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# Synthesis, Isomerism, and Hypotensive Activity of Thiethane-Containing Hydrazones of Uracilylacetic Acid

**S. A. Meshcheryakova[b], V. A. Kataev[b], K. V. Nikolaeva[b], V. N. Perfilova[a, 1], D. D. Borodin[a], and I. N. Tyurenkov[a]**

[a] *Volgograd State Medical University, pl. Pavshikh Bortsov 1, Volgograd, 400131 Russia*

[b] *Bashkirian State Medical University, Ufa, Bashkirtostan, Russia*

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**Abstract**—By the reaction of 2-[6-methyl-1-(thiethane-3-yl)uracil-3-yl]acetic acid hydrazide with aryl aldehydes and acetophenone derivatives, acylhydrazones have been obtained, which exist in DMSO solutions as a mixture of two stereoisomers of an $E_{C=N}$-isomer, due to the hindered internal rotation around the hydrazide bond. It has been found that the compounds synthesized exhibit a hypotensive activity.

*Keywords: uracil, thiethane, acylhydrazones, E,Z-isomers, hypotensive activity*

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## INTRODUCTION

The role of arterial hypertension as one of the key risk factors in the development of stroke, myocardial infarction, cardiac insufficiency, myocardial ischemia, and cardiac death has been well studied and is beyond question [1, 2]. According to the data of epidemiological studies, AH accounts for 30 to 50% of the global burden of disease in the world; this indicator among the population of the Russian Federation is 38% [3]. AH in our country has been and remains one of the most important medical and social problems since it is the main factor determining the high mortality in Russia. According to the data of the Ministry of Health, it was the cause of 18.3% of lethal outcomes in 2012 [4, 5].

Despite the fact that to date there is a wide selection of hypotensive drugs, the number of persons with high AP who are nonsusceptible to pharmacotherapy steadily increases [6]. About 60% of patients with AH in Russia take hypotensive drugs; however, positive results are observed only in 21.5% [7, 8]. Many hypotensive drugs used in medicinal practice are characterized by a slow development of the clinically significant decrease in AP and have limitations owing to side effects or the impairment of quality of life, which largely restricts their use. A search for, and the development of, novel highly effective and low-toxic hypotensive drugs of long-term action remain urgent problems in modern pharmacology and pharmaceutical chemistry.

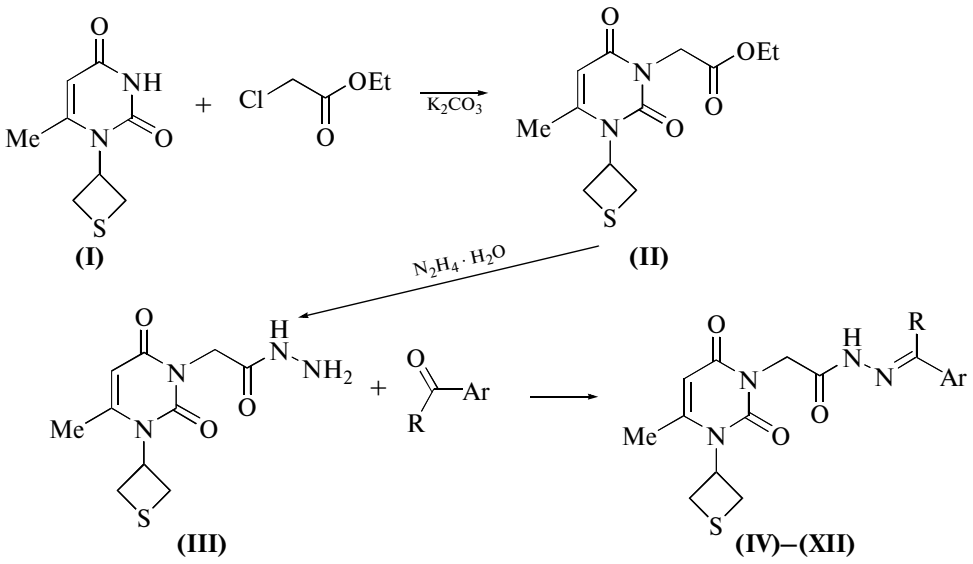
Abbreviations: AH, arterial hypertension; AP, arterial pressure; SAP, systolic arterial pressure; HR, heart rate.

[1] Corresponding author: phone: +7 (905) 395-54-51; fax: +7 (8442) 97-81-80; e-mail: vnperfilova@mail.ru.

Uracil is present, as a structural fragment, in molecules of many biologically active compounds having a wide spectrum of pharmacological activity; novel drugs are being successfully synthesized by its modifications. On the other hand, thiethanes and their derivatives found in the plants of *Berkheya angustifolia* and *Cullumia squarrossa* and in glands of some mammals of the Mustelid family, which exhibit anti-inflammatory, sedative, and insecticide activities, are promising objects for the synthesis of potentially biologically active compounds. The goal of the present study was the synthesis of thiethane-containing hydrazones of uracilylacetic acid and a search for compounds possessing a hypotensive activity in this series.

