



Synthesis and structure of novel dithioderivatives of 3-pyrrolin-2-one

Liliya S. Kosolapova ^a, Enze S. Rabbanieva ^a, Darya P. Gerasimova ^b,
Sergey V. Efimov ^c, Olga A. Lodochnikova ^b, Vladimir V. Klochkov ^c,
Almira R. Kurbangalieva ^a*

a: A.M. Butlerov Institute of Chemistry, Kazan Federal University , Kazan 420008, Russia

b: A.E. Arbuzov Institute of Organic and Physical Chemistry , Federal Research Center “Kazan Scientific Center of Russian Academy of Sciences”, Kazan 420088, Russia

c: Institute of Physics, Kazan Federal University , Kazan 420008, Russia

* Corresponding author: akurbang@kpfu.ru

Abstract

Unsaturated γ -lactams (3-pyrrolin-2-ones) are an important class of five-membered nitrogen-containing heterocycles that play a significant role as structural motifs in numerous natural products and synthesized compounds with a wide range of biological activities. These motifs are also successfully used as intermediates in organic transformations and allow access to more diverse compounds and previously inaccessible structures. In this work, method for the synthesis of two types of novel heterocyclic compounds containing an unsaturated γ -lactam ring and two sulfur atoms was developed. Reactive and easily available substrates of 5-methoxy-2(5*H*)-furanone series were involved into the reactions with ammonia and benzylamine and converted into the corresponding dithioderivatives of 5-hydroxy-3-pyrrolin-2-one, difficult to access by other methods. The molecular and crystal structures of four novel sulfur-containing compounds were characterized by single-crystal X-ray diffraction. These heterocyclic systems are promising candidates for further functionalization and biological screening.

Key findings

- Novel dithioderivatives of 3-pyrrolin-2-one were obtained from the reactions of the corresponding 5-methoxy-2(5*H*)-furanones with ammonia or benzylamine.
- Molecular and crystal structure of novel heterocycles, containing γ -lactam ring and two sulfur atoms was characterized by single crystal X-ray diffraction.
- 5-Alkoxyfuranone based method is attractive for the synthesis of different heterocycles, possessing lactam ring, difficult to access by other methods.

© 2025, the Authors. This article is published in open access under the terms and conditions of the Creative Commons Attribution (CC BY) license (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted reuse of the work in any medium provided the original work is properly cited.

1. Introduction

Nitrogen-containing heterocyclic compounds have garnered considerable attention due to their abundance in nature, great medical and biological importance and numerous applications in various fields ranging from medicinal chemistry to material science [1,2]. α,β -Unsaturated γ -lactams (1,5-dihydro-2*H*-pyrrol-2-ones, also referred to as 3-pyrrolin-2-ones) have occupied a prominent place among five-membered *N*-heterocycles by virtue of their

diverse medicinal values [3–5]. Derivatives of 3-pyrrolin-2-one exhibit an impressive repertoire of biological activities, including antimicrobial, anti-inflammatory, anti-tumor, analgesic, antiviral, nootropic, antiaggregant, and many others. In addition, 3-pyrrolin-2-one functional derivatives are widely used as versatile scaffolds for organic synthesis and development of novel biologically active compounds [6].

To date, a number of methods have been proposed for the synthesis of pyrrolinones using different precursors,

Accompanying information

Article history

Received: 18.12.25

Revised: 19.01.26

Accepted: 22.01.26

Available online: 22.01.26

Keywords

3-Pyrrolin-2-one; Unsaturated lactam; 2(5*H*)-Furanone; Sulfur-containing heterocycle; *bis*-Thioether; Molecular structure

Funding

This work was funded by the subsidy allocated to Kazan Federal University for the State Assignment in the Sphere of Scientific Activities (project No. FZSM-2023-0018).

Supplementary information

Supplementary materials:

Transparent peer review:

Sustainable Development Goals



such as acetylene, allene, ketene, pyrrole, furanone, azirine, azetine, aldehyde and keto acids, amino alcohols, amides, imides, enamines, and imines [4,7–9]. In this series, reactions of various 2(5*H*)-furanone derivatives with nitrogen-containing nucleophiles provide a simple, convenient and versatile way to obtain structurally similar 3-pyrrolin-2-ones [7,10–12]. The formation of lactam ring in these reactions is achieved under mild conditions, and a broad range of amino compounds can be involved as reactants into the interaction with furanones, namely, ammonia, primary aliphatic and alicyclic amines, amino alcohols, amino acids, alkylarylamines, and hetarylamines.

In our recent studies, we applied a facile approach for the synthesis of 1-benzyl and 1-(4-methylbenzyl) derivatives of 3-chloro- and 3-bromo-5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-ones, possessing arylsulfanyl [13–17] or 4-phenyl-1,2,3-triazolyl [18] group in the fourth position of the lactam ring, based on the interaction of the corresponding 4-substituted 5-methoxy-2(5*H*)-furanones with benzyl-type amines. Thioethers of *N*-substituted 5-hydroxy-3-pyrrolin-2-ones have shown the ability to form a wide range of stereochemically different phases during crystallization, including examples of spontaneous resolution of enantiomers [14,15,17,18]. The available literature on the synthesis and properties of pyrrolinone thioethers [19–23] and sulfur heterocycles, containing γ -lactame ring [24,25] remains scarce.

In this work, we aimed to expand on furanone based approach to obtain novel sulfur-containing derivatives of 3-pyrrolin-2-one, possessing two sulfur atoms. Here, we show that reactive and easily available starting materials of 5-methoxy-2(5*H*)-furanone series can be successfully converted by the treatment with ammonia or benzylamine into the corresponding derivatives of 5-hydroxy-3-pyrrolin-2-one, difficult to access by other methods.

