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α-THIOUREIDOALKYLATION OF 4-ALKYL- AND 4-PHENYLTHIOSEMICARBAZIDES

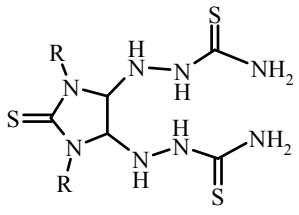
G. A. Gazieva[1]*, M. I. Struchkova[1], and N. G. Kolotyrkina[1]

Previously unknown 1,3-dialkyl-4,5-bis[4-alkyl(phenyl)thiosemicarbazido]imidazolidine-2-thiones and 4,5,7-trialkylperhydroimidazo[4,5-e]-1,2,4-triazine-3,6-dithiones have been synthesized by the α-thioureidoalkylation of 4-alkyl(phenyl)thiosemicarbazides using 1,3-dialkyl-4,5-dihydroxyimidazolidine-2-thiones.

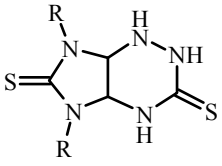
Keywords: 4-alkyl(phenyl)thiosemicarbazides, 1,3-dialkyl-4,5-bis(4-alkyl(phenyl)thiosemicarbazido)-imidazolidine-2-thiones, 1,3-dialkyl-4,5-dihydroxyimidazolidine-2-thiones, α-thioureidoalkylation.

Thiosemicarbazides have been of considerable interest in synthetic organic chemistry for many years. They are readily available and, thanks to the presence of several active reaction centers, are widely used as multipurpose reagents in organic synthesis, especially in the preparation of biologically active thiosemicarbazones and of nitrogen- and sulfur-containing heterocyclic compounds, e.g. thiazoles, thiadiazoles, triazoles, pyrazoles, thiadiazines, pyrimidines, etc. [1-6]. Thiosemicarbazide based substances show anticancer [1, 2, 7], antiparasitic [3, 4], and antimicrobial [5, 6] activity.

We have previously studied the α-thioureidoalkylation reaction of a thiosemicarbazide to give the 1,3-dialkyl-4,5-bis(thiosemicarbazido)imidazolidine-2-thiones **1a**,**b** and the 5,7-dialkylperhydroimidazo[4,5-*e*]-1,2,4-triazine-3,6-dithiones **2a**,**b** [8].



1a,b



2a,b

1, 2 a R = Me, **b** R = Et

Dedicated to L. I. Belen'kii on the occasion of his eightieth birthday.

* To whom correspondence should be addressed, e-mail: gaz@ioc.ac.ru.

[1]N. D. Zelinsky Institute for Organic Chemistry, Russian Academy of Sciences, 47 Leninsky Pr., Moscow 119991, Russia.

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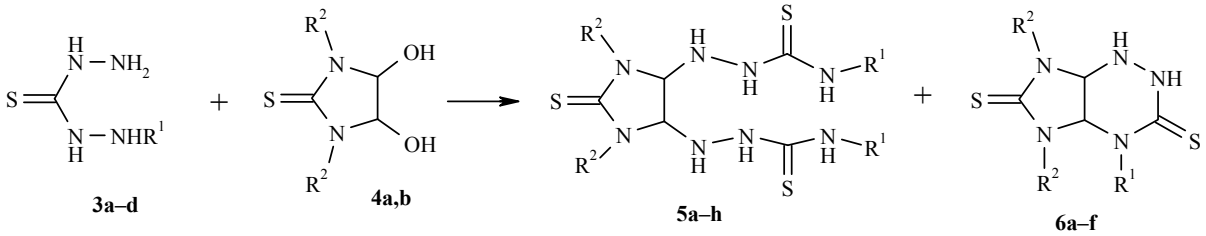
In this work we have now studied the reaction of the 4-alkyl- and 4-phenylthiosemicarbazides **3a-d** with the 4,5-dihydroxyimidazolidine-2-thiones **4a**,**b** and the effect of the substituent at position 4 of the thiosemicarbazide **3** on the reaction routes and yields. The α-thioureidoalkylation was carried out at 50-90ºC under HCl catalyzed conditions in water, isopropyl alcohol, or their mixture (depending on the solubility of the thiosemicarbazide). The highest yields of the 1,3-dialkyl-4,5-bis(4-alkyl(phenyl)thiosemicarbazido)imidazolidine-2-thiones **5a-h** (70-82%) were achieved by carrying out the reaction at 70-80ºC for 2 h. At lower temperature over 24 h the reaction mixture contains about 40% of the unreacted initial **3a-d** and **4a**,**b** materials. At 90ºC the dihydroxyimidazolidinethiones **4a**,**b** give 30-35% of 1,3-dialkyl-2-thioxoimidazolidin-4-ones (thiohydantoins [8]) and this leads to a lowering of the yields of compounds **5a-h**.



