Synthesis of 6-amino-4-aryl-5-cyano-3-(3-cyanopyridin-2-ylthiomethyl)-2,4-dihydropyrano[2,3-*c*]pyrazoles and their hydrogenated analogs. Molecular structure of 6-amino-5-cyano-3-(3-cyano-4,6-dimethylpyridin-2-ylthiomethyl)-4-(2-nitrophenyl)-2,4-dihydropyrano[2,3-*c*]pyrazole

L. A. Rodinovskaya,[a]★ A. V. Gromova,[a] A. M. Shestopalov,[a] and V. N. Nesterov[b]

[a]N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 119991 Moscow, Russian Federation. Fax: +7 (095) 135 5328. E-mail: shchem@dol.ru

[b]A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, 28 ul. Vavilova, 119991 Moscow, Russian Federation. Fax: +7 (095) 135 6549

Substituted 3-hydroxypyrazoles, which were prepared based on ethyl esters of substituted 4-(pyridin-2-ylthio)- or 4-(1,4-dihydropyridin-2-ylthio)acetoacetic acids and hydrazine hydrate, were used in the synthesis of 6-amino-4-aryl-5-cyano-3-(pyridin-2-ylthiomethyl)-2,4-dihydropyrano[2,3-*c*]pyrazoles. The molecular and crystal structure of 6-amino-5-cyano-3-(3-cyano-4,6-dimethylpyridin-2-ylthiomethyl)-4-(2-nitrophenyl)-2,4-dihydropyrano[2,3-*c*]pyrazole was established by X-ray diffraction analysis.

Key words: malononitrile, arylidenemalononitriles, 4-(3-cyanopyridin-2-ylthio)acetoacetic esters, 6-(3-ethoxycarbonyl-2-oxopropylthio)-1,4-dihydropyridine, 2-(pyrazol-5-ylmethylthio)pyridine, 2-(pyrazol-5-ylmethylthio)-1,4-dihydropyridine, pyrano[2,3-*c*]pyrazoles, X-ray diffraction analysis.

Due to the presence of several reaction centers, 4-(3-cyanopyridin-2-ylthio)acetoacetic esters serve as convenient starting reagents in the synthesis of difficultly accessible 4-hydroxy-1*H*-thieno[2,3-*b*;4,5-*b*]dipyridin-2-ones,[1] 2-amino-3-cyano-5-oxo-5,6-dihydro-4*H*-pyrano[2,3-*d*]pyrido[3′,2′:4,5]thieno[3,2-*b*]pyridines, and 3-alkoxycarbonyl-6-amino-5-cyano-(3-cyanopyridin-2-ylthiomethyl)-4*H*-pyrans.[2]

Taking into account that 4-(3-cyanopyridin-2-ylthio)acetoacetic esters **1** contain the nucleophilic centers along with electrophilic centers, such as carbonyl carbon atoms, we decided to use these compounds in reactions with hydrazine. Thus, the reaction of ester **1** with hydrazine afforded 2-(3-hydroxy-1*H*-pyrazol-5-ylmethylthio)pyridine **2** (Scheme 1, Table 1).

It is known that pyrazoles are convenient reagents for the synthesis of 6-amino-5-cyano-2,4-dihydropyrano[2,3-*c*]pyrazoles.[3—12] We also used compound **2** in the synthesis of pyrano[2,3-*c*]pyrazoles (see Scheme 1). The reactions of pyrazole **2** with arylidenemalononitriles **3a—f** in ethanol in the presence of catalytic amounts of triethylamine afforded pyranopyrazoles **5a—f** (method *A*). Most probably, these reactions proceed through the corresponding Michael adduct **4**, whose subsequent cyclization gives rise to pyrano[2,3-*c*]pyrazoles **5**. We prepared compounds **5c—f** also by the three-component reactions of pyrazole **2**, malononitrile **6**, and the corresponding aldehyde **7c—f** (method *B*). The synthesis according to methods *A* and *B* produced compounds in comparable yields. It should be emphasized that pyranopyrazoles containing the methyl-

Table 1. Physicochemical parameters of 6-amino-4-aryl-5-cyano-3-(3-cyano-4,6-dimethylpyridin-2-ylthiomethylene)-2,4-dihydropyrano[2,3-*c*]pyrazoles (**5**)

Compound	M.p. /°C	Yield (%) (method)	Found / Calculated (%) C	H	N	Molecular formula
5a	238—239	82 (*A*)	63.48 / 63.75	4.22 / 4.38	20.06 / 20.28	$C_{22}H_{18}N_6OS$
5b	231—233	87 (*A*)	60.93 / 61.10	3.78 / 3.96	19.24 / 19.43	$C_{22}H_{17}FN_6OS$
5c	248—249	83 (*A*), 82 (*B*)	57.34 / 57.51	3.56 / 3.73	21.12 / 21.34	$C_{22}H_{17}N_7O_3S$
5d	256—257	85 (*A*), 80 (*B*)	57.04 / 57.26	3.34 / 3.55	17.26 / 17.42	$C_{23}H_{17}F_3N_6OS$
5e	215—216	81 (*A*), 72 (*B*)	60.97 / 60.71	4.36 / 4.12	23.47 / 23.60	$C_{21}H_{17}N_7OS$
5f	233—234	84 (*A*), 86 (*B*)	56.94 / 57.12	3.60 / 3.84	19.67 / 19.98	$C_{20}H_{16}N_6OS_2$