2. Experimental

2.1. General

Benzylamine and 1,2-ethanedithiol (all Aldrich) were used as received without further purification. All solvents were purified and distilled by standard procedures. IR spectra were recorded on a Bruker Vertex 70 FTIR spectrometer fitted with a Pike MIRacle ATR accessory. NMR spectra were measured on a Bruker Avance III 400 spectrometer at 400.17 MHz (¹H) and 100.62 MHz (¹³C) at 20 °C, Bruker Avance III HD 700 spectrometer at 700.13 MHz (¹H) and 176.06 MHz (¹³C) at 25 °C in acetone-*d*₆. The chemical shifts (δ) are expressed in parts per million (ppm) and are calibrated using residual undeuterated solvent peak as an internal reference (acetone-*d*₆: δ_{H} 2.05; δ_{C} 29.8). Analytical thin layer chromatography (TLC) was carried out on Sorbfil PTLC-AF-A-UF plates using UV light (254 nm) as the visualizing agent. The melting points were measured on a Boetius hot stage and were not corrected.

2.2. X-ray structure determinations

Single crystal X-ray diffraction analysis was performed on a Bruker Kappa Apex automatic four-circle diffractometer at a temperature of 296(2) K: graphite monochromator, $\lambda[\text{Mo K}\alpha] = 0.71073 \text{ \AA}$, ω/ϕ scanning mode with a step of 0.5°. Data collection and indexing, determination, and refinement of unit cell parameters for crystals were carried out using the APEX3 software package. Spherical absorption correction was performed using the SADABS software [26]. Using OLEX2 [27], structures were solved by direct methods using the SHELXT program [28] and refined by full-matrix least-squares on *F*² using the SHELXL program [29]. Non-hydrogen atoms were refined anisotropically. Positions of H(N/O) hydrogen atoms were determined from difference electron density maps and refined isotropically. The remaining hydrogen atoms were refined using a riding model. Figures and analysis of intermolecular interactions were performed using MERCURY [30] and PLATON [31] programs. The crystal data, data collection, and structure refinement details are summarized in Table S1.

The crystallographic data for the structures 6–9 have been deposited in the Cambridge Crystallographic Data Centre and are freely available on request on the website www.ccdc.cam.ac.uk/data_request/cif. X-Ray diffraction data were obtained in the Collective Spectro-Analytical Center of FRC Kazan Scientific Center of RAS.

2.3. Chemical Synthesis

7-Hydroxy-2,3-dihydro[1,4]dithiino[2,3-*c*]furan-5(7*H*)-one (2) [32], 7-methoxy-2,3-dihydro[1,4]dithiino[2,3-*c*]furan-5(7*H*)-one (3) [33], 3,4-dichloro-5-methoxy-2(5*H*)-furanone (4) [34] and 4,4'-(ethane-1,2-diyl)disulfanediy]bis(3-chloro-5-methoxyfuran-2(5*H*)-one) (5) [32] were synthesized according to the known methods.

2.3.1. 7-Hydroxy-2,3,6,7-tetrahydro-5*H*-[1,4]dithiino[2,3-*c*]pyrrol-5-one (6)

Cooled aqueous ammonia solution (25%, 3 mL, 40 mmol) and a 1:2 mixture of ethanol and diethyl ether (3 mL) were added to a compound 3 (0.25 g, 1.2 mmol). The reaction mixture was stirred at $-13 \div -10 \text{ }^\circ\text{C}$ for 24 h (monitored by TLC). A precipitate formed during the reaction was filtered off, washed with ether and recrystallized from ethanol to afford heterocycle 6 as colorless solid. Yield 91% (0.21 g), m.p. 162–163 °C. *R*_f 0.11 (acetone-toluene, 1:2). IR, ν , cm^{-1} : 3000–3500 (OH, NH), 1662 (C=O), 1568 (C=C). ¹H NMR (acetone-*d*₆, 400 MHz, ppm): δ 3.12–3.40 (m, 4H, SCH₂), 5.27 (d, 1H, OH_B, ³*J*_{AB} = 9.8 Hz, ⁴*J*_{BX} = 0.0 Hz), 5.45 (dd, 1H, C(7)_{HA}, ³*J*_{AB} = 9.8 Hz, ³*J*_{AX} = 1.6 Hz), 7.57 (br s, 1H, NH_x). ¹³C{¹H} NMR (acetone-*d*₆, 100 MHz, ppm): δ 25.9, 27.4 (SCH₂), 82.0 (C(7)), 121.9 (C(4a)), 144.4 (C(7a)), 168.5 (C(5)). Found (%): C, 38.18; H, 3.85; N, 7.27; S, 34.04. C₆H₇NO₂S₂. Calculated (%): C, 38.08; H, 3.73; N, 7.40; S, 33.89.

2.3.2. 6-Benzyl-7-hydroxy-2,3,6,7-tetrahydro-5H-[1,4]dithiino[2,3-c]pyrrol-5-one (7)

A solution of benzylamine (0.33 mL, 3.0 mmol) in diethyl ether (10 mL) was added dropwise to a stirred mixture of compound **3** (0.41 g, 2.0 mmol) and ether (10 mL). The reaction mixture was refluxed for 26 h. After cooling to room temperature, the precipitate was filtered off, washed with ether and recrystallized from a mixture of benzene and tetrachloromethane (10:1) to give heterocycle **7** as colorless solid. Yield 71% (0.40 g), m.p. 166–167 °C. R_f 0.31 (acetone-toluene, 1:4). IR, ν , cm^{-1} : 3000–3500 br (OH), 1656 (C=O), 1580 (C=C_{lact}), 1498 (C=C_{arom}). ^1H NMR (acetone- d_6 , 400 MHz, ppm): δ 3.21–3.28 (m, 2H, SCH₂), 3.28–3.36 (m, 2H, SCH₂), 4.29, 4.84 (both m, 1H each, AB quadruplet, CH₂N, $^2J_{\text{HH}} = -15.2$ Hz), 5.18 (d, 1H, C(7)H, $^3J = 9.9$ Hz), 5.55 (d, 1H, OH, $^3J = 9.9$ Hz), 7.17–7.41 (m, 5H, H_{arom}). $^{13}\text{C}\{^1\text{H}\}$ NMR (acetone- d_6 , 100 MHz, ppm): δ 26.1, 27.5 (SCH₂); 43.3 (CH₂N); 84.0 (C(7)); 122.0 (C(4a)); 128.1, 128.9, 129.4, 138.9 (C_{arom}); 142.6 (C(7a)); 166.2 (C(5)). Found (%): C, 55.81; H, 4.62; N, 5.08; S, 22.93. C₁₃H₁₃NO₂S₂. Calculated (%): C, 55.89; H, 4.69; N, 5.01, S, 22.95.

