4-Methyl-3,4-dihydro-2-quinolone (III), with mp 98°C [9], and 4-methyl-3,4-dihydro-1-isoquinolone (IV), with mp 81°C* [8], were similarly obtained from α-phenylethylacetylhydroxamic acid and PPA.

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*For optically active compounds.

INVESTIGATION OF NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES.

37.* REACTION OF o-AMINO MERCAPTO DERIVATIVES OF PYRIDINE AND PYRIMIDINE WITH ESTERS OF β-HALO-α,γ-DIKETO ACIDS

L. G. Levkovskaya, I. E. Mamaeva, O. S. Anisimova, and T. S. Safonova

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The synthesis of two-ring 1,4-thiazine systems was previously accomplished on the basis of the reaction of o-amino mercapto derivatives of pyridine and pyrimidine with dicarbonyl compounds — halo β-keto esters and halo β-diketones. In the present paper it is shown that the primary products of this reaction are S-β-ketoalkylmercapto derivatives, which are subsequently cyclized to the corresponding hydroxy amino compounds. The latter are converted to N-acylamino-S-β-carbethoxy (keto)alkylmercapto derivatives under the influence of an alkaline agent. The indicated compounds were isolated and characterized [2, 3].

Continuing our recent research [2, 3] to obtain biologically active substances among derivatives of two-ring 1,4-thiazine systems we investigated the reaction of o-amino mercapto derivatives of pyridine and pyrimidine with tricarbonyl compounds — esters of β-halo α, γ-diketo acids.

We have shown that the reaction of 2-mercapto-3-amino-6-chloropyridine (I) and 4-methoxy-5-amino-6-mercaptopyrimidine (II) with esters of β-chloro-β-acylpyruvic acids in the presence of a slight excess of alkaline agents such as KOH, NaH, and triethylamine leads to the formation of the previously unknown heterocyclic systems — oxazolidino[3,2-d]pyrido[2,3-b]- and oxazolidino[3,2-d]pyrimido[4,5-b]-1,4-thiazines (VIIa-g).

In analogy with the reaction of o-amino mercapto derivatives of pyridine and pyrimidine with dicarbonyl compounds, we assumed that the initial step in the reaction of I and II with esters of β-halo α, γ-diketo acids is evidently alkylation of the sulfur atom to give intermediate III (see the scheme below), which subsequently undergoes cyclization to hydroxy amino compound IV. The conditions for the destructive cleavage of IV at the C_6-C_7 bond, as a result of which the corresponding N-oxamoyl-S-β-ketoalkylmercapto derivatives Va-e (Table 1) are

*See [1] for communication 36.

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow 119021.

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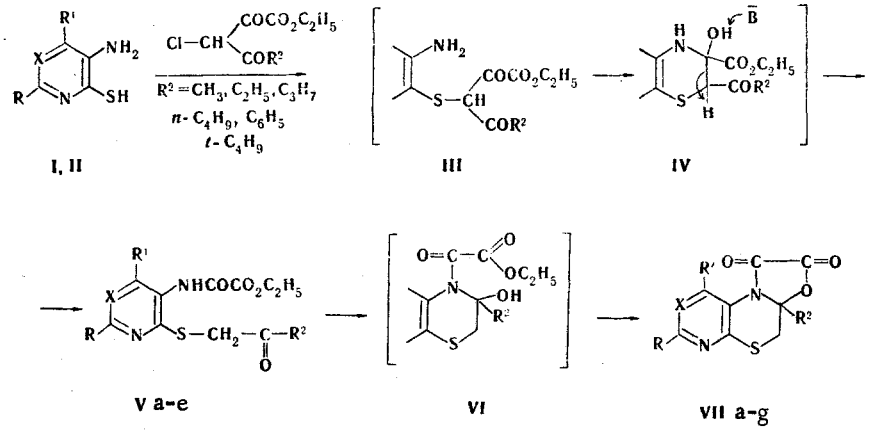
TABLE 1. Characteristics of Va-e and VIIa-g

