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HETEROCYCLES CONTAINING NITROGEN AND SULFUR. PART 49*. SYNTHESIS OF DERIVATIVES OF NEW HETEROCYCLIC SYSTEMS: 1,2-DIOXOCYCLOPENTA(HEXA)[*g*]OXAZOLIDINO-[3,2-*f*]PYRIMIDO[4,5-*b*][1,4]THIAZINE, 1,2-DIOXOCYCLOPENTA(HEXA)-[*g*]IMIDAZOLIDINO[3,2-*f*]PYRIMIDO[4,5-*b*][1,4]THIAZINE, AND 1,2-OXAZINO[5,4-*g*]PYRIMIDINO[4,5-*b*][1,4]THIAZINE

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The reaction of 4-methoxy-5-amino-6-mercaptopyrimidine with 2-oxo-1-chlorocyclopentyl(hexyl)glyoxalate esters gave derivatives of the previously unknown tetracyclic systems 1,2-dioxocyclopenta(hexa)[g]oxazolidino[3,2-f]pyrimido[4,5-b][1,4]thiazines, which are transformed by ammonium acetate into derivatives of 1,2-dioxocyclopenta(hexa)[g]imidazolidino[3,2-f]pyrimido[4,5-b]-[1,4]thiazines. Derivatives of the new tricyclic 1-oxazino[5,4-g]pyrimido[4,5-b][1,4]thiazine system were obrtained by reaction of 6-carbethoxy-7-acetylpyrimido[4,5-b][1,4]thiazines with hydroxylamine.

The reactions of 5-amino-6-mercaptopyrimidines with esters of β-halo-α,γ-diketoacids in the presence of alkaline agents result in oxazolidino[3,2-*f*]pyrimido[4,5-*b*][1,4]thiazines [2]. We have extended this research and used as tricarbonyl component in those reactions some cyclic derivatives of β-halo-α,γ-diketoacid esters: the ethyl esters of 2-oxo-1-chlorocyclopentyl-1-glyoxalic and 2-oxo-1-chlorocyclohexyl-1-glyoxalic acids (IIa, b).

We found that 4-methoxy-5-amino-6-mercaptopyrimidine (I) reacts with compounds IIa, b in DMF in the presence of sodium hydride at 18-20°C to give new tetracyclic systems: 1,2-dioxo-11-methoxycyclopenta-[*g*]oxazolidino[3,2-*f*]pyrimido[4,5-*b*][1,4]thiazine (IVa) and 1,2-dioxo-12-methoxycyclohexa[*g*]oxazolidino[3,2-*f*]-pyrimido[4,5-*b*][1,4]thiazine (IVb).

The structures of compounds IVa, b are confirmed by the presence in the IR spectra of a band at 1820 cm^{-1} characteristic of a lactone CO group and a band due to the amide CO group in the region of 1745 cm^{-1}. Such bands have been observed in our previously synthesized oxazolidino[3,2-*f*]pyrimido[4,5-*b*][1,4]thiazines [2].

The following explanation can be given for the formation of the tetracyclic systems IVa, b and also for the previously obtained oxazolidinopyrimidothiazines and oxazolidinopyridothiazines [2].

First, the mercapto group of I is alkylated with the formation of derivatives of structure A, which is followed by cyclization to the spirocompounds B. The alkaline agent detaches a proton from the hydroxyl group in a B compound. The stabilization of the resulting anion results in regeneration of the carbonyl group, the breakage

* See [1] for Part 48.

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of the C(6)—C(7) bond, and the production of the open form C. There is a reactive ketogroup in structure C, which favors the transition of form C to the cyclic tautomeric form D. The stabilization of the latter by closure of the lactone ring irreversibly shifts the reaction to the formation of the tetracyclic systems IVa, b.