3a–d **4a,b** **5a–h** **6a–f**

3a, 5a,b, 6a,b R^1 = Me, **3b, 5c,d, 6c,d** R^1 = Et, **3c, 5e,f, 6e,f** R^1 = *i*-Bu, **3d, 5g,h** R^1 = Ph;
4a, 5a,c,e,g, 6a,c,e R^2 = Me, **4b, 5b,d,f,h, 6b,d,f** R^2 = Et

TABLE 1. Characteristics and High Resolution Mass Spectra* of Compounds **5a-f** and **6a**,**b**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C (decomp.)	Yield, %
		C	H	N	S		
5a	$C_9H_{20}N_8S_3$					255-257	77-79
5b	$C_{11}H_{24}N_8S_3$					205-207	80-82
5c	$C_{11}H_{24}N_8S_3$					232-234	74-76
5d	$C_{13}H_{28}N_8S_3$					225-227	74-77
5e	$C_{15}H_{32}N_8S_3$	42.74 / 42.83	7.69 / 7.67	26.71 / 26.64	22.78 / 22.87	216-218	71-74
5f	$C_{17}H_{36}N_8S_3$	45.66 / 45.50	8.13 / 8.09	24.91 / 24.97	21.37 / 21.44	184-186	73-76
5g	$C_{19}H_{24}N_8S_3$	49.49 / 49.54	5.27 / 5.25	24.38 / 24.33	20.79 / 20.88	186-189	70-73
5h	$C_{21}H_{28}N_8S_3$					196-198	71-74
6a	$C_7H_{13}N_5S_2$	36.39 / 36.34	5.72 / 5.66	30.23 / 30.27	27.61 / 27.72	262-264	2-5
6b	$C_9H_{17}N_5S_2$	41.62 / 41.67	6.68 / 6.61	27.05 / 27.00	24.60 / 24.72	230-232	2-5

* Mass spectrum:
5a – found, *m/z* 359.0867 $[M+Na]^+$; calculated, $[M+Na]^+$ 359.0865;
5b – found, *m/z* 387.1177 $[M+Na]^+$; calculated, $[M+Na]^+$ 387.1178;
5c – found, *m/z* 387.1182 $[M+Na]^+$; calculated, $[M+Na]^+$ 387.1178;
5d – found, *m/z* 391.1521 $[M–H]^-$; calculated, $[M–H]^-$ 391.1515;
5h – found, *m/z* 487.1527 $[M–H]^-$; calculated, $[M–H]^-$ 487.1515

In addition to the derivatives **5a**,**b** the reaction of compounds **4a**,**b** with the thiosemicarbazide **3a** also gives the imidazotriazines **6a**,**b** in 2-5% yields. The ^{1}H NMR spectra of the reaction masses of imidazolidinethiones **4a**,**b** and thiosemicarbazones **3b**,**c** evaporated to dryness show both signals for compounds **5c-f** and also for the 4,5,7-trialkylperhydroimidazo[4,5-*e*]-1,2,4-triazine-3,6-dithiones **6c-f** with low intensity (typical multiplets for the bridging CH protons at 5.25-5.42 and proton singlets for two NH groups at 5.7-5.8 and 9.4-9.6 ppm being observed).

