Synthesis of isomeric 3-phenyl-5-(pyridylmethylene)-2-thiohydantoins and their *S*-methylated derivatives. Molecular and crystal structures of (5*Z*)-3-phenyl-5-(pyridin-2-ylmethylene)-2-thiohydantoin and (5*Z*)-2-methylthio-3-phenyl-5-(pyridin-2-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one

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Three procedures were used for the synthesis of α-, β-, and γ-pyridyl-substituted (5*Z*)-3-phenyl-5-(pyridylmethylene)-2-thiohydantoins: the reaction of 2-thiohydantoin with the corresponding aldehyde in AcOH in the presence of AcONa, the two-step one-pot synthesis with the use of the same starting compounds, and three-component condensation of aryl isothiocyanate, glycine, and aldehyde in AcOH. Alkylation of the resulting thiohydantoins with iodomethane in the presence of a base afforded the corresponding *S*-methylated derivatives, *viz.*, 2-methylthio-3-phenyl-5-(pyridylmethylene)-3,5-dihydro-4*H*-imidazol-4-ones. The structures of (5*Z*)-3-phenyl-5-(pyridin-2-ylmethylene)-2-thioxoimidazolin-4-one and (5*Z*)-2-methylthio-3-phenyl-5-(pyridin-2-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one were established by X-ray diffraction analysis.

Key words: thiohydantoins, 2-alkylthio-3,5-dihydroimidazolones, condensation, pyridinecarboxaldehydes, *S*-alkylation, crystal and molecular structure.

2-Thiohydantoins (4-oxoimidazolidine-2-thiones) and their *S*-alkylated derivatives (2-alkylthio-3,5-dihydro-4*H*-imidazol-4-ones) have attracted attention as convenient synthetic intermediates containing both electrophilic and nucleophilic C atoms and also because these compounds have a broad spectrum of biological activities. The hydantoin and thiohydantoin fragments are responsible for antiarrhythmic[1] and antihypertensive[2,3] activities. In addition, thiohydantoins have found application as fungicides and herbicides.[4] Due to the presence of the nucleophilic C atom at position 5 of the thiohydantoin ring, various substituents can be introduced at this position, and 5-substituted thiohydantoins are also used in therapeutic practice.[5—14]

In many cases, coordination of sulfur- and nitrogen-containing compounds to transition metal ions enhances their antiviral and antitumor activities.[15] From this point of view, 2-thiohydantoins and their *S*-alkylated derivatives, which contain endo- and exocyclic donor atoms of various nature and can exist as either neutral molecules or monoanions,[16—18] are of interest as ligands for the preparation of metal chelate complexes. The introduction of substituents containing additional donor atoms at position 5 of the thiohydantoin ring makes it possible to prepare chelate complexes in which coordination occurs through the N atom of the thiohydantoin ring and the electron-donating atom of the substituent at position 5.[19—21] For example, the reaction of N(3)-unsubstituted 5-(2-pyridylmethylene)hydantoin with copper(II) chloride affords a supramolecular complex, in which two N atoms form a chelate coordination bond with the Cu^{II} ions and the organic fragments are linked through hydrogen bonds.[19] These systems are of considerable interest, because a transition metal ion introduced into supramolecular crystalline systems imparts the optical, conducting, and magnetic properties to these compounds, due to which such materials hold promise as conductors and ferromagnets in nonlinear optics.

In the present study, we synthesized 5-pyridylmethylene-substituted thiohydantoins **1a—c** and their *S*-alkylated analogs **2a—c** and investigated their structures (Scheme 1).

