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Cocrystals of 6-propyl-2-thiouracil: N—H···O *versus* N—H···S hydrogen bonds

Maya Tutughamiarso and Ernst Egert*

Institut für Organische Chemie und Chemische Biologie, Goethe-Universität Frankfurt, Max-von-Laue-Strasse 7, 60438 Frankfurt am Main, Germany
Correspondence e-mail: egert@chemie.uni-frankfurt.de

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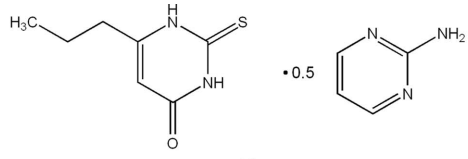
In order to investigate the relative stability of N—H···O and N—H···S hydrogen bonds, we cocrystallized the antithyroid drug 6-propyl-2-thiouracil with two complementary heterocycles. In the cocrystal pyrimidin-2-amine–6-propyl-2-thiouracil (1/2), $C_4H_5N_3{\cdot}2C_7H_{10}N_2OS$, (I), the 'base pair' is connected by one N—H···S and one N—H···N hydrogen bond. Homodimers of 6-propyl-2-thiouracil linked by two N—H···S hydrogen bonds are observed in the cocrystal *N*-(6-acetamidopyridin-2-yl)acetamide–6-propyl-2-thiouracil (1/2), $C_9H_{11}N_3O_2{\cdot}2C_7H_{10}N_2OS$, (II). The crystal structure of 6-propyl-2-thiouracil itself, $C_7H_{10}N_2OS$, (III), is stabilized by pairwise N—H···O and N—H···S hydrogen bonds. In all three structures, N—H···S hydrogen bonds occur only within $R_2^2(8)$ patterns, whereas N—H···O hydrogen bonds tend to connect the homo- and heterodimers into extended networks. In agreement with related structures, the hydrogen-bonding capability of C=O and C=S groups seems to be comparable.

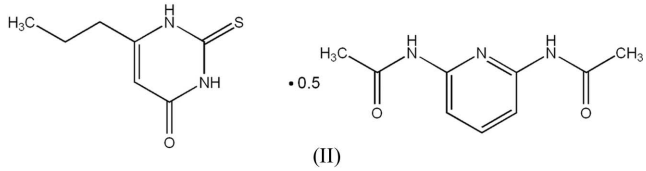
Comment

Hydrogen-bond interactions with an S atom as an acceptor are important in biological processes. For example, sulfur-containing nucleosides are components of the anticodon of transfer RNAs. They exhibit the same arrangement of hydrogen-donor and -acceptor groups as unmodified nucleosides, but the replacement of an O with an S atom induces changes in their properties and interactions. The thio residue can be selectively photoactivated, so that it is used as an intrinsic photolabel to probe the nucleic acid structure and to identify interactions within nucleic acids or between nucleic acids and proteins (Favre *et al.*, 1998). Furthermore, the enhanced base-pairing specificity of thionucleosides can be utilized, for example, in the design of antisense oligonucleotides (Testa *et al.*, 1999).

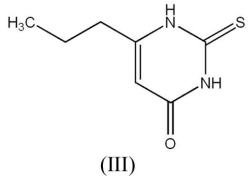
Because of its reduced electronegativity, an S atom should be a weaker hydrogen-bond acceptor than an O atom. Many theoretical and experimental investigations have been concerned with the stability of the N—H···O and the N—H···S hydrogen bonds, but no clear trend has emerged. *Ab initio* energy calculations (Šponer *et al.*, 1997; Basilio Janke *et al.*, 2001) and a study of the thermodynamics of RNA duplexes containing thiouridine (Testa *et al.*, 1999) showed that a base pair connected by an N—H···O hydrogen bond is more stable than that connected by an N—H···S hydrogen bond. In the case of 2-thiouridine, the Watson–Crick base pair with adenine, which is connected by an N—H···O hydrogen bond, is preferred over the wobble base pair with guanine, which is linked by an N—H···S hydrogen bond. In contrast, 4-thiouridine increases the stability of the wobble base pair compared with the Watson–Crick base pairing. However, the IR spectroscopic red shift of the N—H stretching frequency indicated that N—H···S is comparable or even stronger than the N—H···O interaction (Lautié & Novak, 1980; Biswal & Wategaonkar, 2009).



(I)



(II)



(III)

In order to study the stability of the N—H···S hydrogen bond in the presence of a competitive carbonyl O atom as an acceptor, we cocrystallized pyrimidin-2-amine and *N*-(6-acetamidopyridin-2-yl)acetamide, respectively, with the antithyroid drug 6-propyl-2-thiouracil, also known as propylthiouracil. It inhibits the synthesis of thyroid hormones and has been used for the treatment of hyperthyroidism caused by Graves' disease (Cooper, 2005). Because of its risk of serious liver injury, 6-propyl-2-thiouracil is used as a second-line drug for patients who are intolerant of other therapies (Bahn *et al.*, 2009).

