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Reaction of 3-Oxo-3-R^1-*N*-R^2-propanethioamides with 2-Amino-5-R-pyridines

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Abstract—Direction of a reaction between 3-oxo-3-R^1-*N*-R^2-propanethioamides and 2-amino-5-R-pyridines in acetic acid depends on the structure of initial thioamides: at R^1 = Me, R^2 = Ar, Et 2-methyl-7-R-4*H*-pyrido[1,2-*a*]-pyrimidine-4-thiones are obtained, and at R^1 = Ar, R^2 = Me form 1-methyl-5-(*N*-methylaminothiocarbonyl)-4,6-diaryl-1,2-dihydropyridine-2-thiones.

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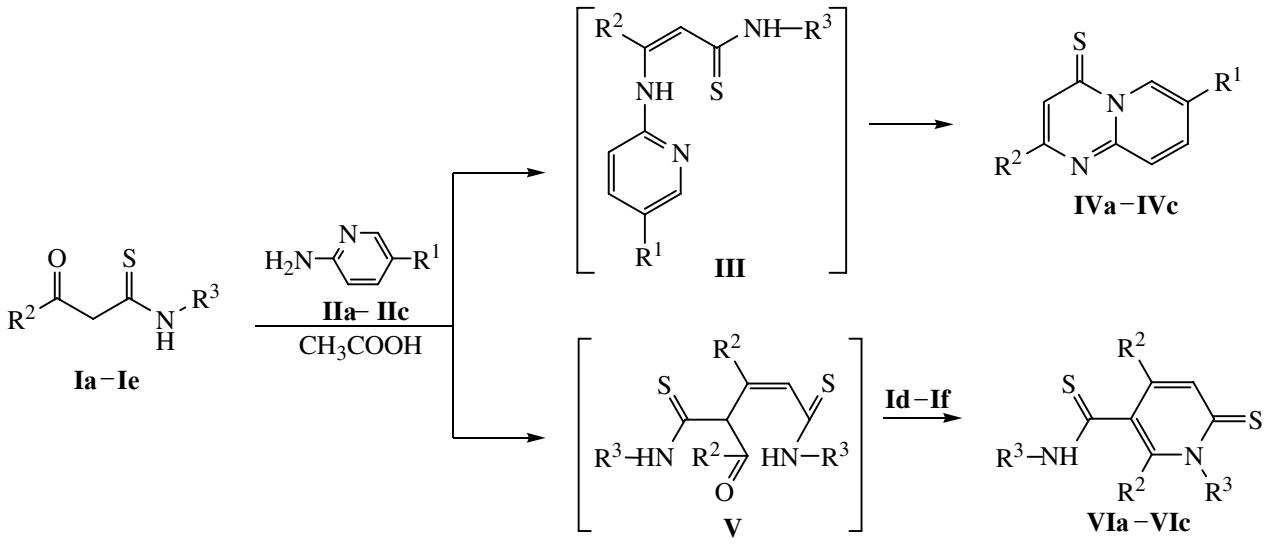
3-Oxo-3-R^1-*N*-R^2-propanethioamides possess several reactive sites capable of multiple chemical reactions providing a possibility to prepare from these substances other classes of organic compounds, first of all from the heterocyclic series [1–4]. However among published data except for [5] information is lacking on the dependence of reactivity on the structure of 3-oxo-3-R^1-*N*-R^2-propanethioamides for the majority of these reactions has been studied by examples of *N*-aryl-3-oxobutanethioamides as the most accessible representatives of this class compounds. We recently developed [6] a preparative procedure for 3-oxo-3-R^1-*N*-R^2-propanethioamides (R^1, R^2 = Alk, Ar) thus significantly extending the range of substrates involved into reactions and revealing the effect of substituent structure R^1 and R^2 on the direction of transformations of 3-oxo-3-R^1-*N*-R^2-propanethioamides.

