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The ratio of 3- and 5-nitro isomers formed in the nitration of 2-pyridones with nitric acid is determined by the reaction temperature but is independent of the concentration of the nitrating agent. The presence of a phenyl group in the 6 position of the α -pyridone ring hinders incorporation of a nitro group in the 5 position.

Many electrophilic substitution reactions of 2-pyridones proceed with incorporation of a substituent in the 5 position. It has been reported that primarily 3-nitro isomers are formed by nitration [1, 2], but in the case of 1-methyl-2-pyridone and 6-phenyl-2-pyridone we have established that this sort of orientation is observed only at low temperatures and that raising the temperature leads to an increase in the percentage of the 5-nitro isomer [3, 4]. The literature contains contradictory data with respect to the site of incorporation of a substituent in the nitration of unsubstituted 2-pyridone and 1-methyl-2-pyridone [2, 4-7].

In the present research we set out to ascertain the effect of the temperature on the orientation in the nitration of 2-pyridones with different structures. For this, we selected 2-pyridone (I), 1-ethyl-2-pyridone (II), and 1-propyl-2-pyridone (III), which do not have substituents attached to a heteroring carbon atom, in order to eliminate the effect of steric factors on the ratio of the ortho and para isomers [8]. For comparison we studied the nitration of 1-methyl-6-phenyl-2-pyridone (IV).

We used 70 and 98% nitric acid, since that gives fewer undesired dinitro compounds than a nitrating mixture but the same isomer ratios and overall yields of nitration products [4].

Nitro compounds V-XIV were isolated in individual form by means of column chromatography (see Tables 1 and 2). Their structures were proved by their PMR spectra by comparison with the spectra of starting pyridones I-IV and 3- and 5-nitro-1-methyl-2-pyridones, which are described in [9], and from the multiplicities [triplet 5-H signal for the 3-nitro isomers (V-VII) and doublet 3-H signal for the 5-nitro isomers (IX-XI)] and the constants of coupling of the 5-H and 3-H protons with the adjacent protons on the basis of the previously found principle that $J_{3.4} > J_{4.5}$ (see Table 3) [3].

According to the data in Table 1, at 20°C the nitration of pyridone I proceeds with considerably greater difficulty than the nitration of 1-alkylpyridones Π -IV and only in the 3 position. Pyridones Π -IV form 3- (VI-

Starting pyridone	Reac- tíon temp., °C	70% HNO	Recovered			
		3-NO2	5 NO2	ratio of 3- and 5-NO ₂ isomers	3,5-di-NO ₂	starting pyridone, %
2-Pyridone (I)	20 90	18 (V) 48 (V)	27 (IX)	1.74		64
l-Ethyl-2- pyridone (II)	20 90 20*	46 (VI) 48 (VI) 16 (VI)	25 (X) 41 (X) 8 (X)	1,81 1,17 2,0	5 (XIII) 45 (XIII)	33
l-Propyl-2- pyridone (III)	20 90	42 (V11) 42 (V11)	25 (XI) 38 (X1)	1,68 1,11	13 (XIV)	48
l-Methyl-6- phenyl-2- pyridone (IV)	20 90	80 (VIII) 46 (VIII)	16 (XII) 46 (XII)	5.00 1,00		=

TABLE 1. Yields and Ratios of the Products of Nitration of 2-Pyridones (V-XIV)

* The nitration was carried out with 98% HNO₃ (sp. gr. 1.5).

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I, V, IX R=R'=H; II, VI, X, XIII $R=C_2H_5$, R'=H; III, VII, XI, XIV $R=C_3H_7$, R'=H; IV, VIII, XII $R=CH_3$, $R'=C_6H_5$

VIII) and 5-nitropyridones (X-XII) with significant predominance of the former. The ratio of 3- and 5-nitro isomers obtained from pyridones I and II is 1.7-1.8 but increases to five for 1-methyl-6-phenyl-2-pyridone (IV) because of the fact that the phenyl group in the 5 position hinders approach of the attacking group.

Raising the temperature to 90°C leads to equalization of the rates of nitration in both positions (the ratio of the 3-nitro and 5-nitro isomers is 1.00-1.17 for all of the investigated pyridones).

Thus we have shown a distinct dependence of the orientation on the temperature in the nitration of 2-pyridones with different structures. An increase in the nitric acid concentration has almost no effect on the isomer ratio but only increases the amount of dinitro compounds XIII and XIV.