We chose pyrimidin-2-amine because of its adjacent amine and imine groups resembling the donor–acceptor site of adenine. Since it has a mirror plane bisecting the molecule along the C—NH_2 bond, one pyrimidin-2-amine molecule may be hydrogen bonded to two 6-propyl-2-thiouracil molecules. Indeed, the asymmetric unit of cocrystal (I), namely pyrimidin-2-amine–6-propyl-2-thiouracil (1/2), contains two 6-propyl-2-thiouracil molecules and one pyrimidin-2-amine molecule (Fig. 1). The plane of the pyrimidin-2-amine mol-

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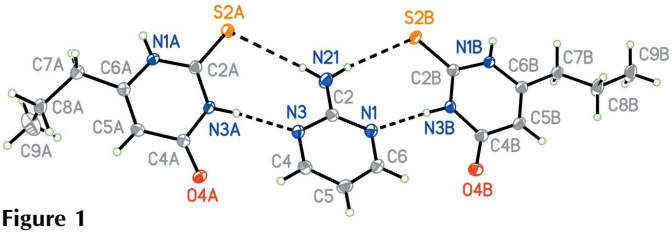

Figure 1
A perspective view of (I), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. Dashed lines indicate hydrogen bonds.

ecule forms dihedral angles of 17.1 (1) and 10.6 (1)° with those of the thiouracil rings of molecules *A* and *B*, respectively. Different propyl side-chain conformations are observed: in molecule *A*, methyl C atom C9*A* and thiouracil ring atom C6*A* are synclinal, with the C8*A*—C9*A* bond almost perpendicular to the plane of the ring, while in molecule *B* they are antiperiplanar, with a dihedral angle of 32.7 (2)° between the plane of the thiouracil ring and the plane through the side chain (Table 1). Each 6-propyl-2-thiouracil molecule is hydrogen bonded to the pyrimidin-2-amine molecule by an $R_2^2(8)$ motif (Bernstein *et al.*, 1995) characterized by one N—H···S and one N—H···N hydrogen bond. The O atoms participate in N—H···O interactions (Table 2) connecting the 6-propyl-2-thiouracil molecules into *C*(6) chains running along the *b* axis. The packing of (I) shows layers parallel to (101) containing circular arrangements of four adjacent trimeric units with an $R_8^8(34)$ hydrogen-bond pattern (Fig. 2).

Its participation in the 'base pairing' of (I) suggests that the S atom competes as an acceptor with the O atom. Hence, we were also interested in whether both S and O atoms can be hydrogen bonded simultaneously to a complementary molecule. Since 6-propyl-2-thiouracil possesses an acceptor–donor–acceptor site, we cocrystallized it with *N*-(6-acetamidopyridin-2-yl)acetamide, which exhibits a donor–acceptor–donor site.

Cocrystal (II), namely *N*-(6-acetamidopyridin-2-yl)acetamide–6-propyl-2-thiouracil (1/2), contains three symmetry-independent complexes, each consisting of two 6-propyl-2-thiouracil molecules and one *N*-(6-acetamidopyridin-2-yl)acetamide molecule (Fig. 3). The molecular structures of the six propylthiouracil and the three *N*-(6-acetamidopyridin-2-yl)acetamide molecules are very similar. The r.m.s. deviation from the mean plane through the non-H atoms of each 6-propyl-2-thiouracil molecule varies from 0.012 to 0.028 Å, confirming their planarity. All side chains show an extended conformation, with C8 antiperiplanar to N1 and C9 antiperiplanar to C6 (Table 3). Both N—H bonds of the *N*-(6-acetamidopyridin-2-yl)acetamide molecules are directed to the same side of the side chains as the pyridine N atom, while the methyl groups are antiperiplanar to ring atoms C2 and C6 (Table 4). Thus, dihedral angles ranging from 12.6 (1) to 15.6 (1)° are formed between the planes through one of the amide groups and the pyridine ring (Table 5). The hydrogen-bond patterns within the three complexes are also identical. The 6-propyl-2-thiouracil molecules are linked into dimers by an $R_2^2(8)$ motif involving two N—H···S hydrogen bonds. In

