SYNTHESIS AND STUDY OF SOME ELECTROPHILIC REACTIONS OF 2-PHENYL-3-HYDROXYPYRIDINE N-OXIDES

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In a previous series of papers on aromatic substitution in 2-phenyl-3-hydroxypyridine and its derivatives we observed a variable orientation of the electrophilic reagents, depending on their type and the conditions of running the reaction. Thus, the reactions in alkaline media (aminomethylation, iodination, azo-coupling) proceed with involvement of the β-pyridinol nucleus [1-3]. In contrast, during sulfonation and nitration, which proceed in strongly acid medium, the p-position of the phenyl ring undergoes substitution [4, 5]. In view of the cited data it was interesting to study the aromatic substitution of the 2-aryl-3-hydroxypyridine N-oxides and compare it with the known properties of the unoxidized compounds. Besides this, a study of the biological properties of the 2-aryl-3-hydroxypridine N-oxides had independent interest.

For this we synthesized a number of 2-aryl-3-hydroxypyridine N-oxides and on the example of 2-phenyl-3-hydroxypyridine N-oxide studied the effect of the N-oxide group on the orientation of aminomethylation, iodination, nitration and sulfonation. Despite the fact that the N-oxidation of 3-hydroxypyridine proceeds in practically quantitative yield, the oxidation of the 2-aryl-3-hydroxypyridine under analogous conditions led to a low yield of the corresponding N-oxides. The optimum conditions for the N-oxidation of the 2-aryl-3-hydroxypyridines were found to be the use of more concentrated H_2O_2 solution. Here the yield of the N-oxides was 70-85%.

The aminomethylation of 2-phenyl-3-hydroxypyridine proceeds under the conditions for the aminomethylation of 2-methyl-3-hydroxypyridine and initially gives the Mannich 6-mono-base, and then the 4,6-bis-base. A study of the aminomethylation of (I) disclosed that in this case the N-oxide group does not affect either the reactivity of the β-pyridinol ring or the orientation of the substitution. The existence of 6-substitution during the aminomethylation of (I) follows from an examination of the IR spectrum of the obtained compound in chloroform, which contains the band of a free hydroxyl group in the 3550 cm^{-1} region. The band of a free OH group is absent in the IR spectrum of the Mannich bis-base (which is soluble in CCl_4, in contrast to the mono-base), which testifies to the substitution of the second aminomethyl group in the 4 position.

In contrast to 2-phenyl-3-hydroxypridine, the iodination of which proceeds only in the 6 position, the oxidized base forms the 4,6-diiodo compound, i.e., in this reaction the N-oxide group increases the reactivity of the β-pyridinol ring, especially the 4 position, as a result of which the substitution proceeds simultaneously in the 4 and 6 positions. The structure of (XI) was confirmed by the NMR spectrum, which was taken in 1 N NaOD solution. The existence of disubstitution greatly simplifies the spectrum of the protons of the pyridine ring and, instead of the three quadruplets in the spectrum of the starting product, only one signal is present in the 4.25 ppm region, the intensity of which corresponds to one C_3H proton, in which connection the intensity of the signal from the protons of the aryl ring (3.65 ppm) corresponds, the same as in the starting product, to 5 protons.

The sulfonation and nitration of (I) was of interest in the planned study of the effect of the N-oxide group on the orientation of substitution in the phenyl ring. Earlier this effect had been established while studying the nitration of 2-phenylpyridine and its N-oxide [6]. As our study disclosed, the sulfonation and nitration of (I), analogous to the unoxidized base, proceeds under the same conditions and is directed to the p-position of the phenyl ring. The structure of the nitro and sulfo compounds was confirmed by the counter synthesis of (XII) and (XIII), both by the sulfonation and nitration of (I) and by the N-oxidation of the 2-(4'-sulfophenyl)-and 2-(4'-nitrophenyl)-3-hydroxypyridines (Scheme 1).

