2-PYRIDONES

VI.* NITRATION OF 6-PHENYL-2-PYRIDONE

N. P. Shusherina and T. I. Likhomanova

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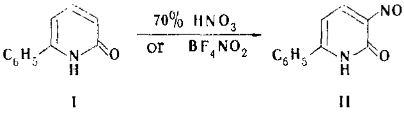
The nitration of 6-phenyl-2-pyridone with 70% nitric acid, nitronium tetrafluoroborate, and acetyl nitrate has been studied for the first time. It was shown that, depending on the reaction temperature, the nitro group enters the 3 or 5 position of the heterocyclic ring. 3-Nitro-6-(p-nitrophenyl)-2-pyridone is formed by the action of fuming nitric acid on 6-phenyl-2-pyridone. The structures of the nitropyridones obtained were proved by PMR spectroscopy.

It is known [1, 2] that the nitration of 2-pyridones proceeds at the 3 and 5 positions to give mono- and dinitro derivatives. The data relative to which of the possible mononitro isomers is obtained under various conditions are extremely contradictory [3-5].

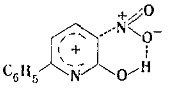
In the present paper we have studied for the first time the nitration of 6-phenyl-2-pyridone by the action of various nitrating agents – 70% nitric acid, nitronium tetrafluoroborate, fuming nitric acid, and acetyl nitrate (in the cold and at 90°C). In the case of this aryl-2-pyridone, in which both reactive positions are free for electrophilic attack, it was of interest to ascertain the site of entry of the nitro group into the pyridone ring and the possibility of selective nitration in the pyridone or benzene ring, as we have previously demonstrated for 6-phenyl-2-pyrone [6].

The nitration of 6-phenyl-2-pyridone (I) with 70% nitric acid in the cold gives one compound (in 60% yield), which, judging from the analytical data, is the mononitrophenylpyridone; its purity was confirmed by thin-layer and gas–liquid chromatography. This same compound is formed in 40% yield by the action of nitronium tetrafluoroborate (in nitromethane solution) on 6-phenyl-2-pyridone in the cold. The 3-nitro-6-phenyl-2-pyridone structure (II) of the nitro compound was proved by means of its PMR spectrum (see below).



The entry of the nitro group only into the 3 position of the pyridone ring during nitration in the cold does not agree with the direction of other electrophilic substitution reactions for 2-pyridones (for example, chlorination [7, 8] and iodination [9]), which proceed only (or primarily) at the 5 position under these conditions.

As was described for 3-hydroxypyridine [10-12], the reason for this sort of orientation during the nitration of 6-phenylpyridone in the cold is possibly the formation of a "chelate" bond between the hydroxyl and nitro groups in the transition state. If this assumption is correct, one might have expected a change in



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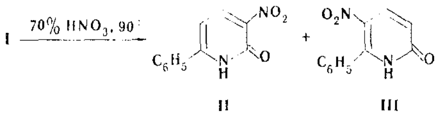
the orientation during nitration of this pyridone under more severe temperature conditions that prevent the formation of a hydrogen bond. In fact, if the nitration of 6-phenylpyridone is carried out with 70% nitric acid while heating (90°), primarily 5-nitro-6-phenyl-2-pyridone (III) is obtained, together with a lesser amount of the 3-nitro isomer (II) [in a ratio of 3 : 2, judging from the results of gas–liquid chromatography (GLC)].



The same mixture of isomers was obtained by nitration of 6-phenyl-2-pyridone with acetyl nitrate at 90°. Thus in the investigated examples of the nitration of 6-phenyl-2-pyridone, the site of entry of the nitro group is determined by the temperature conditions of the reaction rather than by the character of the nitrating agent.

The structures of mononitro isomers II and III were proved by means of the PMR spectra. The assignment of the bands in the PMR spectra* of nitro compounds II and III was made by comparing them with the spectra of the starting 6-phenyl-2-pyridone and 5,6-cyclohexano-2-pyridone (V) and with the spectra of 4,6-dimethyl-2-pyridone [13] and 2-pyrone [14] (Fig. 1 and Table 1).

