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SPECTROSCOPIC STUDY OF THE KETO-ENOL EQUILIBRIUM OF N-ARYLDIACETYLTHIO-ACETAMIDES AND THEIR REACTIVITY

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An NMR study of the equilibrium between keto-enol tautomeric forms of N-aryl- diacetylthioacetamides enables us to estimate their population ratio in solvents of increasing polarity. An X-ray analysis confirmed the structure of the thermodynamically most stable tautomer. We presume that the course of heterocyclization processes with N-aryldiacetylthioacetamides is affected by the structure of the reacting tautomeric form. The treatment of N-aryldiacetylthioacetamides with oxalyl or bromoacetyl bromides leads to thiazolidine derivatives. The reactivity of the 5-methylene group in the obtained thiazolidin-4-one derivatives was investigated.

Keywords: anilide of 3-oxoalkanethioic acids, N-aryldiacetylthioacetamide, keto-enol equilibrium, thiazolidin-4-one.

Recently it has been shown that anilides of 3-oxoalkanethioic acids are of particular interest due to their capacity to react in different ways, depending on reagents and reaction conditions, both with dielectrophiles or dinucleophiles, usually leading to heterocyclic compounds [1].

Modification of 3-oxoalkanethioic acid anilide in position 2 leads to novel interesting building blocks. Due to this exceptionally polyfunctional reactivity such anilides have a wide synthetic potential [2–6]. Our continual interest on this area encouraged us to undertake a study of the structure and reactivity of N-aryldiacetylthioacetamides **1**. Although keto-enol equilibrium of the derivatives of 3-oxoalkanethioic acid amides has been studied [7], a spectroscopic study concerning equilibrium of the tautomeric forms of 2-substituted acid amides such as N-aryldiacetylthioacetamides **1** has not been described yet.

The introduction of an acetyl group at position 2 of N-arylacetylthioacetamide creates β,β'-dioxo-(thioxo)system involving a ready movement of the CH proton along the intramolecular hydrogen bonds (Scheme 1).

A perspective view of the molecule of compound **1a** with the crystallographic atom numbering scheme is shown in Fig. 1.

The ^{1}H NMR spectra of compound **1a** recorded in a polar solvent such as DMSO-d_6 indicated the presence of a signal of one OH group at 16.3 ppm, characteristic of the enol form **A**, NH amide proton at 12.00 ppm, and one signal of two equivalent CH_3 groups at 2.2 ppm (6H).

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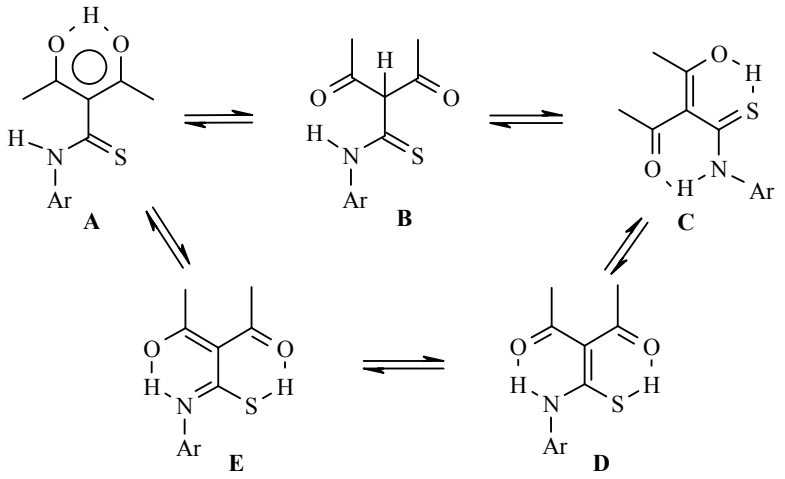
The ^{13}C NMR spectra of compound **1a** clearly confirm the presence of only one form **A** with characteristic signals of the C=S group carbon atom at 189.05 ppm and C=O carbon atoms in acetyl groups at 194.9 ppm; the sp^3 carbons of CH_3 groups appear as one signal at 23.3 ppm.