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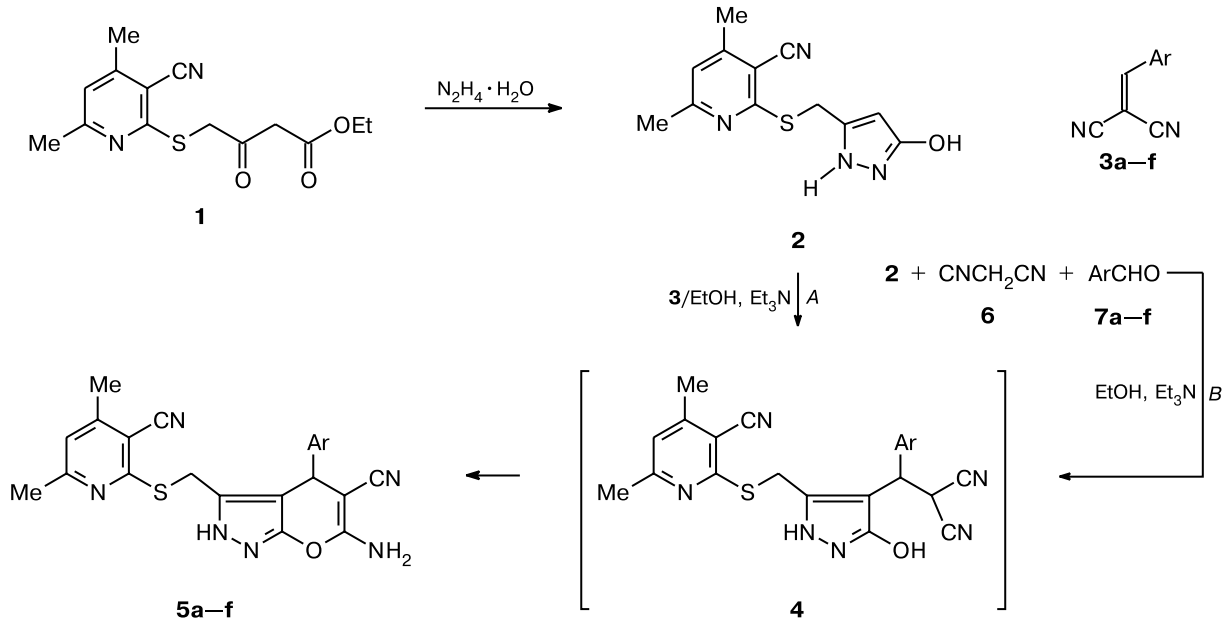
Scheme 1



3, 5, 7: Ar = Ph (**a**), 4-FC_6H_4 (**b**), 2-$NO_2C_6H_4$ (**c**), 2-$CF_3C_6H_4$ (**d**), 3-C_5H_4N (**e**), 2-C_4H_3S (**f**)

thiopyridine substituents at position 2 were synthesized for the first time.

The structures of pyranopyrazoles **5** were confirmed by physicochemical methods (Table 2). The ^{1}H NMR spectra of compounds **5** have characteristic signals among which are singlets for the protons of the NH and NH_2 groups at δ 12.32—12.54 and 6.69—6.99, respectively, as well as for the H(4) proton of the pyran ring at

Table 2. Spectroscopic data for 6-amino-4-aryl-5-cyano-3-(3-cyano-4,6-dimethylpyridin-2-ylthiomethylene)-2,4-dihydropyrano[2,3-*c*]pyrazoles (**5**)

Compound	IR, ν/cm^{-1}		^{1}H NMR (DMSO-d_6), δ (*J*/Hz)							
	CN (pyran/ pyridine ring)	NH, NH_2	Me(4′) (s, 3 H)	H(5′) (s, 1 H)	Me(6′) (s, 3 H)	Ar	NH (s, 1 H)	NH_2 (s, 2 H)	H(4) pyran ring	SCH_2 (2 H)
5a	2200, 2220	1640 (δ), 3220, 3340, 3428	2.41	7.02	2.51	7.16 (m, 5 H, Ph)	12.32	6.69	4.67	4.03, 4.16 (both d, 1 H each, *J* = 14.6)
5b	2200, 2218	1648 (δ), 3224, 3320, 3428	2.31	7.09	2.48	6.70, 7.11 (both t, 2 H each, C_6H_4, *J* = 9.2)	12.41	6.78	4.70	4.09, 4.23 (both d, 1 H each, *J* = 14.7)
5c	2200, 2220	1648 (δ), 3220, 3320, 3424	2.40	6.98	2.44	7.30 (d, 1 H, H(6), C_6H_4, *J* = 8.2); 7.36 (t, 1 H, H(5), C_6H_4, *J* = 8.2); 7.58 (t, 1 H, H(4), C_6H_4, *J* = 8.2); 7.67 (d, 1 H, H(3), C_6H_4, *J* = 8.2)	12.41	6.81	5.39	4.11, 4.22 (both d, 1 H each, *J* = 14.5)
5d	2208, 2224	1648 (δ), 3220, 3320, 3432	2.37	7.08	2.43	7.25 (d, 1 H, H(6), C_6H_4, *J* = 7.8); 7.32 (dd, 1 H, H(5), C_6H_4, *J* = 7.8, *J* = 7.1); 7.48 (d, 1 H, H(3), C_6H_4, *J* = 7.8); 7.58 (dd, 1 H, H(4), C_6H_4, *J* = 7.8, *J* = 7.1)	12.54	6.99	5.01	4.04 (s)

