INVESTIGATION OF NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES. 44.* NEW HETEROCYCLIC SYSTEMS. DERIVATIVES OF IMIDAZOLIDINO-[3,2-f]PYRIDO[2,3-b]-AND IMIDAZOLIDINO[3,2-f]PYRIMIDO[4,5-b]-1,4-THIAZINES. SYNTHESIS AND STRUCTURE

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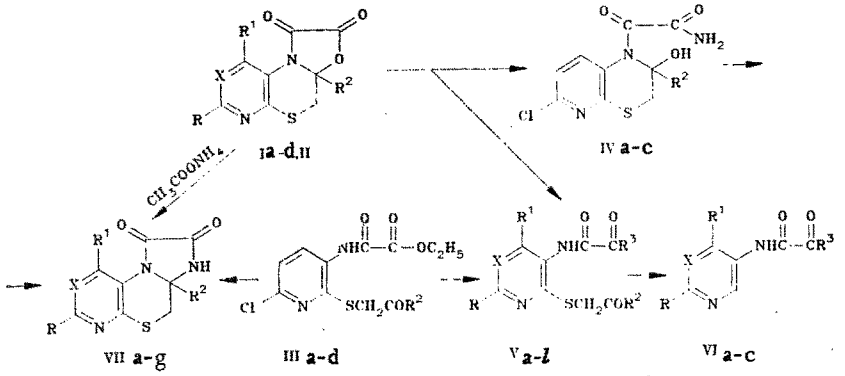
New representatives of heterocyclic systems, imidazolidino[3,2-f]-pyrido-[2,3-b]- and imidazolidino[3,2-f]pyrimido[4,5-b]-1,4-thiazines, have been obtained. Intermediate compounds of 5N-oxalamides-6-hydroxy-7H-pyrido[2,3-b]-1,4-thiazine have been isolated and characterized. Amides of N-(pyridyl-3)- and N-(pyrimidyl-5)-oxaminic acids have been obtained.

We have previously reported [2] that interaction of o-aminomercapto derivatives of pyridine and pyrimidine with esters of β-halogeno-α,γ-diketoacids results in formation of derivatives of oxazolidino[3,2-f]pyrido[2,3-b]-1,4-thiazines (I, II). However, in the case of 2-mercapto-3-amino-6-chloropyridine and esters of β-isovalerylpyruvic acids the reaction is arrested at the stage of formation of the corresponding esters of N-(pyridyl-3) oxaminic acid (IIIa, b).

As a continuation of these studies we have investigated the chemical properties and transformations of compounds I-III under the action of nucleophilic agents. It has been found that compounds I and II react extremely easily with ammonia and amines. Depending on the reaction conditions, the reaction proceeds either with retention of the tricyclic system, or with the ring opening of the oxazolidine cycle only, or with the opening of both oxazolidine and thiazine cycles at the $C_{(2)}$—O and $N_{(5)}$—$C_{(6)}$ bonds. Thus, according to [3], interaction of Ia-d and II with ammonium acetate in glacial acetic acid at 80-100°C gives rise to derivatives of new heterocyclic systems, imidazolino[3,2-f]pyrido-[2,3-b]-1,4-thiazine (VII a-d) and imidazolino [3,2-f]pyrimido[4,5-b]-1,4-thiazine (VII g, Table 1).



Ia—d, Va—f, h—k, VIb, VIIa—f X=CH, R=Cl, R¹=H; II, Vg, l, VIa, VIIg. X=N, R=H; R¹=OCH₃, R²=C₂H₅, Ia, IIIc, IVa, Va,e,i, VIIa R²=CH₃; Ib, IVb, Vb,j, VIIb. R²=C₂H₅; Ic, IIId, IVc, Vc,f,k, VIIc R²=C₃H₇; IIIa, Vd,h, VII R²=C₆H₅; Id, VIId R²=n-C₄H₉; IIIb, VIIe R²=t-C₄H₉; Va—d R³=H; Ve,f, VIb,c R³=NHCH₂C₆H₅; Vh—k,l R³=morpholyl; Vg, VIa R³=H

*For communication 43, see [1].