In contrast to other electrophilic substitution reactions, nitration primarily in the 3 position indicates a factor that promotes or the orientation, the effect of which decreases as the temperature is raised. This sort of dependence of ortho-para orientation on the temperature has been observed in the nitration of phenols (with nitric acid under conditions that exclude their nitrosation [10]), for which this phenomenon is associated with prior to coordination of the nitrating agent with the ring substituent [2]. The possibility of coordination between the nitro group in the 3 position and the hydroxyl group of the tautomeric hydroxypyridine forms, which stabilizes the transition state, was previously assumed in [3, 11]. The fact that there is also a relationship between the temperature and the orientation for 1-alkyl-2-pyridones (although to a lesser extent than for NH-pyridones) makes it possible to assume the possibility of this sort of coordination for the protonated forms of 1-alkyl-2-pyridones.

EXPERIMENTAL

The PMR spectra of the compounds were recorded with a Varian T-60 spectrometer with hexamethyldisiloxane as the internal standard.

<u>1-Methyl-6-phenyl-2-pyridone (IV).</u> A 14.5-g (0.087 mole) sample of 6-phenyl-2-pyridone was added to a solution of sodium methoxide (from 2 g of sodium and 25 ml of methanol), after which 8.5 ml (0.11 mole) of dimethylsulfate was added with stirring in the course of 15 min. The mixture was then heated at 90°C for 9 h, after which it was neutralized with 10 ml of 25% aqueous sodium hydroxide and extracted with chloroform. The chloroform extract was washed with water and dried with magnesium sulfate, and the solvent was removed by distillation. The residual oil began to crystallize when cyclohexane was added. Workup gave 5 g (33%) of pyridone IV with mp 65°C. IR spectrum: 1680 cm⁻¹ (pyridone CO). Found: C 77.8; H 6.1; N 8.0%. C₁₂H₁₁NO. Calculated: C 77.8; H 5.9; N 7.6%.

Com-	Name	mp. °G	Found, %			Empirical	Calc., %		
pound			CHN		N	formula	c	н	N
VI	3-Nitro-1-ethy1-2- pyridone	120-121 (from benzene)	49,9	4,7	16,5	C7H8N2O3	50.0	47	16.6
X	5-Nitro-1-ethyl-2- pyridone	(from toluene)	50,4	4,9	16,6				
VII	3-Nitro-1-propy1-2- pyridone	35	52,7	5.5	14,9	$C_8H_{10}N_2O_3$	52,8	5.5	15,3
XI	5-Nitro-1-propyl-2- pyridone	8081 (from hexane)	53,0	5,7	15,3				
VIII	3-Nitro-1-methyl-6- phenyl-2-pyridone	166—167 (from benzene)	62,7	4,3	12,5	$C_{12}H_{2}O_{3}$	62.6	4,3	12.2
XII	5-Nitro-1-methyl-6- phenyl-2-pyridone	137—139							
XIII	3,5-Dinitro-1-ethyl-2- pyridone	131 (from toluene)	40,0	3,4	19,4	C7H7N3O5	39,8	3,2	19,7
XIV	3,5-Dinitro-1-propyl-2- pyridone	116—117	42,3	4,1	18,9	$C_8H_8N_3O_5$	42,2	3,9	18,5

TABLE 2. Constants and Results of Analysis of Nitro-2-pyridones

TABLE 3. PMR Spectra of I-XII

Com-		Chemical shifts, ppm				Co	Coupling constants, Hz				
pound	Solvent	3-11	4- J I	5-11	6-11	1 _{3,4}	J _{3,5}	J _{4,5}	14,6	J 5.6	
V IX VI X VII XI III VIII XII	$d_{6} - DMSO$ $d_{6} - DMSO$ $CDCl_{3}$ $CDCl_{5}$ $CDCl_{5}$ CCl_{4} $CH_{2}Cl_{2}$ $CH_{2}Cl_{2}$ $CH_{2}Cl_{2}$	6,67d 6,5 d 6,37d 6,6d 6,6d	8,7d 8,33d 8,3d 8,05d 8,4d 8,0d 8,1d 8,1d	6,67m 6,35m 6,43m 6,17 d 6,1d	8,13d 8,87d 7,88d 8,63d 8,63d 7,2 -7 ,6 m (C ₆ H ₅) 7,2-7,6 m (C ₆ H ₅)	$\frac{10}{10}$ $\frac{10}{10}$ $\frac{10}{10}$ $\frac{10}{10}$		8 8 7 8 	3 3 2 3 3 3 3 3 1	$\begin{array}{c} 6\\ \hline 6\\ \hline 6\\ \hline \\ -\\ -\\ -\\ -\\ -\\ -\\ -\\ -\\ -\\ -\\ -\\ -\\ -$	

