Synthesis and investigation of properties of the selected five- and six-membered heterocycles containing exocyclic atoms of sulfur and selenium, with potential biological activity

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Summary of professional accomplishments
as a part of postdoctoral degree conferral procedures

Pedagogical University of Cracow
of the National Education Commission
Kraków 2016

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1. Summary of professional accomplishments as a basis for postdoctoral degree procedures,

pursuant to Art. 16 Paragraph 2 of the Act of 14 March 2003 on Academic Degrees and Academic Title and Degrees and Title in Art (Journal of Laws no. 65, item 595, with amendments).

I hereby present the cycle of six scientific papers published in academic journals indexed in the JCR between 1999 and 2015. The papers describe the research in the field of organic chemistry titled: "**The synthesis and examination of properties of selected 5 and 6-membered heterocyclic compounds containing exocyclic sulfur and selenium atoms and their potential biological activity"**.

According to bibliometric analysis the overall IF of the presented cycle amounts to 5.705, which corresponds to 90 points according to Ministry of Science and Higher Education.

1.1. List of papers constituting the core of the habilitation dissertation. Description and an assessment of my personal contribution to the papers creation

H-1. Tejchman W., Korohoda M. J., "Introduction of selenium to heterocyclic compounds. Part VII. Synthesis of 3-alkyl-5-benzylidene- and 3-alkyl-5-cinnamylidene-2-seleno-rhodanines", *Polish J. Chem*., 1999, 73, 1315-1322, (ISSN: 0137-5083), IF - 0.595.

My contribution to the preparation of the publication was to:

- the creating of research concept
- developing methods for the preparation of quaternary thiazolinium salts from 3-alkyl-5-benzylidene- and 3-alkyl-5-cinnamylidenerhodanine
- development of a method of converting the above-mentioned salt of the appropriate 3-alkyl-5-benzylidene- and 3-alkyl-5-cinnamylidene-2-selenorhodanine under the influence of gaseous Hydrogen selenide
- construction of apparatus, allowing safe operation with the gaseous Hydrogen selenide
- elaborating of collected data, taking part in the text preparation
- manuscript editing and submitting it to the Journal
- participation in preparing the answer to the Reviewers comments
- I am the first author of this publication

My share in participation of this publication is estimated at 70%

H-2. Żylewska A., Tejchman W., Korohoda M. J., Żylewski M., "Synthesis of 1,4,6-trisubstituted 2[1*H*]-pirimidineselenones", *Heterocycles,* 2003, 60, 2749 – 2760, (ISSN: 0385-5414 print / 1881-0942 online), DOI: 10.3987/COM-03-9865, IF-1,082, 15 pkt. MNiSW

My contribution to the preparation of the publication was to:

- developing methods for the preparation of quaternary pyrimidynium salts from 1,4,6-trisubstituted 2[1*H*]-pyrimidinethiones
- development of a method of converting the above-mentioned salt of the appropriate 1,4,6-trisubstituted 2[1*H*]-pyrimidineselenones under the influence of gaseous Hydrogen selenide
- I was involved in the interpretation of the results of spectral measurements and text editing of the publications

My share in participation of this publication is estimated at 35%

H-3. Tejchman W., Zborowski K., Łasocha W., Proniewicz L. M., "Selenomaltol – synthesis, spectroscopy and theoretical calculations", *Heterocycles,* 2008, 75, 1931 – 1942, (ISSN: 0385-5414 print / 1881-0942 online), DOI: 10.3987/COM-08-11337, IF-0.98, 20 pkt. MNiSW

My contribution to the preparation the publication consisted of:

- main contribution to the research concept preparing
- development of a method for preparing of selenomaltol with using tetraphosphorus dekaselenide generated in the reaction medium from selenium and phosphorus
- optimizing the reaction conditions to achieve the highest possible efficiency of the process
- interpretation of IR spectra and EI MS spectra
- preparation of the first manuscript version and discussion with the other Authors
- submission of the final manuscript version to the Journal
- participation in answering the Reviewers comments
- I was involved in the interpretation of the NMR data and calculation results

I am the first author of this publication and the corresponding author

My share in participation of this publication is estimated at 60%

H-4. Tejchman W., Proniewicz L. M., Zborowski K., "Molecular properties of selenomaltols: new interesting ligands for bioactive metal complexes", *J. Phys. Org. Chem.* 2015, 28, 533 – 541, (ISSN: 2015–3230 print / 1099-1395 online) DOI: 10.1002/poc.3443 IF – 1,38, 20 pkt. MNiSW

My contribution to the preparation the publication consisted of:

- main contribution to the research concept preparing
- preliminary interpretation of calculated data and preparing the first manuscript version that was the subject of further discussion
- manuscript editing and submitting to the Journal
- taking part in the discussion with the Reviewers

I am the first author of this publication and the corresponding author

My share in participation of this publication is estimated at 45%

H-5. Tejchman W., Żesławska E., Zborowski K., Nitek W., Żylewski M., „The synthesis, molecular structure and spectra properties of sulfur and selenium deferiprone analogues", *ARKIVOC*, 2015, VII, 216 – 230, (ISSN: 1551-7004 print / 1551-7012 online) DOI: 10.3998/ark.5550190.p009.262, IF – 1,165, 20 pkt. MNiSW

My contribution to the preparation the publication consisted of:

- developing concept of work
- a modified method for preparing thiodeferipne tiodeferipronu using Lawesson's Reagent and HMDSO
- developing method for the preparation selenodeferiprone using Woollins' Reagent and HMDSO
- optimize the reaction conditions to achieve the highest possible efficiency of the process
- interpretation of IR spectra and EI MS
- I took part in text editing of the publication
- conducting correspondence with the editor and answering to reviewers
- I also took part in the interpretation of the NMR data and calculation results

I am the first author of this publication and the corresponding author

My share in participation of this publication is estimated at 60%

H-6. Żesławska E., Nitek W., Tejchman W., "The synthesis and crystal structures of the homologues of epalrestat", *Journal of Chemical Crystallography*, 2015, 45, 151 – 157, (ISSN: 1074-1542 print / 1572-8854 online) DOI 10.1007/s10870-015-0577-z, IF- 0,503, 15 pkt. MNiSW

My contribution to the preparation the publication consisted of:

- share in developing concept of work
- develop a modified method for preparing rhodanine 3-karboxyalkyl acids
- develop a modified condensation method rhodanine 3-karboxyalkyl acids with cinnamic aldehyde and α-methyl-cinnamic aldehyde
- interpretation of the spectra IR, EI MS, ^{1}H NMR i ^{13}C NMR
- I took part in text editing of the publication

My share in participation of this publication is estimated at 60%

Total nuber of articles: 6

Totality IF: 5,705

The synthesis of all the compounds described in papers **H-1** to **H-6** was conducted at Laboratory of Chemistry, Pedagogical University of Cracow. (Previously Independent Unit of Chemistry, next Department of Chemistry, afterwards Unit of Chemistry and Chemistry Teaching, currently Laboratory of Chemistry). The IR and UV spectra were also obtained at Laboratory of Chemistry.

The EI MS and ES MS spectra of the compounds described were conducted at Regional Laboratory of Physicochemical Analysis and Structural Research, Faculty of Chemistry, Jagiellonian University and Department of Biochemistry and Neurobiology, University of Science and Technology.

Combustion analysis was conducted at Elemental Analysis Laboratory, Faculty of Chemistry, Jagiellonian University.

^{1}H NMR, ^{13}C NMR and ^{77}Se NMR spectra were conducted at NMR Spectroscopy Laboratory, Department of Chemistry, Jagiellonian University Medical College and Jagiellonian Centre for Innovation Ltd. in Kraków.

The crystallographic structure was examined at Department of Crystal Chemistry and Crystal Physics, Faculty of Chemistry, Jagiellonian University.

Calculations of the energy of resonance structures and locations of the bands in ^{1}H NMR and ^{13}C NMR spectra were conducted by dr Krzysztof Zborowski at Department of Chemical Physics, Faculty of Chemistry, Jagiellonian University thanks to cooperation with Interdisciplinary Centre for Mathematical and Computational Modelling, University of Warsaw (project G17-8) and Academic Computer Centre CYFRONET AGH.

2. Description of the conducted research and obtained results

2.1. Introduction

The synthesis of new chemical compounds that do not exist in nature is important to many fields of economy. The synthesis of substances having specific biological activity to be used in medicine is one of the dynamically developing areas. Natural remedies have been used for a long time, however, very often they are not effective enough. What is more, their price is very often high due to the limited access to the natural resource or the low quantity of the bioactive component in the animal or plant derived raw material. This is why new bioactive substances are being sought.

Antibiotic therapy is a very important element of treating patients with bacterial infections. However, since antibiotics were introduced to medicine the microorganisms have been acquiring resistance to the substances used.[i] Significant growth in the resistance of many pathogenic bacteria strains to medicine commonly used poses a vital threat to public health. This is why it is essential to precisely define drug resistance and look for new substances able to fight pathogens.[ii]

The research into bioactivity of derivatives of 2,4-thiazolidinediones (rhodanines) suggest that rhodanines usually have greater bioactivity than their oxygen analogues.[iii] It will certainly be interesting to have the possibility to compare characteristics of a specific chemical compound depending on the type of the heteroatom coming from the same group of the periodic table.

The atomic radius of selenium and sulfur are similar. What is more their electronegativity on Pauling scale is similar and the C=Se double bond has a similar nature as the C=S[iv] bond. It may be expected that replacing sulfur with selenium will result in at least similar or grater bioactivity of appropriate isologous derivatives. The case of replacing oxygen with sulfur is similar. On the other hand, it is known that selenium compounds are often more toxic than then their sulfur analogues,[v] which is a serious obstacle in medical use. The fact that the derivatives

where selenium atom is part of a stable system have toxicity comparable with toxicity if their sulfur analogues brings some hope for medical use of the compounds containing selenium.[vi]

The toxicity of selenium organic compounds has been known for a long time. Excess of selenium in everyday diet results in atrophy of the cardiac muscle, nails, tooth decay, apathy.[vii] However, in 1957 it was proved that selenium deficiency in diet result in serious illnesses. The body is prone to liver degeneration, muscle dystrophy and hair loss.[viii]

In their monograph devoted to selenium organic compounds Klayman and Günther in one of the chapters analyse the potential therapeutical use of these compounds. Their antiparasitic, antibacterial and antifungal use was described. The properties of selenium isologues of the substances used as hypnotic and sedative drugs i.e. thiobarbiturates and phenothiazines were also examined. Similar research was conducted into compounds demonstrating anti-inflammatory activity and influencing autonomic nervous system. It was established that selenopurine and selenopyrimidine bases have similar antineoplastic activity as their sulfur analogues.[ix]

The connection between the quantity of selenium in the body with cancer incidence rate has been know since the 1950s. However, the mechanisms of its protective activity have not been fully examined yet. It seems that one of the elements of protective activity of this element is its presence in the active centre of the antioxidant enzymes. One of the best known enzymes is glutathione peroxidase GSH-P_x, which eliminates free radicals that develop during the processes happening in the body.[x]

One of the antioxidant factors is 2-phenyl-1,2-benzisothiazol-3[2H]-one also known as ebselen. It demonstrates antioxidant activity and activity similar to glutathione peroxidase. The compound has little toxicity in comparison to other compounds containing selenium, which probably results from a different way of its metabolism in the body.[xi]

Antibacterial activity is demonstrated by, among other things, selenazole derivatives, which hinder the development of Gram-positive and Gram-negative bacteria.[xii] Similar activity characterises the derivatives of 1,2,3-selenadiazole.[*xiii*]

In the light of the research presented it can be expected that sulfur and selenium analogues of the bioactive compounds having in their structure an oxygen atom will also be bioactive. It is possible that their activity will even be greater than of their analogues containing oxygen.

