SYNTHESIS OF 3-CARBOXYALKYLTHIAZOLIDINE-2-THIONE 4-THIOSEMICARBAZONES AND THEIR DERIVATIVES

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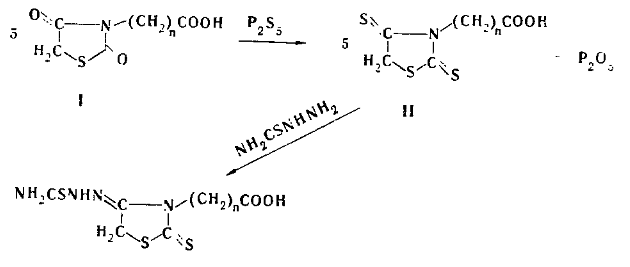
3-Carboxyalkylthiazolidine-2-thion-4-ones react with phosphorus pentasulfide to give 4-thiono analogs, which react with thiosemicarbazide to give the corresponding 4-thiosemicarbazones. 5-Substituted derivatives were obtained by condensation of the oxo compounds with 3-carboxyalkylthiazolidine-2-thione-4-thiosemicarbazones.

Thiazolidine-2,4-dione 2,4-thiosemicarbazones [1, 2], which are potentially of interest as antithyroid and antituberculous preparations [3-5], unfortunately are unsoluble in water and do not give stable salts in aqueous solutions.

We have obtained water-soluble thiazolidine-2-thion-4-one 4-thiosemicarbazones with a hydrophilic carboxyalkyl grouping in the 3 position. 3-Carboxymethylthiazolidine-2-thion-4-one [6] and other 3-carboxyalkylthiazolidine-2-thion-4-ones (I) were converted to 3-carboxyalkylthiazolidine-2,4-dithiones (II) by reaction with phosphorus pentasulfide. The thiono grouping in the 4 position of the thiazolidine derivatives is extremely reactive [7-9]. In fact, 3-carboxyalkylthiazolidine-2,4-dithiones readily form 3-carboxyalkylthiazolidine-2-thion-4-one 4-thiosemicarbazones (III).

The 3-carboxyalkylthioazolidine-2-thion-4-one 4-thiosemicarbazones are soluble in water and are readily recrystallized from it; it was observed that the solubility decreases as the length of the carboxyalkyl residue increases.



IIIa n=1; b n=2; c n=3; d n=5

In order to confirm the structure of the 3-carboxyalkylthiazolidine-2-thion-4-one 4-thiosemicarbazones we synthesized their arylidene derivatives with p-nitrobenzaldehyde (IVa-d) and 5-bromoisatin (Va-d) (Table 1); these derivatives are yellow or red substances that are soluble in most organic solvents.

Thiosemicarbazones III are characterized by two absorption bands with maxima at 252-256 nm (the p−π band of the thioamide fragment) and 294-296 nm (the p−π transition of the $-\ddot{S}-\underset{|}{C}=S$ dithiocarbonate chromophore). The introduction of 5-bromoisatin residues in the 5 position leads to the development of a broad band with maxima and inflections at 397-420 nm because of the formation of the $R-\overset{\xrightarrow{e}}{\underset{|}{C}_6H_3}-\underset{|}{C}=\underset{|}{C}-\underset{|}{C}=\dot{N}-$ chromophore. Superimposition of the π−π * transition of the aryl group on the second absorption band (λ_{max} 290-291 nm) and of the p−π transition of the $>C_6H_3-\underset{|}{\ddot{N}}-\underset{|}{C}=O$ phenyliminocarbonyl chromophore on the first band λ_{max} 244-249 nm) occurs simultaneously.

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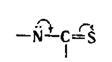
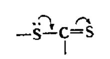
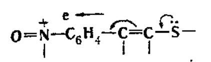
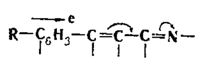
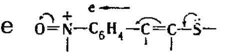
TABLE 1. 3-Carboxyalkylthiazolidine-2-thion-4-one 4-Thiosemicarbazones and Their Derivatives

Compound	mp, °C	Empirical formula	Found, %		Calc., %		Yield, %
			N	S	N	S	
IIIa	206—207 (dec.)	$C_6H_8O_2N_4S_3$	21,0	36,0	21,2	36,4	72
IIIb	186 (dec.)	$C_7H_{10}O_2N_4S_3$	19,9	34,4	20,1	34,6	79
IIIc	175	$C_8H_{12}O_2N_4S_3$	19,0	32,5	19,2	32,9	81
IIId	166—168	$C_{10}H_{16}O_2N_4S_3$	17,2	29,9	17,5	30,0	69
IVa	238—240	$C_{14}H_{10}O_3N_5S_3Br$	14,6	20.0	14,8	20,4	79
IVb	232—233	$C_{15}H_{12}O_3N_5S_3Br$	14,3	19.9	14,4	19,8	87
IVc	220—221	$C_{16}H_{14}O_3N_5S_3Br$	13,8	19,0	14,0	19,2	88
IVd	215	$C_{18}H_{18}O_3N_5S_3Br$	13,2	18,1	13.3	18,2	90
Va	219—220 (dec.)	$C_{13}H_{11}O_4N_5S_3$	17,6	24,3	17.6	24,2	82
Vb	226 (dec.)	$C_{14}H_{13}O_4N_5S_3$	16,6	22,9	17,0	23,4	84
Vc	212	$C_{15}H_{15}O_4N_5S_3$	16.3	22,3	16,4	22,6	81
Vd	182	$C_{17}H_{19}O_4N_5S_3$	15,1	20,8	15.4	21,2	91