Thio-substituted imidazolones and imidazolinones containing the pyridine fragment have attracted our interest primarily in relation to coordination chemistry of such compounds. Compounds **1a** and **2a** containing the α-pyridyl fragments are promising ligands for the preparation of chelate complexes, in which the electron-do-

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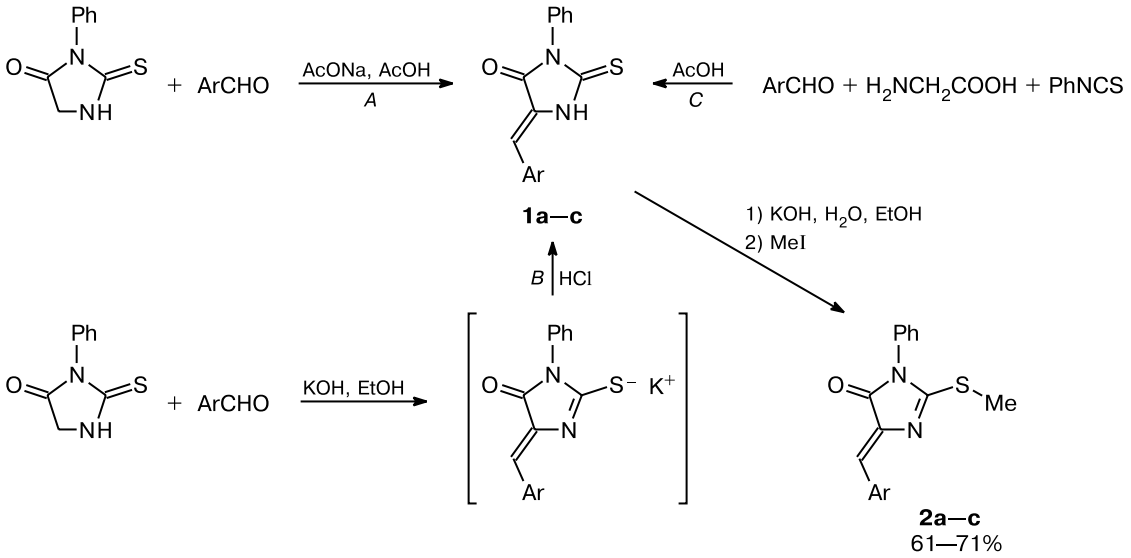
Scheme 1



1, **2:** Ar = 2-pyridyl (**a**), 3-pyridyl (**b**), 4-pyridyl (**c**)

nating N atoms of the pyridine and thiohydantoin rings are involved in coordination. Compounds **1b,c** and **2b,c** containing the β- and γ-pyridyl fragments are of interest from the viewpoint of the synthesis of dimeric and polymeric complexes. Both N atoms of the thiohydantoin ligand and its S atom can coordinate a metal ion. It should be noted that a few transition metal complexes with thiohydantoins have been described in the literature (see above), but the data on the ability of *S*-alkylated thiohydantoins to be involved in coordination are lacking.

Three procedures for the preparation of 5-arylidene-2-thiohydantoins have been documented (see Scheme 1). The procedure *A* involves the reaction of 2-thiohydantoin with the corresponding aldehyde in acetic acid in the presence of an equimolar amount of anhydrous sodium acetate[14] and works well with a large series of aromatic or heteroaromatic aldehydes.

The procedure *B* is based on the two-step one-pot synthesis with the use of the same starting compounds. In the first step, thiohydantoin reacts with aldehyde in the presence of potassium hydroxide in anhydrous ethanol. In the second step, the potassium salt of 5-arylidene-2-mercapto-3,5-dihydro-4*H*-imidazol-4-one is hydrolyzed with dilute hydrochloric acid.[14]

The procedure *C* involves three-component condensation of aryl isothiocyanate, glycine, and aldehyde in acetic acid on heating. This method has been proposed in 1950s, but it has found little practical use because of low yields of the target compounds.[22]

In the present study, we examined the possibility of using the methods *A*—*C* for the synthesis of 5-pyridylmethylene-substituted thiohydantoins **1a—c**. The results of this investigation are given in Table 1.