## RESULTS AND DISCUSSION

Thiethane-containing acylhydrazones (**IV**)–(**XII**) were synthesized from 6-methyl-1-(thiethane-3-yl)uracil (**I**) obtained by the thiirane–thiethane rearrangement in the reaction of equimolar amounts of 6-methyluracil and 2-chloromethylthiirane in water in the presence of potassium hydroxide [10]. The *N*-alkylation of compound (**I**) by the ethyl ether of monochloroacetic acid in the presence of potassium carbonate in acetone led to ether (**II**), which readily reacted with a fivefold molar excess of hydrazine hydrate in ethanol to form hydrazide (**III**) with a yield of 53%. Acylhydrazones (**IV**)–(**XII**) were synthesized by the reaction of hydrazide (**III**) with aryl aldehydes and aryl ketones without the use of acid catalyzers with yields of 48–89% (Scheme).




**(IV)** R = H, Ar = Ph; **(V)** R = H, Ar = Ph(4NMe$_2$); **(VI)** R = H, Ar = Ph(2OH); **(VII)** R = H, Ar = Ph(4OMe); **(VIII)** **R** = H, Ar = Ph(5Br, 2OH); **(IX)** R = Me, Ar = Ph; **(X)** R = Me, Ar = Ph(4Cl); **(XI)** R = Me, Ar = Ph(4Br); **(XII)** R = Me, Ar = Ph(4NH$_2$).

**Scheme.** Synthesis of thiethane-containing acylhydrazones.

The structures of the compounds synthesized were confirmed by spectral methods (IR, $^1$H, and $^{13}$C NMR spectroscopies) and the data of elemental analysis. Thus, $^1$H NMR spectra of compounds **(II)**–**(IV)**, **(VII)**, and **(X)**–**(XII)** indicate the retention of the thiethane cycle; they contain two characteristic pseudotriplets in the ranges of 3.07–3.14 and 4.12–4.21 and a multiplet in the range of 6.02–6.12 ppm, which belong to the protons of the thiethane group and NCH, respectively [10]. In the $^{13}$C NMR spectra of **(VIII)** and **(IX)**, signals of thiethane carbon atoms are also recorded [11]. Signals at 31.40–31.47 and 46.95–47.01 ppm belong to C2, C4, and C3 atoms of the thiethane cycle, respectively.

The $^1$H NMR spectrum of compound **(III)** contains a double set of resonance signals, indicating the *E,Z*-isomerism due to the hindered rotation around the C–N bond, which is typical of hydrazides. The chemical shifts of protons of $CH_2CO$ and $NH_2$ groups of the Z-conformer are in a stronger field, and the signals of the hydrazide proton of NH, the methyl group, and the proton in position 5 of the uracil fragment are in a weaker field compared with the signals of the *E*-isomer (Table 1). The sterically more stable *Z*-isomer prevails.

The spectra of compounds **(IV)**, **(VII)**, **(X)–(XII)** also contain two sets of resonance signals (Table 1). However, it is known that acylhydrazones can exist as four stereoisomeric forms, due to the geometric *E*, *Z*-isomerism relative to the C=N-bond and the conformational isomerism (*E*',*Z*') owing to the hindered rotation around the N-CO bond. According to the literature data, acylhydrazones of aryl aldehydes [12] and acetophenones [13, 14] occur only in the single form of the *E*-isomer relative to the multiple C=N bond. Consequently, the doubling of signals in the $^1$H NMR spectra is caused by the hindered rotation around the N–CO bond. The signals from protons of the $CH_2CO$ group of the *Z*'-conformer of acylhydrazones **(IV)**, **(VII)**, and **(X)**–**(XII)** are shifted to a higher field, and the signals of protons of the HC=N or $CH_3C$=N groups, to a lower field compared with the corresponding signals of *E*'-conformer [14, 15]. The signal from the proton of the NH group of the *Z*'-conformer of compounds **(X)**–**(XII)** is recorded in the high-field region [15], and that of compounds **(IV)** and **(VII)**, in the low-field region compared with the corresponding signal of *E*'-isomer [14], which probably depends on the structure of the hydrazone fragment.

The screening of compounds with hypotensive action among the thiethane-containing hydrazones of uracilylacetic acid revealed that compounds **(V)** and **(VI)** do not affect SAP; compounds **(VII)**, **(VIII)**, **(IX)**, **(X)**, and **(XII)** have a weakly pronounced hypotensive effect and reduce SAP from 4.1 to 5.8%. Compounds **(III)**, **(IV)**, and **(XI)** most significantly reduce SAP, to the maximal extent at 90 min of observation, by 13.9, 14.3, and 21.2%, respectively, compared with the initial parameters. In the control group of animals, no changes in SAP were observed (Table 2).