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STEREOCHEMICAL CHARACTERISTICS AND BIOLOGICAL ACTIVITY OF ENANTIOMERIC (R)- AND (S)-4-METHYL-4-ETHYL-5-METHYLENETHIAZOLIDINES

Tohir Kh. Abdullaev
Institute of Chemistry of the National Academy of Sciences of Tajikistan, Senior researcher of the Laboratory of Organic Synthesis, Candidate of Chemical Sciences, Associate Professor
https://orcid.org/0000-0003-2630-8540

Ibragim R. Askarov
Andijan State University, Professor of the Department of Chemistry, Doctor of Chemistry, Honored Inventor of Uzbekistan, Chairman of the TABOBAT Academy of Uzbekistan
https://orcid.org/0000-0003-1625-0330

Muzafar D. Isobaev
Institute of Chemistry of the National Academy of Sciences of Tajikistan, Professor of the Laboratory of Organic Synthesis, Doctor of Chemical Sciences
https://orcid.org/0000-0001-5664-1956

Elmurod Kh. Pulatov
Institute of Chemistry of the National Academy of Sciences of Tajikistan, Chief Researcher of the Laboratory of Organic Synthesis, Doctor of Chemical Sciences
https://orcid.org/0000-0002-0052-5961

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Keywords:
Heterocycles, tautomerism, PMR spectroscopy, quantum chemical calculation, optically active thiazolidinthione, biological activity

Abstract

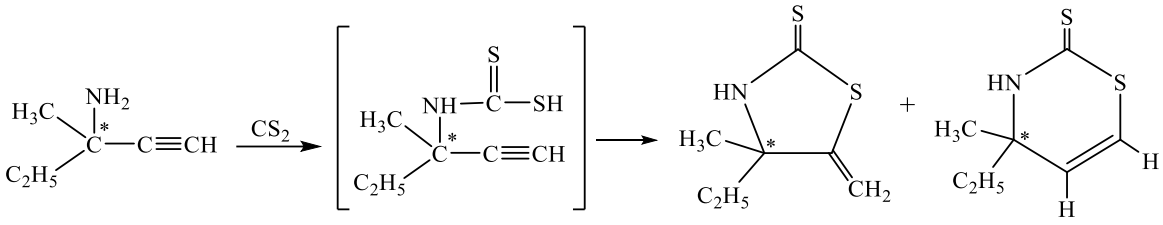
The paper presents some visions of the reaction of formation of sulfur-containing heterocycles. In the case of five-membered structures of the thiazolidine heterocycle type, a thione-thiol tautomeric equilibrium occurs, associated with the migration of a proton between the endocyclic nitrogen atom and the exocyclic sulfur atom. Data on thermodynamic characteristics and information on the stability of various configuration states make it possible to plan further reactions, depending on the selected conditions for their implementation.

Biological tests of racemic and optically active “4-methyl-4-ethyl-5-methylenethiazolidin-2-thiones” showed that they have different degrees of bacteriostatic and bactericidal action in relation to various strains of bacteria.

How to Cite

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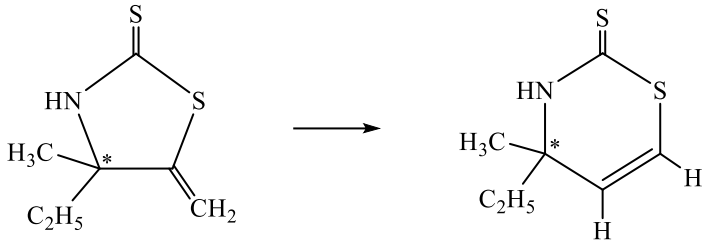
The reaction of acetylenic amines with carbon disulfide was first described by the authors of **[1-3]**. It should be noted that the formation of by-products, as well as the nature of the resulting products from the point of view of structural features, was not given sufficient attention. In the case under consideration, some visions of the reaction of the formation of sulfur-containing heterocycles are presented. It was found that in this case the reaction proceeds with the formation of predominantly five-membered heterocycles **1** and in very small quantities of six-membered thiazine isomers **2**, in accordance with the scheme [**3, 4**].



a **b**

The reaction was carried out in an alcohol medium. The reaction progress was monitored by thin-layer chromatography (TLC) and IR spectroscopy by the disappearance of the triple bond and the appearance of signals from the corresponding functional groups.

