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CONDENSED THIENOPYRIMIDINES. 19*. STUDY OF THE HETEROCYCLIZATION OF 2-HYDRAZINO-6,6-DIMETHYL-5,6-DIHYDRO-8H-PYRANOTHIENO[2,3-*d*]PYRIMIDIN-4-ONE

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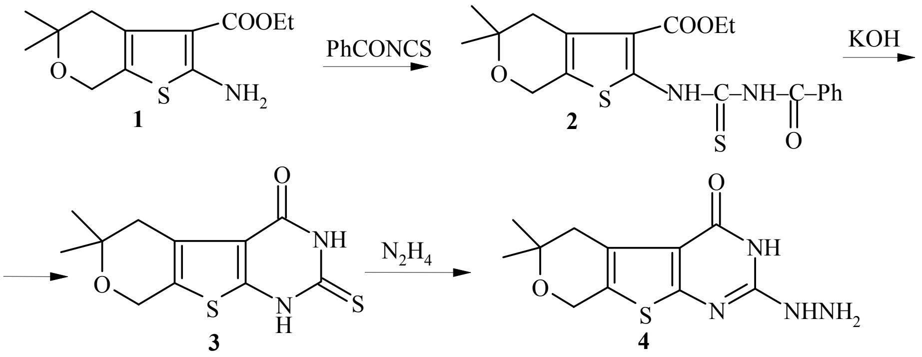
Novel condensed pyrano[4',3':4,5]thieno[3,2-e]triazolo[3,4-b]pyrimidine derivatives have been synthesized from 2-amino-3-carbethoxy-5,5-dimethyl-4,5-dihydro-7H-thieno[2,3-c]pyran.

Keywords: pyran, pyrimidine, thienopyrimidine, thienopyran, thiophene.

The synthesis of 2-amino-3-carbethoxy-5,5-dimethyl-4,5-dihydro-7H-thieno[2,3-*c*]pyran (**1**) has been reported in [2]. It serves as a starting material for the development of methods for preparing novel pyranothienopyrimidines, the structures of which have been identified by X-ray analysis.

The reaction of compound **1** [2] with benzoylisothiocyanate gave the corresponding 2-N'-thioureido derivative **2**. Treatment of the latter with an aqueous alcoholic solution of potassium hydroxide caused an intramolecular cyclization to give the 6,6-dimethyl-2-thioxo-5,6-dihydro-8H-pyrano[4',3':4,5]thieno[2,3-*d*]-pyrimidin-4-one (**3**). Condensation of this with concentrated hydrazine hydrate then gave the corresponding 2-hydrazino-substituted compound **4**.



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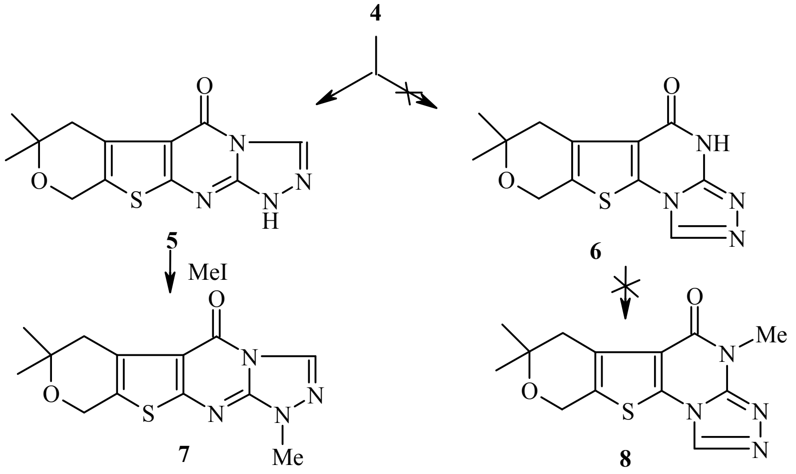
The heterocyclization of compound **4** with ethyl orthoformate gave a product which might be assigned the structure **5** or **6**. Alkylation of this product with methyl iodide gave an N-methyl derivative whose X-ray analysis proved that the structure corresponded to **7**.

The modest accuracy of the X-ray analytical data obtained did not permit a detailed discussion of the geometrical parameters but did allow us unambiguously to solve the problem of the structure of **7**.



The structure of the molecule of **7** is given in Fig. 1 together with the numbering for the non-hydrogen atoms and the bond lengths and the values of the valence angles are given in Table 2. Overall, they are in agreement with standard values and allow us to judge the nature of the valence bonds, i.e. to determine unambiguously the structure of compound studied.