Table 1. Yields of thiohydantoins **1a—c** prepared according to the methods *A*—*C*

Thiohydantoin	Yield of the target compound (%)		
	A	*B*	*C*
1a	Traces	95	Traces
1b	50	7	61
1c	75	11	60

It was found that different procedures of condensation with pyridinecarboxaldehyde are optimal for particular compounds **1a—c**. For example, the methods *A* and *C* are unsuitable for 2-pyridinecarboxaldehyde, and the method *B* proved to be the only preparative procedure for the synthesis of 5-(pyridylmethylene)thiohydantoin **1a**. To the contrary, the method *B* is inapplicable for condensation with 3- and 4-pyridinecarboxaldehydes because of low yields of the target products. Unexpectedly, three-component condensation (method *C*), which has been considered earlier to be of little use, was not only as good as other known methods as applied to the synthesis of compound **1b** but also affords arylidenethiohydantoin in higher yields.

In the presence of substituents at both N atoms, condensation of hydantoins with aromatic aldehydes produces two possible geometric isomers (*Z* and *E*), whereas condensation of unsubstituted hydantoin gives only the *Z* isomer of 5-benzylidenehydantoin, which was accounted for by isomerization through the tautomeric equilibrium involving the proton transfer from the N(1) atom.[23] This signifies that the substituent at the N(3) atom is not of decisive importance for geometric

Table 2. Crystallographic data and details of the structure solution and refinement of compounds **1a** and **2a**

Parameter	**1a**	**2a**
Molecular formula	$C_{15}H_{11}N_3OS$	$C_{16}H_{13}N_3OS$
Molecular weight	281.33	295.35
Color, habitus	Yellow prisms	Yellow platelets
Crystal dimensions/mm	0.5×0.3×0.3	0.72×0.35×0.08
Crystal system	Monoclinic	Monoclinic
Space group	*P*2(1)/*n*	*Pbcm*
a/Å	12.912(5)	8.486(2)
b/Å	6.552(4)	23.474(5)
c/Å	15.383(8)	7.2250(10)
α/deg	90	90
β/deg	94.57(4)	90
γ/deg	90	90
V/Å^3	1297.3(11)	1439.2(5)
Z	4	4
Calculated density/g cm^{-3}	1.440	1.363
Linear absorption coefficient/cm^{-1}	0.247	0.227
F(000)	584	616
θ/deg	2.15—25.06	2.40—24.96
Reflection indices	$-6 \le h \le 10$, $-7 \le k \le 7$, $-18 \le l \le 18$	$0 \le h \le 10$, $0 \le k \le 27$, $0 \le l \le 8$
Number of measured reflections	4088	840
Number of independent reflections	1982 (R_{int} = 0.0243)	840 (R_{int} = 0.0000)
Number of reflections with $I > 2\sigma(I)$	1514	839
Refinement variables	225	155
Goodness-of-fit on F^2	0.845	1.047
R Factors based on reflections with $I > 2\sigma(I)$	R_1 = 0.0354, wR_2 = 0.1008	R_1 = 0.0300, wR_2 = 0.0809
R Factors based on all data	R_1 = 0.0613, wR_2 = 0.1147	R_1 = 0.0300, wR_2 = 0.08
Residual electron density/e·Å^{-3}, ρ_{min}/ρ_{max}	0.178/−0.201	0.149/−0.158

isomerism. However, it has earlier been demonstrated[24] that condensation of aromatic aldehydes with 3-methylthiohydantoin produces only (*Z*)-5-benzylidenethiohydantoins, whereas condensation with 1-methylhydantoin affords a mixture of both possible geometric isomers. We isolated all three thiohydantoins **1a—c** as one isomer. The (*Z*) configuration of compound **1a** was unambiguously established by X-ray diffraction analysis.

2-Thiohydantoins were subjected to alkylation with iodomethane in the presence of a base to prepare the corresponding *S*-methylated derivatives **2a—c** (see Scheme 1).

The molecular and crystal structure of compound **2a** was established by X-ray diffraction analysis.

