Chemistry of Heterocyclic Compounds, Vol. 37, No. 5, 2001

DERIVATIVES OF CONDENSED THIENOPYRIMIDIMINES. 13*. SYNTHESIS AND STRUCTURE OF PYRANO[4',3':4,5]THIENO-[3,2-*e*]-1,2,4-TRIAZOLO[2,3-*c*]PYRIMIDINES

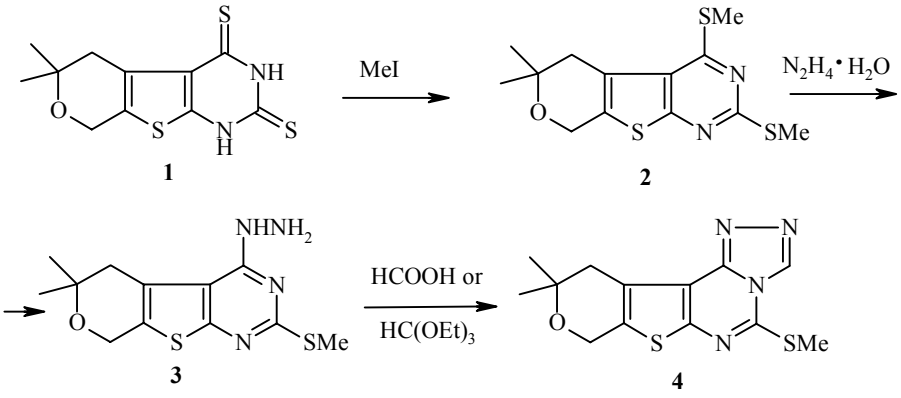
A. Sh. Oganisyan[1], A. S. Noravyan[1], A. A. Karapetyan[1], M. S. Aleksanyan[1], and Yu. T. Struchkov[2]

Methods for the synthesis of 5-substituted 10,10-dimethyl-10,11-dihydro-8H-pyrano[4',3':4,5]thieno[3,2-e]-1,2,4-triazolo[2,3-c]pyrimidines have been developed. An X-ray crystallographic study of 5-(2-ethoxymethylhydrazino)-10,10-dimethyl-10,11-dihydro-8H-pyrano[4',3':4,5]thieno[3,2-e]-1,2,4-triazolo[2,3-c]pyrimidine has been carried out.

Keywords: dithioxopyrimidine, pyranothienopyrimidine, pyranothienotriazolopyrimidines.

The synthesis of 2,4-dithioxopyranothienopyrimidine **1** has been described [2]. We have used it as a starting material for the further development of methods for the preparation of derivatives of pyranothienopyrimidines.

Treatment of the dithioxypyrimidine **1** with methyl iodide in the presence of potassium hydroxide gave the 2,4-dimethylthio derivative **2**. The 4-hydrazino-2-methylthiothienopyrimidine **3** was synthesized by condensation of compound **2** with hydrazine hydrate. It was shown that substitution of the methylthio group occurred only at position 4 of the pyrimidine ring. Condensation of the 4-hydrazinopyrimidine **3** with either formic acid or its orthoester gave a derivative of the triazol[4,3-*c*]pyrimidine series **4**.



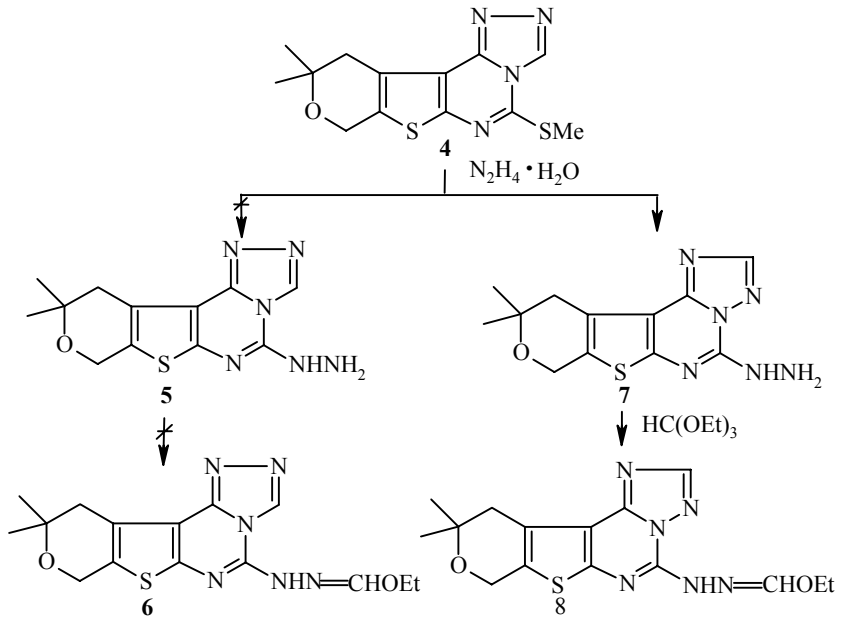
1 **2** **3** **4**

* For paper 12 see [1].

