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Effect of the Structure of 1- and 3-Methylpyrimidin-4-ones on the Rate of Nucleophilic Substitution of the 2-Methylsylfanyl Group

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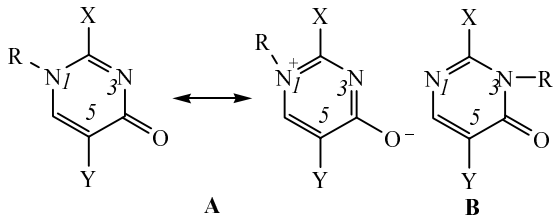
Abstract—Rate constants for substitution of the 2-methylsulfanyl group in 1- and 3-methyl-2-methylsulfanylpyrimidin-4-ones and their 5-fluoro analogs were measured in the reaction with butylamine, alkaline hydrolysis, and methanolysis. The rate of substitution in 1-methyl isomers having a zwitterionic structure is greater by a factor of ~2 than the rate of substitution in 3-methyl isomers with conjugated double bonds in the ring. The presence of a fluorine atom in position *5* accelerates nucleophilic substitution in 1-methyl isomers, while 5-fluoro-3-methyl-2-methylsulfanylpyrimidin-4-ones react at a lower rate than their 5-unsubstituted analogs. According to the NMR data, the reactions involve formation of a tetrahedral intermediate. Anchimeric effect of the methyl group on N^1 hampers attack by basic reagent on the C^6 atom.

Comparison of properties of the isomeric products formed by replacement of hydrogen on the N^1 and N^3 atoms of pyrimidinones or pyrimidinethiones by various groups or sugar residues attracts persistent interest of researchers. This concerns their stability [1], structure and conformation [2], fragmentation under electron impact [1, 3], physical properties [4], behavior under conditions of radiolysis [5] and electrolysis [6], chemical reactivity [7, 8], and biological activity [9]. Interest in biological activity of 1- and 3-isomers arises to a considerable extent from the fact that in natural bases glycosyl group is attached to N^1. Factors responsible for such a selective glycosylation still remain unclear [10]. The NH acidity of uracils (pyrimidine-2,4-diones) constitutes an important problem from the viewpoint of both chemistry and biology. Biological aspects of this problem include H-bonding [11] and activity of enzymes for which uracils are substrates [12, 13].

Unlike pyrimidin-2-ones and uracils, replacement of hydrogen at the nitrogen atom in pyrimidin-4-ones and fused systems containing a pyrimidin-4-one moiety leads to isomers **A** and **B**, which formally differ from each other by arrangement of double bonds in the ring:



A **B**

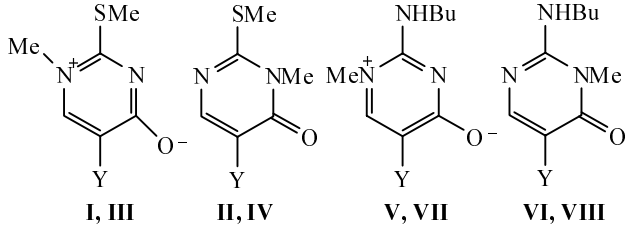
R = H, Me; X = H, AlkS, AlkO, AlkNH; Y = H, F.

As follows from the results of quantum-chemical calculations of tautomers **A** and **B** (R = H) [1, 14], isomers **B** are more stable (by ~8–11 kcal/mol). This is consistent with the known transformation of 1-methylpyrimidin-4-one **A** (R = Me, X = Y = H) into 3-methyl isomer **B** (R = Me, X = Y = H) on heating above 150°C [15]. According to the ^{13}C NMR data [16], zwitterionic structure of 1-methylpyrimidin-4-ones **A** (R = Me) predominates in solution. Presumably, this is the reason why potentially tautomeric compounds in organic solvents (where stabilization of the zwitterionic structure via solvation is weak) exist mainly as structures **B** (R = H) [16].

Up to now, no unambiguous interpretation was proposed for the different reactivities of isomers **A** and **B**. Theoretical assumptions are hardly valuable for solutions where substrates are capable of forming hydrogen bonds, while the available experimental data are scanty, some-

times contradictory, and mostly qualitative. Noncatalytic H–D exchange at C^2 in 1-methylpyrimidin-4-one in D_2O at 90–100°C is faster by a factor of 3 than analogous reaction with its 3-methyl isomer [17]. Under conditions of base catalysis, 5-fluoro-1-methylpyrimidin-4-ones readily exchange hydrogen at C^6 for deuterium, whereas 5-fluoro-3-methylpyrimidin-4-ones do not undergo H–D exchange under the same conditions [18]. The rates of exchange of alkylsulfanyl groups in the reactions of 1- and 3-methyl-2-methylsulfanylpyrimidin-4-ones with 2-(diethylamino)ethane-1-thiol in ethanol are similar, but they differ by an order of magnitude for the corresponding 5-fluoro derivatives [8]. Aminolysis of 3-methyl-2-methylsulfanylpyrimidin-4-one in pure methylamine smoothly occurs at room temperature and takes 4 days, whereas analogous reaction with 1-methyl-2-methylsulfanylpyrimidin-4-one requires heating for a weak at 65°C [19]. 2-Benzylsulfanyl-1,6-dimethylpyrimidin-4-one reacts with 2-aminoethanol (in the presence of the corresponding ammonium salt) in boiling ethanol. The reaction with its 3-methyl isomer occurs at 145–150°C [20]. On the other hand, 2-ethylsulfanyl-3,5-dimethylpyrimidin-4-one and 2-ethylsulfanyl-1,5-dimethylpyrimidin-4-one react with 2-aminoethanol in melt under approximately similar conditions, at 195 and 205°C, respectively [21]. Nucleophilic substitution at position *2* in isomeric 7-methylhypoxanthine derivatives is more facile when the pyrimidine ring therein has a *p*-quinoid structure [22].

In the present work we measured the rates of replacement of the 2-methylsulfanyl group in 1- and 3-methyl-2-methylsulfanylpyrimidin-4-ones **I** and **II** and their 5-fluoro analogs **III** and **IV** in the reaction with butylamine, alkaline hydrolysis, and methanolysis. The conditions were selected in such a way that the rate-determining stage involved neutral molecule of the substrate. Here, we took into account that the reactivities of isomers **I**, **II** and **III**, **IV** are difficult to compare in a medium where acid catalysis is possible: the isomers are characterized by different basicities but cations derived therefrom have similar structures [16].



