It was found, as a result of the studies, that compounds Ia-d and IIIa-d do not possess antiinflammatory activity. Among compounds previously synthesized, significant antiinflammatory activity was found only for 2-(4'-bromoanilino)5-carboxy-6-methylnicotinamide, which decreased swelling of the inflamed paw by 39.3% at a dose of 50 mg/kg, but was inferior to orthophen in potency. It has previously been reported that the sodium salt of this compound has antiplatelet aggregational activity, inhibiting aggregation by 39.3% and having low toxicity (LD_{50} equal to 448 mg/kg) [1].

Thus, from a search among 2-arylamino-5-carboxy-6-methylnicotinamides, compounds were found that have high antiaggregational activity and low toxicity. In addition, one of the compounds tested showed both antiaggregational and antiinflammatory activity. All this indicates the promise of further work with 2-arylamino-5-carboxynicotinamides for use in medical practice.

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SYNTHESIS AND IMMUNOTROPIC ACTIVITY OF DERIVATIVES OF PYRIMIDINES

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The production of immunomodulating agents has important significance for modern immunology and practical medicine [9], since it reveals the possibility of the correction of the immunity in a series of pathological states of man and animals [4, 8]. In recent years, a whole series of natural and synthetic compounds possessing immunomodulating properties has been isolated and investigated. In spite of the large number of agents able to show an immunomodulating influence, the search for preparations with the purposeful immunostimulating or immunosuppressing effect is continuing [13, 16, 23].

Derivatives of pyrimidine pertain to promising classes of immunomodulators, whereby the presence of antioxidant properties in some of them (methyluracil, oxymetacil) is considered to be an important link in the mechanism of their immunomodulating action [6].

Among 22 studies derivatives of pyrimidine [5], the most active stimulators of the phagocytic activity of leukocytes and macrophages in vivo and in vitro proved to be deriva-

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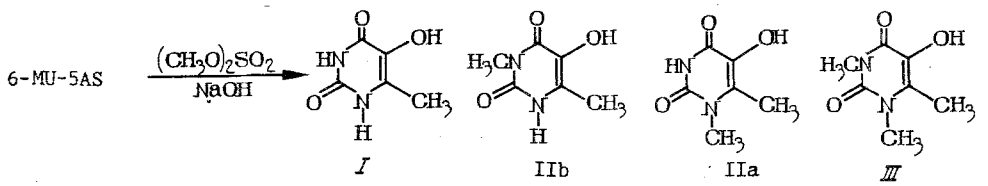
tives such as 5-hydroxtmethyluracil, 2-methyl-4-amino-6-hydroxypyrimidine, 6-methyluracil, and superacil (2-amino-4-methyl-6-hydroxypyrimidine).

There is a known method for the synthesis of 5-hydroxy-6-methyluracil (I) [18] in seven stages with the total yield of 9% by means of the reaction of monochloroacetic acid with sosium sec.-butylate. The resulting sec.-butoxy acid is treated with thionyl chloride, and the acid chloride which is formed converted to sec.-butyloxyacetate, the self-condensation of which by the action of sodium methoxide gives sec.-butyl-α,γ -dialkoxyacetate. The treatment of the last with thiourea gives 5-sec.-butoxy-6-sec.-butoxymethyl-2-thiouracil, which



is converted by monochloroacetic acid to 5-sec.-butoxy-6-sec.-butoxymethyluracil. The treatment of the last with hydriodic acid gives the desired product.

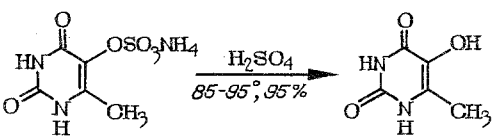
There is a known method for the synthesis of (I) by the oxidation of 6-methyluracil with potassium permanganate in acetic acid at 20-40°C with the yield of 25% [14].

There is a known method for the synthesis of 5-hydroxypyrimidines by the oxidation of pyrimidine derivatives with potassium persulfate or ammonium perfulfate in an alkaline medium at 0-20°C for 24 h with the subsequent hydrolysis of the reaction mixture with hydrochloric acid at 100°C [19], and the oxidation of 6-methyluracil with solid potassium persulfate in an alkaline medium [1]. Only (I) can be isolated by these methods, and it has the purity of not more than 92%; the purification from the initial 6-methyluracil [1, 14, 19] is difficult since it has low solubility in water and is insoluble in organic solvents, which does not allow the utilization of the method of column chromatograhy.

