ISSN 1068-1620, Russian Journal of Bioorganic Chemistry, 2014, Vol. 40, No. 3, pp. 300–307. © Pleiades Publishing, Ltd., 2014.
Original Russian Text © S.A. Meshcheryakova, V.A. Kataev, K.V. Nikolaeva, V.N. Perfilova, D.D. Borodin, I.N. Tyurenkov, 2014, published in Bioorganicheskaya Khimiya, 2014, Vol. 40, No. 3, pp. 327–334.

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

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Received October 15, 2013; in final form, November 11, 2013

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

DOI: 10.1134/S1068162014030108

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.

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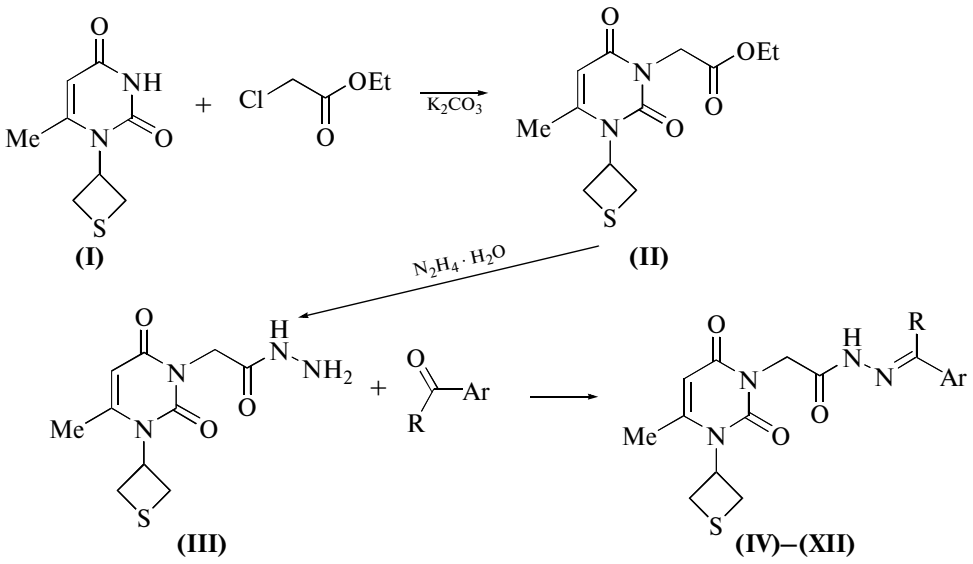
Uracil is present, as a structural fragment, in molecules of many biologically active compounds having a wide spectrum of pharmacological activity; novel drugs are being successfully synthesized by its modifications. On the other hand, thiethanes and their derivatives found in the plants of *Berkheya 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).

Table 1. Chemical shifts in ^{1}H NMR spectra of compounds **(II)**–**(IV)**, **(VII)**, and **(X)**–**(XII)**

