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Ring Opening in 1- and 3-Methylpyrimidin-4-ones in the Presence of Bases

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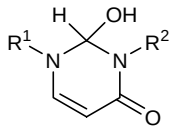
Abstract—According to the data of UV and NMR spectroscopy, 1- and 3-methylpyrimidin-4-ones and their 5-fluoro-substituted analogs in water and DMSO in the presence of bases undergo ring opening with formation of β-formylaminoacrylamide derivatives. The process involves attack by hydroxide ion on the C^2 atom, and its rate in DMSO is higher than in water by three orders of magnitude. Ring opening in 1-methylpyrimidin-4-ones occurs more readily than in the corresponding 3-methyl isomers, while the acyclic products formed from 3-methylpyrimidin-4-ones in DMSO are more stable than those derived from 1-methylpyrimidin-4-ones.

Although pyrimidin-4-ones, some of which exhibit physiological activity [1], have been extensively studied in the past decades [2], only a few data are available on their behavior in the presence of bases. It was reported [3] that 1,4(3,4)-dihydro-1,2,3,5-tetramethyl-4-oxopyrimidinium iodide undergoes hydrolysis to methylamine and organic acids on heating in a boiling 5 M solution of sodium hydroxide. Study of deuterium exchange of 2-H in 3-methylpyrimidin-4-one showed that this compound is slowly hydrolyzed in a 0.3 M solution of NaOH in D_2O at 90°C and that its quaternary salt decomposes at a comparable rate in D_2O at 95°C [4]. According to the kinetic data for bromination at C^5, 1- and 3-methylpyrimidin-4-ones in aqueous solution are converted by 3×10^{-4}% into covalent hydrates **Ia** and **Ib** which are formed from the corresponding cations [5]. The same authors also reported on irreversible opening of the heteroring in covalent hydrate **Ic** obtained from the quaternary salt, presumably with formation of β-formylaminoacrylamide derivative [5, 6]. The ring opening is catalyzed by bases, and the half-conversion period is 350 s at pH 8.7 (30°C).



Ia–Ic

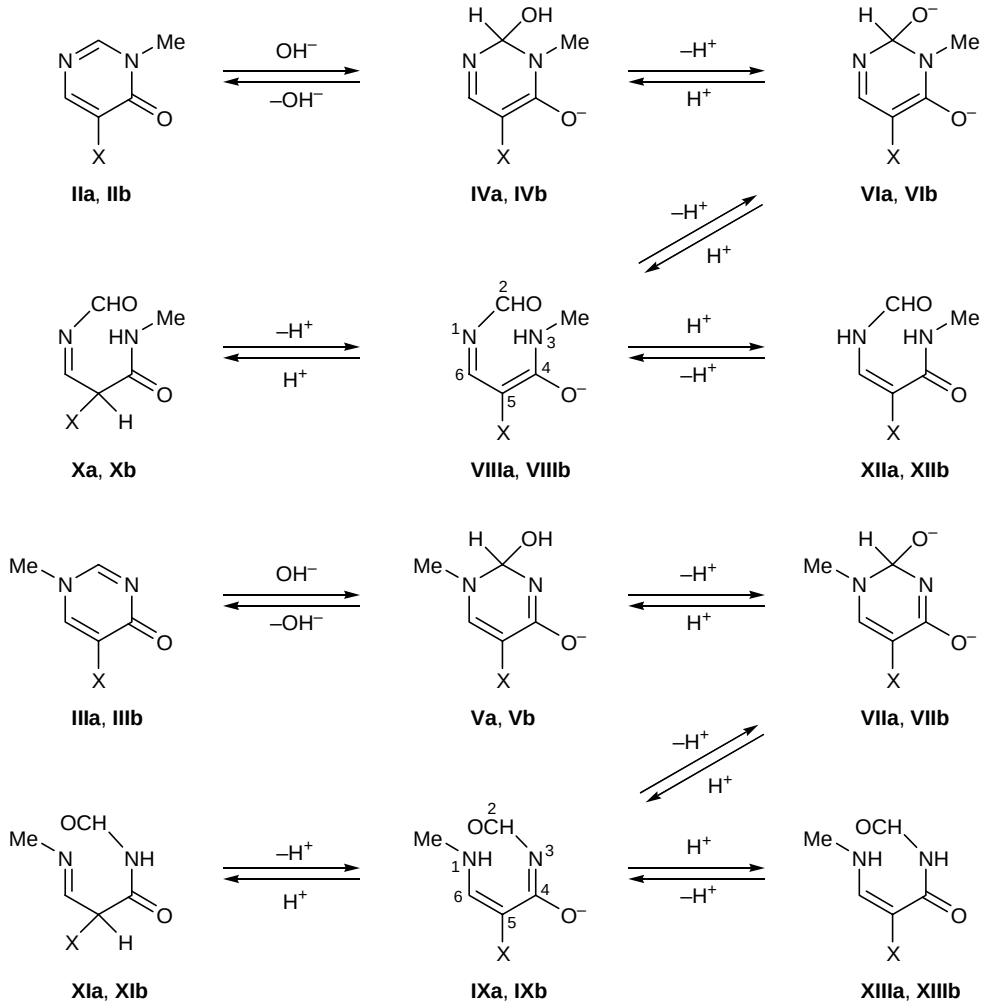
R^1 = Me, R^2 = H (**a**); R^1 = H, R^2 = Me (**b**); R^1 = R^2 = Me (**c**).

