SYNTHESIS AND DIURETIC ACTIVITY OF N-SUBSTITUTED CONDENSED DERIVATIVES OF 3-METHYLXANTHINE WITH ENDOCYCLIC SULFUR ATOM

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Our earlier experiments [1 – 3] showed that nitrogen-containing heteroannelated xanthines possess a wide spectrum of pharmacological activities. However, condensed derivatives of 3-methylxanthine with endocyclic sulfur atom remain virtually uncharacterized with respect to their pharmacological properties. In this connection, we have synthesized hydrated derivatives of thiazolo-, thiazino-, and thiazepino[3,2-f]purines (IIa – c) on the basis of 7-chloroalkyl-8-bromo-3-methylxanthines (Ia – c) [4], and studied some reactions and diuretic activity of the compounds obtained. The pathways of the chemical transformations are illustrated in the scheme below.

As is seen from this scheme, boiling dihalide derivatives Ia – c with sodium sulfide in DMFA led to the previously undescribed 8-methyl-5,7-dioxo-2,3,5,6,7,8-hexahydrothiazolo-(IIa), 9-methyl-6,8-dioxo-3,4,6,7,8,9-hexahydro-2H-1,3-thiazino-(IIb), and 10-methyl-7,9-dioxo-2,3,4,5,7,8,9,10-octahydro-1,3-thiazepino-(IIc) [3,2-f]purines. Alkylation of these intermediates in DMFA in the presence of anhydrous K_2CO_3 yielded the corresponding N-propyl-, allyl-, and butoxycarbonylmethyl derivatives (IIIa – e) with molecules substituted at the uracyl fragment. Interaction of compound IIa with 1-(4-nitrophenoxy)-2,3-epoxypropanone in DMFA in the presence of pyridine allowed us to obtain 8-methyl-6-[2-hydroxy-3-(4-nitrophenoxy)propyl]-5,7-dioxo-2,3,5,6,7,8-hexahydro [3,2-f]purine (IV). Acidic hydrolysis of butyl ester (IIId) led to the formation of (8-methyl-5,7-dioxo-2,3,5,6,7,8-hexahydrothiazolo[3,2-f]purin-6-yl)acetic acid (V). A short-time heating of acid V with amines in dioxane in the presence of a small amount of water led to the synthesis of the corresponding water-soluble salts (VIa – e). Interaction of ester IIId with hydrazine hydrate in DMFA at room temperature resulted in the formation of the hydrazide of (8-methyl-5,7-dioxo-2,3,5,6,7,8-hexahydrothiazolo[3,2-f]purin-6-yl)acetic acid (VII).

The IR spectra of condensed xanthines IIa – c contain characteristic absorption bands at 3100 – 3125 cm^{-1}, belonging to the stretching vibrations of the associated NH group. The absorption of amide carbonyl groups is manifested by two intense bands at 1675 – 1685 and 1660 – 1670 cm^{-1}. The ^1H NMR spectra of xanthines IIa – c exhibit intense singlets at 3.47, 3.17, and 3.76 ppm, caused by the resonance absorption of methyl protons. The methylene protons bonded to the nitrogen atom account for thhe triplet in the region of 4.17 – 4.67 ppm. The absorption of methylene protons bonded to the sulfur atom is manifested by triplets in the interval 3.0 – 4.07 ppm. In addition, the spectra of compounds IIb and IIc contain multiplets due to the methylene protons (C–CH_2–C) at 2.07 and 2.1 ppm, respectively. The mass spectra contain $[M+2]^+$ peaks with relative intensities M^+ : $[M+2]^+$ = 100 : 5, which is evidence of a single sulfur atom per molecule.

The IR spectra of compounds IIIa – e and IV contain no absorption bands corresponding to the stretching vibrations of NH groups of the uracyl fragments of molecules. The spectra of IIId and IIIe show intense bands at 1745 and 1740 cm^{-1}, attributed to the absorption of ester carbonyl groups. The IR spectra of alcohol IV and acid V exhibit bands in the region of 3430 – 3450 cm^{-1}, which are assigned to the stretching vibrations of OH groups. The mass spectrum of butyl ester IIId shows a peak of M^+ with m/z = 338 and a peak of $[M+2]^+$ with m/z = 340. The latter peak has an intensity about 5% of that of the former, which is indicative of a single sulfur atom present in the molecule.

