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CRYSTAL AND MOLECULAR STRUCTURE OF 2H- AND 2-(*p*-TOLYLAMINO)-5,6-DIMETHYLTHIENO[2,3-*d*]PYRIMIDIN-4-ONES

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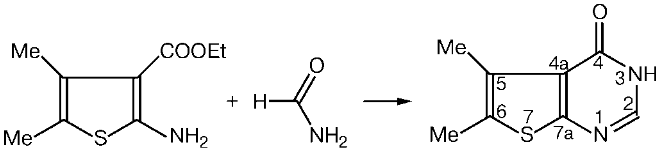
The crystal and molecular structure of 2H- and 2-(p-tolylamino)-5,6-dimethylthieno[2,3-d]pyrimidin-4-ones was investigated by X-ray diffraction. In crystals, the tautomeric form with a localized N(1)=C(2) bond is realized. A comparative analysis of the two structures using the literature data is given to examine the conjugation effect on the geometrical parameters of a pseudoaromatic pyrimidine system.

INTRODUCTION

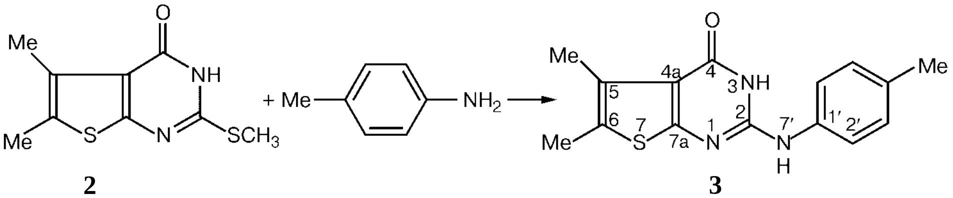
2H-5,6-dimethylthieno[2,3-*d*]pyrimidin-4-one (**1**) and its substituted derivatives, especially those with a heteroatom (oxygen, sulfur, selenium, or amino group) at carbon in the 2 position, may exist in several tautomeric forms. Thus compound **1** exists as three tautomeric forms resulting from migration of the hydrogen atom from N(3) to N(1) or to oxygen at C(4). For this compound, alkylations occur at either N(1) or N(3) atoms, or simultaneously at N(1) and at oxygen bonded to C(4) [1-3]. Therefore it is interesting to determine the tautomeric form of the compound and examine the solid-state methylation reaction.

Compound **1** was synthesized from ethyl 2-amino-4,5-dimethylthiophene-2-carboxylic ether and formamide according to the following scheme:



1

2-(*p*-Tolylamino)-5,6-dimethylthieno[2,3-*d*]pyrimidin-4-one (**2**) has one more arylamino group compared to **1**; due to this, the number of possible tautomeric forms increases to five. Compound **2** was prepared by nucleophilic substitution of the methylthio group of 2-methylthio-5,6-dimethylthieno[2,3-*d*]pyrimidin-4-one (**3**) by *p*-toluidine according to the scheme:



2 **3**

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Compound **3**, in turn, was obtained by alkylation of 2-thioxo-5,6-dimethylthieno[2,3-*d*]pyrimidin-4-one by methyl iodide.

EXPERIMENTAL

Syntheses of parent compounds. *5,6-Dimethylthieno[2,3-d]pyrimidin-4-one.* A suspension of ethyl 2-amino-4,5-dimethylthiophene-3-carboxylic ether (1.0 g, 5 mmol) and formamide (2 ml, 20 mmol) was heated on an oil bath at 120-130°C for 2 h. Then the mixture was cooled and the precipitate was washed with water and dried. Recrystallization form alcohol gave 0.6 g (60%) of a substance with T_m = 267-268°C, R_f = 0.3 (Silufol, acetone:benzene = 1:3).

An analogous procedure with formamide replaced by ammonium rhodanide gave 2-thioxo-5,6-dimethylthieno[2,3-*d*]pyrimidinone-4 with T_m = 313-315°C, R_f = 0.45 (Silufol, acetone:benzene = 1:3).

Methylation of 2-thioxo-5,6-dimethylthieno[2,3-*d*]pyrimidin-4-one in the presence of methyl iodide afforded 2-methylthio-5,6-dimethylthieno[2,3-*d*]pyrimidinone-4 (yield 40%).