While studying base-catalyzed H–D exchange at C^6 in 1- and 3-methyl-5-fluoropyrimidin-4-ones [7], we have found that their UV spectra, as well as the UV spectra of 1- and 3-methylpyrimidin-4-ones in dilute sodium hydroxide solution, slowly and irreversibly change at room temperature. The reason for such spectral changes was not clear, taking into account that the above pyrimidin-4-ones (unlike their quaternary salts) were believed to be stable in media where the concentration of the corresponding cations (which are sensitive to nucleophilic attack) is negligible.

Therefore, we performed a more detailed study of the behavior of these compounds in the presence of bases by UV and NMR spectroscopy. The results of this study are the subject of the present article. The examined compounds were 3-methylpyrimidin-4-one (**IIa**), 5-fluoro-3-methylpyrimidin-4-one (**IIb**), 1-methylpyrimidin-4-one (**IIIa**), and 5-fluoro-1-methylpyrimidin-4-one (**IIIb**) (Scheme 1).

The UV spectra of pyrimidinones **IIa**, **IIb**, **IIIa**, and **IIIb** in a 0.1 M methanolic solution of sodium hydroxide or sodium methoxide at room temperature did not change over a period of tens hours. In the spectra of pyrimidinones **IIa** and **IIb** in aqueous alkali with the same concentration, we observed slow (k_{ap} = 1.8×10^{-6} and 14.1×10^{-6} s^{-1}, respectively) increase in

Scheme 1.



X = H (**a**), F (**b**).

the optical density with simultaneous blue shift of the absorption maximum by 4–6 nm (Fig. 1). Under analogous conditions, the band with its maximum at λ 241 nm disappeared from the UV spectrum of pyrimidinone **IIIa** ($k_{ap} = 3.5\times10^{-6}$ s^{-1}), and a new band appeared at λ 267 nm and attained approximately the same intensity (Fig. 2). The shape and position of the latter resemble the corresponding parameters of the band observed in the UV spectrum of the transformation product (or products) of compound **IIa**. In the case of pyrimidinone **IIIb**, some concurrent processes become appreciable, so that the intensity of the resulting band (λ_{max} 267 nm) progressively falls down. These processes are observed for all compounds in concentrated aqueous solutions (0.35 mol/l) containing 2 equiv of alkali, where the rate of transformation is higher by a factor of 20–30: the intensity of the new band in the UV spectra attains some maximal value and then begins to decrease.

Addition of sodium methoxide to solutions of pyrimidinone **IIa** or **IIb** in DMSO containing 2–3% of methanol (or in the absence of it) leads to fast and irreversible emergence of strong UV absorption bands at λ_{max} 297 (ε = 29570) and 304 nm (ε = 22000), respectively. These bands no longer change over a period of tens hours. After neutralization with 5 M hydrochloric acid, they are replaced by new bands with their maxima at λ 267 (ε = 30000) and 270 nm (ε = 23000), respectively. Addition of a new portion of sodium methoxide to the neutral solution restores the initial pattern (Fig. 3). The same effect was observed when a concentrated aqueous solution of sodium or tetramethylammonium hydroxide was added to a solution of **IIa** or **IIb** in DMSO. It should be noted that, in

