methyl-5-oxo-5*H*-1,3,4-thidiazolo[3,2-*a*]pyrimidyl-2)sulfide (13). 0.01 mol of **6** or **7** was dissolved in 10—15 g of PPA with mild heating, and with vigorous stirring 0.011 mole of ethyl acetate was added dropwise. The reaction mixture was heated for 3 h at 100°C over a boiling water bath. After cooling, the reaction mixture was diluted with 30—50 ml of water. The precipitate was filtered off and recrystallized from aqueous dioxane (1:3).

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Received July 22, 1993;
in revised form October 1, 1993

Interaction of 2-bromo-7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine with methylene-active compounds and acid hydrolysis of its products

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Reactions of 2-bromo-7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine with sodium derivatives of pentane-2,4-dione, malonodinitrile, Meldrum acid, acetoacetic, cyanoacetic and malonic esters have been shown to give the respective substituted derivatives. Azinyl-ylidene tautomerism has been found to be characteristic of these compounds, the latter existing mainly in the ylidene form. The acid hydrolysis of pentane-2,5-dione and cyanoacetic and malonic esters derivatives has been investigated.

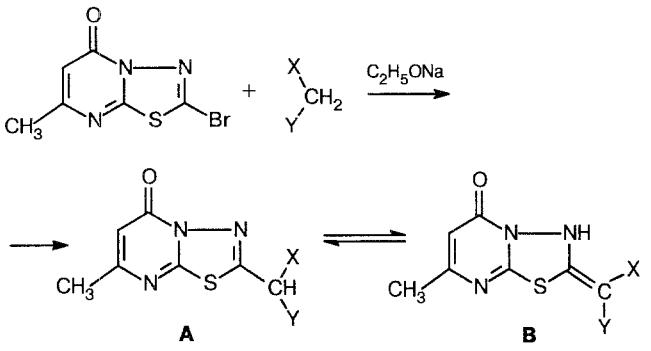
Key words: nucleophilic substitution reaction, 2-bromo-7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine, methylene active compounds (pentane-2,5-dione, malonodinitrile, Meldrum acid, acetoacetic, cyanoacetic, malonic esters), azinyl-ylidene tautomerism, ketonic and acidic cleavage.

In a continuation of our investigations of the reactivity of the bromine atom in 2-bromo-7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine (BTP) under conditions of nucleophilic substitution,[1—3] the interactions of BTP with methylene-active compounds (MC) have been examined. The latter, when converted to sodium derivatives with the use of sodium ethylate in absolute EtOH, participate in the reaction to yield new 1,3,4-thiadiazolo[3,2-*a*]pyrimidine (TP) derivatives (Scheme 1).

We used such MC as pentane-2,5-dione, Meldrum acid (isopropylidenemalonate, 2,2-dimethyl-1,3-dioxane-4,6-dione), malonodinitrile, and acetoacetic, cyanoacetic, and malonic esters. The reaction of MC with BTP proceeds at room temperature. Mild heating or reflux of the reaction mixture accelerates completion of the reac-

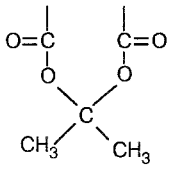
Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 11, pp. 1957—1961, November, 1993.
1066-5285/93/4211-1874 $12.50

Scheme 1



A **B**

1—6

Compound	X	Y
1	—$COCH_3$	—$COCH_3$
2		
3	—CN	—COOEt
4	—CN	—COMe
5	—COOEt	—COOEt
6	—CN	—COOEt

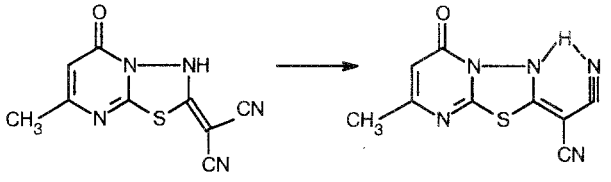
tion. The yields of the target TP vary from 51 to 90 %. The synthesized TP **1—6** are white crystals with high melting points, readily soluble in polar solvents. Characteristics of compounds **1—6** are given in Table 1, ^1H NMR and IR spectra data are presented in Table 2.

