NEW SYNTHESIS OF 2-AMINO-1-THIA-4-CHROMONES

Yu. M. Volovenko, V. A. Litenko,
E. V. Dashkovskaya, and F. S. Babichev

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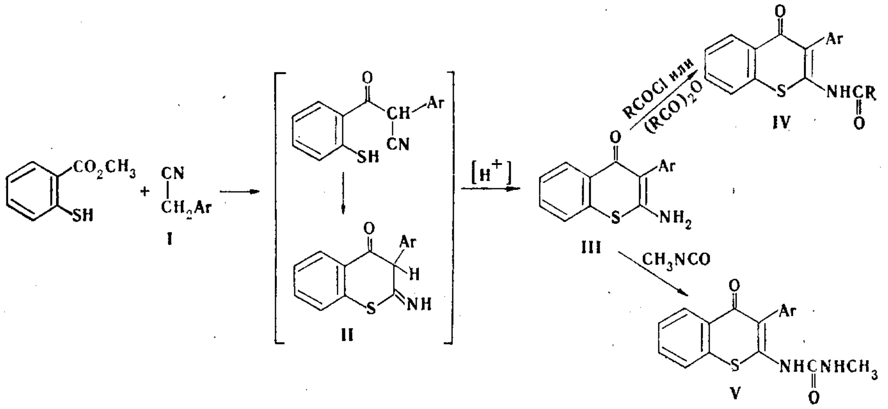
The reaction of arylacetonitriles with methyl thiasalicylate leads to 2-amino-3-aryl-1-thia-4-chromones. The spectral characteristics and the reactions at the amino group were studied.

It is known that 1-thia-4-chromone derivatives display high physiological activity. Effective anti-inflammatory [1] and antivirus [2] preparations are found among these compounds. It seemed of interest to study the possibility of the synthesis of compounds of the 2-amino-1-thia-4-chromone series, since the introduction of an amino group makes it possible to modify the thiachromone molecule. Up until now, there has been only one paper [3] in which the synthesis of unsubstituted 2-amino-1-thia-4-chromone by the traditional multistep method used for the synthesis of 2-aminochromones [4, 5] was presented.

We have found that the reaction of arylacetonitriles (I) with methyl thiasalicylate under basic catalysis conditions leads to 2-amino-3-aryl-1-thia-4-chromones (III) in high yields. The reaction evidently commences with attack by the carbanion generated by the strong base (sodium tert-butoxide) from the arylacetonitrile at the ester group to give an acyl derivative (III) with subsequent addition of the sulfhydryl group to the triple bond of the nitrile:



Two absorption bands of a primary amino group at 3150-3350 cm^{-1} are observed in the IR spectra of the compounds obtained. The absorption of a pyrone carbonyl group lies at 1610-1630 cm^{-1}. A two-proton singlet at 6.6-6.8 ppm, which vanishes when heavy water is added, is observed in the PMR spectra and is due to the signal of the protons of the amino group. The UV spectra are characterized by three absorption maxima at 205 (ε = 42,000), 235 (ε = 37,000), and 335 nm (ε = 15,000). Thus the data from the IR, UV, and PMR spectra constitute evidence for the existence of 2-amino-3-aryl-1-thia-4-chromones in the oxo amino form.

Compounds III remain unchanged when they are refluxed in an acidic medium, in contrast to the structurally similar 2-aminochromones, which are hydrolyzed under these conditions to 4-hydroxycoumarins [4, 5]. The presence of an amino group is confirmed by reactions with acid anhydrides and chlorides, which lead to acylamino derivatives (IV). 2-(3-Methylureido) derivatives (V) are obtained by reaction with methyl isocyanate.