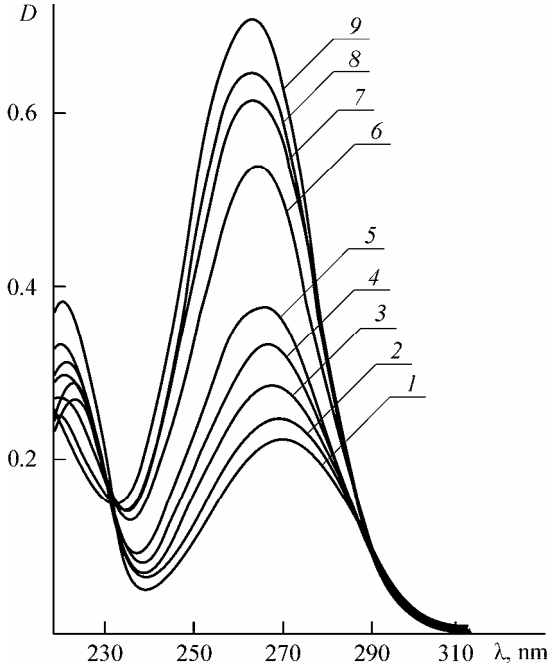


Fig. 1. Variation of the UV spectrum of 3-methylpyrimidin-4-one (**IIa**) ($c = 5.9\times10^{-5}$ M) in a 0.1 M aqueous solution of NaOH at room temperature: (*1*) initial spectrum and spectra recorded after (*2*) 6, (*3*) 26, (*4*) 48, (*5*) 72, (*6*) 142, (*7*) 192, (*8*) 240, and (*9*) 310 h.

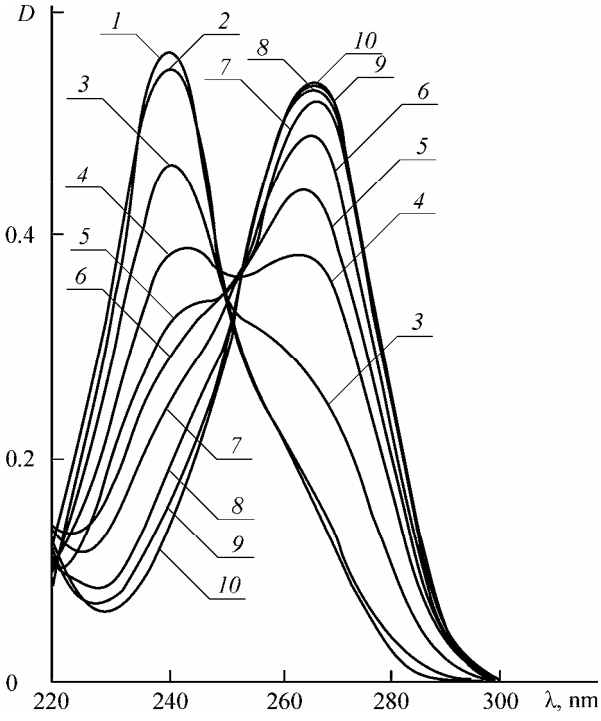


Fig. 2. Variation of the UV spectrum of 1-methylpyrimidin-4-one (**IIIa**) ($c = 4.1\times10^{-5}$ M) in a 0.1 M aqueous solution of NaOH at room temperature: (*1*) initial spectrum and spectra recorded after (*2*) 3, (*3*) 24, (*4*) 48, (*5*) 72, (*6*) 96, (*7*) 120, (*8*) 144, (*9*) 192, and (*10*) 240 h.

contrast to sodium methoxide, NaOH and Me_4NOH do not dissolve in DMSO completely; therefore, their effective concentration is less than 0.1 M.

