UDC 547.745:547.857.1

ACETALS OF LACTAMS AND AMIDES OF ACIDS. COMMUNICATION 78.[1] SYNTHESIS AND BIOLOGICAL ACTIVITY OF 7,8-POLYMETHYLENEPURINE DERIVATIVES

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Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 29, No. 2, pp. 27 – 31, February, 1995.

Original article submitted March 1, 1994.

The condensation of diethylacetal of dimethylformamide with 4-amino-5-ethoxycarbonyl-1,2-polymethyleneimidazoles yielded derivatives of 7,8-polymethylenehypoxanthines that are precursors of 6-amino- and 6-alkylmercapto-7,8-polymethylenepurines and 1-substituted-7,8-polymethylenehypoxanthines. On the basis of the latter, 1,2-trimethylene-4,5,7,8-tetrahydro-6H-imidazo[4.5-e][1.4]diazepine-5,8-dione was obtained. The example of 6-substituted purines was used to study the antiviral activity, and 1-substituted purines were used to study the antihypertensive activity.

This work is a continuation of the investigation of the synthesis of 7,8-methylenepurine derivatives and is aimed at seeking biologically active compounds in this series. Previously, a method for the synthesis of 1,2-polymethylene-4-amino-5-ethoxycarbonylimidazoles (Ia, b) was developed based on Thorpe – Ziegler cyclization [2]. Closure of the pyrimidine ring of the bicycle of the purine series was carried out by the action of ammonia on the molecules of the amidine intermediates (IIa, b), synthesized by the reaction of Ia, b with DMF diacetal [2]. 7,8-Polymethylenehypoxanthines obtained in such a way were, in turn, precursors of 6-chloro- (IVa, b) and 6-mercapto-7,8-polymethylenepurines (Va, b), exhibiting moderate antiviral and antitumor activities [2].

In this study we synthesized a large group of 6-substituted 7,8-polymethylenepurines for biological study using conventional techniques for introducing substituents into the pyrimidine ring. Thus, we synthesized a group of new 6-amino-7,8-polymethylenepurines (IVb – e) by the reaction of previously reported 6-chloro derivatives (IVa, b) [2] with various amines (autoclave, 150°C, 10 h) and a number of 6-alkylthiosubstituted products VIIa-d were obtained by the S-alkylation of 6-mercapto-7,8-polymethylenepurines Va, b.

Polymethylenepurines substituted in position 1 can be obtained by two pathways; the cyclization of amidines IIa, b by heating with various amines (compounds VIIIa – d were obtained by this method), or the alkylation of the 1-unsubstituted hypoxanthine derivative IIIa (VIIIa, e – h). It is known that the alkylation of an oxo heterocycle can occur both at the nitrogen and oxygen atoms, and the ratio of the reaction products is determined in many respects by the chosen conditions (solvent, temperature, type of alkylating agent, etc). As an example, for studying the alkylation of IIIa we chose the reaction of its methylation by methyl iodide in the presence of K_2CO_3 in dry DMF. The studied conversion proved to proceed sufficiently selectively, and finally led to 1-methyl-7,8-trimethylenehypoxanthine VIIIa, whose synthesis by the reaction of amidine IIa and methylamine is described above.

Using TLC, we ascertained that the reaction mixture also contained a small amount of O-alkylated product, 6-methoxy-7,8-trimethylenepurine VIa, obtained by an alternate synthesis via reaction of the chloro derivative IVa described above [2] with sodium methoxide. Similarly, we synthesized 1N-substituted trimethylenehypoxanthines VIIIe – h using other functionally substituted haloalkyl derivatives (α-bromoethylacetate, α-bromo-*p*-nitroacetophenone, benzyl chloride). In this case, N-alkylation is confirmed by the fact that the UV spectra of the derivatives VIIIe – h obtained are very similar and have two maxima at 215 – 218 and 258 nm, while the UV-spectrum of the 6-methoxy derivative VIa has one

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maximum at 262 nm. These data are also supported by the results of mass-spectroscopy. The mass-spectra of all the 1-alkylated derivatives VIIIa-h have typical peaks 189 or 190 formed in the elimination of the functional substituent and related to the 1-methylenehypoxanthine fragment.

