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6-Methyl-2-(3-methyl-5-oxo-2,5-dihydropyrazolyl)-pyrimidin-4(1*H*)-one as CH Acid in Michael Reaction

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Abstract—Addition of 6-methyl-2-(3-methyl-5-oxo-2,5-dihydropyrazol-1-yl)pyrimidin-4(1*H*)-one, a compound with two CH-acidic centers, to 5-benzylidenepyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione proceeds with the participation of the atom C^5 of pyrimidine ring. Under the realized reaction conditions the latter possesses a greater nucleophilicity as a result of the priority ionization. The obtained Michael adduct is unstable in the neutral aqueous medium and is decomposed into initial oxopyrazolylpyrimidinone, pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione, and benzaldehyde.

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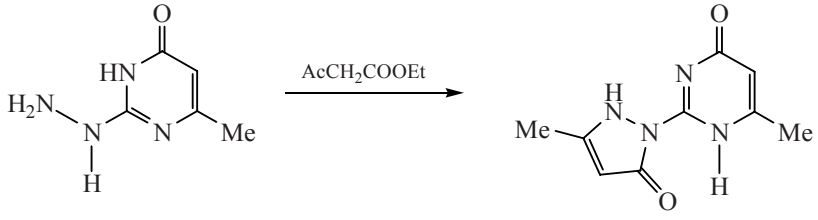
The study of the chemical transformations of 6-methyl-2-(3-methyl-5-oxo-2,5-dihydropyrazol-1-yl)-pyrimidin-4(1*H*)-one (**I**) was practically limited to the investigation of its coupling with aryldiazonium chlorides [1, 2] and condensations with aromatic [3, 4] and heteroaromatic [5, 6] aldehydes. Meanwhile compound **I** is of undoubtable interest as a CH-acidic component of Michael reaction. In view of the presence in the structure of oxopyrazolylpyrimidine **I** of two centers possessing potential CH-acidity, the prediction of the direction of its reaction with the vinylogs of carbonyl compounds becomes possible only taking into account the data on the structure of the ionized form of the reacting component.

The purpose of this work consisted in revealing the priority direction of ionization of oxopyrazolylpyrimidine **I** and in the study of the addition of its ionized form to 5-benzylidenepyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (**II**).

For the synthesis of compound **I** by a method unlike the two-stage one [7,8] we accomplished the condensation of 2-hydrazino-6-methylpyrimidin-4(3*H*)-one (**III**) with ethyl acetoacetate in water and showed that the reaction could be carried out without the intermediate isolation of ethyl acetoacetate (6-methyl-4-oxo-3,4-dihydropyrimidin-2-yl)hydrazone.



III **I**

Analysis of IR spectra of crystalline samples of oxopyrazolylpyrimidine **I** and the related compounds allowed [9] to postulate the structure of **I** as 4-hydroxy-6-methyl-2-(3-methyl-5-oxo-2,5-dihydropyrazol-1-yl)-pyrimidine. We believe that the problem of the structure of compound **I** is more complex, and a possibility of the formation of intramolecular bonds of NH···N and NH···O types involving the appropriate fragments of pyrimidine and pyrazole rings should be considered. Formation of such bonds is promoted, on the first hand, by their coplanar arrangement, and, on the second hand, by the proximity of the indicated

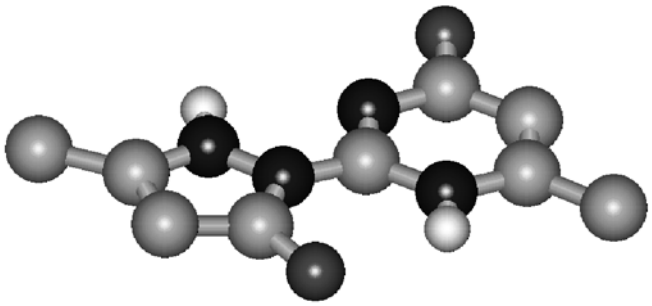
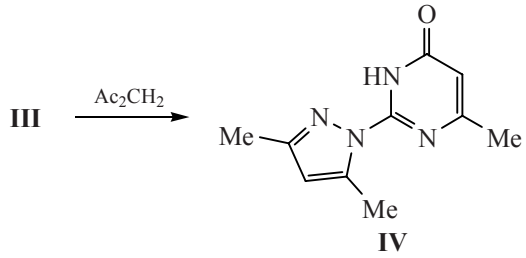