When examining the NMR spectra of the racemic reaction product, it was found that the interaction of carbon disulfide with acetylenic amines is controlled in the direction of the thione group and ethynylthiourea is formed intermediately, which subsequently, under the action of negatively saturated acetylenic carbon atoms at the triple bond, is formed. In one case, five-membered thiazolidine heterocycles **a** are formed, and in the second case, six-membered thiazine products **b**. The ratio of cyclization products and the probability of their formation are determined by the ratio of signals from the geminal protons of the methylene bond in the five-membered and vicinal protons from the six-membered heterocycles, where two types of signals were detected, corresponding to the geminal and vicinal protons of the double bond.



a **b**

It should be noted that according to the integral intensity of the protons of the ethylene groups, the ratios of the reaction products are determined; the amount of thiazine heterocycles **b** is no more than 5%.

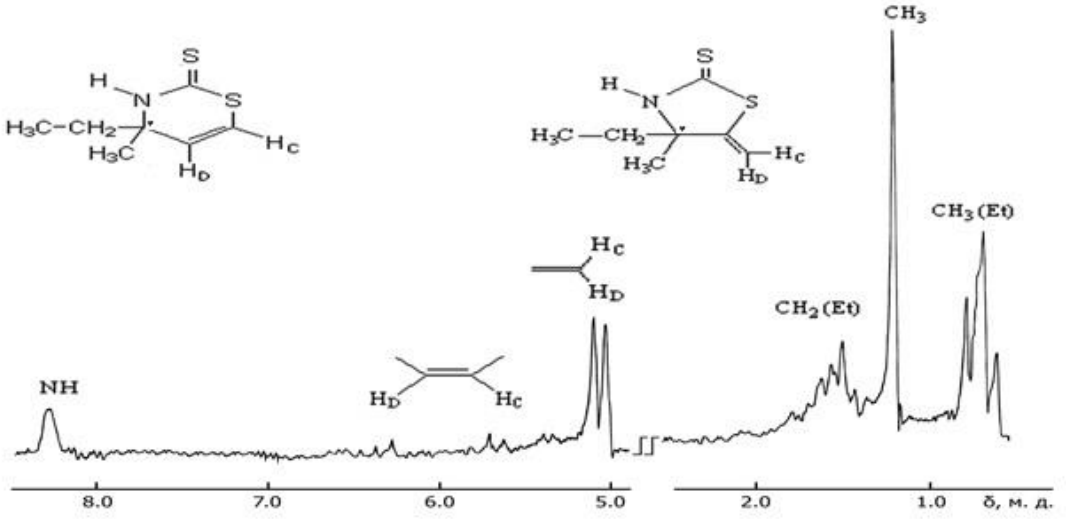
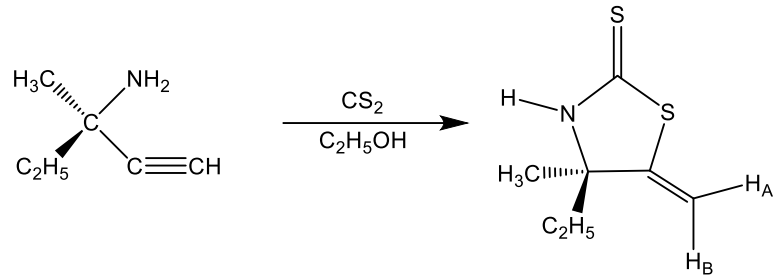
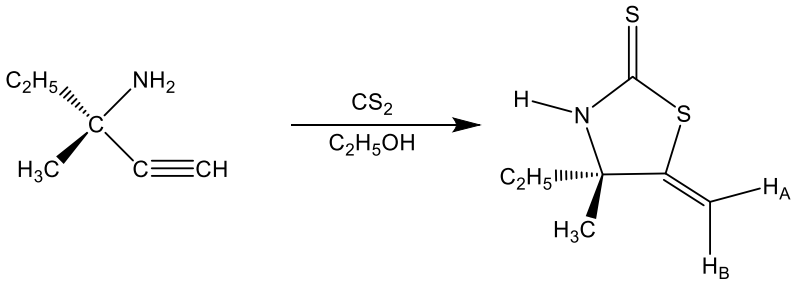


Fig. 1. NMR 1H spectrum (100 MHz) of 4-methyl-4-ethyl-5-methylenethiazolidine (1) with an admixture of six-membered isomer 2 in DMSO-D6 solution.