[1] Center for Investigation of Molecular Structure, Armenian National Academy of Sciences, Erevan 375014; e-mail: admin@msrc.am. [2] Institute of Organoelement Compounds, Russian Academy of Sciences, Moscow 117813, Russia. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, 681-685, May, 2001. Original article submitted April 2, 1999.

 0009-3122/01/3705-0628$25.00

It was expected that the triazolothienopyrimidine **6** would be formed by reaction of 2-methylthio-1,2,4-triazolo[4,3-*c*]thienopyrimidine **4** with hydrazine hydrate and condensation of the compound formed (**5**) with ethyl orthoformate. However it was shown by X-ray crystallography that the new derivatives of the pyranothieno[3,2-*e*]-1,2,4-triazolo[2,3-*c*]pyrimidine series **7,8** were formed by these reactions.



The results obtained show that isomerization of the triazolo ring accompanies substitution of the methylthio group in compound **4** to give the products **7** and **8**. The structure of compound **8** and its bond lengths are shown in Fig. 1.

Atomic coordinates are given in Table 1 and bond angles (ω) are given in Table 2. The geometric parameters of molecules of **8** given in Table 2 have normal values [3, 4] and require no special comments.

As expected, the dihydropyran ring has a weakly distorted half-chair conformation (displacement of atoms $O_{(2)}$ and $C_{(3)}$ from the root mean square plane of the remaining atoms of the ring are -0.325 and 0.398 Å respectively). The tricyclic system including the condensed thiophene, pyrimidine, and triazole rings is virtually planar (individual atoms from the RMS plane of this system are displaced by no more than 0.05 Å). The mutual position of the fragments discussed evidently explains the presence of intramolecular forked hydrogen bonds: $N_{(15)}$–$H_{(15)}$···$O_{(18)}$ (N···O 2.595(3), H···O 2.27 Å, N–H···O 104(2)°) and $N_{(15)}$–$H_{(15)}$···$N_{(14)}$ (N···N 2.726(3), H···N 2.39(2) Å, N–H···N 105(2)°). In sum these indicate the planar trigonal configuration of $N_{(15)}$ (sum of bond angles 360°).

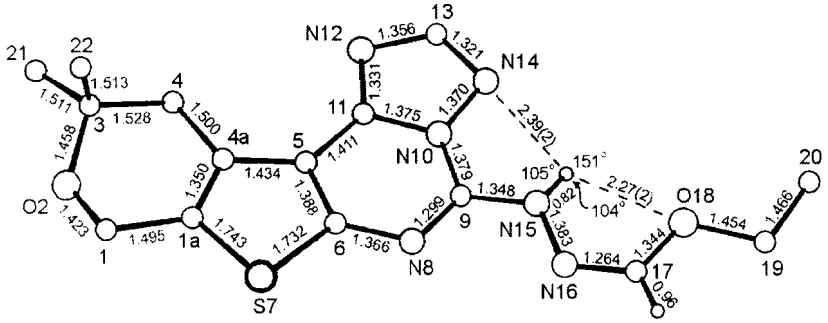


Fig. 1. Structure of the molecule of compound **8** (broken lines indicate hydrogen bonds).