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TABLE 1. Characterization of Compounds IVa-c, Va-l, VIa,b, and VIIa-g

Compound	mp*, °C	R_f (system)	Found					Molecular formula	Calcd., %					Yield, %
			C	H	Cl	N	S		C	H	Cl	N	S	
IVa	287—289	0,51 (a)	41,5	3,4	12,3	14,7	11,4	$C_{10}H_{10}ClN_3O_3S$	41,7	3,5	12,3	14,6	11,1	93
IVb	262—264		43,8	4,2	11,8	14,4	10,8	$C_{11}H_{12}ClN_3O_3S$	43,8	4,0	11,8	13,9	10,6	81
IVc	247—249	0,5 (a)	45,5	4,4	11,8	13,5	10,2	$C_{12}H_{14}ClN_3O_3S$	45,6	4,4	11,3	13,3	10,1	90
Va	208—210		41,4	3,5	12,3	14,5	11,3	$C_{10}H_{10}ClN_3O_3S$	41,7	3,5	12,4	14,6	11,1	71
Vb	207—209	0,5 (a)	43,8	3,9	11,3	13,9	10,6	$C_{11}H_{12}ClN_3O_3S$	43,8	4,0	11,8	13,9	10,6	75
Vc	193—194		45,5	4,6	11,5	13,2	10,1	$C_{12}H_{14}ClN_3O_3S$	45,6	4,4	11,3	13,3	10,1	94
Vd	228—230	0,6 (a)	51,6	3,5	10,3	11,8	9,3	$C_{16}H_{12}ClN_3O_3S$	51,5	3,4	10,2	12,0	9,1	95
Ve	189—190		54,1	4,2	8,7	11,1	—	$C_{17}H_{16}ClN_3O_3S$	54,0	4,2	9,3	11,1	8,5	61
Vf	179—181		55,9	4,6	8,9	10,4	7,6	$C_{19}H_{20}ClN_3O_3S$	56,2	4,9	8,7	10,3	7,9	81
Vg	196—197	0,67 (b)	44,3	4,7	—	18,9	10,8	$C_{11}H_{14}N_4O_4S$	44,3	4,7	—	18,8	10,7	88,6
Vh	145—147		54,4	4,3	8,3	9,8	7,4	$C_{19}H_{18}ClN_3O_4S$	54,3	4,3	8,5	10,0	7,6	96
Vi	105—107		47,0	4,5	10,0	11,7	9,3	$C_{14}H_{16}ClN_3O_4S$	47,0	4,5	9,9	11,7	8,9	80—83
Vj	133—135		46,2	4,6	9,3	10,8	8,4	$C_{15}H_{18}ClN_3O_4S$	46,5	4,6	9,2	10,8	8,2	78
Vk	113—115		49,8	5,2	9,0	10,7	8,4	$C_{16}H_{20}ClN_3O_4S$	49,8	5,2	9,2	10,9	8,3	93
Vl	130—131		48,5	5,3	—	14,3	8,9	$C_{16}H_{20}N_4O_5S$	48,9	5,5	—	15,2	8,7	89
VIa	214—215		43,0	4,2	—	28,4	—	$C_7H_8N_4O_3$	42,9	4,1	—	28,6	—	72
VIb	212—214		57,8	4,0	—	14,7	—	$C_{14}H_{12}ClN_3O_2$	58,0	4,1	—	14,5	—	71
VIIa	298—300	0,35 (a)	44,4	3,0	13,5	15,3	11,7	$C_{10}H_8ClN_3O_2S$	44,5	3,0	13,2	15,6	11,9	96—98
VIIb	263—264	0,39 (a)	46,3	3,6	12,7	14,9	11,4	$C_{11}H_{10}ClN_3O_2S$	46,6	3,5	12,5	14,8	11,3	91—98
VIIc	250—251	0,39 (a)	48,4	4,0	13,8	14,4	10,8	$C_{12}H_{12}ClN_3O_2S$	48,4	4,0	11,9	14,1	10,7	90
VIId	262—264	0,44 (a)	50,4	4,5	11,7	13,7	10,2	$C_{13}H_{14}ClN_3O_2S$	50,1	4,5	11,4	13,5	10,3	88
VIIe	249—250		50,1	4,8	11,3	13,6	10,3	$C_{13}H_{14}ClN_3O_2S$	50,1	4,5	11,4	13,5	10,3	96
VIIf	>300		54,1	3,0	10,7	12,4	9,7	$C_{15}H_{10}ClN_3O_2S$	54,3	3,0	10,7	12,7	9,6	72—93
VIIg	240—241	0,5 (b)	47,2	4,5	—	20,0	11,1	$C_{11}H_{12}N_4O_3S$	47,1	4,3	—	20,0	11,4	69—79

