

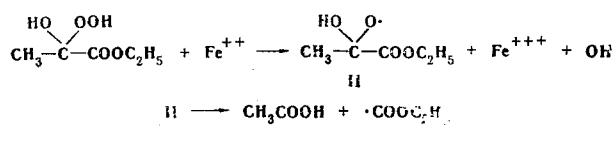
ETHOXYSUBSTITUTION OF METHYL PYRIDINES

R. S. Min and V. S. Aksenov

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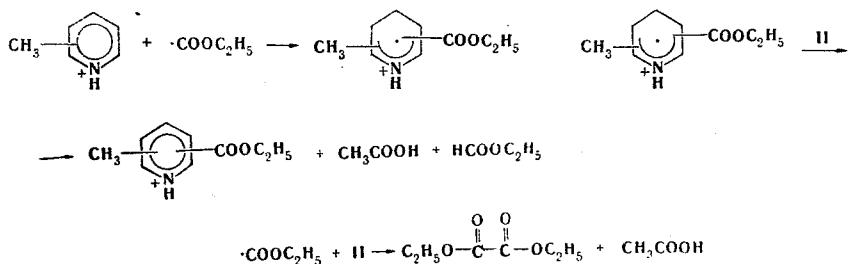
The ethyl esters of pyridine carboxylic acids were obtained by reaction of the ethoxycarbonyl radical with methyl-substituted pyridines. A mechanism is proposed for the carboxylation reaction.

It has recently been shown that radicals of a different type with the radical center on a carbon atom have high reactivities with respect to protonated heteroaromatic bases [1, 2]. The aim of the present research was to study the reaction of the ethoxycarbonyl radical (I) with a number of methyl-substituted pyridines. Radical I was generated by decomposition of ethyl  $\alpha$ -hydroxy- $\alpha$ -hydroperoxypyruvate in the presence of ferrous sulfate.



Ethyl esters of pyridine carboxylic acids (Table 1) were obtained by reaction of radical I with various methyl-substituted pyridines. The results presented in Table 1 constitute evidence for the high selectivity of the ethoxycarbonyl radical in reactions with protonated bases; the activity of the ring 2 position increases on passing from the unprotonated base to the protonated base. The reaction of radical I with the unprotonated base is less selective and gives lower yields of the substitution products. In this case one observes primarily dimerization of radical I to give diethyl oxalate. The formation of diethyl oxalate also occurs in reactions with the protonated bases but to a considerably lesser extent.

The proposed participation of radical II in the step involving detachment of a hydrogen atom requires the presence of two molecules of ethyl  $\alpha$ -hydroxy- $\alpha$ -hydroperoxypruvate for the formation of one molecule of pyridine carboxylic acid ester. In the reaction of radical I with 2,6-dimethylpyridine, ethyl 2,6-dimethylnicotinate is obtained along with ethyl 2,6-dimethylisonicotinate. The formation of the former can be explained, first, by the absence of a hydrogen atom in the most reactive 2 and 6 positions and, second, by the higher statistical weight of the 3 position as compared with the 4 position. It follows from Table 1 that a change in the peroxide-base molar ratio does not affect the isomer ratio. The isomer ratio was determined by gas-liquid chromatography (GLC) and PMR spectroscopy. The ethyl esters of the pyridine carboxylic acids were identified by interpretation of the PMR spectra of mixtures of the isomers without isolation of the individual compounds.



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TABLE 1. Yields of Mixtures of Isomers

Base	Base—peroxide ratio	Isomer ratio (%)	Yield of mixture of isomers, %
Pyridine*	3:1	2(39):4(34):3(27)	Traces
Pyridine	3:1	2(68):4(32)	31
4-Picoline	3:1	2(34)	34
2-Picoline	1:1	4(28):6(72)	31
	3:1	4(32):6(68)	25
	1:3	4(28):6(72)	63
3-Picoline	3:1	2(61):4(29):6(10)	35
2,6-Dimethylpyridine	3:1	4(90):3(10)	33

\*The unprotonated base.

#### EXPERIMENTAL

Gas-liquid chromatography of the compounds was carried out with an LKhM-8MD chromatograph with a column 1 m long. The stationary phase was 15% polymethylphenylsiloxyane oil on Chromaton N-AW-DMCS. The IR spectra of thin layers of the compounds were recorded with a UR-20 spectrometer. The PMR spectra were recorded with a Tesla BS487C spectrometer.

Pyridine Carboxylic Acid Ethyl Esters. A solution of 0.05 mole of  $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$  in 15 ml of water and ethyl  $\alpha$ -hydroxy- $\alpha$ -hydroperoxypyruvate, obtained by the dropwise addition of 0.05 mole of 34%  $\text{H}_2\text{O}_2$  to 0.075 mole of ethyl pyruvate at  $-10^\circ$ , were added simultaneously with stirring and cooling to  $0-5^\circ$  to 0.15 mole of the heterocyclic base in 20 ml of water and 0.15 mole of concentrated  $\text{H}_2\text{SO}_4$ . At the end of the reaction, the mixture was poured over ice, and the aqueous mixture was neutralized with 2%  $\text{NaOH}$  solution and extracted with diethyl ether. The excess solvent was removed and the mixture of isomers was separated by vacuum distillation and investigated by PMR spectroscopy and GLC. The yields were calculated on the basis of the reagent used in insufficient amounts under the condition of equimolecular reaction of the heteroaromatic base with the ethyl  $\alpha$ -hydroxy- $\alpha$ -hydroperoxypyruvate. The reaction with unprotonated pyridine was carried out similarly but without the participation of concentrated  $\text{H}_2\text{SO}_4$ .

#### LITERATURE CITED

1. F. Minisci, *Synthesis*, 1, 1 (1973).
2. R. Bernardi, T. Caronna, R. Galli, F. Minisci, and M. Perchinunno, *Tetrahedron Lett.*, 645 (1973).