A new method for the synthesis of 5-amidinobarbiturates

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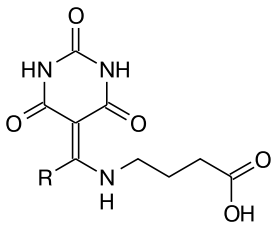
The reactions of 5-[arylamino(methylthio)methylene]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-triones with different aliphatic and aromatic amines were studied. A series of 5-amidinobarbiturates was synthesized. A new and preparatively convenient method for their synthesis appropriate for the use in the combinatorial chemistry was developed.

Key words: barbituric acids, thioimidates, thioamides, amidines.

Barbituric acid derivatives, such as Nembutal, Barbital, and Benzobamil, are known drugs with soporific or antispasmodic effect. Substances of this class manifest a wide range of biological activity.[1—4]

The data on barbituric acid derivatives **1** possessing antitumor and immodulating activity were published.[5—7] For the purpose of searching for new compounds manifesting activity of these types, a series of barbituric acid derivatives **2** with the amidine group in position 5 of the pyrimidine cycle was synthesized by the reactions of barbituric acids with carbodiimides.[7] In spite of certain achievements, the method developed is substantially restricted by a small arsenal of commercial carbodiimides and provides only amidines with the same substituents at the nitrogen atoms of the amidine group. It should be mentioned that the reaction is very sensitive to air moisture.



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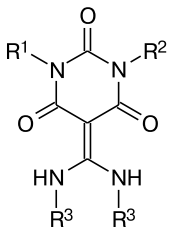

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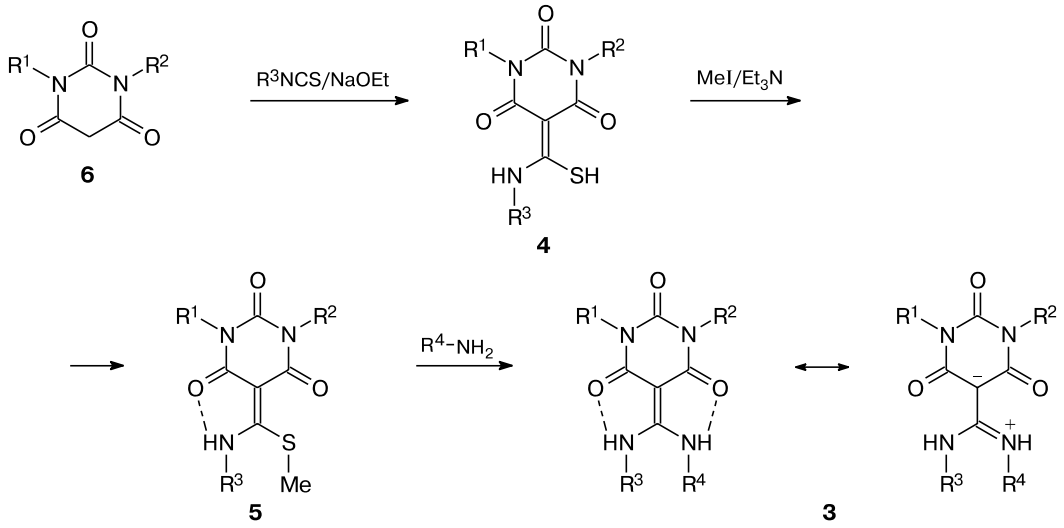
To develop a new, more general and preparatively convenient method for the synthesis of 5-amidinobarbiturates **3**, we synthesized thioamides **4**, which further transformed into thioimidates **5**, and the latter were involved in the reactions with aliphatic and aromatic amines (Scheme 1).

Starting thioimidates **5** were obtained by the two-step synthesis from barbituric acids **6**. In the first step, pyrimidinetriones **6** were condensed with various aryl isothiocyanates using a modified procedure.[8] No substantial differences in reactivity were found for barbituric acids in the reactions with isothiocyanates, except for 1,3-dimethylbarbituric acid. For the latter we had to apply another order of reactant loading. The structures of synthesized thioamides **4** were confirmed by the data of the ^{1}H NMR spectra and elemental analysis. In the second step, thioamides **4** reacted with methyl iodide to form methyl thioimidates **5** similarly to the process described[8] for compounds **5** with the substituents $R^1 = R^2 = H$. The structures of thioimidates **5** were confirmed by the presence of the signal from the SMe group at 2 ppm in the ^{1}H NMR spectra of these compounds. Amidines **3** were synthesized in 50—90% yields by the reactions of thioimidates **5** with amines in a DMF solution. The reactions of methyl thioimidates **5** with various types of amines were studied. It was shown that the primary aliphatic amines, benzylamines, tryptamines, and histamine react smoothly with thioimidates **5** and form amidines **3** in high yields according to the procedure developed. The reactions of compound **5** with aromatic amines occur somewhat more slowly and require the use of larger aniline excess. At the same time, this does not affect the yield of the final compounds, and *N*,*N*-diarylamidines **3** were obtained in high yields. Secondary amines are the least reactive compounds. For instance, the reactions of thioimidates **5** with morpholine, dimethylamine, and piperidine occur very slowly, and we succeeded to isolate only the starting compounds contaminated with resin-like decomposition products of the amidines formed.