Therefore, (I) (oxymetacil) was not obtained with the purity of 99-100%, until now, by any of the methods indicated, and 5-hydroxy-1,6-dimethyluracil (II) and 5-hydroxy-1,3,6-trimethyluracil (III) were not known at all.

The object of the present investigation was the development of new methods for the synthesis of (I) with 99-100% purity and the new compounds (II) and (III), and the study of their immunotropic activity.

An easy method for the synthesis of (I), with the yield of 99-100%, was developed using the hydrolysis of 6-methyluracil-5-ammonium sulfate (6-MU-5-AS) with sulfuric acid with the utilization of the Elbs reaction according to our altered method [14].



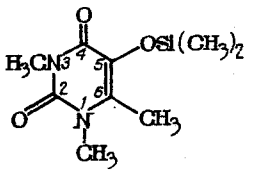
We developed a second method of synthesis where the 6-MU-5-AS in an alkaline medium is treated with dimethyl sulfate in varying proportion prior to the isolation of (I), (II), and (III).

When the ratio of 6-MU-5-AS:NaOH:DMS is 1:1:1, (I) is obtained with the yield of 84%. With the corresponding ratio of 1:4:4, (II) is obtained with the yield of 52.5%, and with the corresponding ratio of 1:10:10, (III) is obtained with the yield of 93%.

The purity and structure of (I)-(III) were proved by the method of TLC, elemental analysis, the IR, UV, and PMR spectra, as well as the GLC of the silylated products [2]. The quantitative content of hydroxy groups was shown by the method of titration [10, 11].

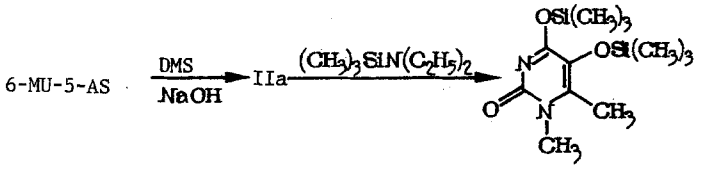
The UV spectrum of the compound (II) at the pH 1-12 does not give a bathochromic shift characteristic of uracils substituted at the tertiary nitrogen atom of the ring [7, 12, 17, 22, 24]. Consequently, the CH_3 group in the compound (II) is situated at the first nitrogen of the ring (IIa).

The ^{13}C NMR spectrum of the silylated (III) (5-trimethyl)-silyloxy-1,3,6-trimethyl-uracil) has chemical shifts of 28.478 and 31.735; this corresponds with CH_3—N(1) and CH_3—N(3):



THE ^{13}C NMR spectrum of the silylated 5-hydroxy-1(3), 6-dimethyluracil has the chemical shift of 27.472 for CH_3—N(1), and the chemical shift of 31.735 is absent. Therefore, the silylated (II) is 4,5-bis(trimethylsilyloxy)-1,6-dimethyluracil, and consequently the un-silylated compound (II), (IIa), is 5-hydroxy-1,6-dimethyluracil.

Therefore, the alkylation of 6-MU-5-AS with dimethyl sulfate in an alkaline medium and the 1:4:4 ratio of 6-MU-5-AS-NaOH:DMS occurs at the position 1.

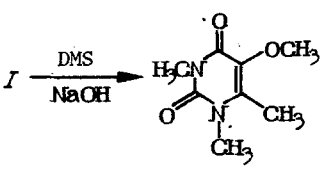


It should be noted that (II) and (III) have the same R_f values. However, (II) is insoluble in organic solvents, and (III) is soluble in organic solvents, and (III) is soluble in chloroform. Therefore, these products are separated readily.

The UV spectra of (I) and (II) at the pH 7 do not differ: the λ_{max} values are 277.8 and 277.2, and the λmin values are 243.7 and 245.1 correspondingly.