TABLE 1. Coordinates of Atoms ($\times 10^4$) and Their Equivalent Isotropic Parameters in the Molecule of Compound **8**

Atom	*x/a*	*y/b*	*z/c*	B_{iso}
$C_{(1)}$	-1961(3)	1978(1)	3672(3)	3.8(1)
$O_{(2)}$	-524(2)	1799(1)	3190(2)	3.5(1)
$C_{(3)}$	-547(3)	1487(1)	1728(3)	3.2(1)
$C_{(4)}$	-1370(3)	838(1)	1806(3)	3.3(1)
$C_{(4a)}$	-2799(3)	905(1)	2601(3)	3.0(1)
$C_{(5)}$	-4013(3)	447(1)	2613(3)	2.8(1)
$C_{(6)}$	-5171(3)	650(1)	3476(1)	3.2(1)
$S_{(7)}$	-4788(1)	1406(0)	4258(1)	3.8(1)
$C_{(1a)}$	-3057(3)	1432(1)	3446(3)	3.2(1)
$N_{(8)}$	-6491(2)	336(1)	3700(2)	3.4(1)
$C_{(9)}$	-6669(3)	-817(1)	3015(3)	3.3(1)
$N_{(10)}$	-5585(2)	-463(1)	2132(2)	3.2(1)
$C_{(11)}$	-4253(3)	-154(1)	1880(3)	3.0(1)
$N_{(12)}$	-3489(2)	-505(1)	933(2)	3.8(1)
$C_{(13)}$	-4418(3)	-1019(1)	661(3)	4.2(1)
$N_{(14)}$	-5700(2)	-1031(1)	1333(3)	3.9(1)
$N_{(15)}$	-7900(2)	-596(1)	3079(3)	4.0(1)
$N_{(16)}$	-9051(2)	-387(1)	3933(3)	4.0(1)
$C_{(17)}$	-10141(3)	-778(1)	4000(3)	3.8(1)
$O_{(18)}$	-10211(3)	-1352(1)	3284(2)	4.1(1)
$C_{(19)}$	-11536(3)	-1737(1)	3560(3)	5.0(1)
$C_{(20)}$	-11516(4)	-2324(2)	2633(4)	6.5(1)
$C_{(21)}$	1096(3)	1381(1)	1460(3)	4.4(1)
$C_{(22)}$	-1263(3)	1938(1)	558(3)	4.4(1)

TABLE 2. Bond Angles ω (deg) in the Molecule of Compound **8**

Angle	ω, deg.	Angle	ω, deg.
$O_{(2)}C_{(1)}C_{(1a)}$	110.8(2)	$S_{(7)}C_{(6)}N_{(8)}$	121.2(2)
$C_{(1)}O_{(2)}C_{(3)}$	114.9(2)	$C_{(1a)}S_{(7)}C_{(6)}$	90.1(1)
$O_{(2)}C_{(3)}C_{(4)}$	109.1(2)	$C_{(6)}N_{(8)}C_{(9)}$	115.4(2)
$O_{(2)}C_{(3)}C_{(21)}$	104.1(2)	$N_{(8)}C_{(9)}N_{(10)}$	121.5(2)
$O_{(2)}C_{(3)}C_{(22)}$	109.5(2)	$N_{(8)}C_{(9)}N_{(15)}$	124.3(2)
$C_{(4)}C_{(3)}C_{(21)}$	110.7(2)	$N_{(10)}C_{(9)}N_{(15)}$	114.2(2)
$C_{(4)}C_{(3)}C_{(22)}$	112.6(2)	$C_{(9)}N_{(10)}C_{(11)}$	124.2(2)
$C_{(21)}C_{(3)}C_{(22)}$	110.5(2)	$C_{(9)}N_{(10)}N_{(14)}$	125.4(2)
$C_{(3)}C_{(4)}C_{(4a)}$	111.4(2)	$C_{(11)}N_{(10)}N_{(14)}$	110.4(2)
$C_{(4)}C_{(4a)}C_{(1a)}$	121.0(2)	$C_{(5)}C_{(11)}N_{(10)}$	116.0(2)
$C_{(4)}C_{(4a)}C_{(5)}$	127.1(2)	$C_{(5)}C_{(11)}N_{(12)}$	134.7(2)
$C_{(1a)}C_{(4a)}C_{(5)}$	111.8(2)	$N_{(10)}C_{(11)}N_{(12)}$	109.3(2)
$C_{(1)}C_{(1a)}C_{(4a)}$	123.4(2)	$C_{(11)}N_{(12)}C_{(13)}$	102.1(2)
$C_{(1)}C_{(1a)}S_{(7)}$	123.5(2)	$N_{(12)}C_{(13)}N_{(14)}$	117.8(2)
$C_{(4a)}C_{(1a)}S_{(7)}$	113.1(2)	$N_{(10)}N_{(14)}C_{(13)}$	100.5(2)
$C_{(4a)}C_{(5)}C_{(6)}$	112.9(2)	$C_{(9)}N_{(15)}N_{(16)}$	118.3(2)
$C_{(4a)}C_{(5)}C_{(11)}$	131.8(2)	$N_{(15)}N_{(16)}C_{(17)}$	115.1(2)
$C_{(6)}C_{(5)}C_{(11)}$	115.2(2)	$N_{(16)}C_{(17)}O_{(18)}$	123.5(2)
$C_{(5)}C_{(6)}S_{(7)}$	111.2(2)	$C_{(17)}O_{(18)}C_{(19)}$	114.5(2)
$C_{(5)}C_{(6)}N_{(8)}$	127.7(2)	$O_{(18)}C_{(19)}C_{(20)}$	108.5(3)

