Fused polycyclic nitrogen-containing heterocycles
17.* 4-Hydroxy-3-phenyl-2-(2-pyridylimino)- and 4-hydroxy-2-phenyl-3-(2-pyridyl)thiazolidines and related thiazolo[3,4-*a*]quinoxalines**

V. A. Mamedov, N. A. Zhukova, T. N. Beschastnova, Ya. A. Levin, A. T. Gubaidullin, and I. A. Litvinov*

A. E. Arbuzov Institute of Organic and Physical Chemistry,
Kazan Research Center of the Russian Academy of Sciences,
8 ul. Akad. Arbuzova, 420088 Kazan, Russian Federation.
Fax: +7 (843 2) 73 2253. E-mail: mamedov@iopc.knc.ru

The condensation of methyl phenylchloropyruvate with 1-phenyl-3-(2-pyridyl)thiourea and its 3- and 4-picolyl homologs affords the corresponding 4-hydroxythiazolidines, which react with *o*-phenylenediamine to give one of two possible thiazolo[3,4-*a*]quinoxalines containing the pyridyl- or picolylimine substituents at position 1. 3a-Hydroxy-3-phenylimino-1-(2-pyridyl)thiazolo[3,4-*a*]quinoxalin-4-(3*H*,5*H*)-one, which is a covalent hydrate of the final product, was isolated as an intermediate in this reaction.

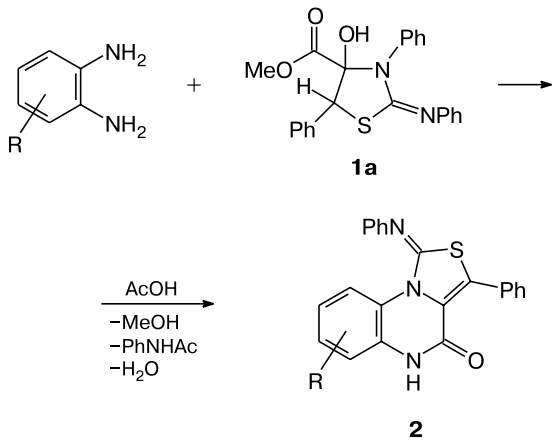
Key words: Hantzsch reaction, 4-hydroxythiazolidines, thiazolo[3,4-*a*]quinoxalines, covalent hydrate, IR spectra, NMR spectra, X-ray diffraction study.

Azolo[*a*]quinoxalines and their 4,5-dihydro derivatives exhibit various biological and pharmacological activities[2—7] and are used in the synthesis of many biologically important compounds and drugs.[8—11] However, unlike the imidazo[1,5-*a*]quinoxaline system, whose synthesis and properties were studied in sufficient detail, the methods for the synthesis of thiazolo[3,4-*a*]quinoxalines, whose first representatives were prepared as late as 1982,[12,13] have received little attention.

Earlier, we have developed a procedure for the synthesis of thiazolo[3,4-*a*]quinoxalines involving the cascade annulation of the thiazolopyrazine system with the benzene moiety by the reaction of the intermediate Hantzsch reaction products, *viz.*, 4-hydroxy-4-methoxycarbonyl-3,5-diphenyl-2-phenyliminothiazolidine **1a** (see Refs 14—19) and its *p*-tolyl, 2-naphthyl, and thiazol-2-yl analogs,[17] with 1,2-phenylenediamines in boiling acetic acid (Scheme 1).

This method is based on the fact that 4-hydroxythiazolidine **1a** exists in solution as an equilibrium mixture[15,19] of two diastereoisomeric forms and their open-chain 1,2-dicarbonyl tautomer, which can react with 1,2-phenylenediamines. It should be noted that ketone carbonyl is present in the protected form (as the geminal hydroxyamino group) in cyclic tautomer **1a** as well. Hence, the latter compound can be considered as the synthetic equivalent of the 1,2-dicarbonyl synthon.

Scheme 1



R = H, Me, NO_2

However, the synthetic potential of 4-hydroxythiazolidines **1** is, on the whole, poorly known.[20,21] In the present study, we examined the possibility of application of this method in the synthesis of thiazolo[3,4-*a*]quinoxalines containing the pyridyl or 3- and 4-picolyl groups, whose presence will allow, if required, the preparation of water-soluble salts of this fused polycyclic heterocycle.

The condensation of chloropyruvate **3** with 3-phenyl-1-(2-pyridyl)thiourea and its picolyl homologs **4b—d** afforded products, which correspond in elemental composition to the expected isomeric 4-hydroxythiazolidines. Unlike 4-hydroxythiazolidine, which we have synthesized

* For Part 16, see Ref. 1.

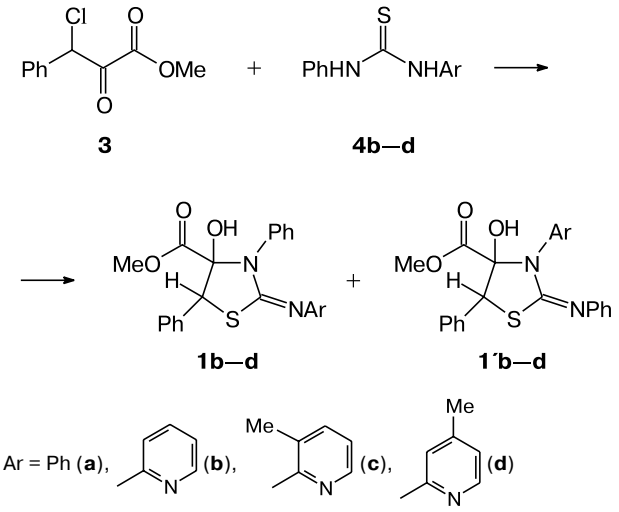
** Dedicated to Academician G. A. Abakumov on the occasion of his 70th birthday.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 11, pp. 2230—2236, November, 2007.