2-(p-Tolylamino)-5,6-dimethylthieno[2,3-d]pyrimidin-4-one. A suspension of 2-methylthio-5,6-dimethylthieno[2,3-*d*]pyrimidin-4-one (1.0 g, 5 mmol) and *p*-toluidine (1.0 g, 10 mmol) was heated on an oil bath at 200-220 °C for 4 h. The reaction mixture was treated with hot water, filtered, and dried. The precipitate was dissolved in a 2% solution of alkali. The residue was filtered off, washed with water, and dried. This gave 0.6 g (60%) of a substance with T_m = 298-300°C (acetone), R_f = 0.61 (Silufol, acetone:benzene = 1:3).

X-ray diffraction analysis. The cell parameters and the space group of crystals **1** and **2** were determined and refined on a Siemens P3 diffractometer. Table 1 lists the main experimental and calculated data. The intensity data were collected on the same diffractometer (θ/2θ scan mode, MoK_α radiation, graphite monochromator).

The structures were solved by direct methods (SHELX-86 [4], on-line mode). The structure refinement was performed by the least-squares method in sequential isotropic-anisotropic approximation using SHELXL-93 [5] for

TABLE 1. Selected Crystal Data and Characteristics of X-Ray Diffraction Experiment for Molecules **1** and **2**

Parameter	**1**	**2**
a, Å	11.090(2)	19.624(5)
b, Å	6.863(1)	26.621(7)
c, Å	11.419(2)	14.146(5)
V, Å^3	821.2(3)	5759(3)
d_{calc}, g/cm^3	1.458	1.316
α, deg	90.0	90.0
β, deg	109.11(3)	128.80(2)
γ, deg	90.0	90.0
Space group	$P2_1/n$, $Z = 4$	$C2/c$, $Z = 16$
No. of reflections	1446 ($I > 0$), 1344 ($I > 2\sigma$)	3641 ($I > 0$), 2510 ($I > 2\sigma$)
$R[I > 2\sigma(I)]$ index	R_1 = 0.0430, wR_2 = 0.1235	R_1 = 0.0336, wR_2 = 0.0902
R (all data)	R_1 = 0.0458, wR_2 = 0.1442	R_1 = 0.0679, wR_2 = 0.0964

TABLE 2. Coordinates (×10^4) and Equivalent Isotropic Thermal Parameters $U = 1/3(U_{11} + U_{22} + U_{33})$ (Å^2×10^3) of Nonhydrogen Atoms in **1**

Atom	*x*/*a*	*y*/*b*	*z*/*c*	*U*
1	2	3	4	5
O(1)	5195(1)	–3670(2)	1334(1)	43(1)
N(1)	2708(1)	40(2)	–1130(1)	40(1)
C(2)	3090(2)	–1629(2)	–1421(2)	39(1)
N(3)	3898(1)	–2858(2)	–609(1)	35(1)

TABLE 2 (Continued)

1	2	3	4	5
C(4)	4441(2)	–2498(2)	654(1)	32(1)
C(4a)	4033(1)	–674(2)	1022(1)	31(1)
C(5)	4395(1)	195(2)	2233(1)	34(1)
C(6)	3849(2)	1988(2)	2196(2)	38(1)
S(7)	2876(1)	2618(1)	716(1)	42(1)
C(7a)	3209(1)	458(2)	107(1)	34(1)
C(8)	5261(2)	–734(3)	3389(2)	47(1)
C(9)	4019(2)	3405(3)	3240(2)	56(1)

TABLE 3. Coordinates ($\times 10^4$) and Equivalent Isotropic Thermal Parameters $U = 1/3(U_{11} + U_{22} + U_{33})$ ($\text{Å}^2 \times 10^3$) of Nonhydrogen Atoms in **2**