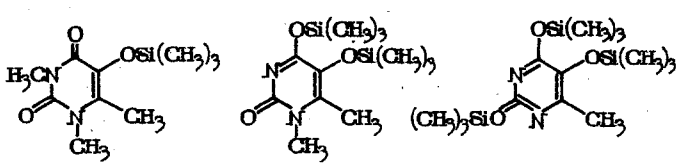
The purification of (II) from the impurity of (I) is performed by crystallization from water.

The treatment of (I) with dimethyl sulfate in an alkaline medium at 0°C with the subsequent raising of the temperature to 100°C leads to the isolation of 5-methoxy-1,3,6-trimethyl-uracil (IV) with the yield of 78% (the 1:4:4 ratio of 6-MU-5-AS:NaOH:DMS):



IV

According to the GLC data, 5-trimethylsiloxy-1,3,6-trimethyluracil, 4,5-bis(trimethylsiloxy)-1,6-dimethyluracil, and 2,4,5-tris(trimethylsiloxy)-6-methyluracil come out in one peak each; this indicates the chromatographic purity of the silylated product and, consequently, the purity of the initial compounds.



The quantitative GLC analysis of the silyl derivatives was performed by the method of internal normalization on a Khrom-5 (Czechoslovakia) chromatograph: the glass column,

length (L) 1.2 m, the internal diameter (d) 3 mm, column filling 5% silicone rubber SE-30 on Inerton Super (0.16-0.20 mm) (Czechoslovakia). The column temperature was 150°C, and the vaporizer temperature was 200°C; the detector temperature was 200°C (catharometer). The gas carrier was helium (50 ml/min); the sensitivity was 2 and 8, and the detector current was 100 mA. The speed of the chart strip was 360 mm/min.

The GLC of 5-trimethylsilyloxy-1,3,6-trimethyluracil was performed on a Khrom-5 (Czechoslovakia) chromatograph with a catharometer on the column of stainless steel, L = 3.7 m, d = 4 mm filled with 5% SE-30, using Inerton Super with the granulation of 0.16-0.20 mm (Czechoslovakia) at the temperature of 60-300°C (program); it was shown that the required product comes out in one peak.

The IR spectra of the compounds (I)-(IV) contain absorption bands in the region of 1660, 1680, and 1720 cm^{-1}, characteristic of the uracil ring ($\nu_{C=O}$, =N—C =O). Absorption bands in the region of 1096-1256 cm^{-1} in the compounds (I)-(III) are characteristic of the alcohol group (= C—OH, ν_{CN}). The absorption bands in the region of 3100 and 3144 cm^{-1} in the compounds (I) and (II) are NH stretching vibrations, whereas these absorption bands are absent for the compounds (III) and (IV).

The ^1H NMR spectrum of the compounds (I)-(IV) show signals of the protons of the uracil fragment: the singlet of the methyl group (1.99-2.3 ppm) [C(6)—CH_3], signals of protons (3.36-3.41 ppm), and the singlets of the methyl groups CH_3—N(1) of the compounds (II), (III), and (IV), the signals of protons, the singlet of the methyl group CH_3—N(3) (3.419 ppm) for the compounds (III) and (IV), and the singlet of the methyl group of OCH_3 in the compound (IV) (3.76 ppm).

The ^{13}C NMR spectrum of the compounds (III) and (IV) contain signals in the region of 159.99 and 159.52 [C, C(4) = O], in the region of 150.33 and 151.101 [C, C(2) = O], in the region of 130.36 and 142.11 [C, C(6) =CH_3], 129.18 and 132.209 [C, C(5)—OH], in the region of 60.476 (C, OCH_3) for the compound (IV), in the region of 31.72 and 31.88 [C, CH_3—N(3)] for the compounds (III) and (IV), signals in the region of 28.53 and 28.036 [C, CH_3—N(1)] for the compounds (III) and (IV), and signals in the region of 17.53 and 12.843 [C, CH_3—(6)].

EXPERIMENTAL (CHEMICAL)

The ^1H NMR and ^{13}C NMR spectra were recorded in the form of the 1% (PMR) and 10-20% (^{13}C) concentrations of the solutions in D_2O or $CDCl_3$ using the AM 300 Bruker NMR spectrophotometer (300 MHz for ^1H and 75.5 MHz for ^{13}C). The chemical shifts are presented relative to TMS in δ ppm.