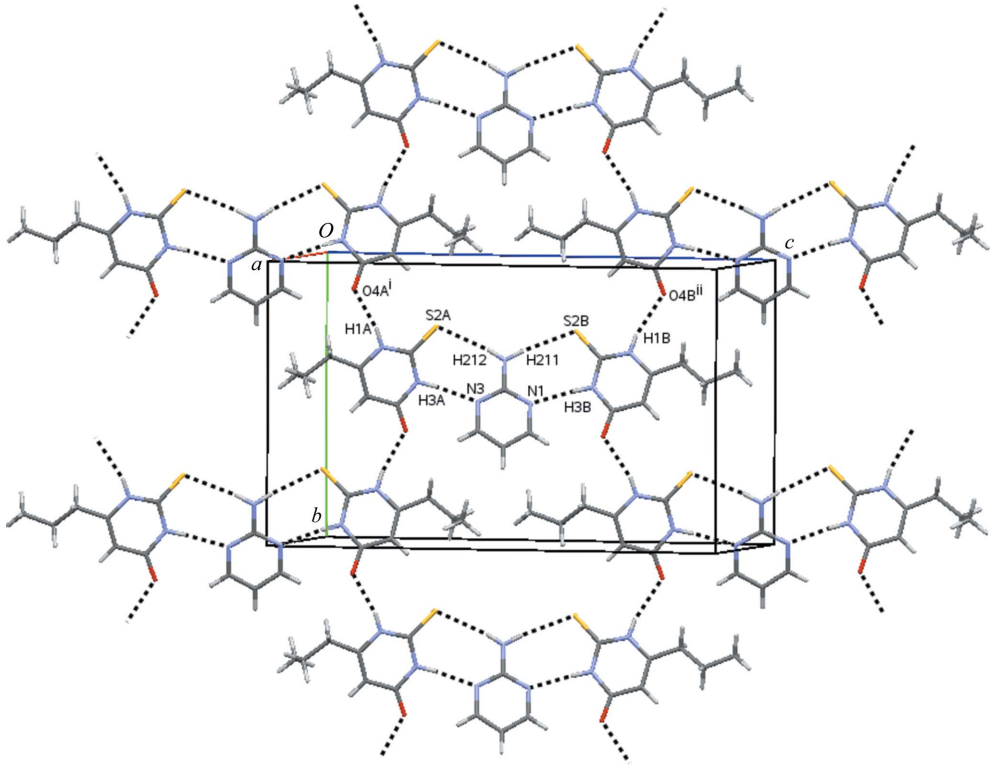

Figure 2
A packing diagram for (I). Dashed lines indicate hydrogen bonds. [Symmetry codes: (i) $-x+2, y-\frac{1}{2}, -z+\frac{1}{2}$; (ii) $-x+1, y-\frac{1}{2}, -z+\frac{3}{2}$.]

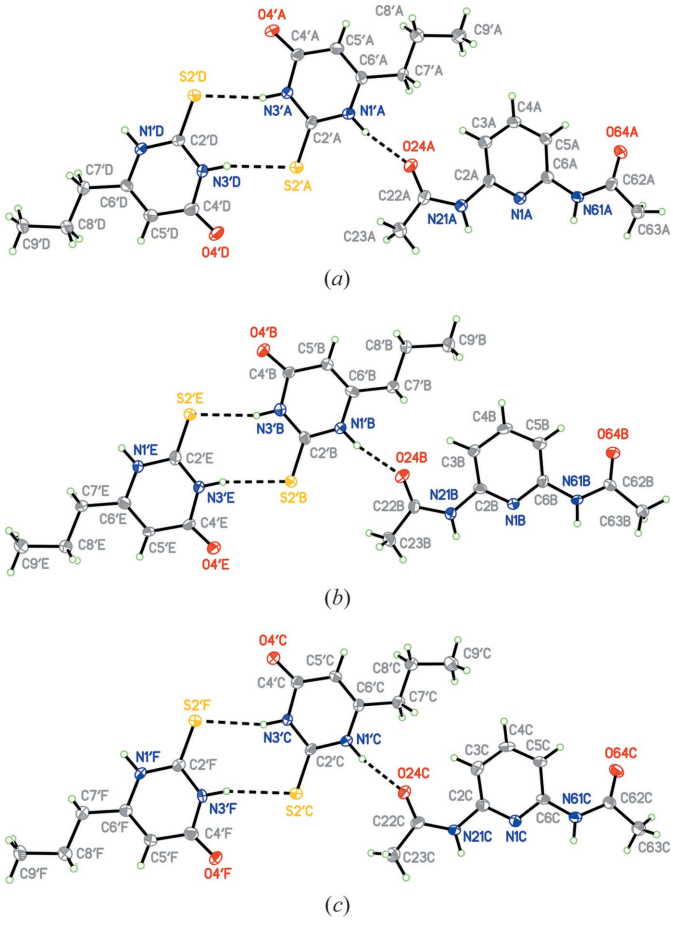

Figure 3
Perspective views of (*a*) the first, (*b*) the second and (*c*) the third symmetry-independent complex molecules in the asymmetric unit of (II), showing the atom-numbering schemes. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. Dashed lines indicate hydrogen bonds.

addition, an N—H···O interaction connects one 6-propyl-2-thiouracil molecule to an *N*-(6-acetamidopyridin-2-yl)acetamide molecule. However, the geometric arrangements of the complexes show some flexibility. The planes through the two 6-propyl-2-thiouracil molecules of a dimer enclose a dihedral angle ranging from 4.4 (1) to 11.9 (1)°, while dihedral angles ranging from 2.0 (1) to 9.7 (1)° are observed between the planes through the pyridine ring and the neighbouring 6-propyl-2-thiouracil molecule (Table 6). In the packing, all three complexes are twisted by 17° with respect to each other and are connected by N—H···O hydrogen bonds into chains running along [310] (Fig. 4). Furthermore, a second chain is formed consisting of N—H···O-bonded symmetry-related complexes aligned along the *b* axis. Altogether, an extended three-dimensional network of hydrogen bonds is observed (Table 7).

