INVESTIGATION OF THE ELECTROPHILIC REACTIONS OF 2-BENZYL-3-HYDROXYPYRIDINE AND ITS N-OXIDE

L. D. Smirnov, V. S. Zhuravlev,
E. E. Merzon, B. E. Zaitsev,
V. P. Lezina, and K. M. Dyumaev

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A comparative investigation of the aminomethylation, azo coupling, and iodination of 2-benzyl-3-hydroxypyridine and its N-oxide has shown that the N-oxide group affects the orientation of iodination but does not affect the direction of aminomethylation and azo coupling. The structures of the newly synthesized compounds were confirmed by the IR and PMR spectra.

An investigation of the electrophilic reactions of 3-hydroxypyridine N-oxide has shown that the principal orienting group is the β-hydroxy group, which directs substitution in the 2 position and then in the 6 position, while the N-oxide group has a para-orienting effect only during iodination [1]. In the case of 2-methyl-3-hydroxypyridine N-oxide, the indicated effect of the N-oxide group was also noted in nitration [2]. In the light of the data presented, it seemed of interest to establish whether the N-oxide group also displays a para-orienting effect in other electrophilic reactions of 2-substituted 3-hydroxypyridines. For this purpose, in the present study we investigated the aminomethylation, azo coupling, and iodination of 2-benzyl-3-hydroxypyridine and its N-oxide. In addition, it was of independent interest to investigate the biological and pharmacological activity of derivatives of 2-benzyl-3-hydroxypyridine N-oxide and to compare these activities with the activities of the unoxidized bases.

The iodination of 2-benzyl-3-hydroxypyridine (I) proceeds in the 6 position and then in the 4 position of the β-pyridol ring [3] with predominant formation of the 6 isomer. The iodination of the corresponding N-oxide (II) under similar conditions proceeds simultaneously in the 6 and 4 positions to give only 4,6-diiodo-2-benzyl-3-hydroxypyridine N-oxide (III). In other words, the N-oxide group increases the reactivity of the 4 position. The structure of III was proved by the PMR spectrum in 1 N NaOD. Only two signals from aromatic protons are present in the spectrum. The signal at 7.02 ppm was assigned to the proton of the pyridine ring, and the second signal at 5.4 ppm was due to the benzene-ring protons. The intensity ratio of these two signals was 1:5; this is evidence in favor of disubstitution.

A comparison of the conditions for the aminomethylation of 2-phenyl- and 2-benzyl-3-hydroxypyridines showed that, as in the case of iodination, replacement of a phenyl group by a benzyl group lowers the reactivity of the pyridine ring, especially of the 4 position. Thus bisaminomethylation of I proceeded under more severe conditions than with 2-phenyl-3-hydroxypyridine. The introduction of an N-oxide group facilitated the aminomethylation but did not affect the orientation of the substitution. Substitution occurs initially in the 6 position; this was shown by the presence of a band at 3600 cm^{-1} (OH) in the IR spectrum of IV and V. The IR spectra of Mannich dibases VI and VII do not contain bands of the stretching vibrations of a free hydroxyl group; this attested to the entry of a second aminomethyl group into the 4 position. The PMR spectrum of V (NR_2 is piperidyl) in dimethyl sulfoxide (DMSO) has signals at 7.70 ppm (pyridine-ring protons) and 7.91 ppm (benzene-ring protons) with an intensity ratio of 2:5; this attests to monosubstitution in the pyridine ring. The signals of the protons of the methylene groups lie at 4.81 and 4.05 ppm, and the protons of the piperidine ring give two multiplets at 3.00 and 2.08 ppm. The spectrum of disubstituted VII (NR_2 is morpholyl) contains the signal of only one proton of the pyridine ring and two singlets corresponding to two CH_2 groups of the aminomethyl grouping at 3.3 and 3.4 ppm.

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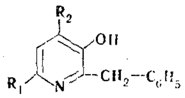
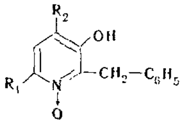
TABLE 1. Aminomethyl and Azo Derivatives of 2-Benzyl-3-hydroxypyridine