TABLE 2. ^{1}H NMR Spectra of Compounds **5a-h** and **6a**,**b**

Compound	Chemical shifts, δ, ppm (*J*, Hz)
5a	2.93 (6H, d, *J* = 4.3, NCH_3); 2.98 (6H, s, NCH_3); 4.15 (2H, s, CH); 6.04 (2H, s, NH); 8.10 (2H, q, *J* = 4.3, NH); 8.80 (2H, s, NH)
5b	0.92 (6H, t, *J* = 6.8, CH_3); 2.92 (6H, d, *J* = 4.0, CH_3); 3.19-3.25 (2H, m, NCH_2); 3.86-3.93 (2H, m, NCH_2); 4.27 (2H, s, CH); 6.01 (2H, s, NH); 8.03 (2H, q, *J* = 3.9, NH); 8.69 (2H, s, NH)
5c	1.08 (6H, t, *J* = 6.9, CH_3); 2.99 (6H, s, NCH_3); 3.45-3.55 (4H, m, NCH_2); 4.20 (2H, s, CH); 6.01 (2H, s, NH); 8.08 (2H, br. s, NH); 8.74 (2H, s, NH)
5d	0.95 (6H, t, *J* = 6.9, CH_3); 1.09 (6H, t, *J* = 7.0, CH_3); 3.18-3.28 (2H, m, NCH_2); 3.42-3.59 (4H, m, $2NCH_2$); 3.86-3.98 (2H, m, NCH_2); 4.33 (2H, s, CH); 5.97 (2H, s, NH); 7.99 (2H, br. s, NH); 8.55 (2H, s, NH)
5e	0.85 (12H, d, *J* = 6.5, CH_3); 1.87-1.96 (2H, m, CH); 3.00 (6H, s, NCH_3); 3.22-3.31 (4H, m, NCH_2); 4.27 (2H, s, CH); 6.05 (2H, s, NH); 7.98 (2H, br. s, NH); 8.77 (2H, s, NH)
5f	0.86 (12H, d, *J* = 6.5, CH_3); 0.95 (6H, t, *J* = 6.6, CH_3); 1.87-1.95 (2H, m, CH); 3.22-3.32 (6H, m, $3NCH_2$); 3.87-3.98 (2H, m, NCH_2); 4.38 (2H, s, CH); 6.03 (2H, s, NH); 7.92 (2H, br. s, NH); 8.63 (2H, s, NH)
5g	3.08 (6H, s, NCH_3); 4.47 (2H, s, CH); 6.40 (2H, s, NH); 7.15 (2H, t, *J* = 7.1, H Ph); 7.31 (4H, t, *J* = 7.5, H Ph); 7.50 (4H, br. s, H Ph); 9.28 (2H, s, NH); 9.83 (2H, s, NH)
5h	0.99-1.05 (6H, m, CH_3); 3.27-3.34 (2H, q, *J* = 7.1, NCH_2); 3.96-4.03 (2H, q, *J* = 7.1, NCH_2); 4.55 (2H, s, CH); 6.38 (2H, s, NH); 7.17 (2H, t, *J* = 6.9, H Ph); 7.33 (4H, t, *J* = 7.4, H Ph); 7.50 (4H, d, *J* = 6.4, H Ph); 9.21 (2H, s, NH); 9.80 (2H, s, NH)
6a	2.95 (3H, s, NCH_3); 3.07 (3H, s, NCH_3); 3.29 (3H, s, NCH_3); 5.25-5.36 (2H, m, CH); 5.83 (1H, s, NH); 9.50 (1H, s, NH)
6b	1.05-1.11 (6H, m, CH_3); 3.28 (3H, s, NCH_3); 3.31-3.71 (4H, m, NCH_2); 5.33-5.42 (2H, m, CH); 5.77 (1H, s, NH); 9.49 (1H, s, NH)