Optically active thiazolidinthiones **(2)-(R)** and **(2)-(S)** were obtained by us by boiling a mixture of excess carbon disulfide with the corresponding o.a. amines **(1)-(R)** and **(1)-(S),** which were separated by disatereomerization [**2, 4, 5]** for 4 hours in alcohol:



(1)-(R) **(2)-(R)**

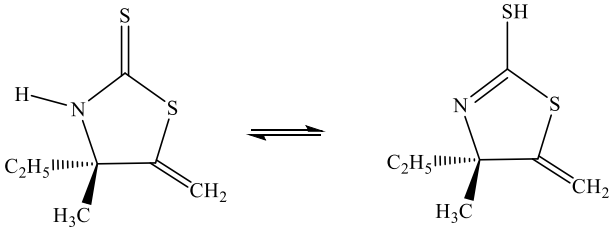


(1)-(S) **(2)-(S)**

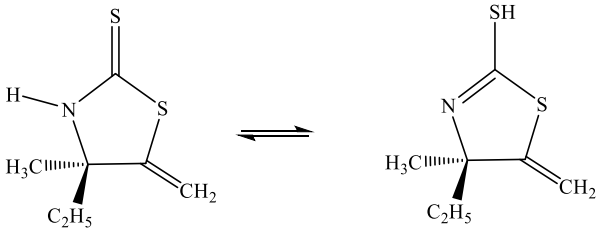
The purified product was obtained by recrystallization from ether. Under similar conditions, racemic **(R+S)**-thiazolidinthione (racemate) was obtained for the purpose of comparing biological activity. The yield of products was 85–90%.

The specific rotation angles were measured using a sodium lamp polarimeter at room temperature and are $[\alpha]_D^{25}$**((2)-(R))**=+3,80^0 (c. 2,11; hlf.), $[\alpha]_D^{25}$**((2)-(S))**=– 4,17^0 (c. 1,99; hlf.).

As expected for five-membered structures of the thiazolidine heterocycle type, a thione-thiol tautomeric equilibrium occurs, associated with the migration of a proton between the endocyclic nitrogen atom and the exocyclic sulfur atom. As indicated in [**6-8**], this equilibrium depends primarily on the conditions of the environment in which the product is found and, in many other cases, on the type of solvent in which it was obtained. In the case of optically active forms, this equilibrium looks as follows:



1a, (S)-(-) **1b, (S)-(-)**



1a, (R)-(+) **1b, (R)-(+)**

The PMR spectra of the obtained compound confirm the proposed structure (Fig. 1). In addition to the main proton signals inherent in the thione structure with a signal from the NH proton in the region of 7.27 ppm, there is also a small peak characteristic of the thiol group proton in the region of 8.10 ppm, which indicates the presence of thione-thiol tautomerism in this compound.

