0.2 ml, 1.44 mmol) was refluxed in 96% EtOH (20 ml). A yellow solid product formed rapidly throughout the volume of the reaction

mixture. The mixture was refluxed with stirring for a further 10 min, and left for 3 days at room temperature. AcOH (1-2 ml) was added, the solid was filtered off, and washed with EtOH. A mixture of compounds **5**+**9** was obtained in 70% yield. According to data of ^{1}H NMR spectroscopy, the ratio of compounds **5** and **9** in the mixture was ~7:2.

Interaction of cyanothioacetamide (3) with enamino ketones 6, 7 was carried out according to a modified procedure from [4]. A mixture of the corresponding enamino ketone **6, 7** (0.11 mol) and cyanothioacetamide (**3**) (0.10 mol) in 96% EtOH (40 ml) was stirred at room temperature for 3 h, and left for 1 day. AcOH (10 ml) was added, the solid was filtered off, and washed with EtOH. For analytical purposes the product was refluxed in AcOH. From enamino ketone **6** a mixture of thiones **4**+**8** was obtained (yield 58%, ratio of isomers according to ^{1}H NMR spectroscopy ~2:1); from enamino ketone **7** a mixture of thiones **5**+**9** was formed (in a ratio of ~4:1) in 66% yield. More rigorous conditions (refluxing) did not increase the product yield but shortened the reaction time to 0.5 h.

Alkylation of Compounds 4+8 and 5+9 with Methyl Iodide and α-Chloroacetamide. A mixture of thiones **4**+**8** or **5**+**9** (5.00 mmol) in warm DMF (5-7 ml) was treated with 10% aqueous KOH (2.60 ml, 5.00 mmol). A small excess of alkylating agent CH_3I (0.35 ml, 5.50 mmol) or α-chloroacetamide (0.5 g, 5.35 mmol) was added to the obtained solution and a solid was precipitated after several seconds. The reaction mass was stirred for 2-3 h, diluted with an equal volume of water, the solid was filtered off, washed with water, then with cold EtOH, and with petroleum ether. For analytical purposes, the substance was recrystallized from a suitable solvent. Chromatographically homogeneous samples of *S*-alkylation products were obtained: **10**+**14**, **11**+**15**, **12**+**16**, **13**+**17**.

1-Methyl-3-methylsulfanyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine-4-carbonitrile (10) and 4-Methyl-2-methylsulfanyl-6,7-dihydro-5*H*-cyclopenta[*b*]pyridine-3-carbonitrile (14) (ratio ~3:2). Yield 89%. Gray-beige finely crystalline powder; mp 125-127°C (EtOH). R_f = 0.75 (acetone–hexane, 1:1). IR spectrum, ν, cm^{-1}: 2225 (C≡N). ^{1}H NMR spectrum (200 MHz), δ, ppm; 2.10-2.22 (4H, m, 6-CH_2 **10** and **14**); 2.39 (3H, s, CH_3 **10**); 2.48 (3H, s, CH_3 **14**); 2.58 (3H, s, SCH_3 **10**); 2.59 (3H, s, SCH_3 **14**); 2.85-3.04 (8H, m, 5,7-$(CH_2)_2$ **10** and **14**). Found, %: C 64.42; H 6.00; N 13.85. $C_{11}H_{12}N_2S$. Calculated, %: C 64.67; H 5.92; N 13.71.

2-[(4-Cyano-1-methyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridin-3-yl)sulfanyl]acetamide (11) and 2-[(3-Cyano-4-methyl-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)sulfanyl]acetamide (15) (ratio ~7:4). Yield 81%. Light-brown crystals; mp 165-170°C (EtOH). IR spectrum, ν, cm^{-1}: 2219 (C≡N). ^{1}H NMR spectrum, δ, ppm: 2.08 (4H, m, 6-CH_2 **11** and **15**); 2.33 (3H, s, CH_3 **11**); 2.42 (3H, s, CH_3 **15**); 2.84 (4H, m, 7-CH_2 **11** and 5-CH_2 **15**); 2.96 (4H, m, 5-CH_2 **11** and 7-CH_2 **15**); 3.93 (2H, s, SCH_2 **15**); 3.94 (2H, s, SCH_2 **11**); 7.18 (2H, br. s) and 7.60 (2H, br. s, C(O)NH_2 **11** and **15**). ^{13}C NMR spectrum, δ, ppm: 17.9; 22.1; 22.8; 23.9; 28.8; 30.2; 32.7; 34.3; 35.1; 104.3; 115.5; 115.9; 133.0; 135.4; 147.9; 150.1; 157.6; 157.7; 159.2; 159.9; 168.5; 168.8; 169.4; 169.6. Found, %: C 58.49; H 5.35; N 17.10. $C_{12}H_{13}N_3OS$. Calculated, %: C 58.28; H 5.30; N 16.99.

1-Methyl-3-methylsulfanyl-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (12) and 4-Methyl-2-methylsulfanyl-5,6,7,8-tetrahydroquinoline-3-carbonitrile (16) (ratio ~5:2). Yield 83%. White finely crystalline powder; mp 89-91°C (EtOH–petroleum ether). R_f = 0.80, acetone–hexane, 1:1. IR spectrum, ν, cm^{-1}: 2222 (C≡N). ^{1}H NMR spectrum (200 MHz), δ, ppm: 1.81 (4H, m, 6,7-$(CH_2)_2$ **12** and **16**); 2.34 (3H, s, CH_3 **12**); 2.44 (3H, s, CH_3 **16**); 2.55 (10H, m, 8-CH_2 **12**, 5-CH_2 **16**, SCH_3 **12** and **16**); 2.80 (4H, m, 5-CH_2 **12** and 8-CH_2 **16**). Found, %: C 66.26; H 6.36; N 13.05. $C_{12}H_{14}N_2S$. Calculated, %: C 66.02; H 6.46; N 12.83.