The tetrahydropyran ring in **7** has the configuration of a distorted half-chair with the O(2) and C(3) atoms deviating from the mean square plane of the remaining ring atoms by -0.33 and 0.42 Å respectively. With the exception of the O(2) and C(3) atoms of the tetrahydropyran ring, the condensed tetracyclic system is essentially planar as might be expected (the greatest deviation from the mean square plane calculated for all of the atoms in the molecule besides O(2), C(3), C(17), and C(18) being -0.14 Å).

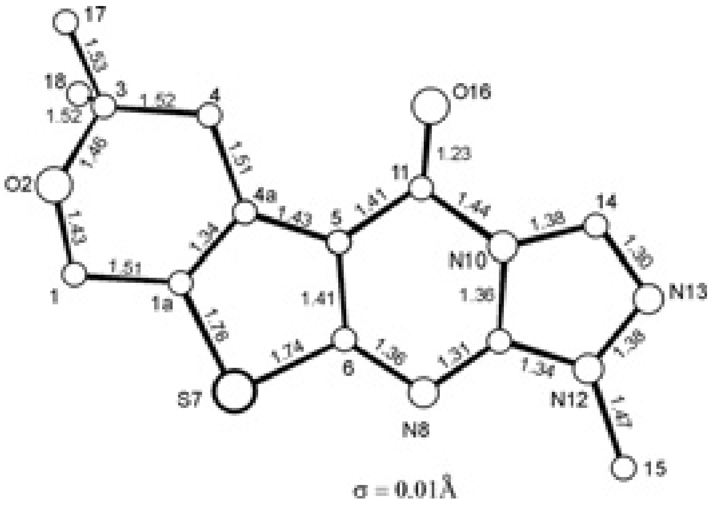


Fig. 1. Structure of the **7** molecule with bond lengths.

TABLE 1. Atomic Coordinates (×10^4) and Their Equivalent Thermal Parameters

Atom	*x/a*	*y/b*	*z/c*	B_{iso}	Atom	*x/a*	*y/b*	*z/c*	B_{iso}
C(1)	549(3)	1521(5)	2333(8)	2.0(2)	C(9)	-1389(3)	1195(5)	7472(8)	1.912(1)
O(2)	1149(2)	1112(3)	2724(5)	2.0(1)	N(10)	-861(2)	936(4)	8253(6)	1.3(1)
C(3)	1403(3)	1411(5)	4173(7)	1.8(2)	C(11)	-227(3)	939(5)	7640(8)	1.6(2)
C(4)	981(3)	1040(5)	5423(8)	1.7(2)	N(12)	-1869(3)	1100(5)	8420(6)	2.1(2)
C(4a)	285(3)	1222(5)	5071(8)	1.4(2)	N(13)	-1682(3)	758(5)	9794(7)	2.4(2)
C(5)	-236(3)	1206(5)	6114(7)	1.6(2)	C(14)	-1065(3)	666(6)	9664(8)	2.0(2)
C(6)	-822(3)	1442(5)	5429(7)	1.3(2)	C(15)	-2564(4)	1221(7)	8095(8)	3.1(2)
S(7)	-713(1)	1685(1)	3525(2)	1.8(1)	O(16)	218(2)	712(4)	8461(8)	2.1(2)
C(1a)	107(3)	1448(5)	3670(8)	1.7(2)	C(17)	1476(3)	2478(7)	4248(8)	2.5(2)
N(8)	-1411(2)	1465(4)	6069(6)	1.6(2)	C(18)	2053(3)	944(4)	4239(9)	2.3(2)

TABLE 2. Valence Angles ω (σ) (deg.)

