STUDY OF SOME ELECTROPHILIC REACTIONS OF 5-BENZYL-3-HYDROXYPYRIDINE 1-OXIDE

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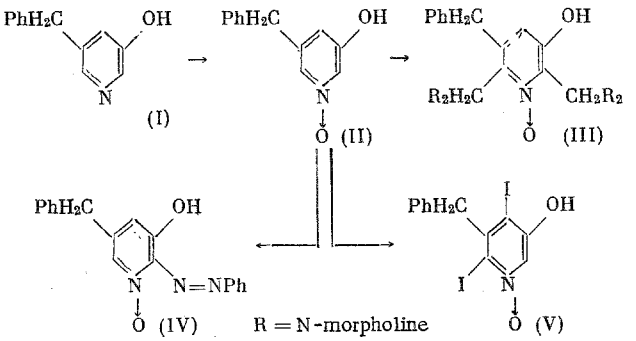
Previously [1] we had studied the aminomethylation and azo-coupling of 5-benzyl-3-hydroxypyridine (I), in which connection we were unable to isolate the corresponding 6-substituted derivatives of (I), whereas 3-hydroxypyridine is easily aminomethylated and azo-coupled in the 6 position [2].

On the example of the 2-benzyl- [3] and 2-phenyl-3-hydroxypyridines [4] it was established that the N-oxide group affects the orientation of iodination, while during aminomethylation it facilitates substitution in the 4 and 6 positions of the hydroxypyridine ring. The indicated phenomenon was also observed in the basic deuterium exchange of these compounds [5].

It seemed interesting to ascertain the effect of the N-oxide group on the orientation of the aminomethylation, azo-coupling, and halogenation of 5-benzyl-3-hydroxypyridine N-oxide (II).

A study of the aminomethylation of (II) confirmed the above-mentioned effect of the N-oxide group. Thus, if (I) is aminomethylated only in the 2 position, then (II) under these conditions easily forms the 2,6-bis-substituted Mannich bases. The structure of the obtained compounds was established on the basis of the IR and NMR spectral data. A broad intense absorption band in the 2600-3200 cm^{-1} region is observed in the IR spectrum of (III) in CCl_4, which is characteristic for an OH group, attached by an intramolecular hydrogen bond (IHB), which indicates that one of the aminomethyl groups is present in the



o-position to the β-hydroxyl. The presence of bis-substitution during the aminomethylation of (II) follows from a comparison of the NMR spectra of (II) and (III). In compound (II) the signals in the 7.44 and 7.33 ppm regions belong to the H^2 and H^6 protons, while the signal at 6.74 ppm belongs to the H^4 proton. The protons of the C_6H_5 group give a multiplet at 7.16 ppm. The signals from the CH_2 group are located at 3.59 ppm. Signals from H^2 and H^6 are absent in the NMR spectrum of (III), which confirms the presence of aminomethyl groups in the 2 and 6 positions of the hydroxypyridine ring. The values of the chemical shifts of the signals from H^4 and C_6H_5 (6.58 and 7.10 ppm) show little change when going from (II) to (III). In addition, two additional singlets at 3.83 and 3.70 ppm arise in the spectrum of (III), which can be assigned only to the protons of the CH_2NR_2 group. The signal from the CH_2Ph group is located at 3.60 ppm. And, finally, two multiplets at 3.50 and 2.50 ppm appear in the spectrum of (III), which are caused by the 16 protons of the two morpholine rings. The ratio in the intensities of the signals in the spectrum of (III)

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confirms the given assignment. As a result, the aminomethylation of (II) proceeds simultaneously in the 2 and 6 positions.

A somewhat different orientation was observed by us in the iodination of (II). Similar to 3-hydroxypyridine 1-oxide [6], the iodination of (II) proceeds with the formation of the 4,6-diiodo derivative (V), the structure of which is also confirmed by the IR and NMR spectra. The IR spectrum of (V) contains a band at 3462 cm^{-1}, which testifies to an IHB of type OH $\cdots$ I, and consequently one of the iodine atoms is found ortho to the OH group. The NMR spectrum of (V) indicates substitution in the 4 and 6 positions of the hydroxypyridine ring. The spectrum of (V), in contrast to the spectrum of (II), lacks signals from H^4 and H^6. The H^2 proton gives a signal at 7.49 ppm, while the protons of the C_6H_5 group give a signal at 7.17 ppm. The signal from the CH_2 group is located at 3.57 ppm. As a result, the iodination of (II) proceeds in the 4 and 6 positions of the hydroxypyridine ring.