The spectrum of 6-phenyl-2-pyridone is divided into parts A and B with respect to the integral 6 : 2, from which it follows that the five protons of the benzene ring and one proton of the pyridone ring correspond to the A group (multiplet at 7.8-8.1 ppm), while the two protons of the pyridone ring correspond to the B group (two doublets at 6.95 and 6.62 ppm). Judging from the data in [13] that $\delta_{3,5} < \delta_{4,6}$, the signal of the proton of the pyridone ring, which is superimposed on the multiplet of the phenyl ring, corresponds to the fourth proton and is found at 7.70 ± 0.1 ppm.

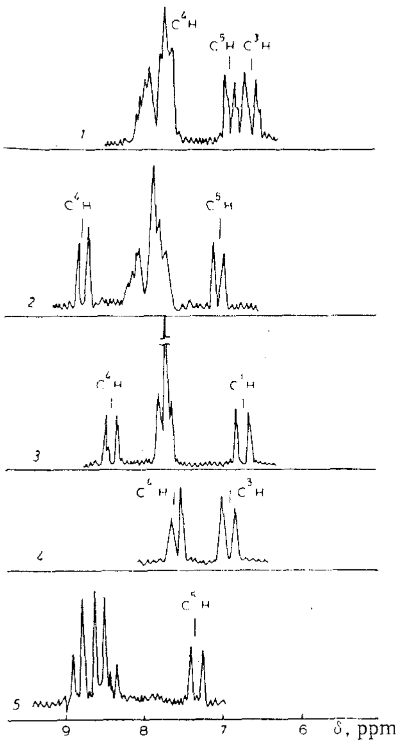


Fig. 1. PMR spectra: 1) 6-phenyl-2-pyridone (I); 2) 3-nitro-6-phenyl-2-pyridone (II); 3) 5-nitro-6-phenyl-2-pyridone (III); 4) 5,6-cyclohexano-2-pyridone (V); 5) 3-nitro-6-(p-nitrophenyl)-2-pyridone (IV).

We confirmed this conclusion by comparison with the spectrum of 5,6-cyclohexano-2-pyridone, which has two doublets at 6.85 and 7.50 ppm, the assignment of which to C^3H and C^4H, respectively, is confirmed by double resonance. When the signal at 2.9 ppm (which corresponds to the CH_2 group in the 7 position) is irradiated, leveling of the intensities occurs only in the doublet at 7.50 ppm. Since this change in intensity may occur due to the long-range interaction of the protons of the CH_2 group only with the proton attached to C^4, the signal at 7.5 ppm consequently corresponds to C^4H, while that at 6.85 ppm corresponds to C^3H.

The assignment of the signals of the B group was made on the basis of the J_{HH} values, which amount to 6.4 Hz for the doublet at 6.95 ppm and 9.2 Hz for the doublet at 6.62 ppm. Since it is known [13, 14] that $J_{4,5} < J_{3,4}$ for 2-pyridones and 2-pyrones, the first doublet should be assigned to C^5H, while the second should be assigned to C^3H. There is only one doublet in the B group in the spectra of mononitro isomers II and III at 7.00 and 6.70 ppm with coupling constants of 8 and 10 Hz, respectively. In conformity with the inequality presented above ($J_{4,5} < J_{3,4}$), these values make it possible to assign the 3-nitro-6-phenyl-2-pyridone structure to II and the 5-nitro-6-phenyl-2-pyridone structure to III.

The shift in the C^4H signals in nitro compounds II and III as compared with the starting 6-phenyl-2-pyridone (I) (because of the proximity of the NO_2 group to this proton) is responsible for the appearance of doublets at stronger field (8.74 and 8.84 ppm, respectively) in their spectra.

The nitration of 6-phenyl-2-pyridone with fuming nitric acid gave only a dinitro compound, which, judging from the PMR spectrum (see Table 1), contains one nitro group in the benzene ring (in the p position) and another in the 3 position of the pyridone ring.