The GLC analysis of the silylated products was performed on the Khrom-5 chromatograph (Czechoslovakia) with the column of glass, L = 1.2 m and d = 3 mm, filled with 5% silicone rubber SE-30 on Inerton Super (0.16-0.20) (Czechoslovakia); the column temperature was 150°C, and the vaporizer temperature was 200°C. The detector temperature was 200°C (catharometer), and the gas carrier was helium (50 ml/min). The sensitivity was 2 and 8, and the detector current was 100 mA; the speed of the chart strip was 360 mm/min, as well as for the column of stainless steel.

The IR spectra were taken on the UR-20 spectrometer, and the TLC was performed on plates of Silufol UV-254 (Czechoslovakia) with the utilization of the 4:1 mixture of alcohol—ammonia as the eluent. Spots of the substances were detected in UV light. The melting temperature was measured on the "Boetius" instrument (Germany).

The data of the elemental analysis satisfy the calculated values.

5-Hydroxy-6-methyluracil (I). Method 1. To 120.8 g (0.505 mole) of 6-MU-5-AS in 800 ml of water at 80°C are added, dropwise with stirring, 62 ml of concentrated H_2SO_4 (114.08 g, 1.16 mole) in the course of 20 min. After 20 min, the mixture is cooled and recrystallized from alcohol prior to the isolation of 722 (100%) of (I) of 100% purity. The mp was 320°C. The purity of the product was determined by the method of UV spectroscopy. $C_5H_6N_2O_3$. The ratio of 6MU-5-AS:H_2SO_4 was 1:2.3. The IR spectrum (ν, cm^{-1}) was as follows. 1130 (≡C—OH), 1260 (CO—NH), 1715 (—C = O), 1380 (δSCH_3), 1660-1670, 3100 (R_2—C = C—R_2), 1660 (NH—CO—NH), and 3260 (OH). According to the TLC data, (I) has one spot with the R_f 0.68. The ^1H NMR (δ, ppm) in D_2O was as follows: 1.99 (s, 3H, C(6)—CH_3) and 4.75 (s, 2H, NH).

TABLE 1. Yield of (I)-(III) Depending on the Ratio of the Initial Substances

No. of experiment	Loading							Ratio 6-MU-5-AS/NaOH/DMS	Obtained			
	6-MU-5-AS		initial uracil		DMS		water, ml		IIa, b		III	
	g	mmole	g	mole	g	mole			g	%	g	%
2	23,9	0,1	4,0	0,1	12,6	0,1	100	1:1:1	13,9*	84,0	0,5	3,2
3	23,9	0,1	8,0	0,2	25,2	0,2	100	1:2:2	14,5*	92,9	1,1	6,4
4	119,6	0,5	60,0	1,5	190,5	1,51	400	1:3:3	43,2**	55,33	16,1	18,92
5	119,6	0,5	60,0	1,5	190,5	1,51	400	1:3:3	41,0**	52,5	13,7	17,55
6	709,5	2,97	360,0	9,0	1145,6	9,08	2000	1:3:3	287,0**	61,3	106,6	20,88
7	78,22	0,327	52,4	1,31	165,2	1,31	300	1:4:4	26,8	52,49	16,3	29,29
8	119,6	0,5	120,0	3,0	378,0	3,0	740	1:6:5	26,1	33,43	46,9	55,12
9	119,6	0,5	160,0	4,0	504,5	4,0	500	1:8:8	15,6	20,0	73,6	86,5
10	119,6	0,5	200,0	5,0	630,6	5,0	500	1:10:10	8,0	10,2	80,0	93,0
11	71,06*	0,5	80,0	2,0	252,0	2,0	300	1:4:4	78,3***	85,0		

*5-Hydroxy-6-methyluracil (I).
**Impurity of (I) (6-7%).
***(III).

Method 2 (Experiment 2). To the solution of 4 g (0.1 mole) of sodium hydroxide, cooled to 30-40°C, are added 23.9 g (0.1 mole) of 6-MU-5-AS, and the mixture is stirred for 10 min. The reaction mixture is cooled to −2°C, and 12.6 g (0.1 mole) (~ 10 ml) of dimethyl sulfate are added dropwise at this temperature for 10 min. After the complete addition of dimethyl sulfate, the cooling is stopped (a lower layer, which does not disappear at this temperature, appears), and the mixture is stirred without heating for 2 h; it is then heated to 100°C (crystals are precipitated after 30-50 min, and the pH is alkaline), boiled for 2 h, and left in the cold. On the following day, the crystals are filtered off and washed with water (40 ml threefold) and acetone (40 ml twice) prior to the isolation of 13.9 g (84%) of (I), which has low solubility in water and is insoluble in organic solvents. The mp 315-318°C.