Compound	Chemical shift, δ, ppm, *J*, Hz						*E*-isomer, %
	$6CH_3$, s	$CH_3C{=}N$, s	$CH_2C{=}H$, s	$CHC{=}N$, s	NH, br s	Other signals	
(II)	2.17	–	4.62	–	–	1.27 (3 H, t, CH_3, Et, *J* 7.1); 3.10–3.14 [2 H, m, $S(CH)_2$]; 4.12–4.16 [2 H, m, $S(CH)_2$]; 4.25 (2 H, q, OCH_2, Et, *J* 7.1); 5.69 (1 H, s, H5); 6.02–6.08 m (1 H, s, NCH)	–
(III)	2.08 (*E*) 2.14 (*Z*)	–	4.42 (*Z*) 4.79 (*E*)	–	8.77 (*E*), 9.36 (*Z*)	3.07–3.11 [2 H, m, $S(CH)_2$]; 4.15–4.19 [2 H, m, $S(CH)_2$]; 4.29 (*Z*), 4.54 (*E*) (2H, br s, CH_2); 5.64 (*E*), 5.66 (*Z*) (1 H, s, H5); 6.03–6.07 (1 H, m, NCH)	12
(IV)	2.15 (*E*) 2.18 (*Z*)	–	4.57 (*Z*) 5.01 (*E*)	8.03 (*E*) 8.20 (*Z*)	11.79 (*E*) 11.82 (*Z*)	3.08–3.11 [2 H, m, $S(CH)_2$]; 4.14–4.17 [2 H, m, $S(CH)_2$]; 5.68 (1 H, s, H5); 6.02–6.08 (1 H, m, NCH); 7.43–7.45 (3 H, m, arom); 7.69–7.72 (2 H, m, arom)	78
(VII)	2.16 (*E*) 2.19 (*Z*)	–	4.57 (*Z*) 5.01 (*E*)	7.99 (*E*) 8.16 (*Z*)	11.63 (*E*) 11.66 (*Z*)	3.09–3.14 [2 H, m, $S(CH)_2$]; 3.81 (3 H, s, OCH_3); 4.15–4.21 [2 H, m, $S(CH)_2$]; 5.69 (1 H, s, H5); 6.04–6.11 (1 H, m, NCH); 7.01 (2 H, d, arom, *J* 8.6); 7.67 (2 H, d, arom, *J* 8.6)	79
(X)	2.17	2.24 (*E*) 2.29 (*Z*)	4.68 (*Z*) 5.04 (*E*)	–	10.73 (*Z*) 10.98 (*E*)	3.08–3.11 [2 H, m, $S(CH)_2$]; 4.14–4.17 [2 H, m, $S(CH)_2$]; 5.67 (1 H, s, H5); 6.02–6.10 (1 H, m, NCH); 7.42 (2 H, d, arom, *J* 8.5); 7.63 (2 H, d, arom, *J* 8.5)	76
(XI)	2.14 (*E*) 2.16 (*Z*)	2.25 (*E*) 2.29 (*Z*)	4.69 (*Z*) 5.04 (*E*)	–	10.84 (*Z*) 11.09 (*E*)	3.08–3.11 [2 H, m, $S(CH)_2$]; 4.14–4.17 [2 H, m, $S(CH)_2$]; 5.68 (1 H, s, H5); 6.02–6.10 (1 H, m, NCH); 7.61 (2 H, d, arom, *J* 8.6); 7.77 (2 H, d, arom, *J* 8.6)	78
(XII)	2.16	2.17 (*E*) 2.20 (*Z*)	4.69 (*Z*) 5.04 (*E*)	–	10.54 (*Z*) 10.73 (*E*)	3.09–3.14 [2 H, m, $S(CH)_2$]; 4.16–4.21 [2 H, m, SCH_2]; 5.46 (2 H, s, NH_2); 5.68 (1 H, s, H5); 6.04–6.12 (1 H, m, NCH); 6.57 (2 H, d, arom, *J* 8.5); 7.54 (2 H, d, arom, *J* 8.5)	85

Then we studied the hypotensive action of the most active compounds, which were administered orally at a dose that exceeded twice the effective dose used upon intravenous injection. It was found that compound **(III)** (20 mg/kg) lowered SAP by a maximum of 6.9% after 8 h; 24 h later SAP returned to the initial level. Compound **(IV)** (24 mg/kg) on peroral administration lowered SAP after 5 h of observation by 8.7% relative to the initial level; however, after 24 h, the readings returned to the initial values. Compound **(XI)** (30 mg/kg) exhibited the most pronounced long-term hypotensive activity: SAP slowly decreased by the action of the compound and was after 8 h by 12.9% lower than the initial values (Table 3). In a group of animals to which the reference preparation normodipine was administered at a dose of 1 mg/kg, SAP decreased by a maximum of 12.6% after 8 h of observation to return almost to the initial value 24 h after the administration. In animals receiving lisinopril at a dose of 10 mg/kg and nebilet at a dose of 2 mg/kg, SAP decreased relative to the initial level by 17.9 and 19.2% after 8 h and by 6.4 and 7.3% 24 h after the administration, respectively (Table 3).

A study of the dose–effect dependence upon the oral administration of the most active compound ylidene hydrazide showed that compound **(XI)** at a dose of 15 mg/kg has a mild hypotensive action with a maximum effect by 6 h after the administration. SAP decreased by 10.8% and after 24 h remained by 7.1% lower than the initial values. Increasing the dose of **(XI)** to 60 mg/kg did not increase the hypotensive action, and SAP reduced by 8 h of the experiment by 8.3% relative to the initial value; after 24 h of observation, the decrease was 6.3% (Table 4). In this case, compound **(XI)** has almost no effect on HR.

