SYNTHESIS OF 5-BENZYL-3-HYDROXYPYRIDINE AND ITS N-OXIDE

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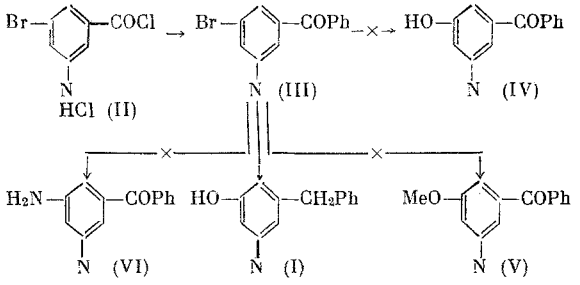
In continuation of studying the rules for the orientation of electrophilic substitution in the series of benzyl-substituted 3-hydroxypyridines, and also for the purpose of ascertaining the mutual effect of the β-pyridol and benzene rings, separated by a CH_2 group, we undertook the synthesis of the previously unknown 5-benzyl-3-hydroxypyridine (I) and its N-oxide.

We used 5-bromonicotinoyl chloride (II) as the intermediate product, which was used to acylate benzene and give 5-bromo-3-benzoylpyridine (III). The bromination of nicotinic acid had been done previously [1] and gave 5-bromonicotinic acid in good yield. Friedel—Crafts acylation had been studied only on the example of nicotinoyl chloride. Our experimental studies disclosed that (II) easily acylated benzene in the presence of anhydrous $AlCl_3$ to give (III). We proposed to accomplish the further conversion of (III) to (I) by first replacing the Br atom by methoxy (V), and then by the hydroxy group to give 3-hydroxy-5-benzoylpyridine (IV), and then convert (IV) to (I) by the Kizhner reaction.



However, contrary to the rules of nucleophilic exchange of halogen atoms for the hydroxy(methoxy) group, the insertion of the electron-acceptor keto group in the β-pyridol ring exerted a negative effect on the ease of cleaving Br atom. In contrast to 3-bromopyridine, for which the satisfactory formation of the 3-hydroxy(methoxy)pyridines was described when it is heated with either alkali or CH_3ONa solution, (III) did not give the 3-hydroxy(methoxy) derivatives (IV) and (V). Attempts to synthesize 3-amino-5-benzoylpyridine (VI) by reacting (III) with NH_3 in the presence of Cu^{2+}, in order to subsequently diazotize (VI) to (IV), also proved unsuccessful.

The above-indicated negative results caused us to turn to another scheme for the synthesis of (I) via the replacement of the benzoyl group by benzyl and the subsequent conversion of 3-bromo-5-benzoylpyridine to (I).

However, (III) was converted directly to (I) in high yield under the conditions of the Kizhner reaction, described for pyridine ketones [2]. The structure of (I) was confirmed by the IR and NMR spectral data. The IR spectrum of (I) in dilute $CHCl_3$ solution has the band of the OH group in the 3585-3600 cm^{-1} region. Since the presence of a benzyl or phenyl group α to the OH group causes the ν_{OH} band to shift by 50-80 cm^{-1} [3], the 3585-3600 cm^{-1} band can be assigned to the free OH group. Consequently, the benzyl group is not α to the OH group.

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Based on the character of the multiplet nature of the signals in the NMR spectrum of (I), and a comparison with the spin–spin coupling constants of the protons in 2-methyl- and 6-methyl-3-hydroxypyridine, it was established that the substitution is directed to the 5 position. A doublet with J = 2.5 Hz lies downfield at 7.75 ppm, and a doublet with J = 1.8 Hz lies at 7.52 ppm. A quadruplet with J = 2.5-1.8 Hz is located further upfield at 6.89 ppm. These values of the spin–spin coupling constants can be obtained only under the condition that substitution was in the 5 position. If it is taken into account that in 3-hydroxypyridine derivatives $J_{24} > J_{46}$ [4], then the two doublets should be assigned to the C_2H and C_6H protons, and the quadruplet to the C_4H proton. In the opposite case the character of the multipleticity from the protons of the pyridine ring would be different. Thus, in the case of the 4-substituted product the spectrum would have doublets from C_6H ($J_{56} \sim 4.5$ Hz) and C_2H ($J_{52} \sim 1$ Hz), and a quadruplet from C_5H. The five protons of the phenyl ring give a signal at 7.38 ppm. The signal from the protons of the CH_2 group lies at 3.75 ppm. The protons of the hydroxyl group and the solvent give one averaged signal in the 4.90 ppm region. The ratio of the intensities of all of the signals in the spectrum confirms the made assignment.