The IR spectrum (ν, cm^{-1}) is as follows: 1130 (=C–OH), 1260 (CO–NH), 1715 (–C = O), 1380 (δ^S CH_3), 1660, 3100 (R_2–C = C–R_2), 1660 (NH–CO–NH), and 3260 (–OH). According to the TLC data, (I) has one spot with the R_f 0.68. The ^1H NMR (δ, ppm) in D_2O is as follows: 1.99 (s, 3H, $C_{(6)}$–CH_3) and 4.75 (s, 2H, NH). The mass spectrum is as follows: M^+ 142, 43 (NH = O), 42 (N = C = O)$^+$, 55 (C_3H_3O)$^+$, 58 (NH–CONH)$^+$, 71 ($^+$O ≡ CNHCO), 86 (NHCONHCO)$^+$, 96, 97, 99 (N_1–H), 114 (M_1–CO)$^+$, and 126.

The mother liquor is extracted with chloroform (threefold portions of 100 ml); the chloroform is distilled off prior to the isolation of 0.5 g (3.2%) of (III) with the mp 183-185°C and the R_f 0.78.

The Experiment 3 is conducted analogously, but with the 1:2:2 ratio of 6-MU-5-AS: NaOH:DMS. The results of the experiment are given in Table 1. The yield of (I) comprises 93%, but according to the TLC data the product is contaminated with an admixture of (III) (6-10%); R_f 0.68 and R_f 0.78.

5-Hydroxy-1,6-dimethyluracil (II). To the solution of 60 g (1.5 mole) of sodium hydroxide in 400 ml of water, cooled to 30-40°C, are added 119.6 g (0.5 mole) of 6-MU-5-AS; the mixture is stirred until the solution is effected. The reaction mixture is cooled to 6-15°C, and 190.5 g (1.51 mole, 143 ml) of dimethyl sulfate are added dropwise at this temperature in the course of 1 h. The temperature is then raised to 85-95°C in the course of 1-2 h, and the mixure is stirred at this temperature for 2 h, cooled, and poured into 200 ml of chloroform. The mixture is stirred for 10 min. The crystals are filtered off and washed (fourfold in 50 ml portions) with water until a neutral reaction is obtained and then acetone (twice in 50 ml portions). The yield of 43.2 g (55.3%) of (II) is obtained; the product has the mp > 270°C, has low solubility in water, and is insoluble in organic solvents. $C_6H_8N_2O_3$. The IR spectrum (ν, cm^{-1}) is as follows: 1096-1256 (C–OH, ν_{C-N}), 1376 (δ^S CH_3), 1604, 1680, 1720 ($\nu_{C=O}$); 1528 ($\nu_{CN} + \delta_{NH}$), 3144 (ν_{NH}), 3226, 3248 ($2\nu_{CN}$), 3328 (OH), 2880, 2928 ($\nu_{C=C}$, $\nu_{aliph\ CH}$), and 1460 (ν_{CH_2}, CH_3). According to the TLC data, 5-hydroxy-1,6-dimethyluracil is contaminated with 5-hydroxy-6-methyluracil (6-7%); R_f 0.78 and R_f 0.68. The experiment 7 was performed analogously using the 1:4:4 ratio of 6-MU-5-AS:NaOH:DMSO.

TABLE 2. Comparison of the Acute Toxicity of the Proposed Compounds with Known Biological Compounds

Compound	LD_{50} for mice with the ip introduction, mg/kg
5-Hydroxy-1,6-dimethyluracil	1000±122,6
5-Hydroxy-1,3,6-trimethyluracil	1500±140,4
5-Methoxy-1,3,6-trimethyluracil	1400±122,6
6-Methyluracil	2700(1928±3780)

Under these conditions, 5-hydroxy-1,6-dimethyluracil was obtained without the impurity of 5-hydroxy-6-methyluracil; according to the TLC data, the product has one spot with the R_f 0.79. The ^1H NMR (δ, ppm) using D_2O is as follows: 2.15 [s, 3H, C(6)—CH_3] 3.265 [s, 3H, CH_3—N(1)], 4.75 (s, NH), and 4.83 (D_2O).