The structures of the synthesized amidines were confirmed by the data of ^{1}H NMR spectroscopy and elemental analysis (Table 1). The existence of the double bond in position 5 of the pyrimidine ring was proved as follows. The spectra of all synthesized amidines **3** and intermediate compounds **4** and **5** contain no signal of the proton at 3—4 ppm characteristic of 5,5r-disubstituted barbituric acids and exhibited two groups of protons of the

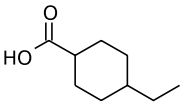
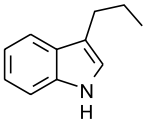
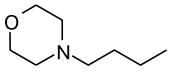
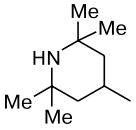
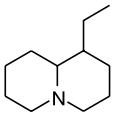
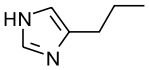
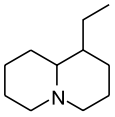
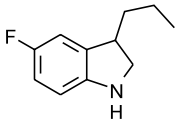
Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 8, pp. 1557—1563, August, 2007.

Scheme 1



R^1 = H (**3a—l, 4a—h, 5a—h, 6a—e**), *cyclo*-C_6H_{11} (**3m,n, 4i, 5i, 6f**), Me (**3p,q,r, 4j,k, 5j,k, 6g**)

R^2 = 4-BrC_6H_4 (**6a**), 4-MeC_6H_4 (**6b**), 4-$MeOC_6H_4$ (**6c**), 2,4-$Me_2C_6H_3$ (**6d**), 2-$EtOC_6H_4$ (**6e**), *cyclo*-C_6H_{11} (**6f**), Me (**6g**)

3	R^2	R^3	R^4	**3**	R^2	R^3	R^4
a	4-BrC_6H_4	Ph	$MeOC_2H_4$	**j**	2-$EtOC_6H_4$	Ph	
b	4-BrC_6H_4	3,5-$F_2C_6H_3$		**k**	2-$EtOC_6H_4$	Ph	
c	4-MeC_6H_4	Ph	$MeOC_2H_4$	**l**	2-$EtOC_6H_4$	Ph	
d	4-MeC_6H_4	Ph	4-$FC_6H_4CH_2$	**m**	*cyclo*-C_6H_{11}	Ph	2-$CF_3C_6H_4CH_2$
e	4-$MeOC_6H_4$	Ph	2-$ClC_6H_4CH_2$	**n**	*cyclo*-C_6H_{11}	Ph	
f	4-$MeOC_6H_4$	4-MeC_6H_4		**p**	Me	Ph	2-$ClC_6H_4CH_2$
g	4-$MeOC_6H_4$	4-MeC_6H_4	4-$CF_3C_6H_4$	**q**	Me	2-ClC_6H_4	
h	4-$MeOC_6H_4$	4-MeC_6H_4	4-MeC_6H_4	**r**	Me	2-ClC_6H_4	4-$CF_3C_6H_4$
i	2,4-$Me_2C_6H_3$	4-ClC_6H_4					

4, 5	R^2	R^3	**4, 5**	R^2	R^3
a	4-BrC_6H_4	Ph	**g**	2,4-$Me_2C_6H_3$	4-ClC_6H_4
b	4-BrC_6H_4	3,5-$F_2C_6H_3$	**h**	2-$EtOC_6H_4$	Ph
c	4-BrC_6H_4	2-ClC_6H_4	**i**	*cyclo*-C_6H_{11}	Ph
d	4-MeC_6H_4	Ph	**j**	Me	Ph
e	4-$MeOC_6H_4$	Ph	**k**	Me	2-ClC_6H_4
f	4-$MeOC_6H_4$	4-MeC_6H_4			

NH-amidine group at 10—13 ppm. It should be mentioned that the ^{1}H NMR spectra of compounds **4f,h,j** contain downfield signals from the protons of the SH groups at 15—16 ppm. Thus, the ^{1}H NMR spectral data indicate the presence of the enamine fragment in the structures of compounds **3—5**. Based on the structures of *N*-monosubstituted (R = H) pyrimidines **3**, we could expect the formation of a mixture of the *cis*- and *trans*-isomers and the double set of signals in the ^{1}H NMR spectra of these compounds. However, the ^{1}H NMR spectra contain only one set of signals from protons. This could be assigned to the easy rotation of the amidine group due to the great contribution of the imino form of compounds **3**. Taking into account the presence of two hydrogen bonds between the NH protons and oxygen atoms of the amide fragments, we have to admit that this assumption is unsatisfactory. Moreover, a more probable reason, in our opinion, is a higher basicity of the amide fragment compared to the anilide fragments of barbituric acids **6**, resulting in the predominant binding of R^3NH with the most basic oxygen atom and the formation of one isomer of thioamides **4** and thioimidates **5**. Probably, upon the formation of amidines the configuration of the enamine fragment remains unchanged, which results in the formation of one of possible isomers.