Compound	mp, °C (from ethanol)	R_f	Found, %					Empirical formula	Calculated, %					Yield, %
			C	H	Cl	N	S		C	H	Cl	N	S	
Va	132—134		45,5	4,1	11,0	8,7	10,1	$C_{12}H_{13}ClN_2O_4S$	45,5	4,1	11,2	8,8	10,1	20,3
Vb	125—127		48,9	4,9	9,9	8,1	9,2	$C_{14}H_{17}ClN_2O_4S$	48,8	4,9	10,1	8,1	9,3	22
Vc	123—125		50,2	5,2	9,9	7,8	8,9	$C_{15}H_{19}ClN_2O_4S$	50,2	5,3	9,9	7,8	8,9	43
Vd	129—131		50,4	5,3	10,2	7,8	9,2	$C_{15}H_{19}ClN_2O_4S$	50,2	5,3	9,9	7,8	8,9	61
Ve	136—137		53,8	3,8	9,4	7,3	8,4	$C_{17}H_{15}ClN_2O_4S$	53,9	3,9	9,4	7,4	8,4	61
VIIa	232—234	0,7	44,3	2,7	13,0	10,5	11,8	$C_{10}H_7ClN_2O_3S$	44,4	2,6	13,1	10,3	11,8	70
VIIb	194—195	0,73	46,5	3,2	12,5	10,1	11,1	$C_{11}H_9ClN_2O_3S$	46,4	3,2	12,5	9,8	11,2	60
VIIc	154—156	0,77	48,4	3,7	11,9	9,3	10,7	$C_{12}H_{11}ClN_2O_3S$	48,2	3,7	11,9	9,4	10,7	61
VIId	145—146	0,8	49,8	4,3	11,5	8,7	10,2	$C_{13}H_{13}ClN_2O_3S$	49,9	4,2	11,4	9,0	10,2	22
VIIe	180—181	0,53	45,1	3,8		15,7	11,6	$C_{10}H_9N_3O_4S$	44,9	3,4		15,7	12,0	22
VIIg	166—168	0,58	47,4	3,8		15,1	11,5	$C_{11}H_{11}N_3O_4S$	47,0	3,9		14,9	11,4	59

formed, are created under the influence of the alkaline agent. The presence of a carbonyl group in the thio ester fragment and an oxalic acid ester residue attached to the



I R=Cl, R^1=H, X=CH; II R=H, R^1=OCH_3, X=N; V a—e R=Cl, R^1=H, X=CH; R^2: a CH_3, b C_3H_7, c n-C_4H_9, d t-C_4H_9, e C_6H_5; VII a—e X=CH, R=Cl, R^1=H; R^2: a CH_3, b C_2H_5, c C_3H_7, d n-C_4H_9; e—g X=N, R=H, R^1=OCH_3; R^2: e CH_3, g C_2H_5

nitrogen atom in the N-oxamoyl-S-β-ketoalkylmercapto derivatives promotes the formation of intermediate two-ring hydroxy amino compound VI, the subsequent formation of a lactone ring from which leads to the formation of three-ring systems VIIa-g (Table 1).

The sequence of reactions leading to the heterocyclic system — oxazolidino[3,2-d]pyrido [2,3-b]-1,4-thiazine — is confirmed by the isolation of intermediate N-oxamoyl-S-β-ketoalkylmercapto derivatives Va-e and their conversion to VIIa, c, d. Thus N-oxamoyl-S-β-ketoalkylmercapto derivatives Va-c were isolated and characterized in the reaction of I with β-chloro-β-acetyl-, β-butyryl-, and β-valerylpyruvic acid esters under mild conditions (at −5 to −10°C); Va-c (if they are not isolated from the reaction mixture) undergo conversion to three-ring lactones VIIa, c, d. This process also occurs during recrystallization and storage in air of the indicated compounds. When esters of β-chloro-β-isovaleryl- and β-chloro-β-benzoylpyruvic acids are used as the carbonyl component in the reaction, the process stops at the step involving the formation of stable oxamic acid esters Vd, e, which cannot be converted to oxazolidino[3,2-d] derivatives under the conditions indicated above. In a study of the reaction of 4-methoxy-5-amino-6-mercaptopyrimidine (II) with esters of β-halo-β-acylpyruvic acids we were unable to isolate the intermediate N-oxamoyl-S-β-ketoalkylmercapto derivatives: the principal reaction products are oxazolidino[3,2-d]pyrimido[4,5-b]-1,4-thiazines (VIIe, g).

