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Abstract

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SYNTHESES AND SOME REACTIONS OF 4-SUBSTITUTED THIOSEMICARBAZIDES

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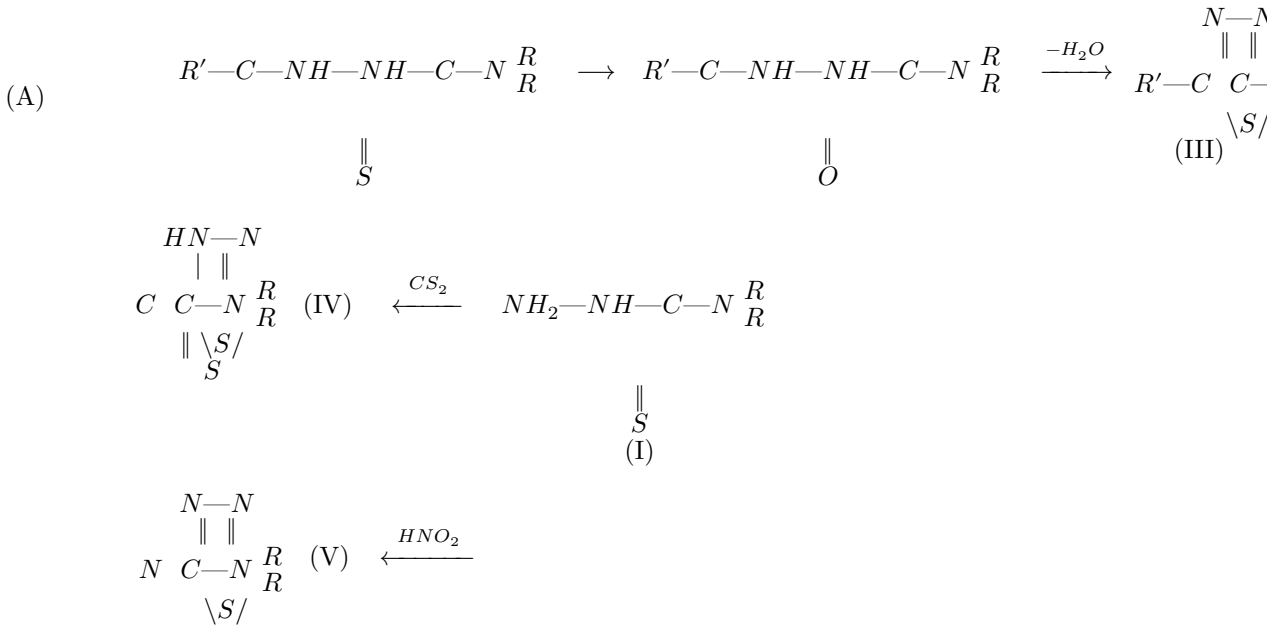
In work on the synthesis of compounds with presumed biological activity, the aim was to obtain 4,4-di-(β-hydroxyethyl)-thiosemicarbazide (VII) and other 4,4-disubstituted thiosemicarbazides (I), with their subsequent conversion into azoles according to the scheme:



Of the compounds of interest to us, only 4,4-dimethyl- and 4,4-diethylthiosemicarbazides ([1]) and 5-dimethylamino-1,2,3,4-thiatriazole ([2]) proved to have been described in the literature.

We tested the possibility of obtaining compound (VII) by Jensen' s method ([1]), which consists in obtaining dialkyldithiocarbaminoacetic acid and reacting its sodium salt with hydrazine hydrate. However, the expected compound (VII) could not be isolated from the reaction mixture. At the same time, it became clear that, after some simplification, this reaction can be successfully applied

to the preparative preparation of 4-monosubstituted thiosemicarbazides. It was found that these compounds can be obtained by successive treatment of the initial amine with carbon disulfide, sodium chloroacetate, and hydrazine hydrate, without isolation of intermediate products, according to the scheme:

$$R\text{—}NH_2 \xrightarrow[NH_4OH]{+CS_2} R\text{—}NH\text{—}C(=S)\text{—}SNH_4 \xrightarrow{ClCH_2COONa} \longrightarrow R\text{—}NH\text{—}C(=S)\text{—}SCH_2COONa \xrightarrow{NH_2\text{—}NH_2} NH_2\text{—}NH\text{—}C(=S)\text{—}NH\text{—}R \quad \text{(B)}$$