The method developed by us for the synthesis of 5-amidinobarbituric acids **3** is general and appropriate for the preparation of the synthesized compounds in large amounts. Since the yield of the target products is high, the procedures are universal and simple, and four centers

Table 1. Melting points, yields, and elemental analysis data for the synthesized compounds

Compound	Yield (%)	M.p./°C	Found / Calculated (%)				Empirical formula
			C	H	N	S	
3a	80	243—244	51.88	4.30	11.85	—	$C_{20}H_{19}BrN_4O_4$
			52.30	4.17	12.20		
3b	62	241—243	55.62	3.62	11.75	—	$C_{27}H_{20}BrF_2N_5O_3$
			55.88	3.47	12.07		
3c	76	212—213	64.11	5.55	13.81	—	$C_{21}H_{22}N_4O_4$
			63.95	5.62	14.20		
3d	62	238—239	67.44	4.42	12.29	—	$C_{25}H_{21}FN_4O_3$
			67.56	4.76	12.61		
3e	96	244—245	62.88	4.22	11.48	—	$C_{25}H_{21}ClN_4O_4$
			62.96	4.44	11.75		
3f	95	296—298	62.35	5.22	18.45	—	$C_{24}H_{24}N_6O_4$
			62.60	5.25	18.25		
3g	47	210—212	61.37	4.11	11.24	—	$C_{26}H_{21}F_3N_4O_4$
			61.18	4.15	10.98		
3h	72	265—267	68.72	5.18	12.43	—	$C_{26}H_{24}N_4O_4$
			68.41	5.30	12.27		
3i	53	206—208	63.59	4.55	12.50	—	$C_{29}H_{25}ClFN_5O_3$
			63.79	4.62	12.83		
3j	88	177—178	64.15	6.20	10.91	—	$C_{27}H_{30}N_4O_6$
			64.02	5.97	11.06		
3k	85	159—160	62.95	6.50	14.42	—	$C_{26}H_{31}N_5O_5$
			63.27	6.33	14.19		
3l	82	147—148	66.30	7.22	13.71	—	$C_{28}H_{35}N_5O_4$
			66.51	6.98	13.85		
3m	78	185—186	65.77	6.32	10.16	—	$C_{31}H_{35}F_3N_4O_3$
			65.48	6.20	9.85		
3n	86	117—119	70.88	8.35	12.27	—	$C_{33}H_{47}N_5O_3$
			70.56	8.43	12.47		
3p	79	198—199	60.02	4.95	14.46	—	$C_{20}H_{19}ClN_4O_3$
			60.23	4.80	14.05		
3q	85	210—212	60.51	6.42	15.20	—	$C_{23}H30ClN_5O_3$
			60.06	6.57	15.23		
3r	81	227—229	52.79	3.49	12.41	—	$C_{20}H_{16}ClF_3N_4O_3$
			53.05	3.56	12.37		

(*to be continued*)

Table 1 (*continued*)

Compound	Yield (%)	M.p./°C	Found / Calculated (%)				Empirical formula
			C	H	N	S	
4a	69	238—240	48.65	2.93	9.86	7.55	$C_{17}H_{12}BrN_3O_3S$
			48.82	2.89	10.05	7.67	
4b	46	125—128	45.22	2.11	8.96	7.39	$C_{17}H_{10}BrF_2N_3O_3S$
			44.95	2.22	9.25	7.06	
4c	60	181—183	44.87	2.38	8.85	7.33	$C_{17}H_{11}BrClN_3O_3S$
			45.10	2.45	9.28	7.08	
4d	76	221—223	60.85	4.06	11.97	9.32	$C_{18}H_{15}N_3O_3S$
			61.18	4.28	11.89	9.07	
4e	61	215—217	58.88	4.22	11.44	8.35	$C_{18}H_{15}N_3O_4S$
			58.53	4.09	11.38	8.68	
4f	68	207—209	59.21	4.40	11.44	8.77	$C_{19}H_{17}N_3O_4S$
			59.52	4.47	10.96	8.36	
4g	72	155—158	56.56	4.26	10.23	8.22	$C_{19}H_{16}ClN_3O_3S$
			56.79	4.01	10.46	7.98	
4h	65	174—175	60.22	4.30	11.31	8.15	$C_{19}H_{17}N_3O_4S$
			59.92	4.47	10.96	8.36	
4i	91	90—91	64.44	6.75	9.75	7.28	$C_{23}H_{29}N_3O_3S$
			64.61	6.84	9.83	7.50	
4j	69	155—156	53.77	4.32	14.13	9.76	$C_{13}H_{13}N_3O_3S$
			53.50	4.50	14.42	11.01	
4k	55	177—178	47.65	3.68	13.13	10.16	$C_{13}H_{12}ClN_3O_3S$
			47.93	3.71	12.90	9.84	
5a	82	267—269	49.75	3.44	9.88	7.35	$C_{18}H_{14}BrN_3O_3S$
			50.01	3.26	9.72	7.42	
5b	55	242—244	46.48	2.77	9.29	6.51	$C_{18}H_{12}BrF_2N_3O_3S$
			46.17	2.58	8.97	6.85	
5c	83	242—244	46.35	3.10	9.33	7.15	$C_{18}H_{13}BrClN_3O_3S$
			46.32	2.81	9.00	6.87	
5d	81	243—244	61.87	4.49	11.29	8.55	$C_{19}H_{17}N_3O_3S$
			62.11	4.66	11.44	8.73	
5e	80	214—215	59.43	4.66	11.35	8.55	$C_{19}H_{17}N_3O_4S$
			59.52	4.47	10.96	8.36	
5f	93	221—223	60.09	5.01	10.44	8.05	$C_{20}H_{19}N_3O_4S$
			60.44	4.82	10.57	8.07	
5g	76	156—158	58.08	4.45	10.50	7.55	$C_{20}H_{18}ClN_3O_3S$
			57.76	4.36	10.10	7.71	
5h	41	204—205	60.70	4.80	11.00	8.01	$C_{20}H_{19}N_3O_4S$
			60.44	4.82	10.57	8.07	
5i	46	152—154	64.94	6.95	9.81	7.05	$C_{24}H_{31}N_3O_3S$
			65.28	7.08	9.52	7.26	
5j	78	147—148	55.46	5.08	14.03	10.82	$C_{14}H_{15}N_3O_3S$
			55.07	4.95	13.76	10.50	
5k	70	200—201	49.18	4.22	12.21	9.59	$C_{14}H_{14}ClN_3O_3S$
			49.49	4.15	12.37	9.44	