Unlike pyrimidinones **IIa** and **IIb**, the results of the reaction of isomeric compounds **IIIa** and **IIIb** with sodium methoxide strongly depend on the concentration of methanol in dimethyl sulfoxide. Addition of sodium methoxide (0.07 M) to their solutions in DMSO induces almost instantaneous disappearance of the absorption bands belonging to the initial pyrimidinones. In the presence of 3% of methanol, compound **IIIb** behaves similarly, but in the spectrum of 1-methylpyrimidin-4-one (**IIIa**) a band with its maximum at λ 293 nm appears and then gradually disappears ($\tau_{0.5} \approx 14$ min); at a methanol concentration of 2%, the lifetime of this band shortens ($\tau \approx 5$ min). Addition of sodium methoxide to a solution of 5-fluoro-1-methylpyrimidin-4-one (**IIIb**) in DMSO containing 10% of methanol gives rise to a strong band with its maximum at λ 304 nm, which disappears with time ($k_{ap} = 9.4\times10^{-4}$ s^{-1}, $\tau_{0.5} = 12.3$ min; Fig. 4); under analogous conditions, in the spectrum of pyrimidinone **IIIa** a band appears at λ_{max} 294.5 nm ($\tau_{0.5} = 105$ min), and the absorption maximum gradually shifts to 272 nm. In the UV spectrum of a solution of **IIIb** in DMSO in the presence of 20% of methanol we observed initial appearance of a band with its maximum at λ 305 nm, subsequent increase in the absorption intensity at λ_{max} 277 nm ($\tau_{0.5} = 20$ min), and disappearance of the latter ($\tau_{0.5} = 400$ min); in the spectrum of **IIIa**, a band at λ_{max} 270 nm slowly increased in intensity ($\tau_{0.5} = 40$ h) and then disappeared even more slowly. The observed patterns resemble the behavior of these compounds in aqueous alkali (Fig. 2).

We believe that the strong long-wave absorption bands appearing in the UV spectra of 3-methylpyrimidin-4-ones and 1-methylpyrimidin-4-ones in the presence of bases belong to the corresponding open-chain anions, **VIII** and **IX**, respectively (Scheme 1). These anions could be formed as a result of attack by hydroxide ion on the C^2 atom in pyrimidinones **II** and **III**. Cleavage of the C^2–N^1 or C^2–N^3 bond is likely to be determined by the stability of anion **VIII** or **IX**, which depends on the degree of charge delocalization in the open-chain system. Unlike 3-methyl-substituted compounds **II**, the conjugation chain in anions **IXa** and **IXb** derived from 1-methylpyrimidin-4-ones **III** is shorter, regardless of the C^2–N bond being broken. Therefore, the lower stability of anions **IXa** and **IXb** may be attributed to localization of the negative charge. Anions **VIII** and **IX** are readily protonated

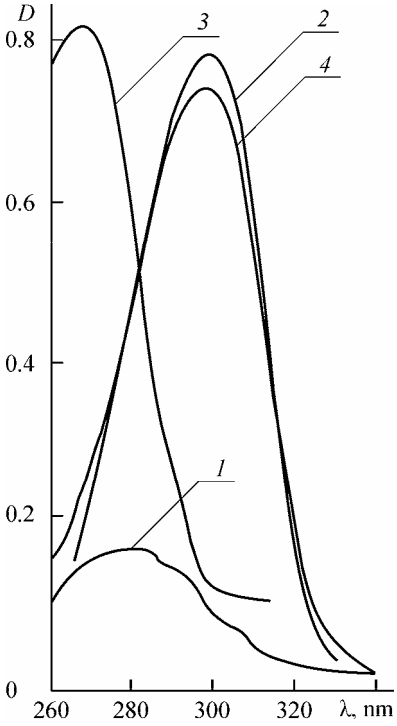


Fig. 3. Variation of the UV spectrum of 3-methylpyrimidin-4-one (**IIa**) ($c = 3\times10^{-5}$ M) in a DMSO solution containing 0.09 mol/l of sodium methoxide at 20°C: (*1*) before addition of NaOMe, (*2*) 5 min after addition, (*3*) after neutralization with 5 M hydrochloric acid, and (*4*) after addition of a new portion of sodium methoxide.