Scheme 1



The ^1H and ^{13}C NMR spectra of compound **1a** indicated that the enol **A** is the dominating form in polar solvents such as DMSO-d_6. Compounds **1** enolize to form a stable intramolecular hydrogen bond between two oxygen atoms of acetyl groups (Scheme 1).

All ^1H and ^{13}C NMR spectra of compound **1a** recorded in solvents of lower polarity (chloroform, benzene) show the presence of keto form **B** and other forms **C**, **D**, and **E** as well as enol form **A**. The relative populations of tautomers **B** and **C–E** in solvents of different polarity was deduced from the signals of OH, NH, CH_3 groups in the ^1H NMR spectra (Table).

The presence of keto form **B** in nonpolar solvent is demonstrated by a characteristic sp^3 carbon shift at 80 ppm in the ^{13}C NMR spectrum. This is confirmed by the singlet of CH (1H) at 5.7 ppm in the ^1H NMR spectrum and the singlet of NH amide proton at 10.9 ppm as well as of CH_3 groups at 2.44 ppm (6H).

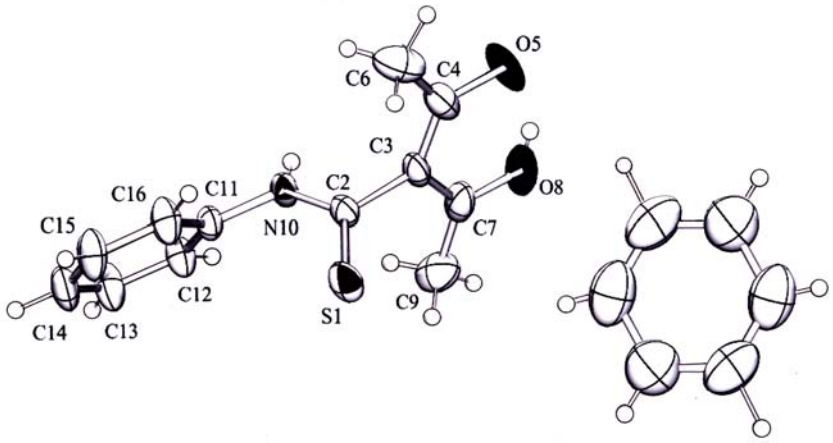


Fig. 1.

TABLE. Diagnostic chemical shifts of tautomeric forms **A–E** of compound **1a** in solvents of various polarity and their relative population

Solvent	ε	Form	%	δ, ppm			
				OH	NH	CH_3	CN
$CDCl_3$	4.81	**A**	66	16.3	8.9	2.2	—
C_6D_6	2.28	**A**	66.5	16.7	8.5	1.9	—
DMSO-d_6	46.68	**A**	100	16.3	12.0	2.1	—
$CDCl_3$	4.81	**B**	7.2	—	10.9	2.4	5.7
C_6D_6	2.28	**B**	6.6	—	9.6	1.9	5.4
$CDCl_3$	4.81	**C–E**	26.3	16.4	9.7	1.6; 2.1	—
C_6D_6	2.28	**C–E**	26.8	16.9	10.9	1.9; 1.7	—

The presence of the enol OH singlet at 16.4 ppm in $CDCl_3$ and C_6D_6 solutions indicated the possible existence of form **C**, being different from form **A**.

The generation of form **C** can be rationalized by the shift of the CH proton to the oxygen atom of the acetyl group with the formation of an intramolecular hydrogen bond between the oxygen of OH group and the sulfur atom of the thioamide group. Differences in the chemical shifts between hydrogen atoms of OH and NH groups in tautomers **A** and **C** confirm that these atoms encounter a new steric situation.

In nonpolar solvents (benzene, chloroform) the NMR spectra display also signals of other tautomers: **D** and **E**, interconverting rapidly with **C** on the NMR time scale.

