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ARYLAMIDES OF SUBSTITUTED THIOCARBOXYLIC ACIDS

III. Cyclizing Arylamides of Acetylthioacetic Acid

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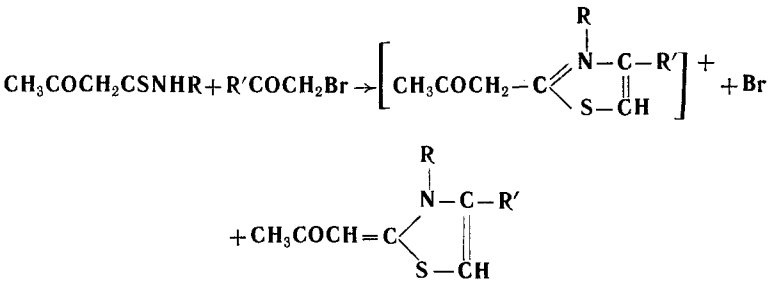
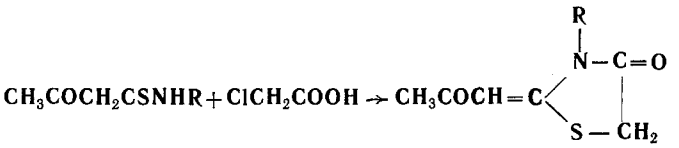
Cyclization of arylamides of acetylthioacetic acid with ω-bromoacetophenone gives mixtures containing hydrobromides of 2-(acetylmethylene)-3,4-diarylthiazolines and 2-(acetylmethylene)-3,4-diarylthiazolines, and from these mixtures hitherto undescribed substituted 4-thiazoline derivatives were isolated by chromatography. 2-(Acetylmethylene)-3-aryl-4-thiazolidones were obtained for the first time by reacting arylamides with acetylthioacetic acid with monochloroacetic acid in the presence of fused sodium acetate in glacial acetic acid.

It is known that thioamides of acids when reacted with α-halogenocarbonyl compounds give thiazole derivatives [1, 2]. It was shown that arylamides of acetylthioacetic acid, containing a secondary thioamide group, react both with α-halogenoketones and with α-halogenocarboxylic acids. In the former case, cyclization results in formation of a mixture of hydrohalide salt of a substituted 4-thiazoline with a small quantity of a methylene base:



α-Halogenocarboxylic acids react with arylamides of acetylthioacetic acid to give methylene bases of substituted 4-thiazolidones.



Among derivatives of 4-thiazoline and 4-thiazolidone are valuable physiologically active compounds [3, 4].

Substituted 4-thiazolines and 4-thiazolidones are used as intermediates in synthesizing cyanine dyes [5], and they also find application in other ways [6]. In this connection, it was of interest to prepare substituted 4-thiazolines and 4-thiazolidones hitherto undescribed in the literature.

Cyclization of arylamides of acetylthioacetic acid with ω-bromoacetophenone has now been investigated. Reaction was effected by boiling equimolecular amounts of reactants together in ethanol [7]. The end product was a yellow crystalline mixture of 2-acetonyl-3,4-diarylthiazolinium bromide and the methylene base, – 2-(acetylmethylene)-3,4-diarylthiazoline, bromide. It was not possible to isolate the hydrobromide of the methylene base pure, as hydrogen bromide split off on recrystallization.

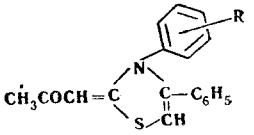
The methylene bases were obtained pure by column chromatography on Al_2O_3 of ethanol solutions of the end products. 2-(Acetylmethylene)-3,4-diarylthiazolines (Table 1) are white or colored, and are readily soluble in chloroform, soluble in ethanol, and insoluble in water.

Arylamides of acetylthioacetic acid react with monochloroacetic acid to give 2-(acetylmethylene)-3-aryl-4-thiazolidones. The reaction is effected by boiling with glacial acetic acid and fused sodium acetate [8]. A few minutes after the onset of reaction the color of the solution changes, and a slight, pale precipitate forms. Precipitate formation is most rapid in the reaction of monochloroacetic acid with p-phenetidyl acetylthioacetic acid.