The crystallographic data and details of the structure solution and refinement of compounds **1a** and **2a** are given in Table 2. The selected bond lengths, bond angles, and torsion angles in molecules **1a** and **2a** are listed in Tables 3 and 4, respectively. The molecular structure of **1a** is shown in Fig. 1, *a*. The thiohydantoin and pyridine rings of molecule **1a** are planar and virtually coplanar. The plane of the benzene ring at the N(3) atom forms an angle of 59° with the plane of the five-membered ring of the ligand. The five-membered thiohydantoin ring shows a pronounced tendency toward bond delocalization (all bond lengths in the ring, except for the C(7)—C(8) bond length,* are noticeably smaller than the average values). The same is true for the C(6)—C(7) and C(5)—C(6) bonds. The former bond is somewhat longer than the standard C=C double bond, whereas the latter bond is, correspondingly, shorter than the single bond. A similar

Table 3. Selected interatomic distances (*d*) and bond angles (ω) for compound **1a**

Bond	*d*/Å	Angle	ω/deg
S(1)—C(9)	1.642(3)	C(9)—N(2)—C(7)	113.2(2)
N(2)—C(9)	1.358(3)	C(9)—N(3)—C(8)	111.52(18)
N(2)—C(7)	1.372(3)	N(2)—C(9)—S(1)	127.18(19)
N(3)—C(9)	1.399(3)	N(2)—C(7)—C(8)	105.79(19)
N(3)—C(8)	1.404(3)	N(3)—C(8)—C(7)	104.0(2)
C(7)—C(8)	1.481(3)	N(2)—C(9)—N(3)	105.5(2)
C(5)—C(6)	1.458(3)	C(7)—C(6)—C(5)	125.0(3)
C(6)—C(7)	1.346(3)	C(7)—C(6)—H(6)	116.3(14)

* Hereinafter, the atomic numbering scheme used in the discussion of the molecular and crystal structures of compounds **1a** and **2a** and in Tables 2 and 3 corresponds to that presented in Fig. 1.

Table 4. Selected interatomic distances (*d*) and bond angles (ω) for compound **2a**

Bond	*d*/Å	Angle	ω/deg
S(1)—C(1)	1.725(3)	C(1)—N(2)—C(2)	105.3(2)
N(1)—C(1)	1.392(4)	C(3)—N(1)—C(1)	107.5(2)
N(1)—C(3)	1.390(4)	N(2)—C(1)—S(1)	126.7(2)
N(2)—C(1)	1.295(3)	N(2)—C(2)—C(3)	109.6(2)
N(2)—C(2)	1.397(4)	N(2)—C(1)—N(1)	114.9(2)
C(2)—C(3)	1.345(4)	N(1)—C(3)—C(2)	102.6(2)
C(3)—C(4)	1.493(4)	C(4)—C(2)—N(2)	129.3(3)

bond distribution has been observed earlier in analogous N(3)-unsubstituted 5-(2-pyridylmethylene)thiohydantoin[18] and 5-(2-pyridylmethylene)hydantoin[18,20] studied by X-ray diffraction. In molecule **1a**, as in the *N*-unsubstituted analogs,[18,20] the N(1) and N(2) atoms are involved in an intramolecular hydrogen bond (N(1)—H(1), 2.203 Å). Apparently, this hydrogen bond additionally stabilizes the (*Z*) configuration of compound **1a**.

The overall view of molecule **2a** and the atomic numbering scheme are presented in Fig. 1, *b*. The pyridine and thiohydantoin rings of molecule **2a** are in a single plane. The benzene ring is orthogonal to the plane of the heterocycles. In contrast to thiohydantoin **1a**, molecule **2a** adopts the second possible conformation, in which conjugation between the pyridine ring and the double bond persists. In molecule **1a**, the N atom of the pyridine ring forms a hydrogen bond with the NH group of thiohydantoin, whereas the N atom in compound **2a** is oriented in the opposite direction. In molecule **2a**, there is a CH...N interaction between the H atom at C(6) and the N(2) atom, which can be considered as a weak intramolecular hydrogen bond.[25]