To synthesise heterocyclic compounds with an exocyclic selenium atom I used in my research as the starting compounds the derivatives of **2-thio-thiazolidine-4-one, 1,4,6-trisubstituted 2[1*H*]-pyrimininones and pyrimidinethiones, 3-hydroxy-2-methyl-4-pyrone and 3-hydroxy-1,2-dimethyl-4[1*H*]-pyridinone.**

2.2. The review of synthesis methods of heterocyclic compounds containing exocyclic oxygen, sulfur and selenium atom in the process of building a skeleton containing appropriate heteroatoms

There are two basic methods to synthesise five- and six-membered heterocyclic ring systems containing exocyclic oxygen, sulfur or selenium atoms.

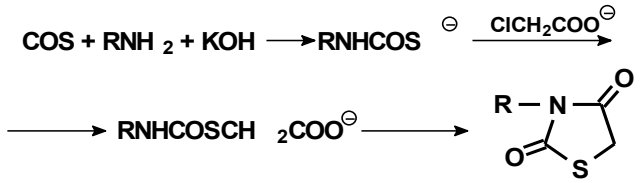
In the first one, appropriate skeleton is built out of components, whereas in the second one, a specific heteroatom is replaced with a different heteroatom in already built system.

The method of building a heterocyclic system skeleton from the appropriate elements containing heteroatoms is widely used to obtain heterocyclic compounds containing oxygen or sulfur. It is not usually used to synthesise compounds having a C=Se group. It is possible to obtain selenium analogues of the appropriate thioderivatives, for example isoselenocyanate, however, their practical uses in laboratory is very difficult. What is more, these compound are highly toxic, very often have an acrid smell and are unstable.[xiv]

The compounds containing exocyclic selenium atom are usually obtained in the process of replacing the oxygen or sulfur atom with selenium in an already obtained heterocyclic system. This method is also used to obtain derivatives containing an exocyclic sulfur atom from appropriate oxygen analogues. In some cases, the sulfur atom is replaced with an oxygen atom to obtain oxygen analogues. This procedure is also used when obtaining an oxygen analogue is not possible in another way or occurs with low efficiency.

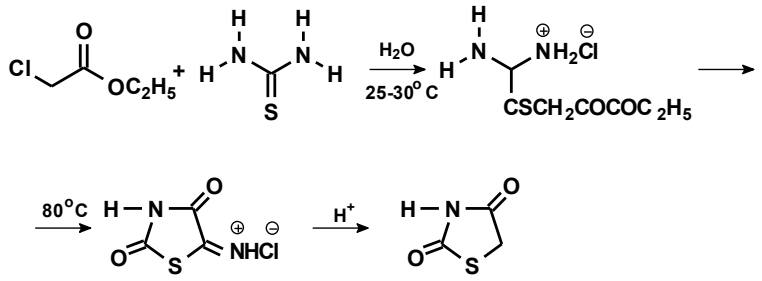
2.2.1. Synthesis of thiazolidine-2,4-diones

Thiazolidine-2,4-diones are very often used as the starting compounds to synthesise sulfur analogues. There are a few known methods to synthesise the thiazolidine-2,4-dione system. Most of them were devised at the end of the 19th or the beginning of the 20th century. One of the oldest methods of thiazolidine-2,4-dione synthesis is the reaction proposed by Holmber in 1909. It bases on the reaction of carbon oxysulfide with ammonia and potassium hydroxide.[xv] The modification of the method is based on replacing ammonia with primary amines and allows to obtain thiazolidine-2,4-diones derivatives substituted at the N-3 position. (Scheme 1).



Scheme 1. Synthesis of thiazolidine-2,4-diones from carbon oxysulfide

A convenient method to synthesise this system is also the reaction of α-chloroacetic acid or its esters with thiourea or N-substituted thioureas. When the reaction is conducted at the temperature of 25 – 30°C it results in thiouronium salts, which undergo ring closure to 2-iminothiazolidine-4-ones after heating the reaction mixture to the temperature of around 80°C. In the acidic environment at the temperature of around 110°C 2-iminothiazolidine-4-ones undergo hydrolysis to thiazolidine-2,4-diones. (Scheme 2).



Scheme 2. Synthesis of thiazolidine-2,4-diones from thioureas.

In some cases the direct synthesis of thiazolidine-2,4-diones derivatives does not bring expected results. It is possible then to replace the sulfur atom in thiazolidine-2,4-dione with an oxygen atom when exposed to chloroacetic acid. (Scheme 3).

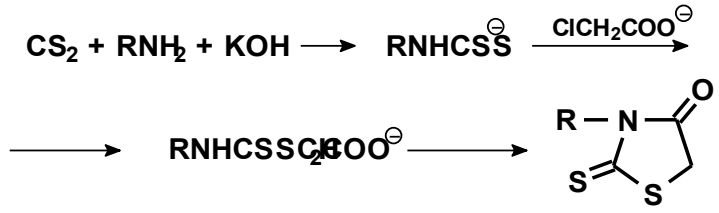
Scheme 3. Obtaining thiazolidine-2,4-dione in sulphate reduction of 2-thiothiazolidine-4-ones

2.2.2. Synthesis of 2-thiothiazolidine-4-ones

The methods to synthesise the system of 2-thiothiazolidine-4-one (rhodanine) are fully described in the overview studies.[xvi,xvii] I am going to focus on a few selected methods I used in my research. The methods have been modified by me in order to simplify the procedure and increase efficiency.

One of the oldest methods used to synthesise rhodanine derivatives having or not substitutes at the N-3 and N-5 positions is the reaction of ammonium dithiocarbamate with α-

halogenocarboxylic acids or their salts.[xviii] Dithiocarbamate are obtained in the reaction of carbon disulphide ewith ammonia or primary amines and sodium hydroxide. Their reaction with sodium chloroacetate leads to connections easily undergoing cyclocondensathion to appropriate rhodanine derivatives when exposed to hydrochloric acid (Scheme 4).



Scheme 4. Synthesis of 2-thiothiazolidine-4-ones from dithiocarbamates

The method has also been adopted to synthesise rhodanine derivatives having a carboxyalcyl group at the N-3 position. Amino acids having the amino group at the final carbon atom react with carbon disulphide and chloroacetic acid in the presence of bases.

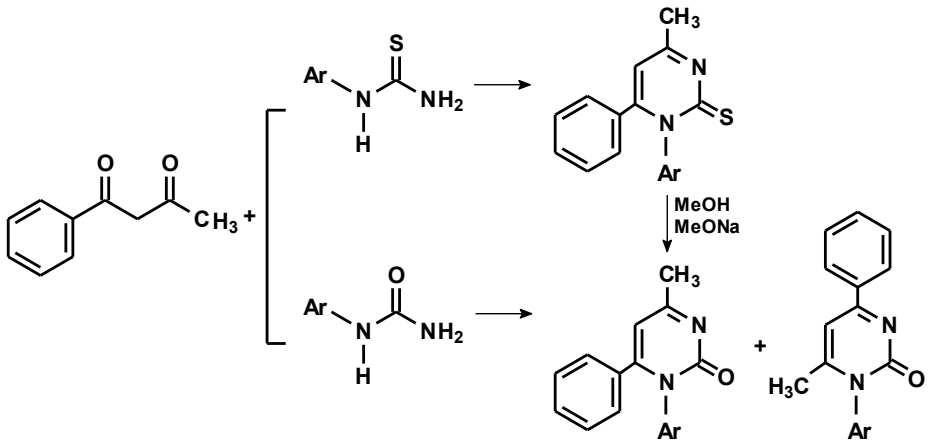
The rhodanine derivatives having a substitute at the N-3 position may also be obtained in the reaction of alkyl- or arylisothiocyanines with α-mercaptoacetic acid or its esters. The resulting intermediate product, after acidifying the reaction environment, undergoes cyclisation to 3-substituted rhodanine.[xix] (Scheme 5).

Scheme 5. Synthesis of 2-thiothiazolidine-4-ones from isothiocyanines

2.2.3. Synthesis of unsimetrically 1,4,6-trisubstituted 2[1H]-pyrimidones and pyrimidinethiones

The synthesis reaction of 1,4,6-trisubstituted 2[1*H*]-pyrimidiones and pyrimidinethiones was investigated by Katoh *et al*. Conducting the reaction of benzoylacetone with N-phenylurea they obtained 1,4-diaryl-6-methyl-2-[1*H*]pyrimidinone and 1,6-diaryl-4-methyl-2-[1*H*]pyrimidinone. Similar reactions conducted with N-arylthiourea lead to 1,6-diaryl-4-methyl-2-[1*H*]pyrimidinethiones only.[xx] These compounds were easily transformed to

appropriate 2-[1*H*]pyrimidinones when treated with methyl iodide in the presence of sodium methoxide in methanol. (Scheme 6).

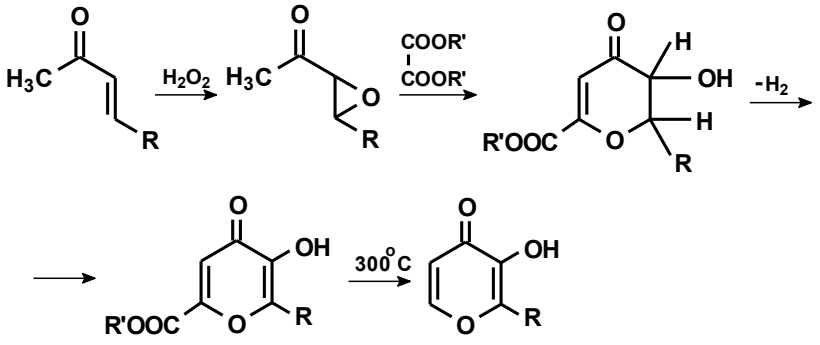


Scheme 6. Synthesis of 1,4-diaryl-6-methyl- and 1,6-diaryl-4-methyl-2[1*H*]-pyrimidinones

2.2.4. Synthesis of 3-hydroxy 2-methyl-[4H]-pyran-4-one (maltol)

Maltol in nature can be found in European larch (*Larix deciduas*), the Katsura (*Cercidiphyllum japonicum*) and plants in the Pinacae family. It is produced in the biosynthesis process from saccharides belonging to the hexose group.[xxi]

On the industrial scale it can be produced from, among other things, unsaturated ketones. The first stage of the reaction is epoxidation of ketone. The resulting epoxide undergoes cyclization with dicarobxylic acid esters and then dehydrogenation. The final stage of the reaction is decarboxylation conducted in high temperature.[xxii] (Scheme 7).

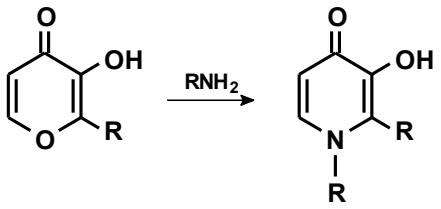


Scheme 7. Synthesis of 3-hydroxy 2-methyl-[4*H*]-pyran-4-one (maltol)

2.2.5. Synthesis of 3-hydroxy-1,2-dimethylpyridin-4[1H]-one (deferiprone)

The synthesis of 3-hydroxy-1,2-dimethylpyridin-4[1*H*]-one system (deferiprone) was first conducted at the laboratory of Professor Hider in 1980. In the method used maltol was the

starting compound, which in the reaction with methylamine was transformed to deferiprone.[xxiii] Until today it is the only method of synthesising this system described in the scientific literature.



Scheme 8. Synthesis of 3-hydroxy-1,2-dimethylpyridine-4[1*H*]-one (deferiprone)

2.3. Methods of synthesising heterocyclic compounds with the exocyclic atom of sulfur or selenium through replacing the oxygen atom in the carbonyl group with a sulfur or selenium atom

The research aimed at obtaining sulfur and selenium analogues of compounds containing a carbonyl group have been conducted for a long time. It is connected with their greater toxicity and expected therapeutic activity, as well as the possibility to use the resulting compounds as intermediates in further synthesis.

