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Reaction of 6-amino-5-nitrosouracil with thiourea: Structure of the hydrolysis product

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The interaction of 6-amino-5-nitrosouracil with thiourea in aqueous acidic solution results in the 6-amino-5-formamidinosulfenimino-2,3,4,5-tetrahydropyrimidine-2,4-dione di-*p*-toluenesulfonate that is subjected to hydrolysis with the formation of 5-formamidinosulfeniminobarbituric acid *p*-toluenesulfonate monohydrate.

Keywords: Nitrosouracil derivative; Thiourea; Hydrolysis; Crystal structure

1. Introduction

The interaction of O-containing nitrogen compounds with a range of sulfur derivatives often bring about the formation of a covalent nitrogen-sulfur bond. In this type of chemistry, the intermediate product of the reaction may be an ether of low stability whose rearrangement is accompanied by the rupture of the nitrogen-oxygen covalent bond (transformation 1 in scheme 1).

Using this route, sulfamic acids [1, 2] were obtained from hydroxylamines and sulfur dioxide (transformation 2 in scheme 1), while the interaction of 1,4-benzoquinonemonooximes with arylsulphenyl chlorides results in arylsulphinyl-1,4-benzoquinonimines (transformation 3 in scheme 1) [3]. The protection of nitrogen-oxygen covalent bond can be achieved by the condensation of sulfur chlorides with 1,2-dioximes [4] or with 6-amino-5-nitrosopyrimidines [5].

The further rearrangement of thus formed N-oxides of 1,2,5-thiadiazoles into the sulfamic acids was proved to be possible only in the presence of water (scheme 2) [6]. This reaction is recognized as one of several examples where the oxygen of a nitroso group is replaced

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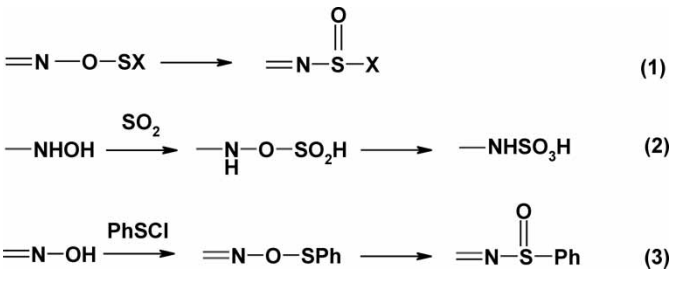
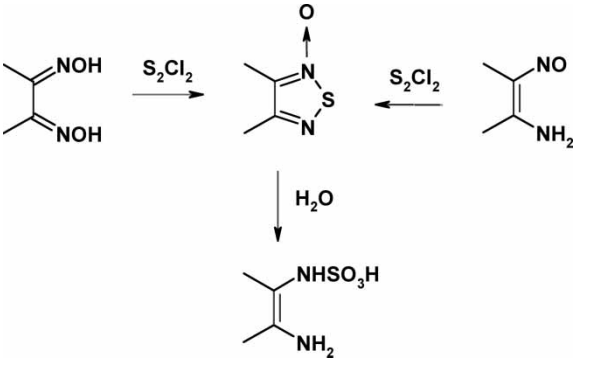


SCHEME 1

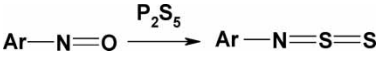


SCHEME 2

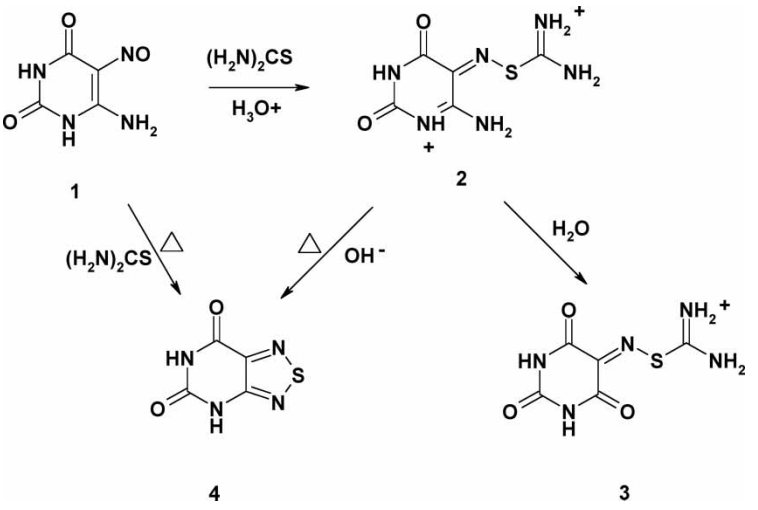
by sulfur. Another example is the attempted preparation of *p*-dimethylamino thionitrosobenzene by treatment of *p*-dimethylaminonitrosobenzene with phosphorus pentasulfide, where *p*-dimethylamino *N*-thiosulfinylaniline was unexpectedly formed (scheme 3) [7].