1066-5285/07/5611-2308

earlier from symmetrical *N*,*N*′-diphenylthiourea,[14—19] thiazolidines can be derived as two regioisomeric forms **1b—d** and **1′b—d** from its unsymmetrical pyridyl analogs (Scheme 2).

Scheme 2



According to the ^{1}H NMR and IR spectra of the reaction products, the ratio of the components in these mixtures strongly depends on the conditions, under which the spectra are measured, and on the nature of the substituent Ar, as well as on the conditions of isolation and purification of the products. The detailed discussion of the regio- and diastereomeric compositions of these products is beyond the scope of the present study. However, it should be noted that new peaks appeared in the ^{1}H NMR spectra during the storage of the solutions (Table 1), which is indicative of a gradual complication of the tautomeric composition of these products. In particular, the number of initial singlets for the methoxy and methine protons in the spectra of product **1c+1′c** is doubled with time. For two other products under study, the appearance of multiplets is observed. For solutions of all three products, the sum of the integrated intensities of the peaks for these groups remains equal to 1 : 3 at least, for 1 day, the chemical shifts being also unchanged.

The nature of the tautomerism responsible for the complication of the ^{1}H NMR spectra is, apparently, the same as that of the above-mentioned tautomerism of compound **1a**[15] (Scheme 3).

The spectra can be additionally complicated due to the fact that cyclic tautomers **1b—d** and **1′b—d** exist as two diastereomers, and open-chain tautomer **5** consists of two "subtautomers" resulting from the amidine tautomerism (in the major tautomer, the C=N bond is conjugated with the pyridyl substituent, which is more electron-withdrawing than the phenyl substituent).[22,23]

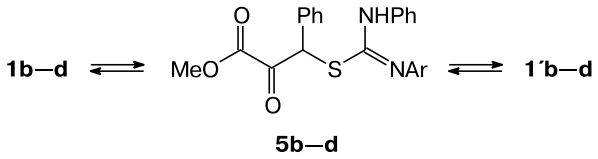
Table 1. Changes with time in the ratio of the isomers* of 4-hydroxythiazolidines in DMSO-d_6 at room temperature

Sample	Isomer	δ_H**		I_{rel} (%)		
		OMe	SC<u>H</u>(Ph)	0	0.5 h	24 h
1b + **1′b** + **5b**	*1*	3.17	5.02	0	2	5
	2	3.18	5.05	0	0	4
	3	3.19	5.00	0	3	22
	4	3.58	5.38	100	84	54
	5	3.60	5.20	0	4	8
	6	3.61	5.46	0	7	7
1c + **1′c** + **5c**	*1*	3.15	4.97	0	5	27
	2	3.56	5.30	100	95	73
1d + **1′d** + **5d**	*1*	3.14	4.99	0	7	5
	2	3.17	4.97	0	6	22
	3	3.58	5.31	100	74	64
	4	3.59	5.18	0	13	9

* Calculated by averaging the relative integrated intensities of the methoxy and methine protons.

** The chemical shifts remain unchanged during the measurements.

Scheme 3

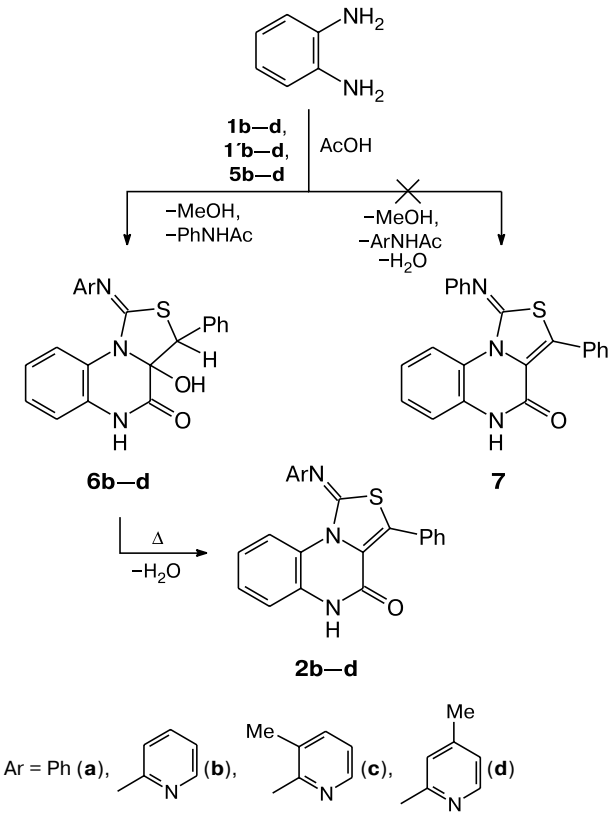


The IR spectra of crystalline samples of the reaction products have many features in common with the IR spectrum of a crystalline sample of cyclic thiazolidine **1a**, which has been comprehensively studied.[15] These spectra do not contain absorption bands at 3400 cm^{-1} characteristic of ν_{N-H} vibrations, which should be present in the IR spectra of the open-chain isothioureide structures.[15] At the same time, these spectra show broad absorption bands at 3452 cm^{-1} (**1b**), 3440 cm^{-1} (**1c**), and 3448 cm^{-1} (**1d**), which can be assigned to ν_{O-H} vibrations of the hydroxy groups of 4-hydroxythiazolidines **1** and/or **1′**. Therefore, like the reaction of chloropyruvate **3** with *N*,*N*′-diphenylthiourea described earlier,[15] the reactions with *N*-phenyl-*N*-pyridylthioureas **4b—d** also produce compounds having the cyclic structure (4-hydroxythiazolidines) in the crystalline phase as the final products.