Thus, compound **(XI)** injected intravenously at a dose of 15 mg/kg lowers AP by 21.2% compared with the initial level. When administered orally, this compound is most effective at a dose of 30 mg/kg; in the magnitude of the effect, it is as good as amlodipine and is comparable with lisinopril and nebivolol, which

Table 2. Changes in SAP in rats* after intravenous injection of thiethane-containing uracilylacetic acid hydrazones

Compound, dose, mg/kg	Time, min			
	Initial value	30	60	90
Control, –	122.1 ± 6.8 –	124.3 ± 5.5 **1.8**	122.3 ± 2.5 **0.2**	122.9 ± 2.6 **0.6**
(II), 11.4	127.0 ± 3.5	123.0 ± 3.2 **–3.1**	126.7 ± 5.9 **–0.3**	125.0 ± 6.4 **–1.6**
(III), 10	128.4 ± 3.2 –	117.7 ± 10.8 **–8.4**	112.0 ± 4.9# **–12.8**	110.6 ± 1.1# **–13.9**
(**IV**), 12	134.0 ± 9.8 –	129.9 ± 10.1# **–3.0**	124.0 ± 9.9# **–7.5**	114.8 ± 9.5# **–14.3**
(V), 13.4	124.6 ± 10.1 –	124.9 ± 22.7 **0.3**	125.4 ± 22.7 **0.7**	124.2 ± 24.0 **–0.3**
(VI), 12.4	124.6 ± 5.6 –	126.8 ± 8.3 **2.9**	128.1 ± 11.3 **1.6**	126.6 ± 10.8 **1.8**
(VII), 13	125.8 ± 6.6 –	121.8 ± 14.8 **–3.2**	120.2 ± 14.9 **–4.4**	119.0 ± 12.3 **–5.4**
(VIII), 15	138.6 ± 19.0 –	134.9 ± 13.5 **–2.6**	136.1 ± 15.5 **–1.8**	132.9 ± 18.3 **–4.1**
(**IX**), 12	124.7 ± 5.2 –	115.7 ± 16.7 **–7.2**	115.6 ± 27.6 **–7.3**	118.9 ± 25.2 **–4.6**
(**X**), 12.5	134.7 ± 7.0 –	135.7 ± 7.5 **0.7**	128.8 ± 14.5 **–4.3**	129.0 ± 8.7 **–4.2**
(XI), 15	125.7 ± 5.5 –	116.5 ± 10.6# **–7.3**	108.1 ± 10.1# **–14.0**	99.0 ± 12.5# **–21.2**
(XII), 13	122.7 ± 11.4 –	120.6 ± 9.1 **–1.7**	120.4 ± 12.5 **–1.8**	115.6 ± 13.7 **–5.8**

* The upper line shows SAP ($M \pm S$, where M is the average value, and S is the standard deviation) and the lower line shows changes in SAP in percent of the initial value.

The data are confident relative to the control group ($p < 0.05$).

enables one to consider a further study of its effect on the cardiovascular system promising.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker AMX-300 spectrometer (Germany) with a working frequency of 300 MHz and a Bruker Avence III-500 device (Germany) with a working frequency of 500.13 MHz. ^{13}C NMR spectra were recorded on a Bruker AMX-300 spectrometer (Germany) with a working frequency of 75 MHz with complete proton decoupling and modulation of the C-H coupling constant. Residual signals of the solvent DMSO-d_6 were used as an internal standard. IR spectra were measured on an Infralum FT-02 device (Russia) in KBr disks, and the melting temperature was determined in a capillary on a PTP(M) device. TLC was carried out on Silufix plates using ethanol as a mobile phase; the detection was with UV light and iodine vapors.

6-Methyluracil (OOO Polisintez, Russia) and 6-methyl-1-(thiethane-3-yl)uracil (29 ± 3%) [10] were used.

The data of ^{1}H NMR spectra of compounds (**II**)–(**IV**), (**VII**), and (**X**)–(**XII**) are given in Table 1.