Of fundamental interest is the related reaction of 6-amino-5-nitrosopyrimidines and thiourea, which results in the formation of 1,2,5-thiadiazolo-[3,4-d]-pyrimidines. 5-Formamidinosulfeniminopyrimidine-2,4-dione was proposed by Timmis [8] to be an intermediate in the formation of thiadiazole from the coupling of thiourea and nitrosopyrimidines. However, the compound has not been isolated, and the mechanism of this reaction is still under the question.

In the course of our study we have observed, that the interaction of 6-amino-5-nitrosouracil, **1** with thiourea in aqueous acidic solution results in the replacement of oxygen of nitroso group by the isothiouronium fragment. The product of this reaction, 6-amino-5-formamidinosulfenimino-2,3,4,5-tetrahydropyrimidine-2,4-dione, **2** was isolated in the solid state as its *p*-toluenesulfonate salt. This salt is stable in the solid state, but labile in aqueous solution. ^{1}H NMR (DMSO-d_6) analysis revealed that in solution there is mixture of tautomers with the prevalence of the bicyclic product. In the aqueous solution the hydrolysis of the amino group at the 6-position of the uracil ring occurs, which results in the formation of 5-formamidinosulfeniminobarbituric acid, **3** in practically quantitative yield. This paper



SCHEME 3



SCHEME 4

describes the first time isolation of this intermediate product and its crystal structure in the form of a *p*-toluenesulfonate monohydrate (scheme 4). The heating of an aqueous solution of **2** and its treatment by alkali results in the formation of 1,2,5-thiadiazolo[3,4-d]pyrimidine, **4**.

2. Results and discussion

Structure of compound **3** in the form of its *p*-toluenesulfonate monohydrate has been studied by single crystal X-ray diffraction analysis. The ORTEP drawing of the salt is shown in figure 1. The presence of lattice water in the complex is obvious as shown in its crystal structure. It blocks the amide hydrogen *via* NH···O hydrogen bond, N2-H2···O1W 2.797(5) Å. The skeleton of organic cation is composed of two planar parts, uracil moiety and the imide side branch, this

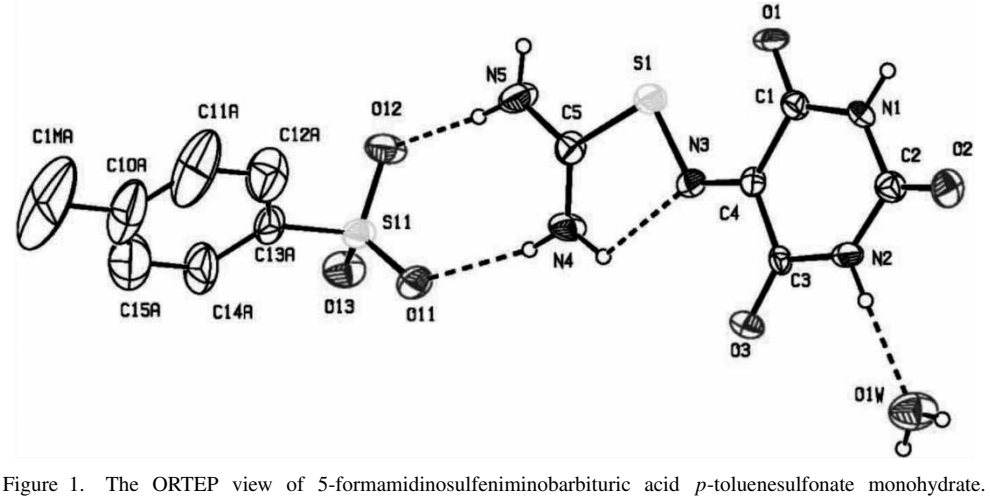


Figure 1. The ORTEP view of 5-formamidinosulfeniminobarbituric acid *p*-toluenesulfonate monohydrate. Non-functional hydrogen atoms are omitted, only one position for the disordered toluene moiety is shown. The thermal ellipsoids are shown in 30% probability level.

fragment being stabilized by the intramolecular N4-H4b···N3 hydrogen bond, 2.710(5) Å. The displacement from coplanarity is indicated by the dihedral angle between the plane of uracil ring and the plane of the five-membered H-bonded ring, H4b-N4-C5-S1-N3 equal to 9.8(1)°. The value of the N3-S1 covalent bond of 1.671(4) Å essentially differs from the standard value for the single bond, and mediates between the single S-N (1.74 Å) and double S=N (1.54 Å) covalent bonds. The close value of S-N bond lenght is typical for sulfenamides and 1,2,5-thiadiazoles [9]. According to Saegebarth and Cox [10] these effects could be explained by 3d orbitals used for d_π-bonding by S. The exclusion is the bonding order in the 2-oxides of 1,2,5-thiadiazoles, where the S1-N2 distance corresponds to the value of a single bond [11]. In **3** the C5-N4 and C5-N5 bond distances being of 1.299(6) Å and 1.319(5) Å, correspondingly are consistent, while the angle C5-S1-N3 of 96.6(2)° is a bit smaller than the value of C-S-C angle in the studied thiouronium salts [12–18].

