STUDY OF SOME ELECTROPHILIC REACTIONS OF 6-HYDROXY(METHOXY)-2-BENZYL-3-HYDROXYPYRIDINES

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A study of electrophilic substitution in the 6-hydroxy(methoxy)-2-phenyl-3-hydroxypyridines disclosed that the insertion of hydroxy and methoxy groups in the 6-position changes the course of the reaction. Thus, the azo-coupling of the indicated compounds takes place in the 5-position [1], which is unreactive in the case of 2-phenyl-3-hydroxypyridine. Consequently, the principal orienting agents in these compounds are the hydroxy and methoxy groups that are found in the 6-position of the β-pyridinol ring. At the same time, the nitration and sulfonation of the 6-hydroxy(methoxy)-2-phenyl-3-hydroxypyridines, similar to 2-phenyl-3-hydroxypyridine, is directed to the p-position of the phenyl ring and proceeds under the same conditions [2].

It was interesting to ascertain the rules for the electrophilic substitution of the 6-hydroxy- (I) and 6-methoxy-2-benzyl-3-hydroxypyridines (II). For this purpose we studied the aminomethylation, azo-coupling, iodination and sulfonation of (I) and (II), and also of 6-methoxy-2-benzyl-3-hydroxypyridine N-oxide (III). It proved that the sulfonation of (I), (II), and (III) proceeds under the same conditions as in the case of 2-benzyl-3-hydroxypyridine, and is directed to the p-position of the phenyl ring. The structure of the obtained compounds was established by the NMR spectra. Starting with the ratios of the integral areas of the individual signals in the spectra of the sulfonic acid, the two doublets at 7.00 and 6.38 ppm must be assigned to the C_4H and C_5H protons of the pyridine ring. Consequently, substitution in the pyridinol ring fails to occur. The formation of two groups of symmetrical signals at 7.30 and 7.68 ppm, the intensity of which corresponds to four protons, in place of one multiplet from the five protons of the starting product, testifies to the fact that the sulfonation is directed to the benzene ring. The symmetrical character of the spectrum corroborates the direction of the substitution in the p-position. The singlet from the protons of the methoxy group lies at 3.58 ppm. An analogous picture is also observed in the case of sulfonic acids (II) and (III). As a result, the insertion of hydroxy and methoxy groups in the 6-position of the β-pyridinol ring fails to affect the orientation of the sulfonation.

In contrast to 6-methoxy-2-phenyl-3-hydroxypyridine, 6-methoxy-2-benzyl-3-hydroxypyridine fails to undergo substitution in azo-coupling, aminomethylation and iodination reactions, which indicates a reduction in the reactivity of the β-pyridinol ring when the phenyl group is replaced by benzyl. However, 6-methoxy-2-benzyl-3-hydroxypyridine N-oxide enters into these reactions, giving the 5-substituted derivatives, the structure of which was established by the IR spectra: an intense absorption band in the 3600-3500 cm^{-1} region, caused by the stretching vibrations of the free OH group, testifies to the absence of a substituent in the 4-position, and consequently, that the substitution is directed to the 5-position of the β-pyridinol ring. In the opposite case, the formation of an intramolecular hydrogen bond between the OH group and the substituent would shift this band by 500-800 cm^{-1}. As a result, in the case of (III), despite the presence of two functional groups (OH and N-oxide), which direct substitution to the 4-position, the principal orienting agent is the methoxy group in the 6-position.

In contrast to (II), 3,6-dihydroxy-2-benzylpyridine easily undergoes aromatic substitution, which in this case proceeds both in the 5- and the 4-position, which testifies to their equal reactivity. The 4-benzeneazo- and 5-benzeneazo-3,6-dihydroxy-2-benzylpyridines were isolated when the azo-coupling of

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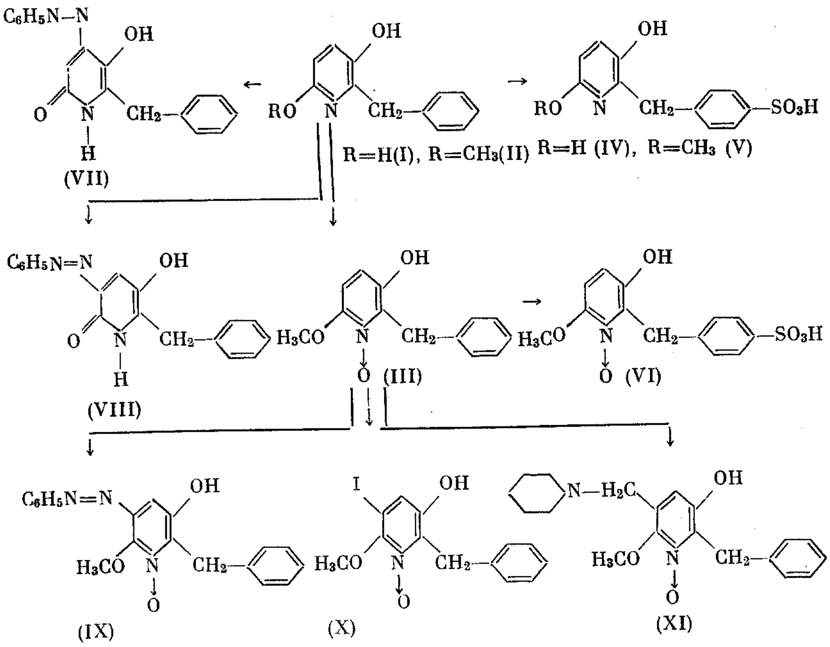

(I) with phenyldiazonium chloride was run under weakly alkaline conditions. Their structure was confirmed by the IR spectra. An intense absorption band at 3620 cm^{-1} is observed in the IR spectrum of 5-benzeneazo-I in $CHCl_3$, which is caused by the stretching vibrations of the free β-hydroxyl group. This band is shifted to 2960 cm^{-1} in the IR spectrum of 4-benzeneazo-I in $CHCl_3$, which testifies to the presence of an intramolecular hydrogen bond of the OH. . . $N\lessgtr$ type. The absorption bands of $\nu_{C=O}$ at 1650 cm^{-1} are observed in both spectra, since the indicated dihydroxypyridine exists in neutral solution in the pyridone form.