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TABLE 1. 2-Amino-3-aryl-1-thia-4-chromones

Compound	Ar	mp, °C	Found, %	Empirical formula	Calculated, %	Yield, %
IIIa	C_6H_5*	186	N 5,6; S 12,7	$C_{15}H_{11}NOS$	N 5,5; S 12,6	60
IIIb	2-ClC_6H_4†	201	Cl 12,3; S 11,3	$C_{15}H_{10}ClNOS$	Cl 12,3; S 11,1	66
IIIc	3-BrC_6H_4†	239	Br 24,3; S 9,6	$C_{15}H_{10}BrNOS$	Br 24,1; S 9,7	96
IIId	4-$(C_2H_5O)C_6H_4$†	213	N 4,8; S 10,8	$C_{17}H_{15}NO_2S$	N 4,7; S 10,8	81
IIIe	3,4-$(CH_3O)_2C_6H_3$*	294—295 (dec.)	N 4,5; S 10,2	$C_{17}H_{15}NO_3S$	N 4,5; S 10,2	91
IIIf	2,3,4-$(CH_3O)_3C_6H_2$*	212	N 4,3; S 9,3	$C_{18}H_{17}NO_4S$	N 4,0; S 9,3	86

*From toluene.
†From 2-propanol.

EXPERIMENTAL

The PMR spectra were recorded with a ZKR-60 spectrometer with tetramethylsilane as the internal standard. The IR spectra of potassium bromide pellets of the compounds were recorded with a UR-20 spectrometer. The UV spectra of solutions in methanol were recorded with a Specord UV-vis spectrophotometer.

2-Amino-3-aryl-1-thia-4-chromones (III). A mixture of 0.03 mole of the alkyl ester of thiasalicylic acid, 0.03 mole of the arylacetonitrile, and 0.12 mole of sodium tert-butoxide in 40 ml of pyridine was refluxed for 3 h, after which the pyridine was removed by heating in vacuo, and the residue was transferred to 200 ml of water and neutralized by stirring with 17 ml of 50% acetic acid. The precipitate was removed by filtration and washed with water. The constants and yields of III are presented in Table 1.

2-Acetamido-3-(2-chlorophenyl)-1-thia-4-chromone (IVa). A 0.6-g (2.2 mmole) sample of 2-amino-3-(2-chlorophenyl)-1-thia-4-chromone (IIIb) and 0.3 ml (3.1 mmole) of acetic anhydride were refluxed in 2 ml of pyridine for 3 h, after which the pyridine was evaporated in vacuo, and the residue was treated with water. The solid material was removed by filtration and washed with sodium bicarbonate solution to give 0.4 g (72%) of a product with mp 211-212°C (from n-propanol). Found: Cl 10.7; N 4.1; S 9.8%. $C_{17}H_{12}ClNO_2S$. Calculated: Cl 10.7; N 4.2; S 9.7%.

2-Acetamido-3-(3-bromophenyl)-1-thia-4-chromone (IVb). This compound, with mp 234°C (from toluene), was obtained in 82% yield from 2-amino-3-(3-bromophenyl)-1-thia-4-chromone (IIIc) by a method similar to that used to prepare IVa. Found: Br 21.2; N 3.9; S 8.6%. $C_{17}H_{12}BrNO_2S$. Calculated: Br 21.4; N 3.7; S 8.6%.

2-Benzamido-3-(4-ethoxyphenyl)-1-thia-4-chromone (IVc). A 0.6-g (2 mmole) sample of 2-amino-3-(4-ethoxyphenyl)-1-thia-4-chromone (IIId) and 0.4 ml (3.3 mmole) of benzoyl chloride were refluxed in 5 ml of pyridine for 2 h, after which the pyridine was removed by heating in vacuo. The residue was treated with water, and the solid material was removed by filtration and washed with sodium bicarbonate solution to give 0.8 g (97%) of a product with mp 218°C (from 2-propanol). Found: N 3.6; S 8.4%. $C_{24}H_{19}NO_3S$. Calculated: N 3.5; S 8.0%.