2.3.1. Application of phosphorus pentasulfide to create the C=S bond

In the process of replacing the oxygen atom in the carbonyl group with a sulfur atom a whole series of derivatives of thioesters, thioketones, thioamides and other is produced.

One of the reagents used to replace the oxygen atom in the carbonyl group with a sulfur atom is phosphorus pentasulfide, P_4S_{10}. It has been used for a long time, since the second half of the 19th century.[xxiv,xxv]

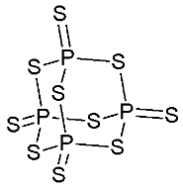


Figure 1. Structure of phosphorus pentasulfide

It is used, among other things, to synthesise dithiocarboxylic acid esters, which are versatile precursors of compounds having antibacterial, antifungal and antineoplastic activity.[xxvi]

At present the reagent is widely used in combination with hexamethyldisiloxane, among other things, to synthesise sulfur analogues of esters, lactones, lactames, amides and ketones.[xxvii]

2.3.2. Application of Lawesson's reagent in C=S bond creation

In recent years 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-dithione, commonly known as Lawesson's reagent (LR), gained great popularity as a sulfurising reagent. The compound was synthesised for the first time by Leher *et al.* in 1956 during the research into reactions of aromatic compounds with phosphorus pentasulfide.[xxviii] In their work they observed that the reactions have to be conducted in a specific range of temperatures. If the temperature was too low, they did not obtain the expected products, whereas if the temperature was too high, tar was produced. The authors suggested that the compounds obtained exist as dimers, which are stable due to electrostatic force between polarized phosphor-sulfur bonds.

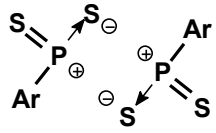
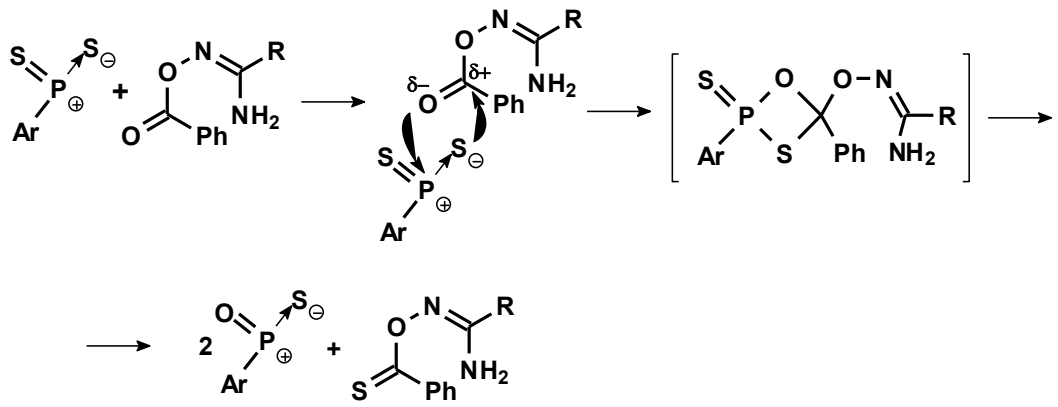


Figure 2. Proposed structure of products of P_4S_{10} reaction with aromatic compounds.

The application of this reagent was popularised by Lawesson *et al.* by conducting synthesis of thioketones with it.[xxix] The replacement of the oxygen atom with a sulfur atom with LR is usually conducted by dissolving the reagents in toluene, xylene, dioxane or pyridine and the reaction is conducted in the boiling temperature of the solvent. It is highly important to select the appropriate stoichiometric ratio of the reagents and time of the reaction, as there are known cases of introducing sulfur atoms in two different places of the heterocyclic system when the time of the process was extended.[xxx]

The probable mechanism of replacing an oxygen atom with a sulfur atom with LR might be presented with the example of reaction to obtain O-thiobenzoyl-*β*-aminopropioamidoximes.[xxxi]



Scheme 9. Expected functioning mechanism of LR

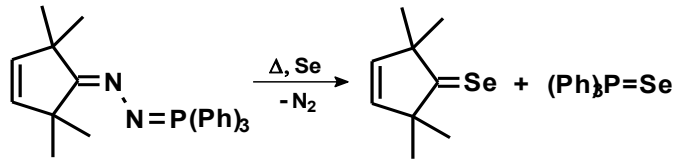
The Lawesson's reagent might also be used solvent-free. The reaction between Lawesson's reagent and xanthine derivatives stimulated with microwaves allowed to obtain sulfur analogues of, among other things, caffeine and theobromine containing exocyclic sulfur atoms at the C-6 position and C-6 and C-2 positions.[xxxii]

2.4. Method of introducing selenium atom in place of other heteroatom

Various selenating reagents are used to replace other heteroatom with a selenium atom with simultaneous production of a C=Se bond. There are methods devised that use elemental selenium, sodium hydroselenide, hydrogen selenide, tetraphosphorus decaselenide, potassium selenocyanate, bis(trimethylsilyl) selenide, tetraethylammonium tetraselenotungstate $(Et_4N)_2WSe_4$, and 2,4-diphenyl-1,3,2,4-diselenadiphosphetan-2,4-diselenide, commonly known as Woolins' reagent (WR).[xxxiii] In the further parts of the paper I am going to focus on the methods of introducing selenium into heterocyclic system that I have used in my research only.

2.4.1. Reactions with selenium

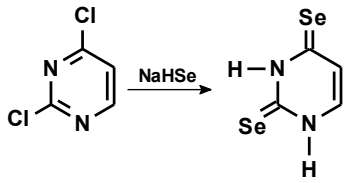
An example of using grey selenium to obtain selenoketones is the reaction of replacing triphenylphosphonium group in triphenylphosphoranylidenohydrazones. The occurring elimination of the nitrogen particle from the compound obtained led directly to producing appropriate selenoketone. The method was used to obtain mainly cyclic selenoketones with good efficiency.[xxxiv,xxxv] (Scheme 10)



Scheme 10. Synthesis of cyclic selenoketones

2.4.2. Reactions with sodium hydroselenide

One of the first suggestions to use sodium hydroselenide anion to create the C=Se bond was put forward by Mauner, who obtained selenium derivatives of pyrimidine and purine in the process of replacing halogen with a selenium atom.[xxxvi] (Scheme 11)



Scheme 11. Synthesis of [1*H*]-pyrimidine-2,4-diselenone

Similar reaction was also successfully conducted when obtaining selenium derivatives of pyridines. Shestopalov *et al.* obtained 4,5,6-trisubstituted-3-cyano-2-selen-[1*H*]-pyridines from 4,5,6-trisubstituted-3-cyano-2-chloropyridines.[xxxvii]

Sodium hydroselenide, which is the main source of hydroselenide anions necessary to conduct these reactions, was obtained through saturating alcohol solution of sodium hydroxide with hydrogen selenide under nitrogen. Due to the toxicity of hydrogen selenide and its irritating smell, this method was very uncomfortable.

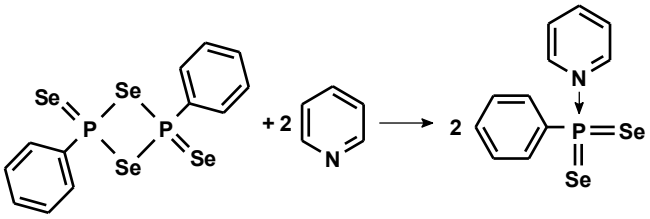
Klayman and Griffin devised a very easy method to generate sodium hydroselenide. In their method, grey selenium reacted with sodium borohydride in ethanol in the atmosphere of nitrogen. The alcohol solution of sodium hydroselenide had relatively high pH (ca. 8) and could be safely used for further synthesis.[xxxviii]

2.4.3. Application of Woollin's reagent in creating C=Se bond

In recent years Woollin's reagent (WR) has gained wide recognition as a selenating reagent. Its first synthesis was conducted during research into organophosphorus ring systems with a general formula $(RP)_xSe_y$. They were obtained in the reaction of cyclophosphines $(PR)_5$ (R = Me, Et, 4-$Me_2NC_6H_4$, Ph) with grey selenium.[xxxix] Heterocyclic compounds containing

phosphor and selenium were described in detailed in review papers.[xl,xli] A method allowing to obtain great quantities of WR, ca. 150g, was also devised.[xlii]

Woollin's reagent is a dimer $(PhPSe_2)_2$, which in reaction conditions decomposes to a monomer PhPSe2, which is the actual selenating reagent. It exhibits a very unusual bonding situation: phosphorus is in the formal oxidation state of +V but only tricoordinated. Due to the fact that the $\sigma^3\lambda^5$ coordination sphere of phosphates is not saturated they exhibit high Lewis acidity. It has been recently demonstrated that stabilising this bond system without high volume substitutes is possible when pyridine is used.[xliii]



Scheme 12. WR stabilisation with pyridine

High Lewis acidity of the phosphor atom in the Woollin's reagent is the reason why it easily reacts with nucleophilessuch as, among other things, methanol, alkynes or dienes. What is more, it may easily undergo nucleophile attack of the oxygen atom from the carbonyl group. As a result, it leads to the replacement of the oxygen atom with a selenium atom and results in a selenocarbonyl compound.

3. Description of own research

3.1. Research goal

In nature there are a lot of compounds that contain heteroatoms. They are usually oxygen or nitrogen atoms. The group of compounds containing sulfur atoms is also quite numerous. Sulfur-containing amino acids, methionine and cysteine, are very important for living organisms. Thiamine containing a fragment of thiazole is also important. There are also thiols and thioethers in nature.

There are much fewer compounds in nature that contain selenium atoms. Selenomethinine and selenocystein seem to be the most important ones. They are present in proteins having important physiological functions. The examples are gluthathione peroxidases (GP_x),[xliv] thiredoxine reductase (TrxR),[xlv] and iodothyronine deiodinases (D1).

The main aim of my research was to devise a method of synthesising previously unknown sulfur and selenium analogues of five- and six-membered hetercyclic compounds containing oxygen and having proven bioactivity. Conducting the synthesis of such compounds will allow to compare physicochemical properties of sulfur and selenium analogues with the precursor compounds containing oxygen. In case of obtaining compounds of sufficient stability, it will be possible to compare their bioactivity.

All these factors made me decide to continue the research into the synthesis of rhodanine derivatives and selenium rhodanine analogues substituted at the N-3 and C-5 positions and expand it to the synthesis of sulfur and selenium analogues of 2[1H]-pyrimidinones, maltol and deferiprone, after I defended my PhD thesis.

I would like to express my deepest gratitude and thank all the colleagues who contributed to the research.

3.2. Synthesis of rhodanine selenium analogues [Paper H-1]

Starting the research into the synthesis of 3-alkyl-5-benzylidene- and 3-alkyl-5-cinnamylidene-2-selenorhodanin was the continuation of previous research into the synthesis of appropriate 2-selenorhodanine derivatives having an aryl substitute at the N-3 position. The aim of the undertaken research was to compare the influence of the type of the substitute at the N-3 position on the reactivity of the rhodanine system and susceptibility to activity of appropriate selenating agent.

The starting compounds used for the synthesis were 3-alkyl-5-bezylidenerhodanines and 3-alkyl-5-cinnamylidenerhodanines. These derivatives were obtained in the Knoevenagel reaction between 3-akylrhodanines and benzaldehyde and cinnamaledehyde respectively. The condensation reaction was done according to the procedure that I had modified basing on previous work.[xlvi] The modification was to use acetic anhydride as a solvent that was also a dehydrating agent.