Ethyl ether of 2-[6-methyl-1-(thiethane-3-yl)uracil-3-yl]acetic acid (II). A suspension of compound (**I**) (4.0 g, 20 mmol) and calcined ground potassium carbonate (4.14 g, 30 mmol) in acetone (125 mL) were boiled on a flask heater for 30 min, and the ethyl ether of monochloroacetic acid (2.45 g,

Table 3. Comparison of the effects of thiethane-containing hydrazones of uracilylacetic acid and reference preparations on SAP administered orally to rats

Compound, dose, mg/kg	Time after the onset of the experiment, h								
	initial value	1	2	3	4	5	6	8	24
Control, –	127.7 ± 3.6	128.6 ± 2.1	127.0 ± 3.2	130.2 ± 3.7	128.4 ± 2.3	129.2 ± 1.4	127.9 ± 2.0	128.6 ± 1.9	128.8 ± 1.6
	–	0.7	–0.5	2.0	0.6	1.2	0.2	0.7	0.9
(III), 20	127.3 ± 1.2	130.0 ± 1.7	127.3 ± 3.2	127.3 ± 4.1	122.0 ± 3.2	126.1 ± 6.0	125.0 ± 9.8	118.5 ± 6.4	125.7 ± 2.8
	–	2.1	0.0	0.0	–4.2	–1.0	–1.8	–6.9	–1.3
(IV), 24	127.2 ± 0.2	130.3 ± 4.2	123.8 ± 3.1	126.2 ± 11.5	126.8 ± 8.2	116.2 ± 12.0	121.3 ± 13.2	131.0 ± 3.1	129.3 ± 2.4
	–	2.5	–2.6	–0.8	–0.3	–8.7	–4.6	3.0	1.7
(XI), 30	128.0 ± 3.8	125.5 ± 2.1$^{\#\&}$	119.8 ± 0.2$^{\#\&}$	116.3 ± 3.8$^{\#}$	112.0 ± 3.8$^{\#}$	109.2 ± 1.2$^{\#\&}$	106.3 ± 9.0$^{\#}$	111.5 ± 2.1	119.3 ± 16.0
	–	–2.0	–6.4	–9.1	–12.5	–14.7	–16.9	–12.9	–6.8
(Normodipin), 1	125.0 ± 1.2	125.7 ± 1.5	124.8 ± 3.0	118.9 ± 2.2	115.1 ± 4.7	112.1 ± 5.7	111.4 ± 5.1	109.2 ± 5.9	120.8 ± 2.7
	–	0.5	–0.2	–4.9	–7.9	–10.3	–10.8	–12.6	–3.4
(Diroton), 10	129.2 ± 0.7	124.0 ± 6.0	118.9 ± 1.8	115.4 ± 2.2	113.3 ± 0.9	107.4 ± 3.9	106.2 ± 2.8	106.1 ± 3.1	120.9 ± 0.7
	–	–4.0	–8.0	–10.7	–12.3	–16.9	–17.8	–17.9	–6.4
(Nebivolol), 2	128.2 ± 2.4	119.1 ± 4.8	118.0 ± 2.6	115.3 ± 3.5	112.7 ± 1.2	106.7 ± 3.1	105.0 ± 2.5	103.7 ± 2.7	118.9 ± 8.1
	–	–7.1	–8.0	–10.1	–12.1	–16.8	–18.1	–19.2	–7.3

* The upper line shows SAP ($M \pm S$, where M is the average value, and S is the standard deviation), and the lower line shows changes in SAP in percent of the initial value.
$^{\#}$ The data are confident relative to the group of animals receiving the reference preparation normodipin ($p < 0.05$).

Table 4. Dose dependence of the effect of compound (**XI**) on SAP upon peroral administration to rats

Dose, mg/kg	Time after the onset of the experiment, h								
	initial value	1 h	2 h	3 h	4 h	5 h	6 h	8 h	24 h
Control, –	123.4 ± 1.4	123.6 ± 2.2 0.1	123.9 ± 1.5 0.4	123.6 ± 1.5 0.1	123.3 ± 2.3 –0.1	123.7 ± 1.8 0.2	123.9 ± 1.0 0.4	125.0 ± 0.6 1.3	124.9 ± 1.3 1.2
15	125.4 ± 1.3	122.4 ± 1.8 –2.4	119.0 ± 4.5 –5.1	114.4 ± 7.5 –8.8	114.0 ± 2.8 –9.1	114.3 ± 3.6 –8.9	111.9 ± 6.7 –10.8	112.9 ± 4.2 –10.0	116.6 ± 6.9 –7.1
30	128.0 ± 3.8	125.5 ± 2.1[#] –2.0	119.8 ± 0.2[#] –6.4	116.3 ± 3.8[#] –9.1	112.0 ± 3.8[#] –12.5	109.2 ± 1.2[#] –14.7	106.3 ± 9.0[#] –16.9	111.5 ± 2.1 –12.9	119.3 ± 16.0 –6.8
60	130.3 ± 1.5	127.9 ± 2.2 –1.9	125.4 ± 2.3 –3.8	122.2 ± 1.9 –6.2	121.3 ± 1.7 –6.9	119.6 ± 3.2 –8.3	120.2 ± 3.0 –7.8	119.6 ± 2.3 –8.3	122.1 ± 5.8 –6.3

* The upper line shows SAP ($M \pm S$, where M is the average value, and S is the standard deviation) and the lower line shows changes in SAP in percent of the initial value.

