**Химия и биологическая активность синтетических и природных соединений**

# КИСЛОРОД- И СЕРУСОДЕРЖАЩИЕ ГЕТЕРОЦИКЛЫ

*Под редакцией докт. хим. наук* ***В.Г. Карцева***

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# 1,3-Dithiolo[4,5-*d*]pyrimidines: Synthesis and properties

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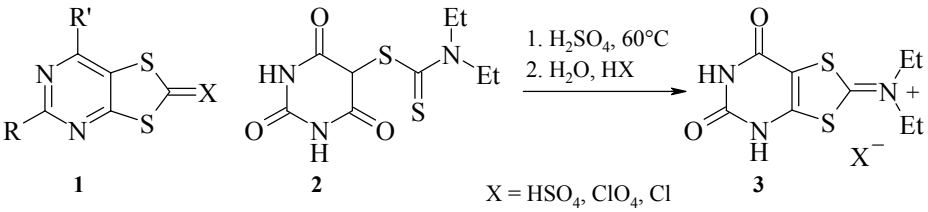
## Introduction

A novel heterocyclic system, 1,3-dithiolo[4,5-*d*]pyrimidine **1**, has been prepared and characterized. We aimed at synthesizing the derivatives of uracil-fused 1,3-dithiol-2-selones and their use in preparation of strongly electron-donating tetrathiafulvalenes bearing an uracil function. We proposed that uracil-fused tetrathiafulvalenes will be capable of forming strong intermolecular complementary hydrogen bonds like nucleic acid. In this paper, we will overview the synthesis and properties of dioxo- and amino-oxo-1,3-dithiolo[3,4-*d*]pyrimidines as well as of dioxo- and aminooxopyrimido-fused tetrathiafulvalenes.

## Synthesis of 5,7-dioxo(4*H*,6*H*)-1,3-dithiolo[4,5-*d*]pyrimidine-2-diethylimmonium salts 3

We synthesized uracil-fused 1,3-dithioles [1–3] from the derivatives of barbituric acid. Reaction of 2-diethylaminothiocarbonylthiobarbituric acid **2** with conc. sulfuric acid (at 60°C) was found to yield target heterocyclic system **3**. Upon dilution with conc. HCl and acetone, chloride **3** precipitated as colorless crystals (Scheme 1).

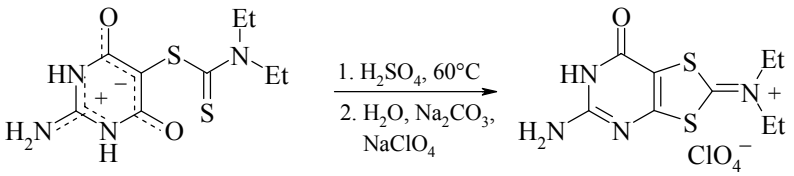
*Scheme 1*




## 5-Amino-7-oxo(6*H*)-1,3-dithiolo[4,5-*d*]pyrimidine-2-diethylimmonium salts

Isocytosine-fused 1,3-dithiole system [4] was synthesized from 5-diethylaminothio-carbonylthio-2-amino(1*H*,5*H*)pyrimidine-3,6-dione **4**. Cyclisation was performed in conc. sulfuric acid. Upon dilution with aqueous perchlorate, compound **5** was precipitated (in neutral solution) with sodium perchlorate. Solubility of this colorless salt in water is lower than that of salts **3**. Salt **5** is well soluble (as a weak base) in dilute acids (Scheme 2).

*Scheme 2*

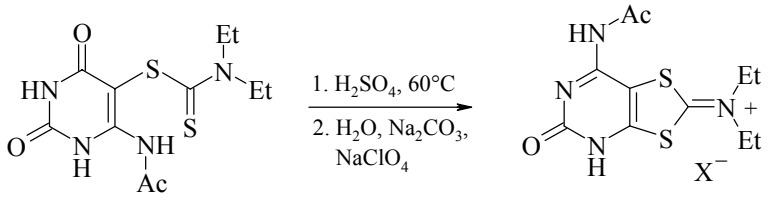



**4** **5**

**7-Amino-5-oxo(4*H*)-1,3-dithiolo[4,5-*d*]pyrimidine-2-diethylimmonium salts**

Cytosine-fused 1,3-dithiole system [5] was synthesized from derivatives of 6-aminouracil, viz. from 5-diethylaminothiocarbonylthio-6-acetylaminouracil **6**. Cyclization was performed in conc. sulfuric acid. Upon dilution and neutralization, we precipitated perchlorate **7** with sodium perchlorate. But cyclization of non-acetylated 6-aminouracil derivative gave salts **3** rather than the desired salt (Scheme 3).