This method of obtaining 4-monosubstituted thiosemicarbazides, by virtue of its simplicity, has an advantage over the method of Pulvermacher ([3]), the drawback of which lies in the laboriousness of synthesizing the isothiocyanates that serve as the starting substances for that method. By scheme B, a series of 4-alkyl- and 4-arylthiosemicarbazides was obtained; the new compounds are given in Table 1.

Not having obtained 4,4-di-(β-hydroxyethyl)-thiosemicarbazide by method ([1]), we attempted to carry out the synthesis of this compound by another route:

$$NH_2\text{—}NH_2 \xrightarrow[KOH]{CS_2} NH_2\text{—}NH\text{—}C(=S)\text{—}SK \xrightarrow{CH_3J} NH_2\text{—}NH\text{—}C(=S)\text{—}SCH_3 \xrightarrow{HN(CH_2CH_2OH)_2} \longrightarrow NH_2\text{—}NH\text{—}C(=S)\text{—}N(CH_2CH_2OH)_2 \quad \text{(VII)}$$

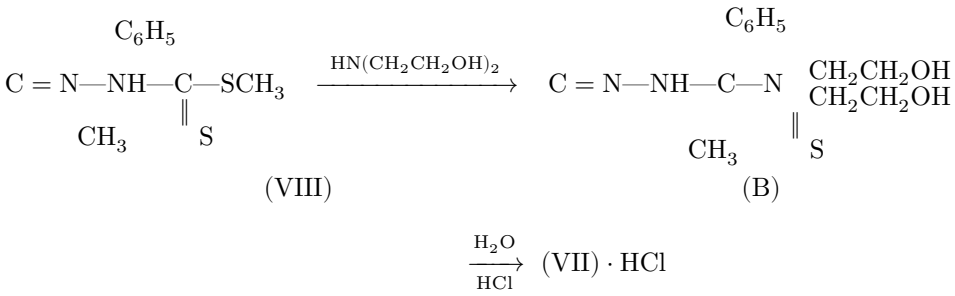
Table 1

4-Monosubstituted thiosemicarbazides
NH_2—NH—C(= S)—NH—R

R	M.p., °C	Yield, %	Empirical formula	N, % found	N, % calc.	S, % found	S, % calc.
$-CH_2CH_2OH$	110-115	36	$C_3H_9ON_3S$	31.20	31.11	23.80	23.70
$-u\text{-}C_6H_{11}$	141-143	57	$C_7H_{15}N_3S$	24.22	24.27	18.52	18.49
$-CH_2CH_2-$	221*	56	$C_4H_{12}N_6S_2$	40.35	40.38	30.75	30.76
$-(CH_2)_6-$	140-142*	35	$C_8H_{20}N_6S_2$	32.30	31.81	24.18	24.24

* With decomposition.

Indeed, as could be expected, the exchange reaction of the thioether group of the methyl ester of dithiocarbazic acid (VI) for diethanolamine did occur, but was accompanied by decomposition. In connection with this, it was not possible to obtain compound (VII) in this case. In attempting to carry out this reaction, instead of (VI) we took the products of its condensation with certain aldehydes and ketones and found that acetophenone methyl dithiocarbazone (VIII) reacts smoothly with diethanolamine, forming in good yield acetophenone 4,4-di-(β-hydroxyethyl)-thiosemicarbazone (IX). The latter is hydrolyzed by cold 1% HCl to give the hydrochloride of compound (VII).