2.3.3. 4,4'-(Ethane-1,2-diylsulfanediy)bis(3-chloro-5-hydroxy-1,5-dihydro-2H-pyrrol-2-one) (8)

Cooled aqueous ammonia solution (25%, 6 mL, 80 mmol) and a 1:2 mixture of ethanol and diethyl ether (3 mL) were added to a compound **5** (0.39 g, 1.0 mmol). The reaction mixture was stirred at $-13 \div -10$ °C for 24 h (monitored by TLC). At first a precipitate of *meso* isomer **8a** was formed during the reaction, which was filtered off, washed with acetone and dried. Evaporation of the mother liquor to about half-volume, and cooling for 24 h, gave a mixture of two diastereomers **8**. The total yield 73% (0.27 g).

Mixture of diastereomers 8. Colorless solid. Yield 30% (0.11 g), m.p. 158 °C (decomp.). IR, ν , cm^{-1} : 3000–3500 br (OH, NH), 1694 (C=O), 1592, 1578 (C=C_{lact}). ^1H NMR (acetone- d_6 , 700 MHz, ppm): δ 3.48–3.72 (m, 8H, SCH₂), 5.71 (dd, 2H, OH_B, $^3J_{\text{AB}} = 10.1$ Hz, $^4J_{\text{BX}} = 1.3$ Hz), 5.73 (dd, 2H, OH_B, $^3J_{\text{AB}} = 9.5$ Hz, $^4J_{\text{BX}} = 1.4$ Hz), 5.84 (dd, 2H, C(5)H_A, $^3J_{\text{AB}} = 10.1$ Hz, $^3J_{\text{AX}} = 1.8$ Hz), 5.85 (dd, 2H, C(5)H_A, $^3J_{\text{AB}} = 9.5$ Hz, $^3J_{\text{AX}} = 1.7$ Hz), 7.92 (br s, 4H, NH_X). $^{13}\text{C}\{^1\text{H}\}$ NMR (acetone- d_6 , 176 MHz, ppm): δ 31.52 (SCH₂); 79.98, 80.04 (C(5)); 122.69, 122.81 (C(3)); 151.86, 151.92 (C(4)); 165.19, 165.24 (C(2)).

Meso-isomer 8a. Colorless solid. Yield 43% (0.16 g), m.p. 159 °C (decomp.). IR, ν , cm^{-1} : 3000–3500 br (OH, NH), 1695 (C=O), 1594 (C=C_{lact}). ^1H NMR (acetone- d_6 , 700 MHz, ppm): δ 3.47–3.71 (m, 4H, SCH₂), 5.71 (d, 2H, OH_B, $^3J_{\text{AB}} = 10.0$ Hz), 5.84 (d, 2H, C(5)H_A, $^3J_{\text{AB}} = 10.0$ Hz), 7.92 (br s, 2H, NH_X). $^{13}\text{C}\{^1\text{H}\}$ NMR (acetone- d_6 , 176 MHz, ppm): δ 31.5 (SCH₂), 80.0 (C(5)), 122.8 (C(3)), 151.9 (C(4)), 165.2 (C(2)). Found (%): C, 33.54; H, 2.80; Cl, 19.78; N, 7.63; S, 17.93. C₁₀H₁₀Cl₂N₂O₄S₂. Calculated (%): C, 33.62; H, 2.82; Cl, 19.85; N, 7.84, S, 17.95.

2.3.4. 4,4'-(Ethane-1,2-diylsulfanediy)bis(1-benzyl-3-chloro-5-hydroxy-1,5-dihydro-2H-pyrrol-2-one) (9)

Cooled solution of benzylamine (0.23 mL, 2.1 mmol) in a 2:1 mixture of diethyl ether and ethanol (7.5 mL) was added dropwise to a stirred mixture of compound **5** (0.27 g, 0.7 mmol) and ether (4 mL). The reaction mixture was stirred at $-13 \div -10$ °C for 3 days (monitored by TLC). The precipitate was filtered off, washed with ether and recrystallized from ethanol to give bis-thioether **9** as a mixture of diastereomers. Colorless solid. Yield 68% (0.26 g), m.p. 163–165 °C (decomp.). R_f 0.49 (acetone-toluene, 1:2). IR, ν , cm^{-1} : 3100–3450 br (OH), 1695 (C=O), 1590, 1499 (C=C_{lact}, C=C_{arom}). ^1H NMR (acetone- d_6 , 700 MHz, ppm): δ 3.46–3.60 (m, 8H, SCH₂), 4.36, 4.81 (both m, 2H each, AB quadruplet, CH₂N, $^2J_{\text{HH}} = -15.4$ Hz), 4.36, 4.82 (both m, 2H each, AB quadruplet, CH₂N, $^2J_{\text{HH}} = -15.4$ Hz), 5.58, 5.61 (both d, 2H each, C(5)H, $^3J = 9.5$ Hz), 5.88 (d, 4H, OH, $^3J = 9.5$ Hz), 7.21–7.35 (m, 20H, H_{arom}). $^{13}\text{C}\{^1\text{H}\}$ NMR (acetone- d_6 , 176 MHz, ppm): δ 31.42, 31.53 (SCH₂); 44.25 (CH₂N); 82.41, 82.45 (C(5)); 122.60, 122.75 (C(3)); 128.18, 128.84, 128.86, 129.40, 138.42 (C_{arom}); 150.16, 150.29 (C(4)); 163.39 (C(2)). Found (%): C, 53.72; H, 4.06; Cl, 13.15; N, 5.17; S, 11.91. C₂₄H₂₂Cl₂N₂O₄S₂. Calculated (%): C, 53.63; H, 4.13; Cl, 13.19; N, 5.21; S, 11.93.