The structures of both the intermediates and the final compounds were confirmed by the data from the IR, PMR, and mass spectra (Table 2) and also by a number of their chemical transformations. Absorption bands at 1700-1730 cm^{-1}, which can be ascribed to the C=O groups of an ester and a ketone, are observed in the IR spectra of Va-e. In contrast to the compounds with open structures, the IR spectra of VIIa-g contain an absorption band at 1820 cm^{-1},

TABLE 2. Spectral Characteristics of Va-e and VIIa-g

Compound	IR spectra, ν, cm^{-1}				PMR spectra, δ, ppm	Mass spectra, m/e (intensity in % relative to the maximum peak)
	NH	lactone C=O	amide C=O	ketone and ester C=O		
Va	3330			1720—1740		
Vb	3330		1700	1720, 1735	0,78; 1,08; 1,57 (protons C_3H_7); 2,55 ($OCH_2\mathbf{CH_3}$, t); 4,21 ($\mathbf{OCH_2}CH_3$, q); 4,10 (2-SCH_2, s)	
Vc	3310		1700	1725, 1730		
Vd	3300		1690	1700, 1740		
Ve	3300		1690	1730		
VIIa		1800—1820	1730—1740		1,14 (CH_3, s); 2,07, 2,35 (two d, 4-CH_2, J_{HH}=12Hz)	*270 (50), 198 (100), 197 (39), 183 (15,5), 171 (17)
VIIb		1820	1735		1,47 ($OCH_2\mathbf{CH_3}$, t); 2,1 ($\mathbf{OCH_2}CH_3$, q); 3,70, 3,90 (two d, 4-CH_2, J_{HH} = 12 Hz)	*284 (58), 212 (100), 211 (44), 198 (34), 183 (75)
VIIc		1820	1730—1740		0,74, 2,08, 2,54 (protons C_3H_7), 3,73, 4,10 two d 4-CH_2, J_{HH} = 12 Hz)	*298 (100), 283 (23), 254 (51,4), 226 (43,6), 211 (28,2), 198 (26), 183 (51)
VIId		1830	1735			*312 (22,5), 240 (16), 198 (100)
VIIe		1810	1750		1,75 (CH_3, s), 3,91 (OCH_3, s), 3,72, 3,95 (two d 4-CH_2, J_{HH}=12Hz)	
VIIg		1820	1745		0,72 ($OCH_2\mathbf{CH_3}$, t), 1,97 ($\mathbf{OCH_2}CH_3$, q) 3,90 (OCH_3, s); 3,63; 4,00 (two d J_{HH} = 12 Hz)	281 (100), 252 (2,7), 224 (8), 209 (49), 197 (30), 180 (13,5), 157 (8,1)

*The ion peaks whose compositions include ^{35}Cl are indicated for VIIa-d.

which can be assigned to a lactone C=O group, and an absorption band of an amide C=O group at 1730-1750 cm^{-1}. In the PMR spectra of VIIa-g the signal of the protons of the 4-CH_2 group, because of the presence of an asymmetric carbon atom in the 4a position, is represented in the form of two doublets with geminal coupling constant J_{HH} = 12 Hz, in contrast to the compounds with open structures (Va-e), in the spectra of which the signal of the S—CH_2 group is represented by a singlet.

Molecular-ion peaks with mass numbers 270/272, 284/286, 298/300, 312/314, and 281 are observed in the mass spectra of VIIa-d, g. Simultaneous elimination of CO and CO_2 groups from the lactone ring of the molecular ion is characteristic for the fragmentation of the indicated compounds. The intense $[M - 72]^{+\cdot}$ peaks correspond to the $[M - CO - CO_2]^{+\cdot}$ ion, whereas in the case of VIIa, b these peaks are the most intense peaks in the spectra. The subsequent fragmentation of the $[M - 72]^{+\cdot}$ ion takes place mainly via two pathways: with elimination of a hydrogen atom, evidently the hydrogen atom in the α position relative to the sulfur atom, and with elimination of the R^2 substituent are observed along with the ions enumerated above in the spectrum of VIIc,d,g.

The determination of the molecular weight of VIIg by an osmometric method gave a value corresponding to the empirical formula of this compound.