Fig. 1. Optimized geometry of the molecule of 6-methyl-2-(3-methyl-5-oxo-2,5-dihydropyrazol-1-yl)-pyrimidin-4(1*H*)-one (**I**) (the hydrogen atoms in 1 and 2 positions of pyrimidine and pyrazole rings are shown).

atoms (Fig. 1). Considering the IR spectrum of oxopyrazolylpyrimidine **I** , one can see that the band at 3110 cm^{-1} corresponding to the stretching vibrations of groups NH is shifted significantly to low frequencies in comparison with the analogous band in the spectrum of model substance, 2-(3,5-dimethylpyrazol-1-yl)-6-methylpyrimidine-4(3*H*)-one (**IV**) (ν_{NH} 3350 cm^{-1}). We obtained pyrazolylpyrimidinone **IV** by the reaction of hydrazinopyrimidine **III** with 2,4-pentanedione at elevated temperature without a solvent.



IV

The absorption bands of the carbonyl groups of pyrimidine ring near 1676 cm^{-1} and pyrazole ring at approximately 1639 cm^{-1} also were subjected to a low-frequency shift relative to the bands of the same origin in the spectra of compound **IV** ($\nu_{C=O}$ 1698 cm^{-1}) and 1-(pyrimidine-2-yl)-5-pyrazolone that have a fixed 5-oxo-2,5-dihydro configuration [10].

The strong interatomic interactions in the molecule of oxopyrazolylpyrimidine **I** may be concluded from the similarity of its UV of spectrum with the spectrum of the ionized form of pyrazolylpyrimidine **IV** (λ_{max} 230, 245 sh, and 274 nm) (Fig. 2) that indicates the parallel processes of the transfer of the NH group protons of the of pyrimidine ring to the carbonyl group of pyrazole ring and of the pyrazole ring NH proton to the pseudo-deprotonated pyrimidine cycle. A similar migration of protons leads to the formation of

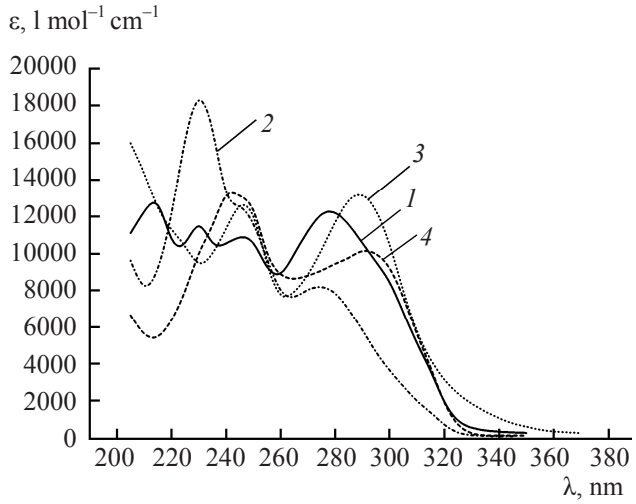
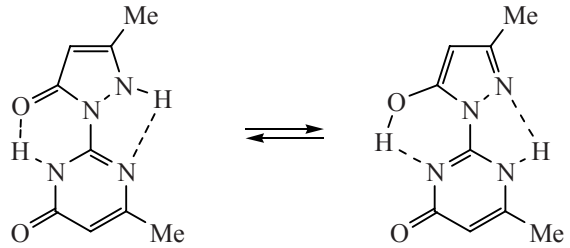


Fig. 2. UV spectra of (*1*) 6-methyl-2-(3-methyl-5-oxo-2,5-dihydropyrazol-1-yl)-pyrimidin-4(1*H*)-one (**I**), (*2*) 2-(3,5-dimethylpirazol-1-yl)-6-methylpyrimidin-4(3*H*)-one (**IV**) in the presence of equimolar quantity of sodium ethoxide, (*3*) 6-methyl-2-(3-methyl-5-oxo-2,5-dihydropyrazol-1-yl)-pyrimidine-4(1*H*)-one (**I**) in the presence of equimolar quantity of sodium ethoxide, and (*4*) 2-(3,5-dimethyl-pyrazol-1-yl)-6-methylpyrimidin-4(3*H*)-one (**IV**).

equilibrium mixture of tautomers **Ia** and **Ib** identified by the absorption bands in the spectrum of compound **I** with maxima at 230, 245 and 277 nm. The presence of the first band is caused by $\pi \rightarrow \pi^*$ transitions in the hydroxypyrazole ring, which is of aromatic nature, and of two other bands, by $n \rightarrow \pi^*$ transitions in pyrazolone and pyrimidine rings, respectively.