(*to be continued*)

Table 2 (*continued*)

Compound	IR, ν/cm^{-1}		^{1}H NMR (DMSO-d$_6$), δ (*J*/Hz)							
	CN (pyran/ pyridine ring)	NH, NH_2	Me(4′) (s, 3 H)	H(5′) (s, 1 H)	Me(6′) (s, 3 H)	Ar	NH (s, 1 H)	NH_2 (s, 2 H)	H(4) pyran ring	SCH_2 (2 H)
5e	2176, 2216	1652 (δ), 3256, 3292, 3344	2.39	7.10	2.48	7.25 (dd, 1 H, H(5), C_5H_4N, *J* = 4.3, *J* = 7.8), 7.47 (d, 1 H, H(6), C_5H_4N, *J* = 7.8); 8.36 (m, 2 H, H(2), H(4), C_5H_4N)	12.50	6.97	4.76	4.10, 4.25 (both d, 1 H each, *J* = 14.5)
5f	2188, 2220	1644 (δ), 3188, 3312, 3376	2.39	7.34	2.51	6.86 (dd, 1 H, H(4), C_4H_3S, *J* = 3.3, *J* = 5.2); 6.94* (d, 1 H, H(5), C_4H_3S, *J* = 3.3); 7.35 (d, 1 H, H(3), C_4H_3S, *J* = 5.2)	12.49	6.93*	5.08	4.27 (s)

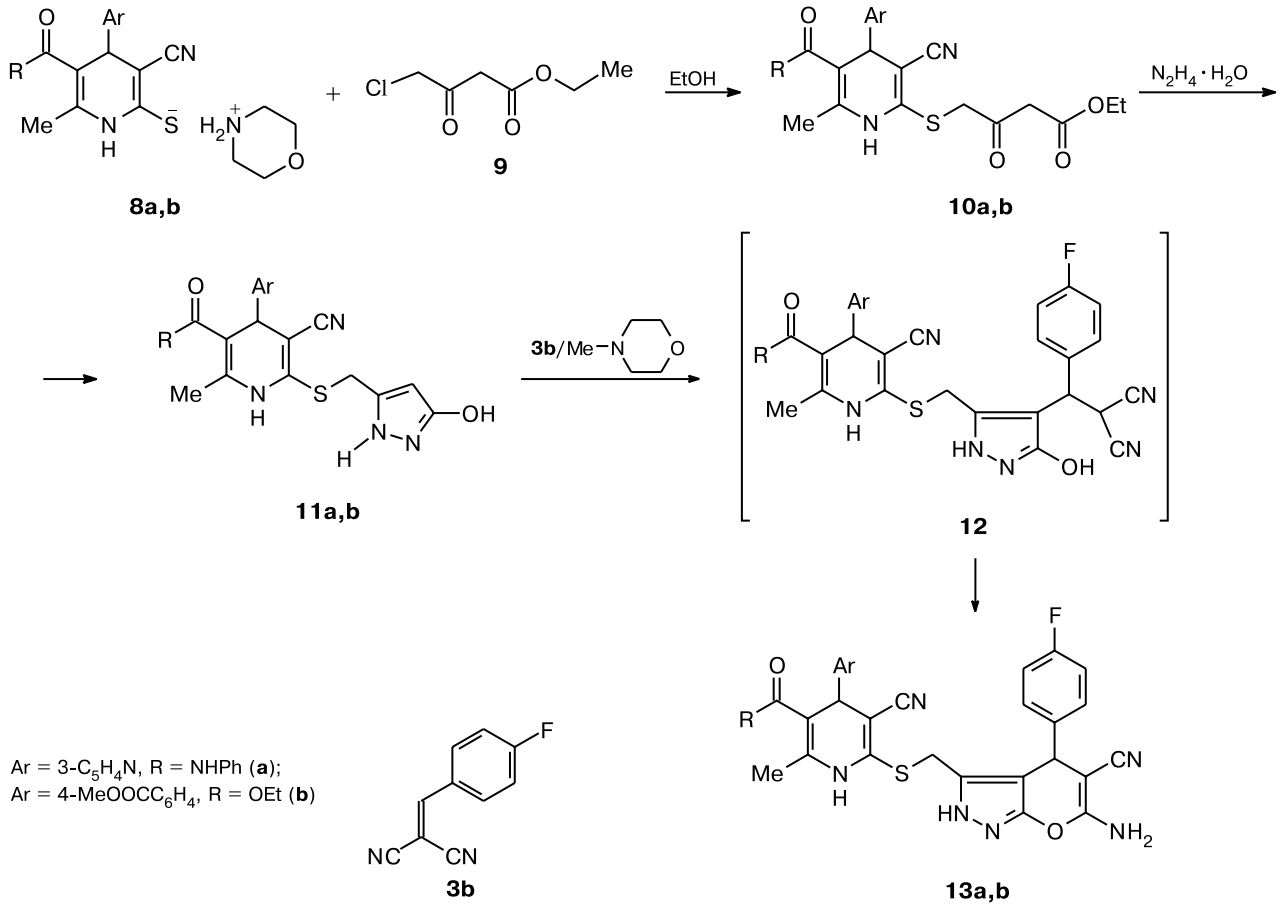
* Signals for the protons overlap with each other.