of a molecule of compounds **3** can be modified, we recommend to use the developed method in the combinatorial chemistry.

Experimental

^{1}H NMR spectra were recorded on a Bruker WM-250 instrument (250.13 MHz) in a DMSO-d_6 solution using Me_4Si as the internal standard. Chemical shifts were measured in the δ scale. The reaction course and individual character of the synthesized substances were monitored by TLC on Sorbfil Uf-254 plates in a chloroform—ethanol (10 : 1) system. Melting points were not corrected.

Starting barbituric acids **6a—g** were purchased from PubChem (National Center for Biotechnology Information, National Library of Medicine, Building 38A Bethesda, MD 20894, USA). The physicochemical characteristics and

yields of the substances are given in Table 1. The characteristics of the ^{1}H NMR spectra of the synthesized compounds are presented in Table 2.

5-[Amino(mercapto)methylene]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-triones 5 (general procedure). Method *A* (for **4a—i**). The corresponding barbituric acid **6** (10 mmol) and aryl isothiocyanate (10 mmol) were added to a solution of sodium ethoxide prepared from sodium (10 mmol) and anhydrous ethanol (40 mL). The mixture was refluxed for 5—10 h, cooled, and kept for 16 h in a refrigerator. A precipitate of thioamide sodium salt **4** was filtered off, washed with a minor amount of alcohol, and dissolved in water. The solution was filtered, and the filtrate was acidified with HCl to pH = 1—2. The precipitate was filtered off, washed with water, and dried. If no precipitate formed upon cooling, the solution was filtered with carbon, and the filtrate was acidified with HCl to pH = 1—2. The precipitate