*Scheme 3*

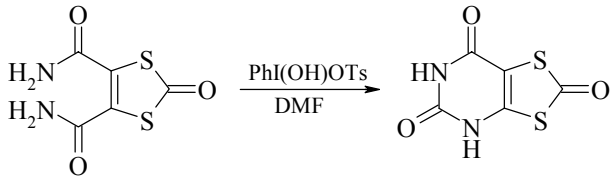



**6** **7**

**1,3-Dithiolo[4,5-*d*]pyrimidine system from 1,3-dithiol derivatives**

Reaction of 1,3-dithiol-2-one-4,5-dicarboxamide **8** with strong oxidant, [hydroxyl(tosyloxy)iodo]benzene, followed by the Hoffmann rearrangement yielded colorless 5,7-dioxo-(4*H*,6*H*)-1,3-dithiolo[4,5-*d*]pyrimidin-2-one **9** [6] (Scheme 4).

*Scheme 4*

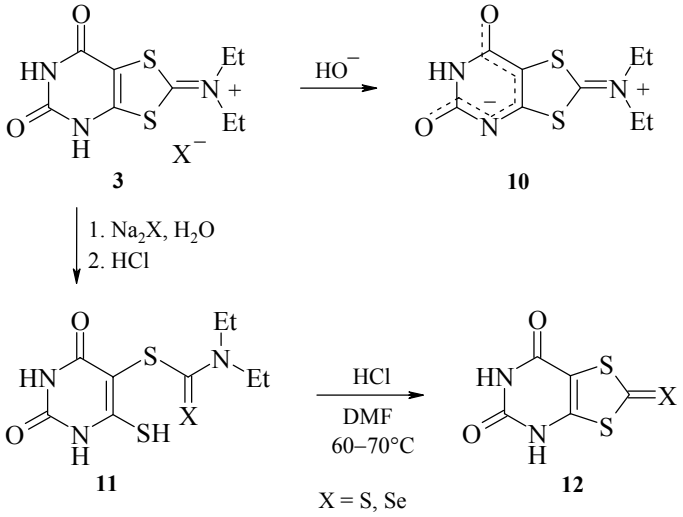



**8** **9**

**Reaction of the salts of compound 3 with nucleophiles**

Just as NH acids (p$K_a$ 3.3, in water) [2], compounds **3** are capable (in the presence of base) of intramolecular salt formation giving betaine **10**. Colorless betaine is water-soluble. Salts of **3** react with strong nucleophiles (sulfides and selenides) in aqueous solutions to yield (via disclosure of the dithiol ring) unusual derivatives of 4-thiobarbituric acid **11**. These compounds are unstable, and undergo cyclization under the action of strong acids yielding yellow 5,7-dioxo(4*H*,6*H*)-1,3-dithiolo[4,5-*d*]pyrimidine-2-thione (**12**, X = S) and red selone **12** (X = Se) [1, 3] (Scheme 5). This selone is an important starting material for further syntheses.

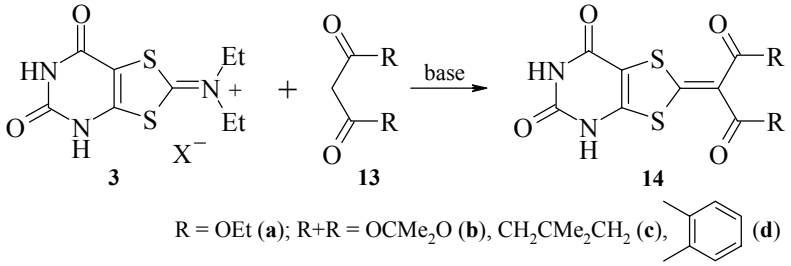
*Scheme 5*




**3** **10** **11** **12**

We observed an unusual condensation of salts of **3** (or betaine **10**) with β-dicarbonyls **13** (in the presence of base in DMF at 90°C) yielding yellow 5,7-dioxo(4*H*,6*H*)-1,3-dithiolo[4,5-*d*]pyrimidine-2-ylidene diethylmalonate **14a**, isopropylidene malonate **14b**, dimedone **14c**, and indan-1,3-dione **14d** (Scheme 6). These compounds are NH acids and are capable of salt formation [7].