*Recrystallization of compounds IVa-c, Va,d,f,h,i,k, VIb, VIIa-d,g from ethanol, Vb,c,e from a 1:2 mixture ethanol—DMF, VIIf from a 2:0.5 mixture of ethanol—DMF, Vj from a 10:1 mixture of ethanol—DMF, Vl from water, Vg from aqueous ethanol, 3:1, and VIa from ethyl acetete.

TABLE 2. Spectral Characterization of Compounds

Compound	IR spectrum, ν*, cm^{-1}				UV spectrum, λ_{max}, nm (log ε)	NMR spectrum, δ, ppm (in C_5D_5N)†
	NH	NH_2	of amides	of ketone		
IVa	3440		1730, 1740			
IVb	3440		1730—1760			0,78 (CH_2CH_3, t), 1,98 (CH_2CH_3, q), 3,52 (7-CH_2, q)
IVc	3440		1670, 1720			0,79, 1,30, 1,98 (protons of C_3H_7), 3,52 (7-CH_2, q)
Va	3380	3230, 3300	1680—1690	1725		
Vb	3390	3295, 3210	1670	1725	208 (4,09), 225 (4,09), 285 (3,94)	0,99 (CH_2CH_3, t), 2,66 (CH_2CH_3, kB), 4,07 (S—CH_2, s), 8,1—8,38 (NH_2, broad s), 10,27 (NH, broad s)
Vc	3400	3300, 3200	1660—1670	1720		
Vd	3400	3310, 3290	1660—1680	1715	208 (4,18), 245 (4,05), 283 (3,84)	
Ve	3300		1670	1730	205 (4,28), 230 (4,36), 284 (3,98)	
Vf	3295		1660, 1700	1720	230 (4,19), 282 (3,97), 308 (3,92)	
Vg	3440—3310	3280, 3250	1665	1720		0,95 (CH_2CH_3, t), 2,53 (CH_2CH_3, q), 3,76 (OCH_3, s), 4,13 (S—CH_2, s), 8,63 (2-CH—, s), 9,23 (NH_2, s), 11,49 (NH)
Vh	3320		1690	1710	248 (4,33), 304 (3,91)	4,71 (S—CH_2, s), 3,76, 4,26 (protons of the morpholine ring), 7,01, 7,1, 8,15, 8,20 (protons of the pyridine ring), 7,54 (protons of C_6H_5)
Vi	3250		1650, 1680	1720		2,23 (CH_3, s), 3,45, 3,98 (protons of the morpholine ring), 4,1 (S—CH_2, s), 7,21, 7,91 (protons of the pyridine ring)
Vj	3310		1680	1720		
Vk	3310		1640, 1680	1720	258 (4,06), 302 (3,90)	0,94, 1,67, 2,66 (protons C_3H_7), 4,01 (S—CH_2, s), 3,75, 4,26 (protons of the morpholine ring), 7.02. 8,14 (protons of the pyridine ring)
VI	3250		1650—1685	1715		0,96 (CH_2CH_3,T), 2,51 (CH_2CH_3, q), 3,79 (OCH_3, s), 4,17 (S—CH_2, s), 8,46 (2-CH, s)
VIa	3440, 3360	3290, 3260	1670			3,79 (OCH_3, s), 8,65 (2-CH, s), 9,61 (6-CH, s)
VIb	3290—3300		1660—1670			
VIIa	3260—3300		1740, 1780		208 (4,07), 244 (4,23), 310 (3,90)	1,67 (3a-CH_3, s), 3,44 (4-CH_2, q)
VIIb	3270		1720—1760		208 (4,06), 244 (4,21), 310 (3,88)	0,78 (CH_2CH_3, t), 2,00 (CH_2CH_3, q), 3,54 (4-CH_2, q)
VIIc	3080—3100		1740—1760		206 (4,01), 244 (4,20), 310 (3,88)	0,79, 1,30, 1,98 (protons of C_3H_7), 3,52 (4-CH_2, q)
VIId	3060—3120		1740, 1760			
VIIe	3030		1750, 1760—1770		240 (4,24), 300 (3,90)	
VIIf	3250		1740—1770			
VIIg	3020		1745—1775			0,82 (CH_2CH_3, t), 1,41 (CH_2CH_3, q), 3,6, 3,66 (4-CH_2, two d.), 3,99 (OCH_3, s), 8,57 (2-CH, s)