2-(3-Methylureido)-3-(4-ethoxyphenyl)-1-thia-4-chromone (Va). A 1.5-g (5 mmole) sample of 2-amino-3-(4-ethoxyphenyl)-1-thia-4-chromone (IIId) and 0.4 ml (7 mmole) of methyl isocyanate were refluxed in 20 ml of dioxane in the presence of a catalytic amount of sodium tert-butoxide for 4 h, and the precipitated crystals were removed by filtration and washed with dioxane to give 1.2 g (74%) of a product with mp 220°C. The reaction product was isolated in analytically pure form. Found: C 65.7; H 5.2%. $C_{19}H_{18}N_2O_3S$. Calculated: C 64.4; H 5.1%.

2-(3-Methylureido)-3-(2-chlorophenyl)-1-thia-4-chromone (Vb). This compound, with mp 229°C (dec.), was obtained in 70% yield from 2-amino-3-(2-chlorophenyl)-1-thia-4-chromone (IIIb) by a method similar to that used to prepare Va. Found: Cl 10.3; S 9.5%. $C_{17}H_{13}ClN_2O_2S$. Calculated: Cl 10.3; S 9.3%.

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INVESTIGATION OF THE REACTIVITY AND TAUTOMERISM OF AZOLIDINES.

41.* REACTION OF 5-BENZYLIDENE-2,4-THIAZOLIDINEDIONES WITH FORMALDEHYDE

A. I. Ginak, V. M. Sokolov,
and S. M. Ramsh

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The reaction of 5-benzylidene-2,4-thiazolidinediones with formaldehyde leads to the formation of only 3-hydroxymethyl-5-benzylidene-2,4-thiazolidenediones in high yields. The structures of the compounds obtained were confirmed by the IR and UV spectra and the results of elementary analysis.

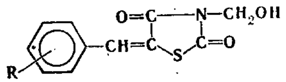
2,4-Thiazolidinediones are ambident compounds that display dual reactivity in reactions with electrophilic reagents [2]. In the alkylation of salts of 2,4-thiazolidinediones in low-polarity solvents the addition of an alkyl group takes place at the N^3 center of the $O-C_2-N_3-C_4-O$ ambident system. An increase in the polarity of the solvent and the hardness of the alkylating agent leads to reaction at the harder center of the ambident system, viz., the oxygen atom.

Alkylation in an alkaline medium proceeds through a step involving the formation of stable salts, the negative charge in the anions of which is delocalized on the oxygen atoms [3]. An investigation of the crystal structure of 2,4-thiazolinedione by x-ray diffraction analysis indicates primary localization of the charge on the oxygen atom bonded to the C_2 atom of the thiazolidine ring [4].

The indicated peculiarities of the distribution of the negative charge in the 2,4-thiazolidinedione anion promote reactions with a hard electrophilic reagent at the oxygen atom attached to the C_2 atom of the thiazolidine ring [2]. Considering the information set forth above, it seemed of interest to continue our study of the dual reactivity of 2,4-thiazolidinediones with formaldehyde as the hard electrophile [5].

The reaction of formaldehyde with 5-benzylidene-2,4-thiazolidinedione was carried out in an organic solvent. The reaction was monitored by thin-layer chromatography (TLC). According to the results of TLC, the formation of only one reaction product is observed in the reaction mixture 2-3 h after the reagents are mixed. The polarity of the solvent has a substantial effect on the reaction rate. The yield of the reaction product increases markedly when the polarity of the solvent is increased, and the reaction time is shortened. Thus the time required to achieve an 80% yield is 2 h when acetone is used as the solvent.

On the basis of the dual reactivity of 2,4-thiazolidinediones in reactions with electrophilic reagents [2], structure I, II, or III can be assigned to the product of the reaction with formaldehyde.



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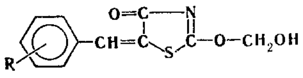

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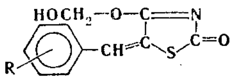

III

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*See [1] for Communication 40.

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