*Scheme 6*

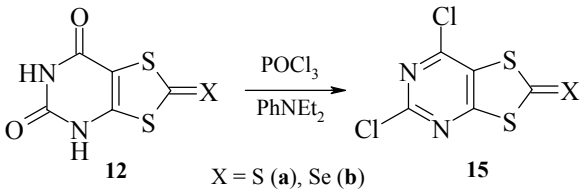



**3** **13** **14**

**Synthesis and properties of 5,7-dihloro-1,3-dithiolo[4,5-*d*]pyrimidine-2-thione and selone (15)** [8]

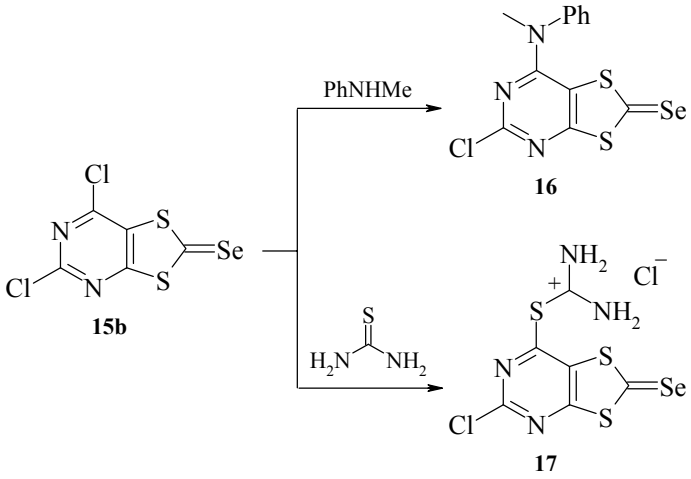
Reaction of thione or selone **12** ($POCl_3$, 90–120°C, in the presence of N,N-diethylaniline) results in dihloroproducts **15a**, **b** (Scheme 7). Deep yellow thione **15a** and deep red-brown selone **15b** are important starting materials for further syntheses. Selone **15b** readily reacts with N-methylaniline (or thiourea) to afford 7-methylphenylamino-5-chloro-1,3-dithiolo[4,5-*d*]pyrimidine-2-selone **16** or chloride of 7-isothiuronio-5-chloro-1,3-dithiolo[4,5-*d*]pyrimidine-2-selone **17** (Scheme 8).