Atom	Molecule **2B**				Molecule **2A**			
	x/*a*	*y*/*b*	*z*/*c*	*U*	*x*/*a*	*y*/*b*	*z*/*c*	*U*
O(1)	5589(1)	–3926(1)	9219(2)	55(1)	6787(1)	–3315(1)	7961(2)	60(1)
N(1)	3697(1)	–5030(1)	7553(2)	42(1)	6045(1)	–2163(1)	9074(2)	46(1)
C(2)	3538(2)	–4549(1)	7381(2)	42(1)	5890(2)	–2637(1)	9111(2)	43(1)
N(3)	4190(1)	–4192(1)	7976(2)	45(1)	6158(1)	–3018(1)	8755(2)	49(1)
C(4)	5075(2)	–4288(1)	8783(2)	42(1)	6607(2)	–2947(1)	8312(2)	46(1)
C(4a)	5270(1)	–4815(1)	8994(2)	37(1)	6808(1)	–2435(1)	8283(2)	41(1)
C(5)	6097(2)	–5066(1)	9757(2)	43(1)	7274(2)	–2226(1)	7898(2)	46(1)
C(6)	6004(2)	–5573(1)	9687(2)	50(1)	7305(2)	–1716(1)	7977(2)	52(1)
S(7)	4911(1)	–5756(1)	8709(1)	51(1)	6774(1)	–1482(1)	8515(1)	56(1)
C(7a)	4559(2)	–5141(1)	8355(2)	39(1)	6497(2)	–2081(1)	8648(2)	42(1)
C(8)	6964(2)	–4805(1)	10557(2)	62(1)	7663(2)	–2536(1)	7462(2)	63(1)
C(9)	6701(2)	–5970(1)	10315(3)	80(1)	7709(2)	–1356(1)	7640(3)	75(1)
C(1′)	1918(2)	–4580(1)	5779(2)	49(1)	5058(2)	–2537(1)	9902(2)	49(1)
C(2′)	1780(2)	–5092(1)	5602(2)	59(1)	4919(2)	–2024(1)	9779(3)	61(1)
C(3′)	943(2)	–5271(1)	4722(3)	72(1)	4503(2)	–1800(1)	10174(3)	75(1)
C(4′)	228(2)	–4963(2)	3995(3)	73(1)	4212(2)	–2067(1)	10696(3)	74(1)
C(5′)	379(2)	–4452(2)	4185(3)	76(1)	4365(2)	–2573(1)	10827(3)	80(1)
C(6′)	1199(2)	–4263(1)	5047(3)	65(1)	4780(2)	–2809(1)	10435(3)	68(1)
N(7′)	2725(1)	–4353(1)	6615(2)	55(1)	5449(1)	–2806(1)	9507(2)	52(1)
C(8′)	–678(2)	–5171(2)	3040(3)	106(1)	3739(3)	–1812(2)	11108(4)	115(1)

nonhydrogen atoms. The H atoms at the heteroatoms N(2) and N(3) were located on difference Fourier maps. The H atoms bonded to the carbon atoms were placed geometrically using the riding model and refined isotropically. The coordinates of the basic atoms obtained in the last cycle of the least-squares refinement are listed in Tables 2 and 3.

DISCUSSION OF RESULTS

The spatial structure of molecules **1** and **2** obtained by X-ray diffraction analysis is shown in Figs. 1 and 2. The independent part of the unit cell of crystal **2** has two molecules. The geometrical parameters of the molecules (bond lengths and angles) are given in Tables 4 and 5.

Analysis of the valence heterobond lengths (Tables 4 and 5) and the experimental positions of H atoms shows that molecules **1** and **2** in crystal exist in tautomeric forms corresponding to the above structural formulas.

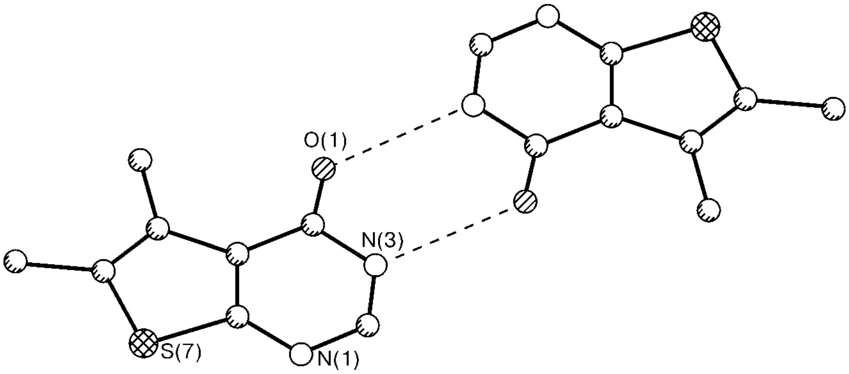

Fig. 1. Spatial structure and H-bonding in the packing of molecule **1** (the numbering is given for some atoms of the basic molecule).