EXPERIMENTAL CHEMICAL PART

The IR spectra were recorded on a Specord IR-75 spectrophotometer (Germany) using samples prepared as vaseline oil suspensions. The ^1H NMR spectra were measured on a

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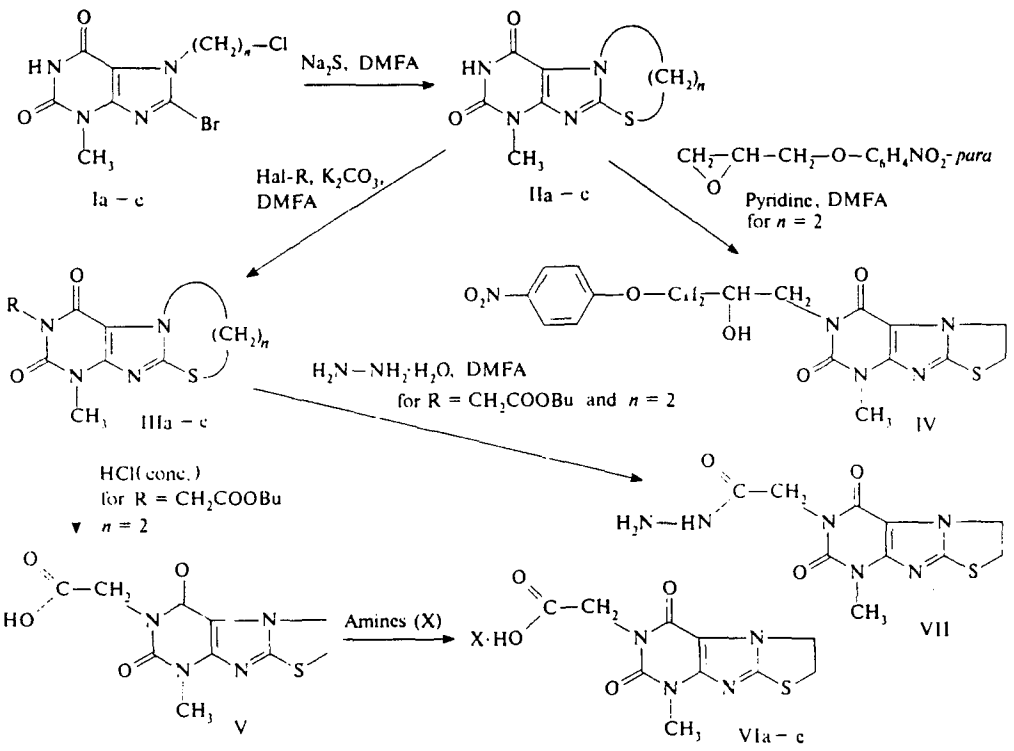

I, II, a: $n = 2$; b: $n = 3$; c: $n = 4$.
IIIa: R = C_3H_7-n, $n = 3$;
b: R = $CH_2CH{=}CH_2$, $n = 3$;
c: R = $CH_2CH{=}CH_2$, $n = 4$;
d: R = CH_2COO-*n*-Bu, $n = 2$;
e: R = CH_2COOBu, $n = 3$.

VIa: X = piperidine;
b: X = morpholine;
c: X = hexamethylenimine;
d: X = diethanolamine;
e: X = diethylamine.

Tesla BS-467 spectrometer (60 MHz) using CF_3COOD as the solvent and HMDS as the internal standard. The mass spectra were obtained on a Varian MAT-311A spectrometer with direct injection of samples into the ion source, operated at an electron-impact ionization energy of 70 eV. The main characteristics of the synthesized compounds are listed in Table 1. The data of elemental analyses agree with the results of analytical calculations.

8-Methyl-5,7-dioxo-2,3,5,6,7,8-hexahydrothiazolo[3,2-f]-purine (IIa). A mixture of 3.07 g (0.01 mole) of compound Ia, 4.8 g (0.02 mole) $Na_2S \cdot 9H_2O$, and 50 ml DMFA is boiled for 3 h and then filtered hot. The precipitate is washed with water and dried. A similar procedure is used to obtain compounds IIb and c.

Alkylation thiazolo-, thiazino-, and thiazepino[3,2-f]-purines (IIIa – e). A mixture of 0.02 mole of compound IIa (IIb or IIc), 2.8g (0.02 mole) anhydrous K_2CO_3, and 50 ml DMFA is boiled for 2 h and then filtered hot. The precipitate is washed with water, and dried.

8-Methyl-6-[2-hydroxy-3-(4-nitrophenoxy)propyl]-5,7-dioxo-2,3,5,6,7,8-hexahydrothiazolo[3,2-f]purine (IV). A solution of 4.5 g (0.02 mole) of compound IIa, 4.3 g (0.022 mole) of 1-(4-nitrophenoxy)-2,3-epoxypropanone, and 1 ml pyridine in 50 ml DMFA is boiled for 30 min. Then the mixture is cooled and diluted with water. The precipitate is filtered, washed with water, and dried.