In spite of the appropriate arrangement of donor and acceptor groups, 6-propyl-2-thiouracil does not form three hydrogen bonds to *N*-(6-acetamidopyridin-2-yl)acetamide in (II), but undergoes homodimerization without participation of the carbonyl O atom. In order to further investigate its preferred hydrogen-bonding interactions, we analysed related crystal structures. Two structures containing 6-propyl-2-thiouracil are present in the Cambridge Structural Database (CSD, Version 5.32 of November 2010, plus two updates; Allen, 2002), namely a 1,4-dioxane solvate (refcode BUWYOH; Okabe *et al.*, 1983) and a charge-transfer complex with diiodine (refcode HAFLAC; Antoniadis *et al.*, 2003). The latter structure is not further considered, since the S atom is connected to the diiodine molecule and hence can hardly participate as a hydrogen-bond acceptor. In the 1,4-dioxane solvate, only the carbonyl O atom takes part in the hydrogen bonding and connects the 6-propyl-2-thiouracil molecules into chains, while no N—H···S interactions are observed. In the solvent-free structure of the selenium analogue of 6-propyl-2-

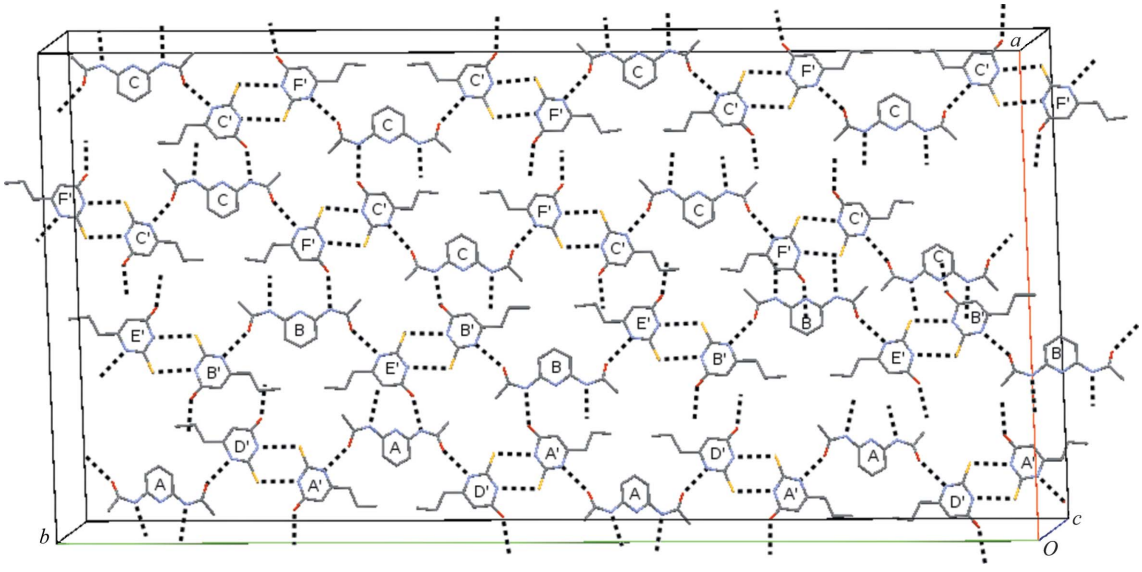

Figure 4
A partial packing diagram for (II). Dashed lines indicate hydrogen bonds. The molecules are designated according to the atom-numbering scheme, with 6-propyl-2-thiouracil molecules marked with primes (see Fig. 3).

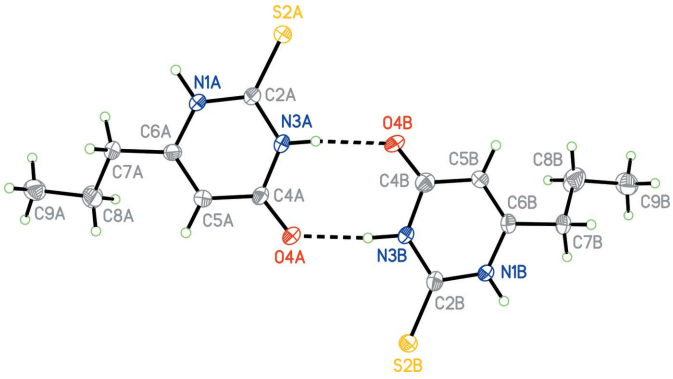

Figure 5
A perspective view of (III), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 50% probability level and H atoms are shown as small spheres of arbitrary radii. Dashed lines indicate hydrogen bonds.

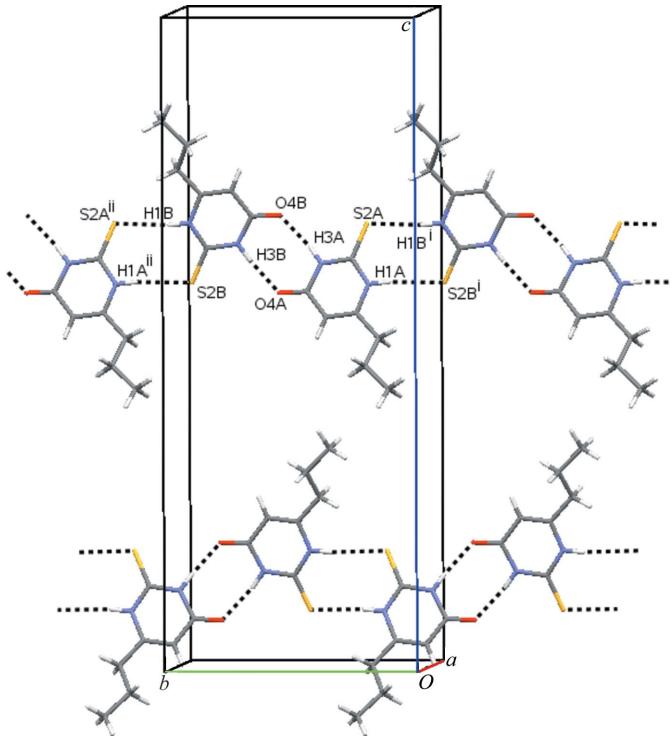

Figure 6
A partial packing diagram for (III), showing chains of dimers running along the *b* axis. Dashed lines indicate hydrogen bonds. [Symmetry codes: (i) $x, y-1, z$; (ii) $x, y+1, z$.]

thiouracil (refcode PELHEU; Antoniadis *et al.*, 2006), the molecules are hydrogen bonded into chains by $R_2^2(8)$ interactions involving either N—H···Se or N—H···O hydrogen bonds. We therefore undertook crystallization experiments with 6-propyl-2-thiouracil alone to study whether similar interactions can be observed.

