ISSN 1070-3632, Russian Journal of General Chemistry, 2012, Vol. 82, No. 10, pp. 1700–1704. © Pleiades Publishing, Ltd., 2012.
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Protolytic Properties of 2-Acylthioacetamides

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Received July 28, 2011

Abstract—Concentration acidity of 2-acylthioacetamides dissolved in DMSO–H_2O was measured by the method of pH-metric titration. The data obtained were extrapolated for the determination of pK_a values of 2-acylthioacetamides in water and DMSO. We found that in aqueous solutions the acidity of thioacetarylamide (pK_a = 5.75–6.01) was almost independent of the nature of substituents in their *N*-phenyl rings, whereas in DMSO solution the nature of substituents significantly affects their ionization constants (pK_a = 7.88–11.70). The graphs were displayed and the acidity of *N*-aryl-3-oxobutanethioamides dependence on the Hammett constants of *meta*- and *para*-substituents in the phenyl rings derived. Water is shown to be a leveling, and DMSO a differentiating solvent for 2-acylthioacetamides.

DOI: 10.1134/S1070363212100106

2-Functionalized methylene-containing thioacetamides are promising starting reagents for both mono- and polynuclear heterocycles [1–5]. But due to the presence of several competing reaction sites, the forecast of the dominant reactions of these substrates is not a simple task. Certain predictions of the reactivity of thioacetamides can be made on the basis of their ionization constants, since they relate directly to the ability of these compounds to generate ambident anions, the intermediates in many reactions [6]. The data on the acidity of thioacetamides allow also the selection of the conditions of their isolation with a maximum yield [7], and contribute to the study of such phenomena as keto–enol–thiol tautomerism [8]. Therefore, the measurement of acidity of thioacetamides is desirable not only from theoretical, but also from practical viewpoint.

Nevertheless, the available literature information on the ionization constants of the methylene-containing thioacetamide is fragmentary and not systematic [9–11]. Moreover, the measurements were performed on single examples in different systems (DMSO–water [9], dioxane–water [10], DMF [11]), that does not permit the correct comparison of the data obtained among themselves or with the pK_a values of other compounds.

In [12], we measured the ionization constants of several methylene-containing tioacetamides in a DMSO–water (1:1) mixture and showed for the first time that 2-acylthioacetamides are slightly more acidic compounds than 2-cyano- and 2-(phenylsulfonyl) thioacetamides. The high acidity and a tendency to keto–enol tautomerism causes increased reactivity of the methylene group of 2-acylthioacetamides compared to other methylene-containing thioacetamides. However, the problem concerning the pK_a of 2-acylthioacetamides in the most frequently used solvents such as water and DMSO remained unresolved.

The aim of this study was to determine the concentration acidity of 2-acylthioacetamides in water and DMSO.

The ionization constants of 2-acylthioacetamides **I–VII** were measured by the method of pH-titration of their solutions in the DMSO–H_2O containing 40, 50, 60, 70, and 80 vol % of DMSO (Table 1).

The calculation of pK_{eff} of 2-acylthioacetamides in solutions containing different amounts of DMSO was carried out by the treatment of the obtained titration curves using Hyperquad 2000 software. To calculate

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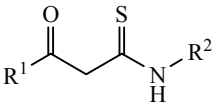
Table 1. Dependence of pK_{eff} of 2-acylthioacetamides on the DMSO–water ratio and Hammett constants of *N*-aryl substituents