EXPERIMENTAL

The IR spectra of mineral oil suspensions of the compounds were recorded with a UR-10 spectrometer. The PMR spectra of C_5D_5N solutions of the compounds were measured with a JNM-4H spectrometer (100 MHz) with tetramethylsilane as the internal standard. Chromatography was accomplished on Silufol UV-254; system 1 [benzene—ethyl acetate—ethanol (17 : 3 : 2)] was used for VIIa-d, and system 2 [benzene—ethyl acetate (1 : 1)] was used for VIIe-g. The determination of molecular weight of VIIg was carried out with a Hewlett—Packard 302 B osmometer. The mass spectra were obtained with an MKh-1303 mass spectrometer with direct introduction of the samples into the source; the ionizing-electron energy was 30 eV, and the temperature of the ionizing chamber was 125°C. Data on the synthesized compounds and their spectral characteristics are presented in Tables 1 and 2.

1,2-Dioxo-4a-alkyl-7-chlorooxazolidino[3,2-d]pyrido[2,3-b]-1,4-thiazines (VIIa-d). A solution of 0.5 g (3 mmole) of I and 0.18 g (3 mmole) of KOH in 15-20 ml of ethanol was added dropwise at −5 to −10°C in the course of 30 min to a solution of 3 mmole of the ethyl ester of the appropriate β-chloro-β-acylpyruvic acid, and the mixture was stirred for 10-15 min. Triethylamine (five to seven drops) was added, the temperature of the reaction mixture was raised to 18-20°C, and the mixture was stirred for 2-3 h. The resulting precipitate was removed by filtration and washed with water and petroleum ether to give VIIa-c. In the case of VIId the reaction mixture was stirred additionally at 18-20°C for 2-3 days.

1,2-Dioxo-4a-ethyl-9-methoxyoxazolidino[3,2-d]pyrimido[4,5-b]-1,4-thiazine (VIIg). A solution of 1.13 g (5.86 mmole) of ethyl β-chloro-β-propionylpyruvate in 5 ml of dimethylformamide (DMF) was added at 5-10°C in the course of 30 min to a solution of 1.0 g (6.36 mmole) of II and 0.17 g (7 mmole) of NaH in 15 ml of DMF, after which the mixture was stirred at 18-20°C for 18-20 h. Water (30 ml) was added, and the mixture was cooled to 0°C. The resulting precipitate was removed by filtration, washed with water, and dried to give 0.92 g (59%) of VIIg with mp 166-168°C (from alcohol). Compound VIIe was similarly obtained.

Ethyl 2-(Isovalerylmethylmercapto-6-chloro-3-pyridyl)- and 2-(Benzoylmethylmercapto-6-chloro-3-pyridyl)oxamates (Vd-e). These compounds were obtained from 9 mmole of ethyl β-chloro-β-isovaleryl- and β-chloro-β-benzoylpyruvates, 1.5 g (9 mmole) of I, 0.5 g (9 mmole) of KOH, and 0.1-0.2 ml of triethylamine under conditions similar to those in the preparation of VIIa-d.

Ethyl-2-(Acetylmethylmercapto-6-chloro-3-pyridyl)oxamate(Va) and 1,2-Dioxo-4a-methyl-7-chlorooxazolidino[3,2-d]pyrido[2,3-b]-1,4-thiazine (VIIa). These compounds were obtained from 3.6 g (18 mmole) of ethyl β-chloro-β-acetylpyruvate, 3.0 g (18 mmole) of I, and 1.4 g (25 mmole) of KOH, as in the synthesis of VIIa-c, except that after 30 min, the precipitate was removed by filtration, washed with water, and dried to give 1.2 g (20.3%) of Va. The filtrate was stirred additionally at 18-20°C for 2-3 h. A total of 2.05 g (40.6%) of VIIa was obtained. When Va could not be separated from the reaction medium, the principal product was VIIa.

Ethyl 2-(Butyrylmethylmercapto-6-chloro-3-pyridyl)- and 2-(Valerylmethylmercapto-6-chloro-3-pyridyl)oxamates (Vb, c). Esters Vb, c were synthesized under similar conditions. Compound VIIc was obtained in 43% yield from the filtrate after separation of Vb. Compound VIId was isolated in 22% yield after stirring the filtrate at 18-20°C for 2-3 days.

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