In addition, the changes in the relative populations of tautomers **A–D** of compound **1a** over the temperature range of 120 K were measured in $CDCl_3$. (Fig. 2).

The diagram shows that remarkable changes in the populations of tautomer **A, B,** and **C** and **D** (counted together) are observed in the temperature range between 303-333 K, whereas in the range 213-03 K the changes are insignificant.

For some years we have employed thioanilide derivatives as starting materials for the synthesis of several biologically active heterocyclic compounds [8].

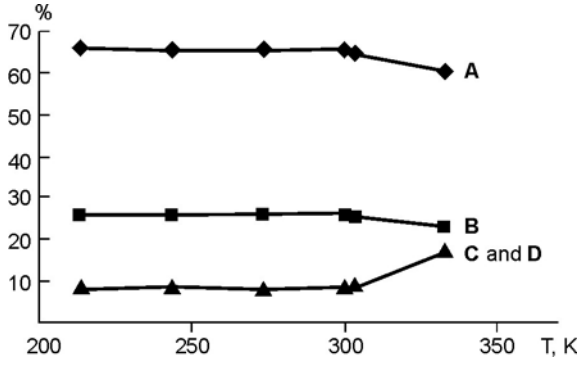


Fig. 2. Dependence of the population of tautomeric forms **A**, **B** and **C**, **D** on temperature.

The presence of several tautomeric forms of N-aryldiacetylthioacetamides **1** increased the number of reactive centers and possible reaction routes. Due to the presence of forms **A–C,** the reaction of thioanilide **1** with dielectrophilic reagents may lead, depending on the dielectrophile and the reaction medium, to the formation of different heterocyclic systems.

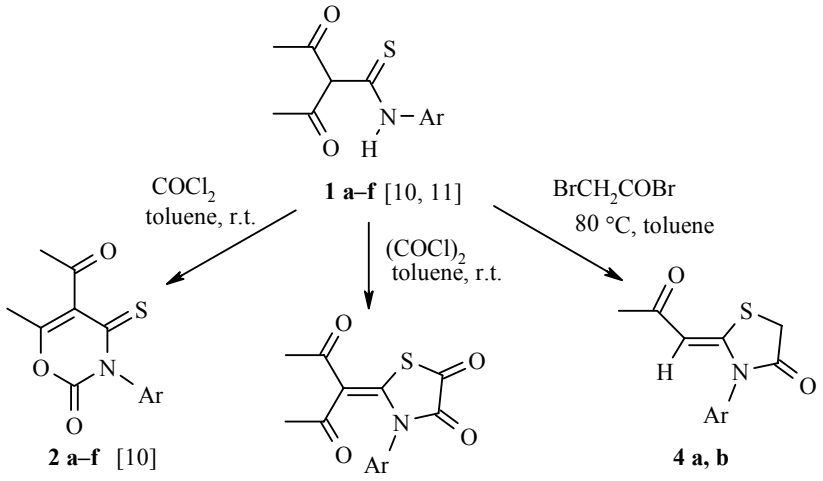
Besides the reactive centers typical of thioamide (electrophylic properties at the thiocarbonyl carbon atom and nucleophilic at thiocarbonyl sulfur and nitrogen atoms), N-aryldiacetylthioacetamides **1** have an additional nucleophilic position at oxygen of one of the acetyl groups. Due to this exceptionally polyfunctional character of compound **1** [9], its reactivity may have a wide synthetic potential.

Moreover, N-aryldiacetylthioacetamides **1** bearing the acetyl group in position 2 may also lose one of the acetyl substituents during the substitution reactions.

The purpose of this paper is to describe our investigations on the participation of appropriate tautomeric forms **A–C** of N-aryldiacetylthio- acetamides **1** in reactions with alkylating and acylating agents in nonpolar medium such as chloroform or toluene.

In our previous investigation [10], with such double acylating reagent as phosgene, 1,3-oxazine derivatives **2** were isolated as the result of O- and N-acylation of N-aryldiacetylthioacetamides **1.** However, a different course of reaction was observed when oxalyl chloride was used. Regiospecific S- and N-thioamide acylation reaction of compound **1** took place (Scheme 2).