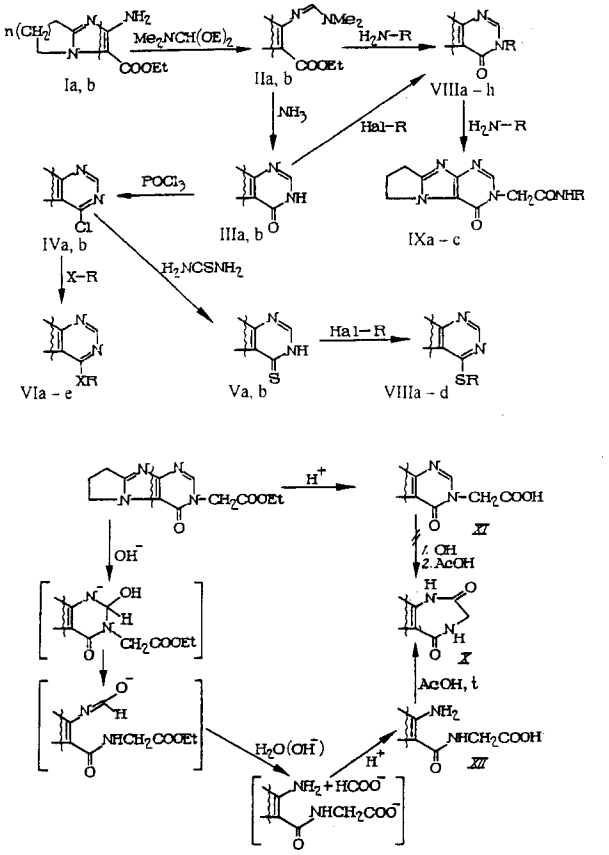
The presence of a functional group in position 1 of the purine cycle makes it possible to obtain other N-substituted polymethylenepurines; thus, amidation of the 1-ethoxycarbonylmethyl derivative VIIIe results in the synthesis of a number of carbamoylmethyl derivatives (IXa – c).

Compound VIIIe is also a starting material for carrying out other lines of research that we started in this work. It is well known that base hydrolysis of 1-ethoxycarbonylmethyl-7-alkylhypoxanthines, followed by heating the intermediates formed in acetic acid, leads to imidazo[4,5-e]diazepine derivatives [3]. Studying a similar reaction using compound VIIIe showed that in this case, the reaction also proceeded easily to form the tricyclic derivative of imidazadiazepinedione (X) in a high yield. The structure of X follows from the elemental analysis data, mass- and ^{1}H NMR spectra. The proton signals from the pyrrole methylene CH_2 groups at 2.87 and 4.22 (t), 2.57 (quintet) ppm and diazepine CH_2 groups at 3.88 (d), NH at 7.80 and 10.80 (br. s) ppm are observed in the NMR spectra (DMF-d_7). The results presented unambiguously confirm the formation of a diazepinedione ring in the course of the studied reaction.

Closer examination of this recyclization allowed us to draw some conclusions concerning the stepwise character of the process of cleavage of the pyrimidine ring and formation of the diazepine ring. First, we carried out acid hydrolysis of the starting ethoxycarbonylmethyl derivative VIIIe to isolate 7,8-trimethylene-1-carboxylmethylhypoxanthine (XI); i.e., we managed to prevent the pyrimidine ring from undergoing cleavage in an acidic medium. The acid obtained is not an intermediate in the purinimidazodiazepine recyclization because it is stable in alkaline medium and does not undergo conversion to a diazepine derivative in an aqueous alcohol solution of alkali. In other words, the presence of an anionic center in the carboxyl group makes the pyrimidine ring stable with respect to the hydroxyl anion under the studied conditions.