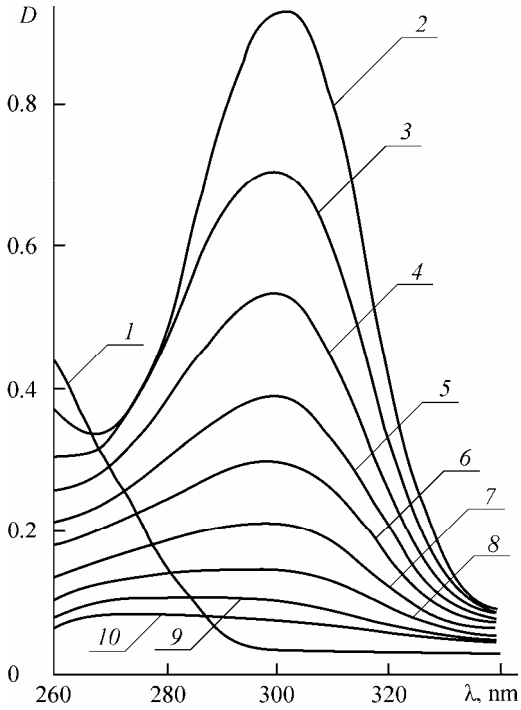


Fig. 4. Variation of the UV spectrum of 5-fluoro-1-methylpyrimidin-4-one (**IIIb**) ($c = 6.4\times10^{-4}$ M) in a DMSO solution containing 10% of methanol and 0.09 mol/l of sodium methoxide at 20°C: (*1*) before addition of sodium methoxide and (*2*) 5, (*3*) 11, (*4*) 16, (*5*) 23, (*6*) 28, (*7*) 36, (*8*) 44, (*9*) 56, and (*10*) 71 min after addition.

with the medium to give β-formylaminoacrylamides **X**/**XII** and **XI**/**XIII**. The latter give rise to UV absorption in the λ region 270–280 nm. These bands gradually disappear as a result of elimination of the formyl group. Compounds **XI** and **XIII** contain a labile imide group, and compounds **XIIa** and **XIIb** may be regarded as vinylogous imides.

Obviously, the above described appearance and disappearance of absorption bands in the UV spectra of 1- and 3-methylpyrimidinones **II** and **III** is governed by the rates of mutual transformations shown in Scheme 1. In the UV spectra of aqueous alkaline solutions (see above) we observed only absorption bands belonging to β-formylaminoacrylamides **X**/**XII** and **XI**/**XIII**, for the rate of formation of anions **IV** and **V** is low while the rate of hydrolytic transformation of anions **VIII** and **IX** is high. The assignment of bands with λ_{max} 270–280 nm to acrylamide derivatives is supported by the known data for structurally related compounds: $Me_2NCH{=}CHCOR$ (R = H, Me, OMe), λ_{max} 270–300 nm [8]; RCONHCH=CHCONHR', λ_{max} 257–263 nm (ε > 17000) [9].

The results of NMR experiments are collected in table. For the sake of convenience, atoms in the open-chain products were given the numbers of the corresponding atoms in the initial pyrimidinones whose NMR spectral parameters are also presented. The spectra are more consistent with the structures of acyclic anions **VIII** and **IX** than of cyclic tautomers **IV** and **V** (Scheme 1). In all cases, the spectra of the products formed from pyrimidinones **II** and **III** in DMSO in the presence of sodium methoxide contain signals typical of aldehyde groups, indicating that the pyrimidine ring is cleaved at the C^2–N bond. The formyl protons in the compounds formed by ring opening in 1-methylpyrimidinones **III** are deshielded by 0.8 ppm, and the vicinal coupling constant $J_{5,6}$ is almost twice as large as that found for ring-opening products derived from 3-methyl isomers **II**. These data suggest the presence of a double $C^5{=}C^6$ bond in anions **IX** and the presence of a conjugated bond system in anions **VIII**.

The spectra of the reaction mixtures obtained from 3-methylpyrimidinones **II** contain a set of signals

Proton and carbon chemical shifts (δ_H, δ_C, ppm) and coupling constants (Hz) in the NMR spectra of pyrimidin-4-ones **IIa**, **IIb**, **IIIa**, and **IIIb** and products of their reaction with sodium trideuteromethoxide in DMSO-d_6 containing 4% of water