Angle	ω(σ)	Angle	ω(σ)	Angle	ω(σ)
O(2)C(1)C(1a)	108.6(6)	C(4a)C(5)C(6)	112.3(6)	N(8)C(9)N(12)	127.3(7)
C(1)O(2)C(3)	114.7(5)	C(4a)C(5)C(11)	128.1(6)	N(10)C(9)N(12)	106.0(6)
O(2)C(3)C(4)	109.5(5)	C(6)C(5)C(11)	119.4(6)	C(9)N(10)C(11)	123.9(6)
O(2)C(3)C(17)	114.4(6)	C(5)C(6)S(7)	110.7(5)	C(9)N(10)C(14)	106.9(6)
O(2)C(3)C(18)	103.5(6)	C(5)C(6)N(8)	127.9(6)	C(11)N(10)C(14)	129.2(6)
C(4)C(3)C(17)	111.9(6)	S(7)C(6)N(8)	121.4(6)	C(5)C(11)N(10)	110.7(6)
C(4)C(3)C(18)	110.0(6)	C(1a)S(7)C(6)	91.1(3)	C(5)C(11)O(16)	130.9(6)
C(17)C(3)C(18)	110.2(6)	C(1)C(1a)C(4a)	125.3(6)	N(10)C(11)O(16)	118.4(6)
C(3)C(4)C(4a)	110.5(6)	C(1)C(1a)S(7)	121.9(5)	C(9)N(12)N(13)	111.5(6)
C(4)C(4a)C(1a)	120.1(6)	C(4a)C(1a)S(7)	112.8(5)	C(9)N(12)C(15)	127.8(6)
C(4)C(4a)C(5)	126.7(6)	C(6)N(8)C(9)	111.1(6)	N(13)N(12)C(14)	104.7(6)
C(1a)C(4a)C(5)	113.2(6)	N(8)C(9)N(10)	126.7(6)	N(13)N(12)C(15)	120.4(6)
				N(10)C(14)N(13)	111.0(6)

Hence we have shown that heterocyclization of the 2-hydrazino derivative **4** with ethyl orthoformate occurs regioselectively to give the product **5**.

EXPERIMENTAL

IR spectra were taken on a UR-20 instrument using vaseline oil and ^1H NMR spectra on a Varian Mercury 300 (300 MHz) instrument. TLC was performed on Silufol UV-254 plates and revealed using iodine vapor.

X-ray Analytical Investigation of Compound 7. Crystals of compound **7** were of low quality but suitable for X-ray analysis for this specific purpose. They were obtained by slow evaporation of an alcoholic solution.

Unit cell parameters and intensities of 1460 independent reflections were measured on a Syntex P2_1, four circle, automatic diffractometer at a temperature of -120°C (λMoKα, θ/2θ scanning, graphite monochromator, θ_{max} = 25°). Crystals rhombic: a = 20.953(4), b = 14.253(3), c = 8.898(1) Å; V = 2657.4(9) Å^3; Z = 8; d_{calc} = 1.451 g/cm^3; space group *Pccn*.

The structure was solved by a direct method and refined in block diagonal least squares analysis in the anisotropic approximation for non-hydrogen atoms. The positions of all the H-atoms were revealed in electron density difference synthesis and included in the refinement with fixed isotropic parameters $B_{\text{iso}} = 5$ Å^2. All calculations were carried out on an IBM Eclipse-S/200 with the INEXTL program [3].

The final values for the difference factors were $R = 0.080$ and $R_w = 0.065$ for 1248 reflections with $I > 7\sigma(I)$. The atomic coordinates are given in Table 1.

2-(N'-Benzoylthioureido)-3-carbethoxy-5,5-dimethyl-4,5-dihydro-7H-thieno[2,3-*c*]pyran (2). Benzoyl isothiocyanate (1.6 g, 10 mmol) was added with stirring to a solution of compound **1** [2] (2.55 g, 10 mmol) in methanol (40 ml). Stirring was continued for 3 h. The precipitated crystals were filtered off and washed with ether to give the product **2** (3.7 g, 90%); mp 208-210°C (pyridine), R_f 0.65 (acetone–hexane, 1:2). IR spectrum (thin film), ν, cm^{-1}: 1680 (amide C=O), 1710 (C=O), 3250-3350 (NH). ^{1}H NMR spectrum (pyridine-d$_5$), δ, ppm (*J*, Hz): 9.15 (1H, s, HNCO); 7.35-8.20 (6H, m, C_6H_5, NHCS); 4.76 (2H, s, 7,7-H_2); 4.50 (2H, q, $J = 7$, $\underline{CH_2}CH_3$); 2.96 (2H, s, 4,4-H_2); 1.36 (3H, t, $J = 7$, $CH_2\underline{CH_3}$); 1.30 (6H, s, 5,5-$(CH_3)_2$). Found, %: C 57.38; H 5.22; N 6.70; S 15.38. $C_{20}H_{22}N_2O_4S_2$. Calculated, %: C 57.41; H 5.26; N 6.69; S 15.31.