The mother liquor remaining after the separation of the crystals is extracted with chloroform (threefold with portions of 200 ml), and the chloroform is distilled off prior to the isolation of 16.1 g (18.93%) of (III) with mp 183-185°C.

The Experiment 6 was performed analogously to Experiment 4; the mixture of (I) and (II) was thereby obtained.

Experiment 9. 5-Hydroxy-1,3,6-trimethyluracil (III). To 119.6 g (0.5 mole) of 6-MU-5-AS is added the solution of sodium hydroxide (160 g, 4 mole) in 500 ml of water, cooled to 15°C. After the complete solution of the 6-MU-5-AS, 504.5 g (4 mole, 379 ml) of dimethyl sulfate are added dropwise for 1.5 h, and the mixture is stirred at 100°C for 2 h and cooled prior to the addition to 200 ml of chloroform. The mixture is stirred for 10 min; the crystals are filtered off and washed with water until a neutral reaction with litmus is obtained (fourfold using 50 ml portions), and acetone (twice with portions of 50 ml). The yield of 15.6 g (0.1 mole) (20%) of (II), was obtained; (II) had the mp > 270°C and the R_f 0.79.

The mother liquor is extracted with chloroform (fivefold with portions of 200 ml); the chloroform is distilled off prior to the isolation of 73.6 g (0.4 mole) (86.5%) of (III) with the mp 183-185°C and the R_f 0.78. $C_7H_{10}N_2O_3$. The product had good solubility in water, chloroform, alcohol, acetone, and benzene, and low solubility in ether; it was insoluble in hexene. The IR spectrum, (ν, cm^{-1}) was as follows: 1082, 1088, 1104, 1230, 1264, 1296 (ν_{CN}), 1376 ($\delta^{s}_{CH_3}$), 1626, 1644, 1696 ($\nu_{C=O}$, =N—C=O), 1088-1230 (≡C—OH), 3336 (OH), 2856, 2929, 2944, and 2954 ($\nu_{C=C}$ and aliph. CH). The ^1H NMR spectrum (δ, ppm) using $CDCl_3$, was as follows: 2.288 [s, 3H, C(6)—CH_3], 3.408 [s, 3H, CH_3—N(1)], and 3.419 [s, 3H, CH_3—N(3)]. The ^{13}C NMR spectrum (δ, ppm) using $CDCl_3$ and TMS was as follows: 159.99 [s, C(4)=O], 150.33 [s, C(2)=O], 130.36 [s, =C(6)—CH_3], 129.18 [s, =C(5) OH], 31.72 [q, CH_3—N(3)], 28.53 [q, CH_3—N(1)], and 12.63 [q, CH_3—C(6)].

The example 10 was conducted analogously with the exception that the ratio of 6-MU-5-AS:NaOH:DMS was 1:10:10 whereby the yield of (II) decreased to 10%, and the yield of (III) increased to 93%.

With the decrease of the ratio 6-MU-5-AS:NaOH:DMS to 1:6:6, (example 7), the yield of (III) decreases to 55%, and that of 5-hydroxy-1,6-dimethyluracil to 33.5%.

Experiment 11. 5-Methoxy-1,3,6-trimethyluracil (III). To the solution of 80 g (2 mole) of sodium hydroxide in 300 ml of water are added, with stirring, 71.06 g (0.5 mole) of (I), and the mixture is cooled to 0°C; 190 ml (252 g, 2 mole) of dimethyl sulfate are added dropwise at this temperature in the course of 40 min. The mixture is then maintained at room temperature for approximately 1 h. All the crystals are dissolved by heating the mixture to 100°C and by stirring it for 4 h. The reaction mixture is cooled to room temperature and then extracted with chloroform (fourfold in portions of 200 ml); the solvent is distilled off, and the crystals are washed with 100 ml of ether prior to the isolation of 78.3 g (85%) of (III) with the mp 103-105°C. $C_8H_{12}N_2O_3$. The R_f was 0.85. The product was readily soluble in water, alcohol, chloroform, and acetone, and had low solubility in ether; it was insoluble in hexane. The IR spectrum (ν, cm^{-1}) was