Ia **Ib**

The consideration of intensities of the bands at 230 (ε = 11460) and 245 (ε = 10850) nm indicates that the ratio of tautomers **Ia** and **Ib** in the mixture is nearly equimolar. The total number of tautomers in the solutions of oxopyrazolylpyrimidine **I** is confirmed by the positive result of the test for the two-component character of the system [11], based on the constancy (within the error) of the ratio of optical densities of two arbitrarily selected solutions at any wavelength (Table 1).

The addition of sodium ethoxide as a base to the equilibrium mixture of tautomers **Ia** and **Ib** produces

Table 1. Optical densities and their functions for the solutions of 6-methyl-2-(3-methyl-5-oxo-2,5-dihydropyrazol-1-yl)-pyrimidine-4(1*H*)-one **I** at the arbitrary wavelengths

Solution	Optical densities of solutions D_i at the wavelength λ, nm			
	230	245	280	300
1	0.6840	0.6716	0.7144	0.5143
2	0.9355	0.8996	0.9914	0.6882
3	1.2006	1.1367	1.2757	0.8794
4	1.4815	1.4089	1.5686	1.0862
D_{av}	1.0754	1.0292	1.1375	0.7920
Functions of optical density	Wavelength λ, nm			
	230	245	280	300
$D_1 - D_{av}$	–0.3914	–0.3576	–0.4231	–0.277
$D_2 - D_{av}$	–0.1399	–0.1296	–0.1461	–0.1038
$D_3 - D_{av}$	0.1252	0.1075	0.1382	0.0874
$D_4 - D_{av}$	0.4061	0.3797	0.4311	0.2942
$D_1 - D_{av}/(D_2 - D_{av})$	2.80	2.76	2.89	2.68
$D_2 - D_{av}/(D_2 - D_{av})$	1	1	1	1
$D_3 - D_{av}/(D_2 - D_{av})$	–0.89	–0.83	–0.94	–0.84
$D_4 - D_{av}/(D_2 - D_{av})$	–2.90	–2.93	–2.95	–2.83

substantial changes in the spectrum: the absorption band at 230 nm disappears completely while the band with the maximum at 277 nm undergoes bathochromic shift by 12 nm and achieves the position of the absorption band of model substance, 3,6-dimethyl-2-(3,5-dimethylpyrazol-1-yl)pyrimidin-4(3*H*)-one (**V**) (λ_{max} = 285 nm) (Fig. 3a). This circumstance convincingly indicates the shift of intermolecular equilibrium to the side of the tautomer (**Ia**) that is characterized by the 4-oxo-3,4-dihydro configuration of pyrimidine ring, and the isosbestic point near 261 nm which occurst in the spectra of the mixtures of compound **I** with sodium ethoxyde at different molar ratios (Fig. 3b) points to the cleavage of the hydrogen bond NH···O and the subsequent formation of the pseudoionized form **A**.