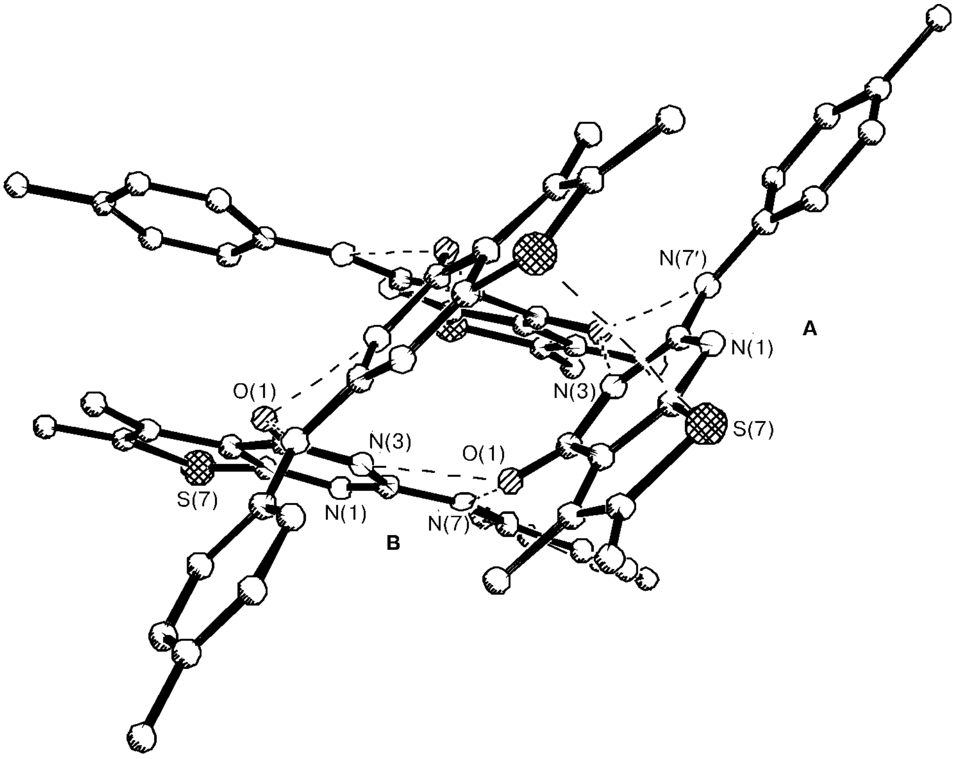

Fig. 2. Spatial structure and the fragment of packing demonstrating the island character of H-bonds in the crystal structure of **2** (basic molecules **A** and **B**).

The pyrimidothiophene nucleus of both molecules and the benzene ring of the toluidine residue in **2** are planar within ±0.015 Å. The minor (up to ±0.08 Å) deviations of the methyl groups at C5 and C6 from the plane of the pyrimidothiophene nucleus seems to be the result of steric hindrances, the anisotropy of the thermal vibrations of atoms, and molecular packing.

In the structure of **2**, the arrangement of the aromatic ring relative to the bicyclic system is of interest from stereochemical viewpoint. The crystallographically independent molecules **2A** and **2B** (Fig. 2) do not differ essentially by appearance, and the benzene ring bonded via the N(7′) atom is virtually coplanar with the pyrimidothiophene nucleus. This is indicated by the values of the torsion angles N(3)–C(2)–N(7′)–C(1′) [–172.9° (**2A**), –177.9° (**2B**)] and C(2)–N(7′)–C(1′)–C(2′) [3.5° (**2A**), 11.3° (**2B**)] defining the arrangement of the aromatic ring.

TABLE 4. Bond Lengths (*d*) and Angles (ω) in **1**

Bond	*d*, Å	Angle	ω, deg	Angle	ω, deg
O(1)–C(4)	1.235(2)	C(2)–N(1)–C(7a)	113.10(13)	C(6)–C(5)–C(8)	124.1(2)
N(1)–C(2)	1.302(2)	N(1)–C(2)–N(3)	124.85(14)	C(4a)–C(5)–C(8)	124.6(2)
N(1)–C(7a)	1.368(2)	C(2)–N(3)–C(4)	124.37(13)	C(5)–C(6)–C(9)	128.3(2)
C(2)–N(3)	1.353(2)	O(1)–C(4)–N(3)	120.74(14)	C(5)–C(6)–S(7)	112.48(12)
N(3)–C(4)	1.391(2)	O(1)–C(4)–C(4a)	126.49(14)	C(9)–C(6)–S(7)	119.21(13)
C(4)–C(4a)	1.440(2)	N(3)–C(4)–C(4a)	112.76(13)	C(7a)–S(7)–C(6)	91.78(7)
C(4a)–C(7a)	1.381(2)	C(7a)–C(4a)–C(5)	113.67(14)	N(1)–C(7a)–C(4a)	127.4(2)
C(4a)–C(5)	1.437(2)	C(7a)–C(4a)–C(4)	117.48(14)	N(1)–C(7a)–S(7)	121.81(12)
C(5)–C(6)	1.366(2)	C(5)–C(4a)–C(4)	128.83(14)	C(4a)–C(7a)–S(7)	110.75(12)
C(5)–C(8)	1.497(2)	C(6)–C(5)–C(4a)	111.30(14)		
C(6)–C(9)	1.502(2)				
C(6)–S(7)	1.736(2)				
S(7)–C(7a)	1.728(2)				