I, III **II, IV** **V, VII** **VI, VIII**

Y = H (**I**, **II**, **V**, **VI**), Y = F (**III**, **IV**, **VII**, **VIII**).

Aminolysis with butylamine. The aminolysis of compounds **I**–**IV** with butylamine was carried out at 145°C in DMSO in the absence of butylammonium salt in order to avoid acid catalysis. The substrate-to-amine ratio was 1 : 100 (pseudofirst-order conditions), and the ratio of DMSO to butylamine was 2 : 1. All 2-butylamino derivatives **V**–**VIII** were isolated and purified, and their structure was confirmed by the NMR, UV, and IR spectra. The reaction rate was monitored by spectrophotometry. A sample of the mixture was diluted with an acid so that the substrate molecule remained neutral while the product was converted into the corresponding cation (Fig. 1). Spectrophotometric study of the reaction of all substrates **I**–**IV** with butylamine showed the absence of side processes. In all cases, the conversion was quantitative: the UV spectra recorded at $\tau=\tau_\infty$ corresponded to the theoretical concentration of the final product. The results of kinetic measurement are shown in Fig. 2. It is seen that the difference in the rates of aminolysis of 1- and 3-methyl isomers is small. Introduction of a fluorine atom into position *5* of the pyrimidine ring reduces the rate of aminolysis of the 3-methyl isomer by a factor of 2.

Alkaline hydrolysis. Products of alkaline hydrolysis of compounds **I**–**IV** are the corresponding uracils **IX**–**XII**. The reaction mechanism was studied previously [23] with 3-methyl-2-methylsulfanylpyrimidin-4-one (**II**) as an example. It was found that the reaction occurs in two steps through intermediate **C** (see Schemes 1 and 2). The rate-determining step is addition of hydroxide ion to

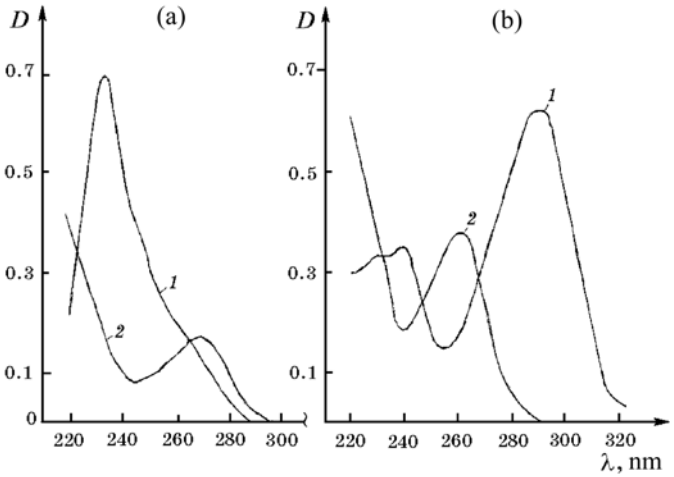


Fig. 1. UV spectra (a) of (*1*) 1-methyl-2-methylsulfanylpyrimidin-4(1*H*)-one and (*2*) 2-butylamino-1-methylpyrimidin-4(1*H*)-one in 0.01 N hydrochloric acid and (b) of (*1*) 5-fluoro-3-methyl-2-methylsulfanylpyrimidin-4(3*H*)-one and (*2*) 2-butylamino-5-fluoro-3-methylpyrimidin-4(3*H*)-one in 0.1 N hydrochloric acid.

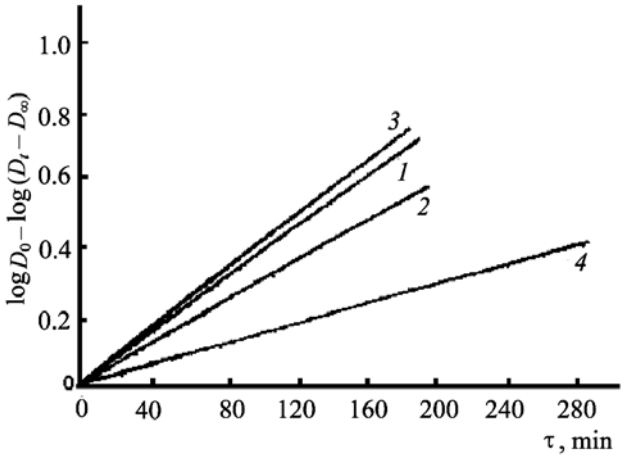


Fig. 2. Semilog kinetic curves for the aminolysis of (*1*)1-methyl-2-methylsulfanylpyrimidin-4(1*H*)-one (**I**), (*2*) 3-methyl-2-methylsulfanylpyrimidin-4(3*H*)-one (**II**), (*3*) 5-fluoro-1-methyl-2-methylsulfanylpyrimidin-4(1*H*)-one (**III**), and (*4*) 5-fluoro-3-methyl-2-methylsulfanylpyrimidin-4(3*H*)-one (**IV**) with butylamine in DMSO at 145°C; concentration, M: substrate, 1.1×10^{-4}, butylamine, 1.1×10^{-2}; $k_{ap} \times 10^{-5}$, s^{-1}: 19.6 (**I**), 11.4 (**II**), 20.9 (**III**), 5.49 (**IV**).

Scheme 1.

$$\mathbf{II} + OH^- \underset{k_2}{\overset{k_1}{\rightleftharpoons}} B \xrightarrow{k_3} \mathbf{XI} + CH_3S^-$$

