INVESTIGATION OF NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES. 40.* 6-CARBETHOXY-7-ACYL-5H-PYRIMIDO[4,5-b]- AND 6-CARBETHOXY-7-ACYL-5H-PYRIDO[2,3-b]-1,4-THIAZINES

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The reaction of 5-amino-6-mercaptopyrimidine and 2-mercapto-3-aminopyridine with esters of β-chloro-α,γ-diketo acids, leads, depending on the pH, to the formation of three-ring and two-ring 1,4-thiazine systems. A preparative method for the production of previously unknown 6-carbethoxy-7-acyl-5H-pyrimido[4,5-b]- and 6-carbethoxy-7-acyl-5H-pyrido[2,3-b]-1,4-thiazines was developed.

In developing our research [2, 3], devoted to the search for biologically active substances in the 1,4-thiazine series, we investigated methods for the synthesis of pyrimido- and pyridothiazine derivatives that contain keto and carbalkoxy groups in the thiazine ring. For this purpose, we studied the reaction of 4-methoxy(4-chloro)-5-amino-6-mercaptopyrimidines (I, II) and 2-mercapto-3-amino-6-chloropyridine (III) with esters of β-halo-α,γ-diketo acids. We demonstrated that, owing to the peculiarities in the structure of the ketone component, the structure of which contains three carbonyl functions, the character of the resulting substances and their properties and structures depend on the conditions under which the process is carried out. Thus it has been previously [3] ascertained that carrying out the reactions of mercaptoamino derivatives of pyridine and pyrimidine with esters of β-halo-α,γ-diketo acids in the presence of a slight excess of alkaline agents such as KOH or NaH promotes the formation of three-ring 1,4-thiazine systems, viz., oxazolidino[3,2-f]pyrido-[2,3-b]- and oxazolidino[3,2-f]-pyrimido[4,5-b]-1,4-thiazines (IVa, b).

In the present research we established that realization of the reaction of I-III with esters of β-halo-α,γ-diketo acids in acidic media leads to the formation of previously unknown two-ring 1,4-thiazine derivatives. Thus, 6-carbethoxy-7-acyl-5H-pyrimido[4,5-b]- and 6-carbethoxy-7-acyl-5H-pyrido[2,3-b]-1,4-thiazines (Va-g) [4] were synthesized by the reaction of mercapto amino derivatives of pyrimidine and pyridine (I-III) with esters of β-chloro-β-acetyl-, β-chloro-β-propionyl-, β-chloro-β-butyryl-, and β-chloro-β-benzolypyruvic acids in the absence of alkaline agents. The process is realized in alcohol or dimethylformamide (DMF), and the pH of the reaction medium is shifted two to five units to the acidic side owing to the liberated hydrogen halide. We assume that the formation of Va-g proceeds via intramolecular cyclization of intermediate A to hydroxy amino compound B with its subsequent dehydration, as in the reaction of I-III with halo-β-dicarbonyl compounds [5, 6].

A number of interesting peculiarities were noted for the reactions of I and III with the ethyl esters of β-chloro-β-benzoyl- and β-chloro-β-butyrylpyruvic acids. Thus, in the reaction of I with β-chloro-β-benzoylpyruvic ester with the use of an equimolar amount of NaH at 60-70°C we isolated and characterized 7-benzoyl-5H-pyrimido[4,5-b]-1,4-thiazine (VI). The formation of the latter probably takes place as a result of saponification of the carbethoxy group in intermediate A and subsequent decarboxylation and cyclization processes. 6-Phenylpyrimido-1,4-thiazine (VII) is formed if the reaction is carried out in the presence of a slight excess of KOH in alcohol with the subsequent addition of a few drops of hydrochloric acid [7]. Acidic cleavage of the benzoylpyruvic fragment of the A molecule, as occurred in [8, 9], to give intermediate A_1 with subsequent cyclization of the latter evidently takes place in this case.

The principal reaction product in the reaction of III with β-chloro-β-butyrylpyruvic ester in DMF in 6-carbothoxy-5H-pyrido[2,3-b]-1,4-thiazine (VIII). The formation of VIII evidently takes place via splitting out of the acyl fragment of the molecule in intermediate A to give ester A_2 and with its subsequent cyclization.

*See [1] for Communication 39.