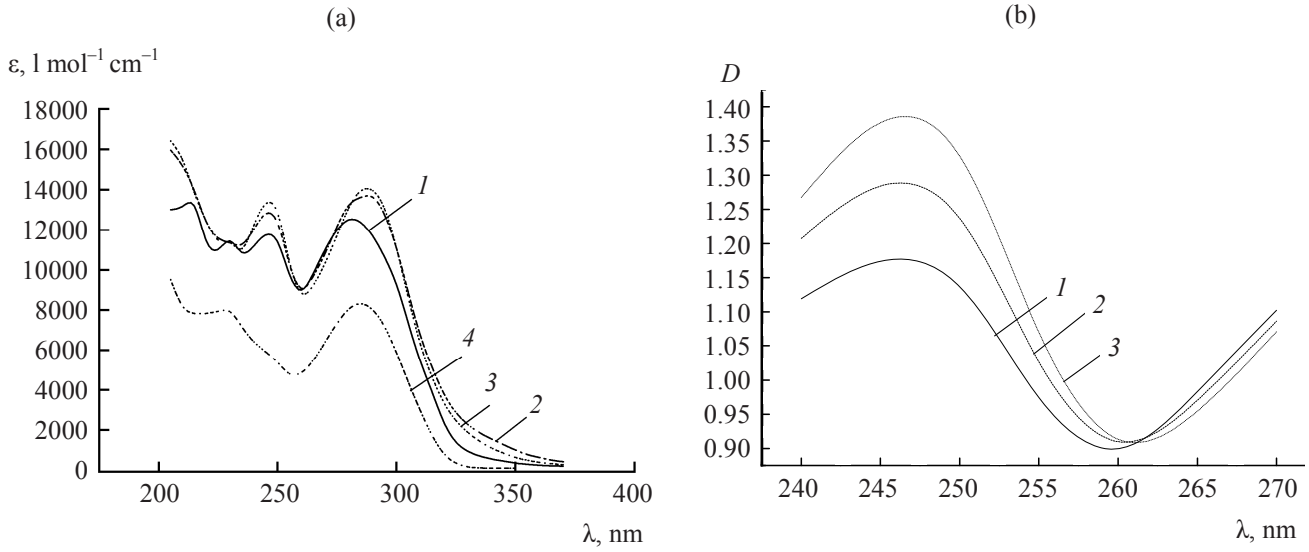
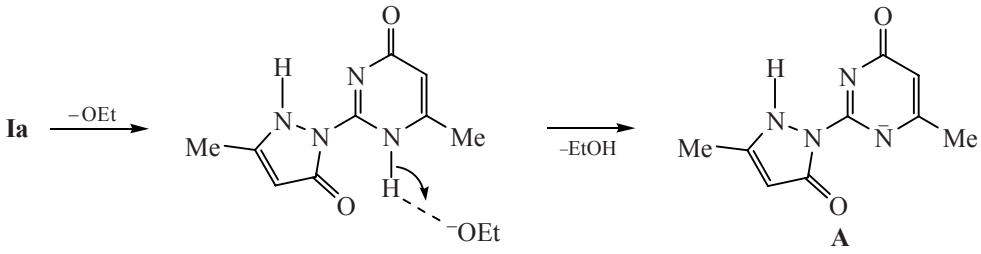
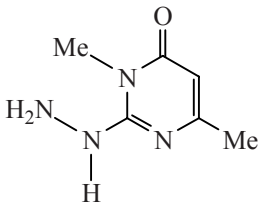


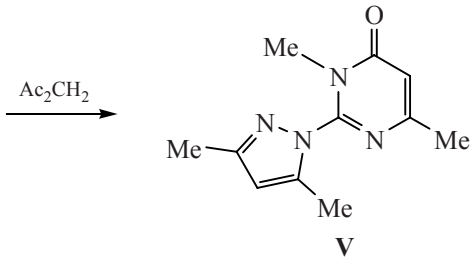
Fig. 3. (a) UV spectra of the mixtures of 6-methyl-2-(3-methyl-5-oxo-2,5-dihydropyrazol-1-yl)-pyrimidin-4(1*H*)-one (**I**) and sodium ethoxide in different molar ratios: (*1*) 1:0.23, (*2*) 1:0.58, (*3*) 1:0.91, and (*4*) of 3,6-dimethyl-2-(3,5-dimethylpirazol-1-yl) pyrimidin-4(3*H*)-one (**V**). (b) Isobestic point in the UV spectra of mixtures of 6-methyl-2-(3-methyl-5-oxo-2,5-dihydropyrazol-1-yl)-pyrimidin-4(1*H*)-one (**I**) and sodium ethoxide in different molar ratios: (*1*) 1:0.23, (*2*) 1:0.58, and (*3*) 1:0.91.



The model compound **V** was synthesized by the condensation of 2-hydrazino-3,6-dimethylpyrimidin-4(3*H*)-one **VI** with 2,4-pentanedione in 1-butanol under the conditions of water removal by the azeotropic distilliation.