Table 2. Data for the ^{1}H NMR spectra of the synthesized compounds

Compound	δ (*J*/Hz)
4a	7.31—7.38 (m, 3 H, CH_{Ar}); 7.42—7.48 (m, 4 H, CH_{Ar}); 7.68—7.72 (m, 2 H, CH_{Ar}); 12.75, 13.62 (both s, 1 H each, NH)
4b	7.02 (t, 1 H, CH_{Ar}, *J* = 7.0); 7.11—7.22 (m, 4 H, CH_{Ar}); 7.66 (d, 2 H, CH_{Ar}, *J* = 7.0); 12.54, 13.58 (both s, 1 H each, NH)
4c	7.23—7.41 (m, 4 H, CH_{Ar}); 7.50—7.54 (m, 1 H, CH_{Ar}); 7.60—7.68 (m, 3 H, CH_{Ar}); 13.54 (s, 1 H, NH)
4d	2.46 (s, 3 H, CH_3); 7.08 (d, 2 H, CH_{Ar}, *J* = 8.0); 7.22—7.48 (m, 7 H, CH_{Ar}); 12.73, 13.80 (both s, 1 H each, NH)
4e	3.69 (s, 3 H, CH_3); 6.98, 7.11 (both d, 2 H each, CH_{Ar}, *J* = 8.8); 7.32—7.48 (m, 5 H, CH_{Ar}); 12.83, 13.85 (both s, 1 H each, NH)
4f	2.35, 3.81 (both s, 3 H each, CH_3); 6.95—6.99 (m, 2 H, CH_{Ar}); 7.13—7.21 (m, 4 H, CH_{Ar}); 7.31 (d, 2 H, CH_{Ar}, *J* = 8.2); 12.60, 13.64 (both s, 1 H each, NH); 15.79 (s, 1 H, SH)
4g	2.13, 2.39 (both s, 3 H each, CH_3); 6.97 (d, 1 H, CH_{Ar}, *J* = 8.0); 7.15 (t, 2 H, CH_{Ar}, *J* = 8.0); 7.38—7.49 (m, 4 H, CH_{Ar}); 12.65, 13.68 (both s, 1 H each, NH)
4h	1.32 (t, 3 H, CH_3, *J* = 7.0); 4.09 (q, 2 H, CH_2, *J* = 7.0); 6.97—7.48 (m, 9 H, CH_{Ar}); 12.60, 13.69 (both s, 1 H each, NH); 17.44 (s, 1 H, SH)
4i	1.18—1.97 (m, 16 H, CH_2); 2.32—2.45 (m, 4 H, CH_2); 4.66—4.73 (m, 2 H, CH); 7.28—7.49 (m, 5 H, CH_{Ar}); 13.98 (s, 1 H, NH)
4j	3.32 (s, 6 H, CH_3); 7.28—7.44 (m, 5 H, CH_{Ar}); 13.96 (s, 1 H, NH); 17.80 (s, 1 H, SH)
4k	3.30 (s, 6 H, CH_3); 7.41—7.46, 7.60—7.65 (both m, 2 H each, CH_{Ar}); 13.84 (s, 1 H, NH)
5a	2.06 (s, 3 H, CH_3); 7.22—7.25 (m, 2 H, CH_{Ar}); 7.31—7.39 (m, 3 H, CH_{Ar}); 7.47 (t, 2 H, CH_{Ar}, *J* = 8.0); 7.62—7.66 (m, 2 H, CH_{Ar}); 11.21, 13.41 (both s, 1 H each, NH)
5b	2.15 (s, 3 H, CH_3); 6.93 (t, 1 H, CH_{Ar}, *J* = 7.0); 7.05—7.16 (m, 4 H, CH_{Ar}); 7.57 (d, 2 H, CH_{Ar}, *J* = 7.0); 11.24, 13.38 (both s, 1 H each, NH)
5c	1.97 (s, 3 H, CH_3); 7.26 (d, 2 H, CH_{Ar}, *J* = 8.4); 7.37—7.48 (m, 2 H, CH_{Ar}); 7.47 (d, 1 H, CH_{Ar}, *J* = 8.0); 7.63—7.66 (m, 3 H, CH_{Ar}); 11.35, 13.66 (both s, 1 H each, NH)
5d	1.99, 2.38 (both s, 3 H each, CH_3); 7.03 (d, 2 H, CH_{Ar}, *J* = 8.0); 7.19—7.45 (m, 7 H, CH_{Ar}); 11.06, 13.72 (both s, 1 H each, NH)
5e	2.00, 3.80 (both s, 3 H each, CH_3); 6.93, 7.07 (both d, 2 H each, CH_{Ar}, *J* = 8.8); 7.27—7.43 (m, 5 H, CH_{Ar}); 11.05, 13.73 (both s, 1 H each, NH)
5f	2.04, 2.33, 3.78 (all s, 3 H each, CH_3); 6.95—6.99 (m, 2 H, CH_{Ar}); 7.14 (d, 2 H, CH_{Ar}, *J* = 8.8); 7.24—7.29 (m, 4 H, CH_{Ar}); 11.12, 13.45 (both s, 1 H each, NH)
5g	2.04, 2.07, 2.34 (all s, 3 H each, CH_3); 6.92 (d, 1 H, CH_{Ar}, *J* = 8.0); 7.05 (t, 2 H, CH_{Ar}, *J* = 8.0); 7.35—7.45 (m, 4 H, CH_{Ar}); 11.10, 13.57 (both s, 1 H each, NH)
5h	1.29 (t, 3 H, CH_3, *J* = 9.0); 2.02 (c, 3 H, CH_3); 4.05 (q, 2 H, CH_2, *J* = 9.0); 6.97—7.11 (m, 3 H, CH_{Ar}); 7.28—7.46 (m, 6 H, CH_{Ar}); 11.02, 13.65 (both s, 1 H each, NH)
5i	1.15—1.85 (m, 16 H, CH_2); 1.96 (s, 3 H, CH_3); 2.26—2.40 (m, 4 H, CH_2); 4.59—4.68 (m, 2 H, CH); 7.25—7.47 (m, 5 H, CH_{Ar}); 13.91 (s, 1 H, NH)
5j	2.03, 3.16 (both s, 6 H each, CH_3); 7.32—7.40 (m, 3 H, CH_{Ar}); 7.46—7.50 (m, 2 H, CH_{Ar}); 13.52 (s, 1 H, NH)
5k	1.95 (s, 3 H, CH_3); 3.19 (s, 6 H, CH_3); 7.37—7.48 (m, 2 H, CH_{Ar}); 7.57 (d, 1 H, CH_{Ar}, *J* = 8.0); 7.65—7.67 (m, 1 H, CH_{Ar}); 13.75 (s, 1 H, NH)
3a	2.87—2.9 (m, 2 H, CH_2); 3.19 (s, 3 H, CH_3); 3.3—3.38 (m, 2 H, CH_2); 7.23—7.29 (m, 5 H, CH_{Ar}); 7.41—7.45 (t, 2 H, CH_{Ar}); 7.62—7.65 (m, 2 H, CH_{Ar}); 11.06, 11.12, 12.30 (all s, 1 H each, NH)
3b	2.90 (t, 2 H, CH_2, *J* = 6.0); 3.18 (d, 2 H, CH_2, *J* = 6.0); 6.93 (m, 1 H, CH_{Ar}); 7.02—7.09 (m, 5 H, CH_{Ar}); 7.22 (d, 2 H, CH_{Ar}, *J* = 8.4); 7.32 and 7.38 (AA´BB´ system, 2 H, CH_{Ar}, *J* = 8.0); 7.63—7.65 (m, 2 H, CH_{Ar}); 10.85, 11.07, 11.19, 12.15 (all s, 1 H each, NH)