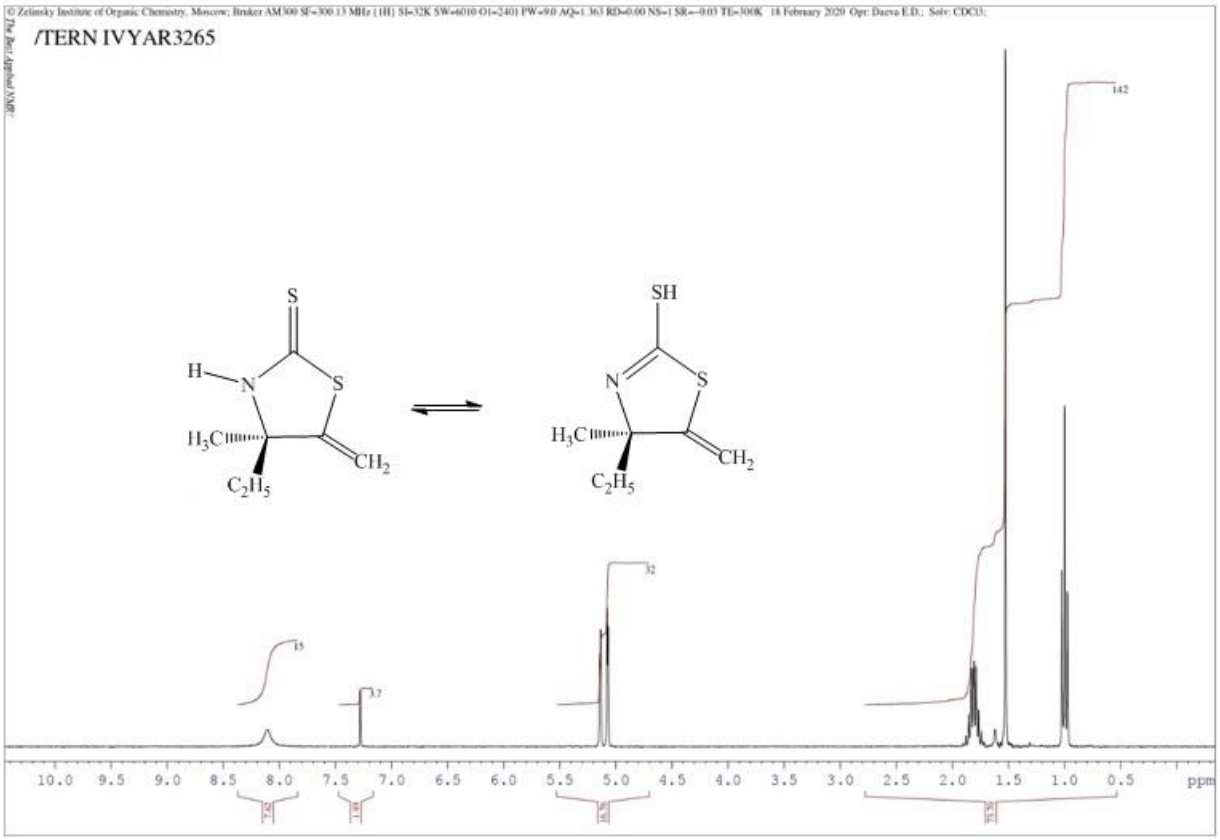


Fig. 1. NMR 1H spectrum (300.13 MHz) of (R)-(+)-4-methyl-4-ethyl-5-methylenethiazolidine (1a, (R)-(+)) in chloroform solution.

In order to clarify the thermodynamic characteristics for the studied structures of the synthesized optically active products in various tautomeric states, we carried out a quantum chemical calculation using the Gaussian computer software package, with the DFT approximation for low-structure states **[9].**

According to the quantum chemical calculations, under neutral conditions, the thione state is the most stable of the two forms (thione-thiol).

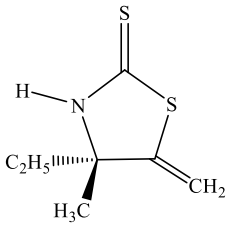
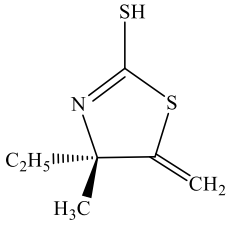
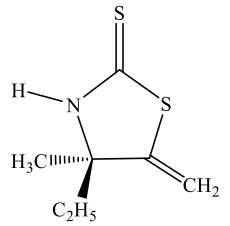
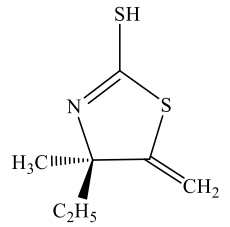
Data on the thermodynamic characteristics and information on the stability of various configurational states make it possible to plan further reactions, depending on the selected conditions for their implementation. Also, the results of quantum chemical calculations provide clear theoretical ideas about the potential reaction centers of the studied structures based on the electron density distribution data.

