Chemistry of Heterocyclic Compounds, Vol.35, No. 6, 1999

NITROGEN AND SULFUR CONTAINING HETEROCYCLES. 50.* SYNTHESIS AND REACTIONS OF 6-OXOPYRIMIDO[4,5-*b*][1,4]THIAZINE-7-CARBOXYLIC ACID DERIVATIVES

T. S. Safonova and A. F. Keremov

Reaction of 5-amino-6 mercaptopyrimidines with diethyl bromomalonate gave ethyl 6-oxopyrimido-[4,5-b][1,4]thiazine-7-carboxylates, from which there was synthesized a series of derivatives at the carboxyl group (amides, hydrazides, and, from the latter, urethanes). Desulfurization of the 6-oxo-pyrimidothiazine-7-carboxylic acid esters gave N-(pyrimidin-5-yl)monoamides of ethyl malonate.

We have previously reported [2, 3] preparative methods and properties for pyrimido[4,5-b][1,4]thiazin-6-one. A study of the biological properties of these compounds has shown that they selectively suppress the growth of tumor cells when compared with the growth of normal cells [4].

In a development of this work, we have undertaken the synthesis and study of the reactions of a series of novel pyrimido[4,5-b][1,4]thiazin-6-ones containing a carbethoxy group at position 7. With this in mind, we examined the reaction of 5-amino-6-mercaptopyrimidines Ia-c with diethyl bromomalonate (II). It was found that reaction of 5-amino-4-chloro-6-mercaptopyrimidine (Ia) with compound II in alcohol in the presence of potassium hydroxide gave 5-amino-4-chloro-6-dicarbethoxymethylthiopyrimidine (IIIa). The structure of pyrimidine IIIa was confirmed by the presence in its IR spectrum of absorption bands for the amino group at 3340 and 3440 and two absorption bands for ν_{CO} from the ester groups at 1735 and 1750 cm^{-1}.

It was, however, not possible to convert IIIa to the corresponding pyrimidothiazin-6-one. This is evidently attributable to the lower nucleophilicity of an amino group at position 5 of the pyrimidine ring due to the I- effect of the chlorine atom.

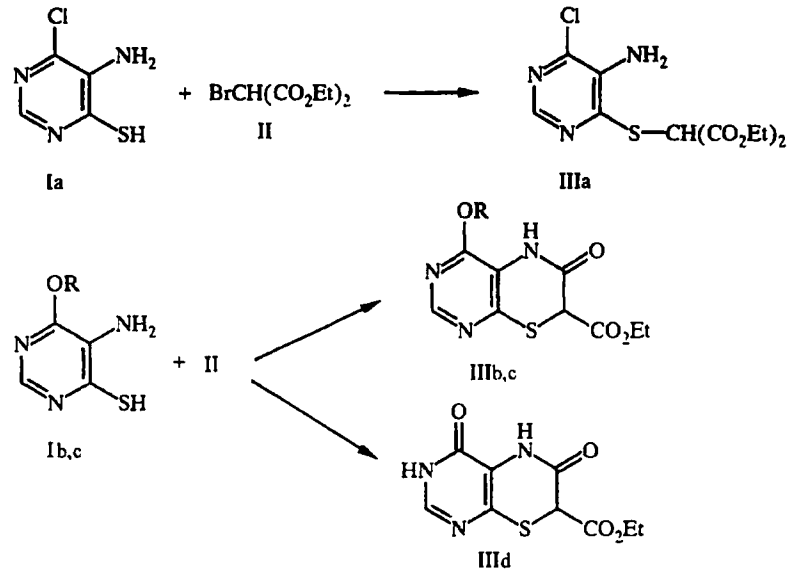
Exchange of the chlorine atom in compound Ia for an alkoxy group significantly raises the nucleophilicity of the amino group and leads to closing of the thiazine ring. Hence reaction of the 4-methoxy- and 4-ethoxy-5-amino-6-mercaptopyrimidines (Ib,c) with ester II under the conditions for preparing IIIa leads to the formation of the ethyl esters of 4-alkoxy-6-oxopyrimido[4,5-*b*][1,4]thiazine-7-carboxylic acids (IIIb,c). If the same reaction between the named components is carried out at 90-95°C without solvent and in the absence of base, the cyclization process is accompanied by hydrolysis of the alkoxy group in position 4 of the pyrimidine ring. Under these conditions, the reaction of pyrimidines Ib,c with ester II gives the ethyl ester of 4,6-dioxopyrimidothiazine-7-carboxylic acid (IIId). The IR spectra of the pyrimidothiazinones IIIb-d show the presence of CO and NH absorption bands from the amide group at 1684-1688 and 3210-3325 respectively and an ester carbonyl group at 1733-1738 cm^{-1}, which agrees with their structure.