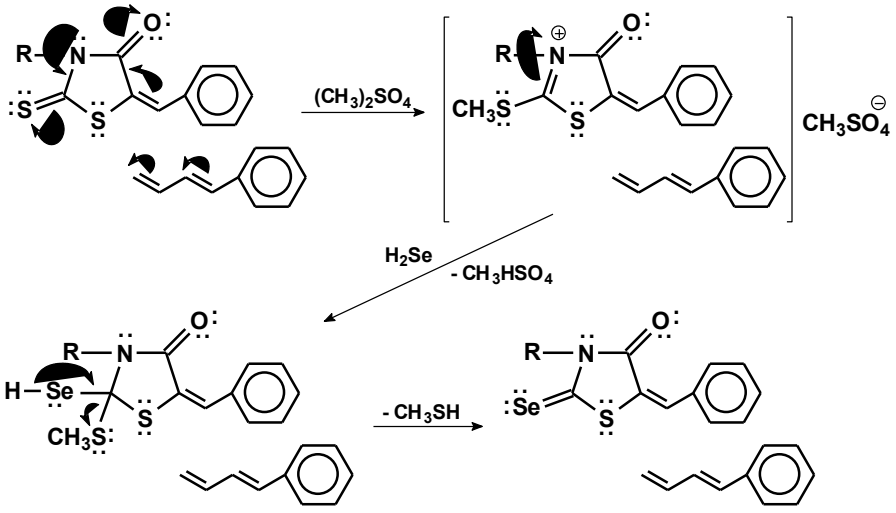
In the previous work on introducing a selenium atom in the place of sulfur in the 2-thioxoimidazolidin-4-one (2-thiohydantoin) system and 2-thiothiazolidin-4-one (rhodanine) system it was proved that to conduct the reaction two criteria have to be met:[xlvii,xlviii]

- a tautometric form having a HS- group and a double bond within the ring have to be formed,

• the sulfur atom from the HS- group has to undergo methylathion, which results in the easily deriving CH_3S- group.

In the work on the synthesis of 3-aryl-5-benzylidene- and 3-aryl-5-cinnamylidene-2-selenothiazolidin-4-ones it was proved that it is possible to replace the arylimine group with selenium in 3-aryl-5-benzelidene- and 3-aryl-5-cinnamylidene-2-aryliminothiazolidine-4-ones.[xlix] The condition to conduct the reaction was obtaining relatively stable ammonium quaternary salts in the process of methylation of nitrogen atom being part of the 2-arylimin group.

Basing on the information given, I decided to check if it is possible to obtain thiazoline quaternary salts from 3-alkyl-5-benzylidene and 3-alkyl-5-cinnamylidene-2-selenorhodanins and check if they will be susceptible to gaseous hydrogen selenide. (Scheme 13)



Scheme 13. Proposed mechanism of replacing sulfur atom with selenium atom

I obtained the expected thiazoline quaternary salt with a SCH_3 through treating the starting compounds 3-alkyl-5-benzylidene and 3-alkyl-5-cinnamylidene-2-selenorhodanins with a tenfold excess of dimethyl sulphate. I did not isolate the salts from the reaction environment. Directly after obtaining I treated them with gaseous hydrogen selenide. As a result of the reaction I obtained 3-alkyl-5-benzylidene and 3-alkyl-5-cinnamylidene-2-selenorhodanin respectively. Conducting the reaction in the protective gas (nitrogen) atmosphere and without it allowed to prove that thiazoline salts having at the C-5 position a cinnamylidene substitute are resistant to oxygen from air, whereas the salts having at C-5 the C-5 position a benzylidene substitute are not. In the presence of the oxygen from the air the salt underwent oxidation which

resulted in 3-alkyl-5-benzylidene-thiazolidine-2,4-dione instead of 2-selenorhodanin. Both benzylidene and cinnamylidene substituents at the C-5 position cause an increase of the electron density within the heterocyclic ring. It seems that greater resistance to oxidation of the thiazoline salts having at the C-5 position a cinnamylidene substituent in comparison to the salts having a benzylidene substituent might be explained through lower electron deficit on the carbon atom at the C-2 position due to the cinnamylidene substituent.

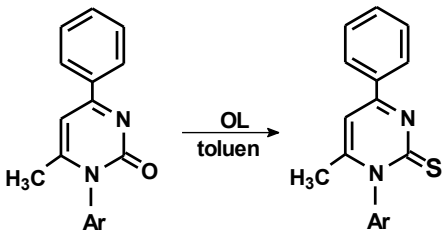
The structure of the compounds obtained was confirmed by elemental analysis and spectroscopic methods. EI MS, IR, UV and ^{1}H NMR.

3.3. Synthesis of selenium analogues of 2[1H]-pyrimidinones [Paper H-2]

A group of compounds having interesting biological properties are 2[1*H*]-pyrimidones derivatives and their sulfur analogues. They have, among other things, antibacterial, antifungal and anti-inflammatory properties.[1]

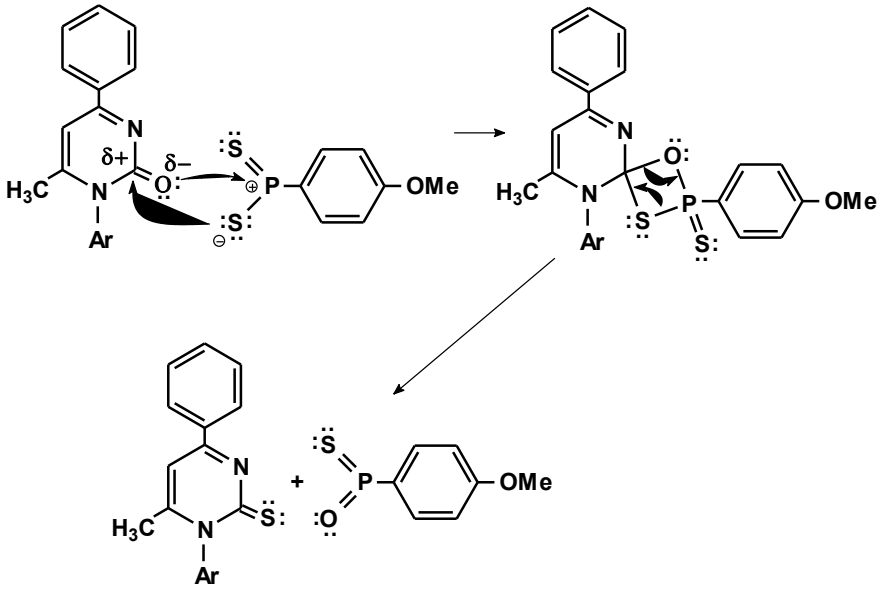
This is why I became interested in obtaining 1,4,6-trisubstituted 2[1H]-pyrimidineselenones. Their synthesis would allow compare the properties of selenium analogues with previously described sulfur and oxygen analogues.

1-aryl-4-methyl-6-phenyl-2[1*H*]-pyrimidinethiones and 1-aryl-6-methyl-4-phenyl-2[1*H*]-pyrimidinethiones were used as the starting compounds. 1-aryl-4-methyl-6-phenyl-2[1*H*]-pyrimidinethiones were obtained in benzoylacetone condensation with appropriate arylthioureas. This method failed in the attempt to obtain 1-aryl-6-methyl-4-phenyl-2[1*H*]-pyrimidinethiones. The synthesis of expected derivatives was conducted in two stages. First, 1-aryl-6-methyl-4-phenyl-2[1*H*]-pyrimidinones were obtained in the reaction of benzoylacetone with N-arylureas.[xx] In the second stage, I transformed 1-aryl-6-methyl-4-phenyl-2[1*H*]-pyrimidinones to appropriate pyrimidinethiones in the reaction with Lawesson's reagent. (Scheme 14).



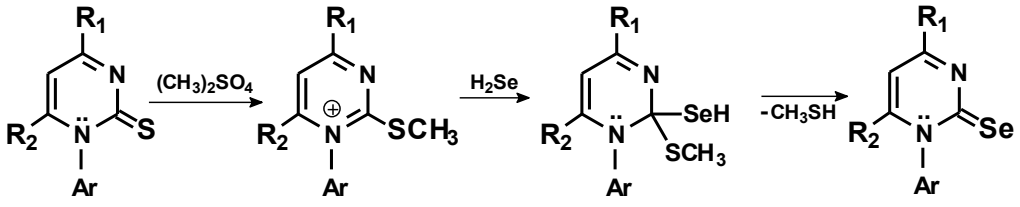
Scheme 14. Synthesis pyrimidinethiones in the reaction with Lawesson's reagent

The probable mechanism of the course of the reaction, analogical to the described previously sulfation mechanism of O-benzoyl- *β*-aminopropioamidoximes[xxxi] is presented in scheme 15.



Scheme 15. Suggested mechanism of replacing exocyclic oxygen atom with sulfur atom in 1-aryl-6-methyl-4-phenyl-2[1*H*]-pyrimidinones

In the previous paper [**H-1**] I stated that one of the conditions of transforming thiones into appropriate selenones is obtaining relatively stable quaternary pyrimidine salts with a positive charge on the nitrogen atom and the SCH_3 group at the C-2 position. In order to obtain them, pyrimidinothiones were treated with dimethyl sulphate under nitrogen. These salts were transformed to appropriate of 1,4,6-trisubstituted 2[1*H*]-pyrimidineselenones under the influence of HSe^- anions coming from gaseous hydrogen selenide. (Scheme 16).



R_1, R_2 = Me lub Ph

Scheme 16. Proposed mechanism of synthesis of 1,4,6-trisubstituted 2[1*H*]-pyrimidine-selenones

The structure of the obtained compounds was confirmed by elemental and spectral analysis: ^{1}H NMR, ^{13}C NMR, UV and IR. It was established that replacing the sulfur atom with a selenium atom that causes no significant changes in ^{13}C NMR spectra. In pyrimidineselenones ^{1}H NMR spectra there were shifts down of the fields coming from the proton at the C-5 position (vinyl) in comparison to pyrimidionothione spectra. This change in chemical shift can be explained through different electronegativity of sulfur and selenium in combination with electron properties of α,β-unsaturated carbonyl system.

For all obtained 1,4,6-trisubstituted 2[1*H*]-pyrimidineselenones 2D NOESY spectra were also examined. Significant NOE signal for both isomers are shown in figure 14.

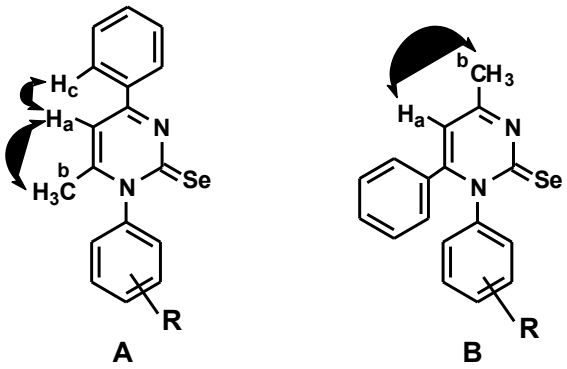


Figure 3. Significant NOE interaction in 1-aryl-6-methyl-4-phenyl-2[1*H*]-pyrimidineselenones (A) and 1-aryl-4-methyl-6-phenyl-2[1*H*]- pyrimidineselenones (B)

The interaction between the proton in the phenyl H_c group and the H_a vinyl proton in the 1,4-diaryl- derivatives is possible only when the phenyl ring and the pyrimidine ring are in the same plane. On the other hand, there are no such interactions between the methyl group and protons of aryl ring substituted at the N-1 position, which suggests that the plane of this ring is strongly bent in relation to the pyrimidine plane. It is possible that both planes are even at the right angle.

Similar situation occurs in the 1,6-diaryl- derivatives, where there are no interactions between aromatic protons of both aryl substituents and between aromatic protons of the phenyl ring and the H_a vinyl proton, which allows to assume that the planes of both aromatic rings of these derivatives are bent in relation to the pyrimidin ring plane.