The packing of the molecules in the crystal exhibits some interesting features. The related by translation cations are combined into a positive chain *via* the couple of NH···O hydrogen bonds, N1-H1···O3(x, y, $z+1$) 2.849(5) Å, and N4-H4b···O1(x, y, $z-1$) 2.869(5) Å (figure 2a). This positive chain is imprisoned between two rows of H-bonded *p*-toluenesulfonate anions, bound

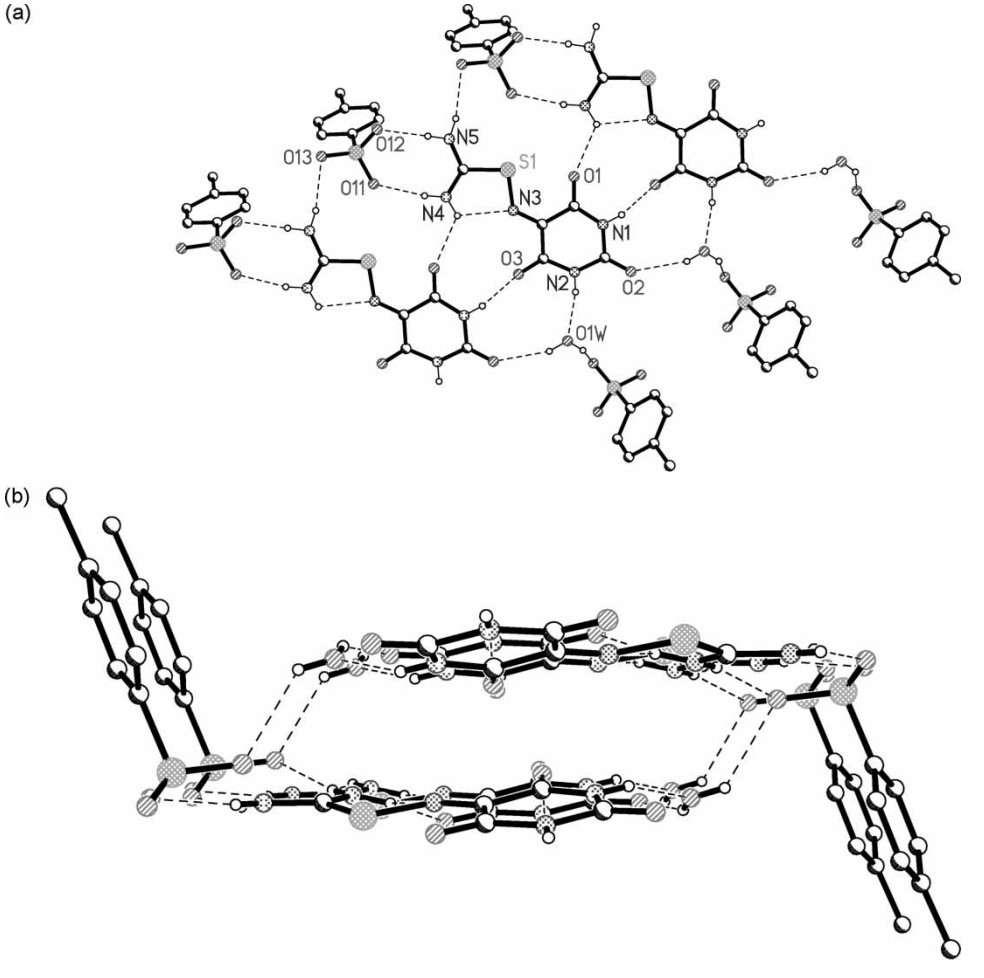


Figure 2. (a) The fragment of the ribbon in 5-formamidinosulfeniminobarbituric acid *p*-toluenesulfonate monohydrate; (b) the association of the neighboring positive chains into a double ribbon.

with the positive chain *via* two NH···O hydrogen bonds using both terminal amino-groups and two oxygens of sulfonic group, from one side, and *via* bridging water molecules from another side, giving rise to the ribbon propagated along *c* direction in the unit cell. All of the donor and acceptor functions of the 5-formamidinosulfeniminobarbituric acid cation participate to form the ribbon. Molecules of water and tetrahedral sulfonic anions bind formamidinium cations to form the six-membered associates characterized by a two-fold screw axis symmetry (figure 2b), with the arrangement of the components very close to that found in S-benzylisothiouronium cyclohexanesulfonate [13] (Refcode EBIFOK in Cambridge Structural Database [19]).