The crystal structure of 6-propyl-2-thiouracil, (III), is isostructural with PELHEU (Fig. 5). The thiouracil rings of the two independent molecules are planar [r.m.s. deviations = 0.006 (*A*) and 0.016 Å (*B*) for all non-H atoms] and the propyl side chains are again extended but slightly twisted, with the planes through the ring and the side chain enclosing dihedral angles of 26.0 (2)° in *A* and 29.8 (2)° in *B* (Table 8). The 6-propyl-2-thiouracil molecules are connected into vaulted chains running along the *b* axis by two kinds of hydrogen-bond interactions (Table 9). Although both show the same $R_2^2(8)$ graph set, the hydrogen-bond pattern consists of either two N—H···O or two N—H···S interactions (Fig. 6). In the crystal packing, two adjacent chains form a tubular arrangement stabilized by van der Waals interactions (Fig. 7).

In (I)–(III), 6-propyl-2-thiouracil exhibits different side-chain conformations. The dihedral angle between the planar thiouracil ring and the plane through the side chain varies from 2.3 (1) to 89.4 (1)°, although an extended arrangement is preferred. Since sufficient donor groups are available both O and S atoms participate in the hydrogen bonding. The N—H···O hydrogen bonds have different functions: they connect hydrogen-bonded 6-propyl-2-thiouracil molecules either with themselves [in (I)] or with the other cocrystal component [in (II)], thus forming chains, or they stabilize homodimers of 6-propyl-2-thiouracil with an $R_2^2(8)$ pattern [in (III)]. In contrast, the S atoms are only involved in $R_2^2(8)$ hydrogen-bond formation linking the 6-propyl-2-thiouracil molecules into a heterodimer [in (I)] or into a homodimer [in (II) and (III)].

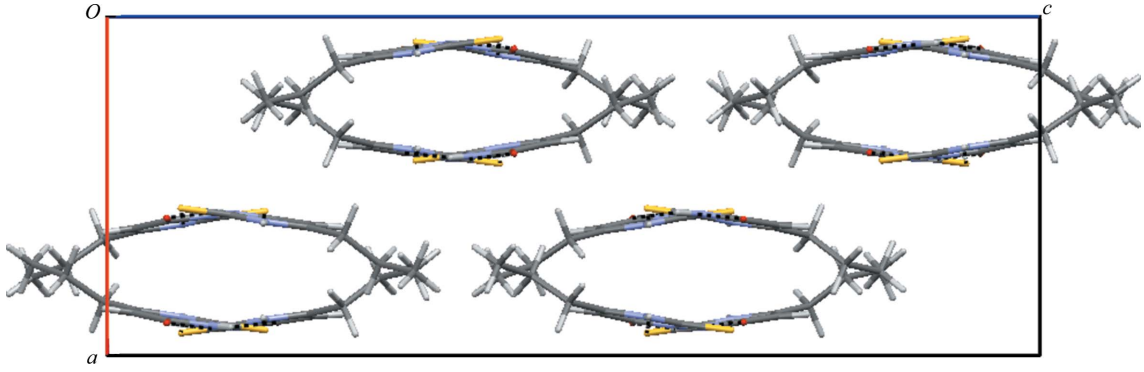

Figure 7
A packing diagram for (III), viewed down the *b* axis, showing the tubular arrangement of chains. Dashed lines indicate hydrogen bonds.

From the hydrogen-bond interactions in the three structures [(I)–(III)], it is not evident whether an N—H···O or an N—H···S hydrogen bond is stronger. A CSD search of six-membered ring compounds with hydrogen-bonding sites similar to 2-thiouracil yielded four different types of $R_2^2(8)$ patterns. 19 entries showed $R_2^2(8)$ motifs characterized by two N—H···O hydrogen bonds; the S atoms take part as acceptors only in five of them [refcodes LACJIJ (Tashkhodzhaev *et al.*, 2002), XUHJIY (Pawlowski *et al.*, 2009), XEXWAZ, XEXWED and XEXWIH (Balalaie *et al.*, 2006)], whereby chains stabilized by N—H···S hydrogen bonds are observed only in XUHJIY. Nine structures contain two different $R_2^2(8)$ patterns with either two N—H···O or two N—H···S hydrogen bonds [refcodes CASPUI (Hu *et al.*, 2005), CUKBOA (Hori *et al.*, 2009), GEMCAC (Read *et al.*, 1988), PABPAL (Chierotti *et al.*, 2010), RAPNAY (Long *et al.*, 2005), TURCIL01 (Tiekink, 1989), TURCIL02 (Munshi & Guru Row, 2006), WIVJAM (Coxall *et al.*, 2000) and ZEWDOU (Ferrari *et al.*, 1995)]. Furthermore, six entries showed $R_2^2(8)$ interactions consisting of two N—H···S hydrogen bonds [refcodes FALWOF (Orzeszko *et al.*, 2004), JESWEK (Xue *et al.*, 2006), MTURAC (Hawkinson, 1975), PABNIR (Chierotti *et al.*, 2010), VOKBUT (Luo *et al.*, 2008) and ZUWMUZ (Branch *et al.*, 1996)]. In three of these structures, the O atoms do not participate in hydrogen bonds. Finally, $R_2^2(8)$ motifs with one N—H···O and one N—H···S hydrogen bond are only observed in EAZTHY (Voutsas *et al.*, 1978).