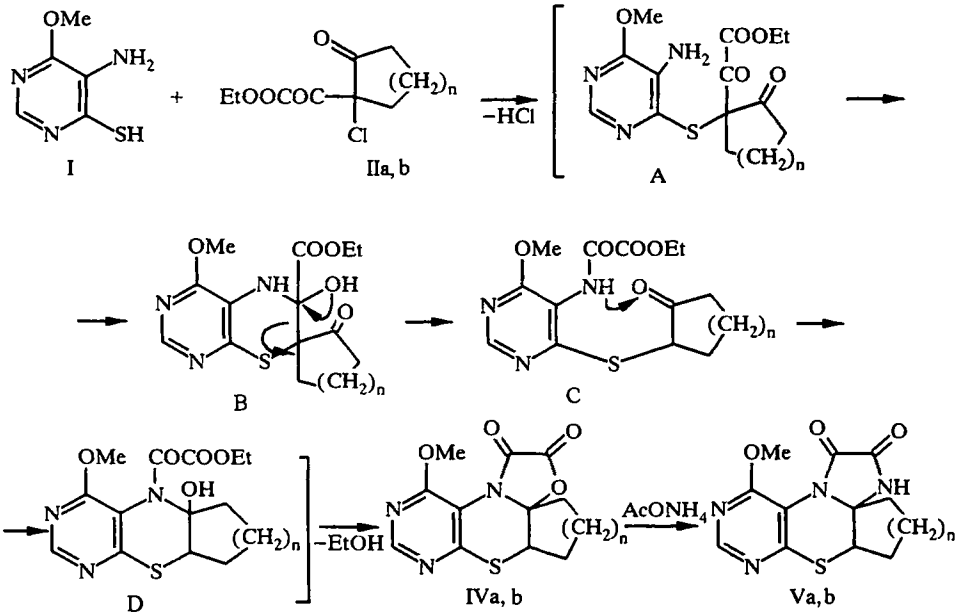
Unfortunately, we were unable to isolate the intermediate substances A-D from the reaction mixture, but previously we had observed the formation of cyclic compounds of types B and D, such as 5-N-oxalamides, 6-oxy-6-alkyl-5,6-dihydropyrido[2,3-*b*][1,4]thiazines [3], and 6-oxy-6-alkyl-5,6-dihydropyrimido[4,5-*b*][1,4]thiazines [4]. It has been shown that the latter can exist in cyclic and open tautomeric forms, and in the latter case, as derivatives of 5-amino-6-(β-ketoalkylthio)pyrimidines.

Also, we have shown [2] that 2-mercapto-3-amino-6-chloropyridine reacts with esters of β-halo-α,γ-diketoacids under mild conditions in a way that can be halted at the stage of the formation of substances of C type: the corresponding derivatives of pyridyl-3-oxaminic acid, which were isolated under these reaction conditions, characterized, and transformed to oxazolidinopyridothiazines.

In research on derivatives with systems IVa, b, we observed that heating with ammonium acetate in glacial acetic acid at 80°C transformed them into previously unknown heterocyclic systems: 1,2-dioxo-11-methoxycyclopenta[*g*]imidazolidino[3,2-*b*]pyrimido[4,5-*b*][1,4]thiazine (Va) and 1,2-dioxo-12-metoxycyclohexa-[*g*]imidazolidino[4,5-*b*][1,4]thiazine (Vb) with yields of 69 and 94% respectively.

The IR spectra of compounds Va,b differ from that of compoumds IVa,b by the presence of the absorption band from the NH group in the region 3180 cm^{-1}, broad absorption band from C=O amide groups are at 1730 - 1760 cm^{-1} and 1700 – 1735 cm^{-1} respectively.

The reactions of 5-amino-6-mercaptopyrimidines with β-halo-α,γ-diketoacid esters in neutral or weakly acid media result not in oxazolidinopyrimidothiazines but in 6-ethoxycarbonyl-7-acylpyrimido[4,5-*b*][1,4]thiazines (IIIa-c) [5]. These compounds contain reactive keto and ester groups and can thus provide for conversion to derivatives of tricyclic systems that have not been described in the literature, which are of interest for making biologically active substances.