In the present study we investigated a reaction of 3-oxopropane-thioamides **Ia–If** with 2-amino-5-R-pyridines **IIa–IIc**. Presumed products of this reactions were expected to be 4*H*-pyrido[1,2-*a*]pyrimidine-4-thiones, 2*H*-pyrido[1,2-*a*]pyrimidine-2-thiones, 4*H*-pyrido[1,2-*a*]pyrimidine-4-imines, and 2*H*-pyrido[1,2-*a*]-pyrimidine-2-imines. We established that this reaction, like that of ethyl acetoacetate with 2-amino-pyridines [7] occurred selectively, and its direction depended on the structure of 3-oxopropane-thioamides **Ia–If** (see the scheme). It turned out that the condensation of thioamides **Ia–Ic** with 2-amino-5-R-pyridines **IIa–IIc** in acetic acid resulted in 2-methyl-7-R-4*H*-pyrido-[1,2-*a*]pyrimidine-4-thiones **IVa–IVc**, whereas thioamides **Id–If** in the presence of 2-amino-5-R-pyridines **IIa–IIc** under the same conditions unexpectedly suffered self-condensation into 1-methyl-5-(*N*-methylaminothio-carbonyl)-4,6-diaryl-1,2-dihydro-pyridine-2-thiones **VIa–VIc**.

In the ^{1}H NMR spectra of pyrido[1,2-*a*]pyrimidine-4-thiones **IVa–IVc** the characteristic protons signals of CH_3-2, H^3, H$^{6–9}$ appear respectively at 2.42–2.45, 7.56–7.59, and 7.64–10.19 ppm, and in the spectra of 1,2-dihydropyridine-2-thiones **VIa–VIc** the characteristic proton signals of $NHC\underline{H}_3$, CH_3-1, H^3, $N\underline{H}CH_3$ are observed respectively at 2.83–2.85, 3.35–3.45, 6.65–6.72, and 8.93 ppm. The IR spectra of compounds **IVa–IVc** contain characteristic absorption bands of C=N groups and Ar at 1590 and 3100 cm^{-1} respectively, and the spectra of compounds **VIa–VIc** , absorption bands of C=N, Ar, and NH groups at 1570–1580, 3050, and 3400 cm^{-1} respectively.

The spectral characteristics and the melting point of compound **IVa** were identical to those of the previously published for 2-methyl-4*H*-pyrido[1,2-*a*]-pyrimidine-4-thione which had been synthesized from 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one and phosphorus pentasulfide [8], thus proving unambiguously the structure of compounds **IVa–IVc**. These data show also that in 2-amino-pyridines **IIa–IIc** in contrast to 3-amino-5-R-1,2,4-triazoles [9] in reactions with 3-oxo-3-R^1-*N*-R^2-propanethioamides the exocyclic amino group is more reactive than the endocyclic imino group NH^1.

Scheme.



II, IV, R^1 = H (a), Me (b), Br (c); R^2 = Me (**Ia–Ic, IVa–IVc**), Ph (**Id, VIa**), *p*-$MeOC_6H_4$ (**Ie, VIb**), *ï*-ClC_6H_4 (**If, VIc**); R^3 = Ph (**Ia**), *p*-ClC_6H_4 (**Ib**), Et (**Ic**), Me (**Id–If, VIa–VIc**).

Note that the data of ^{1}H NMR and IR spectra of compounds **VIa–VIc** cannot unambiguously prove whether these substances are 1-methyl-5-(*N*-methyl-aminothiocarbonyl)-4,6-diaryl-1,2-dihydropyridine-2-thiones or 2-methylimino-5-(*N*-methylaminothiocarbonyl)-4,6-diaryl-2*H*-thiopyrans. To establish the structure of the self-condensation products we registered the ^{13}C NMR spectrum of compound **VIa**. Two characteristic signals were observed in this spectrum in the downfield region (181.6 and 187.5 ppm) identified as signals of the carbon atoms of the two thiocarbonyl groups. The is fact unambiguously indicates that compounds **VIa–VIc** are 1-methyl-5-(*N*-methylaminothiocarbonyl)-4,6-diaryl-1,2-dihydropyridine-2-thiones.

The self-condensation of compounds **Id–If** in acetic acid was initiated not only by 2-amino-5-R-pyridines **IIa–IIc** but also at replacing these bases by aniline or *N,N*-dimethylaniline. However at boiling a toluene solution of thioamides **Id–If** with 2-amino-5-R-pyridines **IIa–IIc** no reaction between the initial substances was observed.

Our data unambiguously demonstrate that the direction of the reaction between 2-amino-pyridines and 3-oxo-3-R[1]-*N*-R[2]-propanethioamides is governed exclusively by the structure of substituents R[1] and R[2]. It should be stressed that unlike the process described in [5] the reactions under study occur selectively providing the possibility to obtain products in fair yields (27–65%) without applying special procedures of separation and purification.