The process is described by the following kinetic equation:

$$k_{ap} = k_1 [OH^-].$$

Tables 1 and 2 contain the apparent rate constants for hydrolysis of compounds **I**–**III**, depending on the alkali concentration and temperature. The process strictly follows the first-order kinetics. The catalytic second-order rate constants k_{OH} were determined from the slope of the linear dependence of $\log k_{ap}$ on the activity of hydroxide ions (a_{OH}), and the thermodynamic parameters were estimated from the $\log k_{ap}$–$1/T$ relation. According to the data in Tables 1 and 2, the rate of alkaline hydrolysis of 1-methyl isomer **I** is more than twice as high as that found for 3-methyl isomer **II**. Introduction of a fluorine atom into position *5* of the pyrimidine ring only slightly increases the reaction rate. The absence of side processes in the hydrolysis of compounds **I**–**III** is confirmed by almost quantitative yields of the corresponding uracils, which were calculated from the UV spectra, and by similarity of the spectral patterns observed for the reaction mixture (Fig. 3; d, e) and an artificial mixture consisting of the substrate and the product (Fig. 3; a, b). A different pattern was found for 5-fluoro-3-methyl-2-methylsulfanylpyrimidin-4-one (**IV**) (Fig. 3; c, f). Unlike artificial mixtures, the absorption intensity at λ 292 nm (corresponding to absorption maximum of the hydrolysis product) in the spectra of the reaction mixtures decreases with time, and the final spectrum (at $\tau = \tau_\infty$) corresponds to the spectrum of 5-fluoro-3-methyluracil (**XII**) anion formed in an amount of 60% of the theoretical value. Analogous transformation was observed for the UV spectrum of **IV** in a 0.1 N alkali solution kept for a long time at room temperature. Increase in the intensity of high-frequency absorption in the initial period cannot be attributed to methanethiolate ion, for such absorption was not observed in the hydrolysis of pyrimidinones **I**–**III**; moreover, the contribution of the entire theoretical amount of methanethiol to the above absorption could be no more than 30%.*

Table 1. Apparent (k_{ap}) and catalytic (k_{OH}) rate constants for hydrolysis of 1- and 3-methyl-2-methylsulfanylpyrimidin-4-ones **I** and **II** and 5-fluoro-1-methyl-2-methylsulfanylpyrimidin-4(1*H*)-one (**III**), 60°C, $I = 0.5$ M

Alkali concentration, M	pH[a]	$k_{ap} \times 10^4$, s^{-1}		
		I	**II**	**III**
0.049	11.31	4.43	1.82	5.95
0.097	11.48	9.32	4.03	11.97
0.147	11.55	13.40	5.73	18.17
0.198	11.65	19.17	8.28	26.50
0.298	11.78	26.50	12.50	41.67
0.395	11.98	37.83	16.73	–
$k_{OH} = k_{ap}/a_{OH}$, $l\ mol^{-1}\ s^{-1}$		6.29×10^{-3}	2.85×10^{-3}	9.5×10^{-3}

[a] At 60°C.

Table 2. Apparent rate constants for hydrolysis of 1- and 3-methyl-2-methylsulfanylpyrimidin-4-ones **I** and **II** and 5-fluoro-1-methyl-2-methylsulfanylpyrimidin-4(1*H*)-one (**III**) in a 0.145 N aqueous solution of sodium hydroxide at 45–70°C ($I = 0.5$ M) and parameters of the Arrhenius equation

Temperature, °C	$k_{ap} \times 10^4$, s^{-1}		
	I	**II**	**III**
70	25.2	13.4	35.5
60	13.4	5.7	18.8
50	6.4	2.7	9.4
45	4.5	1.5	6.3
E_a, kJ/mol	61.2	83.4	61.2
ln A	11.8	18.0	12.0

* UV spectrum of methanethiolate ion in H_2O: $\lambda_{max} = 238.5$ nm, $\varepsilon = 5045 \pm 200\ l\ mol^{-1}\ cm^{-1}$.