TABLE 2. UV Spectra of III-V

Compound	Chromophores							
								
	λ_{max}, nm	$\lg \varepsilon_{max}$	λ_{max}, nm	$\lg \varepsilon_{max}$	λ_{max}, nm	$\lg \varepsilon_{max}$	λ_{max}, nm	$\lg \varepsilon_{max}$
IIIa	252	4,34	294	4,16	—	—	—	—
IIIb	255	4,27	295	4.12	—	—	—	—
IIIc	256	4.27	295	4.15	—	—	—	—
IIId	255	4.23	295	4.13	—	—	—	—
IVa	249	4,41	290*	—	—	—	399, 415*	4.40—4,38
IVb	248	4.46	291	3,82	—	—	390*, 415	
IVc	245	4,45	290	3,68	—	—	397, 420*	
IVd	244	4,41	290	3,61	—	—	398, 418*	4.29—4.31
Va	245	4,27	278	4,17	375	4,46	—	—
Vb	245	4,27	278	4,01	376	4,42	—	—
Vc	244	4,34	278	4,07	378	4,47	—	—
Vd	243	4,33	278	4,05	378	4,51	—	—

*Inflections on the absorption curve.

The introduction of a p-nitrobenzylidene grouping in the 5 position of thiosemicarbazone III leads to the development of a new band with a maximum at 375-378 because of the formation of the  chromophore. Electron transfer in the dithiocarbonate chromophore is hindered as a result of drawing together of the electrons from the S atom in the 1 position, and the maximum in the second band is shifted hypsochromically to 278 nm, where there is superimposition of the $\pi-\pi^*$ transitions of the phenyl rings. Similarly, there is also a hypsochromic shift of the maxima in the second band to 243-245 nm (Table 2).

EXPERIMENTAL

The UV spectra of methanol solutions of the compounds were recorded with an SF-4A spectrophotometer.

3-Carboxyalkylthiazolidine-2,4-dithiones (II). These compounds were obtained by reaction of 0.02 mole of 3-carboxyalkylthiazolidine-2-thion-4-ones (I) with 0.89 g of purified phosphorus pentasulfide in 25 ml of dioxane with vigorous stirring and refluxing in a flask equipped with a reflux condenser for 1 h. The resulting solutions were clarified with activated charcoal and used without additional purification in the subsequent syntheses.

3-Carboxyalkylthiazolidine-2-thion-4-one 4-Thiosemicarbazones (III). These compounds were obtained by refluxing 0.02 mole of a freshly prepared dioxane solution of 3-carboxyalkylthiazolidine-2,4-dithiones with 1.82 g (0.02 mole) of thiosemicarbazide in 20 ml of methanol for 2-3.5 h until hydrogen sulfide evolution ceased. The corresponding thiosemicarbazones were precipitated by cooling the mixture for 24 h or by the addition of the minimum amount of water. Crystallization from water gave dirty-yellow and orange crystalline products.

5-Arylidene-3-carboxyalkylthiazolidine-2-thion-4-one 4-Thiosemicarbazones (IV, V). A mixture of 5 mmole each of thiosemicarbazone III and 5-bromoisatin (or p-nitrobenzaldehyde) in 20 ml of ethanol was refluxed for 2 h with 0.5 g of NH_4Cl and 0.5 ml of NH_4OH. Red, bordeaux-red, or yellow precipitates formed after 10-15 min. After 24 h, the mixture was diluted with water, acidified with HCl, and filtered. The products were crystallized from acetic acid or dioxane.

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REACTION OF 2-IMINO-3-ARYL-4-OXOTHIAZOLIDINES WITH PHENYL ISOTHIOCYANATE

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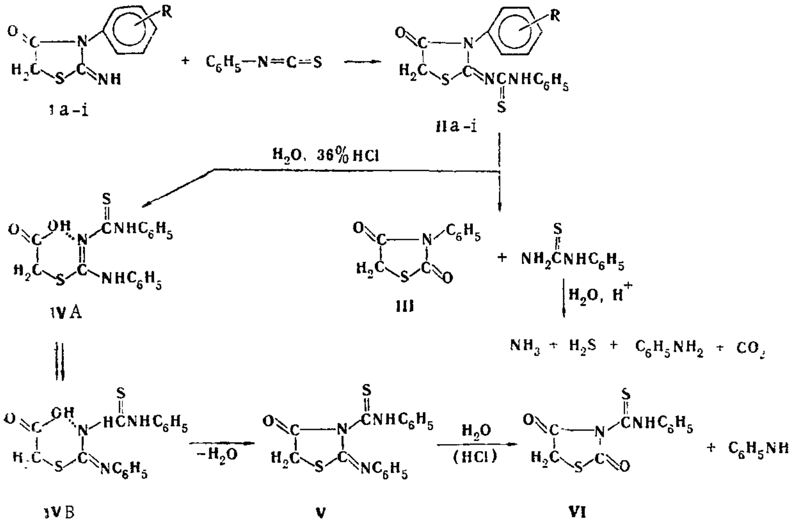
2-Phenylthiocarbamoylimino-3-aryl-4-oxothiazolidines, which are hydrolyzed at the C=N and $N_3=C_4$ bonds of the thiazolidine ring to give 3-arylthiazolidine-2,4-diones, N-phenylthiocarbamoylarylpseudothiohydantoic acids, and 3-phenylthiocarbamoylthiazolidine-2,4-dione, were synthesized by reaction of 2-imino-3-aryl-4-oxothiazolidines with phenyl isothiocyanate.

In order to obtain compounds with possible physiological activity we investigated the addition of phenyl isothiocyanate to the imino group of 2-imino-3-aryl-4-oxothiazolidines Ia-i to give 2-phenylthiocarbamoylimino-3-aryl-4-oxothiazolidines IIa-i in high yields.



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