Signal	C^2	C^4	C^5	C^6	NMe	Coupling constants		
						5-H–6-H	5-F–6-H	C^5–F
3-Methylpyrimidin-4-one (**IIa**)								
δ_H[a]	8.42	–	6.38	7.89	3.39	5.7	–	–
δ_C	153.4	161.3	114.9	154.1	34.2	–	–	–
Product **VIIIa**								
δ_H[a]	8.41	–	4.39	7.13[b]	2.64	8.0	–	–
δ_C	170.2	174.7[b]	99.6	154.0[b]	25.4	–	–	–
5-Fluoro-3-methylpyrimidin-4-one (**IIb**)								
δ_H[a]	8.36	–	–	8.06	3.53	–	2.6	–
δ_C	149.0	155.1	149.8	136.5	33.7	–	–	251
δ_H[a,c]	8.30	–	–	8.04	3.60	–	2.2	–
δ_C[c]	149.0	157.9	150.4	137.0	34.7	–	–	251
Product **VIIIb**								
δ_H[a]	8.42	–	–	7.29	2.70	–	14.0	–
δ_C	173.4	163.8	139.7	137.6	25.3	–	–	220
δ_H[a,d]	8.46	–	–	6.84	2.79	–	27.8	–
δ_C[d]	171.5	164.8	136.1	125.3	25.8	–	–	228
1-Methylpyrimidin-4-one (**IIIa**)								
δ_H[a]	8.26	–	6.01	7.69	3.56	7.56	–	–
δ_C	153.6	169.2	111.1	143.8	39.9	–	–	–
Product **IXa**[e]								
δ_H[a]	9.20	–	4.63	7.45	2.55	13.0	–	–
δ_C	174.0	180.9	93.9	148.2	30.0	–	–	–
5-Fluoro-1-methylpyrimidin-4-one (**IIIb**)								
δ_H[a]	8.23	–	–	8.10	3.62	–	6.35	–
δ_C	150.8	162.2	146.8	129.2	39.6	–	–	255
Product **IXb**[e]								
δ_H[a]	9.19	–	–	6.92	2.75	–	27.8	–
δ_C	173.9	164.3	137.4	131.1	34.2	–	–	218

[a] Chemical shifts of protons at the corresponding carbon atom.
[b] Broadened signal.
[c] In D_2O.
[d] In a solution of NaOD in D_2O.
[e] Major isomer.

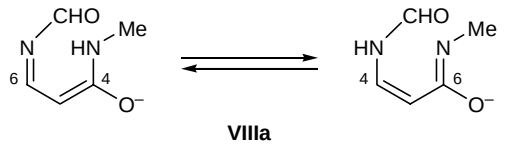
belonging to only one product which does not change over a period of 100 min. In the case of 1-methyl-substituted compounds **III**, we observed two sets of signals in the NMR spectra, and the intensity of both these decreased in parallel with time. On the basis of the coupling constants, the major set of signals was assigned to the *trans* isomer of anion **IX**, and the minor, to the *cis* isomer. After addition of 1 equiv of CD_3ONa to a solution of 5-fluoro-1-methylpyrimidin-4-one (**IIIb**) in DMSO-d_6 containing 3–4% of water, signals of the initial compound disappeared from the ^1H NMR spectrum in 1 min, and the spectrum contained signals from aldehyde protons (δ 9.19 and 9.28 ppm) at a ratio of ~15:1, doublet signals from 6-H (δ 6.92 and 6.76 ppm, J = 27.8 and 12.0 Hz, respectively), and singlets from N-methyl groups (δ 2.75 and 2.95 ppm). These signals may be assigned to the *trans*- and *cis* isomers (with respect to the H and F atoms) of *N*-formyl-2-fluoro-3-methylaminoacrylamide or anion **IXb**; elimination of the formyl group therefrom (δ 8.43 ppm, s) gives *trans*-2-fluoro-3-methylaminoacrylamide (δ 6.62 ppm, d, J = 29 Hz).

After 15 min, the concentration of the hydrolysis products attains 30–40%. Later on, signals of compound **IXb** disappear completely from the spectrum. Elimination of the formyl group from anion **IXa** occurs at a lower rate, although opening of the heteroring in pyrimidinone **IIIa** in DMSO in the presence of sodium methoxide is as fast as in **IIIb**.

Proton abstraction from the hydroxy group in cyclic anions **IV** and **V** should give dianions **VI** and **VII** which are common for tautomeric anions **VIII** and **IX**. If the hydroxy hydrogen atom in structures **IV** and **V** is replaced by methyl group, no open-chain isomer is formed. In fact, reactive hydroxide ions are generated by hydrolysis of sodium methoxide with water present in DMSO. In dry DMSO, the reaction does not occur even on addition of 2 equiv of sodium methoxide, whereas in the presence of 3–4% of water 1 equiv of MeONa is sufficient to complete the process. These findings are consistent with the data obtained by UV spectroscopy, according to which compounds **II** and **III** in methanol and in 0.1 M solutions of sodium hydroxide or methoxide in methanol do not change for a long time (in contrast to aqueous alkalies; see above).