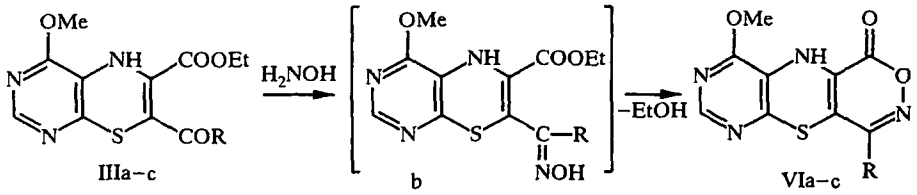


IIa, IVa, Va n = 1; IIb, IVb. Vb n = 2;
II, IV, V a n = 1; b n = 2

We also examined the reactions of compounds IIIa-c with hydroxylamine, but although we varied the reaction conditions, in all cases we obtained complicated mixture of substances with low melting points, from which we were able to isolate in the pure state only representatives of the previously undescribed heterocyclic system 1,2-oxazino[5,4-*g*]pyrimido[4,5-*b*][1,4]thiazine (VIa-c) with a yield of about 14%.

TABLE 1. Characteristics of Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %				mp,°C	IR spectrum, ν, cm^{-1}	Yield, %
		C	H	N	S			
IVa	$C_{12}H_{11}N_3O_4S$	48,93 49,13	3,51 3,78	14,14 14,33	10,89 10,93	183...184	1820, 1745	46
IVb	$C_{13}H_{13}N_3O_4S$	50,50 50,80	4,43 4,26	13,92 13,68	10,38 10,42	218...218,5	1840, 1745	55
Va	$C_{12}H_{12}N_4O_3S$	49,15 49,30	4,23 4,14	19,18 19,17	10,70 10,97	243...244	1760...1730, 3180	69
Vb	$C_{13}H_{14}N_4O_3S$	50,71 50,96	4,98 4,61	18,07 18,29	10,64 10,47	243...244	1735, 1700, 3180	94
VIa	$C_{10}H_8N_4O_3S$	45,41 45,46	3,03 3,05	21,27 21,20	12,26 12,13	193...195	1720, 3300	14
VIb	$C_{10}H_{10}N_4O_3S$	47,11 47,47	4,00 3,62	19,99 20,13	11,29 11,52	183...185	1720, 3320	13
VIc	$C_{12}H_{12}N_4O_3S$	49,51 49,30	4,03 4,14		11,00 10,97	134...135	1710, 3310	14



IIIa, VIa R = Me; IIIb, VIb R = Et;
IIIc, VIc R = Pr

The structures of compounds VIa-c are confirmed by the IR spectra, which contain bands from the NH and CO groups in the regions of 3320-3300 and 1720-1710 cm^{-1} respectively.

The PMR spectrum of compound VIa had signals from CH_3, OCH_3, and NH groups and from a proton in position 2 in the pyrimidine ring, which agrees well with the proposed structure of that compound.

EXPERIMENTAL

The IR spectra were recorded with a Perkin-Elmer 457 spectrometer in oil; the PMR spectra were recorded with a Varian XL-200 instrument, internal standard TMS. The reaction was tracked and the purity of the compounds was verified by TLC on Silufol UV-254 plates in the benzene-ethyl acetate system, 1:1, development in UV light.

Table 1 gives the characteristics of the synthesized compounds.

The ethyl esters of 2-oxo-1-chlorocyclopentyl-1-glyoxalic acid and of 2-oxo-1-chlorocyclohexyl-1-glyoxalic acid (IIa, b) were made by the [6] method.

The method of [5] was used to prepare 4-methoxy-6-ethoxycarbonyl-7-acetylpyrimido[4,5-*b*][1,4]thiazine (IIIa), 4-methoxy-6-ethoxycarbonyl-7-propionylpyrimido[4,5-*b*][1,4]thiazine (IIIb), and 4-methoxy-6-ethoxycarbonyl-7-butyrylpyrimido[4,5-*b*][1,4]thiazine (IIIc).

