STUDY OF NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES.

46.* NEW HETEROCYCLIC SYSTEMS — DERIVATIVES OF PYRIDO[3′,2′:5,6][1,4]THIAZINO[3,4-c]- AND PYRIMIDO-[5′,4′:5,6][1,4]THIAZINO[3,4-c][1,2,4]TRIAZINES. SYNTHESIS, PROPERTIES

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Representatives of new heterocyclic systems were obtained — pyrido[3′,2′:5,6][1,4]thiazino[3,4-c]- and pyrimido[5′,4′:5,6][1,4]thiazino[3,4-c][1,2, 4]triazines. Hydrazides of N-(pyrid-3-yl)- and N-(pyrimid-5-yl)oxamic acids were isolated and characterized. Their acylation products were investigated.

We have previously reported [2] that the reaction of o-aminomercapto derivatives of pyridine and pyrimidine with esters of β-halo-α,γ-diketo acids, leads to the formation of oxazolo[3,2-d]pyrido[2,3-b]- and oxazolo[3,2-d]pyrimido[4,5-b]-1,4-thiazines (Ia-d, II) or esters of N-(pyridyl-3)oxamic acid (IIIa, c-f).

In the present work, in order to conduct a further search for new biologically active compounds in the 1,4-thiazine series, we continued the investigation of the chemical properties and transformations of compounds I-III under the action of nucleic agents, using hydrazine hydrate and phenylhydrazine as such. It was found that when treated with hydrazine hydrate in alcohol at 18-20°C, tricyclic derivatives Ia-c, II undergo a transformation proceeding with a simultaneous opening of the oxazole and thiazine rings at the $C_{(2)}-O$ and $N_{(10)}-C_{(3a)}$ bonds, similarly to reactions with ammonia and amines [3]. As a result, hydrazides of N-(pyrid-3-yl)- and N-(pyrimid-5-yl)oxamic acids (IVa-c and V, respectively) are formed in a high yield (90-99%) (see Table 1). The action of phenylhydrazine or its hydrochloride on thiazines Ia, c in alcohol in the presence of triethylamine leads to the formation of phenylhydrazides (IVg, h).

Hydrazides IVe, f and phenylhydrazide IVk were also obtained by treatment of esters of (pyrid-3-yl)oxamic acid IIIe, f with hydrazine hydrate and phenylhydrazine, respectively. The identity of hydrazide IVc, synthesized both from ester IIIc and from the tricyclic compound Ic was proved by comparison of their analytical and spectral characteristics. Acylation of hydrazides IVc and IVf by β-bromopropionyl chloride and acetic anhydride leads to acylhydrazides IVi, j, *l*. It was found that hydrazides IVa-c, e, f, V are quantitatively converted by the action of alcoholic and ethereal solutions of HCl into the derivatives of heterocyclic systems — pyrido[3′,2′:5,6][1,4]thiazino[3,4-c]- and pyrimidino[5′,4′:5,6][1,4]thiazino[3,4-c][1,2,4]triazines (VIa-c, e, f, VII) [4], the formation of the latter clearly proceeding in analogy with the data in [5], via oxamino compounds "A" with their subsequent dehydration.

The derivatives of pyridothiazino[1,2,4]triazines can also be obtained from esters of N-(pyrid-3-yl)oxamic acid without isolation of the corresponding hydrazides. Thus, treatment of esters IIId, f by hydrazine hydrate in ethanol medium, followed by boiling of the reaction mixture with addition of hydrogen chloride leads to compounds VId, f.

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*For communication 45, see [1].

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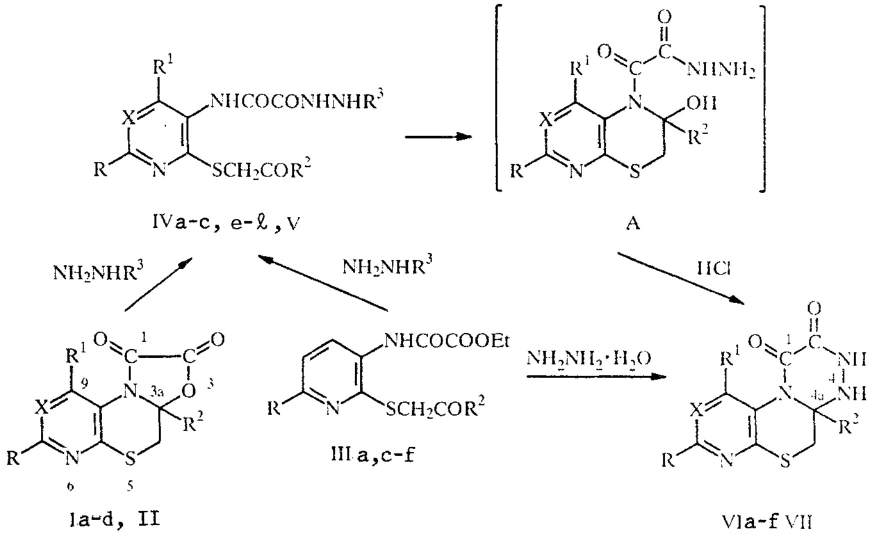