To substantiate the mechanistic scheme of reactions we have studied we take into account the difference both in electronic and steric factors in the structure of thioamides **Ia–Ic** and **Id–If**.

Since aryl substituents are stronger acceptors than alkyls it may be concluded that the difference in the reactivity of thioamides **Ia–Ic** and **Id–If** originates apparently from the higher acidity of methylene groups and the higher nucleophilicity of *N*-methylthiocarbonyl groups of thioamides **Id–If** compared to these characteristics of the same groups in thioamides **Ia–Ic**. Aryl substituents at the carbonyl carbon in thioamides **Id–If**, bulkier than the methyls of thioamides **Ia–Ic**, are likely to provide steric hindrances to the nucleophilic attack of the amino group of 2-aminopyridines **IIa–IIc** on the carbonyl atom C[3] in thioamides **Id–If** but do not hamper the proton abstraction from the methylene (enol) group of these thioamides.

Thioamides **Ia** and **Ib** are known to react in acetic acid with aniline and other aromatic amines leading to the formation of enaminothiones [10–12]. It is therefore presumable that thioamides **Ia–Ic** reacting with 2-amino-5-R-pyridines **IIa–IIc** form enaminothiones **III** that further undergo cyclization into pyrido[1,2-*a*]pyrimidine-4-thiones **IVa–IVc**.

Inasmuch as 3-oxopropanethioamides **Id–If** contain an active methylene group, they would be capable to generate carbanions that would attack as nucleophiles

the carbonyl group of thioamides **Id–If** giving intermediates **V**. The latter apparently suffer intramolecular attack of the thioamide group on the carbonyl leading to the formation of 1,2-dihydro-pyridine-2-thiones **VIa–VIc**.

EXPERIMENTAL

NMR spectra of solutions of compounds in DMSO-d_6 were registered on a spectrometer Varian-300 at operating frequencies 300 (^{1}H) and 75 MHz (^{13}C), internal reference TMS. IR spectra were recorded on UR-20 instrument from KBr pellets.

2-Methyl-7-R-4*H*-pyrido[1,2-*a*]pyrimidine-4-thiones IVa–IVc. A solution of 10 mmol of 3-oxo-*N*-arylpropanethioamides **Ia–Ic** and 10 mmol of 2-amino-5-R-pyridine **IIa–IIc** in 7 ml of AcOH was heated for 4 h at 100°C, cooled, and thione **IVa–IVc** was separated by filtration.

2-Methyl-4*H*-pyrido[1,2-*a*]pyrimidine-4-thione (IVa). Yield 1.144 g (65%), mp 156–158°C (from AcOH) (158°C [7]). IR spectrum, ν, cm^{-1}: 1260, 1310, 1380, 1420, 1590, 3100. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.45 s (3H, CH_3-2), 7.56 s (1H, H^3), 7.64 m (1H$_{arom.}$), 7.85 d (1H, H^9, *J* 8.7), 8.11 m (1H$_{arom.}$), 10.10 d (1H, H^6, *J* 7.5). Found, %: C 61.20; H 4.33; N 16.17; S 18.40. $C_9H_8N_2S$. Calculated, %: C 61.34; H 4.58; N 15.90; S 18.19.

2,7-Dimethyl-4*H*-pyrido[1,2-*a*]pyrimidine-4-thione (IVb). Yield 1.007 g (53%), mp 140–142°C (from ethanol). IR spectrum, ν, cm^{-1}: 1260, 1280, 1320, 1430, 1500, 1590, 3100. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.42 s (3H, CH_3-2), 2.54 s (3H, CH_3-7), 7.57 s (1H, H^3), 7.80 d (1H, H^9, *J* 8.8), 8.02 d (1H, H^8, *J* 8.8), 9.92 s (1H, H^6). Found, %: C 62.94; H 5.53; N 14.57. $C_{10}H_{10}N_2S$. Calculated, %: C 63.13; H 5.30; N 14.72.