[#] The data are confident relative to the control group ($p < 0.05$).

20 mmol) was added. After 2 h, more monochloroacetic acid ethyl ether (1.23 g, 10 mmol) was added, and the boiling was continued for 5 h. The reaction mass was cooled, and the sediment was filtered. The solvent was removed in a vacuum, and the residue was recrystallized from hexane. Yield 4.24 g (74%); R_f 0.54; mp 40–42°C; IR (ν, cm^{-1}): 1750 (C=O), 1703 (C2=O), 1656 (C4=O), 1626 (C=C), 1418, 1389 (C–N), 1208 (C–O–C). Found, %: C 50.81, H 5.59, N 9.97. $C_{12}H_{16}N_2O_4S$. Calculated, %: C 50.69, H 5.67, N 9.85.

2-[6-Methyl-1-(thiethane-3-yl)uracil-3-yl]acetic acid hydrazide (III). A 85% solution of hydrazine hydrate (2.94 g, 50 mmol) was added to a solution of compound (**II**) (2.84 g, 10 mmol) in EtOH (50 mL) and boiled for 3 h. The reaction mixture was cooled at 0°C for 12 h, and the sediment was filtered, washed with water, and dried. Yield 1.43 g (53%); R_f 0.35; mp 199–201°C (EtOH); IR (ν, cm^{-1}): 3211, 3322 (NH), 1692 (C2=O), 1654 (C4=O, C=O), 1609 (C=C), 1464, 1439, 1385 (C–N). Found, %: C 44.44, H 5.19, N 20.74. $C_{10}H_{14}N_4O_3S$. Calculated, %: C 44.71, H 5.11, N 20.89.

A general method for obtaining acylhydrazones (IV)–(XII) Aryl aldehyde or acetophenone (2.4 mmol) was added to a solution of hydrazide (**III**) (0.54 g, 2 mmol) in EtOH (15 mL). The mixture was boiled and cooled. The sediment was filtered, washed with EtOH, and dried.

2-[6-Methyl-1-(thiethane-3-yl)uracil-3-yl]acetic acid phenylmethylidene hydrazide (IV). A reaction mixture was boiled for 3 h. Yield 89%; R_f 0.67; mp 233–235°C (PrOH); IR (ν, cm^{-1}): 3198, 3067 (NH), 1712 (C2=O), 1664, 1657 (C4=O, C=O, C=N), 1615 (C=C), 1438, 1409, 1299 (C-N). Found, %: C 57.11, H 4.99, N 15.81. $C_{17}H_{18}N_4O_3S$. Calculated, %: C 56.97, H 5.06, N 15.63.

2-[6-Methyl-1-(thiethane-3-yl)uracil-3-yl]acetic acid (4-dimethylaminophenyl)methylidene hydrazide (V). A reaction mixture was boiled for 2 h. Yield 53%; R_f 0.46; mp 241–243°C (*i*-PrOH); IR (ν, cm^{-1}): 3172, 3053, 2946 (NH), 1734 (C2=O), 1678, 1646 (C4=O, C=O, C=N), 1611 (C=C), 1527, 1411 (C–N). Found, %: C 57.02, H 5.64, N 17.29. $C_{19}H_{23}N_5O_3S$. Calculated, %: C 56.84, H 5.77, N 17.44.

2-[6-Methyl-1-(thiethane 3-yl)uracil-3-yl]acetic acid (2-hydroxyphenyl)methylidene hydrazide (VI). A reaction mixture was boiled for 2 h. Yield 53%; R_f 0.66; mp 262–264°C (*i*-PrOH); IR (ν, cm^{-1}): 3221, 3057 (OH, NH), 1712 (C2=O), 1664, 1657 (C4=O, C=O, C=N), 1615 (C=C), 1438, 1409, 1299 (C–N). Found, %: C 54.58, H 5.01, N 14.73. $C_{17}H_{19}N_4O_4S$. Calculated, %: C 54.39, H 5.10, N 14.92.