3.4. Synthesis of 3-hydroxy-2-methyl-4-selenopyrone (selenomaltol) [Paper H-3]

Continuing the research into 6-membered heterocyclic compounds with an exocyclic sulfur or selenium atom I started work on the synthesis of compounds that are selenium analogues of derivatives having an α-hydroxyketone system. This group contains, among other things: maltol (3-hydroxy-2-methyl-4-pyrone), ethylomaltol (2-ethyl-3-hydroxy-4-pyranone), deferiprone (3-hydroxy-1,2-dimethylpyridin-4(1H)-one), kojic acid (5-Hydroxy-2-(hydroxymethyl)-4H-pyran-4-one) and propanoic acid ((2*S*)-2-Amino-3-(3-hydroxy-4-oxopyridin-1-yl).

Maltol, just like other compounds containing an α-hydroxyketone group, is known to be a very good ligand in coordination chemistry.[li] It is an excellent chelating ligand for, among other things, Fe^{3+}[lii] and Mn^{2+} ions.[liii] Sulfur analogues of maltol are also known for their ability to coordinate metal ions. Thiomaltol (3-hydroxy-2-methyl-4-thiopyrone) is a very good chelating ligand for Fe^{3+} and Ni^{2+}ions.[liv]

Bearing in mind the possibility of changing the ligand properties resulting from a greater atomic radius of selenium in comparison to the radius of sulfur and oxygen atoms I planned a synthesis of selenomaltol (3-hydroxy-2-methyl-4-selenopyrone), which had not been previously described in scientific literature, so that it would be possible to compare its physic-chemical properties with the properties of oxygen and sulfur analogues.

The methods of introducing exocyclic selenium atom through the use of sodium hydroxide or gaseous hydrogen selenide, which I had devised earlier, proved to be ineffective. As a result, I decided to use tetraphosphorus decaselenide that I generated *in situ* from grey selenium and red phosphorus to transform maltol into selenomaltol.[lv] The reaction was conducted in toluene under argon in the presence of HMDSO (hexamethyldisiloxane) as a catalyst.

The combination of tetraphosphorus decaselenide and HMDSO had previously been successfully used in sulphurisation reaction by T. J. Curphey.[xxvii]

In most cases decribed in the work mentioned, the addition of HMDSO positively influenced the reaction course and resulted in the yield increase. Curphey examined carefully the influence of HDMSO on the reaction course and found that during the sulphurisation reaction when only P_4S_{10} is used the reaction environment becomes more electrophilic because polithiophosphates are produced, among which $P_4O_6S_4$ might be an extreme example (Figure 4), which leads to the development of undesirable by-products and lowers the yield of the reaction. HMDSO reacting with the developing by-products leaves only the appropriate sulphurising agent.

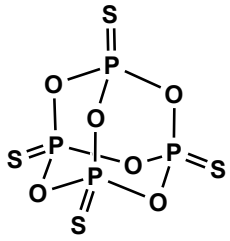
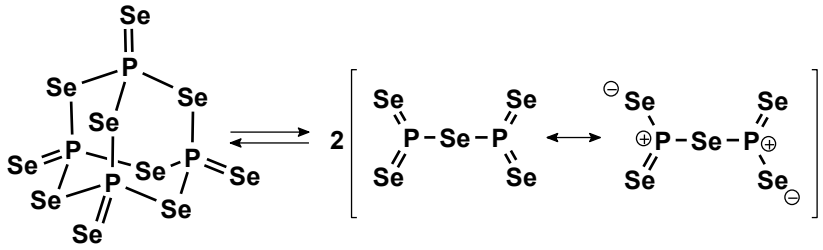


Figure 4. Structure of $P_4O_6S_4$, one of by-products developing in process of replacing oxygen atom in carbonyl group with sulfur atom

Because P_4Se_{10} has an analogous structure to P_4S_{10}, I assumed that in the reaction conditions it would undergo dissociation according to the pattern know for phosphorus pentasulfide. (Scheme 17).

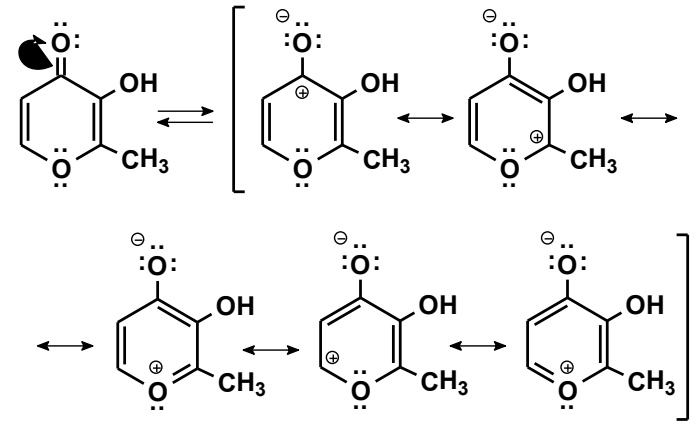


Scheme 17. P_4Se_{10} dissociation

I assumed that in a solution tetraphosphorus decaselenide would dissociate to a monomer and both forms would be present in equilibrium. I also assumed that monomer would develop to its mesomeric form, diselenophosphinate ylide, which is the primary reacting agent in the process of replacing the oxygen atom with a selenium atom.

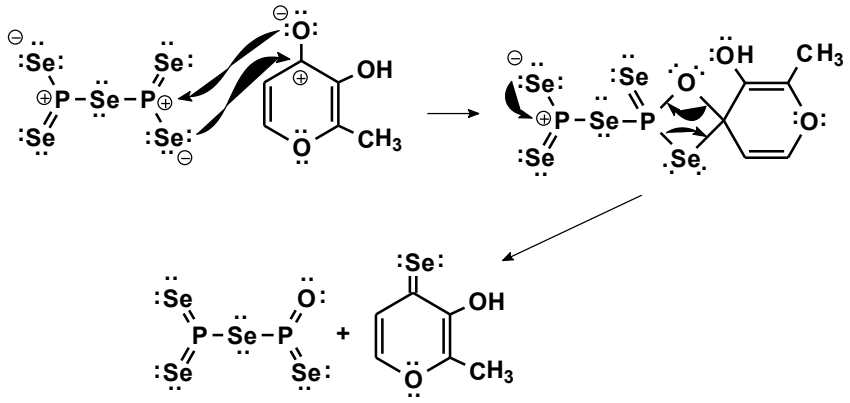
I also assumed that, due to the similarity of chemical properties of selenium and sulfur, the use of HMDSO in the reaction of introducing a selenium atom in the place of the oxygen atom would also have a positive effect on the course of the process, just like in case of sulphurisation reaction.

The necessary condition to effectively conduct the reaction of replacing the oxygen atom with a selenium atom is the presence of the positive charge on the carbon atom and the negative on the oxygen atom in the carbonyl group in maltol particle. The condition is met by at least one of the possible resonance structures, which can be proposed for maltol particle. (Scheme 18)



Scheme 18. Possible resonance structures present in maltol

Replacing the oxygen atom with a selenium atom in maltol particle with the use of P_4Se_{10} probably runs according to the following mechanism. (Scheme 19)



Scheme 19. Probable mechanism of replacing oxygen atom with selenium atom in maltol

Replacing the oxygen atom with a selenium atom was confirmed through elemental analysis and mass spectrometry (EI MS). In theory, each of the oxygen atoms can be replaced with a selenium atom in the maltol particle. As a result, there could be three isomers of selenomaltol, isomer A, isomer B and isomer C. (Figure 5)

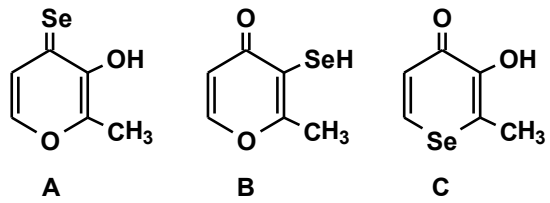


Figure 5. Possible selenomaltol isomers

The fact that the reaction led to isomer A was confirmed by spectral IR analysis, ^{1}H NMR and ^{13}C NMR. The conclusive proof that isomer A was obtained was determining crystallographic structure of the selenomaltol particle. The atom arrangement in the selenomaltol suggests that between the proton in hydroxyl group and the selenium atom exists weak intramolecular hydrogen bond. Primitive cell structure of the monocrystal was also investigated. Selenomaltol crystallises in monoclinic structure, the $P2_1/c$ space group. Lattice parameters of selenomaltol are very similar to the lattice parameters of thiomaltol, which had already been described.[liv] Thiomaltol also crystallises in monoclinic structure and similarly to selenomaltol belongs to the $P2_1/c$ space group.

The experimental IR and NMR spectra were compared to the results obtained by calculation methods with a good agreement of results. The only exception was significant variance in chemical shift determined experimentally and calculated theoretically in the ^{13}C NMR spectrum for the carbon atom bound directly with the selenium atom. The variance was ca. 22 ppm and was caused by the effect of a heavy atom shielding a light atom, which is described in literature. [lvi,lvii]

There are three possible tautomeric structures possible for isomer A. N1, N2 and N3 (Figure 6). Tautomeric equilibria constants were calculated for these structures and on their basis it was proved that among the three tautomeric structures structure N1 containing a ketoenol group has the greatest stability.

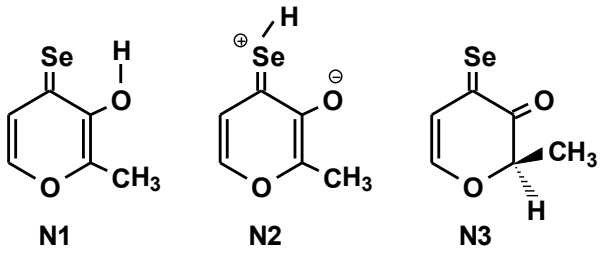


Figure 6. Possible tautomers for isomer A

The results of the conducted research and the results of calculations prove that when treating maltol with tetraphosphorus decaselenide in the presence of MDSO the exocyclic oxygen atom AT C-4 is replaced with a selenium atom.

Because scientific literature also describes properties of ethylomaltol (2-ethylo-3-hydroxy-4-pyrone) and its sulfur analogue, I obviously tried to obtain its selenium analogue.

Despite many attempts with various selenation agents I did not obtain selenoethylomaltol. The problem remains unsolved and will be investigated further.

3.5. Examination of properties of selenium analogues of maltol using theoretical methods [Paper H-4]

The research into the selenium maltol analogues through calculations was started in the paper previously described. [**Paper H-3**]. The calculation of energy differences between tautomeric forms allowed to prove that N1 tautomer is a dominant form over N2 and N3 tautomers in the mix. (Figure 6). Calculations of the tautomerization phenomenon of selenomaltol were continued in paper **H-4.** The work also investigates slenomaltol aromaticity. Both tautomery and aromaticity have a great influence on the properties and reactivity of the compounds where they occur. The presence of various ligand tautomeric and ionic forms in the complex compounds, protonated or deprotonated (Figure 7) might result in a very unexpected reaction course in which they take part.

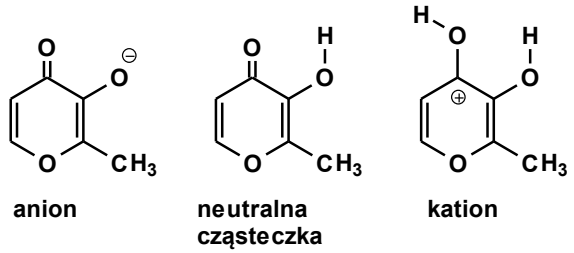


Figure 7. Structure of various maltol forms

Maltol and its sulfur and selenium analogues may create with metal ions whole series of complex compounds of significant pharmacological, biological or industrial importance. Chelating properties of maltol and its sulfur and selenium analogues depend to a great extent on the tautomeric form they occur in. Because maltol and its analogues systems have certain aromaticity, in complex compounds created with them energetic effects resulting from metal ions chelation might occur, as well as effects resulting from ligands aromaticity. Although the entropy change occurring during metal ions chelation by ligands having at least two coordinating places is so great that it masks the effects causeh by their aromaticity.