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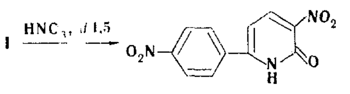
* We thank N. M. Sergeev for his assistance in the interpretation of the spectra.



IV

A doublet at 7.33 ppm, which should be related to C^5H on the basis of the $J_{4,5}$ value (8 Hz, compare with the above), and a multiplet are observed in the spectrum; the multiplet includes two doublets at 8.43 and 8.69 ppm, which are characteristic for p-substituted phenyl systems, and a C^4H doublet at 8.84 ppm.

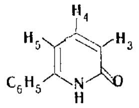
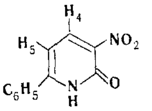
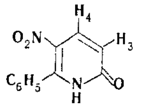
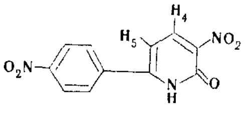
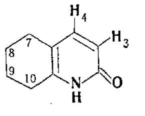
Thus the nitration of 6-phenyl-2-pyridone with 70% nitric acid, nitronium tetrafluoroborate, and acetyl nitrate proceeds only in the heterocyclic ring to give 3- and 5-mononitro isomers, while 3-nitro-6-(p-nitrophenyl)-2-pyridone (IV) is formed in the reaction with fuming nitric acid.

EXPERIMENTAL

The products of the nitration of 6-phenyl-2-pyridone were subjected to GLC with a Pai-104 analytical chromatograph with a flame ionization detector; the device had a column 1.5 m long and 4 mm in diameter and QF 1%. The carrier gas was nitrogen, the flow rate was 100 cm^3/sec, and the temperature was 200°. The IR spectra of mineral-oil suspensions were recorded with an IKS-22 spectrometer.

3-Nitro-6-phenyl-2-pyridone (II). A) Nitration of 6-phenyl-2-pyridone with 70% HNO_3 in the cold. A 3-g sample of 6-phenyl-2-pyridone (I) (mp 197° [15]) was added with vigorous stirring in the course of 20 min to 4.5 ml of 70% (sp. gr. 1.41) HNO_3, and the mixture was stirred at room temperature for 20 h. It was then poured into ice water, and the resulting crystals were removed by filtration. The crystals were washed thoroughly with water until they were neutral and were then dried at 60° to give 2.2 g (60%) of 3-nitro-6-phenyl-2-pyridone (II) with mp 276-277° (dec., from methanol). One spot with R_f 0.07 was detected by chromatography on Al_2O_3 (in methanol); investigation of the substance by GLC showed the presence of a single substance with a retention time of 4 min and 20 sec. IR spectrum, cm^{-1}: 1690 (amide $\nu_{C=O}$), 1500 (ν_{NO_2}). Found: C 61.1; H 4.0; N 13.1%. $C_{11}H_8N_2O_3$. Calculated: C 61.1; H 3.7; N 12.9%.

TABLE 1. Parameters of the PMR Spectra* of 2-Pyridone Derivatives

Compound	Formula	Chemical shifts, ppm			Constants, Hz		
		δ_3	δ_4	δ_5	$J_{3,4}$	$J_{3,5}$	$J_{4,5}$
I		6,62	7,70	6,95	9,2	1,0	6,4
II		—	8,74	7,00	—	—	8,0
III		6,70	8,40	—	10,0	—	—
IV		—	8,84	7,33	—	—	8,0
V		6,85	7,50	—	8,0	—	—

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* The PMR spectra of solutions of I-V in dimethyl sulfoxide were recorded with a Varian T-60 spectrometer at 60 MHz. The chemical shifts are presented in parts per million with respect to the internal standard (hexamethyldisiloxane).