2-[6-Methyl-1-(thiethane-3-yl)uracil-3-yl]acetic acid (4-methoxyphenyl)methylidene hydrazide (VII). A reaction mixture was boiled for 3 h. Yield 88%; R_f 0.82; mp 214–215°C (PrOH); IR (ν, cm^{-1}): 3181, 3084 (NH), 1716 (C2=O), 1663, 1654 (C4=O, C=O, C=N), 1607 (C=C), 1419, 1411, 1388 (C–N), 1274, 1261 (C–O). Found, %: C 55.74, H 5.03, N 14.27. $C_{18}H_{20}N_4O_4S$. Calculated, %: C 55.66, H 5.19, N 14.42.

2-[6-Methyl-1-(thiethane-3-yl)uracil-3-yl]acetic acid (5-bromo-2-hydroxyphenyl)methylidene hydrazide (VIII). A reaction mixture was boiled for 2 h. Yield 59%; R_f 0.65; mp 176–178°C (*i*-PrOH); IR (ν, cm^{-1}): 3224, 3068 (OH, NH), 1706 (C2=O), 1670, 1653 (C4=O, C=O, C=N), 1623 (C=C), 1477, 1418,

1383 (C–N), 1273 (C–O); ^{13}C NMR (δ, ppm): 19.10 (6 CH_3); 31.40 [$S(CH_2)_2$)]; 45.69 (3 CH_2); 46.95 (NCH); 100.11 (C5); 110.78 ($C5_{arom}$); 118.39 ($C3_{arom}$); 122.38 ($C1_{arom}$); 127.59 ($C6_{arom}$); 133.52 ($C4_{arom}$); 139.54 (N=CH); 151.58 ($C2_{arom}$); 153.95 (C6); 155.60 (C2); 161.17 (C4); 168.24 (3 CH_2–C=O). Found, %: C 45.16, H 3.86, N 12.47. $C_{17}H_{17}BrN_4O_4S$. Calculated, %: C 45.04, H 3.78, N 12.36.

2-[6-Methyl-1-(thiethane-3-yl)uracil-3-yl]acetic acid phenylethylidene hydrazide (IX). A reaction mixture was boiled for 6 h. Yield 72%; R_f 0.79; mp 192–194°C (*i*-PrOH); IR (ν, cm^{-1}: 3307): 3307 (NH), 1687 (C2=O), 1662, 1621 (C4=O, C=O, C=N, C=C), 1426, 1399, 1364 (C–N). Found, %: C 58.10, H 5.36, N 15.10. $C_{18}H_{20}N_4O_3S$. Calculated, %: C 58.05, H 5.41, N 15.04.

2-[6-Methyl-1-(thiethane-3-yl)uracil-3-yl]acetic acid (4-chlorophenyl)ethylidene hydrazide (X). A reaction mixture was boiled for 5 h. Yield 57%; R_f 0.68; mp 201–203°C (*i*-PrOH); IR (ν, cm^{-1}): 3125, 3083 (NH), 1718 (C2=O), 1662, 1647, 1607 (C4=O, C=O, C=N, C=C), 1480, 1413, 1349 (C–N). Found, %: C 53.07, H 4.68, N 13.91. $C_{18}H_{19}ClN_4O_3S$. Calculated, %: C 53.13, H 4.71, N 13.77.

2-[6-Methyl-1-(thiethane-3-yl)uracil-3-yl]acetic acid (4-bromophenyl)ethylidene hydrazide (XI). A reaction mixture was boiled for 4 h. Yield 82%; R_f 0.73; mp 251–253°C (BuOH); IR (ν, cm^{-1}): 3191, 3075 (NH), 1718 (C2=O), 1661, 1627 (C4=O, C=O, C=N, C=C), 1435, 1417, 1364 (C-N); ^{13}C NMR (δ, ppm): 13.55 (N=C–$\underline{C}H_3$); 19.15 (6 CH_3); 31.47 [$S(CH_2)_2$)]; 46.16 (3 CH_2); 47.01 (NCH); 100.24 (C5); 122.80 ($C4_{arom}$); 128.25 ($C3,5_{arom}$); 131.32 ($C2,6_{arom}$); 137.06 ($C1_{arom}$); 148.02 (N=$\underline{C}$-CH_3); 151.68 (C6); 153.95 (C2); 161.23 (C4); 169.32 (3 CH_2–$\underline{C}$=O). Found, %: C 47.99, H 4.18, N 12.29. $C_{18}H_{19}BrN_4O_3S$. Calculated, %: C 47.90, H 4.24, N 12.41.