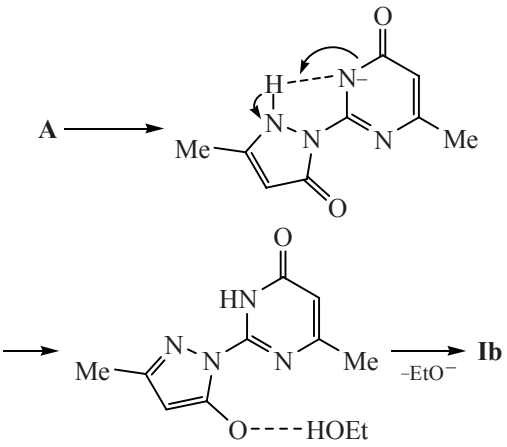


VI



V

The observed isosbestic point occurs in a narrow interval of the oxopyrazolylpyrimidine **I** and sodium ethoxide molar ratio, and this fact together with the increase in the optical density of the solutions of their mixtures at the increase in the molar content of the base indicates that the pseudoionized form **A** is protonated via the migration of the proton of pyrazole ring followed by formation of tautomer **Ib**:



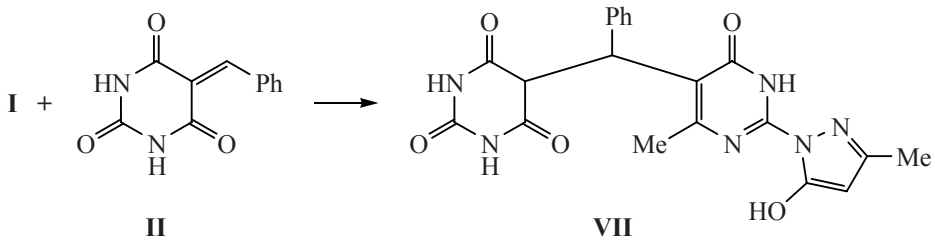
The retention of hydrogen bond NH···N is confirmed additionally by the similarity of the spectra of compound **I** in the presence of equimolar quantity of sodium ethoxide (λ_{max} 245, 289 nm) and of neutral form of pyrazolylpyrimidine **IV** (λ_{max} 242, 292 nm) (Fig. 2).

The break of the hydrogen bond NH···O is illustrated also by the shift of the band of the stretching vibrations of the pyrazole ring carbonyl group in the spectrum of the oxopyrazolylpyrimidine **I** monosodium salt by 10 cm^{-1} to the region of higher frequencies in comparison with the analogous band in the IR spectrum of the demetallated compound **I**.

Varying temperature does not affect noticeably the process of pseudoionization of oxopyrazolylpyrimidine **I**. The UV the spectra of the equimolar mixtures of compound **I** and sodium ethoxide recorded at the temperature of the mixture 25.5, 45.5, 55.3, and 65.1°C, are identical, and the difference in the molar absorption coefficients ε of the mixtures at the arbitrarily selected wavelength does not exceed 5% (Table 2). The revealed similarity of the spectra of the mixtures of compound **I** with sodium ethoxide indicates the invariability of the structure of the psevdoionized form **A** over a wide range of temperatures.

The pseudoionization of pyrimidine ring leads to an increase in its nucleophilicity that determines preferred addition of of benzylidenebarbituric acid **II** to the indicated CH-acidic center of oxopyrazolylpyrimidine **I** molecule. Actually, by the reaction of compounds **I** and **II** in boiling ethanol in the presence of an equimolar quantity of sodium ethoxide we obtained and isolated a single reaction product, (2,4,6-trioxo-1,2,3,4,5,6-hexahydropyrimidin-5-yl)[2-(5-hydroxy-3-methylpyrazol-1-yl)-6-methyl-4-oxo-3,4-dihydropyrimidin-5-yl]phenylmethane (**VII**).