EXPERIMENTAL

IR spectra of nujol mulls were recorded with a UR-10 instrument, ^{1}H NMR spectra were recorded with a Varian T-60 spectrometer, and mass spectra with a MX-1303 with an ionizing voltage of 70 eV. TLC was carried out on Silufol UV-254 plates developed with iodine vapor. Calculations were carried out with the INEXTL program [5] with an Eclipse S/200 computer.

6,6-Dimethyl-2,4-dimethylthio-5,6-dihydro-8H-pyrano[4',3':4,5]thieno[2,3-*d*]pyrimidine (2). Methyl iodide (2.82 g, 0.02 mol) in ethanol (10 ml) was added dropwise at 40-50°C to a solution of thienopyrimidine **1** (2.84 g, 0.01 mol) and potassium hydroxide (1.12 g, 0.02 mol) in ethanol (50 ml). Stirring was continued for 2 h. The reaction mixture was diluted with water (50 ml). The precipitate was filtered off, washed with water, and dried to give pyrimidine **2** (2.6 g, 83%); mp 133-134°C (ethanol). R_f 0.52 (ether–benzene, 1:1). ^{1}H NMR spectrum (pyridine-d_5), δ, ppm: 4.70 (2H, s, 8-CH_2); 2.96 (2H, s, 5-CH_2); 2.60 (3H, s, 2-SCH_3); 2.54 (3H, s, 4-SCH_3); 1.30 (6H, s, 6-$(CH_3)_2$). Mass spectrum, *m/z* (I_{rel}, %): 312 (M^+) (100), 297 (17), 262 (46), 254 (18), 239 (18). Found, %: C 50.01; H 5.42; N 8.90; S 30.80. $C_{13}H_{16}N_2OS_3$. Calculated, %: C 49.82; H 5.22; N 9.11; S 30.79.

4-Hydrazino-6,6-dimethyl-2-methylthio-5,6-dihydro-8H-pyrano[4',3':4,5]thieno[2,3-*d*]pyrimidine (3). A mixture of compound **2** (3.12 g, 0.01 mol), 98% hydrazine hydrate (5 ml), and butanol (10 ml) was boiled for 8 h. After cooling the precipitate was filtered off, washed with water, and dried to give pyrimidine **3** (2.6 g, 88%); mp 237-238°C (butanol). R_f 0.47 (ethanol–chloroform, 2:1). IR spectrum, ν, cm^{-1}: 1620 (C=N), 3150-3350 (NH–NH_2). ^{1}H NMR spectrum (pyridine-d_5), δ, ppm: 4.86 (2H, s, 8-CH_2); 4.66 (3H, br. s, $NHNH_2$); 3.03 (2H, s, 5-CH_2); 2.66 (3H, s, S-CH_3); 1.28 (6H, s, 6-$(CH_3)_2$). Found, %: C 48.50; H 9.62; N 18.61; S 21.39. $C_{12}H_{16}N_4OS_2$. Calculated, %: C 48.60; H 9.38; N 18.90; S 21.55.

10,10-Dimethyl-5-methylthio-10,11-dihydro-8H-pyrano[4',3':4,5]thieno[3,2-*e*]-1,2,4-triazolo[4,3-*c*]-pyrimidine (4). A. A mixture of compound **3** (2.96 g, 0.01 mol) and ethyl orthoformate (15 ml) was boiled for 5 h. After cooling, the precipitate was filtered off, washed with ether, and dried to give the triazolopyrimidine **4** (2.3 g, 78%); mp 267-269°C (ethanol). R_f 0.48 (butanol–pyridine, 2:1). ^{1}H NMR spectrum (pyridine-d_5), δ, ppm: 8.87 (1H, s, 3-CH); 4.80 (2H, s, 8-CH_2); 3.33 (2H, s, 11-CH_2); 2.62 (3H, s, S-CH_3); 1.33 (6H, s, 10-$(CH_3)_2$). Found, %: C 50.52; H 4.28; N 20.26; S 12.06. $C_{13}H_{14}N_4OS_2$. Calculated, %: C 50.11; H 4.52; N 20.41; S 11.70.