* For communication 49 see [1].

Center for Chemistry of Drugs - All-Russian Research Chemical-Pharmaceutical Institute, Moscow 119021, Russia. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 822-828, June, 1999. Original article submitted May 22, 1998.

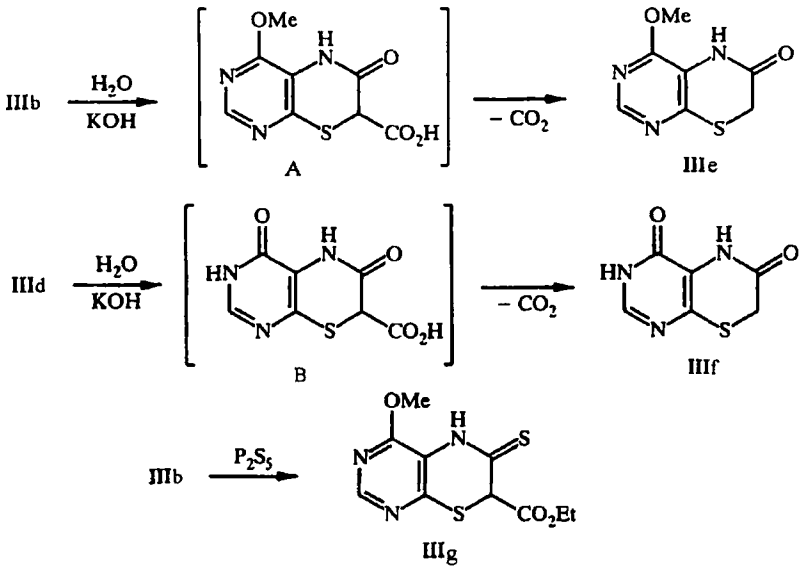
0009-3122/99/3506-0733$22.00©1999 KluwerAcademic/Plenum Publishers

Attempts to hydrolyze esters IIIb,d by heating them with aqueous alcoholic alkali solution and subsequent acidification with hydrochloric acid gave the pyrimidothiazinones IIIe,f in 90-92% yield. Evidently, the initial products of these reactions are the corresponding acids A and B. They are unstable and are decarboxylated under rather mild conditions to give the pyrimidothiazinones IIIe,f.



Ib, IIIb R = Me; Ic, IIIc R = Et

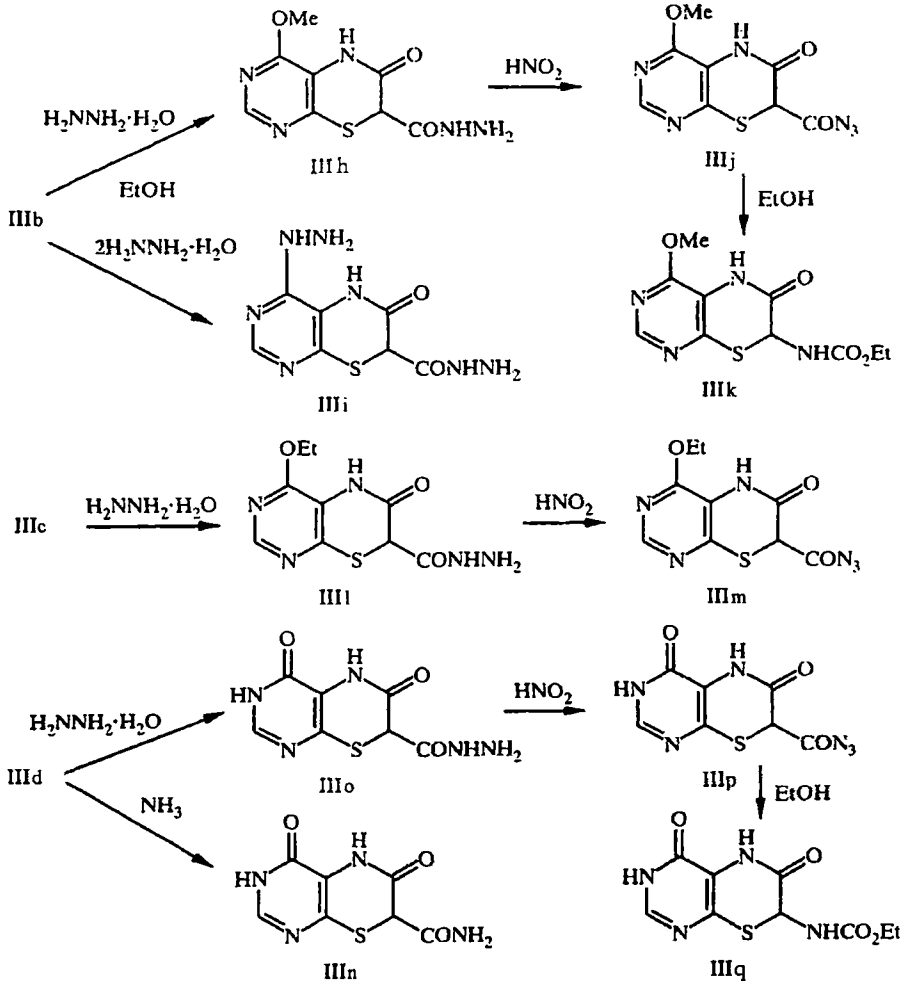
The IR spectra of compounds IIIe,f show the absence of absorption bands for the ester groups and, according to their analytical characteristics, are identical to the corresponding 4-methoxy- and 4-oxopyrimidothiazin-6-ones obtained previously [2]. Compound IIIb under heating with phosphorus pentasulfide in toluene gives the thione IIIg. Its structure was confirmed by the presence in the IR spectrum of absorption bands for the ester and thioamide groups.