The structure of bispyrimidylphenylmethane **VII** is confirmed by the ^1H NMR spectrum, which contains the characteristic [12] signal of the proton of exocyclic methine group at 5.9 ppm. Alongside the presence of



the signal of the proton at the C^5 atom of the trioxopyrimidine ring near 3.4 ppm, in the spectrum a signal is absent in the region of 6 ppm characteristic of the proton of the pyrimidine ring methine group in oxopyrazolylpyrimidine (**I**). At the same time the position of the signal of the proton at the C^4 atom of the pyrazole ring, which in the spectrum of compound **I** occurs at about 5.2 ppm, is changed considerably to appear at 7.3 ppm. Due to the ovelap of the signals of the methyl group protons and of solvent in the spectrum of bispyrimidylphenylmethane **VII** we registered the spectrum of this compound dissolved in deuterated trifluoracetic acid and established the equivalence of these signals and found their chemical shift, which equaled 3.30 ppm.

Compound **VII** is extremely instable even in neutral aqueous solutions. Already during suspending bispyrimidylphenylmetane **VII** in water it begins to partially decompose, and at boiling it undergoes complete irreversible degradation. By extracting the hydrolyzate with ethyl acetate and by the subsequent study of the compositions of aqueous and organic phases by TLC it was shown by comparison with reference compounds that the products of compound **VII** decomposition are pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione [R_f 0.82 (A)], oxopyrazolylpyrimidinone **I** [R_f 0.47 (A)], and benzaldehyde [R_f 0.43 (B)].

EXPERIMENTAL

The ^{1}H NMR spectra were registered on a Briker WM-400 spectrometer (operating frequency 400.13 MHz), solvent DMSO-d_6 [except 3,6-dimethyl-2-(3,5-dimetylpirazol-1-yl)pyrimidin-4(3*H*)-one **V**] (solvent $CDCl_3$), internal references were the signals of the residual protons of the solvents. The IR spectra were registered on a Shimadzu FTIR-8400S spectrophotometer from KBr tablets. The UV spectra were taken on a SF-26 spectrophotometer in the temperature-controlled quartz cells with the optical layer thickness 1 cm, in ethanol at the concentration of substances ~ 1×10^{-4} mol l^{-1}. For testing on the *n*-component composition were used solutions of 6-methyl-2-(3-methyl-5-oxo-2,5-dihydropyrazol-1-yl)-pyrimidin-4(1*H*)-one **I** of the following concentrations: 0.54×10^{-4} (solution 1), 0.74×10^{-4} (solution 2), $1.05\cdot10^{-4}$ (solution 3) and 1.28×10^{-4} (solution 4) mol l^{-1}. The individuality of compounds was monitored by the TLC on the Silufol UV-254 plates in the following systems: 1-butanol–acetic acid 1:1 + 5 drops of water (eluent A), acetone–heptane 2:3 (eluent B), 1-butanol–acetic acid–water, 1:1:1 (eluent C), 1-butanol–acetic acid, 1:1 + 2 drops of water (eluent D) and acetone–heptane, 2:1 (eluent E). Developing of the spots corresponding to compounds **I**–**VI** was achieved by UV irradiation, the spots of compound **VII** were developed by treatment

Table 2. Molar absorption coefficients of the mixtures of 6-methyl-2-(3-methyl-5-oxo-2,5-dihydropyrazol-1-yl)-pyrimidine-4(1*H*)-one **I** with sodium ethoxide at various temperatures and wavelengths

Temperature, °C	Molar absorption coefficients ε (l mol^{-1} cm^{-1}) at wavelength λ, nm			
	230	255	270	295
25.5	9468	9430	8865	12245
45.5	9921	9589	9281	12342
55.3	9835	9549	9281	12342
65.1	9752	9433	9244	12194

with iodine vapor followed by the UV irradiation of the chromatographic plate. Elemental analysis was carried out on a Leco CHNS-932 analyzer.

Commercial 5-benzylidenepyrimidinee-2,4,6-(1*H*,3*H*,5*H*)-trione **II** was purified by recrystallization from a mixture of anhydrous acetic acid and DMF (4:1), repeated washing with benzene, and drying at 80°C for 8 h.

2-Hydrazino-6-methylpyrimidin-4-(3*H*)-one **III** and 2-hydrazino-3,6-dimethylpyrimidin-4-(3*H*)-one **VI** were synthesized according to procedures [8] and [13] respectively.