We obtained the intermediate of the recyclization under consideration, 1,2-trimethylene-4-amino-5-(N-carboxymethyl)carbamidoimidazole (XII), by boiling VIIIe in an aqueous alcohol solution of alkali. Heating XII in AcOH results in the tricycle X; this fact supports the assumption that XII is an intermediate in the process of diazepinedione formation.

Thus, the opening of the pyrimidine ring is likely to be the first step in the studied pyridine-diazepine transformation. Earlier it was shown that in the case of 4-pyrimidinediones of the para-quinoid structure, such a cleavage was accompanied by a nucleophilic attack at position 2 in the pyrimidine ring followed by liberation of formic acid [4]. In this study, we used the method reported in [5] based on catalytic dehydration of formic acid (formed in the recyclization process) when treated with acetic anhydride in the presence of sulfuric acid. The quantity of carbon monoxide released suggests that cleavage of the pyrimidine ring goes to 85% completion under these conditions (see the experimental part). Therefore, the scheme for the formation of imidazodiazepinedione can be presented as follows:



n = 1 (Ia – Va), n = 3 (Ib – Vb);

n = 1: R = H (IXa), Me (VIIIa), Et (VIIIb), CH_2CH_2OH (VIIIc), $CH_2CH_2CH_2OH$ (VIIId), CH_2COOMe (VIIb), CH_2COOEt (VIIIe), CH_2Ph (VIIIf, IXb, VIIa), $CH_2CHOHCH_2OH$ (IXc), $CH_2COC_6H_4NO_2$-*p*(VIIIg), 1-methyl-4-nitro-5-imidazolyl (VIId); X = O, R = Me (VIa); X = NH, R = CH_2Ph (VIe), XR = morpholino (VIb);

n = 3: R = CH_2Pt (VIIIh), CH_2COOMe (VIIc); X = NH, R = CH_2Pt (VIc); XR = morpholino (VId)

CHEMICAL EXPERIMENTAL PART

The mass-spectra of the compounds synthesized were recorded on a Varian MAT 112 (50 eV) spectrometer, and the temperature of the ionization chamber was 140°C. The ^{1}H NMR spectra were obtained on a Varian XL-200 instrument with TMS as the internal standard. Melting points were determined on a Boetius heating stage.

Determination of the formate ion was based on the catalytic dehydration of acetic anhydride in the presence of a

catalyst, a strong acid (H_2SO_4), in accordance with the following reaction:

$$HCOOH + (CH_3CO)_2O \xrightarrow{H^+} 2CH_3COOH + CO.$$

The carrier gas (CO_2) removed the carbon monoxide-formed into a gasometer filled with 40% KOH. The amount of formate ion in a sample was calculated from the CO volume.

Elemental analysis data are consistent with the calculated values for the structures assigned. Physical and chemical properties of the compounds synthesized are given in Table 1.

6-Methyloxy-7,8-trimethylpurine (VIa). A solution of chloropurine IVa (1.94 g, 10 mmole) and MeONa (obtained from 0.69 g of metallic Na and 30 ml of MeOH) was refluxed for 20 min and evaporated; the residue was dissolved in water (10 ml), extracted with $CHCl_3$ (100 ml), dried over $CaCl_2$, evaporated, and ground with hexane.

6-Morpholino-7,8-trimethylenepurine (VIb). Morpholine (2.175 g, 25 mmole) was added to a solution of chloropurine IVa (1.95 g, 10 mmole) in acetonitrile (30 ml), kept in an autoclave for 10 h at 150°C; then the reaction mixture was evaporated, the residue was ground with *i*-PrOH, filtered off, and washed with *i*-PrOH and heptane.

6-Benzylamino-7,8-pentamethylenepurine (VIa). VIa was obtained from chloropurine IVb and benzylamine by a procedure similar to that used for obtaining VIb.