2-Methyl-7-bromo-4*H*-pyrido[1,2-*a*]pyrimidine-4-thione (IVc). Yield 1.53 g (60%), mp 198–200°C (from AcOH). IR spectrum, ν, cm^{-1}: 1250, 1310, 1430, 1540, 1590, 3100. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.44 s (3H, CH_3-2), 7.59 s (1H, H^3), 7.79 d (1H, H^9, *J* 8.9), 8.22 d (1H, H^8, *J* 8.9), 10.19 s (1H, H^6). Found, %: C 42.14; H 2.50; N 11.17. $C_9H_7BrN_2S$. Calculated, %: C 42.37; H 2.77; N 10.98.

1-Methyl-5-(*N*-methylaminothiocarbonyl)-4,6-diaryl-1,2-dihydropyridine-2-thiones VIa–VIc. A solution of 10 mmol of 3-oxo-*N*-methyl-3-arylpropanethioamides **Id–If** and 10 mmol of 2-amino-5-R-pyridine **IIa–IIc** in 7 ml of AcOH was heated for 12 h at 100°C, cooled, and thionepyran **VIa–VIc** was separated by filtration.

1-Methyl-5-(*N*-methylaminothiocarbonyl)-4,6-diphenyl-1,2-dihydropyridine-2-thione (VIa). Yield 0.717 g (41%), mp 324–326°C (from DMSO). IR spectrum, ν, cm^{-1}: 1320, 1360, 1430, 1490, 1580, 3050, 3400. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.83 d (3H, NHC$\underline{H}_3$, *J* 4.0), 3.35 s (3H, CH_3-1), 6.72 s (1H, H^3), 7.48–7.58 m (8H$_{arom.}$), 8.01 m (2H$_{arom.}$), 8.93 br.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 32.6 ($HNCH_3$), 35.22 (CH_3-1), 86.7 (C^3), 122.1 (Ar), 126.8 (Ar), 128.2 (Ar), 128.6 (Ar), 128.9 (Ar), 130.0 (Ar), 130.5 (Ar), 134.8 (Ar), 137.1 (Ar), 139.1 (Ar), 161.3 (C^6), 181.6 (C=S), 187.5 (C^2). Found, %: C 68.30; H 5.31; N 8.07; S 18.03. $C_{20}H_{18}N_2S_2$. Calculated, %: C 68.54; H 5.18; N 7.99; S 18.29.

1-Methyl-5-(*N*-methylaminothiocarbonyl)-4,6-bis-(4-methoxyphenyl)-1,2-dihydropyridine-2-thione (VIb). Yield 0.676 g (33%), mp 295–297°C (from DMSO). IR spectrum, ν, cm^{-1}: 1330, 1360, 1420, 1500, 1570, 3050, 3400. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.85 d (3H, NHC$\underline{H}_3$, *J* 3.8), 3.45 s (3H, CH_3-1), 3.82 s (3H, CH_3O), 3.84 s (3H, CH_3O), 6.65 s (1H, H^3), 6.97 d (2H, *p*-C_6H_4, *J* 8.1), 7.19 d (2H, *p*-C_6H_4, *J* 8.3), 7.39 d (2H, *p*-C_6H_4, *J* 8.1), 7.99 d (2H, *p*-C_6H_4, *J* 8.3), 8.82 q (1H, NH, *J* 3.8). Found, %: C 64.10; H 5.65; N 6.57. $C_{22}H_{22}N_2O_2S_2$. Calculated, %: C 64.36; H 5.40; N 6.82.

1-Methyl-5-(N-methylaminothiocarbonyl)-4,6-bis-(4-chlorophenyl)-1,2-dihydro-pyridine-2-thione (VIc). Yield 0.564 g (27%), mp 291–293°C (from DMSO). IR spectrum, ν, cm^{-1}: 1320, 1360, 1440, 1490, 1550, 1600, 3000, 3400. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.87 d (3H, NHC$\underline{H}_3$, *J* 4.1), 3.38 s (3H, CH_3-1), 6.77 s (1H, H^3), 7.47 d (2H, *p*-C_6H_4, *J* 8.1), 7.53 d (2H, *p*-C_6H_4, *J* 8.4), 7.62 d (2H, *p*-C_6H_4, *J* 8.1), 8.08 d (2H, *p*-C_6H_4, *J* 8.4), 9.29 q (1H, NH, *J* 4.1). Found, %: C 56.99; H 4.10; N 6.47. $C_{20}H_{16}Cl_2N_2S_2$. Calculated, %: C 57.28; H 3.85; N 6.68.

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