The condensation of pyridyl-containing thiazolidines **1b—d** + **1′b—d** with *o*-phenylenediamine, like that of diphenylthiazolidine **1a**, affords the expected thiazolo[3,4-*a*]quinoxalinones **2b—d**. However, unlike thiazolidines prepared from other unsymmetrical *N*,*N*′-disubstituted thioureas, which give mixtures of isomeric thiazolo[3,4-*a*]quinoxalines in the reactions with *o*-phenylenediamine,[18,19] the compounds under study give ex-

clusively quinoxalines **2b—d** (rather than mixtures) containing the pyridylimine groups at position 1, *i.e.*, the condensation is accompanied by elimination of aniline but not of 2-aminopyridine or 2-aminopicolins. Therefore, we solved the problem of the synthesis of thiazolo[3,4-*a*]quinoxalines containing the pyridyl or picolyl groups (Scheme 4).

Scheme 4



Unlike the reaction of thiazolidine **1a** with *ortho*-phenylenediamine yielding the final product in 3—5 min, the reactions of pyridyl-containing thiazolidines **1b—d** with *ortho*-phenylenediamine are completed in ~1 h under analogous conditions. Slower rates of the reactions under consideration allow the isolation of intermediate products. The formation of a crystalline precipitate different from the final product is observed 5 min after the beginning of refluxing. Using the reaction of thiazolidine **1b** as an example, we demonstrated that this compound is a covalent hydrate (compound **6b**) of the final thiazolo[3,4-*a*]quinoxaline **2b**. The structure of compound **6b** was established by spectroscopic methods and X-ray diffraction.

Molecule **6b** occupies a general position in the tetragonal unit cell (Fig. 1). The crystal structure includes a DMSO molecule. In the crystal, the solvent molecule is

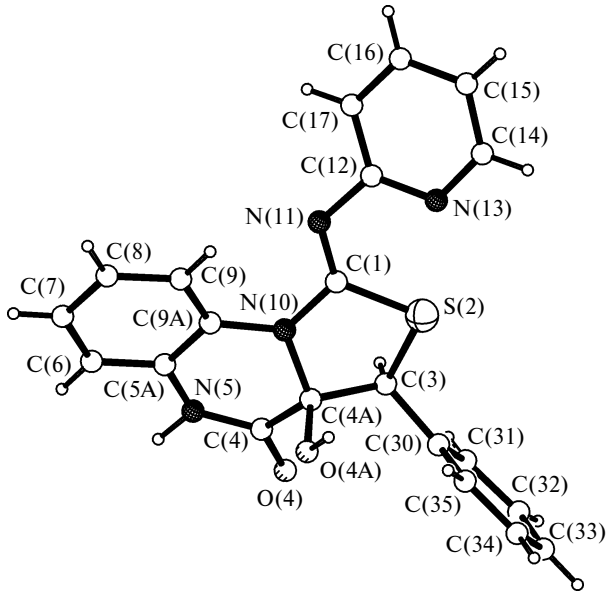


Fig. 1. Molecular geometry of compound **6b** in the crystal structure. The DMSO solvent molecule is omitted.

disordered over two positions with occupancies of 0.53 and 0.47. The molecule of compound **6b** is chiral, and compound **6b** crystallizes in the noncentrosymmetric space group $P2_12_12_1$. However, the refinement of the experimental data showed that the structure is a racemic twin with a ratio of 0.55 : 0.45. This did not allow us to determine the absolute configurations at the chiral carbon atoms. The relative configurations at the C(3) and C(4a) atoms are *S* and *R*, respectively. The phenylimine group has a *Z* configuration.

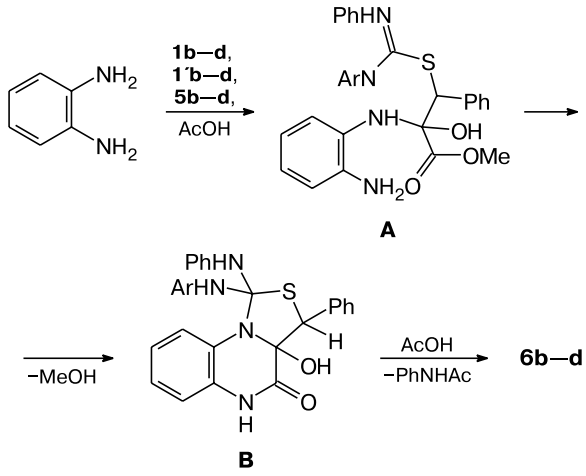
The presence of sp^3-hybridized carbon atoms in the tricyclic moiety of compound **6b** is responsible for the nonplanarity of this fragment and hinders the formation of π—π interactions characteristic of the crystal packing of the thiazolo[3,4-*a*]quinoxaline systems.[17,19] At the same time, the presence of the DMSO solvent molecule in the crystal hinders the formation of hydrogen-bonded dimers through N—H...O pairwise interactions characteristic of such compounds. This phenomenon has been discussed in detail in our earlier study.[24] In the case under consideration, hydrogen-bonded chains are formed along the crystallographic 0*a* axis *via* O—H...O hydrogen bonds; N—H...O interactions are observed between the carbamoyl group and the oxygen atom of the DMSO molecule.

Upon further heating in acetic acid, covalent hydrate **6b** loses the water molecule and is transformed into thiazolo[3,4-*a*]quinoxaline **2b** in virtually quantitative yield.