1,2-Dioxo-11-methoxycyclopenta[*g*]oxazolidino[3,2-*f*]pyrimido[4,5-*b*][1,4]thiazine (IVa). To a solution of 2.62 g (16.7 mmole) of 4-methoxy-5-amino-6-mercaptopyrimidine I and 0.4 g (16.7 mmole) of NaH in 20 ml of anhydrous DMF we added at 18-20°C 3.0 g (13.7 mmole) of compound IIa. The reaction mixture was kept for 72 h at 18-20°C and then poured into 20 ml of cooled water. The resulting precipitate was filtered off, washed with water, dried, and crystallized from ethanol.

1,2-Dioxo-12-methoxycyclohexa[*g*]oxazolidino[3,2-*f*]pyrimido[4,5-*b*][1,4]thiazine (IVb) was obtained by analogy with compound IVa from 1.0 g (6.4 mmole) of 4-methoxy-5-amino-6-mercaptopyrimidine I, 0.16 g (6.66 mmole) of NaH, and 1.2 g (5.15 mmole) of compound IIb in 10 ml of DMF. Crystallized from ethanol, R_f 0.83.

1,2-Dioxo-11-methoxycyclopenta[*g*]imidazolidino[3,2-*f*]pyrimido[4,5-*b*][1,4]thiazine (Va). A solution of 1.2 g (4.1 mmole) of compound IVa and 3 g (39 mmole) of ammonium acetate in 45 ml of glacial CH_3COOH was heated for 2 h at 80°C, then cooled and poured into 65 ml of water, the solution being neutralized with aqueous ammonia and evaporated under vacuum to a volume of 45 ml, and then cooled to 0-3°C. The resulting precipitate was filtered off, washed with water, and crystallized from 3:1 aqueous ethanol.

1,2-Dioxo-12-methoxycyclohexa[*g*]imidazolidino[3,2-*f*]pyrimido[4,5-*b*][1,4]thiazine (Vb) was obtained by analogy with compound Va from 0.75 g (2.44 mmole) of compound IVb and 2.0 g (26 mmole) of ammonium acetate. Crystallized from aqueous ethanol, 3:1.

4-Methoxy-6-oxo-9-methyl-5,6-dihydro[1,2]oxazino[5,4-*g*]pyrimido[4,5-*b*][1,4]thiazine (VIa). A solution of 0.7 g (2.39 mmole) of compound IIIa, 0.16 g (2.39 mmole) of hydroxylamine hydrochloride, and 0.19 g (2.39 mmole) of sodium acetate in 25 ml of 80% ethanol was refluxed for 8 h and then cooled, the precipitate was filtered off, washed with water, and crystallized from ethanol; R_f 0.92. PMR spectrum ($CDCl_3$): 2.11 (3H, s, CH_3); 3.97 (3H, s, CH_3); 6.28 (1H, w. s, NH); 8.06 ppm (1H, s, $C_{(2)}$ in pyrimidine).

4-Methoxy-6-oxo-9-ethyl-5,6-dihydro[1,2]oxazino[5,4-*g*]pyrimido[4,5-*b*][1,4]thiazine (VIb): was obtained by analogy with compound VIa from 0.6 g (1.95 mmole) of compound IIIb, 0.14 g (1.95 mmole) of hydroxylamine hydrochloride, and 0.16 g (1.95 mmole) of sodium acetate. Crystallized from ethanol, R_f 0.68.

4-methoxy-6-oxo-9-propyl-5,6-dihydro[1,2]oxazino[5,4-*g*]pyrimido[4,5-*b*][1,4]thiazine (VIc): was obtained by analogy with compound VIa from 0.63 g (1.95 mmole) of compound IIIa, 0.14 g of hydroxylamine hydrochloride, and 0.16 g (1.95 mmole) of sodium acetate. Crystallized from ethanol, R_f 0.68.

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