δ 4.67—5.39. The IR spectra of compounds **5** show two absorption bands of the CN group at ~2200 and ~2220 cm^{-1}.

We also synthesized pyrano[2,3-*c*]pyrazoles based on hydrogenated pyridines (Scheme 2). Alkylation of morpholinium 1,4-dihydropyridine-2-thiolate **8a** with ethyl 4-chloroacetoacetate **9** in ethanol afforded 2-(3-ethoxycarbonyl-2-oxopropylthio)-1,4-dihydropyridine **10a**. The reaction of ester **10a** with hydrazine hydrate gave rise to 2-(pyrazol-5-ylmethylthio)-1,4-dihydropyridine **11a**.

The reaction of pyrazole **11a** with 4-fluorobenzylidenemalononitrile (**3b**) in ethanol in the presence of *N*-methylmorpholine yielded pyranopyrazole **13a**. The re-

Scheme 2

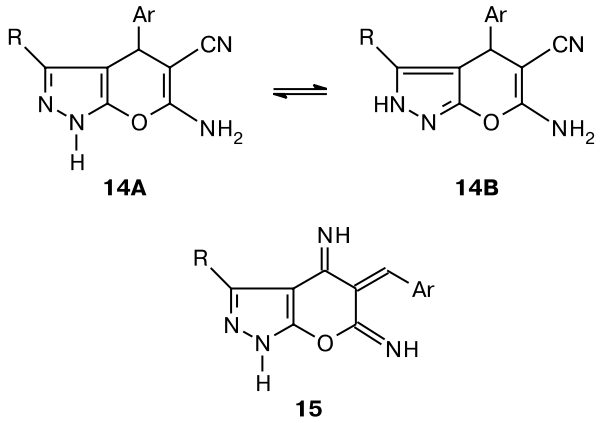


action proceeded, apparently, through intermediate **12**. Compounds **11b** and **13b** were synthesized according to a simplified procedure. Ester **10b** was generated in the reaction mixture and then subjected to the reaction with hydrazine hydrate without purification. Pyrazole **11b** thus prepared was also used in the synthesis of the target compound **13b** without purification.

The structures of compounds **10**, **11**, and **13** were confirmed by physicochemical methods. Among the characteristic signals, the ^{1}H NMR spectra of 2-pyrazolylmethylthio-1,4-dihydropyridines **11** have signals for the protons of the NH groups at δ ~11.50 (pyridine ring) and ~9.55 (pyrazole ring), for the H(4) proton of the pyrazole ring at δ 5.37 and 5.40, and for the H(4) protons of the pyridine ring at δ 4.62 and 4.81. The IR spectra of compounds **13** have two absorption bands of the CN group. The ^{1}H NMR spectra of these compounds have characteristic signals for the protons of the pyridine ring along with characteristic signals for the H(4) protons of the pyran ring as singlets at δ 4.61 and 4.89, a signal of the NH_2 group at δ 6.9, and signals for the aryl protons.

The above data for pyranopyrazoles **5** and **13** did not allow us to unambiguously decide between two alternative tautomeric forms, **14A** or **14B**, in which these compounds can exist.

In the literature, there is no consensus of opinion regarding the structures of pyranopyrazoles derived from pyrazol-5-ones. For example, the structure of diiminopyranopyrazoles **15** was assigned to the reaction products in the study,[13] whereas the structures of 1,4-dihydropyrano[2,3-*c*]pyrazoles (**14A**)[3–9] or their tautomers, *viz.*, 2,4-dihydropyrano[2,3-*c*]pyrazoles (**14B**),[10–12] were alternatively proposed by other researchers.



To unambiguously establish the structures of compounds **5**, we carried out X-ray diffraction study of compound **5c** and demonstrated that the latter is 6-amino-5-cyano-3-(3-cyano-4,6-dimethylpyridin-2-ylthiomethyl)-4-(2-nitrophenyl)-2,4-dihydropyrano[2,3-*c*]pyrazole. The overall view of the molecule is shown in Fig. 1. The bond lengths and bond angles are given in Tables 3 and 4, respectively.