TABLE 1. Physical and Chemical Properties of the Compounds Synthesized

Compound	Yield, %	M. p., °C (solvent)	Empirical formula
IVa	68	191 – 193 (toluene)	$C_9H_{10}N_4O$
IVb	72	178 – 199 (2-propanol)	$C_{12}H_{15}N_5$
IVc	55	128 – 129 (methanol)	$C_{17}H_{19}N_5$
IVd	76	195 – 197 (2-propanol)	$C_{14}H_{13}N_5O$
VIIa	68	148 – 149 (2-propanol)	$C_{15}H_{14}N_4S$
VIIb	52	109 – 111 (2-propanol)	$C_{11}H_{12}N_4SO_2$
VIIc	63	155 – 156 (2-propanol)	$C_{13}H_{16}N_4SO_2$
VIId	45	247 – 249 (decomp, DMF)	$C_{12}H_{11}N_{74}SO_2$
VIIIa	68*	271 – 272 (2-propanol)	$C_{95}H_{10}N_4O$
VIIIb	50	216 – 217 (2-propanol)	$C_{10}H_{142N4}O$
VIIIc	45	231 – 233 (DMF)	$C_{10}H_{12}N_4O_2$
VIIId	43	171 – 173 (2-propanol)	$C_{11}H_{14}N_4O_2$
VIIIe	89	119 – 121 (2-propanol)	$C_{12}H_{14}N_4O_3$
VIIIf	53	177 – 180 (2-propanol)	$C_{15}H_{14}N_4O$
VIIIg	47	244 – 246 (DMF)	$C_{16}H_{13}N_5O_4$
VIIIh	55	135 – 137 (DMF)	$C_{17}H_{19}N_4O$
IXa	99	300 (water)	$C_{10}H_{11}N_4O_2$
IXb	50	270 – 273 (DMF)	$C_{17}H_{17}N_5O_2$
IXc	59	228 – 229 (methanol)	$C_{13}H_{17}N_5O_4$
Xa	83	> 300 (water)	$C_9H_{10}N_4O_2$
XI	80	200 – 202 (ethanol)	$C_{10}H_{10}N_4O_3$
XII	34	225 – 228 (decomp. water)	$C_9H_{12}N_4O_3 \cdot H_2O$

* Procedure A; procedure B – 73%.

6-Morpholino-7,8-pentamethylenepurine (VId). VId was obtained from chloropurine IVb and morpholine as in the process used for obtaining VIb.

6-Benzyl-7,8-trimethylenepurine (VIe). VIe was obtained from chloropurine VIa and benzylamine as for VIb.

6-Benzylmercapto-7,8-trimethylenepurine (VIIa). A solution of KOH (0.8 g in 10 ml of water) was added to a suspension of thiopurine Va (0.96 g, 5 mmole) in 10 ml of DMF and 5 ml H_2O and stirred until the Va was completely dissolved. Then benzyl chloride (0.8 g, 6.5 mmole) was added, and the mixture was stirred for 10 min; the precipitate formed was filtered off and washed with water.

6-Methoxycarbonylmethylmercapto-7,8-trimethylenepurine (VIIb). VIIb was obtained from thiopurine and methylbromoacetate by a procedure similar to that used for the synthesis of VIIa.

6-Methoxycarbonylmethylmercapto-7,8-pentamethylenepurine (VIIc). VIIc was obtained from thiopurine Vb and methylbromoacetate by a procedure comparable to that used for the synthesis of VIIa.

6-(1-Methyl-4-nitro-5-imidazolyl)mercapto-7,8-trimethylenepurine (VIId). VIId was obtained from thiopurine Va and 1-methyl-5-chloro-4-nitroimidazole in a procedure similar to that used for the synthesis of VIIa.