Scheme 2



a Ar = Ph, **b** Ar = *p*-ClC_6H_4, **c** Ar = *p*-BrC_6H_4, **d** Ar = *p*-IC_6H_4, **e** Ar = α-$C_{10}H_7$, **f** Ar = β-$C_{10}H_7$

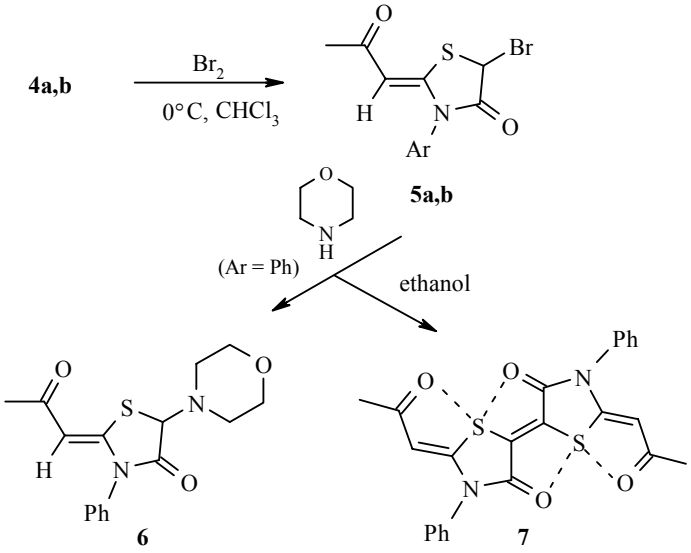
Spectral analysis of the product obtained as a result of heterocyclization with oxalyl chloride confirmed the structure of thiazolidin-4,5-dione derivatives **3**.

The treatment of compound **1** with bromoacetylbromide in boiling toluene leads to the thiazolidin-4-one derivatives **4**. This heterocyclization proceeds as the electrophilic substitution–condensation with participation of the sulfur and nitrogen atoms of a thioamide group with elimination of one acetyl group. Products **4** are assigned the structure of thiazolidin-4-one derivatives on the basis of their spectral data and elemental analysis.

In the ^{13}C NMR and ^{1}H NMR spectra of obtained compounds **4** the specific signals of CH_2 as well as CH= groups confirm that compounds **4** exist only in one geometric configuration. On the basis of this assumption the *Z*-configuration is proposed (Scheme 2).

The bromination reaction of thiazolidin-4-ones **4a,b** leads to products **5a,b**. The treatment of product **5a** with morpholine in boiling ethanol leads to a mixture of two interesting derivatives: red crystalline product **7** insoluble in ethanol and colorless compound **6** with good solubility in ethanol (Scheme 3).

Scheme 3



The above results of the reactions suggest that the participation of the **C** enol form in the process of heterocyclic construction of compounds **3** and **4** is predominant.

On the other hand, from a mechanistic point of view the synthesis of 1,3-oxazine system with phosgene confirms a bielectrophilic attack on the oxygen and the nitrogen (amide) of enol form **A**. When a reactant different than phosgene was used, in the first step, an intermediate seven-membered system of thiazepine can be formed, but Dimroth rearrangement leads to thermodynamically more stable five-membered system.

The heterocyclization process of N-aryldiacetylthioacetamides **1** depends mostly on the medium polarity, population of the tautomers, as well as stability of intermediate systems.

EXPERIMENTAL

Melting points were determined on an electrothermal IA9000 digital mp apparatus and are uncorrected. IR spectra were obtained on a Bruker IFS 48 spectrometer (KBr). ^{1}H and ^{13}C NMR spectra were recorded with a Bruker AMX 500 (500 and 125 MHz, respectively) or AVANCE II 300 (300 and 75MHz, respectively) NMR spectrometer in $CDCl_3$ at room temperature. Mass spectra (EI) were registered with Finnigan 95JS instrument (70 eV). Yields are given for pure products.