The geometry optimization of the 6-methyl-2-(3-methyl-5-oxo-2,5-dihydropyrazol-1-yl)pyrimidin-4(1*H*)-one **I** molecule was carried out by the Fletcher-Reeves method with the use of the HyperChem™ Release 6.03 for Windows Molecular Modeling System.

6-Methyl-2-(3-methyl-5-oxo-2,5-dihydropyrazol-1-yl)-pyrimidin-4(1*H*)-one (I). A mixture of 1.26 g of hydrazinopyrimidine (**III**) and 1.17 g of ethyl acetoacetate in 30 ml of water was refluxed for 1 h. The precipitate formed on cooling was filtered off and recrystallized from water, and after drying at 80°C for 7 h was obtained 0.79 g (43%) of compound **I**, mp 203°C (published: mp 204°C [8]), R_f 0.45 (C). ^{1}H NMR spectrum, δ, ppm: 2.19 s (3H, Me), 2.23 s (3H, Me), 5.20 s (1H, CH), 5.96 s (1H, CH), 11.55 br.s (1H, NH).

2-(3,5-Dimethylpyrazol-1-yl)-6-methylpyrimidin-4(3*H*)-one (IV). A mixture of 1 g of hydrazinopyrimidine (**III**) and 0.71 g of 2,4-pentanedione was maintained at 120–130°C for 1 h. On cooling the hardened reaction mixture was ground with 5 ml of benzene, the precipitate was filtered off, washed with benzene, and dried in air. Dry product was recrystallized from water and after drying at 80°C for 7 h we obtained 0.57 g (39%) of compound (**IV**), mp 140°C (published data: mp 135–137°C [14]), R_f 0.73 (D). ^{1}H NMR spectrum, δ, ppm: 2.21 s (3H, Me), 2.25 s (3H, Me), 2.58 s (3H, Me), 6.11 s (2H, CH), 11.67 br.s (1H, NH).

3,6-Dimethyl-2-(3,5-dimethylpirazol-1-yl)pyrimidin-4(3*H*)-one (V). To a suspension of 0.5 g of *N*-methylhydrazinopyrimidine (**VI**) in 30 ml of anhydrous 1-butanol heated to 110°C was added 0.32 g of 2,4-pentanedione. The mixture was refluxed with the Dean–Stark trap for 2 h. After slow cooling the mixture was filtered to remove an insignificant amount of precipitate, and the filtrate was evaporated in a vacuum to dryness. The solid residue was recrystallized from cyclohexane, and 0.3 g (52%) of compound **V** was isolated. After drying in a vacuum mp 115°C, R_f 0.58 (E). ^{1}H NMR spectrum, δ, ppm: 2.26 s (3H, Me), 2.27 s (3H, Me), 2.34 s (3H, Me), 3.39 s (3H, MeN), 5.99 s (1H, CH), 6.29 s (1H, CH). Found, %: C 60.53; H 6.47; N 25.67.. $C_{11}H_{14}N_4O$. Calculated, %: C 60.47; H 6.21; N 25.09.

(2,4,6-Trioxo-1,2,3,4,5,6-hexahydropyrimidin-5-yl)[2-(5-hydroxy-3-methylpyrazol-1-yl)-6-methyl-4-oxo-3,4-dihydropyrimidin-5-yl]phenylmethane (VII). A mixture of 1.03 g of oxopyrazolylpyrimidine **I** and 1.08 g of benzylidenebarbituric acid **II** in 35 ml of anhydrous ethanol containing 0.37 g of sodium ethoxide was refluxed for 2 h. On cooling, the suspension was acidified by adding a calculated quantity of acetic acid, then stirred for 5 min, the prcipitate formed was filtered off and recrystallized twice from the glacial acetic acid. The purified product was boiled with 20 ml of anhydrous benzene and after drying in a high vacuum we obtained 0.43 g (20%) of compound **VII**, mp > 300°C, R_f 0.76 (C). The ^{1}H NMR spectrum, δ, ppm: 3.42 s (1H, CH), 5.88 s (1H, CH), 6.90–7.11 m (5H, the pHs), 7.34 m (2H, CH+OH). Found, %: C 55.16; H 3.70; N 18.23. $C_{20}H_{18}N_6O_5$. Calculated, %: C 56.87; H 4.30; N 19.90.

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