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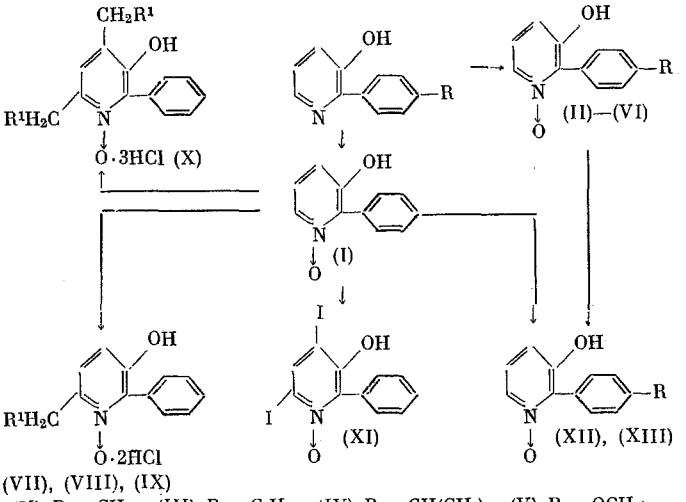
TABLE 1. Derivatives of 2-Phenyl-3-Hydroxypyridine N-Oxide

Compound	Yield, %	Mp., °C	Found, %		Empirical formula	Calculated, %	
			C	H		C	H
(I)	75	260—261	70,38 70,45	4,82 4,79	$C_{11}H_9O_2N$	70,58	4,81
(II)	70	214—215	72,00 72,10	5,58 5,58	$C_{12}H_{11}O_2N$	71,84	5,40
(III)	85	205—206	72,33 72,40	5,91 6,00	$C_{13}H_{13}O_2N$	72,53	6,04
(IV)	74	236—237	73,32 73,30	6,32 6,53	$C_{14}H_{15}O_2N$	73,36	6,55
(V)	72	237—238	66,23 66,10	5,00 4,95	$C_{12}H_{11}O_3N$	66,35	5,06
(VI)	73	233—234	59,49 59,40	3,59 3,47	$C_{11}H_8O_2NCl$	59,58	3,61
(VII)	93	160—161	52,95 53,00	5,70 5,75	$C_{14}H_{18}O_2N_2Cl_2$	53,00	5,68
(VIII)	89	170—171	53,68 53,50	5,37 5,40	$C_{16}H_{20}O_3N_2Cl_2$	53,50	5,58
(IX)	90	163—164	57,00 56,95	6,00 6,10	$C_{17}H_{22}O_2N_2Cl_2$	57,20	6,16
(X)	91	191—192	56,00 56,10	6,90 6,91	$C_{23}H_{34}O_2N_3Cl_3$	56,20	6,93
(XI)	90	199—200	30,90 31,00	1,94 1,75	$C_{11}H_7O_2J_2N_2$	31,10	1,65
(XII)	83	350(decompn.)	49,10 49,20	3,50 3,68	$C_{11}H_9O_5NS$	49,40	3,37
(XIII)	88	237—238	56,22 56,70	3,66 3,40	$C_{11}H_8O_4N_2$	56,9	3,45



(II) R = CH_3; (III) R = C_2H_5; (IV) R = $CH(CH_3)_2$ (V) R = OCH_3;

(VI) R = Cl; (VII) $R^1 = N(CH_3)_2$; (VIII) R^1 = N⟨⟩O;

(IX); (X) R = N⟨⟩; (XII) R = SO_3H; (XIII) R = NO_2

Scheme 1

The structure of (XII) was confirmed by the NMR spectrum, which was taken in $(CH_3)_2SO$. The protons of the pyridine ring form two groups of multiplets, the intensity of which corresponds to one C_6H and two C_3H protons. As a result, substitution in the pyridine ring is exluded. For this reason the character of the spectrum of the protons of the phenyl ring changes sharply, which unequivocally testifies that the reaction is directed to this ring: two groups of signals arise in place of the signal from the 5 protons of the aryl ring, in which connection the intensity of each of them corresponds to only two protons. The symmetrical appearance of this signal testifies that only the p-position of the phenyl ring is substituted.

As a result, the N-oxide group fails to affect the orientation of electrophilic reactions that are directed to the phenyl ring of 2-phenyl-3-hydroxypyridine.

EXPERIMENTAL METHOD

The NMR spectra were obtained for 5-8 mole % solutions in either NaOD or DMSO on an NA-100 spectrometer (100 MHz); the accuracy of measuring the chemical shifts (δ) was ± 0.02 ppm; dioxane was

used as the internal standard. The IR spectra were taken on a UR-20 spectrometer in either $CHCl_3$ or CCl_4 solution (concentration = 2×10^{-4}-3×10^{-5} M/liter). The yields and constants of the synthesized compounds are given in Table 1.