There are no signals of methylene group protons at 5.1 ppm in the ^1H NMR spectra of compounds **1—6**. This anomalous fact can be explained[4] by the phenomenon of azinyl-ylidene tautomerism previously unknown for the 1,3,4-thiadiazolo[3,2-a]pyrimidine series. Analysis of the IR spectra of TP **1—6** indicates the presence of an absorption band in the 3380—3450 cm^{-1} interval, indicative of an NH group. The presence of the NH group is evidence of a methylene proton hydride shift to the N-3 nitrogen atom of the 1,3,4-thiadiazole ring.

Thus, for compounds **1—6** the ylidene form (**B**) is favorable, rather than the azinyl form (**A**). This draws attention to the fact that compounds **1—6** have abnormally high melting points, though the majority of TP melt at considerably lower temperatures.[1,2,5,6]

Presumably, the MC fragments in position 2 of TP and the hydrogen atom of the NH group form «pseudo-cycles» by hydrogen bonding. For example, in the IR spectrum of compound **3** two absorption bands, indicating two nitrile groups, are observed at 2189 and 2212 cm^{-1}, which proves the non-equivalence of these two groups, caused by the involvement of one of them in a «pseudo-cycle» (**3B**).

Scheme 2



3A **3B**

In addition to the cyano group, the carbonyl group of ketone **1** or the ester group of compounds **2** and **6** can contribute to the formation of «pseudo-cycles»

Of considerable interest are the structures of TP **4** and **5**, which contain fragments of acetoacetic and cyanoacetic esters, because for compound **4** not only the carbonyl group of the ketone fragment, but also the ethoxycarbonyl group can participate in cycle formation. In compound **5** both the cyano group and the ester group can participate in cycle formation.

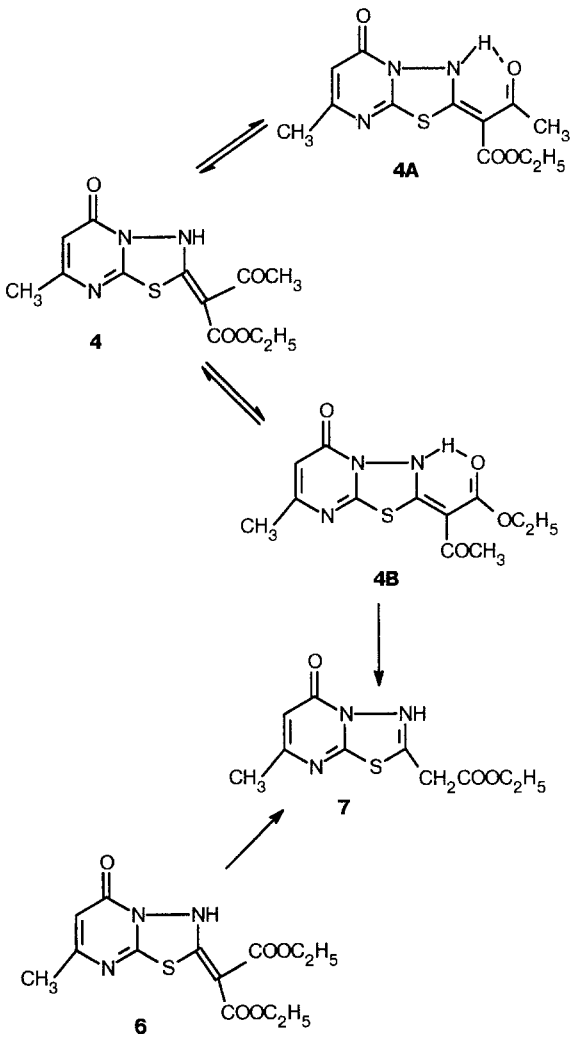
We have confirmed the structure of compound **4** by its chemical decomposition in an acidic medium. Preliminary experiments have shown that in a 5 % solution of phosphoric acid decomposition of the acetoacetic fragment without change of the TP ring takes place. Compound **7** (75 % yield) proved to be a final product of compound **4** degradation. Formation of TP **7** can be accounted by the acidic cleavage of compound **4B** according to Scheme 3.

