SULFONATION OF PYRIDINE, 3-HYDROXYPYRIDINE, AND THEIR N-OXIDES

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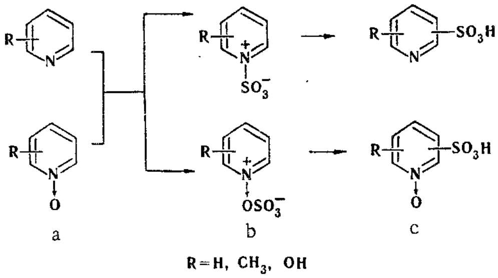
UDC 547.822.6'823:542.945.22

The sulfonation of pyridine derivatives and their N-oxides in fuming sulfuric acid was studied. 3-Hydroxypyridine N-oxide is sulfonated in the 2 position of the pyridine ring. A probable scheme for the substitution is proposed.

The sulfonation of pyridine, like that of its N-oxide, requires extremely severe conditions and proceeds in the 3 position rather than the 4 position of the pyridine ring [1, 2]. To explain the peculiarities of the behavior of pyridine derivatives and their N-oxides in sulfonation, a number of assumptions have been made: the actual sulfonating agent is free SO_3 contained in the fuming sulfuric acid [3], pyridine N-oxide reacts in the form of a salt [4], and, finally, in analogy with nitration, under the sulfonation conditions pyridine derivatives and their N-oxides react in the protonated form [2, 5, 6].

However, these assumptions give rise to a number of contradictions. The inert character of 2-, 3-, and 4-hydroxypyridines in sulfonation is incomprehensible in this case. The behavior of N-methyl-2-hydroxypyridine, which is readily sulfonated [6], is less understandable.

Greater clarity can be achieved if one proceeds from the fact that a complex of sulfur trioxide with the heterocycle (a → b, see the scheme below) is initially formed in sulfonation in fuming sulfuric acid. This complex is then catalytically rearranged at higher temperatures to give the corresponding sulfonic acid (b → c).



The production of pyridine sulfotrioxide in 65% fuming sulfuric acid [7] confirms the possibility of the a → b transition. To prove the b → c transition, we carried out the sulfonation of pyridine in 18% fuming sulfuric acid, during which the amount of SO_3 in mole fractions was equal to or less than the amount of base used.

In contrast to the results in [4], heating at 220-230°C in the presence of a mercury sulfate catalyst led to pyridine-3-sulfonic acid. Under these same conditions, pyridinesulfonic acid N-oxide was obtained from pyridine N-oxide.

Under conditions analogous to the sulfonation of pyridine and with a reactant mole fraction ratio of 1:2.5, 3-hydroxypyridine forms 25% of 3-hydroxypyridine-2-sulfonic acid. The yield does not change when the reactant mole fraction ratio is decreased to 1:1.

The sulfonation of 3-hydroxypyridine N-oxide under the conditions and with the reactant ratio indicated above is accompanied by deoxygenation, and the product yield is 25%.

Scientific-Research Institute of Organic Intermediates and Dyes, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 813-815, June, 1973. Original article submitted December 12, 1972.

From the results presented, one should probably acknowledge that the determining step is rearrangement b → c (see the scheme on previous page). The ease of rearrangement with subsequent formation of the sulfonic acid depends, in addition to other factors, on the stability of complex b. If one takes into account that its stability depends on the strength of the base used [8], the reason for the decrease in the yields in the sulfonation of 2-, 3-, and 4-picolines and 2,6-dimethylpyridine as compared with pyridine [3] becomes comprehensible. The relatively low yields of sulfonic acids from the 2-, 3-, and 4-hydroxypyridines are also explained by the high stability of their adducts with sulfur trioxide due to transmission of the +M effect of the OH group from the corresponding position of the pyridine ring.