(*to be continued*)

Table 2 (*continued*)

Compound	δ (*J*/Hz)
3c	2.34 (s, 3 H, CH_3); 2.86—2.9 (m, 2 H, CH_2); 3.19 (s, 3 H, CH_3); 3.25—3.37 (m, 2 H, CH_2); 7.10 (d, 2 H, CH_{Ar} *J* = 8.4); 7.22—7.29 (m, 5 H, CH_{Ar}); 7.41—7.45 (t, 2 H, CH_{Ar}); 11.04, 11.11, 12.36 (all s, 1 H each, NH)
3d	2.37 (s, 3 H, CH_3); 3.98 (d, 2 H, CH_2, *J* = 5.5); 6.98—7.43 (m, 13 H, CH_{Ar}); 10.93, 11.29, 12.48 (all s, 1 H each, NH)
3e	3.79 (s, 3 H, CH_3); 4.08 (d, 2 H, CH_2, *J* = 5.5); 6.92 and 7.05 (AA´BB´ system, 4 H, CH_{Ar}, *J* = 8.7); 7.19—7.42 (m, 9 H, CH_{Ar}); 10.91, 11.29, 12.55 (all s, 1 H each, NH)
3f	2.30 (s, 3 H, CH_3); 2.60 (t, 2 H, CH_2, *J* = 6.4); 2.99 (m, 2 H, CH_2); 3.78 (s, 3 H, CH_3); 6.69 (s, 1 H, CH_{imide}); 6.95—6.98 (m, 2 H, CH_{Ar}); 7.11—7.15 (m, 4 H, CH_{Ar}); 7.22 (d, 2 H, CH_{Ar}, *J* = 8.0); 7.48 (d, 1 H, CH_{imide}, *J* = 1.2); 10.93, 11.00, 11.74, 12.25 (all s, 1 H each, NH)
3g	2.12, 3.81 (both s, 3 H each, CH_3); 6.81 (s, 4 H, CH_{Ar}); 6.95 (d, 2 H, CH_{Ar}, *J* = 9.0); 7.09 (t, 4 H, CH_{Ar}, *J* = 9.2); 7.27 (d, 2 H, CH_{Ar}, *J* = 8.2); 11.16, 12.82, 12.89 (all s, 1 H each, NH)
3h	2.14 (s, 6 H, CH_3); 3.81 (s, 3 H, CH_3); 6.73—6.82 (m, 8 H, CH_{Ar}); 6.94 and 7.08 (AA´BB´ system, 4 H, CH_{Ar}, *J* = 9.0); 11.04 (s, 1 H, NH); 12.70 (s, 2 H, NH)
3i	2.04, 2.34 (both s, 3 H each, CH_3); 2.83, 3.11 (both t, 2 H each, CH_2, *J* = 6.8); 6.77—7.38 (m, 11 H, CH_{Ar}); 10.77, 10.90, 11.07, 12.32 (all s, 1 H each, NH)
3j	0.79—0.82 (m, 2 H, CH_2); 1.19—1.22 (m, 5 H, CH_2 + CH_3); 1.33—1.38 (m, 1 H, CH); 1.50—1.53, 1.81—1.83 (both m, 2 H each, CH_2); 2.0—2.04 (m, 1 H, CH); 2.60—2.64, 4.00—4.03 (both m, 2 H each, CH_2); 6.98—7.45 (m, 9 H, CH_{Ar}); 11.01, 11.07, 12.0, 12.31 (all s, 1 H each, NH)
3k	1.21 (t, 3 H, CH_3, *J* = 7.0); 1.51—1.55 (m, 2 H, CH_2); 2.12—2.19 (m, 6 H, CH_2); 2.81—2.84 (m, 2 H, CH_2); 3.46—3.48 (m, 4 H, CH_2); 3.99—4.04 (m, 2 H, CH_2); 6.95—7.45 (m, 9 H, CH_{Ar}); 10.91, 11.04, 12.30 (all s, 1 H each, NH)
3l	0.55 (s, 6 H, CH_3); 0.82—0.91 (m, 8 H, 2 CH_3 + CH_2); 1.21 (t, 3 H, CH_3, *J* = 7.0); 1.60—1.64 (m, 2 H, CH_2); 3.48—3.52 (m, 1 H, CH); 4.00—4.05 (m, 2 H, CH_2); 6.95—7.47 (m, 9 H, CH_{Ar}); 10.87 (d, 1 H, NH *J* = 8.8); 11.06, 12.43 (both s, 1 H each, NH)
3m	1.05—1.85 (m, 16 H, CH_2); 2.25—2.40 (m, 4 H, CH_2); 4.08 (d, 2 H, CH_2, *J* = 5.5); 4.54—4.74 (m, 2 H, CH); 6.90—7.42 (m, 9 H, CH_{Ar}); 11.29, 12.55 (both s, 1 H each, NH)
3n	1.09—1.82 (m, 30 H, CH_2); 2.28—2.41 (m, 4 H, CH_2); 2.60 (d, 2 H, CH_2, *J* = 11.0); 2.90—3.04 (m, 2 H, CH_2); 4.51—4.71 (m, 2 H, CH); 7.16—7.44 (m, 5 H, CH_{Ar}); 11.25, 12.67 (both s, 1 H each, NH)
3p	3.16 (s, 6 H, CH_3); 4.09 (d, 2 H, CH_2, *J* = 5.5); 7.18—7.42 (m, 9 H, CH_{Ar}); 11.42, 12.67 (both s, 1 H each, NH)
3q	1.09—1.82 (m, 14 H, CH_2); 2.62 (d, 2 H, CH_2, *J* = 11.0); 2.87—3.01 (m, 2 H, CH_2); 3.21 (s, 6 H, CH_3); 7.26—7.53 (m, 3 H, CH_{Ar}); 7.55 (m, 1 H, CH_{Ar}); 11.24, 12.37 (both s, 1 H each, NH)
3r	3.28 (s, 6 H, CH_3); 6.89—7.34 (m, 8 H, CH_{Ar}); 13.06, 13.11 (both s, 1 H each, NH)