As can be seen from Fig. 1 and Table 3, the distribution of the double bonds in the pyrano[2,3-*c*]pyrazole fragment of molecule **5c** differs from that reported in the literature.[3–9] The difference electron density synthesis

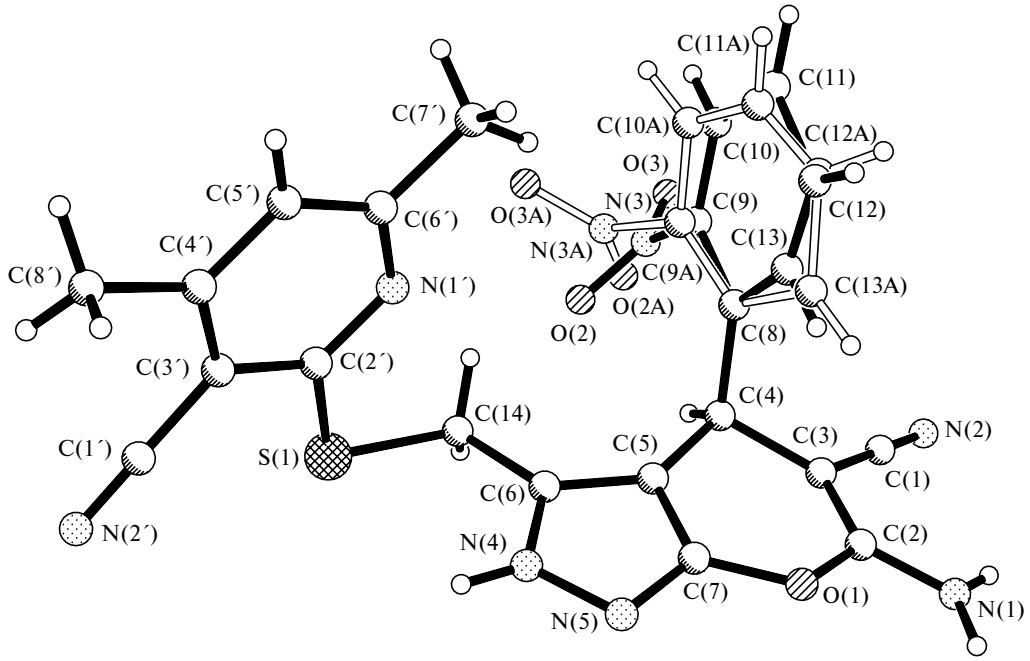


Fig. 1. Overall view of the molecule of 6-amino-5-cyano-3-(3-cyano-4,6-dimethylpyridin-2-ylthiomethyl)-4-(2-nitrophenyl)-2,4-dihydropyrano[2,3-*c*]pyrazole (**5c**).

Table 3. Selected bond lengths (*d*) in molecule **5c**

Bond	*d*/Å	Bond	*d*/Å
S(1)—C(2′)	1.779(4)	C(2)—C(3)	1.375(6)
S(1)—C(14)	1.801(4)	C(3)—C(1)	1.426(6)
O(1)—C(7)	1.372(5)	C(3)—C(4)	1.530(6)
O(1)—C(2)	1.385(5)	C(4)—C(5)	1.498(6)
N(4)—C(6)	1.345(5)	C(4)—C(8)	1.537(6)
N(4)—N(5)	1.385(5)	C(5)—C(6)	1.401(5)
N(5)—C(7)	1.314(5)	C(5)—C(7)	1.404(5)
N(2)—C(1)	1.153(6)	C(6)—C(14)	1.517(5)
N(1)—C(2)	1.340(5)		

Table 4. Selected bond angles (ω) in molecule **5c**

Angle	ω/deg	Angle	ω/deg
C(2′)—S(1)—C(14)	101.2(2)	C(5)—C(4)—C(8)	111.5(3)
C(7)—O(1)—C(2)	114.7(3)	C(3)—C(4)—C(8)	112.1(3)
C(6)—N(4)—N(5)	113.0(3)	C(6)—C(5)—C(7)	102.6(3)
C(7)—N(5)—N(4)	102.2(3)	C(6)—C(5)—C(4)	135.3(3)
N(1)—C(1)—C(3)	178.3(5)	C(7)—C(5)—C(4)	122.0(4)
N(1)—C(2)—C(3)	128.2(4)	N(4)—C(6)—C(5)	106.9(3)
N(1)—C(2)—O(1)	109.7(3)	N(4)—C(6)—C(14)	121.9(3)
C(3)—C(2)—O(1)	122.1(4)	C(5)—C(6)—C(14)	131.1(3)
C(2)—C(3)—C(1)	117.5(4)	N(5)—C(7)—O(1)	119.6(3)
C(2)—C(3)—C(4)	124.9(3)	N(5)—C(7)—C(5)	115.2(4)
C(1)—C(3)—C(4)	117.6(4)	O(1)—C(7)—C(5)	125.2(3)
C(5)—C(4)—C(3)	105.8(3)	C(6)—C(14)—S(1)	114.4(3)

unambiguously revealed that the hydrogen atom is bound to the N(4) atom, as opposed to the earlier studies[3—9] in which the position at the N(5) atom has been assigned to this atom. The X-ray diffraction analysis as well as detailed studies of the structures of analogous compounds performed by us earlier[10—12] demonstrated that there are no tautomeric forms of these compounds.

In molecule **5c**, the pseudoaxial *ortho*-nitrophenyl substituent is disordered over two positions with equal occupancies (see Fig. 1). The dihedral angle between the planes of the phenyl rings is 20.4°. Apparently, the reaction gives rise to two conformers of the Michael adduct, which differ in the orientation of the *ortho*-nitrophenyl substituent with respect to the H(4) atom, and subsequent cyclization of these conformers affords compound **5c** characterized by the above-described disorder of the substituent. Like in the related compounds studied by us earlier,[14] this substituent is also in the *sp* orientation with respect to the hydrogen atom at the C(4) atom. It can be seen (see Fig. 1) that the H(4) atom is located between two oxygen atoms, *viz.*, O(2) and O(2A), and forms nonvalent contacts with the latter atoms (the distances between the atoms are smaller than the sums of their van der Waals radii[15]).