3. Results and Discussion

Two types of sulfur-containing compounds of 2(5H)-furanone series were considered as promising precursors for the synthesis of the corresponding dithioderivatives of 3-pyrrolin-2-one. The interaction of mucochloric acid **1** with 1,2-ethanedithiol in the presence of triethylamine resulted in the formation of fused bicyclic compound **2** [32], which was further converted into a methoxy derivative of dithiiofuranone **3** (Scheme 1). *Bis*-thioether **5**, which combines two 2(5H)-furanone moieties, bridged through their carbon atoms C(4) by the 1,2-ethanedithiol fragment, was obtained from mucochloric acid **1** in two steps by initial reaction with alcohol under acidic catalytic conditions, followed by thiolation of furanone **4** by the use of dithiol in the presence of a base [32].

Bicycle **3** and *bis*-thioether **5** were involved in the reaction with nitrogen-containing nucleophiles to afford the corresponding dithioderivatives of 3-pyrrolin-2-one **6–9**, possessing a hydroxy group at the saturated carbon atom of the γ -lactam ring (Scheme 2). Reactions were carried out under cooling by mixing compounds **3** and **5** with aqueous ammonia solution or benzylamine in diethyl ether-ethanol medium. The structure of novel synthesized compounds **6–9** obtained as stable colorless solids was confirmed by IR, ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopy, and single crystal X-ray diffraction (Figures S1–S8, Table S1).

Characteristic features of the IR spectra of pyrrolinones **6–9** are a broad band of medium intensity in the range of 3000–3500 cm^{-1} assigned to the stretching vibra-

tions of the hydroxy (for **6–9**) or both OH and NH groups (for the *N*-unsubstituted compounds **6** and **8**), and a strong band at 1656–1695 cm^{-1} corresponding to the lactam carbonyl group (Figures S6–S8).

The ^1H NMR spectra of compounds **6–9** recorded in the deuterated acetone contain signals for the methine proton at the saturated carbon atom of the lactam ring (δ 5.18–5.85 ppm), the proton of the hydroxy group (δ 5.27–5.88 ppm) and a multiplets in the range of 3.12–3.72 ppm, characteristic for the methylene protons of the $-\text{SCH}_2\text{CH}_2\text{S}-$ moiety (Figures S1–S5). The signal for the NH proton appeared as a broad singlet in the range of 7.57–7.92 ppm in the ^1H NMR spectra of compounds **6** and **8**.

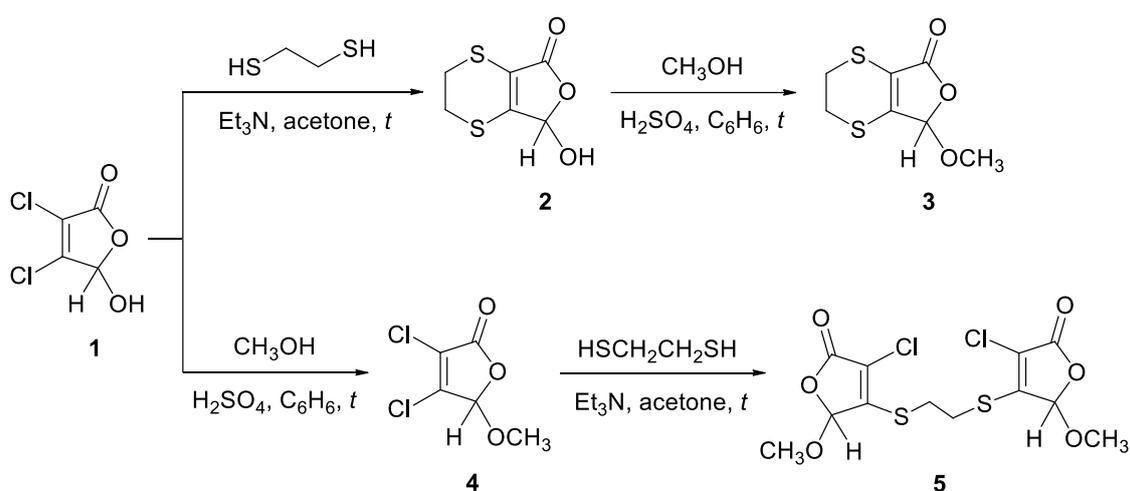
In the case of *bis*-thioethers **8** and **9**, a doublet signal set in the ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra evidenced the formation of two diastereomers (*meso* and *dl*) of these products. The less soluble *meso* isomer **8a** was obtained in pure form and characterized by spectral methods (Figures S4, S7b) and single crystal X-ray diffraction.

It should be noted, that similar to heterocycles **6** and **7** other fused bicyclic compounds were synthesized earlier in two steps from 5,6-dihydro-1,4-dithiine-2,3-dicarboxylic anhydride and amines followed by reduction using sodium borohydride [24,25]. To the best of our

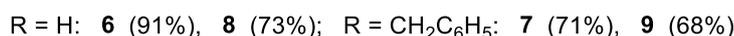
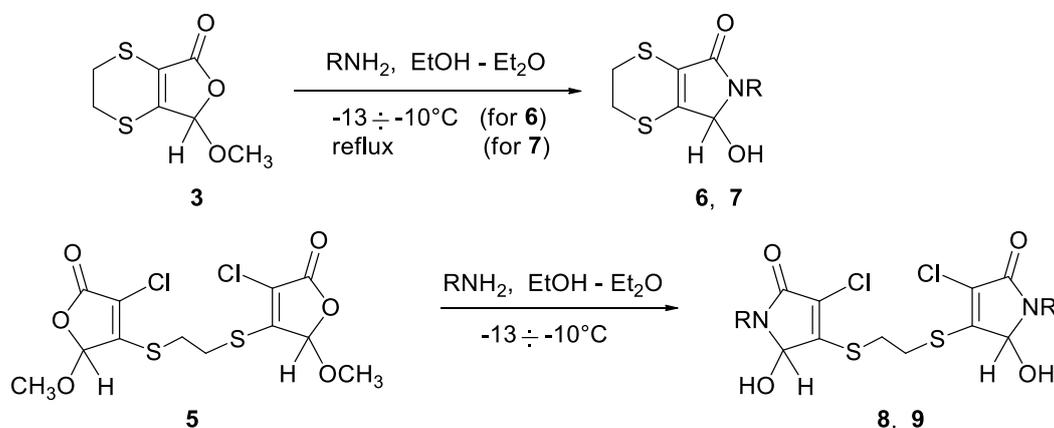
knowledge, compounds **8** and **9** are first representatives of *bis*-thioethers with a dithiol linker joining the two lactams together through their C(4) atoms.

