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Microwave Activation in the Synthesis of Nitrogen Heterocycles, *N*-Oxides of Pyridine Series

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Abstract—Oxidation of heterocycles of the pyridine series under conditions of microwave irradiation was studied. It is established that oxidation of pyridine and 4-methylpyridine with hydrogen peroxide results in the corresponding *N*-oxides, and oxidation of 3-(piperidin-2-yl)pyridine gives δ-oximino-δ-(pyridyl-3-*N*-oxide)-valeric acid.

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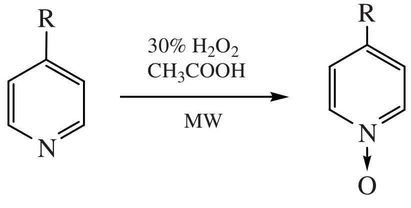
N-oxides of nitrogen heterocycles, of the pyridine series in particular, constantly grow in importance. It is known that electrophilic substituents are more readily introduced into the *N*-oxides of pyridine series than into the initial *N*-heterocycles. The oxidation of the corresponding pyridines with hydrogen peroxides in a glacial acetic acid solution is the most important way to such compounds. The reaction is commonly carried out at 70–80°C for a few hours. Then the reaction mixture is evaporated and the product is extracted with chloroform [1]. The disadvantages of this method are the long reaction duration and the necessity of using a solvent.

We studied pyridine **I** and 4-methylpyridine **II** oxidation with hydrogen peroxide in the glacial acetic acid under microwave irradiation (MW irradiation) according to the scheme:

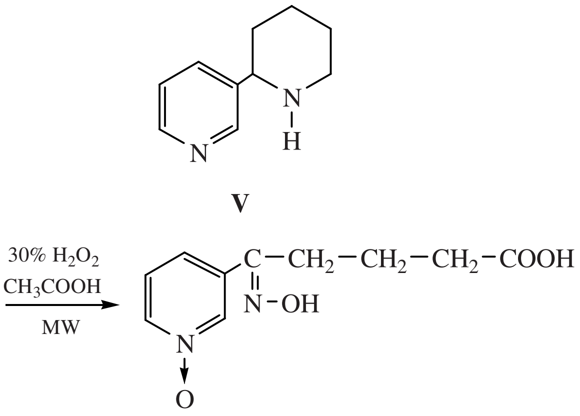


I, II **III, IV**

R = H (**I, II**), Me (**II, IV**).

It was established that pyridine and 4-methylpyridine *N*-oxides (**III** and **IV,** respectively) were synthesized in 20 min at the microwave irradiation of 70 W power. Their structure and identity were proved by independent syntheses, IR and NMR spectroscopy, and thin layer chromatography.

Oxidation of anabasine **V** was studied under similar conditions:



VI

According to the classical procedure, the oxidation of anabasine with 30% hydrogen peroxide in acetic acid was completed in 24 h at heating on a water bath [3]. We established that under MW irradiation this reaction could be successfully carried out in 30 min at the radiation power of 70 W. It should be noted that reaction did not result in anabasine Py–*N*-oxide or complete oxidation to nicotinic acid as it might be

Physicochemical constants of compounds **III**, **IV** and **VI** prepared under classical and MW irradiation conditions

Comp. no.	mp, °C		Yield, %		Formula	Calculated, %		Found, %	
	classical conditions [2, 3]	MW irradiation	classical conditions [1, 3]	MW irradiation		C	H	C	H
III	67	67–68	92	85.2	C_5H_5NO	63.15	5.30	63.19	5.25
IV	184–186	184	90	87.5	C_6H_7NO	66.04	6.47	66.09	6.52
VI	224–227	227	68–72	65.2	$C_{10}H_{12}N_2O_4$	53.57	5.39	53.61	5.36

expected, but led to the opening of the piperidine ring to form δ-oximino-δ-(pyridyl-3-*N*-oxide)valeric acid **VI**.

Compound **VI** is a powder-like substance, poorly soluble in water, alcohol and organic solvents (except DMF), and readily soluble in aqueous ammonia, alkali and acids at heating. Structure of compound **VI** was proved by independent synthesis, IR and NMR spectroscopy, and by its physicochemical constants corresponding to published data [2]. In the IR spectrum of synthesized compounds **III, IV** and **VI** we observed absorption band in the region of 1250–1290 cm^{-1} typical of N→O bond. In the IR spectrum of compound **VI** there is a carboxylic group absorption band at 1710 cm^{-1}.

Physicochemical constants of compounds **III**, **IV** and **VI** consistent with the literature data [2, 3] are listed in the table.

Hence application of microwave activation is a convenient laboratory way to obtain *N*-oxides of nitrogen-containing heterocycles of pyridine series and may be recommended as a highly effective method for preparative synthesis.

EXPERIMENTAL

Pyridine and 4-methylpyridine *N*-oxides (I, II). In a heat-resistant Erlemeyer flask, 5 g of pyridine (4-methylpyridine) was dissolved in 30 ml of the glacial acetic acid and 15 ml of 30% hydrogen peroxide was added. The reaction mixture was exposed to microwave irradiation of 70 W power during 20 min, 4 times by 5 min. To this solution 15 ml of water was added and then water was removed in a vacuum of the water-jet pump. On cooling to room temperature the product precipitated and was recrystallized from benzene.

δ-Oximino-δ-(pyridyl-3-*N*-oxide)valeric acid (III). In a a heat-resistant Erlemeyer flask 5 g of anabasine was dissolved in 30 ml of the glacial acetic acid and 15 ml of 30% hydrogen peroxide was added. The reaction mixture was exposed to microwave irradiation of 70 W power during 30 min, 6 times by 5 min. To this solution 15 ml of water was added and then water was removed in a vacuum of the water-jet pump. On cooling to room temperature the product precipitated and was recrystallized from ethanol. ^1H NMR spectrum, DMSO, δ, ppm: 1.65 m (2H, CH_2), 2.3 m (4H, $COO–CH_2–C H_2$), 7.45 t (1H, H pyridine), 8.23 d (1H, H pyridine), 8.43 s (1H, H pyridine), 11,75 s (1H, C=N–OH), 12.10 s (1H, COOH).

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