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SYNTHESIS AND STUDY OF NEW HETEROCYCLIC COMPOUNDS BASED ON PYRIMIDINE DERIVATIVES

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ABSTRACT
The presented work reflects the synthesis and transformation processes of some thio-substituted compounds on the basis of the thiopyrimidin substances, the study of their antioxidant properties in model reactions and the results of the established relationship between the structure of the synthesized compounds their antioxidant properties. Some transformations of thiouracil compounds obtained from the cyclization of cyanoacetic acid and acetoacetic acid ethyl esters containing methylene active groups and thiourea were also reflected in the presented work.
Keywords: pyrimidine derivatives, antioxidant properties, model reactions, sulfur-substituted compounds.

Introduction

As is well known, pyrimidines are six-membered heterocyclic compounds found in most natural compounds. For example, vitamin B_1 or thymine has a pyrimidine ring. Synthetic derivative-barbituric acid, sleep inducers-beronol, luminol, which are compounds of this type. Nowadays uracil and its various derivatives find broad applications among pyrimidine derivatives. It should be noted that uracil is widely used directly in the biosynthesis of nucleic acids [1-3].

Pyrimidine derivatives, cytosine, thymine and uracil are the important structural motif of nucleic acids that play an important role in the functioning of the living organism [4]. In addition pharmacophore groups containing uracil scaffold, is used against the formation of oncological tumors, the synthesis of new constituent compounds based on them is currently of urgent importance, such as 5-bromouracil and 5-fluorouracil, etc. 5-bromouracil has strong chemical mutagenic properties, so it is used to change hereditary traits by replacing one or another nitrogen base in the matrix of nucleic acid at mutation points. 5-bromouracil has found a wide field of application both as a radiosensitizer and in the treatment of oncological tumors. Among the other derivatives of uracil, 5-oxomethyl-4-methyluracil (pentoxide) and 4-methyluracil (metasyl) are powerful cold remedies. Pentoxyl, metasyl, urosyl, cytosine play an essential role in the formation of the protein part of the blood. 2,6-dioxopyrimidine-4-carboxylic acid is a primary product in the synthesis of nucleic acids [3]. 5-fluorouracil is used as a drug in oncological diseases. [5, 6]. It should be noted that, recently, literature data on the immunotropic, antiradical, and membrane stabilization properties of uracil derivatives have also been found.

Thiouracil derivatives are drugs widely used in the treatment of a number of neurological diseases as Alzheimer's, Parkinson's, Huntington's, migraine, depression and memory impairment.

It is known from the literature that thiouracil derivatives act as an inhibitor of the transcriptase of the human immunodeficiency virus in calming the nervous system.

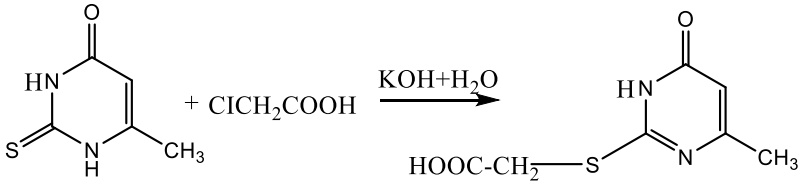
On the basis of before mentioned information, the presented study reviewed the synthesis and research of some conversion processes and synthesized new derivatives of thiouracil compounds obtained from the cyclization of cyanoacetic acid and acetoacetic acid ethyl esters containing methylene active groups and thiourea.

Results and discussion

Synthesis of pyrimidinthio derivatives and some sulfur-substituted compounds based on them

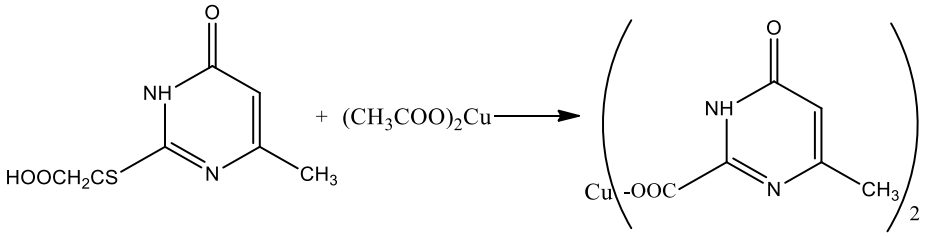
6-Methylthiouracil, which is used as a starting material in research work, was synthesized by multistep reaction from the method known in the literature. In the first step, condensation of thiourea with ester of α-keto acid occurs in the pottasium hidroxide solution in ethaol in a water bath for 30 minutes. After removing ethyl alcohol from the product, the residue is dissolved in water and neutralized with 10% chloride or acetic acid [6-12,24,25].