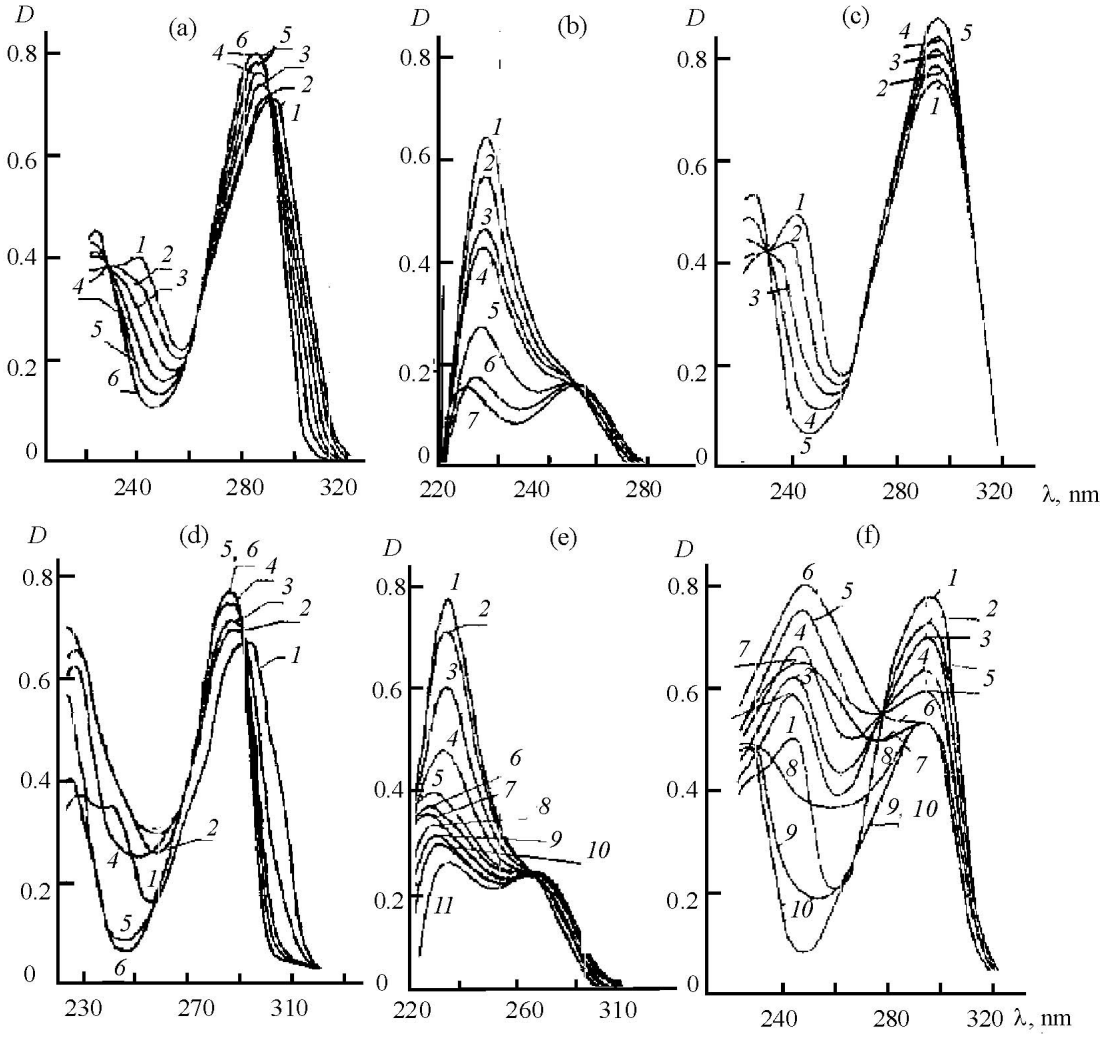


Fig. 3. UV spectra of (a–c) mixtures of pyrimidin-4-ones **II**–**IV** and uracils **X**–**XII** in 0.01 N NaOH and (d–f) reaction mixtures obtained from substrates **II**–**IV** in 0.1 N NaOH: (a) a mixture of 3-methyl-2-methylsulfanylpyrimidin-4(3*H*)-one (**II**) and 3-methyluracil (**X**); fraction of **II**, %: (*1*) 100, (*2*) 80, (*3*) 60, (*4*) 40, (*5*) 20, (*6*) 0; (b) a mixture of 5-fluoro-1-methyl-2-methylsulfanylpyrimidin-4(1*H*)-one (**III**) and 5-fluoro-1-methyluracil (**XI**); fraction of **III**, %: (*1*) 100, (*2*) 90, (*3*) 70, (*4*) 50, (*5*) 30, (*6*) 10, (*7*) 0; (c) a mixture of 5-fluoro-3-methyl-2-methylsulfanylpyrimidin-4(3*H*)-one (**IV**) and 5-fluoro-3-methyluracil (**XII**); fraction of **IV**, %: (*1*) 100, (*2*) 75, (*3*) 50, (*4*) 25, (*5*) 0; (d) 3-methyl-2-methylsulfanylpyrimidin-4(1*H*)-one (**II**); reaction time τ, min: (*1*) 0, (*2*) 7, (*3*) 30, (*4*) 40, (*5*) 100, (*6*) τ_∞; (e) 5-fluoro-1-methyl-2-methylsulfanylpyrimidin-4(1*H*)-one (**III**); τ, min: (*1*) 0, (*2*) 5, (*3*) 15, (*4*) 30, (*5*) 60, (*6*) 90, (*7*) 150, (*8*) 240, (*9*) 330, (*10*) 450, (*11*) τ_∞; (f) 5-fluoro-3-methyl-2-methylsulfanylpyrimidin-4(3*H*)-one (**IV**); τ, min: (*1*) 0, (*2*) 5, (*3*) 15, (*4*) 35, (*5*) 65, (*6*) 100, (*7*) 150, (*8*) 180, (*9*) 270, (*10*) τ_∞.

These findings suggest that, when the rate of hydrolysis of pyrimidinone **IV** is comparable with the rate of formation of 5-fluoro-3-methyluracil, an additional reaction product accumulates in the mixture. This product is then converted into one or more nonabsorbing species, i.e., those lacking specific absorption. According to the data of [24], unsubstituted uracil is fairly stable on heating in alkali, whereas 5-fluorouracil undergoes slow decomposition to give a nonabsorbing product (or products; $\tau_{0.5}$ = 50 h at 80°C in 0.2 N NaOH). Presumably, this transformation is the result of attack by hydroxide ion on the ring C^6 atom, elimination of hydrogen fluoride, and intermediate formation of barbituric acid; the pyrimidine ring in the latter is cleaved under these conditions. The formation of 1-methylbarbituric acid on heating of 5-bromo-3-methyluracil in alkali is explained in a similar way, and its low yield is attributed to slow decomposition to a nonabsorbing product [25]. In order to estimate the contribution of such transformations of 5-fluoro-3-methyluracil (**XII**) in the hydrolysis of pyrimidinone **IV**,

Table 3. Apparent rate constants for decomposition of 1-methyluracil (**IX**), 3-methyluracil (**X**), 5-fluoro-1-methyluracil (**XI**), and 5-fluoro-3-methyluracil (**XII**) in aqueous alkali at 80°C (substrate concentration $c = 7\times10^{-5}$ M, $I = 0.5$ M)[a]

Concentration of alkali, M	$k_{ap} \times 10^6$, s^{-1}			
	IX	**X**	**XI**	**XII**
0.09	[b]	0.45	4.42	6.14
0.43	0.39	1.21	12.80	16.43

[a] Uracil, $k_{ap} = 0.4\times10^{-6}$ s^{-1} (80°C, 0.2 N NaOH); 5-fluorouracil, $k_{ap} = 5.62\times10^{-6}$ s^{-1} (80°C, 0.6 N NaOH [24].

[b] The spectrum did not change over a period of 5 days.

Table 4. Apparent rate constants for decomposition of barbituric (**XIII**), 1-methylbarbituric (**XIV**), and 1,3-dimethylbarbituric acids (**XV**) in aqueous alkali at 80°C

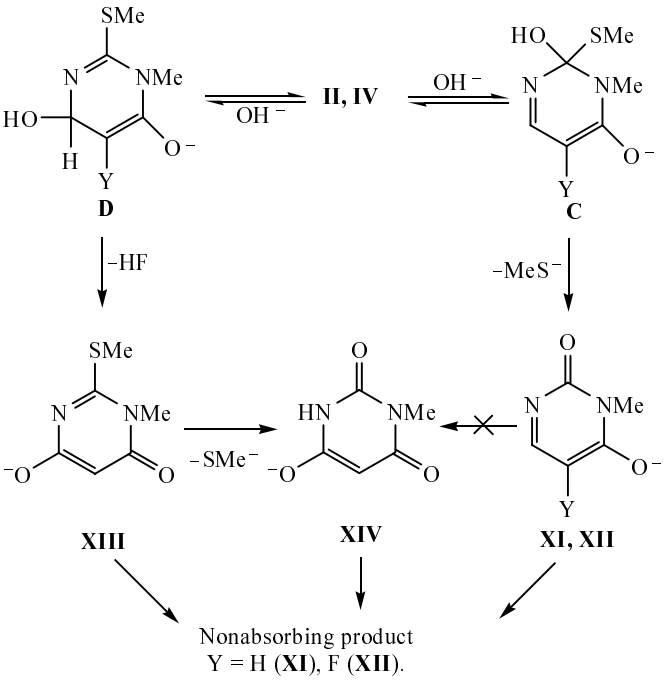
Concentration of alkali, M	$k_{ap} \times 10^5$, s^{-1}		
	XIII	**XIV**	**XV**
0.10[a]	9.33	9.75	1.93
0.43[a]	12.21	20.33	2.83
1.03	13.63	25.08	3.03