The CSD study might suggest that an N—H···O is more stable than an N—H···S interaction, but some structures revealed hydrogen-bond interactions only with C=S as a supposedly weaker acceptor group. Although the $R_2^2(8)$ motif with two N—H···O hydrogen bonds is more abundant in the CSD, it is not formed in two of our three structures. A closer examination of the hydrogen-bonding interactions between 6-propyl-2-thiouracil and pyrimidin-2-amine in (I) revealed unusually large N···S distances [N21···S2*A* = 3.6234 (18) Å and N21···S2*B* = 3.5145 (17) Å]. Presumably the complex is further stabilized by a weak C—H···O interaction, which leads to a slightly twisted arrangement of the molecules. The hydrogen-bond pattern with the O atom as an acceptor appears to be essential for the packing in (I). If the N—H···O hydrogen bond was instead present in the $R_2^2(8)$ motif (an interaction similar to the 2-thiouracil–adenine Watson–Crick base pair), the heterodimer between 6-propyl-2-thiouracil and pyrimidin-2-amine would be further stabilized by a C—H···S instead of a C—H···O interaction and the 6-propyl-2-thiouracil chains linked by N—H···S instead of N—H···O hydrogen bonds. The C—H···S interaction and chains connected by N—H···S hydrogen bonds seem to be less stable, since they are rarely observed in crystal structures (Domagała *et al.*, 2003; Pawlowski *et al.*, 2009).

The hydrogen-bond interactions in (II) can be rationalized by similar arguments. If the homodimer of 6-propyl-2-thiouracil was linked by an $R_2^2(8)$ motif with two N—H···O hydrogen bonds, the N—H···S hydrogen bonds would connect the 6-propyl-2-thiouracil and *N*-(6-acetamidopyridin-2-yl)acetamide molecules into chains. The desired heterodimer with three hydrogen bonds is not observed. This is probably due to the fact that the intramolecular distances between the hydrogen donor and acceptor groups of 6-propyl-2-thiouracil do not match with those of *N*-(6-acetamidopyridin-2-yl)acetamide (pyrimidine–thio N···S *ca* 2.7 Å and pyridine–amide N···N *ca* 2.3 Å). Therefore, formation of the desired complex may result in a strained arrangement; no such cocrystal has yet been reported in the CSD. The hydrogen-bonding interactions in (III) are similar to those of its selenium analogue and to the nine entries from the CSD study (see above). In none of the three structures, (I)–(III), is an $R_2^2(8)$ motif with one N—H···O and one N—H···S hydrogen bond observed.

Obviously, the relative strength of the N—H···O and N—H···S hydrogen bonds cannot be clearly judged, since there are many factors affecting hydrogen-bond formation in the crystal. All donor groups will strive to form hydrogen bonds with available acceptor groups within a favourable crystal packing. This complex situation might explain why previous theoretical and experimental studies revealed different relative stabilities for the N—H···O and N—H···S hydrogen bonds. As a result of our investigation, C=O and C=S are indeed competitive acceptor groups.

Experimental

Crystals of (III) were obtained by solvent evaporation from 6-propyl-2-thiouracil (4.7 mg, 0.028 mmol) dissolved in dimethyl sulfoxide (40 µl). Cocrystallization attempts with 6-propyl-2-thiouracil (3.3 mg, 0.019 mmol) and pyrimidin-2-amine (4.3 mg, 0.045 mmol) from *n*-propanol (350 µl) yielded (I). Single crystals of (II) were obtained during attempts to cocrystallize 6-propyl-2-thiouracil (2.5 mg, 0.015 mmol) and *N*-(6-acetamidopyridin-2-yl)acetamide (2.6 mg, 0.015 mmol) from dimethylacetamide (90 µl). All crystallization experiments were performed at room temperature using commercially available compounds.

Compound (I)

Crystal data

$C_4H_5N_3{\cdot}2C_7H_{10}N_2OS$
M_r = 435.58
Monoclinic, $P2_1/c$
a = 7.6094 (5) Å
b = 12.9888 (6) Å
c = 20.8838 (14) Å
β = 99.179 (5)°
V = 2037.7 (2) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.29 mm^{-1}
T = 173 K
0.60 × 0.20 × 0.15 mm

Data collection

Stoe IPDS II two-circle diffractometer
Absorption correction: multi-scan (*MULABS*; Spek, 2009; Blessing, 1995)
T_{min} = 0.844, T_{max} = 0.958
25516 measured reflections
3819 independent reflections
3163 reflections with $I > 2\sigma(I)$
R_{int} = 0.094

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.037
$wR(F^2)$ = 0.105
S = 1.05
3819 reflections
289 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.30 e Å^{-3}
$\Delta\rho_{min}$ = −0.29 e Å^{-3}

Table 1
Selected torsion angles (°) for (I).