The structure of the obtained compounds was proven using IR and PMR spectra.

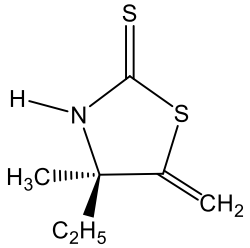
Table 1.

Thermodynamic characteristics of tautomeric states of optically active five-membered heterocycles

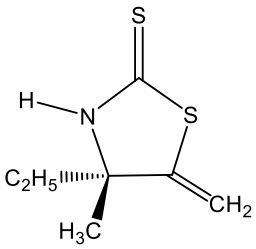
Composition	Structure	Emin, a.u.	E(Thermal), KCal/Mol	CV, Cal/Mol-Kelvin	S, Cal/Mol-Kelvin

1a, (S)-(-)		-1118.784	114.397	41.438	104.469
1b, (S)-(-)		-1118.746	111.840	43.124	107.116
1a, (R)-(+)		-1118.783	114.452	41.362	102.463
1b, (R)-(+)		-1118.749	111.823	43.021	105.850

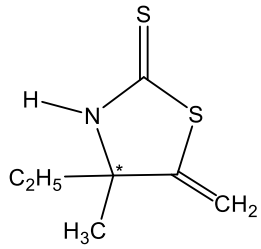
It is known [**10, 11**] that thiazolidinthiones exhibit a wide range of biological activity, including fungicidal properties and growth regulators of higher plant cell cultures. Of particular interest in this regard is the activity of thiazolidinthiones against cotton verticillium wilt. One option for increasing activity is to switch to optically active thiazolidinthiones. A study was conducted on the biological activity of the obtained preparations of "4-methyl-4-ethyl-5-methylenethiazolidin-2-thiones" in optically active form and in the racemate.



(2)-(R)



(2)-(S)



(2)-(R+S) Racemate

A series of successive dilutions were prepared from the presented compounds on a liquid Giss nutrient medium, based on the content of 4 μg to 20,000 μg of the preparation in 1 ml in 12 test tubes. The 13th test tube served as a control for the test culture. A fresh culture of the test microorganism species grown on meat-peptone agar was seeded into each test tube. In all cases, the microbial load was the same - 20,000 microbial bodies in 1 ml. The cultures were incubated at a temperature of 36-37 °C. To study the bacteriostatic effect, the culture on meat-peptone agar was seeded after 24 hours, and to identify the bactericidal effect after 72 hours. Methylene blue was tested as a control. Studies have shown that among the studied preparations **(2)-(R)**, in doses of 156-312 mcg/ml, exhibit bacteriostatic and bactericidal action against Staphylococcus aureus and Staphylococcus epidermidis, Escherichia coli, Klebsiella and Dysentery bacillus, and in doses of 625 mcg/ml against Proteus. **(2)-**

(S) in doses of 312-625 mcg/ml has a bacteriostatic and bactericidal effect against Staphylococcus aureus and Staphylococcus epidermidis, Klebsiella, Proteus, Escherichia coli and Dysentery bacillus. **Racemate**, in doses of 156-312 mcg/ml has bacteriostatic activity against epidermal, Staphylococcus aureus, Proteus and dysentery bacillus, and in doses of 625-1250 mcg/ml against Klebsiella and Escherichia coli.

As a control, methylene blue was tested, which in a dose of 20,000 mcg/ml has a bactericidal effect on blue-green pus bacillus, Escherichia coli and Proteus. In a dose of 625 mcg/ml on Staphylococcus aureus and anthracoid.

Thus, the biological tests conducted on the preparations of racemic and optically active "4-methyl-4-ethyl-5-methylenethiazolidin-2-thiones" showed [**12**] that they have varying degrees of bacteriostatic and bactericidal action against Staphylococcus aureus and Staphylococcus epidermidis, Klebsiella, Proteus, Escherichia coli and Dysentery bacillus.

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