The isolation of intermediate covalent hydrate **6b** of the final product, thiazolo[3,4-*a*]quinoxaline **2b**, allows the refinement of the mechanisms of formation of thiazolo[3,4-*a*]quinoxalines **2** in the reactions under consider-

ation (Scheme 5). These mechanisms have been discussed in our earlier studies.[17,19]

Scheme 5

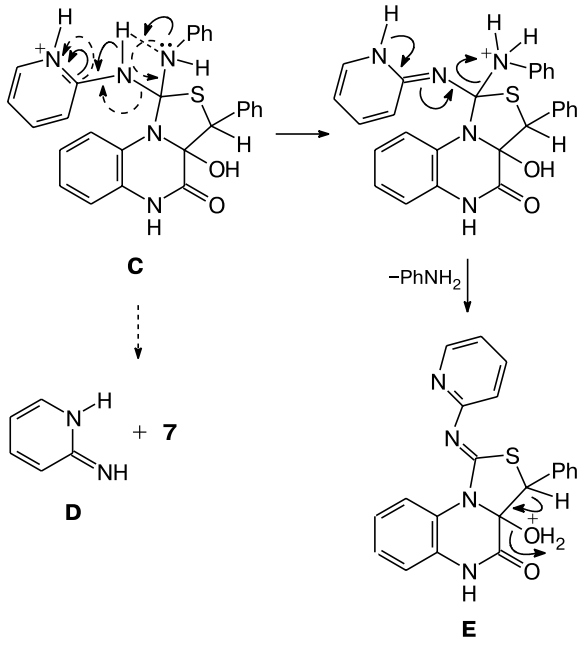


Apparently, the product **A**, which is generated in the first step as a result of the reaction of open-chain ketone **5** and/or its protected cyclic forms **1** or **1´** with *ortho*-phenylenediamine, undergoes intramolecular amidation followed by the addition of the amino group of the aminal system at the amidine carbon atom to give the thiazolo[3,4-*a*]quinoxaline system **B** containing the geminal phenylamino and pyridylamino substituents at position 1. The subsequent acid-catalyzed elimination of aniline (isolated as acetanilide) from the intermediate **B** affords covalent hydrates **6b—d**, whose dehydration under the reaction conditions gives the final products **2b—d**.

The explanation of the formation of only one of two possible isomers of thiazolo[3,4-*a*]quinoxalines containing exclusively the pyridylimine group at position 1 presents another problem. Evidently, this is due to the competitive elimination of the geminal arylamino substituents in the intermediate **B**. Since the reaction is performed in an acidic medium, the higher basicity of the pyridylamino group compared to the phenylamino group (pK_a of 2-aminopyridine and aniline are 7.2 (see Ref. 25) and 4.6 (see Ref. 26), respectively) should lead to the predominant protonation of the aminopyridine moiety and elimination of aminopyridine giving rise to compound **7**. However, this is not the case. The reaction is accompanied by elimination of the phenylamino fragment and gives compound **2**. There are at least two, apparently parallel, factors responsible for this result. These factors are associated with the intramolecular proton or acetyl transfer from the pyridine to phenylamino nitrogen atom.

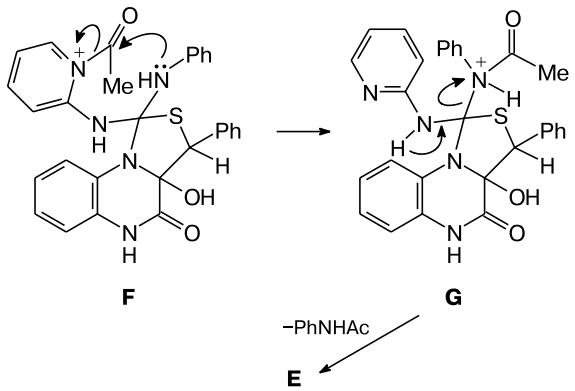
One factor is that aminopyridine can be eliminated from the intermediate **C** (the form of the structure **B** protonated at the pyridine nitrogen atom) only as the tautomer **D** destabilized by the loss of aromaticity,[27] this process being unlikely. The elimination of aniline giving rise to the compound **E**, which is the protonated form of compound **6**, is a more probable process (Scheme 6).

Scheme 6



Another factor is that the preliminary acetylation of the intermediate **B** at the pyridine nitrogen atom with acetic acid affords the intermediate **F**, in which the intramolecular transfer of the acetyl group to the phenylamino nitrogen atom occurs (the intramolecular catalysis of acetylation of amines with pyridine facilitated by the spatial proximity of the pyridine and aniline nitrogen atoms). This gives rise to the intermediate **G**, from which acetanilide is easily eliminated to form the above-considered intermediate **E** (Scheme 7).

Scheme 7



Experimental

The ^{1}H NMR spectra were recorded on a Bruker AVANCE-600 spectrometer (600.00 MHz) in DMSO-d_6. The chemical shifts are given on the δ scale. The IR spectra were measured on a Bruker Vector-22 Fourier-transform spectrometer in KBr pellets. The melting points were determined on a Boetius hot-stage apparatus. Methyl phenylchloropyruvate **3** (see Ref. 28), 1-(2-pyridyl)-3-phenylthiourea, and its picolyl homologs **4b—d** (see Ref. 29) were synthesized according to known procedures.

***N´*-Phenyl-*N*-(2-pyridyl)thiourea (4b).** Phenyl isothiocyanate (6 g, 0.0444 mol) was added to a solution of 2-aminopyridine (4 g, 0.0426 mol) in toluene (50 mL). The reaction mixture was refluxed for 5 h. The white crystals that precipitated were filtered off. The yield was 8.3 g (97%), m.p. 172 °C (*cf.* lit. data[29]: 171—172 °C). IR, ν/cm^{-1}: 3219—2853 (NH); 1598, 1555, 1532, 1495, 1437, 1428. ^{1}H NMR, δ: 7.11 (dd, 1 H, H(5), J = 6.70 Hz, J = 5.20 Hz); 7.21 (dd, 1 H, *p*-H_{Ph}, J = 7.84 Hz, J = 7.45 Hz); 7.23 (d, 1 H, H(3), J = 8.50 Hz); 7.39 (dd, 2 H, 2 *m*-H_{Ph}, J = 7.84 Hz, J = 7.45 Hz); 7.70 (dd, 2 H, 2 *o*-H_{Ph}, J = 7.84 Hz); 7.84 (ddd, 1 H, H(4), J = 8.50 Hz, J = 6.70 Hz, J = 1.40 Hz); 8.31 (d, 1 H, H(6), J = 5.20 Hz); 10.87 (s, 2 H, 2 NH).