N1*A*—C6*A*—C7*A*—C8*A*	162.10 (17)	N1*B*—C6*B*—C7*B*—C8*B*	150.28 (17)
C6*A*—C7*A*—C8*A*—C9*A*	−78.4 (2)	C6*B*—C7*B*—C8*B*—C9*B*	176.90 (17)

Table 2
Hydrogen-bond geometry (Å, °) for (I).

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N21—H211···S2*B*	0.89 (2)	2.63 (2)	3.5145 (17)	173 (2)
N21—H212···S2*A*	0.87 (2)	2.77 (2)	3.6234 (18)	168 (2)
N1*A*—H1*A*···O4*A*^{i}	0.83 (2)	2.17 (2)	2.983 (2)	167 (2)
N3*A*—H3*A*···N3	0.87 (2)	2.06 (2)	2.926 (2)	174 (2)
N1*B*—H1*B*···O4*B*^{ii}	0.82 (2)	2.31 (2)	3.107 (2)	166 (2)
N3*B*—H3*B*···N1	0.88 (2)	2.10 (2)	2.975 (2)	175 (2)

Symmetry codes: (i) $-x+2, y-\frac{1}{2}, -z+\frac{1}{2}$; (ii) $-x+1, y-\frac{1}{2}, -z+\frac{3}{2}$.

Table 3
R.m.s. deviations (Å) of the non-H atoms from the mean ring planes and selected geometric parameters (°) of 6-propyl-2-thiouracil for (II).

Molecule	R.m.s. deviation	N1′—C6′—C7′—C8′	C6′—C7′—C8′—C9′
A′	0.024	178.7 (3)	−178.2 (3)
B′	0.028	−178.2 (3)	178.8 (3)
C′	0.028	176.9 (3)	178.1 (3)
D′	0.018	176.7 (3)	178.0 (3)
E′	0.017	−178.4 (3)	−177.4 (3)
F′	0.012	−178.0 (3)	179.8 (3)

Compound (II)

Crystal data

$C_9H_{11}N_3O_2\cdot 2C_7H_{10}N_2OS$
M_r = 533.68
Orthorhombic, *Fdd*2
a = 37.9355 (12) Å
b = 76.880 (3) Å
c = 10.5666 (3) Å
V = 30817.3 (18) Å^3
Z = 48
Mo *Kα* radiation
μ = 0.25 mm^{-1}
T = 173 K
0.50 × 0.30 × 0.20 mm

Data collection

Stoe IPDS II two-circle diffractometer
Absorption correction: multi-scan (*MULABS*; Spek, 2009; Blessing, 1995)
T_{min} = 0.885, T_{max} = 0.951
108254 measured reflections
14445 independent reflections
10225 reflections with $I > 2\sigma(I)$
R_{int} = 0.129

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.047
$wR(F^2)$ = 0.097
S = 0.91
14445 reflections
985 parameters
1 restraint
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.22 e Å^{-3}
$\Delta\rho_{min}$ = −0.25 e Å^{-3}
Absolute structure: Flack (1983), 6784 Friedel pairs
Flack parameter: 0.12 (7)

Compound (III)

Crystal data

$C_7H_{10}N_2OS$
M_r = 170.23
Orthorhombic, *Pbca*
a = 10.4340 (6) Å
b = 11.1320 (6) Å
c = 28.7090 (17) Å
V = 3334.6 (3) Å^3
Z = 16
Mo *Kα* radiation
μ = 0.33 mm^{-1}
T = 173 K
0.40 × 0.20 × 0.20 mm

Table 4
Selected geometric parameters (°) of *N*-(6-acetamidopyridin-2-yl)acetamide for (II).

Molecule	1	2	3	4
A	−167.1 (4)	179.9 (3)	−166.1 (4)	178.5 (4)
B	167.9 (3)	179.7 (3)	166.5 (3)	179.1 (4)
C	−169.8 (4)	−177.8 (4)	−167.2 (3)	−177.9 (3)

Torsion 1 = N1—C2—N21—C22, torsion 2 = C2—N21—C22—C23, torsion 3 = N1—C6—N61—C62 and torsion 4 = C6—N61—C62—C63.

Table 5
Dihedral angles (°) between the pyridine ring and the amide groups of *N*-(6-acetamidopyridin-2-yl)acetamide [designated by *α* (N21) and *β* (N61)] for (II).

Molecule	*α*	*β*
A	13.4 (1)	15.5 (1)
B	12.6 (1)	14.6 (1)
C	12.6 (1)	15.6 (1)

Table 6
Dihedral angles (°) within the three symmetry-independent complexes for (II).

γ designates the angle between two 6-propyl-2-thiouracil molecules and *δ* designates the angle between the pyridine ring and the central 6-propyl-2-thiouracil molecule; the molecules are designated according to Fig. 4.