A series of derivatives at the carboxyl group was also prepared from compounds IIIb-d. Heating of 4-methoxy derivative IIIb in ethanol with hydrazine hydrate gave hydrazide IIIh. If the same reaction is carried out without solvent with excess hydrazine hydrate then, along with formation of the hydrazide, there occurs exchange of the methoxy group at position 4 for a hydrazine residue and the main reaction product is compound IIIi.

The action of nitrous acid on hydrazide IIIh at 0°C gave the azide IIIj which, when heated in ethanol, was converted to urethane IIIk. Under similar conditions, the 4-ethoxy substituted IIIc gave the hydrazide IIIl and azide IIIm.

Similar reactions were carried out with the 4-oxo derivative IIId. When treated with aqueous ammonia it gave amide IIIn and when IIId was heated with hydrazine hydrate it gave the hydrazide IIIo. From the latter the azide IIIp was synthesized and this was converted to urethane IIIq. The structures of IIIh-q were confirmed by the presence in their IR spectra of absorption bands for the corresponding functional groups.



In connection with data [5] concerning the conversion of cyclopenta[*b*][1,4]benzothiazines *via* desulfurization to cyclopenta[b]indoles we have studied an analogous reaction with compounds IIIb,d. However, it was found that heating IIIb,d with Raney nickel in alcohol gives pyrimidin-5-yl amides of the ethyl malonates IVa,b and not the corresponding pyrrolopyrimidines V (which might have been expected by analogy with the reported work [5]).

Hydrolysis of esters IVa,b in alkaline medium with subsequent acidification gave the acids IVc,d. Hydrazide IVe was prepared from ester IVb.

The structure of compounds IVa-e was confirmed by the presence in their IR spectra of absorption bands for the corresponding functional groups. In the PMR spectra of IVa,b in $CDCl_3$, beside proton signals for the side chains, there were found signals for the protons at $C_{(2)}$ and $C_{(6)}$ of the pyrimidine ring at 8.45 and 7.67 ppm respectively, which also agrees with their structure.