***N*-(3-Methyl-2-pyridyl)-*N´*-phenylthiourea (4c).** Compound **4c** was synthesized as described above starting from 2-amino-3-methylpyridine. The yield was 67%, m.p. 130—135 °C (from EtOH) (*cf.* lit. data[30]: 123—124 °C). Found (%): C, 64.17; H, 5.39; N, 17.27; S, 13.18. $C_{13}H_{13}N_3S$. Calculated (%): C, 64.18; H, 5.33; N, 17.32; S, 13.15. IR, ν/cm^{-1}: 3399—2854 (NH); 1631, 1595, 1573, 1516, 1500, 1468, 1453, 1417. ^{1}H NMR, δ: 2.37 (s, 3 H, Me); 7.11 (dd, 1 H, H(5), J = 7.20 Hz, J = 4.60 Hz); 7.22 (dd, 1 H, *p*-H_{Ph}, J = 7.34 Hz, J = 7.33 Hz); 7.39 (dd, 2 H, 2 *m*-H_{Ph}, J = 7.58 Hz, J = 8.07 Hz); 7.68 (d, 2 H, 2 *o*-H_{Ph}, J = 7.58); 7.73 (d, 1 H, H(4), J = 7.20 Hz); 8.23 (d, 1 H, H(6), J = 4.60 Hz), 9.75 (s, 2 H, 2 NH).

***N´*-(4-Methyl-2-pyridyl)-*N´*-phenylthiourea (4d).** Compound **4d** was synthesized as described above starting from 2-amino-4-methylpyridine. The yield was 79%, m.p. 156—157 °C (from EtOH) (*cf.* lit. data[30]: 161.5—162.5 °C). Found (%): C, 64.17; H, 5.39; N, 17.27; S, 13.18. $C_{13}H_{13}N_3S$. Calculated (%): C, 64.15; H, 5.34; N, 17.30; S, 13.16. IR, ν/cm^{-1}: 3218—2854 (NH); 1615, 1597, 1562, 1531, 1500, 1483, 1447, 1404. ^{1}H NMR, δ: 2.31 (s, 3 H, Me); 6.95 (d, 1 H, H(5), J = 5.00 Hz); 7.08 (s, 1 H, H(3); 7.21 (dd, 1 H, *p*-H_{Ph}, J = 7.58 Hz, J = 7.34 Hz); 7.39 (dd, 2 H, 2 *m*-H_{Ph}, J = 7.58 Hz, J = 8.07 Hz); 7.69 (d, 2 H, 2 *o*-H_{Ph}, J = 7.58 Hz); 8.18 (d, 1 H, H(6), J = 5.00 Hz); 10.77 (s, 2 H, 2 NH).

4-Hydroxy-4-methoxycarbonyl-3,5-diphenyl-2-(2-pyridylimino)thiazolidine (1b) and **4-hydroxy-4-methoxycarbonyl-5-phenyl-2-phenylimino-3-(2-pyridyl)thiazolidine (1´b).** Sodium acetate (3.6 g, 0.0438 mol) was added to a solution of *N´*-phenyl-*N´*-(2-pyridyl)thiourea **4b** (4 g, 0.0175 mol) in CH_2Cl_2 (150 mL). The reaction mixture was cooled to a temperature from −15 to −20 °C, and a solution of methyl phenylchloropyruvate (3.7 g, 0.0175 mol) in CH_2Cl_2 (20 mL) was added dropwise. The reaction mixture was stirred at ~20 °C for 5 h and poured into water. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (2×20 mL). The organic layer and the extract were combined and dried with $MgSO_4$, the solvent was evaporated, and the residue was treated with Pr^{i}OH. A mixture of (**1b+1´b**) was obtained in a yield of 3.4 g (50%). M.p. 137—139 °C (Pr^{i}OH). Found (%): C, 64.72; H, 4.26; N, 9.90; S, 8.38. $C_{22}H_{19}N_3O_3S$. Calculated (%): C, 65.17; H, 4.72; N, 10.36; S, 7.91. IR, ν/cm^{-1}: 3452 (OH); 3059—2853, 1738 (C=O); 1629 (C=N). ^{1}H NMR, δ: 3.17, 3.18, 3.19, 3.58, 3.60, and 3.61 (all s, 3 H, OMe); 5.00, 5.02, 5.06, 5.20, 5.33, and 5.46 (all s, 1 H, CH); 6.63—8.51 (m, 15 H, 2 Ph, H(2)—H(5) pyridine, OH).

4-Hydroxy-4-methoxycarbonyl-2-(3-methyl-2-pyridylimino)-3,5-diphenylthiazolidine (1c) and 4-hydroxy-4-methoxycarbonyl-3-(3-methyl-2-pyridyl)-5-phenyl-2-phenyliminothiazolidine (1´c). Compound **1´c** was synthesized as described above starting from *N*-(3-methyl-2-pyridyl)-*N´*-phenylthiourea **4c**. The yield was 46%, m.p. 130—134 °C (Pr^{i}OH). Found (%): C, 65.55; H, 4.91; N, 9.76; S, 7.38. $C_{23}H_{21}N_3O_3S$. Calculated (%): C, 65.85; H, 5.05; N, 10.02; 11.44; S, 7.64. IR, ν/cm^{-1}: 3440 (OH); 3055—2853 (NH); 1757 (C=O); 1731 (C=O); 1623 (C=N). ^{1}H NMR, δ: 2.00 (s, 6 H, 2 Me); 3.15 and 3.56 (both s, 3 H, OMe); 4.97 and 5.30 (both s, 1 H, CH); 6.90—8.15 (m, 14 H, 2 Ph, H(2)—H(4) pyridine, OH).