[a] The ionic strength was maintained constant at 0.5 M.

we measured the lifetimes of uracils **IX**–**XII** and barbituric acids **XIII**–**XV** (Tables 3, 4). Comparison of the data in Tables 1–4 and those reported in [24] shows that the rate of decomposition of *N*-methyl-substituted uracils **IX**–**XII** is much greater than the rate of decomposition of 5-unsubstituted uracil and 5-fluotouracil and that 1-methylbarbituric acid **XIV** is converted into a nonabsorbing product at a rate exceeding the rate of conversion of 5-fluoro-3-methyluracil (**XII**) by a factor of 12–15. Therefore, the low yield of uracil **XII** cannot be the result of its direct transformation into 1-methylbarbituric acid **XIV** during the hydrolysis of pyrimidinone **IV**. This means that the contribution of the **IV** > **XII** > **XIV** path (if it exists) is small (Scheme 2). Probably, a part of pyrimidinone **IV** is transformed into a nonabsorbing product at a rate comparable with the rate of formation of uracil **XII** via attack by hydroxide ion at the C^6 atom, followed by elimination of HF from intermediate **D** (see Scheme 2). Isomeric 1-methylpyrimidinone **III** is quantitatively converted into 5-fluoro-1-methyluracil (Fig. 3, e). This may be due to the fact that the rate of hydrolysis considerably exceeds the rate of HF elimination and/or due to anchimeric effect of the 1-methyl group, which hinders attack on C^6 by a base in side reaction. Attack by hydroxide ion or water on the C^6 atom in 3-methyl-2-methylsulfanylpyrimidin-4-one (**II**) to give tetrahedral complex like **D** is also possible; however, the latter is stable when no fluorine atom is present in position *5*, and it may play the role of a "depot" in the transformation of pyrimidinone **II** into 3-methyluracil. As shown below, attack by a base on C^6 of the pyrimidine ring is really possible.

Methanolysis of pyrimidin-4-ones I–IV. Unlike aqueous alkali, pyrimidinone **IV** is quantitative converted into 5-fluoro-3-methyluracil (**XII**) at room temperature in a methanolic solution of sodium hydroxide containing 10–15% of water (Fig. 4). According to the data of UV spectroscopy, the reaction involves an intermediate product whose rate of formation is greater by a factor of 35–40 than the rate of its subsequent transformation into uracil **XII** (at a substrate concentration of 10^{-5} to 10^{-4} M). This intermediate was also detected by TLC analysis of the reaction mixture with a substrate concentration of 10^{-2} to 10^{-1} M. Pyrimidinones **I**–**III** in methanolic alkali showed an analogous behavior. As follows from the NMR data, 2-methylsulfanylpyrimidinones **I**–**IV** are rapidly converted into 2-methoxy derivatives **XVI**–**XIX** which then give rise to the corresponding uracils. The different rates of the first and second reaction stages allowed us to isolate 2-methoxy derivatives **XVI**–**XIX** in preparative experiments which were carried out both in the presence of 10–15% of water and in the absence of it. Below are given the half-conversion periods for the transformation of compounds **I**–**IV** into 2-methoxy derivatives **XVI**–**XIX** in 90% CD_3OD containing 2 equiv of NaOD at 20°C (initial substrate concentration 0.11 M).

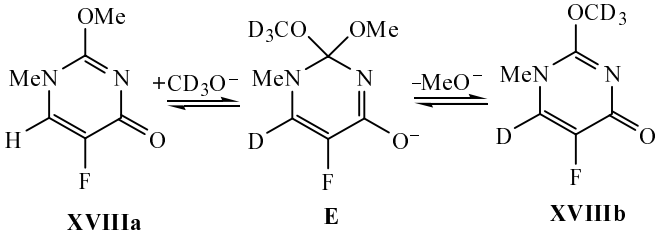
Scheme 2.



Compound no.	**I**	**II**	**III**	**IV**
$\tau_{0.5}$, min	4.0	7.6	2.8	11.0

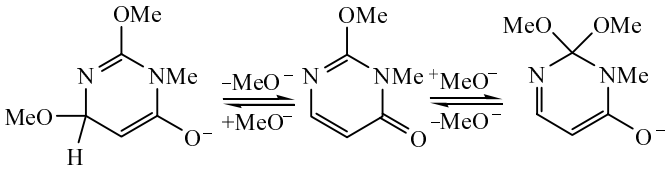
These data indicate approximately the same difference in the reactivities of 1- and 3-methyl isomers **I**–**IV** as that observed in the aminolysis with butylamine and alkaline hydrolysis (see above). The rate of methanolysis was measured by ^{1}H NMR spectroscopy, following variation in the intensity of signals from the *S*- and *N*-methyl groups, as well as from the ring protons. Deviation in the $\tau_{0.5}$ values determined with the use of the above parameters did not exceed 5%. When the reaction was complete, ^{13}C NMR spectra were recorded. They contained signals typical of pure compounds **XVI**–**XIX**. The 6-H signal of pyrimidinone **III** cannot be used in the determination of the reaction rate, for the 6-H proton is instantaneously replaced by deuterium at an alkali concentration of 0.2 M (cf. [18]). A very fast deuterium exchange at C^6 was also observed with 2-methoxy derivative **XVIII** in the same medium. In this case, the intensity of the 2-MeO signal (δ 4.0 ppm) decreased exponentially, while the 1-Me signal (δ 3.55 ppm) did not change its position and intensity; simultaneously, the signal from methanol (δ 3.38 ppm) increased in intensity. Addition of 1 equiv of a 5.8 M solution of $NaOCD_3$ to a solution of compound **XVIII** in DMSO-d_6 led to appearance in the ^{1}H NMR spectrum of a quartet signal from hydroxy proton at δ 4.10 ppm, $J(CH_3–OH) = 4.0$ Hz. We can conclude that H–D exchange at C^6 [18] in pyrimidinone **XVIIIa** is accompanied by replacement of the 2-methoxy group by CD_3O. The rate of replacement of the 2-methoxy group increases as the alkali concentration rises [k_{ap} (s^{-1}) = $-0.001 + 0.0099c_{NaOH}$ (M); $r = 0.99$]; at an alkali concentration of 0.2 M, the rate of methoxy group exchange

Scheme 3.



