# HOMOLYTIC ETHOXYCARBONYLATION OF AMINOPYRIDINES

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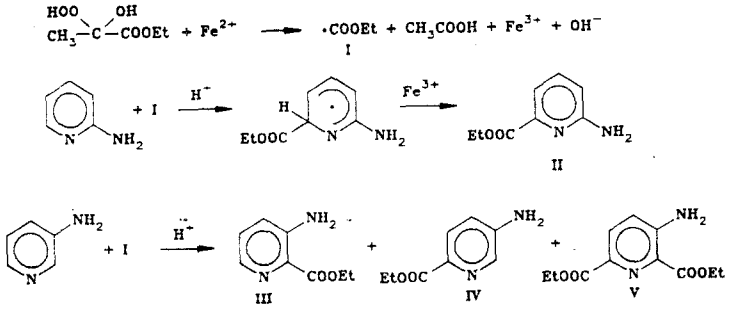
Pyridinecarboxylic acid ethyl esters are formed in the reaction of ethoxycarbonyl radicals with aminopyridines.

It has been previously reported that a mixture of ethyl esters of picolinic and isonicotinic acids is formed in the reaction of protonated pyridine bases with ethoxycarbonyl radicals [1]. In the present research we studied the reaction of ethoxycarbonyl radicals with protonated 2- and 3-aminopyridine. According to the data obtained, ·COOEt radicals generated in the ethyl α-hydroxy-α-hydroperoxypropionate–$Fe^{2+}$ redox system react actively with aminopyridines in an acidic medium to give products of replacement of the hydrogen atom at the α-carbon atom of the heterocyclic ring. This sort of behavior is characteristic for the homolytic substitution of protonated pyridine bases by nucleophilic radicals [2].



The ratios of the products of the reaction of I radicals with aminopyridines were determined by GLC. We used PMR spectroscopy of the isolated compounds to assign the chromatographic peaks to specific compounds. Only one product – ethyl 6-aminopicolinate (II) – was detected by GLC in the reaction of I radicals with 2-aminopyridine in an acidic medium. A mixture of ethyl 3-aminopicolinate (III), ethyl 5-aminopicolinate (IV), and ethyl 3-amino-6-carbethoxypicolinate (V) in a ratio of 8:1:3.5 is formed in the reaction of ethoxycarbonyl radicals with 3-aminopyridine under the same conditions. The formation in this reaction of diadduct V in greater amounts than monoadduct IV indicates that the introduction of an ethoxycarbonyl group activates the heterocyclic ring to further attack by ethoxycarbonyl radicals under the reaction conditions. In addition to ring-substitution products II-V, diethyl oxalate is formed as a result of recombination of I radicals.

Signals of aromatic protons (6.43-8.18 ppm) and characteristic signals of methylene and methyl groups of the ethoxy fragment (4.33 and 1.43 ppm) and of the amino group (4.24 ppm) are observed in the PMR spectrum of II. The ratio of the integral intensities of the aromatic protons and the protons of the $CH_2$, $NH_2$, and $CH_3$ groups is 3:4:3, which indicates the formation of a product of reaction of 2-aminopyridine with one ethoxycarbonyl radical. An analysis of the absorption at 6.43-8.18 ppm constitute unequivocal evidence for incorporation of the ethoxycarbonyl substituent in the 6 position of 2-aminopyridine: the signal that is characteristic for the ring 6-H proton at 8.6 ppm is absent in the spectrum, the signals at 8.14 and 8.00 ppm belong to the 5-H and 4-H protons, and the signals at 6.47 ppm belong to the 3-H proton. The ratio of the intensities of the signals at 7.98-8.18 and 6.43-6.51 ppm (2:1) confirms this assignment. The deshielding effect of the ester group on the ortho protons, which gives rise, as previously noted for such structures [3], to drawing together of the chemical shifts of the 4-H and 5-H protons in the 2-amino-6-carbethoxypyridine (II) molecule, is displayed in the spectrum. In addition to the absorption bands that are

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characteristic for the $NH_2$ group (3355, 3465 $cm^{-1}$), the IR spectrum of II contains absorption bands of C=O and C–O groups at 1710 and 1260 and 1100 $cm^{-1}$, as well as absorption bands of a substituted pyridine ring.

The spectra of III-V were similarly interpreted. The characteristics of the spectra are presented in the experimental section.

## EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The UV spectra of solutions of the compounds in methanol were recorded with a Specord UV-vis spectrophotometer. The PMR spectra of solutions in $CD_3OD$ were obtained with a Tesla BS-597 spectrometer (100 MHz) with hexamethyldisiloxane as the internal standard. Analysis by GLC was carried out with an LKhM-8MD chromatograph with a 200 by 0.3 cm steel column packed with 15% polymethylsiloxane oil on Chromaton N-AW-DMCS.