Just as well as with diethanolamine, compound (VIII) reacts with other sufficiently basic amines*, giving the corresponding thiosemicarbazones (Table 2). According to scheme B, 4-(β-hydroxyethyl)- and 4,4-diethylthiosemicarbazides were synthesized, which proved to be identical with those obtained by

Table 2

4-Substituted thiosemicarbazones of acetophenone
$C_6H_5C(=N—NH—C(=S)—R)CH_3$

R	M.p., °C	Yield, %	Empirical formula	N, % found	N, % calc.	S, % found	S, % calc.
—NH—CH_2CH_2OH	108–109	97	$C_{11}H_{15}ON_3S$	17.50	17.72	—	—
—$N(CH_2CH_2OH)_2$	134–135	95	$C_{13}H_{19}O_2N_3S$	14.86	14.94	11.71	11.38
—N cyclohexyl ring	134–135	90	$C_{13}H_{17}N_3S$	16.99	17.00	13.01	12.96
—N piperidyl ring	101–102	96	$C_{14}H_{19}N_3S$	15.55	16.09	12.03	12.26
—N morpholine ring	105–107	98	$C_{13}H_{17}ON_3S$	15.69	15.96	12.41	12.16

* Found, %: C 55.26; H 6.60. Calculated, %: C 55.51; H 6.76.

* Under analogous conditions, aromatic amines do not react with compound (VIII).

Table 3

4,4-Disubstituted thiosemicarbazides

$$NH_2{-}NH{-}C(=S){-}R$$

R	M.p., °C	Base: empirical formula	Base: N, % found	Base: N, % calcd.	Base: S, % found	Base: S, % calcd.	Hydrochloride: m.p., °C (with decomp.)	Hydrochloride: yield, %	Hydrochloride: N, % found	Hydrochloride: N, % calcd.
— $N(CH_2CH_2OH)_2$	—	$C_5H_{13}O_2N_3S$	—	—	—	—	149–151	67	19.64	19.48
—N-pyrrolidyl	163–165 (with decomp.)	$C_5H_{11}N_3S$	28.48	28.96	22.12	22.06	206–208	98	22.92	23.14
—N-piperidyl	95–96.5	$C_6H_{13}N_3S$	26.12	26.41	19.96	20.12	200–202	76	21.31	21.48
—N-morpholyl	176–177 (with decomp.)	$C_5H_{11}ON_3S$	26.18	26.08	19.81	19.87	164–166	70	21.39	21.26

scheme B, as well as thiosemicarbazides with cyclic residues not previously described (Table 3).

Several of the 4,4-disubstituted thiosemicarbazides obtained by us were converted into azoles according to scheme A. These transformations were carried out by means of reactions described as applied to thiosemicarbazide and 4-monosubstituted thiosemicarbazides ([4]-[8]). 2-Amino-5-alkyl-(aryl)-1,3,4-thiadiazoles (III) substituted at the amino group were obtained by cyclization of the intermediate acyl derivatives (II) with chloroacetyl chloride or concentrated sulfuric acid. Compounds (IV) were synthesized by boiling (I) with carbon disulfide in pyridine. Substituted 5-amino-1,2,3,4-thiatriazoles (V) were obtained by the interaction of the hydrochlorides of thiosemicarbazides (I) with sodium nitrite. Some of the compounds synthesized according to scheme A are given in Table 4.

Experimental Part

Acetophenone methyldithiocarbazone (VIII). To 12.2 g (0.1 g-mol) of the methyl ester of dithiocarbazinic acid ([9]) in 100 ml of alcohol, 12 g (0.1 g-mol) of acetophenone was added, and the mixture was boiled for 10 min. Yield: 21 g (94%) of yellow prisms, m.p. 142–143° (from alcohol). Found, %: N 12.49. $C_{10}H_{12}N_2S_2$. Calculated, %: N 12.50.

4,4-Di-(β-oxyethyl)-thiosemicarbazone of acetophenone (IX). A mixture of 18 g (0.08 g-mol) of (VIII) and 10.5 g (0.1 g-mol) of diethanolamine in 100 ml of methanol was boiled for 9 h. After cooling, the reaction solution was diluted with water until turbidity ceased to appear. After standing for 2 h, 20 g (90%) of light-yellow needles were filtered off and recrystallized from 50% methanol.