2-Acylthioacetamide 				DMSO content (vol %)						
Comp. no.	R^1	R^2	σ_p (σ_m)	0[a]	40[b]	50[b]	60[b]	70[b]	80[b]	100[a]
I	CH_3	Ph	0.00	6.01±0.23	7.9	8.4	9.0	9.3	9.6	10.80±0.23
II	CH_3	4-$CH_3OC_6H_4$	–0.27	5.75±0.39	8.2	8.9	9.5	9.9	11.1	11.70±0.395
III	CH_3	3-ClC_6H_4	(0.37)	5.79±0.42	7.4	7.9	8.5	8.6	9.2	10.00±0.42
IV	CH_3	3-$CF_3C_6H_4$	(0.43)	5.85±0.53	7.3	8.0	8.4	8.5	9.0	9.80±0.53
V	CH_3	4-$NO_2C_6H_4$	0.7	5.98±0.14	6.7	7.0	7.1	7.3	7.5	7.88±0.14
VI	Ph	CH_3	–	7.89±0.11	8.2	8.4	8.5	8.6	8.7	8.89±0.11
VII	Ph	Ph	–	5.18±0.20	7.34	7.83	8.5	9.1	9.4	10.58±0.20

[a] Obtained by approximation. [b] The pK_{eff} values are measured with an accuracy ± 0.1 pK units.

the pK_{eff} values of 2-acylthioacetamides in pure water and DMSO we constructed the plots pK_{eff} = pK_a + nc_{DMSO} (where pK_{eff} is the thioacetamide pK in water–DMSO, pK_a is the acidity of the thioamide in water, n is the slope of the linear dependence, which is a characteristic of the dielectric conductivity of the solvent and the initial acidity of the thioacetamide, c_{DMSO} is the percentage of DMSO content in the solution by volume). The point c_{DMSO} = 0% corresponds to the pK_a value of thioamide in water, from c_{DMSO} at 100% was calculated the pK_a value in DMSO.

The resulting numerical data are listed in Table 1. Based on this information, we have constructed the plots of the pK_{eff} of *N*-aryl-3-oxobutanethioamides **IV** versus the Hammett constants of substituents on the *N*-phenyl ring and the composition by volume of the DMSO–H_2O solutions (Fig. 1) and derived the related equations (Table 2).

As seen from Table 1 and Figs. 1, 2, water and DMSO are leveling and differentiating solvents, respectively. In aqueous solution, the acidity of thioacetamide **IV** (pK_a = 5.75–6.01) practically does not depend on the nature of the substituents in the *N*-phenyl ring (within errors, all the points are actually at the same level), whereas in DMSO solution (pK_a = 7.88–11.70) the nature of these substituents has a significant effect on the ionization constant. It can be concluded that water solvates well the formed ions, whereas DMSO solvates the undissociated molecules.

Similar effect was observed for the solutions of thiophenol in water and in DMSO (pK_a values are 6.6 and 10.3 respectively) [13].

2-Acylthioacetamides are the hetero-analogs of β-dicarbonyl compounds and may exist in the keto (K) and chelate-type enol (E) forms (see the scheme) [8, 12]. The prototropic tautomerism of 2-acylthioacetamides has been studied fairly well [8], while the equilibrium between different forms of the anions of 2-acylthioacetamides remains practically unknown. It

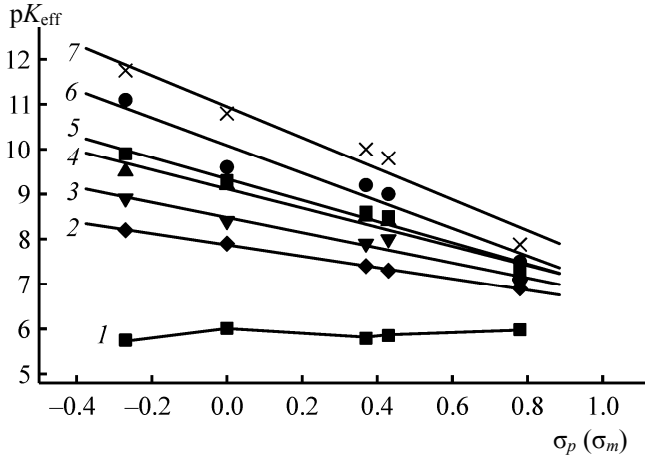


Fig. 1. Plots of pK_{eff} of *N*-aryl-3-oxobutanethioamides **IV** vs. Hammett constants of substituents in the *N*-phenyl rings and the composition by volume of the DMSO–H_2O mixture. Numerals indicate the DMSO concentrations: (*1*) 0, (*2*) 40, (*3*) 50, (*4*) 60, (*5*) 70, (*6*) 80, and (*7*) 100% by volume.