Like in 4*H*-pyrans studied by us earlier,[16—18] the six-membered heterocycle adopts a flattened boat conformation with the O(1) and C(4) atoms deviating from the plane through the remaining four atoms (planar to within ±0.021 Å) by −0.156 and −0.258 Å, respectively. The folding angles along the O(1)...C(4), C(2)...C(7A), and C(3)...C(5) lines are 19.7°, 12.1°, and 163.5°, respectively. The dihedral angle between the bottom of the boat and the plane of the five-membered heterocycle is 11.6°, which indicates that the bicyclic fragment of the molecule is flattened.

The mutual arrangement of the substituents in molecule **5c** is responsible for the occurrence of the intramolecular nonbonded S(1)...H(4A) interaction with the distance (2.70(5) Å) smaller than the sum of the van der Waals radii of these atoms.[15] The plane of the pyridyl substituent is virtually perpendicular to the pyrano[2,3-*c*]pyrazole fragment, as evidenced by the N(4)—C(6)—C(14)—S(1), C(2')—S(1)—C(14)—C(6), and C(14)—S(1)—C(2′)—N(1′) torsion angles of 10.6°, 82.5°, and 10.5°, respectively.

In the crystal, molecules **5c** are linked in infinite ribbons by extensive intermolecular hydrogen bonds: N(4)—H(4A)...N(5) (1 − *x*, 2 − *y*, 1 − *z*) (N(4)...N(5), 2.856(6) Å; N(4)—H(4A), 0.92(5) Å; H(4A)...N(5), 2.13(5) Å; N(4)—H(4A)...N(5) angle, 135(3)°), N(1)—H(1A)...N(2) (1 − *x*, 2 − *y*, 2 − *z*) (N(1)...N(2), 2.989(6) Å; N(1)—H(1A), 0.86 Å; H(1A)...N(2), 2.17 Å; N(1)—H(1A)...N(2) angle, 159°), and N(1)—H(1B)...N(2′) (1 − *x*, 2 − *y*, 1 − *z*) (N(1)...N(2′), 3.169(6) Å; N(1)—H(1B), 0.86 Å; H(1B)...N(2′), 2.38 Å; N(1)—H(1B)...N(2′) angle, 153°).

Analysis of the crystal packing showed the presence of the shortened (3.247(4) Å) intermolecular nonbonded S(1)...S(1) contacts (−*x*, 2 − *y*, 1 − *z*). A search for intermolecular S...S contacts in the Cambridge Structural Database demonstrated that such contacts with distances shorther than 3.10 Å are present between the stacks formed in the crystals of substituted tetrathiofulvalenes, whereas no such examples were found for usual organic molecules.

The remaining geometric parameters in molecule **5c** have standard values.[19]

Experimental

The IR spectra were measured on Perkin—Elmer-577 and Specord M-80 instruments in KBr pellets at a concentration of 0.01 mol L^{-1}. The ^1H NMR spectra were recorded on Bruker AC-300 (300 MHz), Bruker AM-300 (300 MHz), and Bruker WM-250 (250 MHz) instruments (5—10% DMSO-d_6 solutions; Me_4Si as the internal standard). Elemental analysis was carried out on a Perkin—Elmer C,H,N-analyzer. The course of the reactions and purities of the compounds were monitored by thin-layer chromatography on Silufol UV-254 plates using a 5 : 3 hexane—acetone mixture as the eluent; visualization was carried out with iodine vapor.

X-ray diffraction analysis. Triclinic yellow crystals of compound **5c** were grown by slow evaporation of an ethanolic solu-

tion. The X-ray data were collected at 25 °C: a = 7.442(5), b = 9.525(6), c = 16.651(10) Å, α = 73.90(5), β = 85.11(5), γ = 80.78(5)°, V = 1118(1) Å^3, d_{calc} = 1.365 g cm^{-3}, Z = 2, space group P$\bar{1}$.

The unit cell parameters and intensities of 3916 independent reflections were measured on a four-circle automated Siemens P3/PC diffractometer (λMoKα, graphite monochromator, θ/2θ scanning technique to θ_{max} = 27°). The structure was solved by direct methods, which revealed all nonhydrogen atoms, and refined by the full-matrix least-squares method with anisotropic thermal parameters for nonhydrogen atoms. It was found that the *ortho*-nitrophenyl substituent in the molecule is disordered over two positions with equal occupancies (0.5 : 0.5). The hydrogen atom at N(4) was revealed from the difference Fourier synthesis and refined isotropically. The positions of the remaining hydrogen atoms were calculated geometrically and refined with fixed positional and thermal parameters (riding model). The final reliability factors were as follows: R_1 = 0.084 based on 2799 reflections with $I > 2\sigma$ and R_w = 0.238 based on 3818 reflections. All calculations were carried out using the SHELXL-97 program package.