Compound **7** is also formed under the same conditions of acidic cleavage of compound **6** in 90 % yield. Recently a one-pot synthesis of TP **7** from cyanoacetic ester, thiosemicarbazide and acetoacetic ester in polyphosphoric acid has been described.[7]

In our opinion, the chemical cleavage of TP **4** indicates the participation of the ester group of the acetoacetic fragment (**4B**) in the ring formation. Although a ketonic carbonyl group is more active than an ester carbonyl group (due to stronger polarization), we assume that it can not participate in hydrogen bond formation due to its solvation by the polar molecules of the solvent.

We have noticed that if the keto group of **4** is blocked chemically by its transformation into a Schiff base, recyclization of the pseudocycle can be performed

Scheme 3

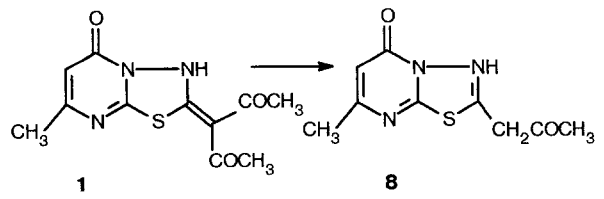


followed by ketonic cleavage leading to compound **8** in 60 % yield.

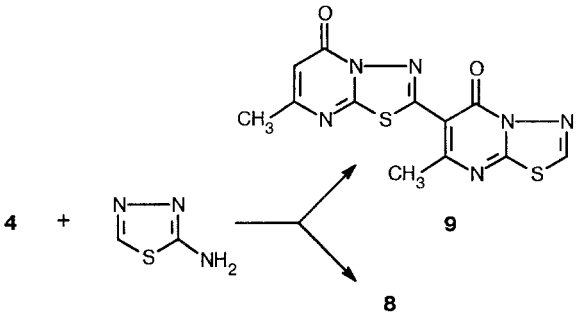
Compound **8** is also formed in the cleavage of diketone **1** with a yield of 80 % (Scheme 4).

The fact that compound **4** exists in the ylidene form has been established by chemical methods. In order to do this the reaction of keto ester **4** with 2-amino-1,3,4-thiadiazole (AT) in polyphosphoric acid was carried out. The reaction of AT with keto esters is well studied and the structures of the intermediates formed during cyclodehydration are safely known. This reaction leads to ketone **8**, but not to 6-(7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine-2-yl)-7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine **9**.

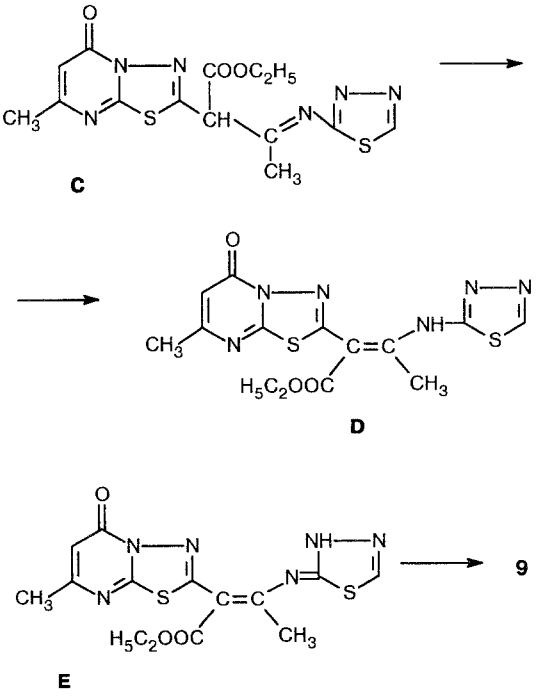
Scheme 4



Scheme 5



The formation of compound **9** should follow the transfer of a hydrogen atom from the methylene carbon atom of the acetoacetic fragment to the endocyclic nitrogen atom of 2-amino-1,3,4-thiadiazole through the intermediates **C**, **D**, **E**.



