CHEMISTRY OF HETEROCYCLIC N-OXIDES AND RELATED COMPOUNDS

13*. ACYLAMINATION OF PYRIDINE N-OXIDE BY ANILINE, p-ANISIDINE, AND THEIR N-p-TOSYL DERIVATIVES

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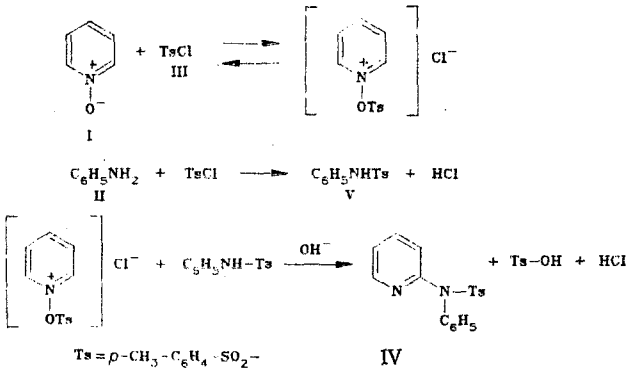
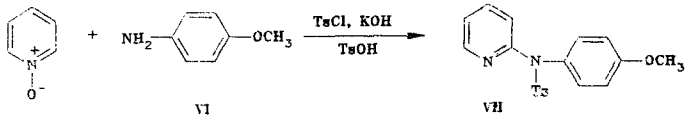
UDC 547.821.3.07:542.958.3

Acylamination of pyridine N-oxide by aniline, p-anisidine, and their tosyl derivatives was carried out in an alkaline medium in the presence of p-tosyl chloride. The reaction proceeds selectively with the formation of the corresponding 2-(N-p-tosyl)anilino- and 2-p-(N-p-tosyl)anisidino-pyridines. The reaction products were converted by acid hydrolysis into the corresponding 2-anilinopyridines.

We have previously described [2] the reaction of reductive acylamination of pyridine N-oxide (I) by aniline II in the presence of p-tosyl chloride (III). The reaction takes 3 h, proceeds in an alkaline medium at room temperature, and leads to the formation of 2-(N-p-tosyl)anilino-pyridine (IV) in a yield of 41%. The acrylamination reaction proceeds according to the scheme



This path of the reaction with the participation of p-tosylanilide (V) is confirmed by the results of the acylamination of pyridine N-oxide by amide V, proceeding under the same conditions in the presence of p-tosyl chloride, with a high yield of compound IV [3]. When p-anisidine (VI) was used for the acylamination of N-oxide I, 2-p-(N-p-tosyl)anisidino-pyridine (VII) was obtained in a yield of 67%.



*For communication 12, see [1].

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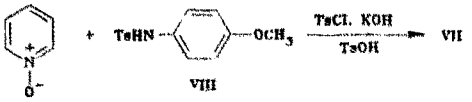
0009-3122/86/2207-0749$12.50

The use of the known p-(N-p-tosyl)anisidine (VIII) as the acylating agent also leads to the formation of compound VII in a yield of 74%.



The structure of compounds IV and VII was confirmed by acid hydrolysis to the corresponding 2-anilinopyridines.

As the above described acylamination reactions are selective, they can be proposed as a convenient method for the synthesis of 2-acylamino-pyridines. Compound VII can serve as an intermediate in the sysnthesis of the pharmacological preparation "Allergil."

EXPERIMENTAL

The course of the reaction and the individual state of the compounds obtained were controlled by TLC on aluminum oxide grade II ot activity, in a chloroform–benzene–alcohol system, 11:4:1 (using iodine vapors as a developer, system A) and by chromatography on paper No. 2 (Rapid, produced in GDR) in a butanol–hydrochloric acid–water system, 5:7:14 (using Dragendorff reagent as a developer).

Reaction of N-oxide I with amine II. A solution of 1 g (10.5 mmoles) of N-oxide I, 0.9 g (10 mmoles) of amine II and 4.7 g (25 mmoles) of compound III in 50 ml of chloroform is shaken with 1.6 g (40 mmoles) of 10% solution of sodium hydroxide for 3 h at room temperature. The aqueous layer is separated and extracted by chloroform. The combined chloroform solutions are dried over sodium sulfate, the solvent is distilled off, and an oily residue is obtained containing besides the desired end product, also unreacted N-oxide (R_{f_A} 0.7, R_{f_B} 0.5) and p-tosyl chloride. The residue is washed consecutively with ether, water, and alcohol to yield 1.34 g (41%) of compound IV, mp 151°C (from alcohol), R_{f_A} 0.9, R_{f_B} 0.97. Found: N 8.9%. $C_{18}H_{16}N_2O_2S$. Calculated: N 8.6%.

Reaction of N-oxide I with amide V. A solution of 0.5 g (5 mmoles) of N-oxide I, 1.28 g (5 mmoles) amide V, and 1.14 g (6 mmoles) of compound III in 30 ml of chloroform is shaken with 1.14 g (28 mmoles) of a 10% solution of sodium hydroxide at room temperature for 2 h. The aqueous layer is separated, extracted by chloroform, and the combined chloroform solutions are dried over sodium sulfate. The solvent is distilled off to yield a semicrystalline mass containing, besides the desired and product, also small amounts of unreacted N-oxide I (R_{f_A} 0.7, R_{f_B} 0.5) and p-tosyl chloride. This mixture is washed with hexane to yield 1.26 g (74%) of compound IV, mp 151°C (from alcohol), R_{f_A} 0.9, R_{f_B} 0.97.