EXPERIMENTAL METHOD

The IR spectra were recorded on a UR-20 spectrophotometer in $CHCl_3$ solution. The NMR spectra were taken on a HA-100 spectrometer. The chemical shifts were measured relative to dioxane and recalculated to HMDS. As the solvent we used 1 N NaOD solution (concentration of (I) = 8 mole %).

3-Bromo-5-benzoylpyridine (III). With stirring and cooling, 500 g (3.75 moles) of $AlCl_3$ was added in 40 min to a solution of 5-bromonicotinoyl chloride hydrobromide (obtained by the bromination of 1 mole of nicotinoyl chloride) in 700 ml of benzene, cooled to 0°C. The mixture was stirred for 1 h at 20°, and then the temperature was raised slowly, and the mixture was refluxed for 5-6 h until the HCl evolution ceased. After cooling, the mixture was poured into an ice-water mixture that had been acidified with HCl, the organic layer was separated, the solvent was removed, and the product was vacuum-distilled. We obtained (V) in 86% yield, bp 194-195° (4 mm), mp 73-74° (from alcohol). Found: C 55.02; H 3.07; Br 30.76%. $C_{12}H_8NOBr$. Calculated: C 55.00; H 3.07; Br 30.50%.

3-Hydroxy-5-benzoylpyridine (IV). A mixture of 0.05 mole of (III) and 0.5 mole of KOH was heated at 120-150° for 2 h. The cooled mixture, after adding 200 ml of water, was filtered, the mother liquor was acidified with 10% H_2SO_4 solution, and the obtained precipitate was separated and dried. After continuous extraction with ether and removal of the solvent we obtained (IV) in 7.6% yield, mp 119-120°. Found: C 72.33; H 4.48; N 7.01%. $C_{12}H_9NO_2$. Calculated: C 72.41; H 4.52; N 7.04%.

3-Hydroxy-5-benzylpyridine (I). With stirring, to a solution of 0.1 mole of (III) in 100 ml of diethylene glycol was added 0.33 mole of hydrazine hydrate, and then 0.5 mole of powdered KOH was sifted in. The mixture was heated under reflux at 155° for 2 h, after which the condenser was replaced by a descending condenser and the temperature was gradually raised to 195°, held there for 4 h, and the diethylene glycol was distilled off using a high vacuum. The residue was dissolved in water (150-200 ml), filtered, the filtrate was acidified with 20% H_2SO_4 solution to pH 6, and the obtained precipitate was separated and dried by continuous extraction in a Soxhlet apparatus. We obtained (I) in 65% yield, mp 136°. Found: C 77.85; H 5.93; N 7.55%. $C_{12}H_{11}NO$. Calculated: C 77.83; H 5.94; N 7.57%.

5-Benzyl-3-hydroxypyridine N-Oxide (VII). To a solution of 10 g of 5-benzyl-3-hydroxypyridine in 50 ml of glacial AcOH was added 20 ml of 30% H_2O_2 solution, and the mixture was heated on the steam bath for 6 h. The solvent was removed in vacuo, the oily residue was treated with alcoholic HCl solution, the alcohol was distilled off, 20 ml of acetone was added, and the solution was let stand for several days. The crystallized 5-benzyl-3-hydroxypyridine N-oxide hydrochloride was filtered, washed with acetone, dried, and recrystallized from alcohol. We obtained (VII) in 41% yield, mp 98-100°. Found: C 60.7; H 5.06%. $C_{12}H_{11}NO_2 \cdot HCl$. Calculated: C 59.8; H 4.9%.

The (VII) hydrochloride was converted to the free base by treating its aqueous solution with 5% $NaHCO_3$ solution to pH 7, mp 124-125° (alcohol). Found: C 71.80; H 5.55; N 6.93%. $C_{12}H_{11}NO_2$. Calculated: C 71.61; H 5.47; N 6.97%.

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CONCLUSIONS

The acylation of benzene with 5-bromonicotinoyl chloride gave 5-bromo-3-benzoylpyridine in high yield, the Kizhner reduction of which led to the synthesis of 3-hydroxy-5-benzylpyridine in good yield.

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