However intermediates **C—E** can not form due to the fact that in ketoester **4** this transfer leads to a TP-ring (with the formation of **4A**). Instead, a transformation giving rise to ketone **8** through the intermediate steps **F→B→G** takes place:

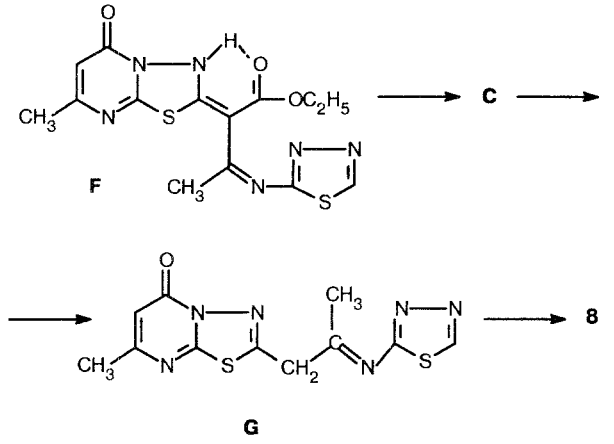


Table 1. Characteristics of the synthesized compounds

Compound	Yield (%)	M.p./ °C	Found (%) / Calculated C	Found (%) / Calculated H	Molecular formula
1	90	305—306	49.95 / 49.79	4.36 / 4.18	$C_{11}H_{11}N_3O_3S$
2	51	> 350 (decomp.)	46.71 / 46.59	3.90 / 3.58	$C_{12}H_{11}N_3O_3S$
3	86	> 350 (decomp.)	46.51 / 46.76	2.31 / 2.17	$C_9H_5N_3OS$
4	88	360—361	48.53 / 48.80	4.30 / 4.43	$C_{12}H_{13}N_3O_4S$
5	89	347—348	47.70 / 47.47	3.67 / 3.62	$C_{11}H_{10}N_4O_3S$
6	69	352—354	48.29 / 47.99	4.63 / 4.64	$C_{13}H_{15}N_3O_5S$
7	87	85—86	47.86 / 47.41	4.59 / 4.37	$C_{10}H_{11}N_3O_3S$
8	60	170—171	48.10 / 48.41	4.41 / 4.06	$C_9H_9N_3O_2S$
10	84	214—215	40.97 / 40.52	4.15 / 4.08	$C_{10}H_{12}N_6OS_2$

Table 2. Spectral characteristics of compounds **1—9**

Compound	IR Spestrum (ν / cm^{-1})	NMR Spestrum (δ, ppm)
1	1700 C=O; 1645 C=O (cycle) 1620 C=C; 1610 C=C; 3420 NH	6.0(s, H, CH); 2.32(s, 3 H, CH_3); 2.17(s, 3 H, CH_3).
2	1690 C=O (cycle); 1712 C=O; 3420 NH	6.01(s, H, CH); 2.41(s, 3 H, CH_3); 2.30(s, 3 H, CH_3); 2.19(s, 3 H, CH_3).
3	1670 C=O (cycle); 2211 CN; 2189 CN; 3450 NH	5.79(s, H, CH); 2.12(s, 3 H, CH_3).
4	1650 C=O (cycle); 1691 C=O; 1696 C=O; 3450 NH	6.02(s, H, CH); 4.10(q, 2 H, CH_2); 2.25(s, 3 H, CH_3); 2.17(s, 3 H, CH_3); 1.17(t, 3 H, CH_3).
5	1630 C=O (cycle); 1642 C=O; 2200 CN; 3420 NH	5.95(s, H, CH); 3.97(q, 2 H, CH_2); 2.12(s, 3 H, CH_3); 1.10(t, 3 H, CH_3).
6	1635 C=O (cycle); 1650 C=O; 1660 C=O; 3380 NH	6.1(s, H, CH); 4.0(q, 2 H, CH_2); 2.22(s, 3 H, CH_3); 1.15(t, 3 H, CH_3).
7	1695 C=O (cycle); 1715 C=O	6.20(s, H, CH); 4.22(s, 2 H, CH_2); 4.0(q, 2 H, CH_2); 2.32(s, 3 H, CH_3); 1.25(t, 3 H, CH_3).
8	1690 C=O (cycle); 1719 C=O;	6.17(s, H, CH); 4.17(s, 2 H, CH_2); 2.25(s, 3 H, CH_3); 2.22(s, 3 H, CH_3).
9	1690 C=O (cycle); 3270 NH; 3390 NH	10.17(s, H, NH); 8.05(s, H, NH); 7.40(s, H, NH); 6.17(s, H, CH); 4.02(s, 2 H, CH_2); 2.20(s, 3 H, CH_3); 1.97(s, 3 H, CH_3).