4-Hydroxy-4-methoxycarbonyl-2-(4-methyl-2-pyridylimino)-3,5-diphenylthiazolidine (1d) and 4-hydroxy-4-methoxycarbonyl-3-(4-methyl-2-pyridyl)-5-phenyl-2-phenyliminothiazolidine (1´d). Compound **1´d** was synthesized as described above starting from *N*-(4-methyl-2-pyridyl)-*N´*-phenylthiourea **4d**. The yield was 67%, m.p. 143—145 °C (Pr^{i}OH). Found (%): C, 65.50; H, 4.88; N, 9.87; S, 7.29. $C_{23}H_{21}N_3O_3S$. Calculated (%): C, 65.85; H, 5.05; N, 10.02; 11.44; S, 7.64. IR, ν/cm^{-1}: 3448 (OH); 3214—2951 (NH); 1748 (C=O); 1613 (C=N). ^{1}H NMR, δ: 2.21, 2.22, 2.31, and 2.34 (all s, 3 H, Me); 3.14, 3.17, 3.57, and 3.58 (all s, 3 H, OMe); 4.97, 4.99, 5.18, and 5.31 (all s, 1 H each, CH); 6.63—8.18 (m, 14 H, 2 Ph, H(2), H(3), H(5) pyridine, OH).

3-Phenyl-1-(2-pyridylimino)thiazolo[3,4-*a*]quinoxalin-4-(5*H*)-one (2b). A solution of *o*-phenylenediamine (0.53 g, 4.90 mmol) and 4-hydroxythiazolidine (**1b+1´b**) (2 g, 4.90 mmol) in AcOH (50 mL) was refluxed for 1 h. The pale-yellow crystals that precipitated were filtered off. Analytically pure compound **2b** was obtained in a yield of 1.39 g (77%). M.p. > 300 °C. Found (%): C, 67.79; H, 3.66; N, 15.01; S, 8.35. $C_{21}H_{14}N_4OS$. Calculated (%): C, 68.09; H, 3.81; N, 15.12; S, 8.65. IR, ν/cm^{-1}: 3185—2857 (NH); 1679 (C=O); 1607 (C=N); 1586, 1564, 1532, 1489, 1462, 1430, 1404. ^{1}H NMR, δ: 7.08 (ddd, 1 H, H(5) pyridine, J = 7.10 Hz, J = 4.80 Hz, J = 0.78 Hz); 7.19 (dd, 1 H, H(6), J = 7.50 Hz, J = 1.60 Hz); 7.22 (ddd, 1 H, H(8), J = 8.40 Hz, J = 7.50 Hz, J = 1.60 Hz); 7.27 (ddd, 1 H, H(7), J = 7.60 Hz, J = 7.60 Hz, J = 1.30 Hz); 7.34 (d, 1 H, H(3) pyridine, J = 8.10 Hz); 7.41—7.43 (m, 3 H, phenyl); 7.55—7.57 (m, 2 H, phenyl); 7.82 (ddd, 1 H, H(4) pyridine, J = 8.10 Hz, J = 7.60 Hz, J = 1.96 Hz); 8.49 (dd, 1 H, H(6) pyridine, J = 4.96 Hz, J = 1.00 Hz); 10.00 (d, 1 H, (H9), J = 8.40 Hz); 11.27 (s, 1 H, NH). The filtrate was treated with a 5% $NaHCO_3$ solution. The precipitate that formed was filtered off, washed with water, dried in air, and recrystallized from DMSO. Compound **2b** was additionally obtained in a yield of 0.08 g (4%). The aqueous layer was extracted with ethyl acetate (3×20 mL). Ethyl acetate was evaporated, the residue was treated with diethyl ether, and the orange precipitate was filtered off. Acetanilide was obtained in a yield of 0.10 g, m.p. 110—113 °C. IR, ν/cm^{-1}: 3292—2853 (NH); 1664 (C=O); 1619, 1599, 1556. ^{1}H NMR, δ: 2.03 (s, 3 H, COMe); 7.21 (dd, 1 H, *p*-H_{Ph}, J = 7.80 Hz, J = 7.32 Hz); 7.27 (dd, 2 H, 2 *m*-H_{Ph}, J = 7.80 Hz,

J = 7.32 Hz); 7.56 (d, 2 H, 2 o-H_{Ph}, J = 7.80 Hz); 9.88 (s, 1 H, NH).

1-(3-Methyl-2-pyridyl)imino-3-phenylthiazolo[3,4-*a*]quinoxalin-4-(5*H*)-one (2c). Compound **2c** was synthesized as described above starting from 4-hydroxythiazolidine **1c**. The yield was 80%, m.p. > 300 °C. Found (%): C, 68.39; H, 4.04; N, 14.45; S, 8.24. $C_{22}H_{16}N_4OS$. Calculated (%): C, 68.73; H, 4.19; N, 14.57; S, 8.34. IR, ν/cm^{-1}: 3185—2853 (NH); 1681 (C=O); 1606 (C=N); 1573, 1532, 1488, 1463, 1447, 1436, 1418. ^{1}H NMR, δ: 2.48 (s, 3 H, Me); 7.01 (dd, 1 H, H(5) pyridine, J = 7.20 Hz, J = 4.80 Hz); 7.21 (dd, 1 H, H(6), J = 7.60 Hz, J = 1.60 Hz); 7.23 (ddd, 1 H, H(8), J = 8.70 Hz, J = 7.30 Hz, J = 1.80 Hz); 7.28 (ddd, 1 H, H(7), J = 7.60 Hz, J = 7.30 Hz, J = 1.30 Hz); 7.42—7.45 (m, 3 H, phenyl); 7.55—7.57 (m, 2 H, phenyl); 7.70 (d, 1 H, H(4) pyridine, J = 7.20 Hz); 8.34 (d, 1 H, H(6) pyridine, J = 4.80 Hz); 10.01 (d, 1 H, H(9), J = 8.60 Hz); 11.28 (s, 1 H, NH).