XVIIIa **E** **XVIIIb**

Scheme 4.



J **XVII** **I**

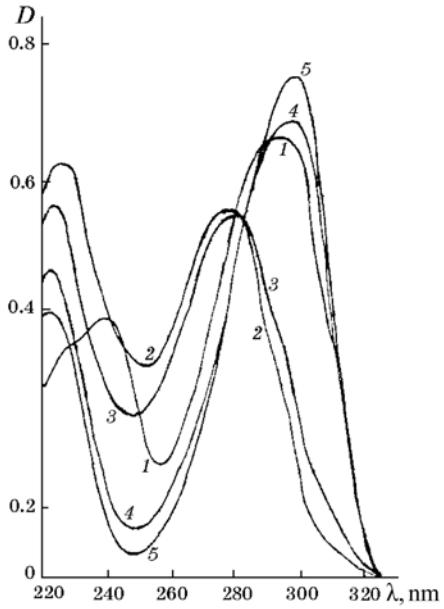


Fig. 4. UV spectra of the reaction mixture in the methanolysis of 5-fluoro-3-methyl-2-methylsulfanylpyrimidin-4(3*H*)-one (**IV**) in alcoholic (86% of methanol) alkali at 20°C after (*1*) 0, (*2*) 4.2, (*3*) 24, (*4*) 192, and (5) 408 h; $c_{NaOH} = 0.1$ M; $c_{IV} = 8.4 \times 10^{-5}$ M.

approaches the rate of methoxylation of substrate **III**, $\tau_{0.5} \approx 2.2$ min. Presumably, this is not an accidental coincidence, for the exchange process undoubtedly involves attack by CD_3O^- ion on the C^2 atom in **XVIIIa**, formation of tetrahedral complex **E**, and elimination of methoxide ion in excess methanol-d_4 (Scheme 3).

Table 5. Proton and carbon chemical shifts (δ and δ_C, ppm) in the NMR spectra of 2-methoxy-3-methylpyrimidin-4-one (**XVII**) and products of addition of 1 equiv of sodium methoxide (adducts **I** and **J**) in DMSO-d_6.

Parameter	C^2	C^4	C^5	C^6	NMe	OMe
2-Methoxy-3-methylpyrimidin-4-one (**XVII**)						
δ	–	–	6.05 [a]	7.71 [a]	3.27	3.95
δ_C	157.4	161.9	107.7	151.9	27.4	56.0
Adduct **I**						
δ	–	–	5.16 [b]	7.34 [b]	3.06	3.15
δ_C	99.5	165.9	95.9	155.6	26.6	48.6
Adduct **J**						
δ	–	–	[c]	[c]	[c]	[c]
δ_C	161.1	167.2	[c]	59.9	36.4	55.9 [d]

[a] $J_{5,6} = 6.5$ Hz.
[b] $J_{5,6} = 6.0$ Hz.
[c] Obscured by the signal of adduct **I**.
[d] 2-MeO group.

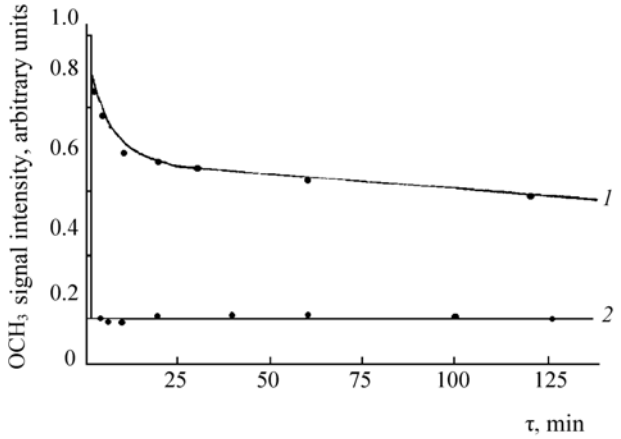


Fig. 5. Variation of the intensity of the methoxy group signal with time in the ^{1}H NMR spectrum of 2-methoxy-3-methylpyrimidin-4(1*H*)-one (**XVII**) in DMSO-d_6 after addition of one equivalent of (*1*) sodium methoxide and (*2*) sodium trideuteromethoxide.

We previously detected by the kinetic method formation of a tetrahedral intermediate in the alkaline hydrolysis of pyrimidinone **II**; it was also shown that its formation is the rate-determining stage [23]. In the present work we made an attempt to obtain spectroscopic proofs for the existence of intermediate **I** by prolonging its lifetime under conditions excluding its decomposition into the hydrolysis products (Scheme 4). After addition of an equivalent amount of sodium methoxide in DMSO-d_6 to substrate **XVII**, all its signals in the ^{1}H NMR spectrum decreased in intensity. Simultaneously, new signals appeared in the spectrum (Table 5), and their intensity attained 90% in several days at room temperature. A similar pattern was observed in a 1 : 1 mixture of dioxane-d_8 and DMSO-d_6. In analogous experiments with sodium trideuteromethoxide, the intensity of the MeO signal of substrate **XVII** (δ 3.95 ppm) almost instantaneously fell down to ~10% and it no longer changed (Fig. 5). Here, the overall intensity of the unresolved signals from the methoxy group in complex **I** and methoxide ion also remained unchanged (it corresponded to one equivalent). The intensities of signals from the other groups changed exponentially, regardless of whether CH_3ONa or CD_3ONa was added.