3. Experimental

6-Amino-5-formamidinosulfenimino-2,3,4,5-tetrahydropyrimidine-2,4-dione di-*p*-toluenesulfonate. The mixture of (0.5 g, 3 mmol) **1**, thiourea (0.7 g, 9 mmol) and of *p*-toluenesulfonic acid (2 g, 12 mmol) in water (15 mL) was stirred at 40–60 °C till the disappearance of the initial uracil in the reactive mixture. The dense colorless mass was filtered off and washed by the small portion of glacial water and air-dried. The yield of **2** is 1 g (56%), mp 270 C. IR (Specord-80, KBr, ν, cm^{-1}): 3360, 3300–3080, 3080–2930, 2910, 2840, 2810, 1800, 1860, 1720, 1670, 1560. ^{1}H NMR (Varian WXP, 300 MHz; DMSO-d_6; δ, ppm; J, Hz) 2.29 (s, CH_3), 6.94 (s, N(4)H), 7.13 (d, CH, $J = 8$), 7.28 (s, N(5)H), 7.50 (d, CH, $J = 8$), 9.41 (s, N(6)H), 9.70 (s, N(4)H), 9.78 (s, N(5)H), 10.07 (s, N(6)H), 10.16 (s, N(2)H), 10.89 (s, N(2)H), 11.61 (s, N(2)H), 12.21 (s, N(1)H).

5-Formamidinosulfeniminobarbituric acid *p*-toluenesulfonate monohydrate (5-formamidinosulfenylimino-1,2,3,4,5,6-hexahydropyrimidine-2,4,6-trione *p*-toluene-sulfonate monohydrate). 6-Amino-5-formamidinosulfenimino-2,3,4,5-tetrahydropyrimidine-2,4-dione di-*p*-toluene sulfonate (0.5 g, 0.9 mmol) was dissolved in water (75 mL) at 40 °C, and the solution was stored at 20–30 °C for 10 days. Then the solution was filtered off, evaporated in vacuum at 20°C till the precipitate appearance and cooled till 10°C. The precipitate was filtered off, and air-dried. **3**: 0.3 g (86%), mp 280 °C. IR (Specord-80, KBr, ν, cm^{-1}): 3560, 3540, 3520, 3500, 3460, 3370–2800, 1780, 1750, 1740, 1720, 1710, 1680, 1660, 1630, 1610, 1590, 1560, 1510. ^{1}H NMR (Varian WXP, 300 MHz; DMSO-d_6; δ, ppm; J, Hz): 2.28 (3H, s, CH_3), 7.13 (2H, d, CH, $J = 8$), 7.50 (2H, d, CH, $J = 8$), 9.22 (2H, s, N(5)H), 9.78 (2H, s, N(4)H), 11.82 (1H, s, N(2)H), 12.21 (1H, s, N(1)H).

Crystallographic data for the structure of **3**·$C_7H_7O_3S$·H_2O has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 262211. Intensity data were collected on a Bruker P4 single crystal diffractometer with CCD area detector (graphite-monochromated Mo-Kα radiation, $\lambda = 0.71073$ Å) using the $\omega - 2\theta$ technique to a maximum 2θ of 52.0°. The structure was solved by direct methods and refined by full-matrix least-squares on F^2 using SHELX–97. It was obvious from electron-density maps that the *p*-toluenesulfonate anion was unequally disordered over two closely related orientations. These aromatic rings were modelled as rigid hexagons with C-C 1.39 Å and tied occupancies refined to 0.668(11)/0.331(11). The H atoms of the disordered methyl groups were not well resolved and in the final refinement they were modelled as six partial-occupancy H atoms equally distributed about the methyl C atoms C1MA and C1MB. All other H atoms were visible in difference maps and were subsequently allowed for as riding on the relevant C, N and O atoms. The Flack value (0.08(10)) shows that the correct direction of the polar axis has been chosen.

Crystal data for **3**·$C_7H_7O_3S$·H_2O: $C_5H_6N_5O_3S$·$C_7H_7O_3S$·H_2O, $M = 405.41$, orthorhombic, $a = 16.616(2)$ Å, $b = 16.947(3)$ Å, $c = 6.583(2)$ Å, $V = 1853.7(7)$ Å^3, space group

$Pna2_1$ (no 33), $Z = 4$, $d_{\text{calcd}} = 1.453\,\text{g/cm}^3$, 16043 reflections measured, 1803 reflections [$I > 2\sigma(I)$] were used in all calculations, $R = 0.0440$, $wR2 = 0.0746$.

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