Reaction of Ethoxycarbonyl Radicals with Aminopyridines. A solution of 13.9 g (0.05 mole) of $FeSO_4 \cdot 7H_2O$ in 15 ml of water and the reagent obtained by the dropwise addition of 5.0 g (0.05 mole) of 34% $H_2O_2$ to 8.7 g (0.075 mole) of ethyl pyruvate at −10°C were added simultaneously with stirring and cooling to 0-5°C to 4.7 g (0.05 mole) of the aminopyridine in 20 ml of water and 14.7 g (0.15 mole) of concentrated $H_2SO_4$. At the end of the reaction the mixture was poured over ice, and the aqueous mixture was neutralized with 2% NaOH solution and extracted with ether. The excess solvent was removed by distillation, and the reaction mixture was analyzed by GLC. For the preparative isolation of the products the excess amounts of the starting compounds were removed by distillation, and the residue was crystallized from pentane or petroleum ether (60-80°C). Compounds III-V were isolated from the mixture of products by liquid adsorption chromatography on $Al_2O_3$ [elution with hexane–ethyl acetate (4:1)]. The yield was calculated on the basis of the amount of ethyl α-hydroxy-α-hydroperoxypropionate used.

Ethyl 6-Aminopicolinate (II). The yield was 0.75 g (30%), and the product had mp 56-58°C (56°C [4]). IR spectrum: 1710 (C=O), 3355, 3465 $cm^{-1}$ ($NH_2$). UV spectrum, $\lambda_{max}$ (log ε): 213 (4.62), 249 (4.37), 337 nm (4.17). PMR spectrum: 1.43 (t, 3H, $CH_3$), 4.33 (q, 2H, $CH_2$), 4.24 (s, 2H, $H_2$), 6.47 (1H, d, $J_{34}$ = 7.0 Hz, 3-H), 8.00 (1H, d, $J_{43}$ = 7.0 Hz, 4-H), 8.14 ppm (1H, d, $J_{54}$ = 7.0 Hz, 5-H). Found: N 16.7%. $C_8H_{10}N_2O_2$. Calculated: N 16.8%.

Ethyl 3-Aminopicolinate (III). The yield was 1.7 g (32%), and the product had mp 131–132°C (132°C [5]). IR spectrum: 1690 (C=O), 3190, 3395, 3430 $cm^{-1}$ ($NH_2$). UV spectrum, $\lambda_{max}$ (log ε): 215 (4.66), 255 (5.53), 345 nm (4.30). PMR spectrum: 1.35 (t, 3H, $CH_3$), 4.35 (q, 2H, $CH_2$), 5.65 (s, 2H, $NH_2$), 6.90 (1H, m, $J_{54}$ = 8.0 Hz, 5-H), 7.06 (1H, m, $J_{45}$ = 8.0 Hz, 4-H), 7.96 ppm (1H, q, $J_{65}$ = 4.2 Hz, $J_{64}$ = 1.5 Hz, 6-H). Found: N 16.7%. $C_8H_{10}N_2O_2$. Calculated: N 16.8%.

Ethyl 5-Aminopicolinate (IV). The yield was 0.2 g (4%), and the product had mp 128-129°C (129-130°C [6]). IR spectrum: 1720 (C=O), 3210, 3315, 3450 $cm^{-1}$ ($NH_2$). PMR spectrum: 1.41 (t, 3H, $CH_3$), 4.35 (q, 2H, $CH_2$), 4.73 (s, 2H, $NH_2$), 7.16 (2H, m, 4-H, 5-H), 7.79 ppm (1H, s, 2-H). Found: N 16.8%. $C_8H_{10}N_2O_2$. Calculated: N 16.8%.

Ethyl 3-Amino-6-carbethoxypicolinate (V). The yield was 0.7 g (14%), and the product had mp 79-81°C. IR spectrum: 1720, 1740 (C=O), 3190, 3300, 3465 $cm^{-1}$ ($NH_2$). UV spectrum, $\lambda_{max}$ (log ε): 215 (4.31), 262 (3.91), 386 nm (3.91). PMR spectrum: 1.43 (t, 3H, $CH_3$), 1.47 (t, 3H, $CH_3$), 4.26 (s, 2H, $NH_2$), 4.32 (q, 2H, $CH_2$), 4.36 (q, 2H, $CH_2$), 7.76 (1H, d, $J_{45}$ = 8.0 Hz, 4-H), 7.80 ppm (1H, d, $J_{54}$ = 8.0 Hz, 5-H). Found: C 55.0; H 6.0; N 11.7%. $C_{11}H_{14}N_2O_2$. Calculated: C 55.4; H 5.9; N 11.8%.

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