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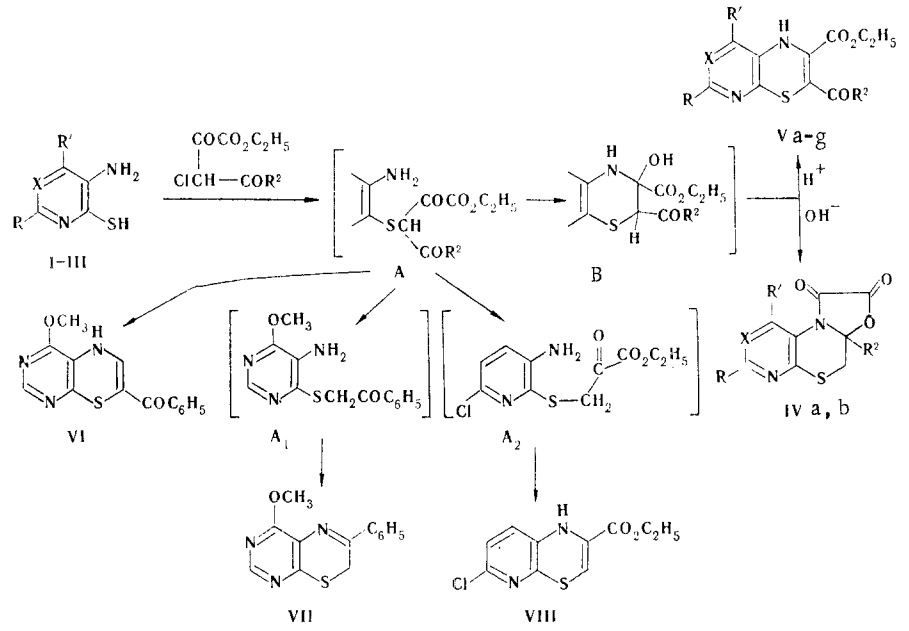

I, IV, Va-d X = N, R = H, R' = OCH_3; II, Ve X = N, R = H, R' = Cl; III, Vf,g X = CH, R = Cl, R' = H; IVa, Va,e,f $R^2 = CH_3$; IVb, Vb,g $R^2 = C_2H_5$; Vc $R^2 = C_3H_7$; Vd = C_6H_5.

Absorption bands at 1700-1730 and 1640-1670 cm^{-1}, which can be assigned to ester and ketone CO groups, are observed in the IR spectra of Va-g. The absorption band at 3380-3390 cm^{-1} was assigned to the NH group. The PMR spectra do not contradict the structures of these compounds.

EXPERIMENTAL

The IR spectra of suspensions of the synthesized compounds in mineral oil were recorded with a Perkin–Elmer 599 spectrometer. The UV spectra of solutions in alcohol were recorded with a Perkin–Elmer 575 spectrophotometer. The PMR spectra were obtained with a JNM-4H spectrometer (100 MHz) with tetramethylsilane as the internal standard. Chromatography was realized on Silufol UV-254 with a benzene–ethyl acetate system (1:1) and development in UV light.

Information on the synthesized compounds and their spectral characteristics are presented in Tables 1 and 2.

4-Methoxy-6-carbethoxy-7-acyl-5H-pyrimido[4,5-b]-1,4-thiazines (Va-c). A solution of 3.18 mmole of 4-methoxy-5-amino-6-mercaptopyrimidine (I) and 2.66 mmole of the ethyl ester of the corresponding β-chloro-β-acylpyruvic acid in 15 ml of DMF was heated at 50°C for 1.5 h, after which it was poured into ice water. The resulting precipitate was removed by filtration, washed with water, and dried.

4-Methoxy-6-carbethoxy-7-benzoyl-5H-pyrimido[4,5-b]-1,4-thiazine (Vd). A solution of 1.03 g (6.55 mmole) of I and 1.34 g (5.25 mmole) of ethyl β-chloro-β-benzoylpyruvate in 10 ml

TABLE 1. Characteristics of Va-g, VI, and VIII

Compound	mp,* °C	R_f	Found, %					Empirical formula	Calc., %					Yield, %
			C	H	Cl	N	S		C	H	Cl	N	S	
Va	131—132	0,74	48,5	4,4	—	14,0	10,7	$C_{12}H_{13}N_3O_4S$	48,8	4,4	—	14,2	10,8	71
Vb	82—84	0,73	50,3	4,7	—	13,4	10,5	$C_{13}H_{15}N_3O_4S$	50,5	4,9	—	13,6	10,4	65
Vc	78—80	0,57	51,6	5,3	—	13,0	9,9	$C_{14}H_{17}N_3O_4S$	52,0	5,3	—	13,0	9,9	60
Vd	95—97		57,2	4,1	—	11,6	9,0	$C_{17}H_{15}N_3O_4S$	57,1	4,2	—	11,8	9,0	30
Ve	196—198	0,63	43,9	3,5	11,5	14,0	10,7	$C_{11}H_{10}ClN_3O_3S$	44,0	3,3	11,8	14,0	10,7	40
Vf	142—144		48,0	3,7	12,0	9,2	11,0	$C_{12}H_{11}ClN_2O_3S$	48,2	3,7	11,9	9,4	10,7	77
Vg	123—125		56,7	3,6	9,8	7,8	8,9	$C_{17}H_{13}ClN_2O_3S$	56,6	3,6	9,8	7,7	8,9	81
VI	254—255		58,8	3,8	—	14,6	11,1	$C_{14}H_{11}N_3O_2S$	58,9	3,9	—	14,7	11,2	42
VIII	150—152	0,88	46,8	3,60	14,1	10,9	12,6	$C_{10}H_9ClN_2O_2S$	46,8	3,5	13,8	10,9	12,5	48

*The compounds were crystallized: Va, e-g and VIII from ethanol, Vb-d from alcohol–water (1:3), and VI from alcohol-DMF (5:1).