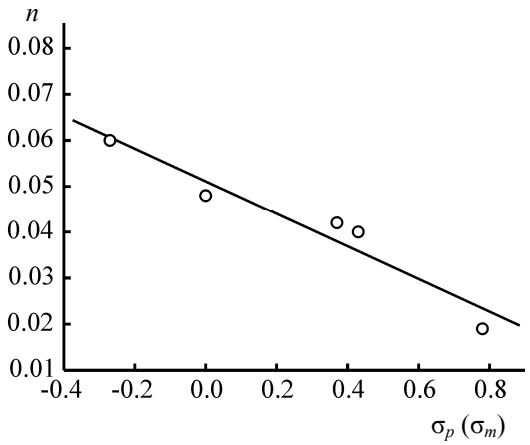


Fig. 2. Influence of Hammett constants on the differentiating effect of DMSO on the acidity of thioacetamides **I–IV**.

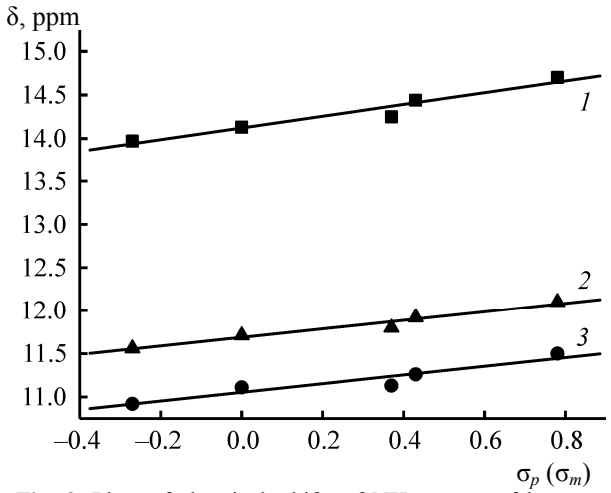


Fig. 3. Plots of chemical. shifts of NH-protons of ketone (*2*) and enol (*3*) forms of thioacetamide **IV** and related sodium salts **VIII–XII** (*1*) vs the Hammett constants (σ_p, σ_m) of their *N*-phenyl substituents.

was postulated only [9] that the acidity of these compounds is due to removing the proton from the hydroxy group of the enol form.

To determine the structure of the resulting anion, we synthesized 2-acylthioacetamides **VIII–XIV** sodium salts and characterized them by the methods of ^{1}H and ^{13}C NMR and IR spectroscopy.

In the ^{1}H NMR spectra of thioacetamide sodium salts in DMSO-d_6 there are characteristic signals of H^2 and NH protons (5.13–5.93 and 12.22–14.79 ppm, respectively), indicating the existence of the tioacetamide anions as the structures **VIIIa–VIIIf** to **XIVa–XIVf**. In the IR spectra of compounds **VIII–XIV** the absorption bands of the C=O fragments are shifted to low-frequency vibrations of values 1590–1600 cm^{-1}.

Table 2. Equations of the plots of pK_{eff} of *N*-aryl-3-oxobutanethioamides **IV** versus Hammett constants of substituens in *N*-phenyl rings and the composition by volume of the DMSO–H_2O mixture

DMSO concentration, vol %	Equation
40	$pK_{eff} = (7.87\pm0.01) - (1.26\pm0.03)\sigma_{p(m)}$
50	$pK_{eff} = (8.48\pm0.09) - (1.68\pm0.22)\sigma_{p(m)}$
60	$pK_{eff} = (9.11\pm0.13) - (2.13\pm0.29)\sigma_{p(m)}$
70	$pK_{eff} = (9.34\pm0.09) - (2.37\pm0.22)\sigma_{p(m)}$
80	$pK_{eff} = (10.08\pm0.21) - (3.07\pm0.46)\sigma_{p(m)}$
100	$pK_{eff} = (10.94\pm0.20) - (3.44\pm0.45)\sigma_{p(m)}$