1-Methyl-7,8-trimethylenehypoxanthine (VIIIa). Procedure A. A mixture of amidine IIa (5 g, 20 mmole) and 50 ml of 25% methylamine ethanol solution was introduced into an autoclave and heated for 10 h at 130°C, then evaporated; the residue was ground with ethanol, and VIIIa was filtered off. Procedure B. A mixture of hypoxanthine IIIa (1.76 g, 10 mmole), potassium carbonate (1.66 g, 12 mmole), and 15 ml DMF was heated to 90°C with stirring, and methyl iodide (1.56 g, 11 mmole) was added. The mixture was kept at this temperature for 10 min and then evaporated; the residue was ground with butanol and filtered off.

1-Ethyl-7,8-trimethylenehypoxanthine (VIIIb). A mixture of amidine IIa (5 g, 20 mmole) and 50 ml of a 25% ethylamine aqueous solution was placed in an autoclave and heated for 10 h at 130°C, evaporated, and the residue was ground with ethanol and filtered off.

1-β-Hydroxyethyl-7,8-trimethylenehypoxanthine (VIIIc). A mixture of amidine IIa (1.25 g, 5 mmole), ethanolamine (0.366 g, 6 mmole), and *p*-toluenesulfonic acid (0.3 g) in 20 ml of toluene was boiled for 30 min; an oily precipitate was formed and solidified under cooling. The solid product was filtered off and washed with toluene and acetone.

1-γ-Hydroxypropyl-7,8-trimethylenehypoxanthine (VIIId). VIIId was obtained from amidine IIa and γ-propanolamine by a procedure similar to that used for the synthesis of VIIIc.

1-Ethoxycarbonylmethyl-7,8-trimethylenehypoxanthine (VIIIe). VIIIe was obtained from hypoxanthine IIIa and ethylchloroacetate similarly to the method used for synthesis of VIIIa (Procedure B).

1-Benzyl-7,8-pentamethylenepurine (VIIIf). VIIIf was obtained from amidine IIa and benzylamine similarly as for synthesis of VIIIc.

1-(*p*-Nitrobenzoyl)methyl-7,8-trimethylenehypoxanthine (Vg). Vg was obtained from hypoxanthine IIIa and α-bromo-*p*-nitroacetophenone by a procedure similar to that used for synthesis of VIIIa.

1-Benzyl-7,8-pentamethylenehypoxanthine (VIIIh). VIIIh was obtained from amidine IIc and benzylamine by a procedure similar to that used for synthesis of VIIIc.

1-Carbamoylmethyl-7,8-trimethylenepurine (IXa). Into a solution of hypoxanthine VIIIe (2.62 g, 10 mmole) in 40 ml of methanol, ammonia was passed for 1 h; the precipitate formed was filtered off and washed with methanol.

1-N-(Benzyl)carbamoylmethyl-7,8-trimethylenehypoxanthine (IXb). A mixture of hypoxanthine VIIIe (1.3 g, 5 mmole) and 1 ml of benzylamine was kept at 120°C for 10 min and cooled; the precipitate formed was filtered off and washed with isopropanol and heptane.

1-N-(2,3-dihydroxypropyl)carbamoylmethyl-7,8-trimethylenehypoxanthine (IXc). IXc was obtained from hypoxanthine VIIIe and 1-amino-2,3-dihydroxypropane by a procedure similar to that used for the synthesis of IXb.

1,2-Trimethylpropylene-4,5,7,8-tetrahydro-6H-imidazo[4,5-e][1,4]diazepine-5,8-dione (X). Synthesis was performed by the method in [3].

1-Carbamoylmethyl-7,8-trimethylenehypoxanthine (XI). A solution of hypoxanthine VIIIe (1.3 g, 5 mmole) in 5 ml of conc. HCl was heated until boiling, cooled down to 20°C, and allowed to stand overnight. The next day, the solution was boiled down; the residue was dissolved in 5 ml of a 3 : 1 ethanol – water mixture, boiled for 4 h, and cooled; the precipitate formed was filtered off and washed with ethanol.

