## STUDY OF THE ORIENTATION OF THE AMINOMETHYLATION OF 2,5-DIHYDROXYPYRIDINE AND N-METHYL-3-HYDROXY-2-PYRIDONE

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The aminomethylation of the 2-hydroxy- and 2-methoxy-3-hydroxypyridines was investigated by us and it was shown that the substitution is directed initially to the 6 position, and then to the 4 position of the pyridine ring [1]. This testifies to the fact that the principal effect on the orientation of electrophilic substitution is exerted by the  $\beta$ -hydroxy group of the pyridine ring. In this connection it seems of interest to ascertain the orientation of aminomethylation for 2,5-dihydroxypyridine (I) and N-methyl-3-hydroxy-2pyridone (II). In addition, the aminomethylation of pyridone (II) is of interest in order to compare the orienting capacity of a phenolic hydroxyl with that of a fixed " $\alpha$ -pyridone" group.

As our study disclosed, the aminomethylation of pyridone (II) proceeds under the same conditions as the aminomethylation of 2,3-dihydroxypyridine.

The obtained Mannich bases represented high-melting crystalline. compounds that are readily soluble in water.

The structure of the synthesized compounds was established by means of the NMR spectra. In the NMR spectrum of the aminomethyl derivative of pyridone (II) is present a symmetrical quartet downfield, which is caused by the spin-spin coupling of the two protons of the pyridine ring. Starting with the spin -spin coupling constants (J = 7.5 Hz), these protons are found at the 4th and 5th carbon atoms. The chemical shifts of the protons for  $C_4H$  and  $C_5H$  in 1 N aqueous NaOD solution are respectively equal to 2.62 and 3.02 ppm (using dioxane as the internal standard). The signals from the four methylene groups of the substituent ( $-N \bigcirc O$ ) are located further upfield at 0.00 and -1.2 ppm. The signal from the  $-CH_2-N$  group lies at 0.28 ppm, whereas the intense peak from  $-NCH_3$  is located in the vicinity of 0.26 ppm.

As a result, the  $\beta$ -hydroxy group exerts an orienting effect on the direction of substitution in pyridone (II). In addition, based on a comparison of the orientation of the aminomethylation for (I) and (II) it is possible to conclude that involvement of the molecule in either the pyridone or the enolic form apparently has little effect on the direction of the substitution.

However, in contrast to (I), attempts to bis-substitute pyridone (II) proved unsuccessful. Our attempts to bis-aminomethylate (I) also proved unsuccessful. At the same time it should be mentioned that even the

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TABLE 1. Aminomethyl Derivatives of N-Methyl-3-hydroxy-2-0Hpyridine RCH<sub>2</sub> dHa Empirical Calculated,% Found, % Yield, мр, °С R % formula Ċ н N G н N 92 58,90 7,12 12,24  $C_{11}H_{16}N_2O_3$ 58,92 7,14 12,50 64,86 12,61 8,08 12,43 89 131 - 13264,81 C12H18N2O2 8.15 210-215 59,26 7,54 15,22  $C_9H_{14}N_2O_2$ 59.34 7.69 15,38 83 (decomp.)

monomethylation of (I) proceeds under much more drastic conditions when compared with 2,3-dihydroxy-pyridine.



A study of the NMR spectrum of the Mannich monobase of (I) disclosed that the substitution is directed to the 6 position of the pyridine ring. This is evidenced by an analysis of the spectrum of the aromatic protons, which consists of two doublets with a spin-spin coupling constant of J = 9.0 Hz, which unequivocally indicates substitution in the 6 position of the ring. The presence of 6-substitution in the aminomethylation of (I) makes it possible to conclude that also in this case the  $\beta$ -hydroxy group exerts the predominant orienting effect.

## EXPERIMENTAL METHOD

<u>6-Dialkylaminomethyl-N-methyl-3-hydroxy-2-pyridones.</u> To a stirred solution of 0.625 g of pyridone (II) in 15 ml of alcohol were added 0.5 g of 30% formaldehyde solution and 0.005 mole of the secondary amine. The reaction mixture was heated on the water bath at 70-80°C for 30 min. The solvent was removed in vacuo, while the residual viscous oil was recrystallized from acetone to give the Mannich base. The yields and melting points are given in Table 1.

<u>6-Morpholinomethyl-2,5-dihydroxypyridine</u>. To a stirred solution of 0.55 g of (II) in 15 ml of alcohol were added 0.43 g of morpholine and 0.5 g of 30% formaldehyde solution. The mixture was heated on the steam bath for 3 h. The solvent was removed, and the residue was dissolved in anhydrous alcohol and then saturated with HCl gas. We obtained 0.94 g (91% yield) of 6-morpholinomethyl-2,5-dihydroxypyridine hydro-chloride, mp 189-190. Found: C 48.51; H 5.96; N 11.25%.  $C_{10}H_{14}N_2O_3 \cdot HCl$ . Calculated: C 48.68; H 6.08; N 11.33%.

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## CONCLUSIONS

1. A study was made of the aminomethylation of 2,5-dihydroxypyridine and N-methyl-3-hydroxy-2-pyridone.

2. The aminomethylation of 2,5-dihydroxypyridine and N-methyl-3-hydroxy-2-pyridone is directed to the 6 position of the pyridine ring.

## LITERATURE CITED

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