Synthesis of 2-Aryl-3-hydroxypyridine N-Oxides (I)-(VI). With stirring, to 0.1 M of the 2-aryl-3-hydroxypyridine in 100 ml of glacial CH_3COOH was added 40 ml of 40-50% H_2O_2 solution. The reaction mass was kept at 90-95°C for 3-4 h, cooled to ~20°, the solvent was removed and acetone was added to the residue. The obtained precipitate was separated, dried, and recrystallized from alcohol.

Aminomethylation of 2-Phenyl-3-hydroxypyridine N-Oxide (I). With stirring, to a solution of 0.005 M of (I) in 5 ml of alcohol were added 0.005 M of the secondary amine and 0.005 M of 30% aqueous formaldehyde solution. The mixture was heated on the water bath for 3-4 h, the solvent was removed, and the residual viscous oil was dissolved in anhydrous alcohol and saturated with HCl. Here we obtained the dihydrochlorides of the 6-dialkylaminomethyl-2-phenyl-3-hydroxypyridine N-oxide (VII)-(X).

By a similar procedure, but using 2 equivalents of the secondary amine and formaldehyde, the Mannich bis-bases were obtained as the trihydrochlorides (see Table 1).

The band of the stretching vibrations of the OH groups is absent in the IR spectrum of a dilute solution of 2-phenyl-4,6-bispiperidinomethyl-3-hydroxypyridine N-oxide in CCl_4, and the band of the bound OH groups is observed in the 2600-3100 cm^{-1} region. Since the band of the bound OH groups does not change on subsequent dilution, and the band of the free OH groups is not observed, the band at 2600-3100 cm^{-1} must be assigned to the bound OH group.

Iodination of 2-Phenyl-3-hydroxypyridine N-Oxide (I). To 0.01 M of (I) in 50 ml of 10% Na_2CO_3 solution was added a mixture of 9 g of I_2 and 9 g of KI in 50 ml of water, and the mixture was stirred at ~100° for 1-2 h. The reaction mixture was neutralized with CO_2, and the obtained precipitate was separated, washed with water, dried, and recrystallized from alcohol. Compound (XI) was obtained.

Sulfonation of 2-Phenyl-3-hydroxypyridine N-Oxide (I). A solution of 0.016 M of (I) and 5 ml of 20% oleum was heated at 110-120° for 4 h. Then the mixture was cooled, poured over ice, and carefully neutralized with $Ba(OH)_2$. The obtained precipitate was separated, the mother liquor was evaporated to dryness, and the residue was recrystallized from alcohol. Compound (XII) was obtained.

Nitration of 2-Phenyl-3-hydroxypyridine N-Oxide (I). With stirring, to a solution of 0.01 M of (I) in 5 ml of conc. H_2SO_4 at 0° was added 0.01 M of HNO_3 (d 1.5) in 1 ml of H_2SO_4. The reaction mixture was stirred at ~100° for 2 h, cooled, poured over ice, and carefully neutralized with ammonia. The obtained precipitate was separated, dried, and recrystallized from alcohol. Compound (XIII) was obtained.

N-Oxidation of 2-(4'-Nitrophenyl)-3-hydroxypyridine. With stirring, to 0.09 M of 2-(4'-nitrophenyl)-3-hydroxypyridine in 20 ml of glacial CH_3COOH was added 50 ml of 40-50% H_2O_2 solution. The reaction mass was kept at 90-95° for 6 h, cooled to ~20°, and the solvent was removed. Compound (XIII) was obtained in 97% yield, mp 237-238° (from alcohol).

N-Oxidation of 2-(4'-Sulfophenyl)-3-hydroxypyridine. A solution of 3 g of 2-(4'-sulfophenyl)-3-hydroxypyridine 30 ml of glacial CH_3COOH and 15 ml of 40-50% H_2O_2 solution were heated at 100-110° for 24 h. We obtained 2.1 g (74.5%) of (XII), mp above 350° (decompn.).

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CONCLUSIONS

1. Some 2-aryl-3-hydroxypyridine N-oxides were synthesized.

2. A study was made of the effect of the N-oxide group on the orientation in electrophilic reactions that proceed both in the β-pyridinol ring and in the phenyl ring of the molecule. The N-oxide group affects the reactivity of the β-pyridinol ring and the orientation of the substitution only in the iodination reaction.

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