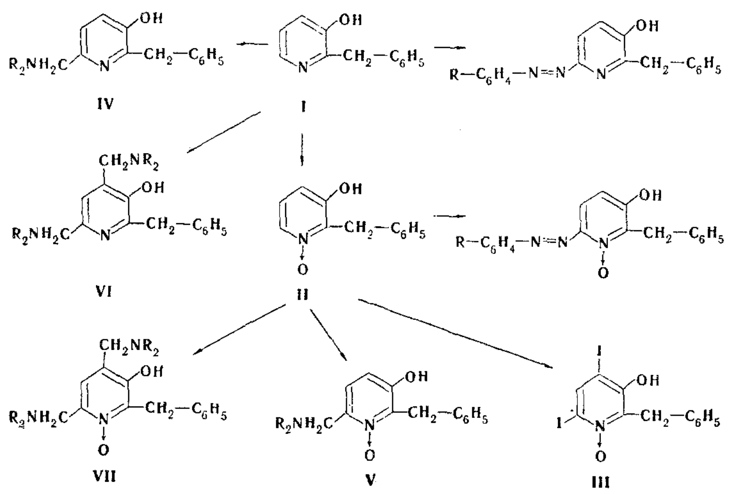


R_1	R_2	mp, °C	Empirical formula	Found, %		Calc., %		Yield, %
				C	H	C	H	
$CH_2NC_5H_{10}$	H	162—163	$C_{18}H_{22}N_2O$	76,4	7,7	76,6	7,8	92,5
$CH_2NC_5H_{10}$	$CH_2NC_5H_{10}$	179—180	$C_{24}H_{33}N_3O$	76,3	8,9	76,0	8,7	90,5
$CH_2NC_4H_8O$	H	144—145	$C_{17}H_{20}N_2O_2$	71,6	6,9	71,8	7,0	93,8
$CH_2NC_4H_8O$	$CH_2NC_4H_8O$	138—140	$C_{22}H_{29}N_3O_3$	69,2	7,6	69,0	7,6	94,3
$C_6H_5N_2$	H	207—208	$C_{18}H_{15}N_3O$	74,6	5,2	74,7	5,2	76,8
$BrC_6H_4N_2$	H	221—223	$C_{18}H_{14}BrN_3O$	58,9	3,7	59,0	3,8	91,0
$NO_2C_6H_4N_2$	H	209—211	$C_{18}H_{14}N_4O_3$	64,5	4,2	64,7	4,2	77,6

TABLE 2. Aminomethyl, Azo, and Iodo Derivatives of 2-Benzyl-3-hydroxypyridine N-Oxides



R_1	R_2	mp, °C	Empirical formula	Found, %		Calc., %		Yield, %
				C	H	C	H	
$CH_2NC_5H_{10}$	H	186—187	$C_{18}H_{22}N_2O_2$	72,4	7,3	72,5	7,4	93,0
$CH_2NC_5H_{10}$	$CH_2NC_5H_{10}$	133—135	$C_{24}H_{33}N_3O_2$	73,2	8,5	72,9	8,3	87,5
$CH_2NC_4H_8O$	H	193—195	$C_{17}H_{20}N_2O_3$	68,4	6,5	68,0	6,7	47,3
$CH_2NC_4H_8O$	$CH_2NC_4H_8O$	199—201	$C_{22}H_{29}N_3O_4$	66,5	7,5	66,2	7,3	83,5
$C_6H_5N_2$	H	207—208	$C_{18}H_{15}N_3O_2$	70,5	4,7	70,7	4,9	78,6
$BrC_6H_5N_2$	H	232—234	$C_{18}H_{14}BrN_3O_2$	56,2	3,6	56,2	3,6	94,3
$NO_2C_6H_5N_2$	H	249—251	$C_{18}H_{14}N_4O_4$	61,5	3,8	61,7	4,0	82,8
I	I	118—120	$C_{12}H_9I_2NO_2$	31,5	2,0	31,8	2,0	91,7



Azo coupling proceeded similarly (at pH 8-9) for I and II. The compounds obtained exist in the azo form in the crystalline state and in $CHCl_3$ solution. Evidence for this is the absence in the IR spectra of the characteristic bands of NH and C = O groups of the hydrazo form, the presence of bands of the azo form (ν_{OH} 3552-3595 cm^{-1}), and the presence of vibrations of the pyridine and phenyl rings (1603 cm^{-1}). The azo group in the synthesized compounds is found in the 6 position, since the IR spectrum contains a band of ν_{OH} stretching vibrations at 3595 and 3552 cm^{-1}, which is characteristic for a free hydroxyl group, and a band at 850 cm^{-1}, which is due to the out-of-plane deformation vibrations of two adjacent CH groups of the pyridine ring. Thus, as in the case of azo coupling, the N-oxide group does not affect the orientation of substitution.

EXPERIMENTAL

The PMR spectra were recorded with an NA-100 spectrometer relative to hexamethyldisiloxane as the internal standard; 5-8 mole % solutions in DMSO or 1 N NaOD were used for the recordings. The IR spectra of $3 \cdot 10^{-4}$ M solutions in CCl_4 or $CHCl_3$ were obtained.

Method Used for Aminomethylation. An equimolecular amount of a secondary amine and a 30% aqueous solution of formaldehyde were added to a solution of 5 mmole of 2-benzyl-3-hydroxypyridine in 5 ml of ethanol, and the mixture was heated for 7-8 h on a water bath, after which the solvent was removed in vacuo. The yields and physicochemical constants of the Mannich bases obtained are presented in Table 1.

The aminomethylation of 2-benzyl-3-hydroxypyridine N-oxide was carried out similarly but, in contrast to the preceding experiment, the mixture was heated for 3-4 h. The yields and physicochemical constants of the compounds obtained are presented in Table 2.

Method Used for Azo Coupling. A solution of the diazonium component (2.7 mmole) and a solution of KOH were added gradually with stirring to a cooled (to 5-10°) solution of 2.7 mmole of 2-benzyl-3-hydroxypyridine in 50 ml of 10% aqueous KOH in such a way that the pH of the medium remained at 8-9. The mixture was held under these conditions for 1 h, after which the mother liquor was neutralized by bubbling CO_2 through it. The precipitate was separated, washed with water, dried, and crystallized from alcohol. The yields and physicochemical constants of the azo derivatives of 2-benzyl-3-hydroxypyridine are presented in Table 1.

The azo coupling of 2-benzyl-3-hydroxypyridine N-oxide was carried out similarly (the yields and physicochemical constants of the products are presented in Table 2).

Method Used for Iodination. A mixture of 9 g of iodine in a potassium iodide solution was added to a solution of 7.4 mmole of 2-benzyl-3-hydroxypyridine N-oxide in 50 ml of 2 N sodium carbonate solution, and the reaction mixture was refluxed for 2-2.5 h and filtered. The mother liquor was neutralized with a weak sulfuric acid solution, and the precipitate was separated, washed with water, dried, and crystallized from alcohol to give the iodo derivative of 2-benzyl-3-hydroxypyridine N-oxide. The yields and physicochemical constants are presented in Table 2.

LITERATURE CITED

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