*Scheme 7*




**12** **15**

*Scheme 8*

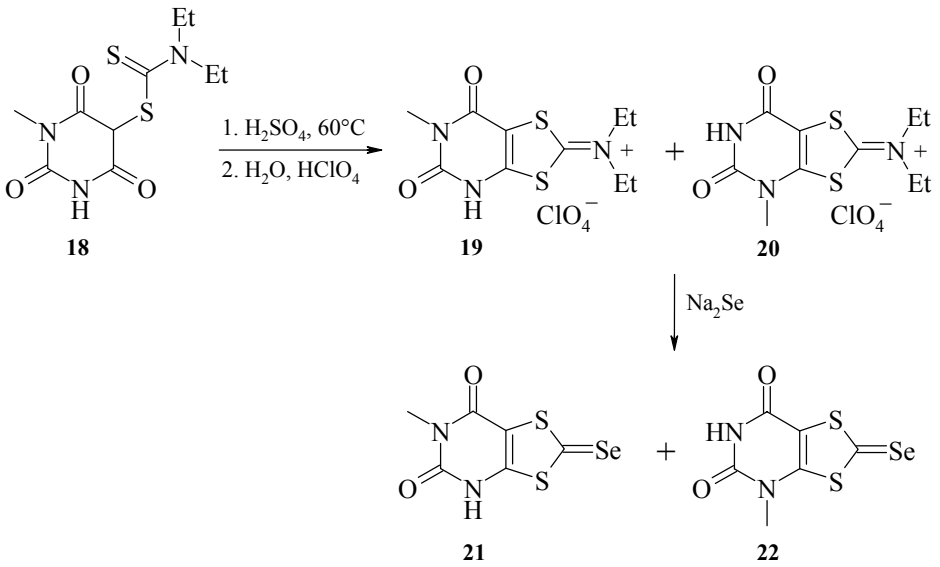



**15b** **16** **17**

**Cyclization of N-methyl-5-diethylaminothiocarbonylthiobarbituric acid** [9]

Aming at synthesizing N-methylsubstituted selone **12**, we found out that cyclization of N-methylbarbituric acid derivative **18** yielded a mixture of 4-methyl- and 6-methyl-substituted salts **19**, **20.** Transformation of these products into selones gave a mixture of 4-methyl- and 6-methylsubstituted selones **21**, **22** (Scheme 9). The isomers were separated chromatographically. 4-Methylselone **22** was a major product.

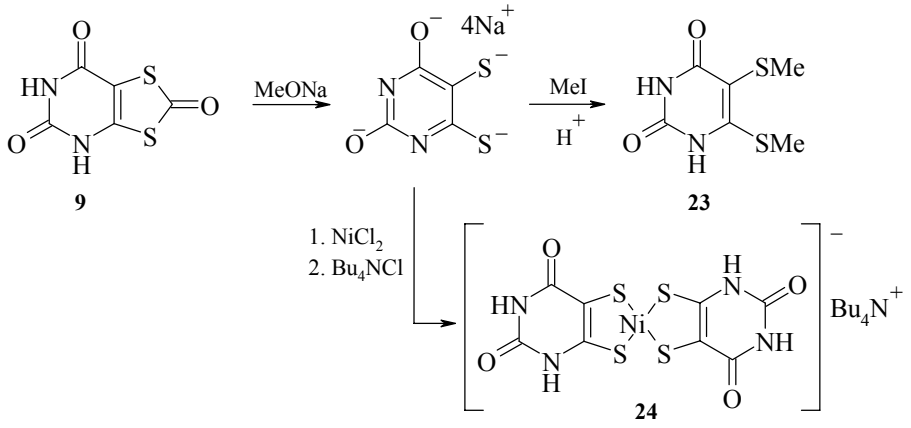
*Scheme 9*




**Transformations of 5,7-dioxo(4*H*,6*H*)-1,3-dithiolo[4,5-*d*]pyrimidine-2-one (9)** [6]

Dithiolone **9** containing polarized S–CO bonds can readily react with strong bases. Reaction of compound **9** with sodium methoxide resulted in dimercaptide methylation of which gave 5,6-di(methylthio)uracil **23**. Reaction of dimercaptide with nickel salt and tetrabutylammonium chloride resulted in interesting deep colored dithiolene complex **24** (Scheme 10).

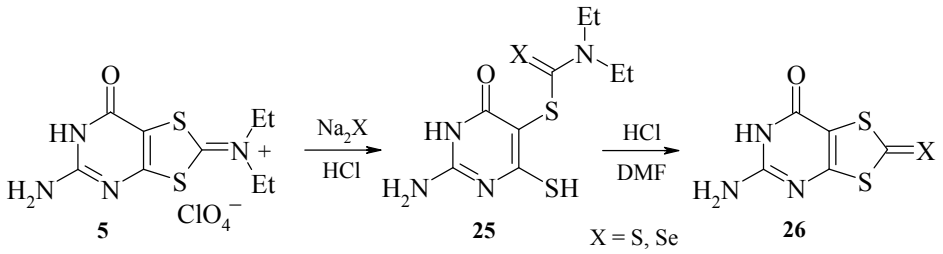
*Scheme 10*



**Synthesis of isocytosine-fused 1,3-dithiol-2-thione and 2-selone** [4]

Diethylimmonium perhlorate **5** easily reacts with sodium sulfide (or sodium selenide) in water to yield 2-amino-5-diethylaminothio(seleno)carbonylthio-6-mercapto(3*H*)pyrimidin-4-one **25**. This unusual compound is unstable and undergoes cyclisization under the action of strong acids (in DMF or acetic acid) yielding yellow 5-amino-7-oxo(6*H*)-1,3-dithiolo[4,5-*d*]pyrimidine-2-thione (**26**, X = S) or red selone (**26**, X = Se) (Scheme 11). This selone is a valuable starting material for further syntheses.