3-Cyano-2-(3-hydroxy-1*H*-pyrazol-5-ylmethylthio)-4,6-dimethylpyridine (2). Hydrazine hydrate (0.5 mL) was added to a solution of ester **1** (1.46 g, 0.005 mol) in ethanol (15 mL). The reaction mixture was refluxed for 1—2 min and kept for 16 h. The precipitate that formed was filtered off and washed with water, ethanol, and hexane. Compound **2** was prepared in a yield of 1.29 g (99%) as a slightly yellowish powder, m.p. 247—248 °C. Found (%): C, 55.74; H, 4.44; N, 21.76. $C_{12}H_{12}N_4OS$. Calculated (%): C, 55.37; H, 4.65; N, 21.52. IR, ν/cm^{-1}: 2228 (CN); 1640 (δ(NH)); 3324 (NH). ^{1}H NMR (300 MHz, DMSO-d_6), δ: 2.42 and 2.55 (both s, 3 H each, Me); 4.34 (s, 2 H, CH_2S); 5.34 (s, 1 H, H(4′)); 7.03 (s, 1 H, H(5)); 10.10 (s, 1 H, NH).

Synthesis of 6-amino-4-aryl-5-cyano-3-(3-cyano-4,6-dimethylpyridin-2-ylthiomethyl)-2,4-dihydropyrano[2,3-*c*]pyrazoles (5) (general procedure). *A.* A mixture of pyrazolylmethylthiopyridine **2** (0.52 g, 0.002 mol), the corresponding arylidenemalononitrile **3a—f** (0.002 mol), and Et_3N (0.1 mL) in ethanol (20 mL) was refluxed for 10 min. After one day, the precipitate that formed was separated, washed with ethanol and hexane, and recrystallized from dioxane or ethanol.

The data for compounds **5a—f** are given in Table 1.

B. A mixture of pyrazolylmethylthiopyridine **2** (0.52 g, 0.002 mol), malononitrile (**6**) (0.13 g, 0.002 mol), the corresponding aldehyde **7c—f** (0.002 mol), and Et_3N (0.1 mL) in ethanol (20 mL) was refluxed for 10 min. The subsequent operations were carried out as described in the method *A*.

5-Cyano-6-(3-ethoxycarbonyl-2-oxopropylthio)-2-methyl-4-(pyridin-3-yl)-1,4-dihydropyridine (10a). Ethyl 4-chloroacetoacetate (**9**) (1.4 mL, 0.01 mol) was added with stirring to a solution of salt **8a** (3.48 g, 0.01 mol) in ethanol (15—20 mL). The reaction mixture was stirred at 40—45 °C for 0.5—1 h, diluted with water (5 mL), and kept in a refrigerator for 1—3 h. The precipitate that formed was filtered off and washed with water, ethanol, and hexane.

Compound **10a** was prepared in a yield of 3.20 g (67%) as a white powder, m.p. 149—150 °C. Found (%): C, 62.91; H, 5.19; N, 11.53. $C_{25}H_{24}N_4O_4S$. Calculated (%): C, 63.01; H, 5.08; N, 11.76. IR, ν/cm^{-1}: 2218 (CN); 1628, 1710, 1730 (δ(CONH)); 3360 (CONH). ^{1}H NMR (300 MHz, DMSO-d_6), δ: 1.20 (t, 3 H, Et, J = 7.1 Hz); 2.07 (s, 3 H, C(6)Me); 3.74 (s, 2 H, CH_2CO); 4.12 (m, 2 H, C$\underline{H_2}$Me); 4.20 (d, 2 H, SCH_2, J = 3.9 Hz); 4.82 (s, 1 H, CH of pyridine); 7.00 (t, 1 H, Ph, J = 7.2 Hz); 7.23 (t, 2 H, Ph, J = 7.8 Hz); 7.36 (dd, 1 H, C(5)H, C_5H_4N, J = 5.2 Hz, J = 7.8 Hz); 7.49 (t, 2 H, Ph, J = 8.5 Hz); 7.60 (d, 1 H, C(6)H, C_5H_4N, J = 7.8 Hz); 8.42 (s, 1 H, C(2)H, C_5H_4N); 8.44 (br.s, 1 H, C(4)H, C_5H_4N); 9.09 (s, 1 H, NH); 9.65 (s, 1 H, NH of pyridine).

5-Cyano-6-(3-hydroxy-1*H*-pyrazol-5-ylmethylthio)-2-methyl-3-(*N*-phenylcarbamoyl)-4-(pyridin-3-yl)-1,4-dihydropyridine (11a). Hydrazine hydrate (0.5 mL) was added to a solution of ester **10a** (2.37 g, 0.005 mol) in ethanol (30 mL). The reaction mixture was refluxed for 1—2 min and kept for 16 h. The precipitate that formed was filtered off and washed with water, ethanol, and hexane. Compound **11a** was obtained in a yield of 1.53 g (69 %) as a white powder, m.p. 185—187 °C. Found (%): C, 62.27; H, 4,31; N, 19.01. $C_{23}H_{20}N_2OS$. Calculated (%): C, 62.15; H, 4.54; N, 18.91. IR, ν/cm^{-1}: 2210 (CN); 1658 (δ(CO)); 3300, 3460 (NH). ^{1}H NMR (300 MHz, DMSO-d_6), δ: 2.11 (s, 3 H, C(6)Me); 4.14 (s, 2 H, SCH_2); 4.82 (s, 1 H, H(4) of pyridine); 5.39 (s, 1 H, H(4) of pyrazole); 7.00 (t, 1 H, Ph, J = 7.2 Hz); 7.23 (dd, 2 H, Ph, J = 7.14 Hz, J = 7.8 Hz); 7.36 (m, 1 H, C(5)H, C_5H_4N); 7.50 (d, 2 H, Ph; 1 H, C(6)H, C_5H_4N, J = 8.5 Hz); 8.37 (s, 1 H, C(2)H, C_5H_4N); 8.42 (br.s, 1 H, C(4)H, C_5H_4N); 9.32 (br.s, 1 H, NH); 9.64 (s, 1 H, NH of pyrazole); 11.56 (br.s, 1 H, NH of pyridine).