Experimental

IR Spectra were obtained on a «UR-20» instrument in the area 3700—400 cm^{-1} for thin layers. ^1H NMR spectra were obtained in DMSO and $CDCl_3$ on a «Tesla BS 487C» spectrometer at 80 MHz, internal standard — HMDS. Melting points were measured on a «Boetius» table.

Initial BTP were obtained according to the previously described procedure.[8] For meldrum acid synthesis see Ref. 9.

General procedure for the synthesis of TP 1—6: 3-(7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine-2-yl)pentane-2,4-dione (**1**); 5-(7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine-2-yl)-1,2,2-dimethyl-1,3-dioxane-4,6-dione (**2**); (7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine-2-yl)malonodinitrile (**3**); ethyl (7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine-2-yl)acetoacetate (**4**); ethyl (7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine-2-yl)cyanoacetate (**5**); diethyl (7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine-2-yl)malonate (**6**).

0.010 mol of the methylene-active compound was added to a solution of sodium ethylate prepared from 15 ml of absolute EtOH and 0.011 mol of metallic sodium at ~20 °C. The reaction mixture was stirred for 20—30 min. Then 0.010 mol of BTP was added and the reaction mixture was stirred for 1—2 h. The reaction mixture was then stirred at 60—80 °C for 40—60 min.

After removal of the solvent the mixture was treated with 30—40 ml of water. The precipitate was filtered off and after drying in the air the product was recrystallized from a dioxane/water mixture (3:1).

Ethyl (7-methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]-pyrimidine-2-yl)acetate (7). *Procedure A.* 2.95 g of TP **4** was added to 10 ml of 5 % solution of H_3PO_4 and 5 ml of EtOH. The reaction mixture was stirred for 30 min on a boiling water bath. After cooling, the reaction product was extracted with $CHCl_3$ (3 × 20 ml). The extract was dried over $MgSO_4$. After removal of the solvent 2.21 g (87.3 %) of **7** was obtained. Compound **7** was recrystallized from a chloroform—hexane mixture (2:1).

Procedure B. 3.25 g of TP **6** was treated with acid at 60—70 °C for 40—50 min similarly to method A. 2.15 g (85 %) of the compound **7** was obtained.

(7-Methyl-5-oxo-5*H*-1,3,4-thiadiazolo[3,2-*a*]pyrimidine-2-yl)propane-2-one (8). *Procedure A.* A mixture of 10 ml of polyphosphoric acid, 1 g of 2-amino-1,3,4-thiadiazole and 2.95 g of TP **4** was heated with stirring for 3 h on a boiling water bath and after cooling was diluted with 40 ml of water. The product was extracted with the mixture $CHCl_3$—C_6H_6 (1:1) (3 × 20 ml) and dried over $MgSO_4$. After removal of the solvents 1.34 g (60 %) of TP **8** was obtained. Product **8** was recrystallized from a water—acetone mixture (1:1).

Procedure B. A suspension of 2.65 g of TP **1** in 10 ml of 5 % aqueous H_3PO_4 and 10 ml of EtOH was heated with stirring on a boiling water bath for 1 h. After cooling the mixture of products was extracted with $CHCl_3$ (3 × 30 ml). After evaporation of $CHCl_3$ 1.78 g (80 %) of TP **8** was obtained. Ketone **8** was characterized as thiosemicarbazone **10**. Characteristics of compounds **1—8**, **10** are given in Tables 1 and 2.

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Received July 22, 1993