Depending on the predicted use of the ligand, various stability constant of the complex compounds created with metal ions might be necessary. An example might be the complex compound with iron ions. They might be used in fighting anaemia or removing the excess of iron ions from the body in case of thalassemia. In the first case, the complex compound with

iron ions has do decompose in the body and free Fe^{2+} ions. In the latter case, iron ions have to be bound by ligands powerfully enough to be excreted from the body.

The possibility to theoretically predict the level of stability of the complex compounds seems to be a very important issue in cases where their therapeutic effect depends on their stability. In case of the compounds that in theoretical calculations are chosen as a potentially useful ligands and have not been obtained yet, it will be possible to make attempts to synthesise them.

This kind of research was undertaken for the whole series of selenium maltol analogues. Quantum chemical calculations were performed by B1LYP/6-311++G** method in the Gaussian'03 package for seven compounds. (Figure 8).

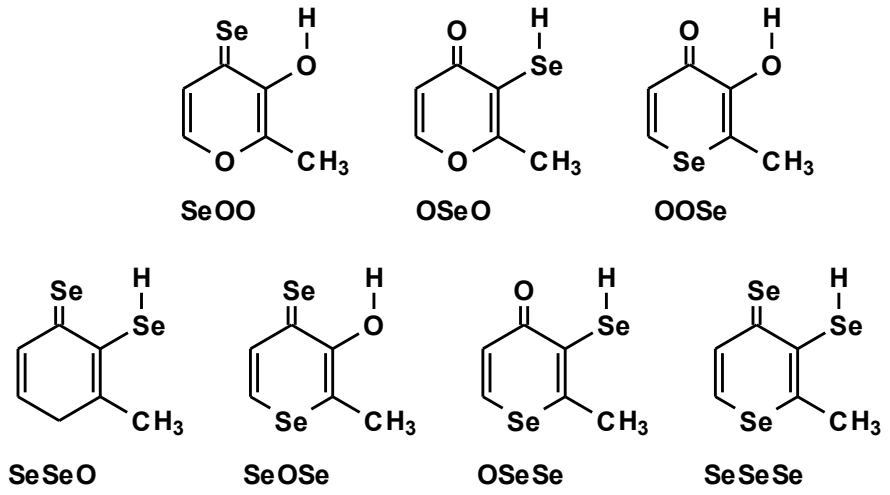


Figure 8. Structure of selenium maltol analogues for which calculations were conducted

Three of them are isomers where one oxygen atom was replaced with a selenium atom. In further three two oxygen atoms were replaced with selenium atoms, whereas in the last examined compound all three oxygen atoms were replaced with selenium atoms. So far only one of these compounds have been obtained through synthesis. 3-hydroxy-2-methyl-4-selenopyrone (selenomaltol), where exocyclic oxygen atom at the C-4 position was replaced with a selenium atom. [**Paper H-3**]

Geometry optimization was conducted for the researched structures and the aromaticity indices were calculated:

HOMA - harmonic oscillator model of aromaticity

NICS - nucleus independent chemical shift

PDI – para-delocalisation index

MCI - multi centre index

ASE - aromatic stabilisation energy

H- H index

The HOMA index is a geometric indicator of aromaticity, the NICS(0) and NICS(1) indices are magnetic indicators of aromaticity, the PDI, MCI and H indices are electron indicators of aromaticity, whereas the ASE index represents the energetic aspect of aromaticity.

The aromaticity indices were calculated not only for the neutral particle, but as well for the deprotonated form (anion) and the protonated form (cation).

The conducted calculations indicated that the anion forms demonstrate very low aromaticity or may even be a bit antiaromatic. The neutral particle of the examined compounds demonstrates an average level of aromaticity, whereas the calculations for cation forms indicate that they are usually considerably aromatic.

Among all the monosubstituted anions the derivative of SeOO has the greatest aromaticity. However, in the case of the OseO derivative, where a selenium atom replaced the oxygen atom which is a part of the hydroxyl group, a significant reduction in aromaticity occurs.

In the case of the OSeO derivative, most aromaticity indicators put its aromaticity between the aromaticity of SeOO and OOSe. In general, the predicted aromaticity of anion selenium maltol analogues is a little greater than their oxygen equivalents.

In the group of the neutral particles of monosubstituted selenium maltol analogues low aromaticity of the OSeO structure is very distinctive, where a selenium atom replaced the oxygen atom which is a part of the hydroxyl group. All the calculated aromaticity indices indicate that its aromaticity is lower than aromaticity of a neutral maltol particle. In case of protonated forms (cations) most aromaticity indices predict lower aromaticity of theselenium than oxygen analogues.

There are interesting results among the compounds containing more than one selenium atom high values of the HOMA index for the derivatives containing a selenium atom in the heterocyclic ring. The remaining aromaticity indicators have values similar to the ones calculated for the monosubstituted analogues.

Relatively high aromaticity level of the derivative where all the oxygen atoms were replaced with selenium atoms was a little surprising as replacing the oxygen atom in the hydroxyl group with a selenium atom lowers aromaticity. This probably results from the fact that two other selenium atoms raise aromaticity.

The presents work is the introduction to the search for new ligands that may create complexes with metal ions where chelatoaromatic effect will be important. On the basis of the

shortly presented calculation results it might be predicted that chelatoaromatic effects in the complex compounds of metal ions with the derivative of the OOSe type should be much stronger than in maltol complexes. OOSe anion has lower aromaticity than the equivalent deprotonated maltol structure. What is more, OOSe cation has a little higher aromaticity than the protonated form of maltol. This results indicate that the difference in electron delocalisation between the anion and cation OOSe forms, which might be recognized as a estimation of the force of aromaticity change in metal complexes, is greater than the predicted difference for the appropriate maltol forms. The chelatoaromatic effects in the complex compounds obtained from OOSe should be a little stronger than in case of maltol complexes. We observe the opposite effect for the SeOO type derivative. In this case the anion has a little greater aromaticity than the equivalent maltol anion. Cation aromaticity is a little lower than aromaticity of the equivalent maltol cation. As a result, chelatoaromatic effects should be a little weaker in this case than in the case of maltol complexes.

The comparison of the calculation results for selenomaltol with the earlier published results for maltol,[lviii] and thiomaltol[lix] allow to state that in all the groups of compounds relative aromaticity is as follows: anion < neutral particle < cation. It is understandable if we take into consideration the changes occurring in the particle structure after replacing the oxygen atom with a sulfur or selenium atom. The structure of the system of electrons constituting the σ binds undergoes significant changes, whereas the structure of the π – electron system changes to a negligible extent.[lx]

The presented compounds constitute a very interesting group of chelating ligands, where the phenomena connected with their aromaticity are additionally present. They can be useful in the synthesis of new bonds potentially having pharmacological activity.

I hope that as a result of the theoretically obtained results it will be possible to optimise the laboratory work. The calculation results should mainly allow to choose structures having the best properties. It will allow for appropriate direction of synthesis.

3.6. Synthesis of 3-hydroxy-1,2-dimethyl-4[1H]-pyridinselenone (selenodeferiprone) [Paper H-5]

Another important heterocyclic system containing an α-ketohydroxy fragment is 3-hydroxy-1,2-dimethyl-4[1*H*]-pyridinone commonly known as deferiprone. For the first time the synthesis of deferiprone was conducted in R. Hider's laboratory in 1980. It was obtained from maltol in the course of replacing the oxygen atom at the 1 position in the 3-hydroxy-2-methyl-4-pirone system with a nitrogen atom.[xxiii] It contains an α-ketohydroxy system, just like

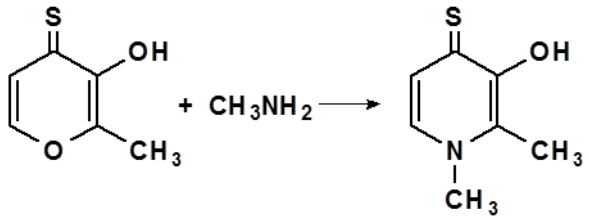
maltol, which makes deferiprone a very good ligand binding, among other things, Fe^{3+} ions. Due to its low toxicity and low susceptibility to oxidation it is used in treating thalassemia in adult[lxi] and children.[lxii]

Deferiprone is a good ligand chelating not only with iron ions, but it may also make complex compounds with ions of other metals. It was proved that with Ga^{3+}, Al^{3+}, In^{3+} ions it makes compounds with similar, high stability. Whereas in case of copper, zinc, calcium and magnesium ions it was established that the stability of their complex deferiprone compounds changes as follows: $Cu^{2+} > Zn^{2+} > Ca^{2+} > Mg^{2+}$.[lxiii]

The compound which is a ligand with such fantastic properties became of interest to me in my research to transform it into sulfur and selenium analogues.

Replacing the oxygen atom in deferiprone with another heteroatom allows to obtain a ligand with a different activity. This is why many research teams have undertaken attempts to obtain sulfur analogues of deferiprone.

In previous research deferiprone was transformed into its sulfur analogue only in the reaction with Lawesson's reagent without a catalyst[lxiv, lxv] or in solvent free conditions in the course of heating with phosphorus pentasulfide.[lxvi] Another method was proposed by Mong *et al.* who obtained thiodeferiprone from thiomaltol replacing the oxygen atom in the ring with N-CH_3 group.[lxvii] (Scheme 20).



Scheme 20. Synthesis of thiodeferiprone from thiomaltol

In my work I used Lawesson's reagent in the presence of hexamethyldisiloxane (HMDSO) as a catalyst to replace the exocyclic oxygen atom at the C-4 position in deferiprone with a sulfur atom. The use of HDMSO resulted in a minor, ca. 10% yield increase in comparison to the methods proposed in the publications mentioned. The reaction was conducted in the atmosphere of a neutral gas at the boiling temperature of toluene (Scheme 21).

Scheme 21. Synthesis of thiodeferiprone

The fact that I obtained thiodeferiprone was confirmed by spectroscopic methods. IR, ES MS, ^{1}H NMR and ^{13}C NMR. In the IR spectrum there is a very characteristic band at 1196 cm^{-1} coming from the stretching vibrations of the C=S group. The identical band was identified in the already mentioned paper by Mong.[lxvii] In the paper the authors also give the location of bands coming from stretching vibrations of the C=S group in thiomaltol (1176 cm^{-1}) and thioethylomaltol (1178 cm^{-1}).

The MS spectrum analysis proved that in the analysed samples there is thiomaltol as well as its dimer. (Figure 9).

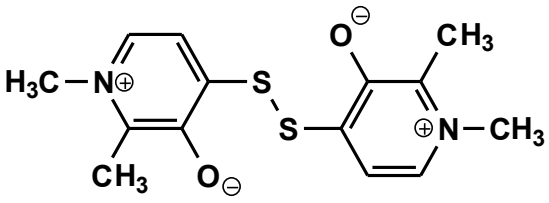


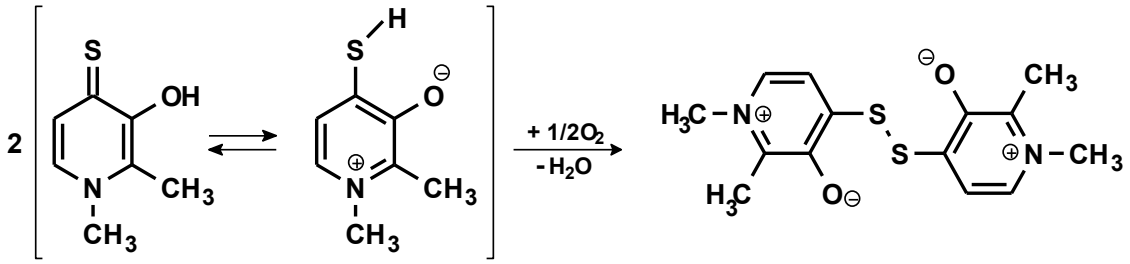
Figure 9. Dimer obtained from thiodeferiprone

In my research I noticed that the peaks coming from dimer always appeared in the spectrum of the examined sample, no matter how it was purified. It indicates that in the conditions of measuring the MS spectrum (temperature of 280°C, in gas phase) partial dimerisation of thiodeferiprone occurs.