<u>Nitration of 2-Pyridone (I).</u> A 10-ml sample of 70% HNO_3 was added dropwise to 1 g of pyridone I, and the mixture was stirred at 20° for 200 h and at 90°C for 2 h. It was then poured over ice, and the mixture was neutralized with 40% sodium hydroxide solution and evaporated to dryness. The residue was extracted with alcohol. Chromatography of the alcohol solution on a plate with silica gel (elution with ethyl acetate) showed the presence of three substances with Rf 0.5, 0.3, and 0.14, which were separated with a column filled with silica gel (elution with ethyl acetate). The following compounds were eluted successively: 5-nitro-2-pyridone (IX) with mp 185°C; 3-nitro-2-pyridone (V) with mp 221-223°C; and starting 2-pyridone (I) with mp 110°C. According to the data in [5, 6], 3-nitro-2-pyridone has mp 224°C, and 5-nitro-2-pyridone has mp 186-188°C.

Nitration of 1-Alkyl-2-pyridones (II-IV) with 70% Nitric Acid (sp. gr. 1.41). A 10-ml sample of HNO_3 was added dropwise to 1 g of the pyridone, and the mixture was allowed to stand at 20°C for 200 h and at 90° for 2 h. It was then poured over ice, and the mixture was neutralized with 40% sodium hydroxide. The resulting solution was extracted with chloroform in an extractor, the extract was dried with MgSO₄, and the solvent was removed from the extract by distillation. Chromatography of the residue with a column filled with silica gel (elution with ethyl acetate) gave 3-nitro and 5-nitro isomers VI-VIII and X-XII in individual form, as well as dinitro compounds XIII and XIV (see Table 2).

<u>Nitration of 1-Ethyl-2-pyridone (II) with 98% Nitric Acid (sp. gr. 1.5).</u> A 15-ml sample of 98% HNO₃ was added dropwise to 1.5 g (0.012 mole) of pyridone II, and the mixture was allowed to stand at 20°C for 70 h. It was then poured over ice, and the mixture was neutralized with 40% sodium hydroxide solution. The precipitated 3-nitro-1-ethyl-2-pyridone (VI) [0.32 g (16%)] was removed by filtration. The aqueous solution was extracted with chloroform in an extractor, the solvent was removed by distillation, and the residual mixture (1.2 g) of 5-nitro-1-ethyl-2-pyridone (X) and 3,5-dinitro-1-ethyl-2-pyridone (XIII) with R_f 0.78 and 0.32 was separated by chromatography with a column filled with silica gel (elution with ethyl acetate) to give 0.15 g (8%) of 5-nitro isomer X and 1.05 g (45%) of dinitropyridone XIII.

LITERATURE CITED

- 1. H. Tomisawa, J. Kabayashi, H. Hongo, and R. Fujita, Chem. Pharm. Bull., <u>18</u>, 932 (1970).
- 2. R. Abramovitch and J. Saha, Adv. Heterocycl. Chem., 6, 254 (1966).
- 3. N. P. Shusherina and T. I. Likhomanova, Khim. Geterotsikl. Soedin., No. 10, 1374 (1972).
- 4. N. P. Shusherina and T. I. Likhomanova, Khim. Geterotsikl. Soedin., No. 12, 1671 (1973).
- 5. A. E. Chichibabin and S. A. Shapiro, Zh. Russk. Fiz. Khim. Obshchestva, 53, 233 (1921).
- 6. A. Binz and H. Meier-Boder, Angew. Chem., 49, 486 (1936).
- 7. A. V. Burton, P. J. Halls, and A. R. Katritzky, J. Chem. Soc., Perkin Trans. II, 1953 (1972).
- 8. C. K. Ingold, Structure and Mechanism in Organic Chemistry, Cornell Univ. Press (1969).
- 9. H. Möhrle and H. Weber, Ber., 104, 1478 (1971).
- 10. A. A. Spryskov and I. K. Barvinskaya, Zh. Org. Khim., 1, 1941 (1965).
- 11. K. Schofield, Quart. Rev., 4, 382 (1950).