B) Nitration of 6-phenyl-2-pyridone with nitronium tetrafluoroborate. A suspension of 0.85 g (5 mmole) of phenylpyridone I in 5 ml of anhydrous nitromethane was placed in a nitrogen-filled four-neck flask equipped with a stirrer, thermometer, and capillary for supplying gas, and a suspension of 0.66 g (5 mmole) of nitronium tetrafluoroborate in 20 ml of nitromethane was added dropwise with stirring at such a rate that the temperature did not exceed 20°. The mixture was allowed to stand overnight, and the nitromethane was removed by distillation. Treatment of the dark-red residue with acetone gave 0.4 g (40%) of nitro-2-pyridone crystals with mp 260-265°; recrystallization from methanol gave a product with mp 276-277° (dec.) that did not depress the melting point of 3-nitro-6-phenylpyridone obtained by nitration of 6-phenyl-2-pyridone with 70% HNO_3 in the cold.

Mixture of 3- and 5-Nitro-6-phenyl-2-pyridones. A) Nitration of 6-phenyl-2-pyridone with 70% HNO_3 at 90°. A 4.8-g sample of phenylpyridone I was added with stirring in the course of 45 min to 48 ml of 70% HNO_3, and the mixture was heated on a boiling-water bath for 1 h until the vigorous evolution of nitrogen oxides had ceased. The mixture was cooled and poured into ice water, and the precipitated crystals were removed by filtration, washed thoroughly with water, and dried at 60° to give 3.8 g (61%) of crystals with mp 230-240° (dec.). IR spectrum, cm^{-1}: 1690 (amide $\nu_{C=O}$) and 1500 (ν_{NO_2}). Found: C 61.1; H 3.8; N 13.0%. $C_{11}H_8N_2O_3$. Calculated: C 61.1; H 3.7; N 13.0%. Gas–liquid chromatography of the nitration product with mp 230-240° demonstrated the presence of two substances in a ratio of 2 : 3 with retention times of 4 min 20 sec and 6 min 45 sec. Two spots with R_f 0.07 and 0.14 were also detected by chromatography on Al_2O_3 (in methanol). A comparison of the retention times and R_f values of a mixture of the isomeric mononitro products with the corresponding values for 3-nitro-6-phenyl-2-pyridone (II) demonstrated that the latter was identical to one of the components of the mixture with R_f 0.07. Five recrystallizations of the mixture of mononitro compounds from methanol gave 3-nitro-6-phenyl-2-pyridone with mp 276-277° (dec.), which did not depress the melting point of an authentic sample of 3-nitro-6-phenylpyridone. The second component with R_f 0.14 and retention time 6 min 45 sec was isolated by heating 1 g of the mixture with 10 ml of methanol. The insoluble portion was separated, and the solution was evaporated to dryness to give crystals with mp 266-270° (from ethanol), which, judging from the PMR spectrum, were 5-nitro-6-phenyl-2-pyridone (III).

B) Nitration of 6-phenyl-2-pyridone with acetyl nitrate at 90°. A total of 13 ml of concentrated HNO_3 (sp. gr. 1.40) was added to a solution of 0.5 g of phenylpyridone I in 13 ml of glacial acetic acid, and the mixture was heated on a boiling-water bath until the evolution of nitrogen oxides had ceased. The mixture was cooled and poured into ice water, and the precipitated yellow crystals were removed by filtration and washed with water (until they gave a neutral reaction) to give 0.32 g (50%) of a mixture of 3- and 5-nitro-6-phenyl-2-pyridones (in a ratio of 2 : 3 according to GLC).

3-Nitro-6-(p-nitrophenyl)-2-pyridone (IV). A 3-g sample of phenylpyridone was added in the course of 40 min to a cooled (0°) 30 ml of fuming HNO_3 (sp. gr. 1.5, 98%), and the mixture was stirred at the same temperature for 1.5 h. It was then poured into ice water, and the precipitated crystals were removed by filtration and washed with water (until they gave a neutral reaction) to give 1.71 g (36%) of a dinitro compound with mp 284-285° (dec., from acetonitrile). According to the PMR spectrum, the product was 3-nitro-6-(p-nitrophenyl)-2-pyridone (IV). IR spectrum, cm^{-1}: 1690 (amide $\nu_{C=O}$) and 1500 (ν_{NO_2}). Found: C 50.6; H 2.7; N 16.0%. $C_{11}H_7N_3O_5$. Calculated: C 50.5; H 2.6; N 16.1%.

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