Ammonolysis or amination of 5-methoxy-2(5*H*)-furanone derivatives represent a simple and convenient method for the synthesis of bicycles **6**, **7** and *bis*-thioethers **8**, **9**. One can expect the formation of unsubstituted at the nitrogen atom N(1) compounds **6** and **8** upon direct thiolation of 5-hydroxy-3,4-dichloro-3-pyrrolin-2-one [35]. However, we have shown that the interaction of this pyrrolinone with ethane-1,2-dithiol in the presence of a base (triethylamine or aqueous potassium hydroxide solution) gave a complex inseparable mixture of several products. Apparently, it is difficult to synthesize compounds **6** and **8** by direct thiolation of 3,4-dichloro-3-pyrrolin-2-one in used reaction conditions.

The structure of bicycle **6** was determined by single crystal X-ray diffraction using colorless crystals obtained from a deuterated acetone solution. According to the X-ray data, the six-membered ring of the molecule **6** in the crystal has a half-chair conformation: the five-atom fragment S(1)C(3)C(4)S(2)C(7) is planar, the C(6A) and C(6B) atoms deviate from this plane by $-0.683(4)$ Å and $0.625(11)$ Å, respectively (Figure 1).



Scheme 1 Synthesis of dithioderivatives of 2(5*H*)-furanone **3** and **5**.



Scheme 2 Synthesis of dithioderivatives of 3-pyrrolin-2-one **6–9**.

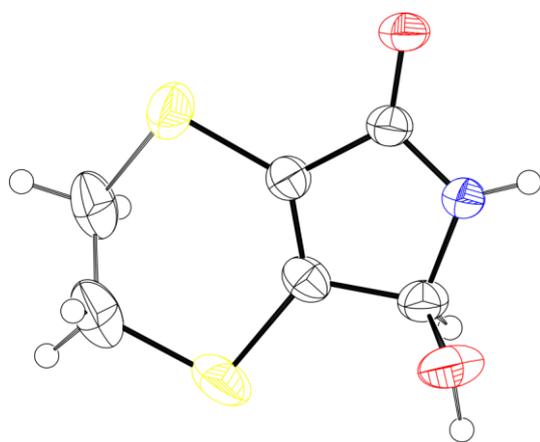


Figure 1 Molecular structure of heterocycles **6** in the crystal.

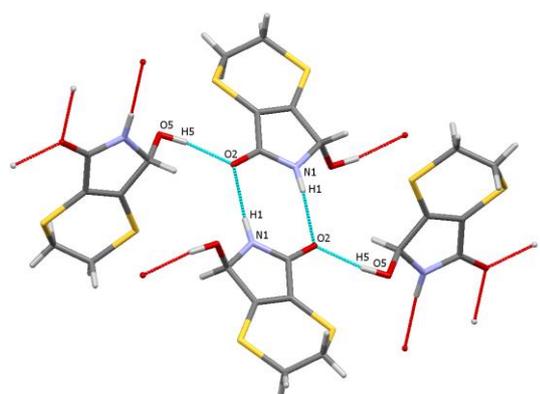


Figure 2 Intermolecular interactions in the crystal of compound **6**.

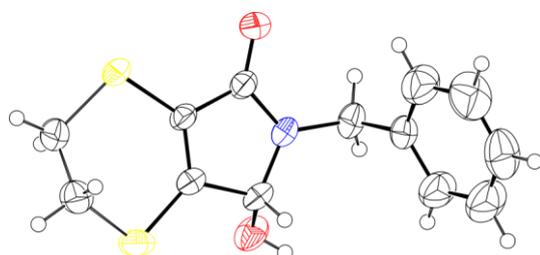


Figure 3 Molecular structure of bicycle **7** in the crystal.

In the crystal, neighboring molecules **6** form centrosymmetric dimers through a hydrogen bond between the hydrogen atom of the amino group and the oxygen atom of the carbonyl group (the N(1)...O(2) distance is 2.938(7) Å). These dimers, in turn, are linked to each other by the interaction of the hydrogen atom of the hydroxy group and the oxygen atom of the carbonyl group (the O(5)...O(2) distance is 2.705(6) Å) (Figure 2).

The X-ray crystallographic analysis revealed that the six-membered cycle of the molecule **7** is characterized by the half-chair conformation (Figure 3). The S(1)C(3)C(4)S(2) fragment is planar, the deviation of C(13A) and C(14A) atoms from the plane is 0.416(16) Å and -0.383(14) Å, correspondingly. The atoms C(13B) and C(14B) deviate from the plane by -0.357(7) Å and 0.449(6) Å, respectively.

The molecules of **7** in the crystal form infinite chains via classical hydrogen bonds between the hydrogen atom

of the hydroxy group and the oxygen atom of the carbonyl group (the O(5)...O(2) distance is 2.726(2) Å) (Figure 4).

The obtained individual *meso* diastereomer **8a** crystallizes as a solvate with two DMSO molecules (Figure 5). The molecules of compound **8a** are linked to the solvent molecules through hydrogen bonds between the hydrogen atom of the hydroxy group and the oxygen atom of DMSO. In the crystal, the molecules of *bis*-thioether **8a** are linked to each other by hydrogen bonds between the hydrogen atoms of the amino groups, on the one hand, and the oxygen atom of the carbonyl group, on the other (Figure 6, Table S2).

Recrystallization of the obtained mixture of isomers **9** from ethanol gave crystals of *meso* form **9a** as verified by X-ray crystallography. The molecules of *meso* form **9a** in the crystal were in the special position in the center of symmetry (Figure 7).

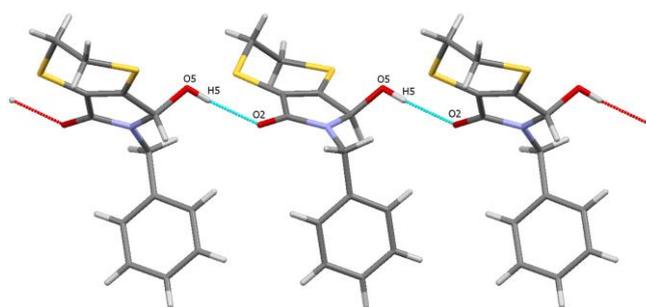


Figure 4 Intermolecular interactions in the crystal of bicycle **7**.