Figure 3 shows the plots of dependence of the chemical shifts of NH protons of ketone and enol forms of thioacetamides **I–IV** and their sodium salts **VIII–XII** on the Hammett constants $\sigma_{m,p}$ of their *N*-phenyl-substituents. These dependences can be expressed by the following equations:

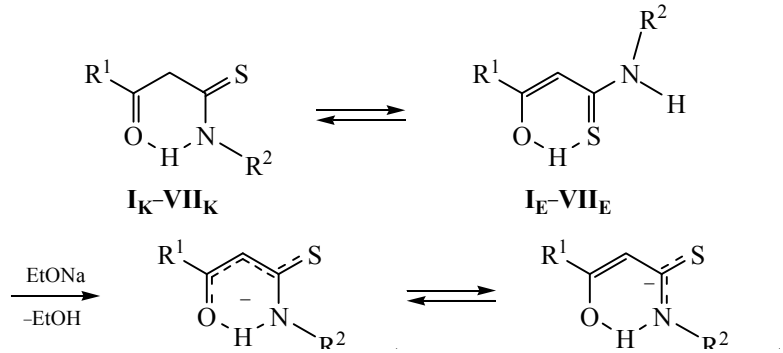
$$\delta_{NH\ salt} = (14.12\pm0.04) + (0.68\pm0.09)\sigma_{p(m)}, \quad (1)$$

$$\delta_{NH\ ketone} = (11.69\pm0.02) + (0.49\pm0.05)\sigma_{p(m)}, \quad (2)$$

$$\delta_{NH\ enol} = (11.05\pm0.04) + (0.50\pm0.09)\sigma_{p(m)}. \quad (3)$$

The appearance of the signals of NH protons in such a weak field indicates that the salts **VIII–XIV**, as well as the initial thioacetamides **I–VII**, are characterized by the formation of strong intramolecular hydrogen bonds of chelate type. It should be noted that in the case of the sodium salts **VIII–XIV** the NH-proton signals are in a weaker field than those of keto and enol forms of 2-acylthioacetamides **I–VII** (13.97–14.70, 11.56–12.10 and 10.92–11.50 ppm, respectively). Consequently, the hydrogen bonds formed in the salts **VIII–XIV** are stronger than those of the keto $\mathbf{I_K}$–$\mathbf{VII_K}$ and enol $\mathbf{I_E}$–$\mathbf{VII_E}$ forms of thioacetamides. This is due to the presence of the conjugation chain and planar structure of salts **VIII–XIV**, and the fact that the energy of hydrogen bonds, in accordance with the principle of hard–soft acids and bases, falls to the following series: NH···O > OH···N > OH···S.

The compounds **VIII–XIV** can be represented by the ambident structures, **VIIIa–XIVa** and **VIIIb–XIVb**, respectively.



I_K–VII_K I_E–VII_E

R^1 = CH_3 (**VIIIa, VIIIb–XIIa, XIIb**), Ph (**XIIIa, XIIIb, XIVa, XIVb**); R^2 = Ph (**VIIIa, VIIIb**), 4-$CH_3OC_6H_4$ (**IXa, IXb**), 3-ClC_6H_4 (**Xa, Xb**), 3-$CF_3C_6H_4$ (**XIa, XIb**), 4-$NO_2C_6H_4$ (**XIIa, XIIb**), CH_3 (**XIIIa, XIIIb**), Ph **(XIVa, XIVb**).

The data obtained allow us to determine the positions of labile protons in the salts **VIII–XIV** only approximately.