TABLE 1. Characteristics of Synthesized Compounds IIIa-q and IVa-e

Compound	Empirical formula	Found, % / Calculated, %				Solvent for crystallization	mp, °C	IR Spectrum, ν, cm^{-1}	Yield, %
		C	H	N	S				
1	2	3	4	5	6	7	8	9	10
IIIa	$C_{11}H_{14}ClN_3O_4S$*	41.68 / 41.31	4.63 / 4.41	12.98 / 13.14	10.19 / 10.02	Ether	94-96	1735, 1750, 3240, 3340, 3440	80
IIIb	$C_{10}H_{11}N_3O_4S$	44.91 / 44.61	4.08 / 4.12	15.93 / 15.60	11.70 / 11.90	Ethanol	132-143	1688, 1733, 3225	70
IIIc	$C_{11}H_{13}N_3O_4S$	46.99 / 46.63	4.71 / 4.63	14.96 / 14.83	11.60 / 11.83	Ethanol	173	1684, 1738, 3165, 3210	53
IIId	$C_9H_9N_3O_4S$	42.64 / 42.34	3.70 / 3.55		12.77 / 12.58	Ethanol	186-187	1670, 1700, 1730, 3215	70
IIIe	$C_7H_7N_3O_2S$*[2]					Ethanol	190-191	1678, 3200, 3325	90
IIIf	$C_6H_5N_3O_2S$*[3]					Water	263-265	1670, 1700, 3220	92
IIIg	$C_{10}H_{11}N_3O_2S_2$				22.63 / 22.47	Benzene	214-216	1730, 1630, 3185	29
IIIh	$C_8H_9N_5O_3S$	37.51 / 37.64	3.60 / 3.55	27.18 / 27.43	12.43 / 12.56	Water	202-203	1625, 1654, 1695, 3130, 3300, 3340	43
IIIi	$C_7H_9N_7O_2S$	32.86 / 32.94	3.70 / 3.55	37.86 / 38.41	12.20 / 12.56	Water	>300	1650, 1690, 3345, 3450	50
IIIj	$C_8H_6N_6O_3S$	35.72 / 36.09	2.59 / 2.27		11.80 / 12.04	Methanol	80	1710, 2183, 3325	77
IIIk	$C_{11}H_{14}N_4O_4S$	44.22 / 44.29	4.65 / 4.73	18.61 / 18.78	10.99 / 10.75	Benzene	150-152	1670, 1730, 3130, 3260	78

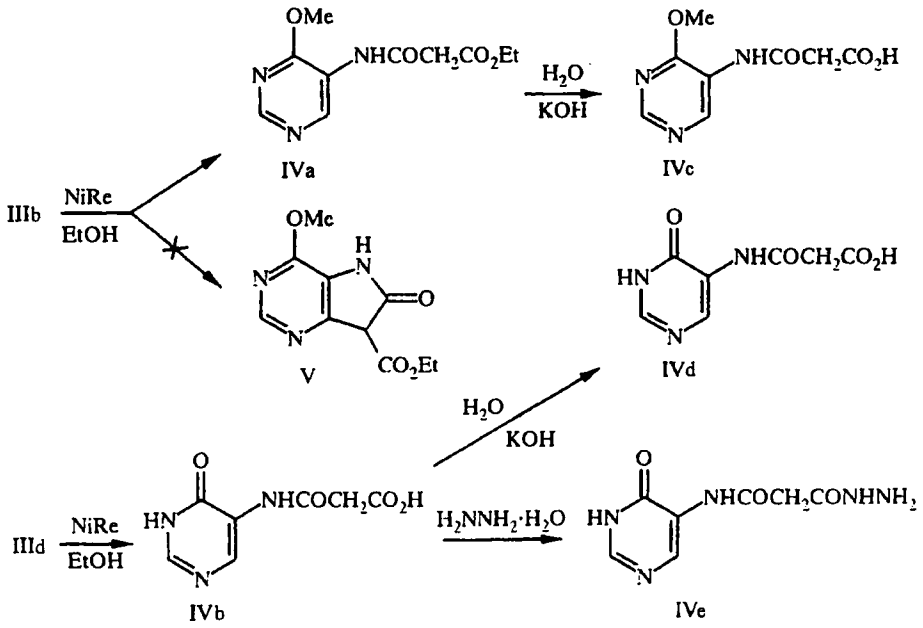
TABLE 1 (continued)

1	2	3	4	5	6	7	8	9	10
IIIl	$C_9H_{11}N_3O_3S$	40.35 40.14	4.15 4.11	25.78 26.01	11.75 11.91	Water	235-236	1660, 1693, 3215, 3275, 3345	96
IIIm	$C_9H_8N_6O_3S$	38.90 38.57	3.00 2.87		11.44 11.44	Ether	108	1695, 2178, 3230, 3370	51
IIIn	$C_7H_6N_4O_3S$	37.55 37.16	2.78 2.67	25.00 24.77	14.32 14.17	Water	255-256	1670, 1690, 3210, 3335	90
IIIo	$C_7H_7N_5O_3S$	34.98 34.85	3.12 2.92	28.93 29.03	13.16 13.30	Water	246-247	1660, 1680, 3225, 3325	60
IIIp	$C_7H_4N_6O_3S$	33.12 33.33	1.64 1.60		12.90 12.71	Ethanol	247-252	1660, 1700, 2189, 3210, 3260	55
IIIq	$C_9H_{10}N_4O_4S$	40.21 40.00	3.97 3.73	20.49 20.73	11.68 11.86	Ethanol	232-233	1670, 1680, 3210, 3295, 3350	78
IVa	$C_{10}H_{13}N_3O_4$	50.02 50.20	5.39 5.48	17.57 17.57		Ethanol	191-193	1695, 1733, 3295	74
IVb	$C_7H_7N_3O_4$	48.10 48.00	5.18 4.92	18.65 18.66		Ethanol	193-194	1700, 1735, 3295	72
IVc	$C_8H_9N_3O_4$	45.55 45.50	4.47 4.29	20.05 19.90		Methanol	159	1697, 1720, 3225	20
IVd	$C_7H_7N_3O_4$	42.78 42.64	3.77 3.58	20.94 21.34		Benzene	294-295	1680, 1735, 3280	20
IVe	$C_7H_9N_5O_3$	40.15 39.81	4.55 4.29	33.12 33.17		Water	210-211	1655, 3285, 3365	54