TABLE 5. Bond Lengths (*d*) and Angles (ω) in **2**

Bond	*d*, Å		Bond	*d*, Å	
	2A	**2B**		**2A**	**2B**
O(1)–C(4)	1.242(3)	1.245(3)	C(6)–C(9)	1.502(4)	1.500(3)
N(1)–C(2)	1.305(3)	1.307(3)	C(6)–S(7)	1.742(3)	1.747(3)
N(1)–C(7a)	1.353(3)	1.366(3)	S(7)–C(7a)	1.725(2)	1.733(2)
C(2)–N(7′)	1.352(3)	1.369(3)	C(1′)–C(2′)	1.381(3)	1.380(3)
C(2)–N(3)	1.378(3)	1.375(3)	C(1′)–N(7′)	1.387(3)	1.383(4)
N(3)–C(4)	1.379(3)	1.378(3)	C(1′)–C(6′)	1.394(3)	1.395(3)
C(4)–C(4a)	1.436(3)	1.426(3)	C(2′)–C(3′)	1.383(4)	1.381(4)
C(4a)–C(7a)	1.392(3)	1.387(3)	C(3′)–C(4′)	1.376(4)	1.381(4)
C(4a)–C(5)	1.432(3)	1.438(3)	C(4′)–C(5′)	1.382(5)	1.367(4)
C(5)–C(6)	1.358(3)	1.360(3)	C(4′)–C(8′)	1.511(4)	1.528(4)
C(5)–C(8)	1.497(3)	1.494(3)	C(5′)–C(6′)	1.368(4)	1.388(4)
Angle	ω, deg		Angle	ω, deg	
	2A	**2B**		**2A**	**2B**
C(2)–N(1)–C(7a)	113.4(2)	113.8(2)	C(9)–C(6)–S(7)	118.9(2)	119.3(2)
N(1)–C(2)–N(7′)	123.6(2)	123.8(2)	C(7a)–S(7)–C(6)	91.9(1)	91.8(1)
N(1)–C(2)–N(3)	122.8(2)	123.1(2)	N(1)–C(7a)–C(4a)	128.7(2)	127.9(2)
N(7′)–C(2)–N(3)	113.6(2)	113.1(2)	N(1)–C(7a)–S(7)	120.9(2)	121.9(2)
C(2)–N(3)–C(4)	125.7(2)	124.4(2)	C(4a)–C(7a)–S(7)	110.4(2)	110.2(2)
O(1)–C(4)–N(3)	118.6(2)	119.7(2)	C(2′)–C(1′)–N(7′)	125.1(2)	125.0(2)
O(1)–C(4)–C(4a)	128.7(2)	126.0(2)	C(2′)–C(1′)–C(6′)	118.0(2)	118.1(3)
N(3)–C(4)–C(4a)	112.7(2)	114.3(2)	N(7′)–C(1′)–C(6′)	116.9(2)	116.9(2)
C(7a)–C(4a)–C(5)	113.6(2)	114.2(2)	C(1′)–C(2′)–C(3′)	119.4(3)	119.9(3)
C(7a)–C(4a)–C(4)	116.6(2)	116.4(2)	C(4′)–C(3′)–C(2′)	123.1(3)	122.7(3)
C(5)–C(4a)–C(4)	129.8(2)	129.3(2)	C(3′)–C(4′)–C(5′)	116.5(3)	116.8(3)
C(6)–C(5)–C(4a)	111.8(2)	111.2(2)	C(3′)–C(4′)–C(8′)	121.9(4)	121.8(3)
C(6)–C(5)–C(8)	123.6(2)	125.2(2)	C(5′)–C(4′)–C(8′)	121.6(3)	121.4(3)
C(4a)–C(5)–C(8)	124.6(2)	123.6(2)	C(6′)–C(5′)–C(4′)	121.7(3)	121.8(3)
C(5)–C(6)–C(9)	128.8(2)	128.1(2)	C(5′)–C(6′)–C(1′)	121.2(3)	120.8(3)
C(5)–C(6)–S(7)	112.3(2)	112.6(2)	C(2)–N(7′)–C(1′)	131.1(2)	129.9(2)