*IR spectrum of compound IVa ν_{OH} 3530, IVb and VIc ν_{OH} 3540 cm^{-1}.
†NMR spectra of Ib were taken in DMSO-d, Vh-k in $CDCl_3$, and Vi in CD_3OD.

It has been shown that the transformation to compounds VIIe,f can be realized using the reaction of esters of N-(pyridyl-3)oxamic acid IIIa,b with ammonia under the above-mentioned conditions. During the reaction of compounds Ia-c with ammonia in glacial acetic acid or its mixture with benzene, the intermediate compounds 5N-oxalimides of 6-hydroxy-7H pyrido[2,3,-b]-1,4-thiazine (IVa-c) were isolated. Compounds IVa,b were transformed into tricyclic compounds VIIa,b by dehydration over P_2O_5.

Contrary to compounds Ia-c, the treatment of oxazolidino[3,2-f]pyrimido[4,5-b]-1,4-thiazine (II) with ammonia, under the conditions described above, leads exclusively to the formation of imidazolidino[3,2-f]pyrimido[4,5-b]-1,4-thiazine (VIIg).

Interaction of compounds I-III with a 25% aqueous ammonia, as well as with primary aliphatic and secondary cyclic amines (benzylamine and morpholine), gives good yields of amides of N-(pyridyl-3)- and N-(pyrimidyl-5)oxaminic acids (Va-ℓ).

We established the identity of amides Vi,k obtained by us from esters IIIc,d and from the cyclic oxazolidino[3,2-f] derivatives Ia,d.

We demonstrated that heating of amides Vg and Vd in glacial acetic acid or with $POCl_3$ leads to imidazolidino[3,2-f]pyrimido- and pyrido-1,4-thiazines (VIIg,f). Cyclization of amide Vg was also observed upon boiling it with an alcoholic HCl solution. However, the yield of compound VIIg did not exceed 28%.

During the reductive desulfurization of amides Vf and Vg in alcohol with Raney nickel amides of N-(pyridyl-3)- and N-(pyrimidyl-5)oxaminic acids (VIa,b) are formed, similarly as in [4].

The structure of synthesized compounds was confirmed by physicochemical methods such as IR, UV, NMR, and mass spectroscopy.

The IR spectra of compounds VIIa-g exhibit absorption bands of the NH group in the region 3030-3290 cm^{-1} and the CO groups in the region of 1730-1780 cm^{-1} (Table 2). The structure of compounds IVa-c and VIIa-g was unequivocally established by its NMR spectrum. In these compounds the signal of the protons of the 7-CH_2 group (IVb,c) and of the 4-CH_2 group (VIIa-c,g), due to the presence of the asymmetric carbon atom in the 6 and 3a positions, show up as two doublets with constant of the geminal interaction $I_{HH} = 12$ Hz, contrary to compounds of the opened structure Vb,g in which the signal of the SCH_2 group protons appears as a singlet.

The mass spectra of imidazolidino[3,2-f]-pyrido- and pyrimido-1,4-thiazines VIIb,g show peaks of molecular ions M^+ with mass numbers 283 and 280, respectively (calculated for the ^{35}Cl isotope). The fragmentation of M^+ proceeds similarly with the stepwise loss of NHCO and CO molecules from the imidazolidine ring. One should point out that the most convenient first step of the fragmentation of M^+ of compounds VIIb,g, as oppossed to the previously studied oxazolidino[3,2-f]-derivatives, consists in elimination of the ethyl group in the α position with respect to the nitrogen atoms of the imidazolidine ring. Consequently, in the spectra of compounds VIIb,g the peaks of ions $[M-C_2H_5]^+$ (40 and 19)*, $M-C_2H_5-CO]^+$ (21 and 26), and $[M-C_2H_5, -CO,-NHCO]^+$ (48 and 22) have higher intensities then peaks of ions $[M-NHCO]^+$ (4 and 8) and $[M-CO_1-NHCO]^+$ (16).