To determine the dominant form of the Na salts, we compared the chemical shifts of carbonyl carbon signals in the spectra of the compounds with intramolecular hydrogen bond PhCO···H and without it. In the ^{13}C NMR spectra the signals of carbonyl carbon of benzoyl fragment of 1-alkyl-2-benzoyl-6-methylthio-3-ethoxycarbonyl-1,2-dihydropyrimidin-2-ones [2] and thioacetamides **XIII, XIV** sodium salts are observed in the range 192.6–193.2 and 187.8–191.5, respectively (the difference is 1.1–5.4 ppm). In the ^{13}C NMR spectrum of β-dicarbonyl compounds the chemical shifts difference of ketone and enol carbon atoms is 10.5–12.8 ppm [14]. Based on these data it is possible to suggest that thioacetamide salts **VIII–XIV** in DMSO solution to a large extent are in the chelate form **VIIIa–XIVa**.

This approach can be explained in terms of the principle of the hard–soft acids and bases: proton is a hard acid and is closely associated with the hard bases, here with primarily the *N*-atom.

EXPERIMENTAL

The NMR spectra of solutions of substances in DMSO-d_6 were recorded on a Varian-300 instrument, operating frequencies 300 MHz (^1H) and 75 MHz (^{13}C), internal reference TMS. The IR spectra were obtained on a UR-20 spectrophotometer from KBr tablets.

2-Acylthioacetamides **I–VII** were synthesized by the method [12]. Their physical and spectral properties correspond to those described in [12].

The dissociation constants of compounds **I–VII** were measured by potentiometric titration with KOH solution (0.033 N) in DMSO–H_2O mixtures (40, 50, 60, 70 and 80 vol %, c = 0.01 M) at 20°C with further processing of the titration curves with the Hyperquad 2000 software. The graphs are constructed using the program Origin 5.0.

Synthesis of 2-acylthioacetamides VIII–XIV sodium salts. A solution of 1 mmol of 2-acylthioacetamide **I–VII** and 1 mmol of sodium ethoxide in 3 ml of anhydrous ethanol was evaporated to obtain a fine-crystalline solid, which was washed with anhydrous diethyl ether (2×3 ml) and dried at 50°C. The yield of salts **VIII–XIV** is quantitative.

3-Oxo-*N*-phenylbutanethioamide VIII Na-salt. mp 220–222°C (decomp.). IR spectrum, cm^{-1}: 3000–2900, 1590, 1520, 1210. ^1H NMR spectrum, δ, ppm: 1.67 s (3H, SH3SO), 5.17 s (1H, CH =), 6.89 m (1H, Ph), 7.18 m (2H, Ph), 7.86 m (2H, Ph), 14.13 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 28.3 (CH_3), 104.6 (C^2), 121.5 (Ph), 122.0 (Ph), 128.2 (Ph), 143.1 (Ph), 180.9 (C^1), 186.1 (C=O). Found,%: C 56.10, H 4.86; N 6.24; S 14.96. $C_{10}H_{10}NNaOS$. Calculated, %: C 55.80, H 4.68; N 6.51; S 14.89.

3-Oxo-*N*-(4'-methoxyphenyl)butanethioamide IX Na-salt. mp 215–218°C (decomp.). IR spectrum, cm^{-1}: 3000–2900, 1600, 1530, 1210. ^1H NMR spectrum, δ, ppm: 1.66 s (3H, CH_3CO), 5.13 s (1H, CH=), 6.77 d

(2H, *p*-C_6H_4, *J* 8.7 Hz), 6.69 d (2H, *p*-C_6H_4, *J* 8.7 Hz), 13.97 s (1H, NH). Found, %: C 53.74, H 5.13; N 5.49; S 13.18. $C_{11}H_{12}NNaO_2S$. Calculated, %: C 53.87, H 4.93; N 5.71; S 13.07.