Analysis of data in Tables 4 and 5 indicates that the S(7)–C(7a) and C(5)–C(6) bonds are slightly shorter than the analogous bonds S(7)–C(6) and C(4a)–C(7a) arranged symmetrically in the thiophene ring. The S(7)–C(7a) and C(5)–C(6) bond lengths averaged over the three X-ray structures (**1**, **2A**, and **2B**) are 1.729 and 1.361 Å, respectively. The S(7)–C(6) and C(4a)–C(7a) bonds arranged symmetrically relative to the above bonds are 1.742 and 1.387 Å, although for "ideal" thiophene, spectroscopic studies [6] showed that S–C is 1.714 Å and C=C is 1.370 Å. The loss of symmetry found for the bond lengths of the thiophene ring may be explained by the effect of the π-electrons of the N(1)=C(2) bond on the heteroaromatic system. The analogous tendency of bond length variation in the thiophene ring with a loss of symmetry in the thiophene ring is also observed in related pyrimidothiophene-containing compounds [7, 8] (Cambridge Structural Database, March, 2000). Another evidence in support of this assumption is lengthening (to 1.307 Å) of the formal double bond N(1)=C(2) with respect to the N=C bonds of 1.265 Å [9], which is observed, for example, in quinazolone alkaloids containing an analogous pyrimidine heterocycle [10, 11].

In **1** and **2**, the N(3) atom is sp^2-hybridized and hence its lone electron pair is simultaneously involved in conjugation with the π-electrons of the C(4)=O and N(1)=C(2) bonds. A consequence of this is pronounced lengthening of the C=O bond to 1.245 Å, which is less pronounced in pyrimidothiophene-containing compounds (1.225 Å) [7, 8] and polymethylene quinazolones (1.211 Å) [10]. In crystals **1** and **2**, the lengthening of the ketone bond may be the result of the action of the intermolecular H-bond involving the C=O group and having an island structure (see below); this was not noted for the packing of the compounds compared above [7, 8, 10].

As opposed to **1**, structure **2** has a *p*-toluidine fragment in the C(2) position. The N(7′) atom is sp^2-hybridized and has a lone electron pair available for conjugation. The participation of the N(7′) atom in conjugation in **2** provides a competing direction for point C(2), due to which C(2)–N(3) is lengthened (to 1.377 Å) compared to the values observed for **1** (1.353 Å). The conjugation between the C=O bond and the lone electron pair of N(3) is strengthened, shortening the N(3)–C(4) bond to 1.379 Å (vs 1.391 Å in **1**).

Analysis of intermolecular contacts (Fig. 1) shows that in crystal **1** the molecules related by the symmetry center due to the N–H...O type H-bond form islands with the distances N(3)...O(1) 2.81 and N(3)H...O(1) 1.99 Å and the angle N(3)–H...O 177°. In crystal, the islands are separated by the distances typical of van der Waals interactions. Molecules **2** also form islands due to N–H...O type H-bonds in crystal (Fig. 2). Island formation, however, involves four molecules: two molecules in the initial position and two molecules transformed by the twofold symmetry axis and approaching the basic molecules (Fig. 2). The geometrical parameters of these intermolecular H-bonds are as follows: the distances O(1)**A**...N(3)**B** 2.90 and O(1)**A**...H(3) 2.08 Å and the angle O–H–N 161°; the distances O(1)**A**...N(7′)**B** 3.05 and O(1)**A**...H(7′) 2.24 Å and the angle O–H–N 156°; the distances O(1)**B**...N(3)**A** 2.77 and O(1)**B**...H(3) 1.96 Å and the angle O–H–N 157°; the distances O(1)**B**...N(7′)**A** 2.90 and O(1)**A**...H(7′) 2.06 Å and the angle O–H–N 155°.

CONCLUSIONS

X-ray diffraction analysis of 2H- and 2-(*p*-tolylamino)-5,6-dimethylthieno[2,3-*d*]pyrimidin-4-ones indicated that a tautomeric form with an N(1)=C(2) bond is realized in their structures. In **1** and **2**, associates of two (1) and four (2) molecules are formed by means of intermolecular H-bonds.

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