TABLE 3. ^{13}C NMR Spectra of Compounds **5a-h** and **6a**,**b**

Compound	Chemical shifts, δ, ppm
5a	30.6 (NCH_3), 32.1 (NCH_3), 76.4 (CH), 182.1 (C=S), 183.0 (C=S)
5b	11.4 (CH_3), 30.6 (NCH_3), 37.6 (NCH_2), 73.0 (CH), 180.4 (C=S), 183.1 (C=S)
5c	14.6 (CH_3), 32.1 (NCH_3), 37.9 (NCH_2), 76.6 (CH), 181.9 (C=S), 182.1 (C=S)
5d	11.4 (CH_3), 14.7 (CH_3), 37.6 (NCH_2), 37.8 (NCH_2), 73.1 (CH), 180.3 (C=S), 181.9 (C=S)
5e	20.0 (CH_3), 27.8 (CH), 32.0 (NCH_3), 50.5 (NCH_2), 76.7 (CH cycle), 182.1 (C=S), 182.4 (C=S)
5f	12.2 (CH_3), 20.6 (CH_3), 28.4 (CH), 38.2 (NCH_2), 51.1 (NCH_2), 74.0 (CH cycle), 180.9 (C=S), 183.1 (C=S)
5g	32.2 (NCH_3), 76.6 (CH), 124.9, 125.5, 128.0, 138.9 (all Ph), 181.2 (C=S), 182.3 (C=S)
5h	11.6 (CH_3), 37.6 (NCH_2), 72.9 (CH), 125.0, 125.5, 128.0, 138.9 (all Ph), 180.5 (C=S), 181.4 (C=S)
6a	31.2 (NCH_3), 33.5 (NCH_3), 40.1 (NCH_3), 72.5 (CH), 75.9 (CH), 182.1 (C=S), 188.8 (C=S)
6b	12.2 (CH_3), 12.7 (CH_3), 38.3 (NCH_2), 39.9 (NCH_3), 70.9 (CH), 74.8 (CH), 180.7 (C=S), 189.8 (C=S)

Hence the nature of the substituent at position 4 of the thiosemicarbazide does not appear to have a major effect on the reaction product yields for **5a-h**, being little lowered upon lengthening or branching the alkyl chain at position 4 of the starting thiosemicarbazide (Table 1). We have previously obtained the imidazotriazines **2a**,**b** (unsubstituted on the N(4) atom) in 5-15% yields [8]. The yield of the 4-substitued imidazotriazines **6** is lower. The 4-methyl derivatives **6a**,**b** are produced in 2-5% yields, the 4-ethyl- (**6c,d**), and 4-isobutyl derivatives (**6e**,f) in trace quantities, but the 4-phenylimidazotriazines are not formed under the conditions studied.

Compound **5b** was investigated for cytotoxic activity in the Institute of Technical Chemistry (Ural Branch, Russian Academy of Sciences) with respect to the cell lines MS (human melanoma) and A549 (human microcellular lung cancer). The compound studied showed weak cytotoxic activity towards the MS cell line (IC_{50} = 238.47 ± 24.19 μM/l) but did not show activity towards the A549 line.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM 300 spectrometer (300 and 75 MHz respectively) using DMSO-d_6 with TMS as internal standard. High resolution mass spectra were recorded on a Bruker microTOF II instrument using electrospray ionization [9]. Measurements were carried out on positive (capillary voltage 4500 V) or negative ions (capillary voltage 3200 V). The mass scanning range was 50-3000 D with external or internal calibration (Electrospray Calibrant Solution, Fluka). Spray injection of the substances was used for solutions in methanol with flow rate 3μl/min. The gas carrier was nitrogen (4 l/min) and the interface temperature 180ºC. Melting points were determined on a Gallenkamp apparatus from the Sanyo Company.

1,3-Dialkyl-4,5-dihydroxyimidazolidine-2-thiones were synthesized by a previously devised method from 1,3-dialkylureas and glyoxal [10]. The 4-alkyl(phenyl)thiosemicarbazides were prepared from hydrazine and the corresponding alkyl(phenyl)isothiocyanate [11].

1,3-Dialkyl-4,5-bis[4-alkyl(phenyl)thiosemicarbazido]imidazolidine-2-thiones 5a-h and **4,5,7-Trialkylperhydroimidazo[4,5-*e*]-1,2,4-triazine-3,6-dithiones 6a,b (General Method)**. Conc. HCl (2 drops) was added to a solution of the 4,5-dihydroxyimidazolidine-2-thione **4a** or **4b** (5 mmol) and the corresponding thiosemicarbazide **3a-d** (10 mmol) in water (10 ml) for compounds **5a-d**, in 2-propanol (10 ml) for compounds **5g**,**h**, or in a mixture of water (7 ml) and 2-propanol (3 ml) for compounds **5e**,**f**. The product was stirred for 2 h at 70-80ºC. After cooling, the precipitated compounds **5c-h** and mixtures of compounds **5a**,**b** and **6a**,**b** were filtered off and recrystallized from methanol. Compounds **5a**,**b** and **6a**,**b** were separated by fractional crystallization from methanol.

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