3-Oxo-*N*-(3'-chlorophenyl)butanethioamide X Na-salt. mp 213–225°C (decomp.). IR spectrum, cm^{-1}: 3000–2900, 1590, 1530, 1210. ^1H NMR spectrum, δ, ppm: 1.69 s (3H, CH_3CO), 5.20 s (1H, CH =), 6.87 d (1 H, 3-ClC_6H_4, *J* 5.1 Hz), 7.17 m (1H, 3-ClC_6H_4), 7.41 d (1 H, 3-ClC_6H_4, *J* 6.1 Hz), 8.53 s (1H, 3-ClC_6H_4), 14.25 s (1H, NH). Found, %: C 47.91, H 3.48; N 5.62; S 12.89. $C_{10}H_9ClNNaOS$. Calculated, %: C 48.10, H 3.63; N 5.61; S 12.84.

3-Oxo-*N*-(3'-trifluoromethylphenyl)butanethioamide XI Na-salt. mp 206–209°C (decomp.). IR spectrum, cm^{-1}: 3050–2900, 1590, 1520, 1220. ^1H NMR spectrum, δ, ppm: 1.70 s (3H, CH_3CO), 5.25 s (1H, CH=), 7.18 d (1 H, 3-$CF_3C_6H_4$, *J* 7.5 Hz), 7.40 m (1H, 3-$CF_3C_6H_4$), 7.80 d (1H, 3-$CF_3C_6H_4$, *J* 8.7 Hz), 8.77 s (1H, 3-$CF_3C_6H_4$), 14.44 s (1H, NH). Found, %: C 46.78, H 3.11; N 5.17; S 11.14. $C_{11}H_9F_3NNaOS$. Calculated, %: C 46.65, H 3.20; N 4.95; S 11.32. 10

3-Oxo-*N*-(4'-nitrophenyl)butanethioamide XII Na-salt. mp 216–220°C (decomp.). IR spectrum, cm^{-1}: 3050–2900, 1600, 1520, 1215. ^1H NMR spectrum, δ, ppm: 1.73 s (3H, CH_3CO) 5.37 s (1H, CH=), 8.8 d (2H, *p*-C_6H_4, *J* 9.3 Hz), 8.26 d (2H, *p*-C_6H_4, *J* 9.3 Hz), 14.70 s (1H, NH). Found, %: C 45.97, H 3.54; N 10.82; S 12.16. $C_{10}H_9N_2NaO_3S$. Calculated, %: C 46.15; H 3.49; N 10.76; S 12.32.

3-Oxo-3-phenyl-*N*-methylpropanethioamide XIII Na-salt. mp 250–255°C (decomp.). IR spectrum, cm^{-1}: 3000–2900, 1600, 1520, 1200. ^1H NMR spectrum, δ, ppm: 2.97 d (3H, CH3, *J* 4.2 Hz), 5.74 s (1H, CH=), 7.62 m (3H, Ph), 7.66 m (2H, Ph), 12.22 br.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 30.9 (CH_3), 98.2 (C^2), 126.4 (Ph), 128.0 (Ph), 128.3 (Ph), 144.2 (Ph), 173.7 (C^1), 191.5 (C=O). Found, %: C 55.83, H 4.93; N 6.44; S 14.73. $C_{10}H_{10}NNaOS$. Calculated, %: C 55.80, H 4.68; N 6.51; S 14.89.

3-Oxo-3-phenyl-*N*-phenylpropanethioamide XIV Na-salt. mp 205–210°C (decomp.). IR spectrum, cm^{-1}: 3000–2900, 1600, 1510, 1200. ^1H NMR spectrum, δ, ppm: 5.93 s (1H, CH =), 6.92 m (1H, Ph), 7.21–7.34 m (5H, Ph), 7.74 m (2H, Ph), 7.96 m (2H, Ph), 14.79 s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 102.1 (C^2), 121.7 (Ph), 122.4 (Ph), 126.6 (Ph), 128.3 (Ph), 128.4 (Ph), 128.9 (Ph), 142.9 (Ph), 143.2 (Ph), 174.7 (C^1), 187.8 (C = O). Found, %: C 65.04, H 4.38; N 4.88; S 11.64. $C_{15}H_{12}NNaOS$. Calculated, %: C 64.97, H 4.36; N 5.05; S 11.56.

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