The fact that the thiodeferiprone dimer is always produced in small quantities during the synthesis apart from the monomeric form was also observed by Mong *et al.* It also results from their research that dimer must exist in the zwitterion form, as only in such case the flat structure of both rings can be preserved.

The researchers also observed that adding D-*threo*-1,4-dimercapto-2,3-butanediol (DTT), which is a strong reducing agent for disulfide bonds, to the thiodeferiprone solution results in quantitative transformation of dimer to monomer. On this basis it can be assumed that the

probable cause of dimer formation is oxidation of its monomeric form with the air oxygen. (Scheme 22).



Scheme 22. Probable course of thiodeferiprone dimer development

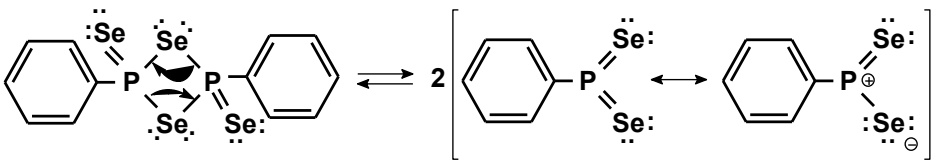
On the other hand, in case of my research, the ^{1}H NMR spectra analysis of thiodeferiprone samples conducted immediately after obtaining it suggests that only monomeric form is present in the solution. In the ^{1}H NMR spectrum of thiodeferiprone characteristic broad band exists, whose chemical shift equals 6.8 ppm and comes from the OH group proton. Probably the speed of dimer development is low enough that it did not develop until the measurement.

Because thiodeferiprone synthesis is well described in subject literature, I decided to focus on devising a method of obtaining selenodeferiprone so that it would be possible to compare the properties of deferiprone, thiodeferiprone and selenodeferiprone.

The attempt to apply the method used to synthesise selenomaltol [**Paper H-3**] failed. Deferiprone proved to be resistant to the activity of tetraphosphorus decaselenide generated in the reaction environment.

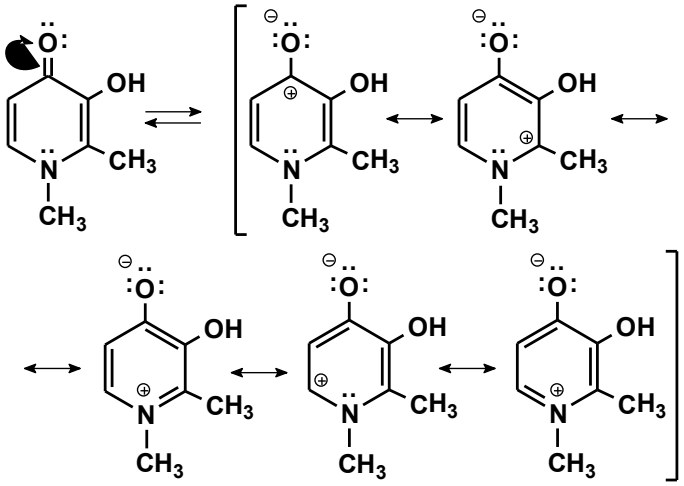
I conducted the synthesis of selenodeferiprone using Woolins' reagent, which I used on deferiprone in the presence of HMDSO in the atmosphere of a neutral gas at the toluene boiling temperature.

Woolins' reagent, just like Lawesson's reagent, dissociates and, as a result, in the solution there is diselenophosphine ylide, which is the appropriate nucleophilic reagent.[xliii] (Scheme 23).



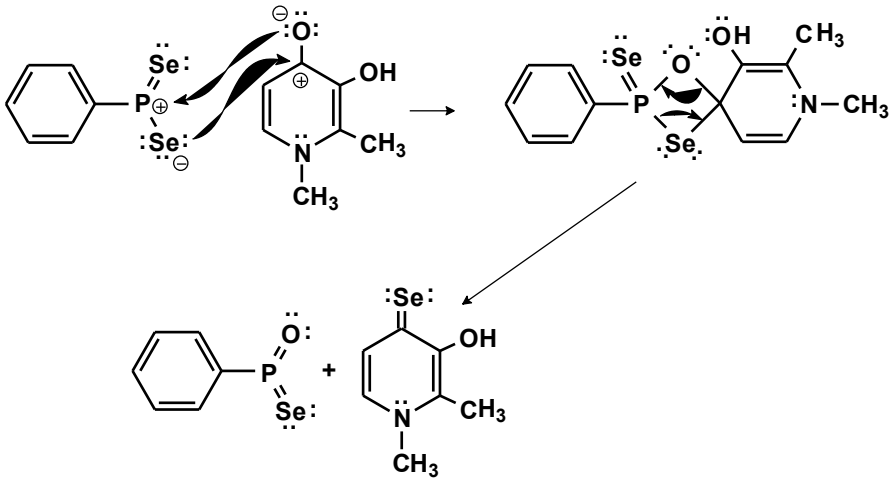
Scheme 23. Woolins' reagent dissociation

Deferiprone particle has a resonance structure which has a positive charge on the carbon atom in the carbonyl group. (Scheme 24).



Scheme 24. Possible resonance structures present in deferiprone

The attack of monomer form of Woolins' reagent on deferiprone particle may occur according to the following, possible reaction mechanism shown in scheme 25.



Scheme 25. Probable mechanism of the reaction of replacing oxygen atom with selenium atom in deferiprone

This mechanism is analogues to the activity mechanism of Lawesson's reagent. On the basis of the results published in the cited paper by Woolins[xliii] and research there cited the assumption that WR works analogically to LR is well justified.

Elemental analysis conducted immediately after receiving the preparation indicates that I obtained a product in a monomer form. The result was confirmed through ^{1}H NMR spectrum analysis, where a very broad band existed with a chemical shift of 8.5 ppm coming from the

OH group proton. The measured values of chemical shifts for ^{1}H NMR and ^{13}C NMR spectra were compared with values calculated theoretically.

The comparison of the experimental and theoretically calculated values of the chemical shifts for thio- and selenodeferiprone is shown in figure 10.

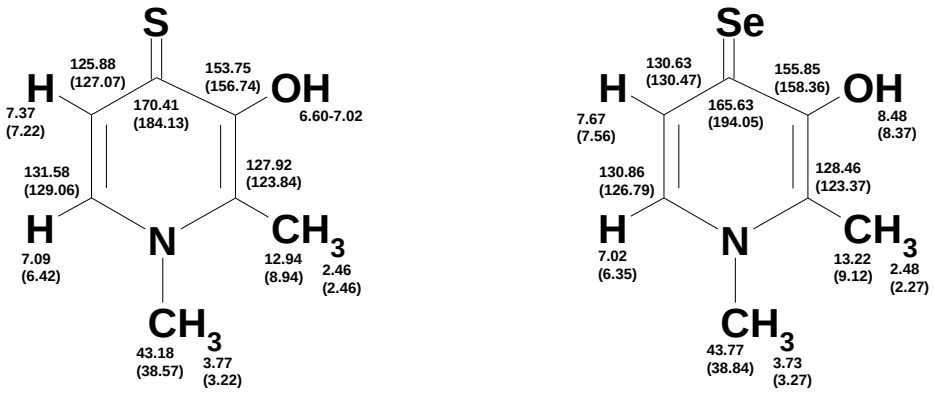


Figure 10. Values of chemical shifts in ^{1}H NMR and ^{13}C NMR spectra for thio- and selenodeferiprone (in brackets theoretically calculated values)

In general, the theoretically calculated values of chemical shifts conform with the experimental values. The observed discrepancies result from the level of theory used for calculations. The only significant difference occurs in the ^{13}C NMR spectra for carbon atoms directly bonded with sulfur and selenium atoms. The differences between the theoretically calculated values and experimental values amount to ca. 14 ppm for the carbon atom bound with the sulfur atom and ca. ok. 29 ppm for the carbon atom bound with the selenium atom. Such discrepancies can be clearly explained by so called "heavy atom effect on the light atom shielding", which is not included in the theoretical model used for our calculathions.[lvi,lvii] This effect was not taken into account in the theoretical model used for calculations. Similar discrepancy between theory and experiment was previously observed in the case of selenomaltol. [**H-3**]

The cohesion between the theoretically calculated and experimental values of chemical shifts confirms the assumption that thio- and selenodeferiprone exist in the solution as monomers.

^{77}Se NMR spectrum was also examined for selenodeferiprone. Only one signal (δ 246.67 ppm) was received, which indicates that there was only one population of selenium atoms in the sample. According to scientific literature[lxviii] the values of chemical shifts for aromatic diselenides are greater than 400 ppm, whereas for the selenocarbonyl group are spread over the

whole range of chemical shifts for selenium, depending on the C=Se bond polarisation and the electric charge.

The negative charge on the selenium atom increases shielding, which results in lower chemical shifts values. For selenodeferiprone it can be achieved in the presence of the mesomeric form having a negative charge on the selenium atom and positive on the nitrogen atom. (Figure 11).

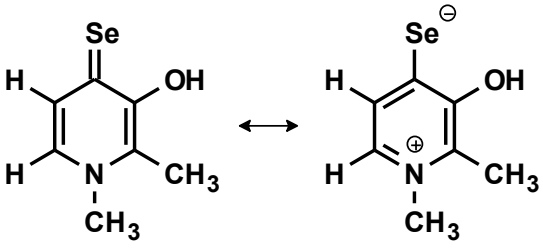


Figure 11. One of the mesomeric forms of selenodeferiprone

The results obtained suggest that in the solution prepared immediately after receiving the preparation selenodeferiprone exist as monomer only.

In order to conduct roentgenographic investigation a monocrystal was grown from the preparation. The structure of the examined compound was solved using SHELXS programme and was further specified using SHELXL programme. The roentgenographic analysis of the selenodeferiprone crystal proved that in the solid state this compound exists in a diselenide form as a zwitterion. (Figure 12).

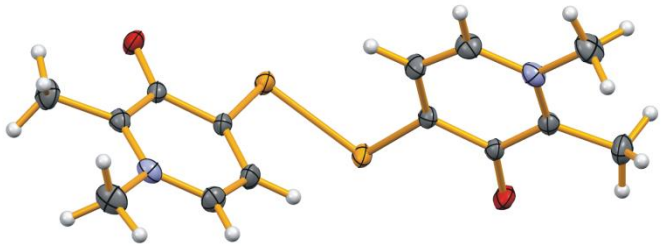


Figure 12. Structure of selenodeferiprone dimer particle

Dimer was created probably due to the long time of crystallisation and the type of solvent used. The monocrystal used to determine crystallographic structure was obtained from 96% ethanol. Slow evaporation of the solvent took two weeks with air access. I suspect that the

oxidation conditions of conducting the process were the reason for the total conversion of the monomer into diselenide.

The crystal obtained was monoclinic, the C2/c space group. The elemental cell contains four particles of the dimer and eight particles of water coming from the solvent used.

Geometric analysis of the diselenide particle demonstrated that the the length of the bonds, the angles between the bonds and the torsion angles are typical for the know diselenide structures.

The experimental results were compared with the result of calculated bond length and the angles between the bonds and showed good compliance.

In the crystal structure of selenodeferiprone dimer there are intramolecular forces through hydrogen bonds. O-H···O bonds are created between phenolic oxygen atoms in the dimer particles and hydrogen atoms in water particles. Each dimer particle is connected with a neighbouring one through hydrogen bonds created with three water particles creating a ring.