2-[6-Methyl-1-(thiethane-3-yl)uracil-3-yl]acetic acid (4-aminophenyl)ethylidene hydrazide (XII). A reaction mixture was boiled for 3 h. Yield 48%; R_f 0.59; mp 198–200°C with decomposition (EtOH : H_2O, 1 : 1); IR (ν, cm^{-1}): 3314, 3174 (NH), 1699 (C2=O), 1662, 1643, 1621 (C4=O, C=O, C=N, C=C), 1518, 1438, 1394 (C–N). Found, %: C 55.87, H 5.49, N 17.99. $C_{18}H_{21}N_5O_3S$. Calculated, %: C 55.80, H 5.46, N 18.07.

Hypotensive activity of compounds (III)—(XII). Experiments were performed on 3.5–4-month-old white nonlinear pubertal female rats weighing 280–320 g, obtained from the Rappolovo Nursery of Laboratory Animals (Russian Academy of Medical Sciences). Rats were maintained in a vivarium under standard conditions and received a diet balanced according to GOST 50258-92.

The study was performed according to the standardized documents: the Order of the Ministry of Health and SR of the Russian Federation of 23.08.2010 no. 708n "Approval of laboratory practice regulations," GOST R-53434-2009 "Principles of proper laboratory practice," and the regulations of the European convention on the protection of vertebrate animals used for experimental and other research purposes (1986).

For measuring SAP and HR, an animal was placed in a box, and a blood pressure cuff with an in-built photosensitive probe was put on the tail. The air was delivered to the cuff under pressure (by 10—15 mmHg higher than the supposed AP) and then slowly let out. The SAP and HR values were automatically fixed on a personal computer connected to a IITC 29 device for the invasive blood pressure measurement (IITC Life Science Inc., United States). The values recorded prior to the administration of compounds under study were taken to be the initial level. The statistical processing of the data was performed by the program Microsoft Excel 2007 using the paired Student's test.

The screening of substances with the hypotensive activity in the series of thiethane-containing hydrazones of uracilylacetic acid was carried out on 72 animals. Twelve groups (six animals in each) were formed: 1, control group of intact animals, which received a 50% aqueous DMSO solution intravenously (iv) in a volume of 0.3 mL per 100 g weight; and 2–12, experimental groups of animals to which the compounds under study were injected iv at a dose that amounted to 1/30 of the molecular weight: (**II**) 11.4 mg/kg, (**III**) 10 mg/kg, (**IV**) 12 mg/kg, (**V**) 13.4 mg/kg, (**VI**) 12.4 mg/kg, (**VII**) 13 mg/kg, (**VIII**) 15 mg/kg, (**IX**) 12 mg/kg, (**X**) 12.5 mg/kg, (**XI**) 15 mg/kg, and (**XII**) 13 mg/kg. A 50% DMSO solution was used as a solvent. The SAP and HR values were recorded 30, 60, and 90 min after the injection of the compounds.

To study the dose–hypotensive effect dependence and the duration of action of compound (**XI**), a leader upon oral administration, in comparison with reference preparations, seven groups of animals were formed, six animals in each: group 1, a control group of intact animals to which a 2% starch mucus (0.2 mL per 100 g weight) was administered; groups 2–4, experimental groups of animals that received compound (**XI**) at a dose of 15, 30, and 60 mg/kg, respectively; groups 5–7, experimental groups of animals to which the reference preparations were administered: nebivolol (nebilet, Berlin-Chemie AG, Germany) at a dose of 2 mg/kg, lisinopril (diroton; Gedeon–Richter, Hungary) at a dose of 10 mg/kg, and normodipine (normodipine; Gedeon–Richter, Hungary) at a dose of 1 mg/kg, respectively. Prior to administration, substances at doses examined and reference preparations were suspended in a 2% starch mucus. The parameters were recorded at 1-h intervals over a period of 8 h and 24 h after the administration of substances using a IITC 29 device for the noninvasive arterial pressure measurement (IITC Life Science Inc., United States).

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Translated by S. Sidorova