TABLE 2. Spectral Characteristics of Va, b, d-g, VI, and VIII

Compound	UV spectrum, λ_{max}, nm (log ε)	PMR spectrum ($CDCl_3$), ppm
Va	257 (3,83); 327 (3,54); 480 (3,15)	1,33 (OCH_2CH_3, t); 4,29 (OCH_2CH_3, q); 2,32 (CH_3, s); 3,98 (OCH_3, s); 6,04 (NH, s); 8,1 (CH, s)
Vb	256 (4,11); 326 (3,81); 476 (3,85)	1,31 (OCH_2CH_3, t); 4,29 (OCH_2CH_3, q); 1,14 ($COCH_2CH_3$, t); 2,64 ($COCH_2CH_3$, q); 3,98 (OCH_3, s); 6,04 (NH, s); 8,12 (CH, s)
Vd	—	0,82 (OCH_2CH_3, t); 3,9 (OCH_2CH_3, q); 4,01 (OCH_3, s); 6,19 (NH, s)
Ve	224 (4,13); 254 (4,14); 295 (3,27); 365 (3,59)	—
Vf	231 (4,14); 247 (4,14); 282 sh (3,35); 370 (3,38)	1,29 (OCH_2CH_3, t); 4,27 (OCH_2CH_3, q); 2,31 (CH_3, s)
Vg	256 (4,17); 362 (3,4)	0,81 (OCH_2CH_3, t); 3,90 (OCH_2CH_3, q); 7,53—7,99 (C_6H_5, m)
VI	—	4,24* (OCH_3, s); 7,1 (6-CH, s); 7,54—7,95 (C_6H_5, m); 8,36 (2-CH, s)
VIII	—	1,29 (OCH_2CH_3, t); 4,26 (OCH_2CH_3, q), 5,67 (NH, s); 5,79 (CH, s); 6,54; 6,76 (pyridine ring protons)

*In CF_3COOH.

of DMF was allowed to stand at 20°C for 7 days, after which it was poured into 150 ml of water. The aqueous mixture was extracted with 100 ml of ether, the extract was dried with Na_2SO_4 and evaporated, and the residual oil was triturated with alcohol and water. The precipitate was removed by filtration and dried. Compound Ve was obtained under similar conditions from 2.0 g (15 mmole) of 4-chloro-5-amino-6-mercaptopyrimidine (II) and 2.9 g (15 mmole) of ethyl β-chloro-β-acetylpyruvate.

2-Chloro-6-carbethoxy-7-acyl-5H-pyrido[2,3-b]-1,4-thiazines (Vf, g). A suspension of 3 mmole of III and 2.6 mmole of ethyl β-chloro-β-acetylpyruvate in 10 ml of ethanol and 2-3 ml of DMF was stirred at 20°C for 2 h, after which it was filtered. The filtrate was evaporated *in vacuo* to one third of its original volume, water was added, and the precipitate was removed by filtration, washed with water, and dried to give Vf. Compound Vg was obtained in the same way, except that the process was carried out in 15 ml of ethanol at 50°C for 1 h.

4-Methoxy-7-benzoyl-5H-pyrimido[4,5-b]-1,4-thiazine (VI). A solution of 0.7 g (4.46 mmole) of I, 0.11 g (4.46 mmole) of NaH, and 1.13 g (4.46 mmole) of ethyl β-chloro-β-benzoylpyruvate in 20 ml of DMF was allowed to stand at 20°C for 24 h, after which it was heated with stirring at 70°C for 14 h. The reaction mixture was then allowed to stand at 0°C for 18 h, and the resulting precipitate was removed by filtration and dried.

4-Methoxy-6-phenylpyrimido[4,5-b]-1,4-thiazine (VII). A solution of 1.0 g (6.36 mmole) of I in 20 ml of ethanol containing 0.5 g (8.9 mmole) of KOH and a solution of 1.63 g (6.36 mmole) of ethyl β-chloro-β-benzoylpyruvate in 10 ml of ethanol were added simultaneously at 20°C to 10 ml of ethanol in the course of 1 h, and the mixture was then stirred at 20°C for 2 h. It was then treated with five drops of concentrated HCl and stirred for 1 h. The precipitate was removed by filtration to give 0.65 g (40%) of VII with mp 171-173°C (from alcohol). The structure of VII was confirmed by data from the IR and PMR spectra and was proved by the fact that it was identical to a sample obtained in [7].

2-Chloro-6-carbethoxy-5H-pyrido[2,3-b]-1,4-thiazine (VIII). A 0.5-g (3 mmole) sample of III and 0.67 g (3 mmole) of ethyl β-chloro-β-butyrylpyruvate were dissolved in 5 ml of DMF, and the mixture was stirred, during which a great deal of heat was evolved, and the solution became red. The solution was cooled to 20°C and stirred for 3 h. It was then allowed to stand overnight, and the resulting precipitate was removed by filtration to give VIII.

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