In this paper I presented a modified method of synthesising thiodeferiprone and a method of synthesising selenodeferiprone, which had not been described in scientific literature before, using organophosphorus reagents. Lawesson's reagent was used to replace the oxygen atom with a sulfur atom, whereas Woolin's reagent was used was used to replace the oxygen atom with a selenium atom. The structure of both obtained compounds was confirmed through MS, IR, ^{1}H NMR and ^{13}C NMR spectra analysis.

3.7. Synthesis and examination of crystal structures of the homologues of epalrestat [Paper H-6]

Continuing the research into five-membered heterocyclic ring systems containing exocyclic sulfur atom I conducted the synthesis of 2-thio-tiazolidino-4-one (rhodanine) having a carboxyalkyl group at the N-3 position.

One of the most important representatives of the compounds group is (5Z)-5-[(20E)-20-methyl-30-phenyl-20-propen-10-ylidene]-4-oxo-2-thioxo-3-thiazolidineacetic acid commonly known as epalrestat. (Figure 13).

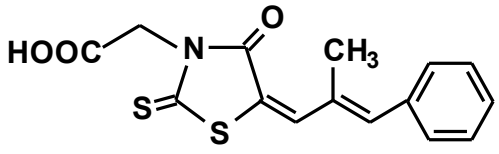
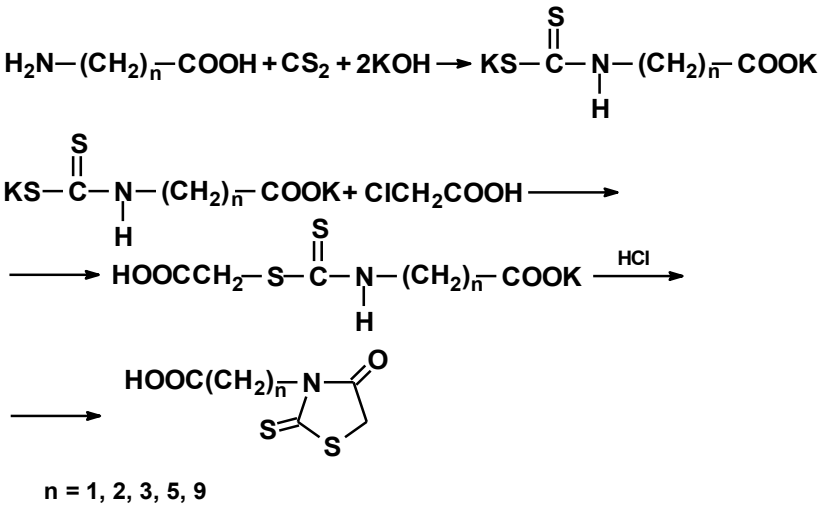


Figure 13. Structure of epalrestat

Epalrestat is a known inhibitor of aldose reductase and is used in treating diabetic neuropathy. At present it is the only effective preparation used for this purpose.[lxix] It was first approved for the clinical use in Japan in 1992. Despite its indisputable merits, new compounds which would have greater effectiveness and lower toxicity than epalrestat are sought.[lxx] Many newly synthesised compounds have at the N-3 position a carboxymethylene group.[lxxi] The presence of a carboxyl group is very important as through it the compounds demonstrating hindering activity bind with hydrophilic fragment of aldose reductase. Another important element is the presence of aromatic group, which is responsible for the contact with hydrophobic pocket.

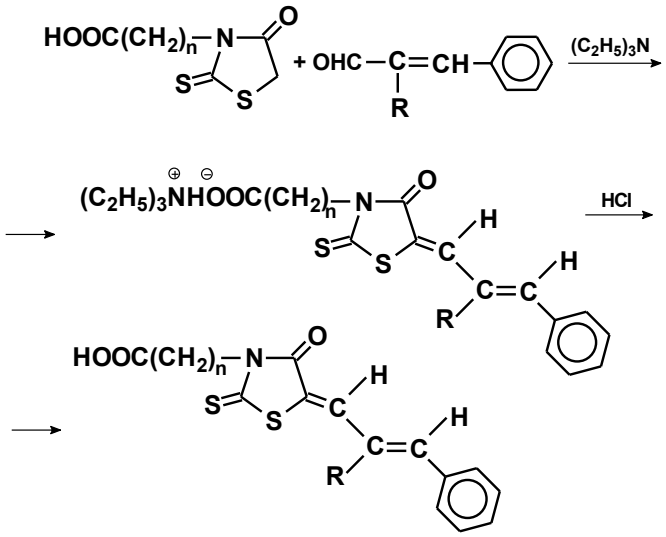
In my research I made an attempt to synthesise a series of epalrestat monologues having at the N-3 position the following groups: carboxymethyl, carboxyethyl, carboxypropyl and carboxybutyl and at the C-5 position a cinnamylidene or 2'-methyl cinnamylidene group. The aim of the undertaken research was to compare the influence of the carbon atom number in the connector between the carboxyl group and the rhodanine fragment on the compound properties. First, I synthesised 3-carboxyalkylrhodanine acids using the method proposed by Körner, which I had modified.[lxxii] (Scheme 26).



Scheme 26. Synthesis of 3-carboxyalkylrhodanine acids

As the starting compounds I used amino acids having a carboxyl or amino group on the opposite ends of the particle. Potassium dithiocarbamate was the result of the reaction with carbon disulphide in the presence of potassium hydroxide. This compound, in the reaction with chloroacetic acid, gave an intermediate product, which very easily underwent cyclisation to appropriate rhodanine-3-carboxyalkyl acid under the influence of hydrochloric acid solution.

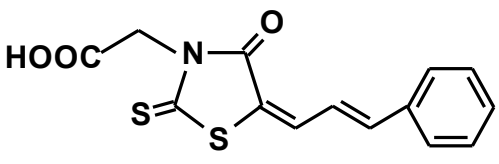
The resulting compounds underwent Knoevenagel condensation with cinnamaldehyde and α-methylcinnamic aldehyde according to the procedure proposed by Fischer and Hibbert, which I had modified.[lxxiii] (Scheme 27).



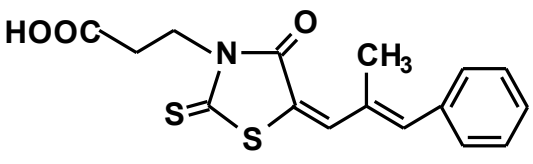
Scheme 27. Condensation of rhodanine-3-carboxyalkyl acids with cinnamaldehyde (R = H) and α- methylcinnamic aldehyde (R = CH_3)

I conducted the reaction of rhodanine-3-carboxyalkyl acids with aldehydes in the presence of excess of triethylamine. As a result of the reaction I obtained quaternary ammonium salts, which were not isolated from the reaction environment. These salts treated with hydrochloric acid resulted in expected derivatives.

The obtained preparations underwent crystallisation to obtain monomeric crystals of the quality enabling roentgenographic examination. The crystals of two compounds were selected from the crystal obtained: 5Z)-5-[(20E)-30-phenyl-20-propen-10-ylidene]-4-oxo-2-thioxo-3-thiazolidine-acetic acid (EPH1) and (5Z)-5-[(20E)-20-methyl-30-phenyl-20-propen-10-ylidene]-4-oxo-2-thioxo-3-thiazolidinepropionic acid (EPH2) (Figure 14). The crystals of remaining compounds were not of quality good enough for roentgenographic examination. Probable lengthening of the connector between the carboxyl group and the rhodanine ring was the reason for creating by other compounds crystals in the form of long threads. In such form they could not be used for examination.



EPH1



EPH2

Figure 14. Structure of rhodanine-3-carboxyalkyl acid derivatives used for examination

The results obtained were compared with the crystallographic examination results described in subject literature, which were conducted for epalrestat. [lxxiv]

The EPH1 crystal used for examination was grown from the mix of DMF and isopropanol. In the crystal received there was one EPH1 particle for one DMF particle. Similar situation was present in the epalrestat crystal after crystallisation from ethanol. There was one epalrestat particle for ethanol particle.[74] Identical result was observed by Igarashi *et al.*, who crystallised epalrestat from methanol.[lxxv] In the EPH2 crystal, which was crystallised from propyl acetate the solvent particles were not present. Both compounds, EPH1 and EPH2, crystallised in the triclinic system. It is possible that increasing the number of carbon atoms in the substituent at the N-3 position blocks the possibility of epalrestat homologues salvation by solvent particles.

Because in the connector between the fragment of the rhodanine ring and the phenyl ring two double bonds exist, EPH1 and EPH2 may have four geometric isomers, 5E,2'E; 5Z,2'Z; 5E,2'Z; 5Z,2'E. Only one of these structures, 5Z,2'E, exists in the EPH1 crystal, just like in EPH2. Epalrestat has also identical structure of this particle fragment.[lxxiv]

Intermolecular forces exist in the crystal structures of the EPH1 and EPH2. In the EPH1 crystal structure strong hydrogen bonds exist between carboxyl group and solvent particles and week hydrogen bonds between hydrogen atoms in the propenylidene chain and oxygen and sulfur atoms in the rhodanine ring. In the EPH2 crystal structure strong hydrogen bonds develop between carboxyl groups of two particles. Dimers that develop in such a way interact with each other through week hydrogen bonds analogues to the ones existing in the EPH1 crystals.

Taking into consideration the similarity of the intermolecular effect in EPH1, EPH2 and epalrestat crystals, it seems justified to assume that the obtained rhodanine-3-carboxyalkyl acids will also demonstrate biological activity. It will be the subject of further research.

4. The summary of the most important achievement in the research on the synthesis and properties of selected heterocyclic systems containing exocyclic sulfur or selenium atom

In the presented series of papers are described methods to synthesise not described earlier in scientific literature selenium analogues of 3,5-disubstituted 2-thio-thiazolidine-4-ones (rhodanins), 1,4,6-trisubstituted 2[1*H*]- pyrimidone, 3-hydroxy-2-methyl-4-pirone (maltol) and 3-hydroxy-1,2-dimethyl-4[1*H*]- pyrimidone (deferipron). The modified methods of the synthesis of rhodanine system having at the N-3 position alkyl and carboxyalkyl substituents

are presented. The modified method of condensation of rhodanine with aromatic aldehydes is described.

The structure of all the obtained selenium analogues and the sulfur analogue which had not been know was confirmed through elemental analysis and spectroscopic methods. IR, I MS, ES MS, ^{1}H NMR, ^{13}C NMR. It was necessary to examine also ^{77}Se NMR spectrum for selenodeferiprone.

For selenomaltol, selenodeferiprone and two epalrestat homologues particle structure was determined through roentgenographic methods and elemental cell structure of the crystals they made was investigated.

Calculation methods were used to predict the stability of the tautomeric structures that might exist in selenomaltol and aromaticity indices were calculated for various selenium maltol analogues.

5. Predicted possibilities of the results application

The obtained results should allow to suggest the synthesis of new compounds having potential antibacterial and antifungal activity. I have high hopes connected with 3-carboxyalkylrhodanine acid derivatives having at the C-5 position elaborate benzylidene and cinnamylidene substituents. Determining their spatial structure through roentgenographic methods might be helpful in investigating the dependency between the compound structure and its biological activity.

The initial research allows to assume that 1,4,6-trisubstituted 2[1*H*]-pyrimidineselenones will demonstrate antibacterial and antifungal activity.

I also hope that the derivatives of selenium analogues of maltol and deferiprone will allow to suggest new ligands, which could be used in treating diabetes, Alzheimer, anaemia or thalassemia. An important issue is examination of the application of sulfur and selenium derivatives of maltol and deferiprone to effective complexation of lead ions, which are characterised by high toxicity.

The applied calculation methods should allow to help plan the synthesis of such structures which will have possibly highest effectiveness.

Kraków, 27 January 2016

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