1-(4-Methyl-2-pyridyl)imino-3-phenylthiazolo[3,4-*a*]-quinoxalin-4-(5*H*)-one (2d). Compound **2d** was synthesized as described above starting from 4-hydroxythiazolidine **1d**. The yield was 83%, m.p. > 300 °C. Found (%): C, 68.48; H, 4.07; N, 14.37; S, 8.19. $C_{22}H_{16}N_4OS$. Calculated (%): C, 68.73; H, 4.19; N, 14.57; S, 8.34. IR, ν/cm^{-1}: 3185—2764 (NH); 1682 (C=O); 1623 (C=N); 1605, 1589, 1559, 1521, 1496. ^{1}H NMR, δ: 2.37 (s, 3 H, Me); 6.92 (d, H(5) pyridine, J = 4.70 Hz); 7.18 (s, 1 H, H(3) pyridine); 7.19 (dd, 1 H, H(6), J = 7.30 Hz, J = 1.60 Hz); 7.21 (ddd, 1 H, H(8), J = 8.40 Hz, J = 7.30 Hz, J = 1.60 Hz); 7.27 (ddd, 1 H, H(7), J = 7.30 Hz, J = 7.30 Hz, J = 1.60 Hz); 7.41—7.45 (m, 3 H, phenyl); 7.54—7.56 (m, 2 H, phenyl); 8.33 (d, 1 H, H(6) pyridine, J = 5.20 Hz); 9.99 (d, 1 H, H(9), J = 8.40 Hz); 11.24 (s, 1 H, NH).

3-Phenyl-1-(2-pyridyl)imino-3a-hydroxythiazolo[3,4-*a*]quinoxalin-4-(3*H*,5*H*)-one (6b). A solution of o-phenylenediamine (0.2 g, 1.90 mmol) and 4-hydroxythiazolidine **1b** (0.75 g, 1.85 mmol) in AcOH (10 mL) was refluxed for 5 min. Pale-yellow crystals that precipitated were filtered off. Analytically pure compound **6b** was obtained in a yield of 0.35 g (50%), m.p. > 300 °C. $C_{21}H_{16}N_4O_2S$. IR, ν/cm^{-1}: 3273—3055 (NH, OH); 1696 (C=O); 1621 (C=N); 1574, 1541, 1496. ^{1}H NMR, δ: 5.31 (s, 1 H, CH); 7.02 (d, 1 H, H(6), J = 8.10 Hz); 7.05—7.74 (m, 12 H, Ph, H(7), H(8), H(3)—H(6) pyridine, OH); 8.52 (d, 1 H, H(9), J = 8.10 Hz); 10.91 (s, 1 H, NH). Compound **6b** (100 mg) was refluxed in AcOH (1 mL) for 50 min. The crystals that precipitated were filtered off. Compound **2b** was obtained in a yield of 90 mg (94%); this compound was identical in all parameters to the sample prepared directly from 4-hydroxythiazolidine **1b** and o-phenylenediamine (see above).

X-ray diffraction study of compound 6b was carried out on an automated four-circle Enraf-Nonius CAD-4 diffractometer. The crystals of $C_{21}H_{16}N_4O_2S \cdot C_2H_6OS$, rhombic, at 20 °C a = 5.590(1), b = 11.526(3), c = 34.806(7) Å, V = 2242.6(8) Å^3, mol. weight = 466.57, d_{calc} = 1.38 g cm^{-3}, Z = 4, space group $P2_12_12_1$. The unit cell parameters and the intensities of 2688 reflections, of which 2286 reflections were with $I > 2\sigma$, were measured at 20 °C (graphite monochromator, λCu-Kα, ω scanning technique, $\theta \leq 74.23°$). The intensities of three check reflections showed no decrease in the course of X-ray data collection. The absorption correction was applied (μ(Cu-Kα) = 24.3 cm^{-1}). The X-ray data were processed with the use of the MolEN program.[31] The structure was solved by direct methods with the use of the SIR program[32] and refined first isotropically and then anisotropically using the SHELXL-97[33] and WinGX[34] program packages. The coordinates of the hydrogen atoms of the hydroxy and amino groups were located in difference electron density maps and refined isotropically. The coordinates of other hydrogen atoms were calculated based on the stereochemical criteria and refined using a riding model. The DMSO molecule is disordered over two positions with occupancies of 0.53 and 0.47. The crystal structure of compound **6b** is a racemic twin with a ratio of 0.55 : 0.45. The final R factors were R = 0.0551 and R_w = 0.1403 based on 2286 reflections with $F \geq 2\sigma$. The figure was drawn with the use of the PLATON program.[35] The atomic coordinates and displacement parameters for compound **6b** were deposited with the Cambridge Structural Database (CCDC 640124).

This study was financially supported by the Russian Foundation for Basic Research (Project Nos 07-03-00613-a and 05-03-33008-a).