Complex	*γ*	*δ*
AA′*D*′	7.3 (1)	9.7 (1)
BB′*E*′	11.9 (1)	2.0 (1)
CC′*F*′	4.4 (1)	7.3 (1)

Data collection

Stoe IPDS II two-circle diffractometer
Absorption correction: multi-scan (*MULABS*; Spek, 2009; Blessing, 1995)
T_{min} = 0.879, T_{max} = 0.937
29872 measured reflections
3131 independent reflections
1990 reflections with $I > 2\sigma(I)$
R_{int} = 0.132

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.046
$wR(F^2)$ = 0.093
S = 0.91
3131 reflections
201 parameters
H-atom parameters constrained
$\Delta\rho_{max}$ = 0.19 e Å^{-3}
$\Delta\rho_{min}$ = −0.25 e Å^{-3}

All H atoms were initially located by difference Fourier synthesis. Subsequently, H atoms bonded to C atoms were refined using a riding model, with methyl C—H = 0.98 Å, secondary C—H = 0.99 Å and aromatic C—H = 0.95 Å, and with U_{iso}(H) = 1.5U_{eq}(C) for methyl or 1.2U_{eq}(C) for secondary and aromatic H atoms. In (II) and (III), H atoms bonded to N atoms were refined using a riding model, with amide N—H = 0.88 Å and U_{iso}(H) = 1.2U_{eq}(N), while in (I) they were refined isotropically. The methyl groups were allowed to rotate about their local threefold axes.

Owing to the systematic absences analysed by the program *XPREP* (Sheldrick, 2008), (II) was solved and refined in the noncentrosymmetric space group *Fdd*2. Structure validation with *PLATON*/*ADDSYM* (Le Page, 1987, 1988; Spek, 2009) detected a pseudo-inversion centre at (0.126, 0.208, 0.466), which is not

Table 7
Hydrogen-bond geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
N21A—H21A···O4′D^{i}	0.88	2.03	2.904 (5)	169
N61A—H61A···O4′E^{ii}	0.88	2.05	2.921 (5)	171
N21B—H21B···O4′A	0.88	2.04	2.906 (5)	170
N61B—H61B···O4′F^{iii}	0.88	2.03	2.893 (5)	169
N21C—H21C···O4′B	0.88	2.01	2.873 (5)	168
N61C—H61C···O4′C^{iv}	0.88	2.07	2.934 (5)	165
N1′A—H1′A···O24A	0.88	2.03	2.892 (4)	167
N3′A—H3′A···S2′D	0.88	2.42	3.279 (3)	166
N1′B—H1′B···O24B	0.88	2.00	2.859 (5)	165
N3′B—H3′B···S2′E	0.88	2.43	3.286 (4)	165
N1′C—H1′C···O24C	0.88	2.09	2.951 (4)	166
N3′C—H3′C···S2′F	0.88	2.45	3.313 (3)	166
N1′D—H1′D···O64A^{v}	0.88	2.00	2.870 (5)	168
N3′D—H3′D···S2′A	0.88	2.45	3.317 (3)	168
N1′E—H1′E···O64B^{vi}	0.88	2.06	2.919 (4)	166
N3′E—H3′E···S2′B	0.88	2.49	3.358 (3)	168
N1′F—H1′F···O64C^{vii}	0.88	2.08	2.944 (4)	166
N3′F—H3′F···S2′C	0.88	2.49	3.359 (3)	168

Symmetry codes: (i) $-x, -y+1, z$; (ii) $-x+\frac{1}{4}, y-\frac{1}{4}, z-\frac{1}{4}$; (iii) $-x+\frac{3}{4}, y-\frac{1}{4}, z+\frac{1}{4}$; (iv) $x-\frac{1}{4}, -y+\frac{5}{4}, z-\frac{1}{4}$; (v) $-x+\frac{1}{4}, y+\frac{1}{4}, z+\frac{1}{4}$; (vi) $-x+\frac{3}{4}, y+\frac{1}{4}, z-\frac{1}{4}$; (vii) $-x+\frac{5}{4}, y+\frac{1}{4}, z+\frac{1}{4}$.

Table 8
Selected torsion angles (°) for (III).

N1A—C6A—C7A—C8A	152.9 (3)	N1B—C6B—C7B—C8B	148.6 (3)
C6A—C7A—C8A—C9A	−174.9 (3)	C6B—C7B—C8B—C9B	−178.8 (3)

Table 9
Hydrogen-bond geometry (Å, °) for (III).

D—H···A	D—H	H···A	D···A	D—H···A
N1A—H1A···S2B^{i}	0.88	2.48	3.341 (2)	165
N3A—H3A···O4B	0.88	1.94	2.797 (3)	163
N1B—H1B···S2A^{ii}	0.88	2.50	3.361 (2)	167
N3B—H3B···O4A	0.88	1.98	2.826 (3)	161

Symmetry codes: (i) $x, y-1, z$; (ii) $x, y+1, z$.

compatible with this space group. Since no correlation matrix elements larger than 0.5 are observed and the Flack (1983) parameter is consistent with a noncentrosymmetric structure, the space group was retained.

For all compounds, data collection: *X-AREA* (Stoe & Cie, 2001); cell refinement: *X-AREA*; data reduction: *X-AREA*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *Mercury* (Macrae *et al.*, 2008) and *XP* (Sheldrick, 2008); software used to prepare material for publication: *publCIF* (Westrip, 2010).

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