was filtered off, washed with water, dried, and crystallized from ethanol. (5*Z*)-5-[Anilino(mercapto)methylene]-1-(4-bromophenyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**4a**), (5*Z*)-1-(4-bromophenyl)-5-{[(3,5-difluorophenyl)amino](mercapto)methylene}pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**4b**), (5*Z*)-1-(4-bromophenyl)-5-{[(2-chlorophenyl)amino](mercapto)methylene}pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**4c**), (5*Z*)-5-[anilino(mercapto)methylene]-1-(4-methylphenyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**4d**), (5*Z*)-5-[anilino(mercapto)methylene]-1-(4-methoxyphenyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**4e**), (5*Z*)-5-{mercapto[(4-methylphenyl)amino]methylene}-1-(4-methoxyphenyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**4f**), (5*Z*)-5-{[(4-chlorophenyl)amino](mercapto)methylene}-1-(2,4-dimethylphenyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**4g**), (5*Z*)-5-[anilino(mercapto)methylene]-1-(2-ethoxyphenyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**4h**), or 5-[anilino(mercapto)methylene]-1,3-dicyclohexylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**4i**) were obtained.

Method *B* (for **4j**,**k**). A solution of sodium ethoxide prepared from sodium (10 mmol) and anhydrous ethanol (40 mL) was slowly (for 2 h) added to a boiling solution of dimethylbarbituric acid (10 mmol) and phenyl or 2-chlorophenyl isothiocyanate (10 mmol) in anhydrous ethanol (50 mL). The mixture was refluxed for 3 h and left to stay for 16 h in a refrigerator. A precipitate of thioamide sodium salt **4** was filtered off, washed with a minor amount of alcohol, and dissolved in water. The solution was filtered, and the filtrate was acidified with HCl to pH = 1—2. The precipitate was filtered off, washed with water, and dried. 5-[Anilino(mercapto)methylene]-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**4j**) and 5-{[(2-chlorophenyl)amino](mercapto)methylene}-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**4k**) were obtained.

5-[Amino(methylthio)methylene]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-triones 5 (general procedure). Methyl iodide (5.5 mmol) and triethylamine (5.5 mmol) were added to a solution of thioamide **4** (5 mmol) in DMF (10 mL), and the mixture was kept at ambient temperature for 1 day. The solution was diluted with water (50 mL), and the precipitate was filtered off, dried, and crystallized from ethanol. (5*Z*)-5-[anilino(methylthio)methylene]-1-(4-bromophenyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**5a**), (5*Z*)-1-(4-bromophenyl)-5-{[(3,5-difluorophenyl)amino](methylthio)methylene}pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**5b**), (5*Z*)-1-(4-bromophenyl)-5-{[(2-chlorophenyl)amino](methylthio)methylene}pyrimidine-

2,4,6(1*H*,3*H*,5*H*)-trione (**5c**), (5*Z*)-5-[anilino(methylthio)methylene]-1-(4-methylphenyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**5d**), (5*Z*)-5-[anilino(methylthio)methylene]-1-(4-methoxyphenyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**5e**), (5*Z*)-5-{methylthio[(4-methylphenyl)amino]methylene}-1-(4-methoxyphenyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**5f**), (5*Z*)-5-{[(4-chlorophenyl)amino](methylthio)methylene}-1-(2,4-dimethylphenyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**5g**), (5*Z*)-5-[anilino(methylthio)methylene]-1-(2-ethoxyphenyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**5h**), 5-[anilino(methylthio)methylene]-1,3-dicyclohexylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**5i**), 5-[anilino(methylthio)methylene]-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**5j**), or 5-{[(2-chlorophenyl)amino](methylthio)methylene}-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**5k**) were obtained.