2-[(4-Cyano-1-methyl-5,6,7,8-tetrahydroisoquinolin-3-yl)sulfanyl]acetamide (13) and 2-[(3-Cyano-4-methyl-5,6,7,8-tetrahydroquinolin-2-yl)sulfanyl]acetamide (17) (ratio ~9:1). Yield 84%. Beige crystals; mp 193-195°C (AcOH) (mp 205-206°C (EtOAc) [4], for isomer **17**: mp 181-184°C (AcOH) [14], 175-177°C [15]). IR spectrum, ν, cm^{-1}: 2219 (C≡N). ^{1}H NMR spectrum, δ, ppm: 1.74 (4H, m, 6,7-$(CH_2)_2$ **13** and **17**); 2.32 (3H, s, CH_3 **17**); 2.43 (3H, s, CH_3 **13**); 2.56 (4H, m, 8-CH_2 **13** and 5-CH_2 **17**); 2.77 (4H, m, 5-CH_2 **13** and 8-CH_2 **17**); 3.90 (2H, s, SCH_2 **17**); 3.91 (2H, s, SCH_2 **13**); 7.15 and 7.58 (4H, br. s, C(O)NH_2 **13** and **17**). ^{13}C NMR spectrum, δ, ppm: 21.4; 22.1; 23.0; 25.2; 28.3; 33.9; 104.3; 115.4; 128.0; 150.7; 156.8; 161.1; 169.6. Found, %: C 59.61; H 5.83; N 16.18. $C_{13}H_{15}N_3OS$. Calculated, %: C 59.75; H 5.79; N 16.08.

Preparation of Thieno[2,3-*b*]pyridine Derivatives 18+20 and 19+21 from Thiones 4+8 and 5+9 according to Thorpe-Ziegler. A suspension of the corresponding mixture of thiones **4**+**8** or **5**+**9** (5.00 mmol) in DMF (5-7 ml) was treated with 10% aqueous KOH (3.0 ml, 5.80 mmol). The obtained solution was treated with α-chloroacetamide (0.5 g, 5.35 mmol), the mixture was refluxed with stirring for 2-3 min, and the reaction mixture was stirred at room temperature for 0.5 h (solid products of *S*-alkylation **11**+**15** and **13**+**17** were precipitated). Further 10% aqueous KOH (3.0 ml) was added to the mixture, which was refluxed for 3-4 min (the solid desired product precipitated). The reaction mixture was stirred for 2-3 h, diluted with an equal volume of EtOH, the product was filtered off, and washed sequentially with EtOH, with water, and once again with EtOH. Analytically pure samples of mixtures of thienopyridine derivatives **18**+**20** and **19**+**21** were obtained.

1-Amino-5-methyl-7,8-dihydro-6*H*-cyclopenta[*d*]thieno[2,3-*b*]pyridine-2-carboxamide (18) and 3-Amino-4-methyl-6,7-dihydro-5*H*-cyclopenta[*b*]thieno[3,2-*e*]pyridine-2-carboxamide (20) (ratio ~4:5). Yield 92%. Finely crystalline khaki-colored powder; mp 295-298°C (decomp.). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.14-2.05 (4H, m, 7-CH_2 **18** and 6-CH_2 **20**); 2.46 (3H, s, CH_3 **18**); 2.63 (3H, s, CH_3 **20**); 2.86 (2H, t, ^3J = 7.5, 6-CH_2 **18**); 2.90 (2H, t, ^3J = 7.5, 5-CH_2 **20**); 2.97 (2H, t, ^3J = 7.5, 7-CH_2 **20**); 3.35 (2H, t, ^3J = 7.2, 8-CH_2 **18**); 6.67 (2H, br. s) and 6.82 (2H, br. s, NH_2 **18** and **20**); 7.11 (4H, br. s, $CONH_2$ **18** and **20**). Found, %: C 58.40; H 5.33; N 17.10. $C_{12}H_{13}N_3OS$. Calculated, %: C 58.28; H 5.30; N 16.99.

1-Amino-5-methyl-6,7,8,9-tetrahydrothieno[2,3-*c*]isoquinoline-2-carboxamide (19) and 3-Amino-4-methyl-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide (21) (ratio ~10:3). Yield 89%. Yellow crystals; mp 230-235°C (mp 248-250°C (*n*-BuOH) [4]). IR spectrum, ν, cm^{-1} 3400, 3320, 3160 (NH_2), 1660 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.77 (8H, m, 7,8-$(CH_2)_2$ **19**, 6,7-$(CH_2)_2$ **21**); 2.44 (3H, s, CH_3 **19**); 2.60 (3H, s, CH_3 **21**); 2.63 (2H, m, 6-CH_2 **19**); 2.72 (2H, m, 5-CH_2 **21**); 2.89 (2H, m, 8-CH_2 **20**); 3.26 (2H, m, 9-CH_2 **19**); 6.84, 6.89, and 7.09 (8H, three br. s, $CONH_2$ and NH_2 **19** and **21**). Found, %: C 60.13; H 5.81; N 16.17. $C_{13}H_{15}N_3OS$. Calculated, %: C 59.75; H 5.79; N 16.08.

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