1,2-Trimethylene-4-amino-5-(N-carboxymethyl)carbamidoimidazole (XII). A solution of hypoxanthine VIIIe (2.62 g, 10 mmole) in a mixture of 10 ml of ethanol, 3 ml of water, and 0.5 g of NaOH was boiled for 2 h, cooled, and HCl was added to pH 7; the precipitate formed was filtered off and washed with water and isopropanol.

Procedure for the determination of formate ion. An accurate weight of 7,8-trimethylene-1-ethoxycarbonylmethylhypoxanthine (0.18951 g) in 4 ml of 20% NaOH was refluxed for 2 h. A 0.4 ml portion of the cooled solution was introduced into a reaction vessel fitted with a bubbler, gas-outlet tube, and a dropping funnel. Then 10 ml of Ac_2O and 2 drops of indicator (2% acetic solution of crystalline violet) were added. Into the dropping funnel, 5 ml of conc. H_2SO_4 was placed. The vessel was connected with a nitrogen gasometer and a source of carbon dioxide; CO_2 was passed through the gasometer until the bubble size in the graduated part of the nitrogen gasometer filled with NaOH became extremely small. Then with no interruption of the CO_2, concentrated sulfuric acid was added dropwise to the vessel from the dropping funnel until the solution in the vessel changed from violet to yellow, at the beginning of the dehydration reaction. The formed CO_2 was collected in the graduated part of the nitrogen gasometer. The carrier gas was passed through until the bubble size became very small again. Calculations were performed taking into account the results of the control experiment.

For analysis, 0.4 ml of the solution containing 18.95 mg of the substance was taken. 1.57 ml of CO was liberated. In the control experiment, 0.03 ml of gas was liberated. The CO volume reduced to normal conditions (at $P = 721$ Torr, $T = 291$ K) is equal 1.37 ml; calculated on the basis of the substance, this is equal to 16.02 mg or 84.6%.

BIOLOGICAL EXPERIMENT PART

The antiviral activity of the compounds were studied against herpes simplex type 1 virus (strain L_2) (HSV), Venezuela horse encephalitis (strain 230) (VHEV), and influenza A/Bethesda (H_2N_2) (IV).

The inhibitory effect of the HSV and VHEV viruses were determined in primary cultures of chick embryo fibroplast (CEF) from suppression of the cytopathic effect of the virus on the cells and the decrease in its infections titer in comparison with the reference, expressed by the TCD_{50} index (the tissue culture infective dose that is cytopathic in 50% of the cultures). The anti-influenza activity of the compounds was investigated in a model of HSV-induced pneumonia in mice caused by the intranasal inoculation of the virus and evaluated from the decreasing lethality in animals in the experimental groups in comparison with the control (untreated) animals, expressed in percent.

We studied the antiviral activity of 15 samples of the new compounds, including 9 samples of 1-substituted 7,8-polymethylenehypoxanthines and 6 samples of 6-substituted 7,8-polymethylenepurines.

In preliminary experiments, it was ascertained that the compounds had no cytotoxic effect on the cells of the CEF culture in concentrations lower than 20 mg/ml. Using higher concentrations, we observed disruption of the cell monolayer because of the death of part of the cells. When the virus-inhibiting effect of the compounds was studied, slight activity was exhibited by a number of 1-substituted 7,8-trimethylenehypoxanthines (VIIIa, VIIIc, VI – IId, VIIIe, IXc) against the VHEV virus. The concentration of the compounds was 5 – 10 log TCD_{50} in comparison with the reference. These compounds had no effect on virus replication. 6-Substituted 7,8-polymethylenepurines were inactive against both viruses.

A theurapeutic effect from compounds VIIIc, VI – IIe (1-substituted 7,8-trimethylenexanthines), and VIIb was ascertained using the model of mouse influenza-induced pneumonia. Administration of 60 mg/kg of these compounds once a day for 5 days led to a 25 – 30% decrease in lethality in the animals in comparison with the untreated reference.