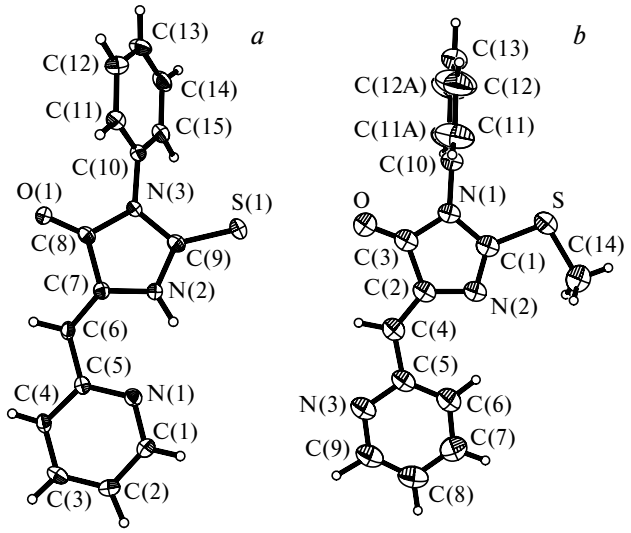


Fig. 1. Molecular structures of compounds **1** (*a*) and **2** (*b*) projected onto the plane of the thiohydantoin ring.

In the crystal structure of compound **1a** (Fig. 2), the molecules are arranged in layers parallel to the crystallographic plane *AC* (see Fig. 2, *a*). In the layers, molecules **1a** are linked to each other *via* intermolecular hydrogen bonds of three types: S(1)...H(4) (2.992 Å), O(1)...H(1)

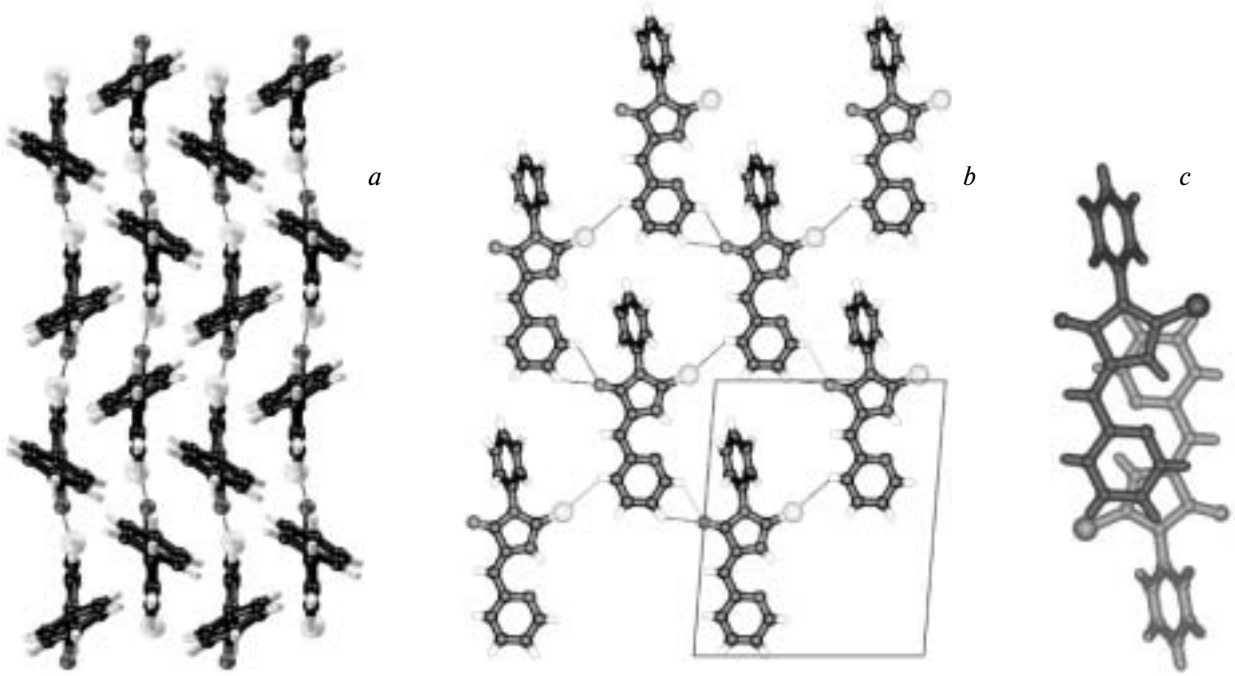


Fig. 2. Crystal structure of compound **1a** (*a*); the packing of the molecules in layers and a hydrogen bond network formed by molecules **1a** (*b*); π—π stacking interactions between the pyridine and thiohydantoin rings (*c*).