3-Carbethoxy-5-cyano-6-(3-hydroxy-1*H*-pyrazol-5-ylmethylthio)-4-(4-methoxycarbonylphenyl)-2-methyl-1,4-dihydropyridine (11b). Ethyl 4-chloroacetoacetate **9** (0.7 mL, 0.005 mol) was added with stirring to a solution of salt **8b** (1.79 g, 0.005 mol) in ethanol (20 mL). The reaction mixture was stirred at 40—45 °C for 0.5 h, diluted with water (10 mL), and kept in a refrigerator for 16 h. The solution was decanted and the resinous residue was dissolved in ethanol (20 mL). Hydrazine hydrate (0.5 mL) was added to the solution. The reaction mixture was refluxed for 1—2 min and kept for 16 h. Then the solution was decanted and a resinous compound was isolated in a yield of 2.2 g (97%). ^{1}H NMR (300 MHz, DMSO-d_6), δ: 1.10 (t, 3 H, Et, J = 7.2 Hz); 3.97 (m, 2 H, Et, J = 7.2 Hz); 2.35 (s, 3 H, C(6)Me); 3.84 (s, 3 H, MeO); 4.20 (s, 2 H, SCH_2); 4.62 (s, 1 H, H(4) of pyridine); 5.37 (s, 1 H, C(4)H of pyrazole); 7.27 (d, 2 H, C_6H_4, J = 8.6 Hz); 7.91 (d, 2 H, C_6H_4, J = 8.6 Hz); 9.55 (s, 1 H, NH); 11.50 (s, 1 H, NH of pyridine).

Synthesis of 6-{-6-amino-5-cyano-4-(4-fluorophenyl)-2,4-dihydropyrano[2,3-c]pyrazol-3-ylthiomethyl}-4-aryl-5-cyano-2-methyl-1,4-dihydropyridines (13a,b). A mixture of the corresponding pyrazolylmethylthiopyridine **11a,b** (0.002 mol), 4-fluorobenzylidenemalononitrile (**3b**) (0.34 g, 0.002 mol), and *N*-methylmorpholine (0.1 mL) in ethanol (20 mL) was refluxed for 10 min. After one day, the precipitate that formed was separated, washed with ethanol and hexane, and recrystallized from dioxane.

Compound 13a. The yield was 0.60 g (49%), m.p. 198—200 °C. Found (%): C, 64.03; H, 4.17; N, 18.29. $C_{33}H_{25}FN_8O_2S$. Calculated (%): C, 64.27; H, 4.09; N, 18.17. IR, ν/cm^{-1}: 1638 (δ(NH_2)); 1710 (CO); 2192, 2200 (CN); 3440 (NH). ^{1}H NMR, δ: 2.08 (s, 3 H, Me); 4.15 and 4.35 (both d, 2 H each, SCH_2, J = 14.7 Hz); 4.80 (s, 1 H, H(4) of pyridine); 4.89 (s, 1 H, H(4) of pyran); 6.73—7.67 (m, 13 H, Ar, NH_2); 8.40 (m, 2 H, Ar); 9.67 (s, 1 H, NH of pyrazole); 12.48 (s, 1 H, NH of pyran).

Compound 13b. The yield was 0.84 г (65%), m.p. 242—244 °C. Found (%): C, 61.18; H, 4.42; N, 13.59. $C_{32}H_{27}FN_6O_5S$. Calculated (%): C, 61.33; H, 4.34; N, 13.41. IR, ν/cm^{-1}: 1640 (δ(NH_2)); 1700 (CO); 2196, 2200 (CN); 3184, 3304, 3384 (NH). ^{1}H NMR, δ: 1.08 (t, 3 H, Me, J = 7.3 Hz); 2.32 (s, 3 H, Me); 3.36 and 3.44 (both d, 2 H each, SCH_2, J = 14.7 Hz); 3.87 (s, 3 H, OMe); 3.98 (q, 2 H, CH_2, J = 7.3 Hz); 4.60 (s, 2 H, H(4) of pyran, H(4) of pyridine); 6.91 (s, 2 H, NH_2); 7.14 (m, 6 H, Ar); 7.90 (d, 2 H, Ar, J = 7.3 Hz); 9.67 (s, 1 H, NH of pyrazole); 12.67 (s, 1 H, NH of pyridine).

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