Reaction of N-oxide I with amine VI. A solution of 1 g (10 mmoles) of N-oxide I, 1.2 g (10 mmoles) of amine VI, and 5.7 g (30 mmoles) of compound III in 60 ml of chloroform is shaken with 2.4 g (40 mmoles) of a 10% solution of potassium hydroxide for 4 h at room temperature. The aqueous layer is separated, extracted by chloroform, and the combined chloroform solutions are dried over sodium sulfate. The solvent is distilled off, and the residue, containing besides the desired end product, also small amounts of unreacted oxide (R_{f_A} 0.7, R_{f_B} 0.5), is washed with water to yield 2.5 g (67%) of compound VII, mp 125°C, (from alcohol), R_{f_A} 0.9, R_{f_B} 1. Found: N 8.0%. $C_{19}H_{19}N_2O_3S$. Calculated: N 7.9%.

Reaction of N-oxide I with amide VIII. A solution of 1 g of N-oxide I, 1.23 g (4 mmoles) of amide VIII, and 5.7 g (3 mmoles) of compound III in 60 ml of chloroform is shaken with 2.24 g (40 mmoles) of a 10% solution of potassium hydroxide at room temperature for 2 h. The aqueous layer is separated and extracted by chloroform. The combined chloroform solutions are dried over sodium sulfate, and the solvent is distilled. A residue forms, containing besides the desired end product, also N-oxide I (R_{f_A} 0.7, R_{f_B} 0.5), and compound III is washed consecutively by ether and alcohol. Yield, 1.22 g (74%) of compound VII, mp 125-126°C (from alcohol), R_{f_A} 0.9, R_{f_B} 1.

Acid Hydrolysis of Compound IV. A 1 g portion (30 mmoles) of compound IV is dissolved in 15 ml of concentrated hydrochloric acid, and the mixture is boiled for 12 h. The reaction

mixture is distilled to dryness, the residue is dissolved in water, the solution is made alkaline with potassium carbonate to pH 8-9, and steam-distilled. The distillate, containing the crystalline product, is extracted by ether. The solvent is distilled to yield 0.45 g (87%) of 2-anilinopyridine, mp 106-107°C; according to the data in [5], mp 106-108°C.

Acid Hydrolysis of Compound VII. A 1 g portion (28 mmoles) of compound VII is dissolved in 5 ml of concentrated hydrochloric acid, and the solution is boiled for 34 h. The reaction mixture is evaporated to dryness, and the residue is dissolved in water, alkaline with potassium carbonate to pH 8-9, and extracted by ether. The ether is distilled off and the residue is treated with benzene. After distillation of benzene, 2-p-anisidinopyridine (IX) is obtained in a yield of 0.40 g (73%), mp 85-87°C (from petroleum ether), according to the data in [6], mp 85°C.

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SYNTHESIS OF SUBSTITUTED 2-PYRIDONES AND 4-AZA-3-FLUORIDONES

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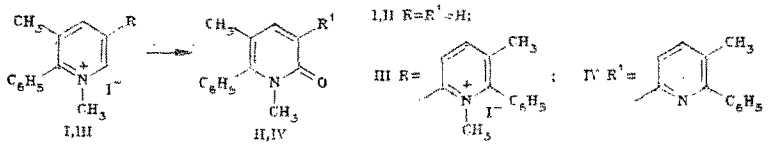
UDC 547.823'836:543.51

Substituted N-methyl-2-pyridones and N-methyl-4-aza-3-fluoridones, a previously unknown group of heterocyclic compounds, were obtained by oxidation of 3-methyl-2-phenylpyridine, 3-methyl-2-phenyl-5-(3'-methyl-2'-phenylpyridin-6'-yl)pyridine iodomethylates, as well as of 4-aza-fluorenes substituted at the 9-position.

For the synthesis of 4-aza-3-fluoridones we used 4-azafluorene, which is obtained by catalytic dehydrocyclization of 3-methyl-2-phenyl-pyridine [1]. It was found that in the synthesis of this pyridine base by phenylation of β-picoline [2], 3-methyl-2-phenyl-5-(3'-methyl-2'-phenyl-3',4'-dehydropiperidin-6'-yl)pyridine is formed in relatively appreciable amounts; the compound readily converts into a similarly substituted β,α-dipyridyl [3].

Having at our disposal practical methods for the preparation of these two pyridine bases, as well as of 4-azafluorene, we turned our attention to the synthesis of new substitutd 2-pyridones and previously unknown 4-aza-3-fluoridones. They are formed by oxidation under alkaline conditions of iodomethylates of the corresponding bases.



For the oxidation of 3-methyl-2-phenylpyridine iodomethylate (I), we used potassium hexacyanoferrate (Fe^{3+}). Irrespective of the time of reaction, 1,5-dimethyl-6-phenyl-2-pyridone (II) is formed in a yield of ~20%; a considerable amount of the starting salt is recovered unchanged.

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 939-942, July, 1986. Original article submitted March 12, 1985.

0009-3122/86/2207-0751$12.50