The iodination of (I) gave negative results in view of the extreme instability of the iodo-substituted product.

EXPERIMENTAL

The NMR spectra were taken on an NA-100 spectrometer in 1 N NaOD solution, using HMDS as the internal standard, while the IR spectra were taken on a UR-20 spectrometer in either CCl_4 or $CHCl_3$ solution.

6-Methoxy-2-benzyl-3-hydroxypyridine N-Oxide. (III). The compound was obtained by the oxidation of (II) as described in [3]. Yield 75%, mp 203-205° (alcohol). Found: C 67.42; H 5.57; N 6.10%. $C_{13}H_{13}NO_3$. Calculated: C 67.53; H 5.63; N 6.06%.

6-Methoxy-2-(4'-sulfobenzyl)-3-hydroxypyridine (V). A solution of 1 g of (II) in 4 ml of 20% oleum was stirred at 40° for 1 h, poured over ice, and salted out with NaCl. The obtained precipitate was separated, and then recrystallized from water. We obtained 1.27 g (92%) of (V), mp 263-264°. Found: C 52.91; H 4.39; S 10.72%. $C_{13}H_{13}NO_5S$. Calculated: C 52.88; H 4.41; S 10.85%.

6-Methoxy-2-(4'-sulfobenzyl)-3-hydroxypyridine 1-Oxide (VI). Obtained in a similar manner as the above, in 95% yield, mp > 300° (decomp.). Found: C 50.21; H 4.16; N 4.56; S 10.31%. $C_{13}H_{13}NO_6S$. Calculated: C 50.16; H 4.18; N 4.51; S 10.28%.

3,6-Dihydroxy-2-(4'-sulfobenzyl)pyridine (IV). Obtained in a similar manner in 97% yield, mp > 300° (decomp.). Found: C 51.29; H 3.89; N 4.96; S 11.42%. $C_{12}H_{11}NO_5S$. Calculated: C 51.25; H 3.92; N 4.98; S 11.39%.

4-Benzeneazo- (VII) and 5-Benzeneazo-3,6-dihydroxy-2-benzylpyridine (VIII). To a solution of 0.0025 mole of (I) in 50 ml of 1 N NaOH solution was added in drops, at 5-10°, a solution of 0.0027 mole of phenyldiazonium chloride in KOH solution, maintaining the pH of the medium in the range 8-9. The reaction mass was stirred for 1 h, and the obtained precipitate was separated, dried, and recrystallized from alcohol. We obtained 0.2 g (26.4%) of (VII), mp 233-235°. Found: C 70.76; H 4.94; N 13.75%. $C_{18}H_{15}N_3O_2$.

Calculated: C 70.82; H 4.92; N 13.77%. The mother liquor from the separation of (VII) was neutralized with dilute H_2SO_4 solution, and the precipitate obtained was separated, dried, and recrystallized from alcohol. We obtained 0.15 g (20%) of (VIII), mp 123-125°. Found: C 70.79; H 4.84; N 13.78%.

6-Methoxy-5-benzeneazo-2-benzyl-3-hydroxypyridine 1-Oxide (IX). Obtained in a similar manner in 76.5% yield, mp 242-243°. Found: C 68.11; H 5.01; N 12.50%. $C_{19}H_{17}N_3O_3$. Calculated: C 68.06; H 5.07; N 12.54%.

6-Methoxy-5-iodo-2-benzyl-3-hydroxypyridine 1-Oxide (X). To a solution of 0.4 g of (III) in 9 ml of 10% Na_2CO_3 solution, with heating on the steam bath, was added in drops a solution of 0.46 g of I_2 and 0.5 g of KI in 10 ml of water, after which the mixture was stirred at the same temperature for 1 h, cooled, and neutralized with dilute H_2SO_4 solution until weakly acid. The precipitate obtained was separated, dried, and recrystallized from alcohol. We obtained 0.31 g (50%) of (X), mp 99-101°. Found: C 43.66; H 3.38; N 3.89; I 35.63%. $C_{13}H_{12}NO_3I$. Calculated: C 43.70; H 3.36; N 3.92; I 33.50%.

6-Methoxy-5-piperidinomethyl-2-benzyl-3-hydroxypyridine 1-Oxide (XI). A solution of 0.005 mole of (III) in 5 ml of water and an equimolar amount of piperidine in 30% aqueous formalin solution was heated at 100° for 3-4 h. The precipitate obtained on cooling the mixture was separated, rubbed with acetone, and filtered. We obtained (XI) in 70% yield; mp 234-236°. Found: C 69.54; H 7.29; N 8.53%. $C_{19}H_{24}N_2O_3$. Calculated: C 69.51; H 7.39; N 8.54%.

CONCLUSIONS

A study was made of the effect of the benzyl group on the reactivity and the orientation of aromatic substitution in the 6-hydroxy(methoxy)-2-benzyl-3-hydroxypyridines and their N-oxides.

LITERATURE CITED

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