References

1. V. A. Mamedov, D. F. Saifina, E. A. Berdnikov, and I. Kh. Rizvanov, *Izv. Akad. Nauk, Ser. Khim.*, 2007, 2055 [*Russ. Chem. Bull., Int. Ed.*, 2007, **56**, No. 10].
2. J.-C. Lancelot, H. Prunier, M. Robba, P. Delagrange, P. Renard, and G. Adam, *Eur. Pat. Appl. EP* 623620 (1994); *Chem. Abstrs*, 1995, **122**, 105922t.
3. A. Noda, H. Noda, T. Imamura, Y. Ono, M. Morita, M. Kai, S. Mine, and S. Goto, *Yakugaku Zasshi*, 1991, **111**, 499; *Chem. Abstrs*, 1992, **116**, 33929b.
4. K. Reddy and C. Rebeiz, *ACS Symp. Ser.*, 1994, 161; *Chem. Abstrs*, 1994, **121**, 101899x.
5. I. Maeba, K. Kitaori, Y. Itaya, and C. Ito, *J. Chem. Soc., Perkin Trans 2*, 1990, **1**, 67.
6. A. Barnes and D. Rowlands, *Ger. Offen.*, 1980, **3**, 750; *Chem. Abstrs*, 1981, **94**, 84164h.
7. R. Neale, S. Fallon, W. Boyar, J. Wasley, L. Martin, G. Stone, B. Glaeser, C. Sinton, and M. Williams, *Eur. J. Pharmacol.*, 1987, **136**, 1.
8. J. Ohmori, M. Shimizu-Sasamata, M. Okada, and S. Sakamoto, *J. Med. Chem.*, 1997, **40**, 2053.
9. R. E. TenBrink, E. J. Jacobsen, and R. B. Gammill, US Pat. 5541324 (1996); *Chem. Abstrs*, 1996, **125**, 195687.
10. H. C. Hansen and F. Watjen, Eur. Pat. Appl. EP 344943 (1989); *Chem. Abstrs*, 1990, **112**, 216962.
11. T. D. Lee and R. E. Brown, US Pat. 4440929 (1984); *Chem. Abstrs*, 1984, **101**, 7202.
12. E. A. Adegoke, A. Babajide, and F. O. Ogunsulire, *J. Heterocycl. Chem.*, 1982, **19**, 1169.
13. E. A. Adegoke and A. Babajide, *J. Heterocycl. Chem.*, 1982, **20**, 1513.
14. V. A. Mamedov and Ya. A. Levin, *Khim. Geterotsikl. Soedin.*, 1996, 1005 [*Chem. Heterocycl. Compd.*, 1996 (Engl. Transl.)].
15. V. A. Mamedov, I. Z. Nurkhametova, R. R. Shagidullin, A. V. Chernova, and Ya. A. Levin, *Khim. Geterotsikl. Soedin.*, 1999, 975 [*Chem. Heterocycl. Compd.*, 1999 (Engl. Transl.)].
16. V. A. Mamedov, I. Z. Nurkhametova, I. Kh. Rizvanov, Yu. Ya. Efremov, and Ya. A. Levin, *Khim. Geterotsikl. Soedin.*, 1999, 1561 [*Chem. Heterocycl. Compd.*, 1999 (Engl. Transl.)].

17. V. A. Mamedov, A. A. Kalinin, A. T. Gubaidullin, I. Z. Nurkhametova, I. A. Litvinov, and Ya. A. Levin, *Khim. Geterotsikl. Soedin.*, 1999, 1664 [*Chem. Heterocycl. Compd.*, 1999 (Engl. Transl.)].
18. V. A. Mamedov, I. Z. Nurkhametova, A. T. Gubaidullin, I. A. Litvinov, and S. Tsuboi, *Heterocycles*, 2004, **63**, 1783.
19. V. A. Mamedov, I. Z. Nurkhametova, S. K. Kotovskaya, A. T. Gubaidullin, Ya. A. Levin, I. A. Litvinov, and V. N. Charushin, *Izv. Akad. Nauk, Ser. Khim.*, 2004, 2462 [*Russ. Chem. Bull., Int. Ed.*, 2004, **53**, 2568].
20. J. V. Metzger, in *Thiazoles and Their Benzo Derivatives in Comprehensive Heterocyclic Chemistry*, Eds A. R. Katritzky and C. W. Rees, Pergamon Press, 1984, Vol. **6**, Chapter 4.19.
21. K. Tanaka, K. Nomura, H. Oda, S. Yoshida, and K. Mitsuhashi, *J. Heterocycl. Chem.*, 1991, 28, 907.
22. P. Jakobsen and S. Treppendahl, *Tetrahedron*, 1977, **33**, 3137.
23. V. G. Granik, *Usp. Khim.*, 1983, **52**, 669 [*Russ. Chem. Rev.*, 1983, **52** (Engl. Transl.)].
24. A. T. Gubaidullin, V. A. Mamedov, and I. A. Litvinov, *Arkivok*, 2004, Part 12, 80.
25. J. A. Joule and K. Mills, *Heterocyclic Chemistry, 4th ed.*, Oxford, Blackwell Science, 2000, p. 92.
26. A. Gordon and R. Ford, *Chemist's Companion*, Wiley-Interscience Publication, New York—London—Sydney—Toronto, 1972.
27. *The Tautomerism of Heterocycles*, J. Marzin Elguero, A. R. Katritzky, and P. Linda, *Adv. Heterocycl. Chem.*, Supplement 1, 1976.
28. V. A. Mamedov and I. A. Nuretdinov, *Izv. Akad. Nauk, Ser. Khim.*, 1992, 2159 [*Bull. Russ. Acad. Sci., Div. Chem. Sci.*, 1992, **41**, 1690 (Engl. Transl.)].
29. E. G. Novikov, K. D. Shvetsova-Shilovskaya, and N. N. Men´shikov, in *Khimiya geterotsiklicheskikh soedinenii* [*Chemistry of Heterocyclic Compounds*], Riga, 1967, **1**, 232—233 (in Russian).
30. Bulgarian Inventor's Certificate, S07 S 157/02, A 01 No. B/00, No. 25136; *RZhKhim*, 1979, 18O426P (in Russian).
31. L. H. Straver and A. J. Schierbeek, *MOLEN. Structure Determination System. Program Description*, Nonius B.V., 1994, **1**, 180.
32. A. Altomare, G. Cascarano, and C. Giacovazzo, *Acta Crystal. (A)*, 1991, **47**, 744.
33. G. M. Sheldrick, *SHELX-97, Release 97-2*, University of Göttingen, Göttingen, 1997.
34. L. J. Farrugia, *J. Appl. Crystal.*, 1999, **32**, 837.
35. A. L. Spek, *Acta Crystal. (A)*, 1990, **46**, 34.

Received June 14, 2007;
in revised form October 23, 2007