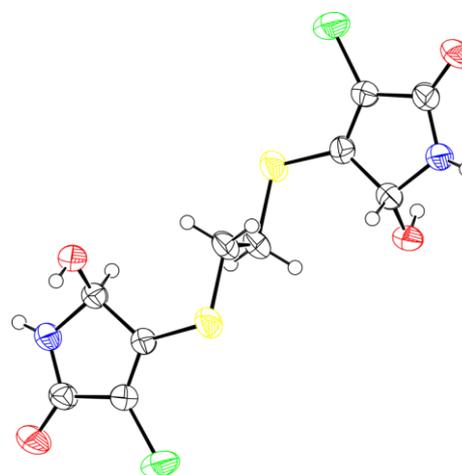


Figure 5 Molecular structure of *meso* isomer **8a** in the crystal.

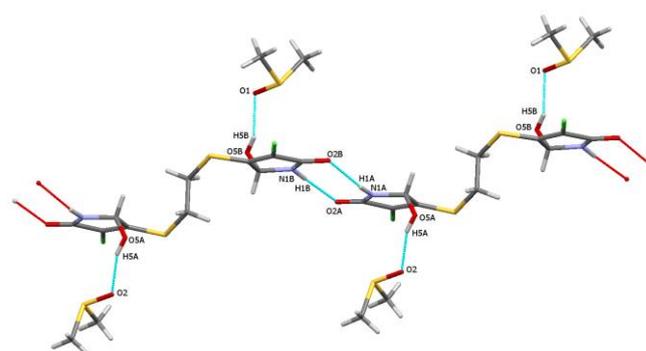


Figure 6 Intermolecular interactions in the crystal of *meso* isomer **8a**.

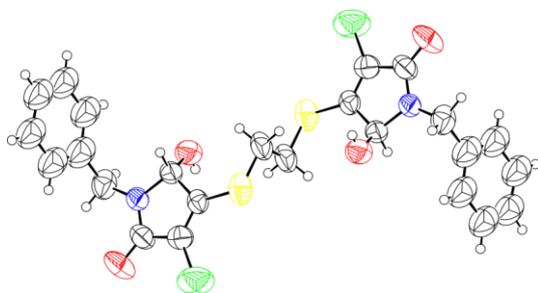


Figure 7 Molecular structure of *meso* isomer **9a** in the crystal.

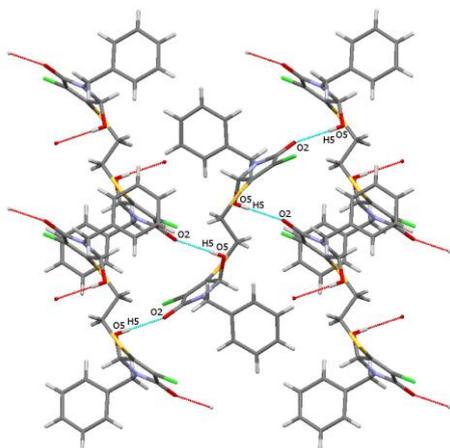


Figure 8 Intermolecular interactions in the crystal of compound **9a**.

The connecting fragment $-\text{SCH}_2\text{CH}_2\text{S}-$ adopts a *transoid* conformation, similar to the studied earlier *meso* isomers of furanone *bis*-thioethers [32]. In the crystal, $\text{O}(5)\text{-H}(5)\dots\text{O}(2)$ hydrogen bonds with an $\text{O}(5)\dots\text{O}(2)$ distance of 2.683(8) Å are observed between the molecules **9a** (Figure 8).

Thus, for all single crystals studied here, hydrogen bonding is a key factor in the formation of compounds structure. In most cases, hydrogen bonds between the hydrogen atom of the hydroxy or amino groups and the oxygen atom of the carbonyl group determine the crystal lattice architecture, forming dimers (*N*-unsubstituted compounds **6** and **8a**) or infinite chains (*N*-benzyl derivatives **7** and **9a**). Interactions with the solvent further stabilize the structure and form special packing motif in the crystal structure of compound **8a**.

4. Limitations

There were some difficulties associated with poor solubility of the synthesized compounds **6–9** in most organic solvents, especially it relates to *bis*-thioether **8**.

5. Conclusions

In this study, we successfully applied the synthesis method, based on the interaction of ammonia and benzylamine with corresponding thioethers of 5-methoxy-2(5*H*)-furanone to the synthesis of novel sulfur-containing derivatives of 3-pyrrolin-2-one, possessing two sulfur atoms.

New representatives of fused bicyclic compounds of 2,3,6,7-tetrahydro-5*H*-[1,4]dithiino[2,3-*c*]pyrrol-5-one series and *bis*-thioethers with a dithiol linker connecting two unsaturated γ -lactams through their C(4) atoms, were synthesized and characterized by spectral methods and single crystal X-ray diffraction. 5-Alkoxy-furanone based method can be effectively utilized for the construction of such and more complex heterocyclic systems, possessing lactam ring, difficult to access by other methods.

Supplementary materials

This manuscript contains supplementary materials, which are available on the corresponding online page.

Data availability statement

The data that supports the findings of this study are available in the supplementary material of this article.

Acknowledgments

None.

Author contributions

Conceptualization: L.S.K., A.R.K.

Data curation: L.S.K., E.S.R., O.A.L., S.V.E.

Formal Analysis: L.S.K., O.A.L., A.R.K.

Funding acquisition: A.R.K.

Investigation: L.S.K., E.S.R., O.A.L., S.V.E.

Methodology: L.S.K., A.R.K.

Project administration: A.R.K.

Resources: O.A.L., V.V.K., A.R.K.

Software: L.S.K., E.S.R., D.P.G., S.V.E.

Supervision: A.R.K.

Validation: L.S.K., E.S.R., V.V.K.

Visualization: E.S.R., D.P.G., O.A.L.

Writing – original draft: L.S.K., E.S.R., D.P.G., O.A.L.

Writing – review & editing: A.R.K.

Conflict of interest

The authors declare no conflict of interest.