Compounds **1a-f** and **2a-f** were prepared according to [11] and [10], respectively.

X-Ray investigation. X-ray analysis of compound **1a** was carried out to determine its structure in the solid state. Compound **1a** with formula $C_{12}H_{13}NO_2S$ crystallizes (from benzene) in the monoclinic system, space group $P2_1/a$, with unit cell parameters a = 948.54(2), b = 1619.18(2), c = 987.69(2) pm, β = 92.473(1)º, V = 515.54(5)·10^6 pm^3, Z = 4. A total of 12 944 reflections (the whole sphere) were collected up to θ = 27.51º and merged to give 3454 independent reflections (R(int) = 0.0251) on a single-crystal sample (size 0.35×0.30×0.15 mm) using a KappaCCD diffractometer and MoKα radiation. The structure was solved by direct methods and

refined by the full-matrix least squares method on F^2 using the SHELX97 program system. All hydrogen atoms were located on a difference Fourier map of electron density. Final *R* indices for $I>2\sigma(I)$ were equal to $R_1 = 0.0506$, $wR_2 = 0.1434$, and $R_1 = 0.0650$, $wR_2 = 0.1534$ for all data. The final difference Fourier map of electron density was featureless with the largest peak and hole at 0.277 and -0.206 e·Å^{-3}, respectively. The structural data have been deposited at the Cambridge Crystallographic Data Centre under the reference number CCDC 672481.

It can be seen that the crystal structure includes solvent molecules, two per unit cell. The pseudo-ring C(3)–C(4)–O(8)–H(8)–O(5)–C(7) is quite flat: no atom deviates from the least-squares plane by more than 0.005 Å. Both oxygen atoms – O(5) and O(8) – share one hydrogen atom, thus forming a very short hydrogen bond (D–A distance 2.433(3) Å, D–H···A angle 151.2(2)º) with O(5) and O(8) being in turn donor or acceptor. This results in a disordered position of the hydrogen atom (either bound to O(5) or O(8) with occupancies converging to 0.3(1)/0.7(1), respectively. Also both oxygens O(5) and O(8) seem to be disordered, which can be inferred from their rather high atomic displacement parameters. However, no precise disorder model could be found, as the coordinates of these atoms are continuously spread rather than limited to two or three definite values. The consequence of this disorder includes somewhat higher R factors. The packing of the crystal structure is dominated by van der Waals interactions, with no strong intermolecular hydrogen bonds.

3-Aryl-2-(diacetylmethylidene)-1,3-thiazolidine-4,5-diones 3a–d (General Method). To 0.01 mol of compound 1 dissolved in 50 cm^3 of dry toluene, oxalyl chloride (1.26 g, 0.01 mol) dissolved in 20 cm^3 of dry toluene was added dropwise, and the mixture was stirred at room temperature. After the reaction was completed and evolution of gaseous HCl stopped, the yellow precipitate was filtered off.

2-(Diacetylmethylidene)-3-phenyl-1,3-thiazolidine-4,5-dione (**3a**). Yellow crystals from toluene–hexane mixture (1:1), yield 60%; mp 214°C. IR, ν, cm^{-1}: 1740 (C=O), 1720 (C=O), 1680 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.8 (3H, s, CH_3); 2.15 (3H, s, CH_3); 7.50-7.78 (5H, m, aromatic protons). ^{13}C NMR spectrum, δ, ppm: 32.67 ($\underline{C}H_3CO$); 29.16 ($\underline{C}H_3CO$); 122.29 (C=); 183.63–200.19 (C=O); 155.93 (S–C–N). Found, %: C 58.02; H 3.78; N 4.87; S 11.12. $C_{14}H_{11}NO_4S$. Calculated, %: C 58.12; H 3.83; N 4.84; S 11.08.