(5*Z*)-5-[Arylamino(alkylamino)methylene]- and (5*Z*)-5-[arylamino(methylene)]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-triones 3 (general procedure). Compound **5** (0.3 mmol) and the corresponding amine (0.33 mmol) were added to DMF (1 mL), and the mixture was boiled for 3 min, cooled to ambient temperature, and diluted with water. The precipitate was filtered off and crystallized from ethanol. (5*E*)-5-{Anilino[(2-methoxyphenyl)amino]methylene}-1-(4-bromophenyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**3a**), (*E*)-5-((2-(1*H*-indol-3-yl)ethylamino)(3,5-difluorophenylamino)methylene)-1-(4-bromophenyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**3b**), (5*E*)-5-{anilino[(2-methoxyphenylamino]methylene}-1-(4-methylphenyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**3c**), (5*E*)-5-{anilino[(4-fluorobenzyl)amino]methylene}-1-(4-methylphenyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**3d**), (*Z*)-5-[(2-chlorobenzylamino)(*p*-anilino)methylene]-1-(4-methoxyphenyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**3e**), (*Z*)-5-imidazole{[2-(1*H*-imidazol-5-yl)ethylamino](*p*-toluidino)methylene}-1-(4-methoxyphenyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**3f**), (*E*)-5-{[4-(trifluoromethyl)phenylamino](*p*-toluidino)methylene}-1-(4-methoxyphenyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**3g**), 5-[bis(*p*-toluidino)methylene]-1-(4-methoxyphenyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**3h**), (*Z*)-5-{[2-(5-fluoro-1*H*-indol-3-yl)ethylamino](4-chlorophenylamino)methylene}-1-(2,4-dimethylphenyl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**3i**), 4-[({anilino[1-(2-ethoxyphenyl)-2,4,6-trioxotetrahydro-5(2*H*)-pyrimidinylidene]methyl}amino)methyl]cyclohexanecarboxylic acid (**3j**), 5-((*Z*)-anilino{[3-(4-morpholinyl)propyl]amino}methylidene)-1-(2-ethoxyphenyl)-2,4,6(1*H*,3*H*)-pyrimidinetrione (**3k**), 5-{(*Z*)-anilino[(2,2,6,6-tetramethyl-4-piperidinyl)amino]methylene}-1-(2-ethoxyphenyl)-2,4,6(1*H*,3*H*)-pyrimidinetrione (**3l**), 5-(anilino{[2-(trifluoromethyl)benzyl]amino{methylene)-1,3-dicyclohexyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**3m**), 5-{anilino[(octahydro-2*H*-quinolizin-1-ylmethyl)amino]methylene}-1,3-dicyclohexyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**3n**), 5-{anilino[(2-chlorobenzyl)amino]methylene}-1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**3p**), 5-{(2-chloroanilino)[(octahydro-2*H*-quinolizin-1-ylmethyl)amino]methylene}-1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)pyrimidinetrione (**3q**), or 5-{(2-chloroanilino)[4-(trifluoromethyl)anilino]methylene}-1,3-dimethyl-2,4,6(1*H*,3*H*,5*H*)-pyrimidinetrione (**3r**) were obtained.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 04-03-32926a).

References

1. A. Kreutzberger, *Arzneimittel-Forschung*, 1978, **28**, 1684.
2. L. R. Morgan, B. S. Jursic, C. L. Hooper, D. M. Neumann, K. Thangaraj, and B. LeBlanc, *Biorg. Med. Chem. Lett.*, 2002, **12**, 3407.
3. M. T. Omar, *Egypt. J. Pharm. Sci.*, 1998, **38,** 281.
4. B. R. Modi, B. D. Mistry, and K. R. Desai, *Orient. J. Chem.*, 1993, **9,** 369.
5. U.S. Pat. 6,335,332; *Chem. Abstrs*, 1999, **130**, 95560.
6. Int. Pat. WO 99/25699; *Chem. Abstrs*, 1999, **131**, 5267.
7. B. S. Jursic, F. Doulle, andE. D. Stevens, *Tetrahedron*, 2003, **59**, 3427.
8. D. Prelicz, Akad. Med., Wroclaw, Pol. *Dissertationes Pharmaceuticae et Pharmacologicae*, 1966, **18**, 1, 31.

Received October 20, 2006;
in revised form May 8, 2007