Additional information

Author IDs:

Liliya S. Kosolapova, Scopus ID 25230267000;

Enze S. Rabbanieva, Scopus ID 57928101500;

Darya P. Gerasimova, Scopus ID 57218115153;

Sergey V. Efimov, Scopus ID 56711366000;

Olga A. Lodochnikova, Scopus ID 6603582369;

Vladimir V. Klochkov, Scopus ID 36742413700;

Almira R. Kurbangaliev, Scopus ID 6603260071.

Websites:

Kazan Federal University, <https://eng.kpfu.ru>;

Arbuzov Institute of Organic and Physical Chemistry, http://iopc.ru/document/main_en.html.

References

- Kerru N, Gummidi L, Maddila S, Gangu KK, Jonnalagadda SB. A Review on Recent Advances in Nitrogen-Containing Molecules and Their Biological Applications. *Molecules*. 2020;25(8):1909. doi:10.3390/molecules25081909
- Kabir E, Uzzaman M. A review on biological and medicinal impact of heterocyclic compounds. *Results Chem*. 2022;4:100606. doi:10.1016/j.rechem.2022.100606

3. López-Francés A, Del corte X, Serna-Burgos Z, Martínez de marigorta E, Palacios F, Vicario J. Exploring the Synthetic Potential of γ -Lactam Derivatives Obtained from a Multicomponent Reaction—Applications as Antiproliferative Agents. *Molecules*. 2022;27(11):3624. doi:10.3390/molecules27113624
4. Siddiqui B, Yadav CS, Faiyyaz M, Akil M, Hassan F, Ahmad A, Ahmad N, Khan AR, Azad I. Comprehensive Review of Dihydro-2H-pyrrol-2-one Derivatives. *ChemistrySelect*. 2025;10(1):e202401807. doi:10.1002/slct.202401807
5. Nguyen NT, Dai VV, Tri NN, Van meervelt L, Trung NT, Dehaen W. Experimental and theoretical studies on the synthesis of 1,4,5-trisubstituted pyrrolidine-2,3-diones. *Beilstein J Org Chem*. 2022;18:1140–53. doi:10.3762/bjoc.18.118
6. Pelkey ET, Pelkey SJ, Greger JG. Reactions of 3-pyrrolin-2-ones. In: Scriven EFV, Ramsden CA. (Eds.) *Advances in Heterocyclic Chemistry*, Vol. 128. Chapter 6. Oxford: Elsevier; 2019, 433–565 pp. doi:10.1016/bs.aihch.2018.10.004
7. Pelkey ET, Pelkey SJ, Greger JG. De Novo Synthesis of 3-Pyrrolin-2-Ones. *Adv Heterocycl Chem*. 2015;:151–285. doi:10.1016/bs.aihch.2015.04.001
8. Schirotti D, Voronov A, Pancrazzi F, Iraci N, Vincenzo giofrè S, Macchi B, Stefanizzi V, Mancuso R, Gabriele B, Pio mazzeo P, Capaldo L, Della ca' N. Direct Access to α,β -Unsaturated γ -Lactams via Palladium-Catalysed Carbonylation of Propargylic Ureas.. *Adv Synth Catal*. 2025;367(5):e202401183. doi:10.1002/adsc.202401183
9. Nakhla MC, Wood JL, Organ MG. Mild Direct Single-Step Conversion of Propargyl Amines to Highly Substituted 3-Pyrrolin-2-ones. *Org Lett*. 2025;27(35):9765–70. doi:10.1021/acs.orglett.5c03109
10. Żurawska K, Byczek-Wyrostek A, Kasprzycka A, Walczak K. 3,4-Dihalo-5-hydroxy-2(5H)-furanones: Highly Reactive Small Molecules. *Molecules*. 2024;29(21):5149. doi:10.3390/molecules29215149
11. Kosolapova LS, Kurbangalieva AR, Valiev MF, Lodochnikova OA, Berdnikov EA, Chmutova GA. Synthesis and structure of the products of the reactions of 3-chloro-5-methoxy-4-[(4-methylphenyl)sulfanyl]-2(5H)-furanone with N,N-binucleophilic agents. *Russ Chem Bull*. 2013;62(2):456–63. doi:10.1007/s11172-013-0064-7
12. Kosolapova LS, Saigitbatalova ES, Latypova LZ, Valiev MF, Gerasimova DP, Kurbangalieva AR. Novel Acid-Catalyzed Transformation of 1-Benzyl-3-Chloro-5-Hydroxy-4-[(4-Methylphenyl)Sulfanyl]-1,5-Dihydro-2H-Pyrrol-2-One. *Molbank*. 2025;2025(2):M2017. doi:10.3390/M2017
13. Lodochnikova OA, Kosolapova LS, Saifina AF, Gubaidullin AT, Fayzullin RR, Khamatgalimov AR, Litvinov IA, Kurbangalieva AR. Structural aspects of partial solid solution formation: two crystalline modifications of a chiral derivative of 1,5-dihydro-2H-pyrrol-2-one under consideration. *CrystEngComm*. 2017;19(48):7277–86. doi:10.1039/C7CE01717K
14. Lodochnikova OA, Zaripova AR, Fayzullin RR, Samigullina AI, Vandyukova II, Potapova LN, Kurbangalieva AR. “Doubly enantiophobic” behavior during crystallization of racemic 1,5-dihydro-2H-pyrrol-2-one thioether. *CrystEngComm*. 2018;20(23):3218–27. doi:10.1039/c8ce00369f
15. Gerasimova DP, Saifina AF, Zakharychev DV, Fayzullin RR, Kurbangalieva AR, Lodochnikova OA. The second example of doubly enantiophobic behavior during crystallization: a detailed crystallographic, thermochemical and spectroscopic study. *CrystEngComm*. 2021;23(21):3907–18. doi:10.1039/D1CE00227A
16. Gerasimova DP, Faizova RG, Zakharychev DV, Saifina AF, Kurbangalieva AR, Lodochnikova OA. Stability and reproducibility of the dimeric motif in the crystals of thioethers of 3-bromo-5-hydroxy-1-(4-methylbenzyl)-1,5-dihydro-2H-pyrrol-2-ones. *J Struct Chem*. 2022;63(10):1616–28. doi:10.1134/S0022476622100080