TABLE 3. Influence of the Compounds on the Reaction of HDT in Mice with the Introduction at the Dose of 0.1 LD_{50} at 1-4 Days after Sensitization (n = 8)

Introduced preparation	Dose, mg/kg	HDT to DNFB: Swelling of the ear
NaCl 0.9% solution (control)	—	45,3±1,1
6-Methyluracil	200	60,2±4,8
5-Hydroxy-1,6-dimethyluracil	100	48,2±1,1
5-Hydroxy-1,3,6-trimethyluracil	150	52,1±1,1
5-Methoxy-1,3,6-trimethyluracil	140	59,5±1,2

as follows: 1100, 1130 (ν_{C-O-C}), 905, 1010 ($\omega_{C=C}$), 1260 ($\nu_{C=O}$), 1050, 1100, 1130, 1260, 1290 (ν_{CN}, $=N-C=O$), 1630, 1690, and 1710 ($\nu_{C=O}$). The ^1H NMR spectrum (δ, ppm) using $CDCl_3$ was as follows: 2.295 [s, 3H, C(6)−CH_3], 3.358 [s, 3H, $CH_3N(1)$], 3.419 [s, 3H, CH_3−N(3)], and 3.755 [s, 3H, OCH_3). The ^{13}C NMR spectrum (δ, ppm) using $CDCl_3$ was as follows: 159.524 [s, C(4) =O], 151.101 [s, C(2) = O], 142.113 [s, = C(6)−CH_3], 132.209 [S, C(5)], 60.476 (s, OCH_3), 31.88 [s, CH_3−N(3)], 28.036 [s, CH_3−N(1)], and 12.843 [s, CH_3−C(6)].

2,4,5-Tris(trimethylsiloxy)-6-methyluracil (V). To 1.42 g of 5-hydroxy-6-methyluracil are added 8 ml of trimethylsilyldiethylamine in a stream of argon; the mixture is heated to 100°C (the product is dissolved after 3-4 h). The excess trimethylsilyldiethylamine is distilled off in vacuo at 120°C/20 mm if Hg stem prior to the isolation of 3.0 g (84%) of (V) with the bp 140-142°C/2 mm of Hg stem. The ^1H NMR spectrum (δ, ppm) using $CDCl_3$ was as follows: 0.22, 0.38, 0.40 [s, 27H, $3Si(CH_3)_3$], and 2.30 [s, 3H, C(6)−CH_3]. The ^{13}C NMR spectrum was as follows: −0.17 q; −0.05 q, +0.11 q [3−$OSi(CH_3)_3$], 18.47 (CH_3−C(6)] 131.60 [C(5)], 154.9 [C(6)], 158.53 [C(2) = O], and 159.88 [C(4) = O].

4,5-Bis(trimethyloxy)-1,6-dimethyluracil (VI). To 1.56 g (0.01 mole) of 5-hydroxy-1,6-dimethyluracil are added 6 ml of trimethylsilyldiethylamine in a stream of argon, and the mixture is heated to 100°C (everything is dissolved after 3 h). The excess treimethylsilyldiethylamine is distilled off at 120°C/20 mm of Hg stem prior to the isolation of 2.5 g (83.2%) of (VI). The product crystallizes, and has the mp 118-120°C. It has good solubility in chloroform. $C_{12}H_{24}N_2O_3Si_2$. According to the GLC data, the product comes out as one peak.

The ^1H NMR spectrum (δ, ppm) using $CDCl_3$ was as follows: 0.188 [s, 18H, $2Si(CH_3)_3$], 2.09 [s, 3H, C(6)−CH_3], and 3.27 [s, 3H, CH_3−N(1)]. The ^{13}C NMR spectrum was as follows: −0.64, 1.04 [s, $Si(CH_3)_3$], 13.321 [CH_3−C(6)], 27.472 [s, CH_3−N(1)], 128.312 [s, C(5)], 134.613 [C(6)], 151.91 [s, C(2) =O], and 160.386 [s, C(4) = O].