EXPERIMENTAL

IR spectra of the synthesized compounds were recorded on a Perkin-Elmer 599 instrument (in paraffin oil), and UV spectra on a Perkin-Elmer 575 spectrophotometer (in alcohol). NMR spectra were measured on JNM-4H (100 MHz and Varian XL-100 instruments using TMS as an internal standard. The purity of compounds was confirmed by thin layer chromatography on Silufol UV-254 plates in the following systems: benzne–ethyl acetate–ethanol 17:5:2 (a) and 5:5:1.5 (b). The chromatograms were visualized in UV light. Electron impact mass spectra were obtained on a Varian MAT-112 mass spectrometer by the method of direct insertion of the sample in the ion source.

*The numbers in parentheses represent the intensities of ion peaks in percent with respect to the maximal peak.

Amides of N-[2-acylmethylthio)-6-chloropyridyl-3]oxaminic Acid (Va-f,h-k). A. A suspension of 2 mmoles of 1,2-dioxo-3a-(alkyl)-7-chlorooxazolidino[3,2-4]pyrido[2,3-b]-1,4-thiazines Ia-c in 10 ml of 25% aqueous ammonia was stirred for 2-3 h at 18-20°. The precipitated solid was filtered off, washed with water, and dried to give amides Va-c. Under analogous conditions the reaction of 2 mmoles of oxazolidino[3,2-f]pyrido-1,4-thiazines Ia-c with 3 mmoles of benzylamine or morpholine in 15-20 ml of ethanol produced compounds Ve,f,i-k.

B. The ethyl ester of the corresponding N-[2-acylmethylthio)-6-chloropyridyl-3]oxaminic acid (IIIa,c,d)(2mmole) was stirred with 2.5-3 mmole of morpholine in 15-20 ml of ethanol. The precipitate was filtered off, washed with water and ether, and then dried to give compounds Vh,i,j. A sample of 8.0 g (26 mmole) of compound IIIa was treated with 25% aqueous ammonia under conditions described for method A to yield amide Vd.

The identity of amides Vi,k obtained according to methods A and B was confirmed by comparing their analytical and spectral characteristics.

Amides of N-(4-Methoxy-6-propionylmethylthio)pyrimidyl-5-oxaminic Acid (Vg,l). To a suspension of 0.83 g (2.83 mmole) of compound II in 50 ml of alcohol 5 ml of 25% aqueous ammonia was added. The substance dissolved and after 10 min a solid precipitated. The reaction mixture was stirred for additional 30 min at 18-20°C. The precipitate was filtered off, washed with water, and dried to give substance Vg. Amide Vl was obtained from 0.7 g (2.5 mmole) of compound II and 0.21 (2.5 mmole) of morpholine in 30-40 ml of ethanol.

Amide of N-(4-Methoxypyrimidyl-5)-oxaminic Acid (VIa). A mixture of 0.74 g (2.48 mmole) of compound Vg and 6.0 g of Raney nickel in 40 ml of ethanol was refluxed for 5 h with vigorous stirring. The catalyst was filtered off, additionally extracted with 20 ml of boiling alcohol, and filtered again. The alcohol filtrates were combined and evaporated under vacuum to dryness to yield amide VIa.

N-Benzylamide-6-chloropyridyl-3)-oxaminic Acids (VIb) and N-Benzylamide of Pyridyl-3-oxaminic Acid (VIc). These were obtained from 0.3 g (0.7 mmole) of compound Ve, 3.0 g of Raney nickel in 20 ml of boiling ethanol during 4 h. The hot solution was filtered. The precipitate was washed twice with 10 ml of hot ethanol. The filtrate and washings were combined and concentrated to 1/3 of the original volume. The precipitate was filtered and dried to give compound VIb. After removal of compound VIb the filtrate was evaporated to dryness; then 5 ml of water was added, and the solid was filtered off and dried to give 0.05 g (27%) of compound VIc, mp 167-168°C (form alcohol). The identity of compound VIc was proved by comparison of its analytical and spectral characteristics with the sample obtained previously [4].