3-(*p*-Chlorophenyl)-2-(diacetylmethylidene)-1,3-thiazolidine-4,5-dione (**3b**). Yellow crystals from toluene–hexane mixture (1:1), yield 70%; mp 175°C. IR, ν, cm^{-1}: 1750 (C=O), 1725 (C=O), 1675 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.9 (3H, s, CH_3); 2.15 (3H, s, CH_3); 7.07-7.68 (4H, m, aromatic protons). ^{13}C NMR spectrum, δ, ppm: 30.9 ($\underline{C}H_3$–CO); 31.3 ($\underline{C}H_3$–CO); 122.2 (C=); 189.63-200.19 (C=O); 157.03 (S–C–N). Found, %: C 51.95; H 2.98; N 4.33; S 9.89. $C_{14}H_{10}ClNO_4S$. Calculated, %: C 51.94; H 3.11; N 4.33; S 9.90.

3-(*p*-Bromophenyl)-2-(diacetylmethylidene)-1,3-thiazolidine-4,5-dione (3c). Yellow crystals from toluene–hexane mixture (1:1), yield 60%; mp 180°C. IR, ν, cm^{-1}: 1750 (C=O), 1720 (C=O), 1685 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.95 (3H, s, CH_3); 2.10 (3H, s, CH_3); 7.06–7.56 (4H, m, aromatic protons). ^{13}C NMR spectrum, δ, ppm: 31.20 ($\underline{C}H_3$–CO); 29.23 ($\underline{C}H_3$–CO); 185.63–200.19 (C=O); 155.98 (S–C–N); 122 (C=). Found, %: C 45.44; H 2.45; N 3.81; S 8.65. $C_{14}H_{10}BrNO_4S$. Calculated, %: C 45.67; H 2.74; N 3.80; S 8.71.

2-(Diacetylmethylidene)-3-(*p*-iodophenyl)-1,3-thiazolidine-4,5-dione (3d). Yellow crystals from toluene–hexane mixture (1:1), yield 50%; mp 160°C. IR, ν, cm^{-1}: 1740 (C=O), 1720 (C=O), 1685 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.9 (3H, s, CH_3); 2.54 (3H, s, CH_3); 7.06–7.56 (4H, m, aromatic protons). ^{13}C NMR spectrum, δ, ppm: 30.9 ($\underline{C}H_3$–CO); 29.8 ($\underline{C}H_3$–CO); 185.63-200.19 (C=O); 152.6 (S–$\underline{C}$–N); 119 (C=). Found, %: C 40.10; H 2.39; N 3.28; S 7.25. $C_{14}H_{10}INO_4S$. Calculated, %: C 40.50; H 2.43; N 3.37; S 7.72.

2-Acetylmethylidene-3-aryl-1,3-thiazolidin-4-ones 4a,b (General Method). To 0.01 mol of compound **3** dissolved in 50 cm^3 of hot (80°C) dry toluene, (1.67 g, 0.01 mol) of ethyl bromoacetate was added dropwise. The mixture was stirred at room temperature for 2 h. The colorless precipitate was filtered off and crystallized from chloroform.

2-Acetylmethylidene-3-phenyl-1,3-thiazolidin-4-one (**4a**). Crystals from chloroform, yield 82%; mp 202-204°C. IR, ν, cm^{-1}: 1720 (C=O), 1660 (C=O). ^{1}H NMR, spectrum, δ, ppm: 2.01 (3H, s, CH_3); 3.85 (2H, s, CH_2); 5.10 (1H, s, CH=); 7.2-7.5 (5H, m, aromatic protons). ^{13}C NMR spectrum, δ, ppm: 31.80 ($\underline{C}H_3$–CO);

40.23 (CH_2); 105.46 (CH=); 145.39 (S–C–N); 172.40 (C=O); 195.91 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 233 $[M]^+$; 218 $[M^+–CH_3]$ (74); 190 $[M^+–CH_3CO]$ (100). Found, %: C 61.33; H 4.66; N 5.83. $C_{12}H_{11}NO_2S$. Calculated, %: C 61.78; H 4.75; N 6.00.