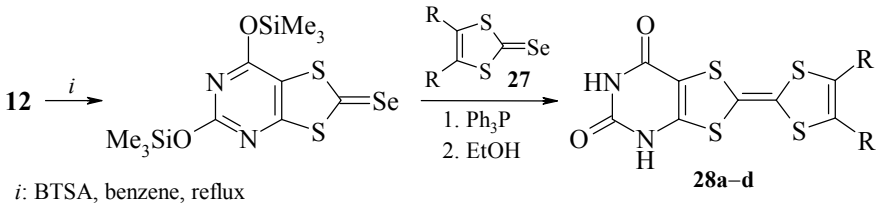
*Scheme 11*



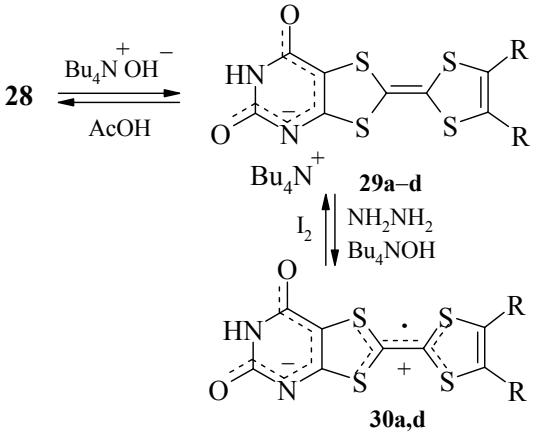

**Synthesis of dioxo- and aminooxopyrimidotetrathiafulvalenes**

We have performed the cross coupling of two 1,3-dithiol-2-selones (**12** and **27**) aiming at preparation of tetrathiafulvalene (TTF) system fused with uracil or isocytosine. A best coupling agent was found to triphenylphosphine. Starting selone has been trimethylsilylated due to its poor solubility in benzene to give disubstituted 4,6-dioxo(3*H*,5*H*)pyrimido-TTFs **28a**–**d** [10–13]. As NH acids, TTFs **28** are capable of salt formation. Tetrabutylammonium salts **29** are being used for purification of poor-soluble TTF **31**. Oxidation of salts **29** with iodine leads to insoluble deep green betaine cation radicals **30** [13, 14] (Scheme 12). The structure of TTFs **28** was confirmed by XRD [12] and mass spectra [15]. These compounds were used to synthesize oligoribonucleotides [16, 17] and H-bonded complexes [18]. Betaines **30a**, **d** exhibit unusually high electroconductivity in pellets [13, 19].

*Scheme 12*



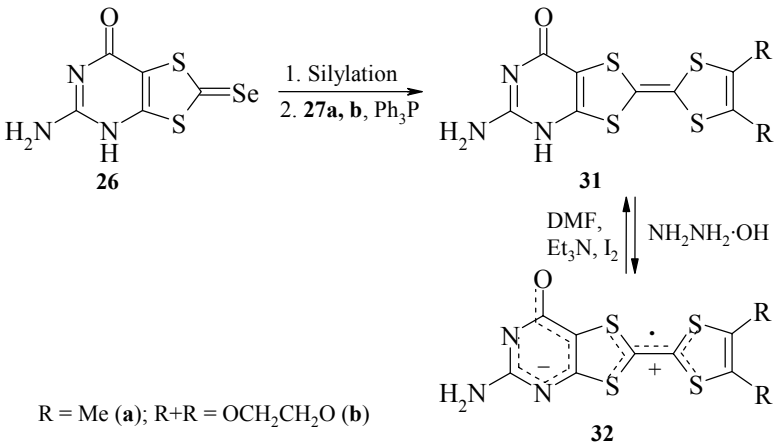

*i*: BTSA, benzene, reflux




R = Me (**a**), SMe (**b**); R+R = $SCH_2CH_2S$ (**c**), $OCH_2CH_2O$ (**d**)

Cross coupling of selone **26** with disubstituted 1,3-dithiol-2-selones resulted in disubstituted 4-amino-6-oxo(5*H*)pyrimidoTTFs **31a**, **b**. Low-soluble selones were purified upon oxidation with insoluble betaine cation radicals **32a**, **b** followed by reduction [19, 20] (Scheme 13). Betaines possess unusually high electroconductivity (single-component organic conductors [13, 19]). The chemical and electrophysical properties of dioxo- and aminooxopyrimidoTTFs have been reviewed in [21, 22].

*Scheme 13*




R = Me (**a**); R+R = $OCH_2CH_2O$ (**b**)

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