17. Gerasimova DP, Zakharychev DV, Saifina AF, Fayzullin RR, Kurbangalieva AR, Lodochnikova OA. Homochiral versus Heterochiral Crystallization of 3-Pyrrolin-2-one Thioether Results in the Score 2:1 in Favor of Homochirality. *Cryst Growth Des*. 2022;22(12):7273–84. doi:10.1021/acs.cgd.2c00916
18. Gerasimova DP, Saigitbatalova ES, Islamov DR, Zakharychev DV, Saifina AF, Kurbangalieva AR, Lodochnikova OA. Reproducibility of a homochiral hydrogen-bonded chain in conglomerate and racemic compound crystals of the triazole derivative of 3-pyrroline-2-one. *J Struct Chem*. 2022;63(9):1434–45. doi:10.1134/S0022476622090062
19. K. donald D, M. cambell M. 3-Chloro-3-cyano-1-(2,4-dimethoxybenzyl)-4-phenylthioazetidin-2-one. *Heterocycles*. 1982;19(11):2087. doi:10.3987/R-1982-11-2087
20. Ito M, Okui H, Nakagawa H, Mio S, Kinoshita A, Obayashi T, Miura T, Nagai J, Yokoi S, Ichinose R, Tanaka K, Kodama S, Iwasaki T, Miyake T, Takashio M, Iwabuchi J. Synthesis and insecticidal activity of novel dihydropyrrole derivatives with N-Sulfanyl, sulfinyl, and sulfonyl moieties. *Bioorganic Med Chem*. 2003;11(4):489–94. doi:10.1016/S0968-0896(02)00476-5
21. Fariña F, Angeles jiménez M, Carmen ortega M, Tito A. Pseudoesters and Derivatives. XXI. The Reaction of 4-Bromo-5-methoxy-3-pyrrolin-2-one with Nucleophiles. *HETEROCYCLES*. 1984;22(5):1179. doi:10.3987/R-1984-05-1179
22. Nikitin KV, Andryukhova NP. Synthesis of N-Substituted -Alkoxy-3-aryl-4-methyl-2,5-dihydro-2-pyrrolones. *Chem Heterocycl Compd*. 2004;40(5):561–9. doi:10.1023/B:COHC.0000037310.26204.24
23. Rudler H, Parlier A, Ousmer M, Vaissermann J. One-pot formation of functionalized pyrrolinones and 2-oxohexahydroindoles from aminocarbene complexes of chromium. *Eur J Org Chem*. 1999;1999(12):3315–3321. doi:10.1002/(SICI)1099-0690(199912)1999:12<3315::AID-EJOC3315>3.0.CO;2-M
24. Ferrucci E, Lissoni F. Foreign inventors in Europe and the United States: Diversity and Patent Quality. *Res Policy*. 2019;48(9):103774. doi:10.1016/j.respol.2019.03.019
25. Jeanmart C, Leger A, inventors; Rhone-Poulenc Industries, assignee. Derivatives of dithiepinol[1,4][2,3-c]pyrrole. United States patent US 4124711. 1978. Nov 7.
26. Krause L, Herbst-Irmer R, Sheldrick GM, Stalke D. Comparison of silver and molybdenum microfocus X-ray sources for single-crystal structure determination. *J Appl Crystallogr*. 2015;48(1):3–10. doi:10.1107/S1600576714022985
27. Dolomanov OV, Bourhis LJ, Gildea RJ, Howard JA, Puschmann H. OLEX2: a complete structure solution, refinement and analysis program. *J Appl Crystallogr*. 2009;42(2):339–41. doi:10.1107/S0021889808042726
28. Sheldrick GM. SHELXT— Integrated space-group and crystal-structure determination. *Acta Crystallogr Sect Found Adv*. 2015;71(1):3–8. doi:10.1107/S2053273314026370
29. Sheldrick GM. Crystal structure refinement withSHELXL. *Acta Crystallogr Sect C Struct Chem*. 2015;71(1):3–8. doi:10.1107/S2053229614024218
30. Macrae CF, Sovago I, Cottrell SJ, Galek PT, McCabe P, Pidcock E, Platings M, Shields GP, Stevens JS, Towler M, Wood PA. Mercury 4.0: from visualization to analysis, design and prediction. *J Appl Crystallogr*. 2020;53(1):226–35. doi:10.1107/S1600576719014092
31. Spek AL. Structure validation in chemical crystallography. *Acta Crystallogr Sect D Biol Crystallogr*. 2009;65(2):148–55. doi:10.1107/S090744490804362X
32. Kurbangalieva AR, Lodochnikova OA, Devyatova NF, Berdnikov EA, Gnezdilov OI, Litvinov IA, Chmutova GA. Structural diversity of interaction products of mucochloric acid and its derivatives with 1,2-ethanedithiol. *Tetrahedron*. 2010;66(52):9945–53. doi:10.1016/j.tet.2010.10.047
33. Latypova LZ. Реакции окисления и восстановления серосодержащих производных 2(5H)-фуранона [Oxidation and reduction reactions of sulfur-containing derivatives of 2(5H)-furanone] [dissertation]. Kazan (Russia): Kazan (Volga region) Federal University; 2013. 215 p. Russian.

34. Mowry DT. Mucochloric Acid. I. Reactions of the Pseudo Acid Group. *J Am Chem Soc.* 1950;72(6):2535-7. [doi:10.1021/jao1162a056](https://doi.org/10.1021/jao1162a056)
35. Frantsuzova LV, Gerasimova DP, Kosolapova LS, Charushin NS, Kurbangalieva AR, Lodochnikova OA. Управление типом стереоизомерного распознавания в ряду 3,4-дигалоген-5-гидрокси-1,5-дигидро-2*H*-пиррол-2-онов посредством варьирования природы галогена в молекуле [Control of the type of stereoisomeric recognition in the 3,4-dihalo-5-hydroxy-1,5-dihydro-2*H*-pyrrol-2-one series by varying the halogen nature in the molecule]. *J Struct Chem.* 2026;67(1):159338. [doi:10.26902/JSC_id159338](https://doi.org/10.26902/JSC_id159338) (In Russian).