2-Acetylmethylidene-3-(*p*-chlorophenyl)-1,3-thiazolidin-4-one (**4b**). Crystals from chloroform, yield 50%; mp 202–204°C. IR, ν, cm^{-1}: 723 (C=O), 1642 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.21 (3H, s, CH_3); 3.9 (2H, s, CH_2); 5.52 (1H, s, CH=); 7.3–7.7 (5H, m, aromatic protons). ^{13}C NMR, δ, ppm: 31.79 ($\underline{C}H_3CO$); 40.23 (CH_2); 101.14 (CH=); 159.60 (S–C–N); 172.40 (C=O); 196.91 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 267 $[M]^+$(88); 252 $[M^+–CH_3]$ (95); 224 $[M^+–CH_3CO]$ (100). Found %: C 53.63; H 3.73; N 5.03. $C_{12}H_{10}ClNO_2S$. Calculated, %: C 53.83; H 3.76; N 5.23.

2-Acetylmethylidene-5-bromo-3-phenyl-1,3-thiazolidin-4-one (**5a**). Compound **4a** (2.3 g, 0.01 mol) dissolved in 20 cm^3 $CHCl_3$ was cooled in ice bath, and bromine (0.8 g, 0.01 mol) dissolved in 20 cm^3 $CHCl_3$ was added dropwise. After 1 h the solvent was removed. Amorphous precipitate was very difficult to purify (decomposition during chromatography).

2-Acetylmethylidene-5-bromo-3-(*p*-chlorophenyl)-1,3-thiazolidin-4-one (**5b**) was prepared similarly from **4b**. Melting points of crude precipitates **5a** 178°C, **5b** 180°C.

IR spectra, ν, cm^{-1}: **5a** – 1720 (C=O), 1643 (C=O), amide 1521 (C=C); **5b** – 1741 (C=O), acetyl group 1652 (C=O), amide group 1521 (C=C).

2-Acetylmethylidene-5-morpholino-3-phenyl-1,3-thiazolidin-4-one (**6**). The mixture of compound **5a** (2.0 g, 0.01 mol) dissolved in ethanol and morpholine (0.87 g, 0.01 mol) was refluxed for 1–2 h. Red needle product **7a** was filtered off from hot solution. After cooling colorless precipitate **6a** was filtered off. Yield 30%. IR spectrum, ν, cm^{-1}: 1720 (C=O), 1643 (C=O), 1521 (C=C). ^{1}H NMR spectrum, δ, ppm: 2.07 (3H, s, CH_3); 2.59 (2H, m, NCH_2); 2.88 (2H, m, NCH_2); 3.78 (4H, m, OCH_2); 5.26 (1H, s, H-5); 5.58 (1H, s, CH=); 7.58-7.23 (5H, m, aromatic protons). ^{13}C NMR spectrum, δ, ppm: 30.78 ($\underline{C}H_3CO$); 49.01 (NCH_2); 66.52 (OCH_2); 72.31, 102.48 (CH=); 156.46 (S–C–N); 171.04 (C=O); 196.24 (C=O). Found, %: C 59.78; H 5.43; N 8.45. $C_{16}H_{18}N_2O_3$. Calculated, %: C 60.06; H 5.70; N 8.80.

2-(Acetylmethylidene)-5-*E*-(2-acetylmethylidene-4-oxo-3-phenyl-1,3-thiazolidinyl-5-ylidene)-1,3-thiazolidin-4-one (**7**). Yield 21%; mp more than 370°C. IR spectrum, ν, cm^{-1}: 1705 (C=O), 1649 (C=O), 1523 (C=C). ^{1}H NMR spectrum, δ, ppm: 2.09 (6H, s, $2CH_3$); 5.70 (2H, s, =CH); 7.48–7.67 (10H, m, aromatic protons). Found, %: C 61.98; H 4.01; N 5.80. $C_{24}H_{18}N_2O_4S_2$. Calculated, %: C 62.32; H 3.92; N 6.06.

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