In contrast to aminomethylation and iodination, only the 2-monosubstituted compounds are formed in the azo-coupling of (II). The absence of 6-substitution must evidently be explained by the greater steric effect of the benzyl group in reactions of this type. The presence of an azo group in the 2 position follows from the IR spectrum of the azo derivative (IV), in which a broad intense absorption band is observed in the 3000-3400 cm^{-1} region, which is caused by an IHB of type OH...N=NPh. Taking into account the inertness of the 4 position in 3-hydroxypyridine and its derivatives in azo-coupling reactions, the structure of 2-benzeneazo-5-benzyl-3-hydroxypyridine can be assigned to compound (IV).

EXPERIMENTAL METHOD

The IR spectra of the (III)-(V) solutions ($3 \cdot 10^{-4}$ M in either CCl_4 or $CHCl_3$) were taken on a UR-20 spectrophotometer. The NMR spectra of 10% solutions of the samples in 1 N NaOD solution were taken on an HA-100 spectrometer. The values of the chemical shifts are expressed on the δ scale.

2,6-bis(Morpholinomethyl)-5-benzyl-3-hydroxypyridine 1-Oxide (III). To a solution of 0.005 mole of (II) in 5 ml of alcohol were added 0.01 mole of morpholine and 0.01 mole of 30% aqueous CH_2O solution, after which the mixture was heated on the steam bath for 2 h, the solvent was removed in vacuo, and the oily residue was treated with alcoholic HCl solution. We obtained the trihydrochloride of (III) in 95% yield, mp 215-217° (alcohol). Found: C 51.99; H 6.39%. $C_{22}H_{32}Cl_3O_4N_3$. Calculated: C 51.90; H 6.29%.

4,6-Diiodo-5-benzyl-3-hydroxypyridine 1-Oxide (V). With stirring, to a solution of 0.005 mole of (II) in 20 ml of 10% Na_2CO_3 solution was added in 30 min a mixture of 0.02 mole of iodine and 0.02 mole of KI in 20 ml of water, maintaining the temperature at ~20°, after which the mixture was allowed to stand overnight at this temperature. Then the mixture was neutralized by the passage of CO_2 gas, and the obtained precipitate was separated and recrystallized from acetone. We obtained (V) in 92% yield, mp 154-155°. Found: C 31.87; H 2.05%. $C_{12}H_9I_2O_2N$. Calculated: C 31.80; H 1.99%.

2-(p-Bromophenylazo)-5-benzyl-3-hydroxypyridine 1-Oxide (IV). With stirring, to a solution of 0.0025 mole of (II) in 50 ml of 10% aqueous KOH solution, cooled to 0-5°C, was gradually added the azo component (from 0.0025 mole of p-$BrC_6H_4NH_2$ and 0.0025 mole of $NaNO_2$) in such a manner that the pH of the medium remained in the range 8-9. The reaction mass was kept at 20° for 1 h, neutralized by the passage of CO_2 gas, and the obtained precipitate was separated, dried, and recrystallized from alcohol. We obtained (IV) in 90.5% yield, mp 142-144°. Found: C 55.42; H 3.58%. $C_{18}H_{14}BrO_2N_3$. Calculated: C 55.67; H 3.61%.

CONCLUSIONS

1. A study was made of the aminomethylation, iodination, and azo-coupling of 5-benzyl-3-hydroxypyridine 1-oxide (II).

2. The insertion of the N-oxide group into the 5-benzyl-3-hydroxypyridine molecule increases the reactivity of the latter in the aminomethylation and iodination reactions.

3. The aminomethylation of (III) leads to the 2,6-bis-substituted Mannich bases, whereas iodination gives the 4,6-disubstituted derivative.

LITERATURE CITED

1. L. D. Smirnov, V. S. Zhuravlev, V. P. Lezina, and K. M. Dyumaev, Izv. Akad. Nauk SSSR, Ser. Khim., 2817 (1973).
2. L. D. Smirnov, V. P. Lezina, V. F. Bystrov, and K. M. Dyumaev, ibid., 198 (1965).

3. L. D. Smirnov, V. S. Zhuravlev, E. E. Merzon, V. P. Lezina, B. E. Zaitsev, and K. M. Dyumaev, Khim. Geterotsikl. Soed., 1880 (1973).
4. L. D. Smirnov, V. I. Kuz'min, A. E. Zbarskii, V. P. Lezina, and K. M. Dyumaev, Izv. Akad. Nauk SSSR, Ser. Khim., 461 (1973).
5. V. P. Lezina, A. U. Stepanyants, V. S. Zhuravlev, L. D. Smirnov, and K. M. Dyumaev, ibid., 1498 (1974).
6. R. Lewicka and E. Plazek, Roczn. Chem., 40, 1875 (1966).