The 2-(acetylmethylene)-3-aryl-4-thiazolidones (Table 2) which we synthesized were colored crystalline substances, soluble in ethanol, and chloroform, soluble with difficulty in aqueous ethanol, partly soluble in hot 10% potassium hydroxide solution, to give yellow solutions. Insoluble in hydrochloric acid.

Table 1

2-(Acetylmethylene)-3-aryl-4-phenylthiazolines

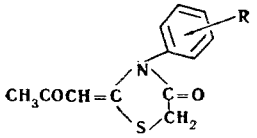


Compound No.	R	Mp, ° C	Formula	Found S, %	Calculated S, %	Yield, %
I	H	215—216	$C_{18}H_{15}NOS$*	11.03; 11.04	10.95	52
II	*p*-CH_3	158—159	$C_{19}H_{17}NOS$	10.26; 10.23	10.43	50
III	*p*-OCH_3	145—146 (decomp)	$C_{19}H_{17}NO_2S$	9.80; 9.77	9.90	52
IV	*o*-OCH_3	192—194	$C_{19}H_{17}NO_2S$	9.98; 9.98	9.90	48
V	*p*-OC_2H_5	132—133	$C_{20}H_{19}NO_2S$	9.34; 9.28	9.48	53

* Found: C 73.79, 73.72; H 5.01, 5.03; N 4.99, 5.09%; M 292.4. Calculated: C 73.65; H 5.14; N 4.77%; M 293.36.

Table 2

2-(Acetylmethylene)-3-aryl-4-thiazolidones



Compound number	R	Mp, ° C	Formula	Found, S %	Calculated S, %	Yield, %
VI	H	204—206	$C_{12}H_{11}NO_2S$	13.46; 13.45	13.75	36
VII	*p*-CH_3	200—202	$C_{13}H_{13}NO_2S$*	12.86; 12.87	13.01	43
VIII	*p*-OCH_3	201—202	$C_{13}H_{13}NO_3S$	11.95; 12.02	12.19	43
IX	*o*-OCH_3	145—146	$C_{13}H_{13}NO_3S$	12.18; 12.26	12.19	40
X	*p*-OC_2H_5	163—164	$C_{14}H_{15}NO_3S$	11.64; 11.63	11.56	50

* Found: C 63.36, 63.32; H 5.31, 5.27; N 6.01, 6.03%; M 256.9. Calculated: C 63.13; H 5.29; N 5.66%; M 247.32.

Experimental

2-(Acetylmethylene)-3,4-diphenylthiazoline (I). 2 g (0.01 mole) ω-bromoacetophenone was added to a solution of 2 g (0.01 mole) acetylthioacetanilide in 8 ml ethanol, and the mixture refluxed for 2 hr. The precipitate which formed on cooling was filtered off and washed with ethanol. The dry solid weighed 2.6 g, it was dissolved in 78 ml EtOH, and column chromatographed on Al_2O_3, eluting with EtOH. After removing the solvent under reduced pressure the yield of pure methylene base was 1.56 g (52%, based on the acetylthioacetanilide), mp 215°–216° C.

The other compounds shown in Table 1 were prepared similarly. With II and III the time for which the reactants were heated together was 25 min, for IV it was 1 hr, and for V, 2 hr.

2-(Acetylmethylene)-3-phenyl-4-thiazolidone (VI). 0.9 g (0.0094 mole) monochloroacetic acid and 1.48 g (0.018 mole) fused NaOAc were added to 1.2 g (0.006 mole) acetylthioacetanilide in 10 ml glacial AcOH and the

whole refluxed for 1 hr 30 min. A pale precipitate appeared 30 min after the commencement of boiling. After cooling, the reaction products were poured into 30 ml cold water. The precipitate formed was filtered off and dried, yield of pure compound 0.5 g, mp 204°-206° C (ex aqueous EtOH). The other 4-thiazolidones given in Table 2, were prepared similarly.

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