B. A mixture of compound **3** (2.96 g, 0.01 mol) and formic acid (15 ml) was boiled for 5 h. The cooled reaction mixture was neutralized with aqueous potassium hydroxide. The precipitated crystals were filtered off, washed with water, and recrystallized from ethanol to give compound **4** (2.2 g, 76.6%) which gave no depression of the melting point when mixed with a sample from method A.

5-Hydrazino-10,10-dimethyl-10,11-dihydro-8H-pyrano[4',3':4,5]thieno[3,2-*e*]-1,2,4-triazolo[4,3-*c*]-pyrimidine (7). A mixture of triazolopyrimidine **4** (3.06 g, 0.01 mol) and 98% hydrazine hydrate (5 ml) in butanol (20 ml) was boiled for 12 h. After cooling the precipitated crystals were filtered off, washed with water, and dried to give pyrimidine **7** (2.2 g, 72%); mp 282-283°C (dimethylsulfoxide). R_f 0.49 (pyridine–chloroform, 3:1). IR spectrum, ν, cm^{-1}: 1630 (C=N), 3100-3320 (NH–NH_2). Found, %: C 50.21; H 4.90; N 28.94; S 11.63. $C_{12}H_{14}N_6OS$. Calculated, %: C 50.00; H 4.98; N 28.96; S 11.03.

5-N-(2-Ethoxymethylhydrazino)-10,10-dimethyl-10,11-dihydro-8H-pyrano[4',3':4,5]thieno[3,2-*e*]-1,2,4-triazolo[4,3-*c*]pyrimidine (8). A mixture of the triazolopyrimidine **7** (2.9 g, 0.01 mol) and ethyl orthoformate (20 ml) were boiled for 3 h. The precipitated crystals were filtered off, washed with ether, and dried to give pyrimidine **8** (2.8 g, 81%); mp 226-228°C (ethanol). R_f 0.51 (pyridine–chloroform–ethanol, 2:1:1). IR spectrum, ν, cm^{-1}: 1620 (C=N), 3150 (NH). Found, %: C 50.40; H 4.96; N 24.18; S 9.02. $C_{15}H_{18}N_6O_2S$. Calculated, %: C 50.21; H 5.02; N 24.24; S 9.24.

X-ray Crystallographic Study of Compound 8. The unit cell parameters and the intensities of 2457 independent reflexions were measured on a Hilger-Watts four-circle automatic diffractometer (λMoKα, θ/2θ scanning, graphite monochromator, θ_{max} = 28°). The crystals were monoclinic: a = 8.900(1), b = 20.594(2), c = 8.954(1) Å; β = 93.35(1)°; V = 1638 Å^3; M = 346.4; d_{calc} = 1.40 g/cm^3; Z = 4; space group $P2_1/a$. The

structure was solved by direct methods and refined by block-diagonal RMS in the anisotropic approximation for non-hydrogen atoms. The positions of the hydrogen atoms were found from a difference Fourier synthesis and refined by disperse in the isotropic approximation with B_{iso} = 5 Å^2. The final residual factors were R = 0.042 and R_w = 0.043 for 1997 reflexions with $I > 4\sigma$. Atomic coordinates are given in Table 1.

This work was carried out within the range of theme 96-999, financed from the state budget of the Republic of Armenia.

REFERENCES

1. A. Sh. Oganisyan and A. S. Noravyan. *Khim. Geterotsikl. Soedin.,* 1388 (1998).
2. A. Sh. Oganisyan, A. S. Noravyan, and G. M. Avetisyan. *Khim. Geterotsikl. Soedin.,* 803 (1998).
3. A. A. Karapetyan, M. S. Alekasanyan, A. Sh. Oganisyan, and Yu. T. Struchkov. *Zh. Strukt. Khim.,* **35**, 197 (1994).
4. F. H. Allen and O. Kennard. *J. Chem. Soc., Perkin Trans. 2*, S1 (1987).
5. R. G. Gerr, A. I. Yanovskii, and Yu. T. Struchkov. *Kristallografiya*, **28**, 1029 (1983).