(8-Methyl-5,7-dioxo-2,3,5,6,7,8-hexahydrothiazolo[3,2-f]-purin-6-yl)acetic acid (V). A solution of 3.4 g (0.01 mole) of compound IIId in 30 ml concentrated HCl is boiled for 2 h. Then the mixture is evaporated in vacuum to half the initial volume and cooled. The precipitate is filtered, washed with water, and dried.

Amine salts of (8-methyl-5,7-dioxo-2,3,5,6,7,8-hexahydrothiazolo[3,2-f]purin-6-yl)acetic acid (VIa – e). A solution of 1.4 g (0.005 mole) of acid V, and 0.005 mole of the corresponding amine in 20 ml dioxane and 1 ml water is boiled for 1 – 2 min and filtered. Then the filtrate is cooled and the precipitate is filtered, washed with ethyl ether, and dried.

Hydrazide of (8-methyl-5,7-dioxo-2,3,5,6,7,8-hexahydrothiazolo[3,2-f]purin-6-yl)acetic acid (VII). To a solution of 3.4 g (0.01 mole) of ester IIId in 20 ml DMFA is added 1.9 ml (0.004 mole) hydrazine hydrate and the mixture is allowed to stand for 24 h at room temperature. The precipitate is filtered, washed with water, and dried.

TABLE 1. Characteristics of Synthesized Compounds

Compound	Yield, %	M.p., °C (solvent)	Empirical formula
IIa	68	> 300 (DMFA)	$C_8H_8N_4O_2S$
IIb	84	> 300 (H_2O-DMFA)	$C_9H_{10}N_4O_2S$
IIc	72	270 – 272 (H_2O-DMFA)	$C_{10}H_{12}N_4O_2S$
IIIa	43	178 – 179 (2-propanol)	$C_{12}H_{16}N_4O_2S$
IIIb	65	177 – 179 (2-propanol)	$C_{12}H_{14}N_4O_2S$
IIIc	68	95 – 97 (methanol)	$C_{13}H_{16}N_4O_2S$
IIId	85	138 – 139 (methanol)	$C_{14}H_{18}N_4O_4S$
IIIe	90	126 – 128 (H_2O – 2-propanol)	$C_{15}H_{20}N_4O_4S$
IV	78	252 – 254 (DMFA)	$C_{17}H_{17}N_5O_6S$
V	88	246 – 248 (dioxane)	$C_{10}H_{10}N_4O_4S$
VIa	76	167 – 169 (H_2O-dioxane)	$C_{15}H_{21}N_5O_4S$
VIb	76	205 – 207 (H_2O-dioxane)	$C_{14}H_{19}N_5O_5S$
VIc	58	230 – 232 (H_2O-dioxane)	$C_{16}H_{23}N_5O_4S$
VId	52	160 – 162 (H_2O-dioxane)	$C_{14}H_{21}N_5O_6S$
VIe	68	212 – 214 (H_2O-dioxane)	$C_{14}H_{21}N_5O_4S$
VII	51	> 300 (DMFA)	$C_{10}H_{12}N_6O_3S$

EXPERIMENTAL BIOLOGICAL PART

The acute toxicity of the synthesized compounds was studied on both male and female white mice weighing 18 – 25 g. The compounds were injected intraperitoneally as an aqueous solution or a fine aqueous suspension stabilized with Tween-80 (for IIIe). The experimental data were processed by the Kerber method [5].

The effect of the compounds studied on the uripoietic function of kidneys was studied in experiments on intact white Wistar male rats weighing 150 – 200 g by the method of Berkhin [6]. The test compounds were injected intraperitoneally at a dose of 20 mg / kg. The LD_{50} values and diuretic characteristics are given in Table 2. As is seen from these data, the synthesized compounds are of low toxicity and produce a diuretic action that is more pronounced (except for VIc) than that of euphyllin.

TABLE 2. Biological Activity of Synthesized Compounds

Compound	LD_{50}, mg / kg	Diuresis, % to control
IIIe	390.0 ± 14.6	158.4
VIa	1220.0 ± 32.1	216.6
VIb	1940.0 ± 55.6	137.5
VIc	640.0 ± 36.0	116.6
VId	1800.0 ± 44.0	137.9
VIe	760.0 ± 28.0	154.2
Euphyllin	194.0	117.8

Special attention should be paid to pyperidine salt of (8-methyl-5,7-dioxo-2,3,5,6,7,8-hexahydrothiazolo[3,2-f]purin-6-yl)acetic acid (VIa), which is virtually nontoxic and produces an almost twofold increases in the diuresis rate.

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