Ia-d; IIIa, c-f; IVa-c, e-*l*; VIa-f) R = Cl, R^1 = H, X = CH; a) R^2 = Me, b) R^2 = Et, c) R^2 = Pr, d) R^2 = Bu, e) R^2 = t-Bu, f) R^2 = Ph; IVa-c, e, f) R^3 = H; IVg-*l*) R^2 = Me, R^3 = Ph, h) R^2 = Pr, R^3 = Ph, i) R^2 = Pr, R^3 = COMe, j) R^2 = Pr, R^3 = $CO(CH_2)_2Br$; k) R^2 = t-Bu, R^3 = Ph, *l*) R^2 = Ph, R^3 = $CO(CH_2)_2Br$; II, V, VII) R = H, R^1 = OMe, R^2 = Et, X = N

The structure of the synthesized compounds was confirmed by the elemental analysis data, and also by their spectral characteristics. In the IR spectra of hydrazides IVa-c, f, e, V bands of stretching vibrations of the NH and NH_2 groups are observed in the 3180 and 3250-3300 cm^{-1} region, and of the amide and ketone C=O in the 1650-1670 cm^{-1} and 1700-1720 cm^{-1} region (see Table 1). In the IR spectra of the tricyclic [1,2,4]triazines VIa-f, VII absorption bands of the NH groups were recorded in the 3200-3250 cm^{-1} region, and of the amide C=O groups in the 1650-1670 cm^{-1} region. The NMR spectra of the hydrazides of N-(pyrid-3-yl)- and N-(pyrimid-5-yl)oxamic acids, similarly as the spectra of the previously discussed amides [3], are characterized by the presence of a singlet signal of the SCH_2 group, which agrees well with the structure proposed for them. The NMR spectra of the corresponding [1,2,4]triazines were not obtained because of the poor solubility of these compounds. In the mass spectrum of pyridothiazino[1,2,4]triazine (VId) the peak of the molecular ion (M^+) with the mass number 346 was observed corresponding to the proposed structure, as well as peaks of ions $[M-CO-NH-NH-CO]^+$ 260 (11), $[M-CO-CO-NH-NH_2]^+$ 259 (10).*

EXPERIMENTAL

The IR spectra of the synthesized compounds were run on a Perkin–Elmer 599 spectrophotometer (in mineral oil). The PMR spectra were measured on a JNM-4H (100 MHz) and Varian XL-100 spectrometers, using TMS as internal standard. The purity of the compounds was confirmed by thin layer chromatography on Silufol UV-254 plates, in a benzene–ethyl acetate–alcohol (17:3:2) system. The chromatograms were developed in UV light. The electron impact mass spectra were obtained on a Varian MAT-112 mass spectrometer, with direct introduction of the sample into the ionic source. The characteristics of the synthesized compounds are given in Table 1.

The elemental analysis data for C, H, N, Cl, S for compounds IVa-c, e-*l*, V, VIa-f, VII correspond to the calculated values.

Hydrazides of N-[2-(Acylmethylthio)-6-chloropyrid-3-yl]oxamic Acid (IVa-c, e, f). A. A 2-mmole portion of compound Ia, Ib, or Ic [2] was stirred with 10 mmoles of hydrazine hydrate in 20 ml of ethanol at 18-20°C for 20-30 min. The precipitate of product IVa, b, or c that separated out was filtered off, washed with alcohol, petroleum ether, and dried.

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*The m/z (I_{rel}, %) values are given.