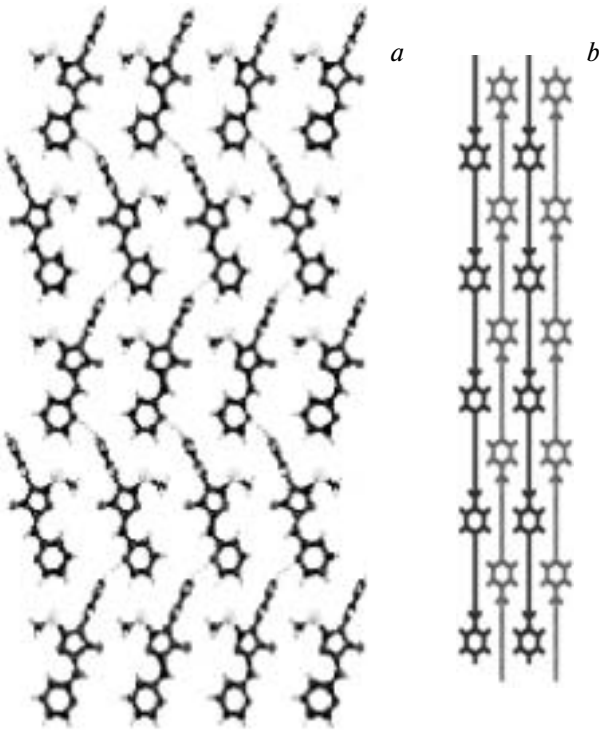


Fig. 3. Crystal structure of compound **2a** and a hydrogen bond network formed by molecules **2a** (*a*); the packing of the molecules in layers (*b*).

(2.598 Å), and O(1)...H(2) (2.445 Å). As a result, each molecule is involved in six hydrogen bonds (see Fig. 2, *b*). (Earlier, it has been demonstrated[25] that the C—H bonds, including even those involved in very weakly polarized Me groups, can participate in hydrogen bonding.) The nearest molecules of the adjacent layers are arranged in a head-to-tail fashion (see Fig. 2, *c*). The distance between the centroids of the pyridine and thiohydantoin rings is 3.667 Å. The distances between the adjacent atoms (C(1)—C(7) and C(2)—C(9)) are 3.303 and 3.365 Å, respectively, which corresponds[27] to a π—π-stacking interaction between the above-mentioned rings.

In the crystal, molecules **2a** are linked to each other *via* CH...N hydrogen bonds between the H(13) atom of one molecule and the N(3) atom of another molecule (the distance between these atoms is 2.50 Å) to form zigzag chains (Fig. 3, *a*). The chains of the molecules are packed in parallel layers (Fig. 3, *b*), which are weakly linked to each other (the distance between the planes of the pyridine rings of the adjacent layers is 3.61 Å).

Experimental

Commercial pyridinecarboxaldehydes (Lancaster) were used in the synthesis without additional purification. 3-Phenyl-2-thiohydantoin was synthesized according to a procedure described earlier.[14] The ^{1}H and ^{13}C NMR spectra (DMSO-d_6) were recorded in $CDCl_3$ on a Varian VXR-400 instrument operating at 400 and 100 MHz, respectively. The IR spectra were measured on a Perkin—Elmer spectrometer as Nujol mulls.

X-ray diffraction study was carried out on a Syntex P21 diffractometer at 153 K (compound **1a**) or 293 K (compound **2a**) (graphite monochromator, λ(Mo-Kα) = 0.71073 Å, ω scanning technique). The absorption corrections were applied based on the intensities of equivalent reflections (T_{min}/T_{max}). The structures were solved by direct methods (SHELXS-97[27]) and refined by the full-matrix least-squares method against F^2 with anisotropic displacement parameters for all nonhydrogen atoms (SHELXL-97[28]). All H atoms were located from difference electron density maps and refined isotropically. Crystallographic data and details of the structure solution and refinement of compounds **1a** and **2a** are given in Table 2.