The presence of sodium methoxide in DMSO-d_6 containing 3–4% of water gives rise to H–D exchange, as follows from sharp increase in intensity of the signal from residual solvent protons. Obviously, this exchange is responsible for the absence of signals from amide or vinylogous imide protons in the spectra of the transformation products. Only in the case of compound **IIb** with insufficient amount of base we observed two signals (δ 8.1 and 9.56 ppm) assignable to structure **XIIb**. The broadened signal at δ 9.56 ppm disappears on addition of sodium methoxide.

The C^6 and C^4 signals in the ^{13}C NMR spectrum of **VIIIa** in DMSO-d_6 are broadened (in contrast to **IXa**). Presumably, the rate of tautomeric proton exchange in anion **VIIIa** at room temperature decreases to a value comparable with the NMR time scale. Analogous signal broadening was observed for some 4-hydroxypyrimidines capable for amine–imine tautomerism [10].



VIIIa

It was difficult to analyze product mixtures in D_2O by NMR spectroscopy. As we already noted, the ring opening in pyrimidinones in aqueous alkali occurs at a much lower rate than in DMSO. On mixing concentrated (0.4 M) solutions of pyrimidinones **IIa** and **IIIa** in D_2O with 2 equiv of NaOD at room temperature, the 65% conversion is attained in 20 and 17 h, respectively. In DMSO, the same conversion is achieved in 1 min or shorter. In aqueous medium, the products can undergo a series of consecutive transformations at different rates; in particular, compounds **Xa** and **XIa** could be formed for which H–D exchange at C^5 is possible. In all cases, after keeping solutions of pyrimidinones **II** and **III** in aqueous alkali, the NMR spectra revealed formation of formyl groups. The data for pyrimidinone **IIb** are given in table; the pyrimidine ring in this compound is cleaved at a relatively high rate. In 3.5 h, the observed set of signals in the NMR spectrum corresponds to only one compound, **VIIIb** or **XIIb**. Comparison of the spectra obtained from solutions in D_2O and DMSO-d_6 shows that in the first case the vicinal coupling constant J(5-F,6-H) is twice as large. This finding should be interpreted in favor of structure **XIIb**, for J(5-F,6-H) = 27.8 Hz (D_2O) corresponds to *trans* arrangement of the fluorine and hydrogen atoms with respect to each other while the value 14 Hz (DMSO-d_6) is typical of *cis* configuration in the conjugated bond system intrinsic to anion **VIIIb**. The spectra of the mixtures obtained by keeping compounds **IIa** and **IIIa** in D_2O in the presence of NaOD lack signals from hydrogen atoms in the 5-position, and the C^5 signals appear as triplets (unlike singlet signals fom the same carbon atoms in the spectra of the mixtures in DMSO-d_6). This means that the hydrogen atom on C^5 is replaced by deuterium. A probable mechanism of H–D exchange involves formation of ketoimino tautomers **Xa** and **XIa**. Here, tautomer **XIa** could be formed from 1-methylpyrimidinone **IIIa** only if the ring opening in anion **Va** occurs at the C^2–N^3 bond. 3-Methyl-substituted isomer **IIa** could give rise to structure **Xa**, regardless of whether C^2–N^1 or C^2–N^3 bond is broken.

EXPERIMENTAL

The UV spectra were measured on an SF-8 spectrophotometer; the spectra of solutions in DMSO were recorded using cells with ground caps. The NMR spectra were recorded on a Bruker DPX-300 spectrometer operating at 300 MHz for ^1H and 75.47 MHz for ^{13}C. The chemical shifts in D_2O and DMSO-d_6 were measured relative to DSS. Samples were prepared as 0.3–0.4 M solutions which were placed in

5-mm NMR ampules. A required amount of a concentrated solution of CD_3ONa (5.1 M) or NaOD (2.6 M) was added. The stock solutions were prepared by dissolving metallic sodium in methanol-d_3 and D_2O, respectively, and their concentrations were determined by titration. A solution of sodium methoxide in DMSO containing no free methanol was prepared as follows. A solution of sodium methoxide in methanol was evaporated to dryness, and the residue was kept in a vacuum desiccator and dispersed in DMSO. The mixture was subjected to centrifugation, and the concentration of sodium methoxide in the supernatant was determined by titration.

The procedures for preparation and properties of 1- and 3-methylpyrimidin-4-ones **II** and **III** were reported previously [10].

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