The corresponding carboxylate derivative 2-((4-methyl-6-oxo-1,6 -di-hydropyrimidin-2-yl)thio)acetate is obtained from the reaction of 6-methylthiouracil with chloroacetic acid in the presence with KOH solution, at room temperature for 20 hours. The reaction scheme of the process is shown below:



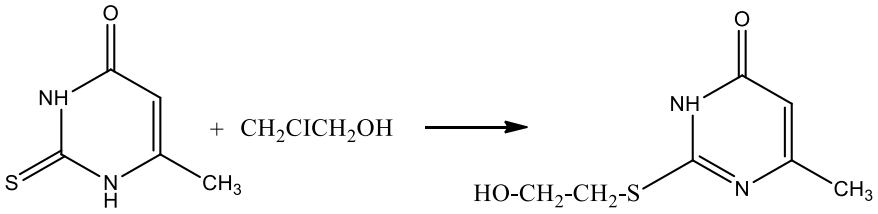
Scheme 1. Synthesis of 2-((4-methyl-6-oxo-1,6 -dihydropyrimidin-2-yl)thio)acetate

A new compound copper salt-Cu-2-((4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)thio)acetate was synthesized from the reaction of carboxylate derivative 2-((4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)thio)acetate and copper-2-acetate.



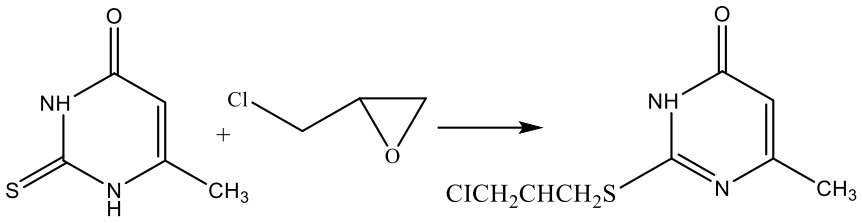
Scheme 2. Synthesis of Cu-2-((4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)thio)acetate

2-((2-hydroxyethyl)thio)-6-methylpyrimidin-4(3H)-one is obtained from the reaction of 6-methylthiouracil with ethylene chlorohydrin in the presence of KOH solution in water according to the following scheme. Usually, this reaction is carried out in a boiling water bath for 6-8 hours.



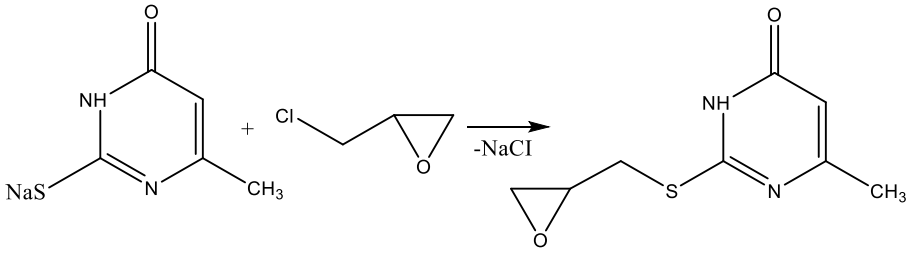
Scheme 3. Synthesis of 2-((2-hydroxyethyl)thio)-6-methylpyrimidin-4(3H)-one

Depends on conditions the reaction of 1,2-epoxy-3-chloropropane with 6-methylthiouracil occurs in two direction. 2-((3-chloro-2-hydroxypropyl)thio)-6-methylpyrimidine-4(3H)-one compound was obtained, if the reaction is proceed in a solution of potassium hydroxide in water:



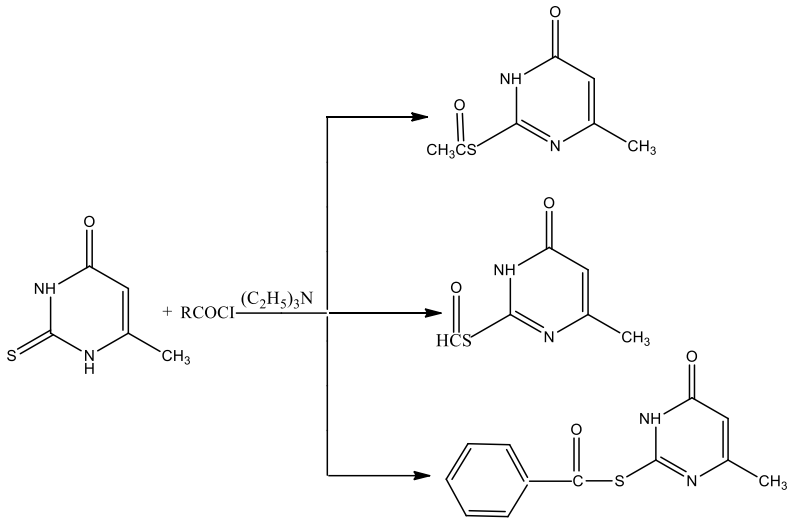
Scheme 4. Synthesis of 2-((3-chloro-2-hydroxypropyl)thio)-6-methylpyrimidin-4(3H)-one

When the reaction is carried out in the second direction, in the first step, sodium mercaptide or sodium 4-methyl-6-oxo-1,6-dihydropyrimidine-2 was synthesized from the interaction of 6-methyluracil with sodium hydroxide. Sulphur-substituted oxiranyl derivative 6-methyl-2-((oxiran-2-ylmethyl)¬thio)-pyrimidin-4(3H)-one was obtained from the interaction of sodium mercaptide with 1,2-epoxy-3-chloropropane in the next step.



Scheme 5. Synthesis of 6-methyl-2-((oxiran-2-ylmethyl)thio)pyrimidin-4(3H)-one

S-acyl derivatives like 2-(methoxythio)-6-methylpyrimidin-4(3H)-one, S-(4-methyl-6-oxo-1,6-S-dihydropyrimidin-2-yl) methanethioate, S-(4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl) benzothioate were obtained from the one pot two component reaction of 6-methylyrasil with acylation reagents as acetylchloride, benzoylchloride in the presence of triethylamine in dimethyl media at 20ºC. It was known from the studies that the acylation process happens in thione sulphur:



Scheme 6. Synthesis of S-acyl derivatives of pyrimidinethiones

Study of antioxidant properties of synthesized compounds

One of the most important problems of modern chemical science is to protect fuels and other petroleum products from the oxidation process during long-term storage or operation. Antioxidant compounds are used to protect fuels and lubricants from oxidation. At present, in the national agriculture alkylphenols, aminophenols, various sulfides, metal salts of dithiophosphate acid, etc. widely used as antioxidants additives.

Numerous scientific articles characterizing the oxidizing properties of sulphur compounds have been published. Sulfides, dithiophosphate, xanthogenate, and sulphur-containing heterocycles were used as a research objects. However, there is not enough information about the antioxidant property of sulphur-containing N-substituted thioureas. Taking into account the above, the antioxidant properties of some synthesized acyclic and cyclic thioureas, as well as their primary products, were studied in model reactions in order to determine the relationship between the structure of N-substituted thiourea derivatives and thioxidizing properties. Cumene was used as a model hydrocarbon to evaluate the antioxidant activity of the synthesized compounds. Because its oxidation mechanism has not been studied enough.