TABLE 1. Characteristics of Compounds IVa-c, e-*l*, V, VIa-f, VII

Compound	Empirical formula	mp, °C	IR spectrum, ν, cm^{-1}				Yield, %
			NH	NH_2	C=O (amide)	C=O (ketone)	
IVa	$C_{10}H_{11}ClN_4O_3S$	156...158	3305	3290	1665	1725	90
IVb	$C_{11}H_{13}ClN_4O_3S$	218...220	3300	3270	1670	1720	98
IVc	$C_{12}H_{15}ClN_4O_3S$	188...190	3290	3270	1650	1715	85...91
IVe	$C_{13}H_{17}ClN4O_3S$	208...210	3300	3250	1650	1710	87...94
IVf	$C_{15}H_{13}ClN_4O_3S$	198...200	3295	3280	1660	1700	85..95
IVg	$C_{16}H_{15}ClN_4O_3S$	196...197	3270	—	1670	1730	82
IVh	$C_{18}H_{19}ClN_4O_3S$	205...207	3250	—	1670	1720	73.5
IVi	$C_{14}H_{17}ClN_4O_4S$	208...210	3230...3260	—	1650	1720	80
IVj	$C_{15}H_{18}ClN_4BrO_4S$	196...198	3230...3270	—	1670	1720	83.5
IVk	$C_{19}H_{21}ClN_4O_3S$	209...211	3230...3260	—	1670	1720	95
IVl	$C_{18}H_{16}ClN_4BrO_4S$	198...200	3240...3280	—	1670	1720	85
V	$C_{11}H_{15}N_5O_4S$	185...186	3320	3230...3270	1650...1670	1720	99
VIa	$C_{10}H_9ClN_4O_2S$	> 300	3220...3240		1650...1670		96
VIb	$C_{11}H_{11}ClN_4O_2S$	> 300	3200...3250		1650...1670		97
VIc	$C_{12}H_{13}ClN_4O_2S$	> 300	3200...3230		1660...1670		100
VId	$C_{13}H_{15}ClN_4O_2S$	> 300	3200...3250		1650...1670		95...100
VIe	$C_{13}H_{15}ClN_4O_2S$	> 300	3200...3250		1650...1670		100
VIf	$C_{15}H_{11}ClN_4O_2S$	> 300	3290		1660...1670		96...98
VII	$C_{11}H_{13}N_5O_3S$	262	3215		1660...1700		85

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*Compound IVa was crystallized from a DMF – H_2O (2:1) mixture; compounds IVb, c, g, h-j, *l* — from a DMF – alcohol (1:2) mixture; compounds IVe, f, k — from alcohol.

B. A 1.3-mmole portion of compound IIIc, IIIe, or IIIf was stirred with 0.5 ml (10 mmoles) of hydrazine hydrate in 20 ml of ethanol under conditions similar to those described for method A. Compounds IVc, e, f were obtained.

IVa. PMR spectrum ($DMSO-D_6$): 2.28 (3H, s, CH_3), 4.08 (2H, s, $S-CH_2$), 4.68 (2H, s, NH_2), 7.3 and 7.81 (the pyridine ring protons), 10.27 and 10.41 ppm (2H, s,s, 2NH).

IVc. PMR spectrum ($DMSO-D_6$): 0.78 (3H, t, $CH_2CH_2C\underline{H}_3$), 1.08 (2H, m, $CH_2C\underline{H}_2CH_3$), 1.57 (2H, t, $C\underline{H}_2CH_2CH_3$), 4.10 (2H, s, $S-CH_2$), 4.70 (2H, s, NH_2), 7.3 and 7.81 (the pyridine ring protons), 10.29 and 10.43 ppm (2H, s,s, $2NH_2$).

Phenylhydrazides of N-[2-Acetylmethylthio)-6-chloropyrid-3-yl)oxamic Acid (IVg, h, k). A. A 1.5-mmole portion of ester IIIa or IIIe was stirred with 0.2 g (1.8 mmoles) of phenylhydrazine in 20 ml of ethanol at 18-20°C for 30 min. The precipitate of product IVh or IVk that separated out was filtered off, washed with alcohol, petroleum ether, and dried.

B. A 0.4-g portion (1.4 mmoles) of oxazolidino(3,2-d) derivative (Ia) was stirred with 0.2 g (1.8 mmoles) of phenylhydrazine in 15-20 ml of ethanol. After 5-10 min, the precipitate of product IVg separated out and after 30-40 min was filtered off, and further treated as described in method A.