* Found, %: Cl 11.27. Calculated, %: Cl 11.10.

*[2] According to [2], mp 193-194°C.

*[3] According to [2], mp 263-265°C.



EXPERIMENTAL

IR spectra were obtained on a Perkin-Elmer 457 spectrometer using vaseline oil. PMR spectra were recorded on a Varian XL-200 instrument using TMS internal standard.

Characteristics for the compounds synthesized are given in the Table 1.

5-Amino-4-chloro-6-mercaptopyrimidine (Ia), 5-amino-6-mercapto-4-methoxypyrimidine (Ib), and 5-amino-4-ethoxy-6-mercaptopyrimidine (Ic) were prepared by method [2].

Diethyl bromomalonate (II) was prepared by method [6].

5-Amino-4-chloro-6-dicarbethoxymethylthiopyrimidine (IIIa). Ester II (2.25 g, 7 mmol) was added to a solution of compound Ia (1.0 g, 6.2 mmol) in ethanol (20 ml) containing an alcoholic solution of potassium hydroxide (10%, 3.5 ml, 6.2 mmol). The reaction mixture was stirred for 30 h at 18-20°C, filtered, and the filtrate evaporated to dryness in vacuo. The oily residue was triturate with water (40 ml) and the solid material filtered off, washed with water, and dried.

Ethyl 4-Methoxy-6-oxopyrimido[4,5-b][1,4]thiazin-6-one-7-carboxylate (IIIb). A mixture of compound Ib (1.0 g, 6.3 mmol) and ester II (1.5 g, 6.6 mmol) in ethanol (30 ml) was refluxed for 3 h. The solution was evaporated to dryness in vacuo, the residue was treated with water, and the insoluble solid material was filtered, washed with water and then alcohol, and dried.

Compound IIIc was prepared similarly.

Ethyl 4,6-Dioxo-3,4-dihydropyrimido[4,5-b][1,4]thiazine-7-carboxylate (IIId). A mixture of compound Ib (1.0 g, 6.3 mmol) and ester II (1.5 g, 6.6 mmol) was heated at 90-95°C for 10-15 min, cooled to 18-20°C, and water (15 ml) was added. The precipitate was filtered, washed with ethanol (4-5 ml), and dried.

6,7-Dihydropyrimido[4,5-b][1,4]thiazine-4,6-dione (IIIf). Ethanol (25 ml) and compound IIId (1.0 g, 3.9 mmol) were added to a solution of potassium hydroxide (0.22 g, 4 mmol) in water (5 ml). The reaction mixture was heated for 2 h at 90-95°C and evaporated to dryness in vacuo. Water (5 ml) was added to the residue and the product was filtered, and the filtrate was acidified with hydrochloric acid. The precipitated material was filtered off, washed with water, and dried.

Compound IIIe was obtained similarly.

Ethyl 4-Methoxy-6-thiopyrimido[4,5-b][1,4]thiazine-7-carboxylate (IIIg). A mixture of compound IIIb (2.0 g, 7.4 mmol) and phosphorus pentasulfide (2.0 g, 9.0 mmol) in anhydrous toluene (30 ml) was refluxed for 15 min. The hot reaction mixture was filtered and the solid residue was extracted with hot toluene. The toluene

solutions were combined and evaporated in vacuo to dryness. The residue was treated with water and the precipitate was filtered off and dried.

4-Methoxy-6-oxopyrimido[4,5-b][1,4]thiazine-7-carboxylic Acid Hydrazide (IIIh). Hydrazine hydrate (2 ml, 4.0 mmol) was added at 60-65°C to a solution of compound IIIb (1.0 g, 3.7 mmol) in ethanol (40 ml) and stirred for 2 h. The reaction mixture was cooled to 18-20°C and the precipitate was filtered off, washed with water and alcohol, and dried.