The oxidation reaction occurring in the presence of α,α-azobisisobutyronitrile initiator, in chlorobenzene solution and at 600°C temperature is used as a model reaction. The oxidation reaction was studied based on automatic compensation of oxygen pressure due to oxygen absorption in a monometric device. In all studied samples, the concentration of AIBN was stable and is 2×10^{-2} mol/l. In order to evaluate the antioxidant properties of the synthesized compounds, the kinetics of their reactions with cumyl hydroperoxide radicals and cumyl hydroperoxide were studied. The concentration of compounds which investigated antioxidant properties was learn in the range of 5×10^{-6} mol/l-3×10^{-4} mol/l. As a part of research work it was found that acyclic and cyclic thioureas, as well as isothiocyanates and benzylrhodanide slow down the oxidation of cumene with the initiator. It should be noted that all the studied compounds also have a catalytic effect on cumyl hydroperoxide, which is obtained as an intermediate product during the oxidation of cumene, and breaks it down into molecular products. The catalytic factor of the synthesized compounds varies between 4500-6000. In conclusion we can say that the studied derivatives of

thiouracil compounds belong to the class of antioxidants with a combined effect. They both break the oxidation chain by reacting with cumyl hydroperoxide radicals, and break cumyl hydroperoxide that obtained from the oxidation of cumene into catalytic molecular products.

Result

In conclusion we can say that for the synthesis heterocyclic thiouracil derivatives and for some transformations interaction of ethyl ether of cyanoacetic acid with thiourea in the presence of sodium ethylate is used.

Methylthiouracil and its sulfur-substituted derivatives were synthesized and investigated from the condensation ethyl ether of cyanoacetic acid with thiourea in the presence potassium hydroxide in ethyl alcohol media. 6-methylthiouracil was synthesized based on the reaction of ethyl ester of acetoacetic acid with thiourea in the presence of sodium hydroxide and ethyl alcohol. Reaction of 6-aminothiouracil with epichlorohydrin, 6-methylthiouracil with benzoyl chloride, formalin, monochloroacetic acid, acetyl chloride, copper (II) acetate, ethylene chlorohydrin, and sodium hydroxide was studied. The antioxidant properties of some of the synthesized compounds were analyzed and determined by model reactions, which break the chain formed by cumyl peroxide radicals and catalytically decomposition of cumyl hydroperoxide, it was determined that the catalytic factor of these compounds varied between 4500-6000.

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PİRİMİDİN TÖRƏMƏLƏRİ ƏSASINDA YENİ HETEROSİKLİK BİRLİKLƏRİN SİNTEZİ VƏ TƏDQİQİ

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XÜLASƏ
Təqdim olunan işdə tiopirimidin maddələri əsasında bəzi tioəvəz edilmiş birləşmələrin sintezi və onların çevrilmə prosesləri, model reaksiyalarda onların antioksidant xassələrinin öyrənilməsi və sintez olunan birləşmələrin strukturu ilə onların antioksidant xassələri arasında müəyyən edilmiş əlaqənin nəticələri öz əksini tapmışdır. Təqdim olunan işdə tərkibində metilen aktiv qrupları və tiokarbamid olan siansirkə turşusu və asetosirkə turşusu etil efirlərinin tsiklləşməsi nəticəsində əldə edilən tiourasil birləşmələrinin bəzi çevrilmələri də öz əksini tapmışdır.
Açar sözlər: pirimidin törəmələri, antioksidant xassələri, model reaksiyaları, kükürdlə əvəzlənmiş birləşmələr.

СИНТЕЗ И ИЗУЧЕНИЕ НОВЫХ ГЕТЕРОЦИКЛИЧЕСКИХ СОЕДИНЕНИЙ НА ОСНОВЕ ПРОИЗВОДНЫХ ПИРИМИДОВ

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РЕЗЮМЕ
В представленной работе отражены процессы синтеза и превращения некоторых тиозамещенных соединений на основе тиопиримидиновых веществ, исследование их антиоксидантных свойств в модельных реакциях, а также результаты установления связи между строением синтезированных соединений и их антиоксидантными свойствами. В представленной работе отражены некоторые превращения тиоурациловых соединений, полученных в результате циклизации этиловых эфиров цианоуксусной кислоты и ацетоуксусной кислоты, содержащих метиленовые активные группы и тиомочевину.
Ключевые слова: производные пиримидина, антиоксидантные свойства, модельные реакции, серозамещенные соединения.