Interpretation of the above findings is not difficult, if we take into account that one equivalent of $NaOCD_3$ participates in the reaction and that OCH_3–OCD_3 exchange is a fast process while the equilibrium shifts toward tetrahedral complex **I** slowly. Also, a steric isotope effect is observed upon elimination of methoxy or drideuteromethoxy group from complex **I** [26]. Here, the equilibrium involves three kinds of adduct **I** molecules, i.e., those containing (1) two methoxy groups, (2) one methoxy and one trideuteromethoxy group, and (3) two trideuteromethoxy groups. The ^{13}C NMR spectra of the final reaction mixture contain weak signals from the substrate and new signals belonging to complex **I** (Table 5). In addition, we also observed signals which were assigned to complex **J** arising from attack by methoxide ion on C^6 in substrate **XVII**. According to the NMR data, analogous transformations occur with 5-fluoro-2-methoxy-3-methylpyrimidine-4(3*H*)-one (**XIX**) on addition of an equivalent amount of sodium methoxide to a solution of **XIX** in DMSO-d_6.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were measured on a Bruker DPX-300 spectrometer operating at 300 MHz for ^{1}H 300 and 75.47 MHz for ^{13}C. The UV spectra were recorded on SF-16, SF-8, and Hitachi 356 spectrophotometers. The IR spectra were obtained on an IKS-24 instrument. pH values were measured using a model 673 pH meter at 60.0±0.1°C in a cell equipped with an agar bridge filled with a solution of KCl. The pH meter was preliminarily calibrated against standard buffer solutions at 60°C (phosphate buffer, pH 6.84; borate buffer, pH 8.96). The pH values were measured before and after kinetic experiment, the deviation did not exceed 0.05 pH units. In experiments performed below 80°C, a water thermostat was used, and in experiments performed at 145°C, a glycerol thermostat.

Kinetic study of the aminolysis of pyrimidinones I–IV with butylamine. Butylamine, 1.1 ml (11 mmol), was added to a solution of 0.11 mmol of compound **I**–**IV** in 2.2 ml of DMSO. A 165-μl sample of the mixture was kept at (145.0±0.1)°C. A 2:1 mixture of DMSO with butylamine (as reference solution) was kept under the same conditions. After cooling, the contents of the ampule were washed off with hydrochloric acid into a volumetric flask, and the solution was adjusted to a spectrophotometric concentration (0.01 M for compounds **I** and **II** and 0.1 M for compounds **III** and **IV**) by addition of hydrochloric acid. The rate of the aminolysis was monitored following the disappearance of UV absorption at λ 298 nm for compound **II,** 312 nm for **IV**, and 240 nm for **I** and **III**. The plot of $\log[D_0/(D_\tau - D_\infty)]$ versus time was linear up to $3\tau_{0.5}$.

Butylamine of analytical grade was dried over sodium hydroxide and distilled over a fresh portion of sodium hydroxide through a column; a fraction with bp 78°C,

$n_D^{20} = 1.405$, was collected. Dimethyl sulfoxide of chemically pure grade was purified over zeolites and distilled; a fraction with bp 85–87°C (25 mm) was collected; the concentration of water in DMSO was checked by ^{1}H NMR spectroscopy.

Kinetic study of the alkaline hydrolysis of 1- and 3-methyl-2-methylsulfanylpyrimidin-4-ones I and II and their fluorinated analogs III and IV. The kinetic measurements were performed by spectrophotometry at 60.0±0.1°C. For determination of the thermodynamic parameters, the measurements were performed at 40–70°C. Quartz cells with ground caps were filled with a solution of alkali (3 ml) and were maintained at a constant temperature (using a water thermostat). A concentrated substrate solution, 5 μl, was added to a final concentration of 8.7×10^{-5} M for 1-methyl isomers or 4.9×10^{-4} M for 3-methyl isomers. The concentration of alkali solutions was checked by titration. The ionic strength was maintained at 0.5 M by adding a required amount of NaCl. The rate of hydrolysis was determined from decrease in the UV absorption intensity at λ 233, 308, and 235 nm for compounds **I**–**III**, respectively. The analytical wavelengths were selected in such a way that the absorption of the hydrolysis products be minimal. All experiments were performed until the optical density no longer changed; this final value was taken as $D_?$. The apparent rate constants k_{ap} were calculated by the formula:

$$k_{ap} = [\ln D_0/(D\tau - D_\infty)]/\tau.$$

Only those k_{ap} values were taken into consideration, for which the spread did not exceed 5%. The time dependence of $\log D_0 - \log(D\tau - D_\infty)$ was linear up to $5\tau_{0.5}$, which confirmed pseudofirst-order of the reaction. The catalytic second-order rate constants k_{OH} were determined from the slope of the linear plot of $\log k_{ap}$ versus activity of hydroxide ions a_{OH}, which was calculated by the equation $p_{OH} = pK_w - pH$. The value $K_w = 9.619\times10^{-14}$ (60°C, NaCl solution) was taken from [27]. pH values at 60°C were measured with the aid of a glass electrode.

Kinetic study of the decomposition of barbituric acids XIII–XV in 0.1–1.0 M solutions of alkali. Experiments were performed in a similar way at 80°C. The rate of decomposition was estimated from the decrease in the UV absorption intensity at λ 260 nm.

Kinetic study of the decomposition of 1- and 3-methyl uracils IX and X and their 5-fluoro analogs XI and XII. Solutions of methyluracils with a concentration of 7×10^{-5} M in 0.09 and 0.41 M alkali solutions were placed in ampules which were sealed and kept at 80°C. Reference solutions were kept under the same conditions. The rate of decomposition was determined from the decrease in the optical density at $\lambda = \lambda_{max}$.

Kinetic study of the methanolysis of pyrimidin-4-ones I–IV. Experiments were performed in NMR ampules. A required amount of the substrate was dissolved in methanol-d_4 to a concentration of 0.11 M. The initial spectrum was recorded relative to DSS as internal standard. A solution of 2 equiv of NaOD in D_2O was then added so that the final solution contained 90% of methanol-d_4. After addition of NaOD/D_2O, the ampule was shaken, and this moment was assumed to be the initial one (no more than 1 min elapsed until the first spectrum was recorded). The rate of the methanolysis was determined from the variation of intensities of signals from the ring protons, as well as from the NMe and SMe groups, relative to the DSS signal intensity.

Sodium metoxide and sodium trideuteromethoxide were prepared by removal of methanol or methanol-d_4 from the corresponding solutions on heating under reduced pressure. The dry residue (which was preliminarily kept in a vacuum desiccator over calcium chloride) was dispersed in DMSO-d_6 until saturation, and the undissolved material was separated by centrifugation. The concentration of sodium methoxide (trideuteromethoxide) in the supernatant was determined by titration.