Weakening of the stability of the complex or carrying out the reaction under conditions that exclude the formation of a complex should, in this case, have facilitated sulfonation. In fact, the increasing tendency of N-substituted 2-hydroxypyridine to undergo sulfonation as compared with the corresponding pyridine base is in opposition to its behavior in nitration [9]; this indicates different mechanisms for substitution in these reactions. The 2 position undergoes substitution in the sulfonation of 3-hydroxypyridine N-oxide. The fact that no melting-point depression was observed for a mixture of oxidized 3-hydroxypyridine-2-sulfonic acid with 3-hydroxypyridinesulfonic acid N-oxide serves as proof of this.

The structures of the pyridine-3-sulfonic acid and its N-oxide obtained under our conditions were proved by comparison with products of known structure and synthesized from the appropriate bases by methods in [3, 10, 11].

EXPERIMENTAL

Pyridine-3-sulfonic Acid (I). A mixture of 16 ml (0.2 mole) of dry pyridine, 1 g of mercury sulfate, and 90 g [47 ml (0.2 mole) of free SO_3] of 18% fuming sulfuric acid was heated to 220-230° and held at this temperature for 15 h. The sulfonic acid product was then isolated by the method in [3] to give 13.1 g (41.2%) of a material with mp 344-345.5° (mp 342-346° [10], 352-256° [3]).

Pyridine-3-sulfonic Acid N-Oxide (II). A mixture of 19 g (0.2 mole of freshly distilled pyridine N-oxide, 1 g of mercury sulfate, and 90 g [47 ml (0.2 mole) of free SO_3] of 18% fuming sulfuric acid was heated to 220-230° and held at this temperature for 17 h. The sulfonic acid product was isolated and purified by the method in [11] to give 11 g (31.2%) of a substance with mp 235-238° (mp 238-243° [11], 237-238° [5]).

Sodium 3-Hydroxypyridine-2-sulfonate (III). A mixture of 18% fuming sulfuric acid (0.07 mole of free SO_3) was heated to 220-230° and held at this temperature for 23 h. The cooled reaction mixture was neutralized with aqueous NaOH to pH 7-7.5 and evaporated to dryness in vacuo. The residue was extracted with acetone to give 4.2 g (44.2%) of the starting 3-hydroxypyridine with mp 115-118°. Prolonged extraction with methanol yielded 4.3 g (21.8%) of III with mp 261-263°. When the sulfonation of 3-hydroxypyridine was carried out with a threefold molar amount of free SO_3 in H_2SO_4 under the conditions described above, the yield of III was 25%.

3-Hydroxypyridine-2-sulfonic Acid N-Oxide (IV). A mixture of 11.1 g (0.1 mole) of 3-hydroxypyridine N-oxide, 1 g of mercury sulfate, and 44.5 g [23.2 ml (0.1 mole) of free SO_3] of 18% fuming sulfuric acid was heated to 220-230° and held at this temperature for 20 h. The cooled reaction mixture was neutralized with aqueous $Ba(OH)_2$ to pH 7-7.5, and the filtrate was evaporated to dryness in vacuo. Extraction of the dry residue with acetone gave 2.05 g of 3-hydroxypyridine with mp 116-200°. The residue was dissolved in the minimum amount of water, and the solution was acidified with the calculated amount of concentrated H_2SO_4 and evaporated to dryness to give 4.2 g (23.1%) of IV with mp 262.5-265° (from alcohol–water). Found: N 7.4%. $C_5H_5NO_5S$. Calculated: N 7.3%. When the sulfonation was carried out in excess SO_3, the yield of IV was 25%.

Oxidation of Sodium 3-Hydroxypyridine-2-sulfonate (III). A mixture of 0.5 g (0.002 mole) of III, 2 ml of 30% H_2O_2, and 20 ml of CF_3COOH was held at 65-70° for 4 h, after which it was treated with 5 ml of concentrated HCl and evaporated to dryness in vacuo. Recrystallization from aqueous alcohol solution gave 0.06 g (12.5%) of a sulfonic acid with mp 265-267°. No melting-point depression was observed for a mixture of this product with IV.

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