2-Chloro-5N-oxalimides of 6-Hydroxy-6-alkyl-7H-pyrido[2,3-b]-1,4-thiazine (IVa-c). Gaseous ammonia was buubled through a suspension of 2 mmoles of compounds Ia-c in 10 ml of glacial CH_3COOH. The reaction mixture warmed up to 100°C and solidified. It was kept for 3 h at 18-20°C and then diluted with 20 ml of water. The precipitate was filtered off, washed with water, and dried to give compounds IVa-c.

1,2-Dioxo-3a-ethyl-9-methoxy-4H-imidazolino[3,2-f]pyrimido[4,5-b]-1,4-thiazine (VIIg). A. A solution of 0.35 g (1.25 mmole) of compound II and 1.8 g (23.2 mmole) of CH_3COONH_4 in 15 ml of glacial acetic acid was heated for 2 h at 80°C. The reaction mixture was poured in 30 ml of water, neutralized with ammonia, evaporated to 15 ml, and cooled with ice-water; the precipitated product was filtered off to give compound VIIg. Mass spectrum, m/z (%): 281 (17), 280 (100), 265 (9), 251 (19), 237 (8), 230 (4), 223 (26), 219 (5), 209 (16), 208 (13), 197 (30), 194 (21), 183 (13), 182 (10), 181 (13), 180 (22), 169 (15), 164 (I), 163 (9), 156 (12), 154 (10), 137 (11), 131 (12), 121 (9), 119 (15), 113 (11), 81 (10), 69 (75), 56 (23).

B. Gaseous ammonia was bubbled during 0.5 h through a suspension of 0.2 g (0.73 mmole) of compound Vg in 10 ml of glacial acetic acid. The mixture was kept for 2 h at 20°C and diluted with 20 ml of water. The precipitate was filtered off to give compound VIIg.

C. Thiazine VII was also obtained from 0.5g (1.78 mmole) of compound II in 10 ml of glacial CH_3COOH under conditions employed in method B.

D. A mixture of 0.43 g (1.45 mmole) of compound Vg, 20 ml of ethanol, and 1 ml of alcoholic HCl was refluxed for 8 h. The precipitate was filtered off and dried to yield 0.06 g (28.6%) of thiazine VIIg. The filtrate gives 0.19 g of the starting amide Vg.

1,3-Dioxo-3a-(aralkyl)-7-chloro-4H-imidazolidino[3,2-f]pyrido[2,3-b]-1,4-thiazines (VIIa-f).

A. Thiazines VIIa-d were obtained from 3 mmoles of 1,2-dioxo-3a-(alkyl)-7-chloroxazolidino [3,2-f]pyrido[2,3-b]-1,4-thiazines Ia-d, 2.0 g of ammonium acetate in 10 ml of glacial acetic acid, or its micture with benzene under conditions analogous to those employed for obtaining compound VIIg (method A) with the only difference that the solutions were refluxed for 5 h. Mass spectrum of compound VIIb, m/z (%): 285 (40), 283 (100), 270 (8), 268 (16), 256 (15), 254 (40), 240 (4), 228 (10), 227 (8), 226 (21), 214 (8), 213 (8), 212 (16), 211 (10), 200 (17), 199 (13), 197 (22), 185 (23), 183 (48), 172 (8), 171 (7), 167 (8), 166 (7), 165 (6), 135 (10), 119 (8), 103 (8), 69 (12), 64 (6), 56 (12), 55 (9).

B. Compounds VIIa,b were obtained by dehydration of 0.09 mmole of compounds IVa,b during 3 days under vacuum on heating over P_2O_5 (heating agent water).

C. Compounds VIIe,f were obtained from 1.5 mmole of the ethyl ester of the corresponding N-[2-acylmethylthio-6-chloropyridyl-3]oxaminic acids (IIa,b) in 10 ml of glacial acetic acid under conditions analogous to the synthesis of compound VIIg (method B).

D. A sample of 7.75 g (22.2 mmole) of compound Vd in 15 ml of $POCl_3$ was refluxed for 15-20 min. The reaction mixture was poured on ice. The precipitate was filtered off, washed with water to neutrality, and dried to give compound VIIf.

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