The investigations conducted showed the activity of 6 new 7,8-polymethylenepurines against RNA-genome viruses (VHEV, IV). Unlike the 6-oxo- and 6-mercapto-7,8-polymethylenepurine derivatives we studied earlier [1], activity against the DNA-genome virus HSV was not found in the compounds examined.

The compounds were studied with respect to the following indices: of acute toxicity with internal administration, influence on the arterial pressure (AP), and analgesic effect.

EXPERIMENTAL METHODS

The ability of hypoxanthine derivatives to influence the AP was studied in white normotensive male rats weighing 220 to 250 g using direct and indirect methods for recording the AP.

In the direct recording method, polyethylene catheters were placed in the left cephalic artery and jugular vein of the urethane-anesthetized normotensive animals (1 g/kg intraperitoneal injection). The AP was measured by a Trantek (USA) pressure gauge through an arterial catheter and recorded on a Ugo Basile Gemini 7070 (Italy) automatic recorder. The compounds were administered through an intravenous catheter as aqueous solutions within the dose range of 0.001 to 1.0 mg/kg.

In the indirect method, the AP was recorded in the caudal artery of animals in boxes at 29°C using a set of instruments produced by IITC company (USA). The compounds were administered in 25 and 50 mg/kg doses. The AP was recorded prior to administration (the starting level of the index was determined) and within 1, 2, 3, and 4 h of administration. In these experiments, spontaneously hypotensive (SH) rats were used [6].

The analgesic effect of 1-substituted hypoxanthine derivatives was examined in male mice weighing 18 – 20 g using thermal (Hot plate [7], Tail flick [8]) and chemical (spasms caused by an intraperitoneal injection of 1% acetic acid [9]) models of painful irritation. The compounds were administered as a screening dose (50 mg/kg) 1 h before the mice were subjected to the painful irritation.

Acute toxicity of the compounds was determined in male mice weighing 18 – 20 g with internal administration. The value of LD_{50} was calculated by the method reported in [10].

RESULTS

The investigations of acute toxicity of the hypoxanthine derivatives showed that LD_{50} for all presented compounds is higher than 1000 mg/kg with internal administration, and therefore, these substances are assigned to the low-toxicity category according to K. K. Sidorov's classification [11].

Experiments on the study of the compounds' effects on the threshold of pain sensitivity in mice showed that the hypoxanthine derivatives exhibited no analgesic action.

Studying the effect of the compounds on the AP in narcotized normotensive rats after intravenous administration showed that the derivatives VIIIe, IXa, and XI caused decreasing AP from the doses 0.01 mg/kg (VIIIe and IXa) and 0.1 mg/kg (X). The reduction in the AP was 20 – 25 Torr and observed within 15 – 20 min after injecting the specified doses; i.e., the hypotensive effect was short-term. A ten-fold increase in the dosage (0.1 and 1.0 mg/kg, respectively) resulted in a slight decrease in the hypotensive effect (as a rule, a 30-Torr decrease in the AP) and an increase in the duration of the effect to 40 – 45 min. It should be emphasized that in the case of administration of compound VIIIe at a 0.1 mg/kg dose, we observed increasing frequency and strength of heart contractions (that was manifested as an 2.5-fold increase in the amplitude of the recording in comparison with the initial recording).

The rest of the compounds of the group presented had no effect on the AP.

Similar results were obtained in studying the influence of the compounds on the AP in SH rats with indirect recording. The compounds IXa, VI, and IId lowered the AP within 1 h after administration of a dose (25 mg/kg); the effect was 25 – 28 Torr relative to the initial level and was observed for 1 h; the initial AP level returned in the third hour of the experiment. The derivative XI in a dose 25 mg/kg demonstrated a hypotensive effect (AP reduction was 20 Torr), but the initial AP value was restored 2 h after administration. We observed no enhancement of the hypotensive effect when compounds VIIIe and IXa were administered in a 50 mg/kg dose (the AP decrease was 30 Torr), but the duration of action increased to 3 h.

The other compounds of this series were inadequate.

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