Compounds IIIl and IIIo were prepared similarly.

4-Hydrazino-6-oxopyrimido[4,5-b][1,4]thiazine-7-carboxylic Acid Hydrazide (IIIi). A mixture of compound IIIb (0.9 g, 3.3 mmol) and hydrazine hydrate (10 ml, 20.0 mmol) was refluxed for 30 min and then cooled to 18-20°C and acidified with acetic acid. The precipitate was filtered off, washed with water and then alcohol, and dried.

4-Methoxy-6-oxopyrimido[4,5-b][1,4]thiazine-7-carboxylic Acid Azide (IIIj). A solution of sodium nitrite (0.35 g, 5 mmol) in water (3 ml) was added at 0°C to a solution of compound IIIh (1.3 g, 5 mmol) in hydrochloric acid (3.5%, 60 ml). The mixture was stirred at this temperature for 30 min. The precipitate was filtered off, washed with water and then alcohol followed by ethyl acetate, and dried.

Compounds IIIm,p were prepared similarly.

7-Carbethoxyamino-4-methoxypyrimido[4,5-b][1,4]thiazin-6-one (IIIk). Compound IIIj (0.6 g, 2.1 mmol) in anhydrous ethanol (50 ml) was refluxed for 3.5 h. The solution was evaporated in vacuo to dryness, the residue was triturated with water, and the precipitate was filtered off and dried.

Urethane IIIq was prepared similarly.

4,6-Dioxo-6,7-dihydropyrimido[4,5-b][1,4]thiazine-7-carboxamide (IIIn). Compound IIId (1.3 g, 5 mmol) in aqueous ammonia (25%, 30 ml) was refluxed for 2 h with simultaneous passage of gaseous ammonia. The reaction mixture was evaporated in vacuo to dryness, the residue was treated with water, and the insoluble precipitate was filtered off, washed with water, and dried.

Ethyl 3-(4-Methoxypyrimidin-5-yl)amino-3-oxopropanoate (IVa). A mixture of compound IIIb (1.0 g, 3.7 mmol) and Raney nickel paste (10 g) in ethanol (50 ml) was refluxed for 5 h. The hot solution was filtered and the catalyst was washed with hot ethanol (2 x 50 ml). The alcohol filtrates were combined and evaporated in vacuo to dryness. The residue was triturated with ether and the precipitate was filtered off and dried.

Compound IVb was obtained similarly.

Malonic Acid N-(4-Methoxypyrimidin-5-yl)amide (IVc). Compound IVa (0.65 g, 3 mmol) was added to a solution of potassium hydroxide (0.5 g, 9 mmol) in water (5 ml) and ethanol (25 ml). The reaction mixture was heated at 60°C for 1 h, evaporated to dryness in vacuo, and the residue was dissolved in water (5 ml) and filtered. The filtrate was acidified with hydrochloric acid and the precipitate formed was filtered and dried.

Acid IVd was prepared similarly.

3-(4-Oxopyrimidin-5-yl)amino-3-oxopropanoic Acid Hydrazide (IVe). Hydrazine hydrate (2 ml, 40 mmol) was added to a solution of compound IVb (0.5 g, 2.2 mmol) in ethanol (20 ml) and then heated for 2 h at 60-65°C. The reaction mixture was cooled to 18-20°C and the precipitate was filtered off, washed with water and then alcohol, and dried.

REFERENCES

1. T. S. Safonova and I. E. Mamaeva, *Khim. Geterotsikl. Soedin.*, No. 1, 101 (1999).
2. T. S. Safonova and M. P. Nemeryuk, *Khim. Geterotsikl. Soedin.*, No. 5, 714 (1966).
3. A. F. Keremov, M. P. Nemeryuk, O. L. Aparnikova, and T. S. Safonova, *Khim. Geterotsikl. Soedin.*, No 10, 1332 (1977).
4. T. S. Safonova, *Directed Search for Novel Anti-Tumor and Anti-Viral Drugs* [in Russian], Zinatne, Riga (1978), p. 51.
5. V. Carelli, P. Marchini, F. Miche, L. Moracci, and J. Liso, *Tetrahedron Lett.*, **35**, 3421 (1967).
6. P. M. Kochergin and R. M. Titkova, *Zh. Org. Khim.*, **30**, 986 (1994).