The synthesis and properties of 1- and 3-methyl-2-methylsulfanylpyrimidin-4-ones **I** and **II**, their 5-fluoro analogs **III** and **IV**, and 1- and 2-butylamino-3-methylpyrimidin-4-ones **V** and **VI** were reported by us previously [16]. Methyluracils **IX**–**XII** were synthesized by acid hydrolysis of the corresponding 2-methylsulfanylpyrimidin-4-ones: 1-methyluracil (**IX**), mp 231–232°C (from water); published data [28]: mp 231°C; 3-methyluracil (**X**), mp 179°C (from ethanol); published data [28]: mp 179°C; 5-fluoro-1-methyluracil (**XI**), mp 257–258°C (from water); published data [29]: mp 263–264°C; 5-fluoro-3-methyluracil (**XII**), mp 194°C (from 50% ethanol); published data [29]: mp 190–191°C. 1-Methylbarbituric acid (**XIV**) was obtained by condensation of *N*-methylurea with diethyl malonate, mp 131–132°C (from ethanol); published data [30: mp 132°C. 1,3-Dimethylbarbituric acid (**XV**) was synthesized by condensation of *N*,*N*'-dimethylurea with diethyl malonate, mp 123°C (from benzene); published data [30]: mp 123°C. Barbituric acid of analytical grade had mp 245°C (from water).

2-Butylamino-5-fluoro-1-methylpyrimidin-4(1*H*)-one (VII). A mixture of 1.15 mmol of 5-fluoro-1-

methyl-2-methylsulfanylpyrimidin-4(1*H*)-one and 11.5 mmol of butylamine was heated for 4 h at 145–150°C under argon in a sealed ampule. Excess butylamine was distilled off under reduced pressure, and the residue was recrystallized from water. Yield 29%, mp 156°C. IR spectrum: νNH 3420, 3250 cm^{-1}. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 7.73 d (1H, 6-H), 6.97 s (1H, NH), 3.29 c (3H, NCH_3). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 152.1 s (C^2), 162.6 d (C^4), 142.65 d (C^5), 128.6 d (C^6), 37.8 s (NCH_3), 19.6 s and 13.8 s (Bu). UV spectrum: 0.1 N HCl: λ_{max} 276 nm (log ε = 3.74); 0.1 N NaOH: λ_{max} 275.5 nm (log ε = 3.56). Found, %: N 21.0. $C_9H_{14}FN_3O$. Calculated, %: N 21.1.

2-Butylamino-5-fluoro-3-methylpyrimidin-4(3*H*)-one (VIII) was synthesized as described above for 1-methyl isomer **VII**; the mixture was heated for 18 h. Yield 27%, mp 113–115°C (from cyclohexane). IR spectrum: νNH 3334 cm^{-1}. ^1H NMR spectrum (DMSO-d_6), δ, ppm: 7.73 s (1H, 6-H), 7.05 s (1H, NH), 3.24 s (3H, NCH_3). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 151.4 s (C^2); 155.4 d (C^4); 142.3 d (C^5); 136.80 d (C^6); 31.8 s (NCH_3); 30.8 s, 28.0 s, 19.65 s, and 13.8 s (Bu). UV spectrum: 0.1 N HCl: λ_{max} 269.5 nm (log ε = 3.55); 0.1 N NaOH: λ_{max} 300 nm (log ε = 3.78). Found, %: N 21.1. $C_9H_{14}FN_3O$. Calculated, %: N 21.1.

1- and 3-Methyl-2-methoxypyrimidin-4-ones and their 5-fluoro analogs (*general procedure*). To a solution of 2.2 mmol of pyrimidinone **I**–**IV** in 15 ml of methanol we added 4.4 mmol of sodium (as a 2.8 M solution in methanol), and the mixture was kept for several hours at room temperature, the progress of the reaction being monitored by TLC (following the disappearance of the initial pyrimidinone). The mixture was neutralized with a 1:1 mixture of hydrochloric acid and methanol, and methanol was distilled off under reduced perssure at room temperature. The dry residue was treated with chloroform or methylene chloride, the extract was passed through a column charged with silica gel (Merck H-60), and the solvent was removed at room temperature.

2-Methoxy-1-methylpyrimidin-4(1*H*)-one (XVI). Yield 75%, mp 144–145°C. ^1H NMR spectrum (CD_3OD), δ, ppm: 7.67 d (1H, 6-H), 6.05 d (1H, 5-H), 4.01 s (3H, OCH_3), 3.55 s (3H, NCH_3). ^{13}C NMR spectrum (CD_3OD), δ_C, ppm: 175.9 s (C^4), 159.5 s (C^2), 147.3 s (C^6), 108.3 s (C^5), 59.2 s (OCH_3), 38.8 s (NCH_3). Found, %: C 51.2; H 5.4; N 19.8. $C_6H_8N_2O_2$. Calculated, %: C 51.4; H 5.7; N 20.0.

2-Methoxy-3-methylpyrimidin-4(3*H*)-one (XVII). Yield 80%, mp 92–95°C; published data [31]: mp 92–95°C. ^1H NMR spectrum (D_2O), δ, ppm: 7.80 d (1H, 6-H), 6.24 d (1H, 5-H), 4.05 s (3H, OCH_3), 3.41 s (3H, NCH_3). ^{13}C NMR spectrum (D_2O), δ_C, ppm: 168.3 s (C^4), 160.8 s (C^2), 155.7 s (C^6), 109.9 s (C^5), 59.1 s (OCH_3), 30.9 s (NCH_3).

5-Fluoro-2-methoxy-1-methylpyrimidin-4(1*H*)-one (XVIII). Yield 71%, mp 178–180°C. ^1H NMR spectrum (D_2O), δ, ppm: 7.84 d (1H, 6-H), 4.00 s (3H, OCH_3), 3.52 s (3H, NCH_3). ^{13}C NMR spectrum (D_2O), δ_C, ppm: 168.2 d (C^4), 156.0 s (C^2), 144.6 d (C^5), 131.5 d (C^6), 57.0 s (OCH_3), 38.2 s (NCH_3). Found, %: C 45.4; H 4.4; N 17.45. $C_6H_7FN_2O_2$. Calculated, %: C 45.6; H 4.4; N 17.7.

5-Fluoro-2-methoxy-3-methylpyrimidin-4(3*H*)-one (XIX). Yield 81%, mp 125–127°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 7.6 d (1H, 6-H), 4.07 s (3H, OCH_3), 3.44 s (3H, NCH_3). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 156.35 d (C^4), 152.9 s (C^2), 146.1 d (C^5), 133.7 d (C^6), 55.8 s (OCH_3), 28.4 s (NCH_3). Found, %: C 45.6; H 4.9; N 17.5. $C_6H_7FN_2O_2$. Calculated, %: C 45.6; H 4.4; N 17.7.

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