3-Phenyl-5-(pyridylmethylene)-2-thioxoimidazolin-4-ones (general procedure). ***A.*** Pyridinecarboxaldehyde (0.64 g, 6 mmol) was added dropwise with stirring to a mixture of 3-phenyl-2-thioxotetrahydro-4*H*-imidazol-4-one (1.0 g, 5.2 mmol), anhydrous sodium acetate (1.16 g, 14.15 mmol), and acetic acid (7.5 mL). The reaction mixture was refluxed with stirring for 4 h, cooled to room temperature, and poured onto ice. The precipitate that formed was filtered off and recrystallized from a 3 : 1 EtOH—DMF mixture.

B. Pyridinecarboxaldehyde (0.56 g, 5.2 mmol) was added dropwise to a solution of 3-phenyl-2-thioxotetrahydro-4*H*-imidazol-4-one (1.0 g, 5.2 mmol) in a 2% ethanolic solution of KOH (14 mL). The reaction mixture was stirred for 12 h. The precipitate that formed was filtered off and dissolved in water, after which the solution was neutralized with dilute HCl to pH 7 with vigorous stirring. The precipitate that formed was filtered off and recrystallized from a 3 : 1 EtOH—DMF mixture.

C. A solution of phenyl isothiocyanate (5.0 g, 37 mmol), glycine (2.78 g, 37 mmol), and pyridinecarboxaldehyde (4.0 g, 37 mmol) in glacial acetic acid (10 mL) was refluxed for 1 h. Then the solution was cooled to room temperature. The precipitate that formed was filtered off and recrystallized from a 3 : 1 EtOH—DMF mixture.

3-Phenyl-(5*Z*)-5-(pyridin-2-ylmethylene)-2-thioxoimidazolin-4-one (1a). M.p. 245 °C (*cf.* lit. data[29]: m.p. 243 °C). ^{1}H NMR, δ: 11.95 (br.s, 1 H, NH); 8.79 (d, 1 H, H(6), Py, J = 4.7 Hz); 7.94 (t, 1 H, H(5), Py, J = 8.3 Hz); 7.80 (d, 1 H, H(3), Py, J = 7.9 Hz); 7.47 (m, 6 H, H(4), Py, Ph); 6.81 (s, 1 H, =CH). IR, ν/cm^{-1}: 3320 (NH); 1750 (C=O); 1600 (C=C).

3-Phenyl-(5*Z*)-5-(pyridin-3-ylmethylene)-2-thioxoimidazolin-4-one (1b). M.p. 217 °C. Found (%): C, 63.63; H, 3.72; N, 14.65. $C_{15}H_{11}N_3OS$. Calculated (%): C, 64.06; H, 3.91; N, 14.95. ^{1}H NMR, δ: 12.45 (br.s, 1 H, NH); 8.94 (d, 1 H, H(2), Py, J = 8.8 Hz); 8.51 (d, 1 H, H(6), Py, J = 8.3 Hz); 8.25 (d, 1 H, H(4), Py, J = 8.3 Hz); 7.42 (m, 6 H, H(5), Py, Ph); 6.71 (s, 1 H, =CH). ^{13}C NMR, δ: 179.0, 163.6, 151.2, 149.5, 136.5, 133.1, 128.7, 123.7, 123.1, 114.8, 108.8. IR, ν/cm^{-1}: 3260 (NH); 1730 (C=O); 1600 (C=C).