Under analogous conditions, the remaining 4-substituted thiosemicarbazones of acetophenone were obtained (Table 2).

Hydrochloride of 4,4-(β-oxyethyl)-thiosemicarbazide. 28.1 g (0.1 g-mol) of (IX) was shaken for 3 h with 300 ml of cold dilute hydrochloric acid containing 0.09 g-mol of HCl. The acetophenone formed upon hydrolysis was extracted with ether, and the excess (IX) was separated. The filtrate was evaporated to a thick mass, which crystallized in a vacuum desiccator over silica gel. The crystals were triturated with absolute alcohol, filtered off, and reprecipitated from alcohol with ether.

Other 4-substituted thiosemicarbazides of acetophenone were hydrolyzed under harsher conditions, i.e., using 3–4% hydrochloric acid.

Table 4

Substituted 2-amino-5-methyl-1,3,4-thiadiazoles (III), 2-amino-1,3,4-thiadiazoline-5-thiones (IV), and 5-amino-1,2,3,4-thiatriazoles (V)

Structure	R	Mp, °C	Yield, %	Empirical formula	N, % found	N, % calc.	S, % found	S, % calc.
(III)	–$N(CH_3)_2$	186–188**	80	$C_5H_9N_3S_2$·HCl	23,52	23,39	17,74	17,82
(III)	–N-piperidyl	43–44,5	88	$C_8H_{13}N_3S_2$	22,72	22,95	17,67	17,48
(III)	–N-morpholinyl	88–90	71	$C_7H_{11}ON_3S_2$	22,82	22,70	17,49	17,30
(IV)	–$N(CH_3)_2$	174–175	34	$C_4H_7N_3S_2$	26,06	26,09	39,69	39,75
(IV)	–N-piperidyl	165–167	72	$C_7H_{11}N_3S_2$	20,97	20,89	32,13	31,84
(IV)	–N-morpholinyl	173–175	25	$C_6H_9ON_3S_2$	20,73	20,68	31,24	31,52
(V)	–$N(CH_3)_2$	48–50* (49–51)	35	$C_3H_6N_4S$	–	–	–	–
(V)	–N-piperidyl	28–29	65	$C_6H_{10}N_4S$	32,71	32,94	19,04	18,82
(V)	–N-morpholinyl	114–115	87	$C_5H_8ON_4S$	32,31	32,55	18,74	18,60

* Characterized as the hydrochloride.
** With decomposition.

upon heating on a water bath. The free bases were isolated with sodium acetate. The new 4,4-disubstituted thiosemicarbazides and their hydrochlorides are given in Table 3.

2-(N-piperidyl)-5-methyl-1,3,4-thiadiazole. To 2 g (0.01 g-mol) of 1-acetyl-4,4-pentamethylenesemicarbazide, obtained by acetylation with acetic anhydride in the cold, 5 ml (0.06 g-mol) of acetyl chloride was added. After one hour the mass was carefully made alkaline with 30% NaOH. The amine was extracted with ether and purified by reprecipitation from ether with petroleum ether. The amine is readily soluble in water and in organic solvents.

2-(N-piperidyl)-1,3,4-thiadiazoline-5-thione. To 1.95 g (0.01 g-mol) of 4,4-pentamethylenethiosemicarbazide hydrochloride in 15 ml of pyridine, 0.9 ml (0.015 g-mol) of carbon disulfide was added, and the mixture was boiled for 4 hours; after cooling it was poured into 100 ml of 2 N HCl. The product that separated was recrystallized from 50% methyl alcohol.

5-(N-piperidyl)-1,2,3,4-thiatriazole. To 1.95 g (0.01 g-mol) of 4,4-pentamethylenethiosemicarbazide hydrochloride in 10 ml of water, with cooling to 0°, a solution of 0.7 g (0.01 g-mol) of sodium nitrite in 10 ml of water was

added dropwise. The substance obtained was recrystallized from petroleum ether.

All the other compounds given in Table 4 were obtained analogously to the last three syntheses.

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Note: Figure translations are in progress. See original paper for figures.