5-Trimethylsiloxy-1,3,6-trimethyluracil (VII). The compound (III) (1.72 g, 0.01 mole) is placed into a two-necked flask of capacity 20 ml in a stream of argon prior to the addition of 5 ml of trimethylsilyldiethylamine (TMSDEA). A reflux condenser with a calcium chloride tube is set up, and the mixture is heated on a boiling water bath. The crystals of (III) are dissolved after 5-10 min. After 1 h, the excess TMSDEA is distilled off at 100°C/80−20 mm of Hg stem prior to the isolation of 2.4 g (100%) of (VII) with the mp 113-115°C. $C_{10}H_{18}N_2O_3Si$. According to the GLC data, the product comes out as one peak. The ^1H NMR spectrum (δ, ppm) using $CDCl_3$ was as follows: 0.26 [s, 9H, $Si(CH_3)_3$], 2.29 [s, 3H, C(6)−CH_3], 3.404 [s, 3H, CH_3−N(1)], and 3.411 [s 3H, CH_3−N(3)]. The ^{13}C NMR spectrum was as follows: −0.814 [s, $Si(CH_3)_3$], 12.483 [C(6)−CH_3], 28.478 [CH_3−N(1)], 31.735 [CH_3−N(3)], 129.231 [C(5)], 130.338 [C(6)], 150.378 [C(2) = O], and 160.055 [C(4) =O].

EXPERIMENTAL (PHARMACOLOGICAL)

Investigations were performed on 320 hybrid white mice of mass 18-20 g, obtained from the "Rappolovo" Nursery of Laboratory Animals AMN RF.

The acute toxicity was determined on 160 hybrid mice of both sexes and the mass 18-20g with the single ip introduction at doses of 50-1600 mg/kg. At 5-10 min after the introduction

TABLE 4. Influence of the Compounds on the Number of AFCs in the Spleen of Mice (n = 8)

Introduced preparation	Dose, mg/kg	No. of AFCs·10^6	p
NaCl 0.9% solution (control)	—	279,0±2,7	
6-Methyluracil	200	751,3±28,6	<0,001
5-Hydroxy-1,6-dimethyluracil	100	978,6±89,1	<0,001
5-Hydroxy-1,3,6-trimethyluracil	150	293,1±15,9	
5-Methoxy-1,3,6-trimethyluracil	140	366,1±6,5	<0,02

of toxic doses, flaccidity, extension of the limbs, decreased mobility, and toxic convulsions were observed in the animals. Onset of death was from cessation of respiration.

The parameters of toxicity were determined by the method of Kerber. The LD_{50} values of compounds for the ip introduction are given in Table 2.

According to the classification of the toxicity of substances [3], the given compounds pertain to the low-toxic group.

The influence of the compounds on the immune system was studied using models of hypersenseitivity of the delayed type (HDT) and the primary immune response to sheep erythrocytes (the determination of the number of antibody-forming cells – AFCs – of the mouse spleen).

The influence of the compounds on the humoral part of the immune response was determined by the method of [16] using the modification of [15]. The compounds were introduced ip at the dose of 0.1 LF_{50} at 1-4 days after immunization.

The HDT to 2,4-dinitrofluorobenzene (DNFB) was produced by the sensitization of animals with the application of 25 µl of the 0.5% solution of DNFB in the 4:1 mixture of acetone and olive oil onto the skin of the abdomen [21]. At 4 days following the sensitization, 20 µl portions of the 0.25% solution of DNFB were trickled onto the ears, first measured with a micrometer. The reaction was evaluated from the swelling of the ear at 24 h after the application of the resolving dose of DNFB. Compounds were introduced at the lose of 0.1 LD_{50} in the course of 4 days commencing from the first day after sensitization. The structural analog of the compound – 6-methyluracil – was introduced in the generally accepted dose (200 mg/kg) by the same scheme (Table 3).

The swelling of the ear in the experimental group was the same as that in the control group; this indicates the absence of suppressive influence on the cellular part of immunity.

The influence of the compounds on the formation of AFCs in the spleen of hybrid male mice is given in Table 4.

Therefore, 5-hydroxy-1,6-dimethyluracil (II) is characterized by marked immunotropic activity, stimulating the humoral immune response at the level of methyluracil.

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