6,6-Dimethyl-2-thioxo-5,6-dihydro-8H-pyrano[4',3':4,5]thieno[2,3-*d*]pyrimidin-4-one (3). A mixture of compound **2** (4.18 g, 10 mmol), potassium hydroxide (1.12 g, 0.02 mol), and aqueous alcohol (50%, 50 ml) was refluxed for 2 h. After cooling, the reaction mixture was acidified with a 10% solution of hydrochloric acid to a weakly acidic reaction. The precipitated crystals were filtered off, washed with water, and dried to give the product **3** (2.4 g, 92.1%); mp 288-290°C (pyridine), R_f 0.47 (chloroform–pyridine, 1:1). IR spectrum (thin film), ν, cm^{-1}: 1690 (C=O), 3400-3420 (NH). Found, %: C 49.28; H 4.32; N 10.39; S 23.93. $C_{11}H_{12}N_2O_2S_2$. Calculated, %: C 49.25; H 4.47; N 10.44; S 23.88.

2-Hydrazino-6,6-dimethyl-5,6-dihydro-8H-pyrano[4',3':4,5]thieno[2,3-*d*]pyrimidin-4-one (4). A mixture of compound **3** (2.68 g, 10 mmol), concentrated hydrazine hydrate (5 ml), and butanol (20 ml) was refluxed for 8 h and then held for ~16 h at room temperature. The precipitated crystals were washed with water and dried to give the product **4** (2 g, 75.5%); mp 308-310°C (butanol), R_f 0.50 (hexane–ethyl acetate, 1:2). IR Spectrum (thin film), ν, cm^{-1}: 1700 (C=O), 3200-3400 ($NHNH_2$). ^{1}H NMR spectrum (pyridine-d$_5$), δ, ppm: 10.8 (1H, s, 3-NH); 5.70 (1H, s, $\underline{NH}NH_2$); 4.40 (4H, s, 8,8-H_2, $NH\underline{NH_2}$); 2.85 (2H, s, 5,5-H_2); 1.18 (6H, s, 6,6-$(CH_3)_2$). Found, %: C 49.52; H 5.18; N 21.13; S 12.09. $C_{11}H_{14}N_4O_2S$. Calculated, %: C 49.62; H 5.26; N 21.05; S 12.03.

7,7-Dimethyl-6,7-dihydro-9H-pyrano[4',3':4,5]thieno[3,2-*e*]triazolo[3,4-*b*]pyrimidin-5-one (5). A mixture of compound **4** (2.66 g, 10 mmol) and ethyl orthoformate (10 ml) was refluxed for 8 h and then held for ~16 h at room temperature. The precipitated crystals were filtered off, washed with ether, and dried to give the product **5** (2.2 g, 75.8%); mp 298-300°C (pyridine), R_f 0.48 (hexane–ethyl acetate–pyridine, 2:1:1). IR spectrum (thin film), ν, cm^{-1}: 1690 (C=O); 3100-3150 (NH). ^{1}H NMR spectrum (pyridine-d$_5$), δ, ppm: 10.4 (1H, s, NH); 9.20 (1H, s, 3-H); 4.42 (2H, s, 9,9-H_2); 2.82 (1H, s, 6,6-H_2); 1.20 (6H, s, 7,7-$(CH_3)_2$). Found, %: C 52.11; H 4.22; N 20.34; S 11.70. $C_{12}H_{12}N_4O_2S$. Calculated, %: C 52,17; H 4.34; N 20.28; S 11.59.

1,7,7-Trimethyl-6,7-dihydro-9H-pyrano[4',3':4,5]thieno[3,2-*e*]triazolo[3,4-*b*]pyrimidin-5-one (7). A mixture of compound **5** (2.76 g, 10 mmol), methyl iodide (1.41 g, 0.01 mol), potassium carbonate (2 g), and methyl ethyl ketone (50 ml) was refluxed for 18 h. The residue after distillation of solvent was washed with water and the precipitated crystals were filtered off and washed with ether to give the product **7** (2 g, 70.0%); mp 211-212°C (ethanol), R_f 0.68 (hexane–ethanol–ethyl acetate, 1:1:1). ^{1}H NMR spectrum (pyridine-d$_5$), δ, ppm: 8.95 (1H, s, 3-H); 4.50 (2H, s, 9,9-H_2); 3.40 (3H, s, 1-CH_3); 2.80 (1H, s, 6,6-H_2); 1.20 (6H, s, 7,7-$(CH_3)_2$). Found, %: C 53.81; H 4.71; N 19.52; S 10.80. $C_{13}H_{14}N_4O_2S$. Calculated, %: C 53.79; H 4.82; N 19.31; S 11.03.

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