C. A 0.24-g portion (1.6 mmoles) of phenylhydrazine hydrochloride and 0.25 ml (0.18 g, 1.7 mmoles), of triethylamine were added to 0.5 g (1.6 mmoles) of compound Ic in 10 ml of ethanol. The mixture was stirred at 18-20°C for 3 h. The precipitate that separated out was filtered off, washed with water, alcohol, and dried. The product obtained was identical with hydrazide IVh obtained by method A, which was confirmed by comparison of their analytical and spectral characteristics.

Acetylhydrazide of N-[2-Butylmethylthio)-6-chloropyrid-3-yl)oxamic Acid (IVi). A 0.5-ml portion (5.2 mmoles) of acetic anhydride was added to a suspension of 0.5 g (1.5 mmoles) of hydrazide IVc in 10 ml of ethanol and the mixture was stirred at 18-20°C for 30 min. In the course of the reaction the precipitate of the initial hydrazide IVc dissolved, and the precipitate of product IVi separated out, which was filtered off, washed with water, and dried.

β-Bromopropionylhydrazide of N-[2-(Butylmethylthio)-6-chloropyrid-3-yl)oxamic Acid (IVj). Hydrazide IVj was obtained in a similar way as hydrazide IVi from 2.0 g (6 mmoles) of hydrazide IVc and 1.1 ml (1.76 g, 10.2 mmoles) of β-bromopropionyl chloride in ether with the difference that anhydrous potassium carbonate was used instead of sodium bicarbonate.

β-Bromopropionylhydrazide of N-[2-(Benzoylmethylthio)-6-chloropyrid-3-yl)oxamic Acid (IV*l*). A 1.1-ml portion (1.76 g, 10.2 mmoles) of β-bromopropionyl chloride in 10 ml of ether was added dropwise to a suspension of 2.0 g (5.5 mmoles) of hydrazide IVf and 1.0 g (12 mmoles) of sodium bicarbonate in 20 ml of absolute ether. The mixture was stirred for 3-4 h at 18-20°C and allowed to stand overnight. The precipitate of product IV*l* that separated out was filtered off, washed with water and petroleum ether.

Hydrazide of N-(4-Methoxy-6-propionylmethylthiopyrimid-5-yl)oxamic Acid (V). A solution of 0.59 g (2.1 mmoles) of thiazine II and 0.11 g (2.1 mmoles) of hydrazine hydrate in 20 ml of ethanol was stirred for 20 min at 18-20°C. The precipitate of hydrazide V that separated out was filtered off, washed with alcohol, and dried.

1,2-Dioxo-4a-(aralkyl)-8-chloro-3,4,4a,5-tetrahydropyrido[3′,2′:5,6][1,4]thiazino[3,4-c][1,2,4]triazines (VIa-f). A. Triazines (VIa-c, e, f) were obtained by boiling for 15-20 min a suspension of 2 mmoles of a hydrazide of the corresponding N-(pyrid-3-yl)oxamic acid (IVa-c, e, f) in 20 ml of ethanol in the presence of 2-3 drops of an alcoholic solution of HCl. The precipitate that separated out on cooling was filtered off, washed with water, and dried.

B. A 0.3-ml portion (6 mmoles) of hydrazine hydrate was added to a solution of 2.0 g (5.5 mmoles) of ester IIId in 20 ml of ethanol and stirred for 20 min. An ethereal solution of HCl (2-3 drops) was added dropwise to the suspension obtained and the mixture was boiled for 20-30 min. The precipitate of product VId that separated out was washed thoroughly with water, alcohol, and petroleum ether. Triazine VIf was obtained in a similar way from 0.5 g (1.3 mmoles) of ester IIIf, 0.1 g (2 mmoles) of hydrazine hydrate with the addition of 2-3 drops of an alcoholic solution of HCl. Mass spectrum, m/z (I_{rel}, %): 76 (100), 77 (20), 101 (25), 102 (77), 103 (46), 104 (52), 133 (27), 159 (27), 186 (17), 259 (10), 260 (11), 346 (3).

1,2-Dioxo-4a-ethyl-10-methoxy-3,4,4a,5-tetrahydropyrimido[5′,4′:5,6][1,4]thiazino[3,4-c][1,2,4]triazine (VII). A suspension of 0.3 g (0.95 mmole) of hydrazide V in 20 ml of ethanol, containing 2 drops of an alcoholic solution of HCl was boiled for 30 min. The product was treated in the same way as compounds VIa-c — by method A.

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