3-Phenyl-(5*Z*)-5-(pyridin-4-ylmethylene)-2-thioxoimidazolin-4-one (1c). M.p. 262 °C (with decomp.). Found (%): C, 63.72; H, 3.85; N, 14.73. $C_{15}H_{11}N_3OS$. Calculated (%): C, 64.06; H, 3.91; N, 14.95. ^{1}H NMR, δ: 12.72 (br.s, 1 H, NH); 8.64 (d, 2 H, H(2), H(6), Py, J = 5.3 Hz); 7.71 (d, 2 H, H(3), H(5), Py, J = 5.3 Hz); 7.42 (m, 5 H, Ph); 6.51 (s, 1 H, =CH). ^{13}C NMR, δ: 179.4, 163.6, 149.9, 139.5, 133.0, 128.8, 128.6, 123.6, 108.6. IR, ν/cm^{-1}: 3260 (NH); 1751 (C=O); 1600 (C=C).

2-Methylthio-3-phenyl-5-(pyridylmethylene)-3,5-dihydro-4*H*-imidazol-4-ones (2a—c) (general procedure). Water (10 mL), EtOH (10 mL), and a 15% aqueous KOH solution (2 mL) were added to the corresponding 3-phenyl-5-(pyridylmethylene)-2-thioxotetrahydro-4*H*-imidazol-4-one (**1a—c**) (1.1 g, 4.1 mmol). After complete dissolution of the precipitate, iodomethane (1.18 g, 0.54 mL, 8.2 mmol) was added, and the reaction mixture was stirred for 2—3 h. The precipitate that formed was filtered off and washed on a filter successively with EtOH and Et_2O.

2-Methylthio-3-phenyl-5-(pyridin-2-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one (2a). The yield was 0.8 r (67%), m.p. 206 °C. Found (%): C, 64.77; H, 4.54; N, 14.25. $C_{16}H_{13}N_3OS$. Calculated (%): C, 65.08; H, 4.41; N, 14.24. ^{1}H NMR, δ: 8.69 (d, 1 H, H(6), Py, J = 8.3 Hz); 8.53 (d, 1 H, H(3), Py, J = 4.4 Hz); 8.03 (t, 1 H, H(4), Py, J = 4.4 Hz); 7.46 (m, 6 H, H(5), Py, Ph); 6.88 (s, 1 H, CH=); 2.70 (s, 3 H, Me). ^{13}C NMR, δ: 173.5, 166.7, 165.2, 151.8, 147.9, 138.1, 134.1, 127.5, 127.2, 125.2, 122.1, 121.1, 11.3. IR, ν/cm^{-1}: 1730 (C=O); 1650 (C=N); 1600 (C=C).

2-Methylthio-3-phenyl-5-(pyridin-3-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one (2b). The yield was 0.85 g (71%), m.p. 167 °C. Found (%): C, 65.22; H, 4.09; N, 14.25; S, 10.63. $C_{16}H_{13}N_3OS$. Calculated (%): C, 65.08; H, 4.41; N, 14.24; S, 10.85. ^{1}H NMR, δ: 9.22 (s, 1 H, H(2), Py); 8.69 (d, 1 H, H(6), Py, J = 8.3 Hz); 8.53 (d, 1 H, H(4), Py, J = 4.4 Hz); 7.46 (m, 6 H, H(5), Py, Ph); 6.88 (s, 1 H, CH=); 2.70 (s, 3 H, Me). ^{13}C NMR, δ: 166.2, 150.8, 148.1, 137.5, 136.1, 128.2, 127.7, 125.7, 122.0, 117.4, 97.0. IR, ν/cm^{-1}: 1740 (C=O); 1610 (C=C); 1650 (C=N).

2-Methylthio-3-phenyl-5-(pyridin-4-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one (2c). The yield was 0.73 g (61%), m.p. 225 °C. ^{1}H NMR, δ: 8.66 (d, 2 H, H(2), H(6), Py, J = 6.1 Hz); 7.97 (d, 2 H, H(3), H(5), Py, J = 6.1 Hz); 7.46 (m, 5 H, Ph); 6.83 (s, 1 H, CH=); 2.71 (s, 3 H, Me). ^{13}C NMR, δ: 202.4, 168.6, 150.3, 141.1, 138.5, 132.2, 129.6, 127.2, 125.0, 120.2, 13.2. IR, ν/cm^{-1}: 1745 (C=O); 1600 (C=C); 1650 (C=N).

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