SYNTHESIS OF CONDENSED STRUCTURES FROM 3-CYANO-2-PYRIDYLACRYLIC ACIDS

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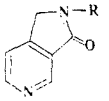
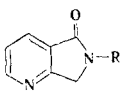
Ammonolysis of the methyl esters of trans-β-(3-cyano-2-pyridyl)acrylic (I) and trans-β-(6-methyl-3-cyano-2-pyridyl)acrylic (II) acids gave the amides of these acids. The addition of bromine, diazomethane, and hydrogen to the double bond of cis- and trans-acids I and II is described. Hydrogenation of the methyl esters of trans-acids I and II over Raney nickel at room temperature and atmospheric pressure occurs with intramolecular cyclization to two-ring lactams – 7-oxo-5,6,8,9-tetrahydropyrid[3,2-c]azepine and 2-methyl-7-oxo-5,6,8,9-tetrahydropyrid[3,2-c]azepine. Under the conditons of acid hydrolysis of acids I and II the elements of water add to the nitrile group with intramolecular cyclization to give, respectively, 3-carboxymethyl-1-oxo-2,3-dihydrofuro[4,3-b]pyridine and 5-methyl-3-carboxymethyl-1-oxo-2,3-dihydrofuro[4,3-b]pyridine, whereas refluxing these acids with aqueous sodium hydroxide gives two-ring lactams – 3-carboxymethyl-1-oxo-2,3-dihydropyrrolo[4,3-b]pyridine and its 5-methyl homolog. The structures of the compounds were confirmed by the UV, IR, PMR, and mass spectra.

Interest in the synthesis of biologically active substances in the lactam series, including lactams condensed with a pyridine ring, has intensified in recent years (for example, see [1]). Thus lactams of the I type, which are cyclic derivatives of o-substituted nicotinic acid, have been studied as analeptics [2]. Some isomeric pyrrolopyridines [3], including lactams with structures of the II type, have been described. However, the methods that have been developed for the synthesis of compounds of this type are extremely complex and do not make it possible to obtain substances with a functional group in the side chain.



I



II

It has been shown [4, 5] that Beckmann rearrangement of the accessible 5-nitroso-6-hydroxyquinolines may be a preparative method for the synthesis of β-(3-cyano-2-pyridyl)acrylic acids (III and IV); we used these acids for subsequent transformations involving the vinyl group.

The polarizing effect of the carboxyl group on the π electrons of the olefinic grouping in acrylic acids of the III and IV type is somewhat weakened because of the competitive effect of conjugation with the aromatic ring. The addition of bromine therefore proceeds rather easily, particularly in the case of cis-acid III, to give a mixture of threo- and erythro-dibromides V. It has been previously noted that the cis-trans isomerization of acids III and IV proceeds very readily [5]. The trans-acid reacts with bromine more slowly to give the erythro form (the PMR spectrum of the product contains two doublets at 5.28 and 5.85 ppm with J = 10.6 Hz). Both cis- and trans-acids III add diazomethane with simultaneous methylation of the carboxyl group to give ester VI, the structure of which was determined on the basis of the results of elementary analysis and data from the UV, IR, and PMR spectra. Similar addition, which establishes the polarized character of the vinyl group, has been noted for other pyridylacrylic acids [6].

Ammonia in an aqueous alcohol medium (at room temperature) does not add to the olefinic bond of the methyl esters (VII and VIII) of trans-acids III and IV. Instead, they undergo smooth ammonolysis to give the corresponding trans-amides IX and X. The signals of olefinic protons are retained in their PMR spectra (for IX, at 7.53 and 7.98 ppm, J = 16 Hz), and the absorption maxima in the UV spectra (265 nm for IX and 268 nm for X) are close to the maxima in the spectra of trans-esters VII and VIII, but the extinctions are somewhat greater.

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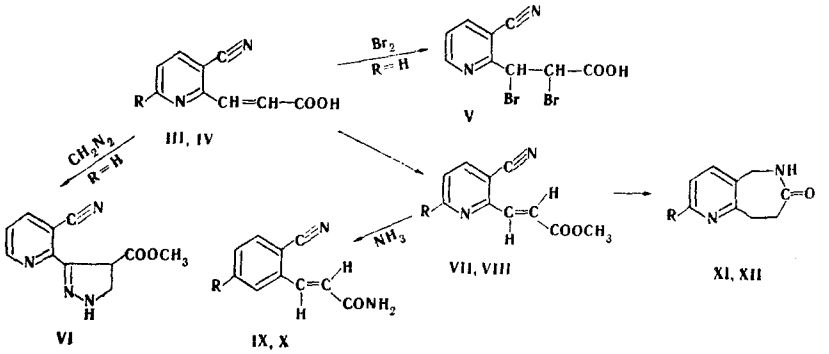
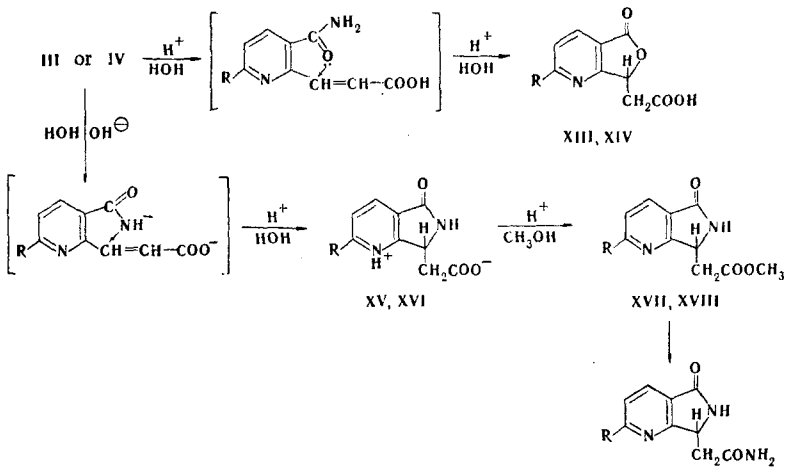


III, VII, IX, XI R = H; IV, VIII, X, XII R = CH_3

The hydrogenation of acids III and IV proceeds in a complex manner to give a multicomponent mixture of reduction products. However, the hydrogenation of esters VII and VIII over Raney nickel at room temperature and atmospheric pressure proceeds smoothly with reduction of both the nitrile group and the vinyl group with simultaneous cyclization to give 7-oxo-5,6,8,9-tetrahydropyrid[3,2-c]azepine (XI) or its 2-methyl homolog (XII), which are representatives of compounds of the previously unknown pyrido[3,2-c]azepine series.

The absorption maximum at 263 nm (log ε 3.59) in the UV spectrum of XI is characteristic for the α band of pyridine. It is shifted bathochromically and hyperchromically as compared with the benzo analog, i.e., 2,3,4,5-tetrahydro[1H]benzo[c]azepin-3-one, for which the maximum [7] lies at 250 nm (log ε 2.42). The PMR spectrum of XII contains two triplets at 3.0-3.6 ppm, which correspond to the CH_2CH_2 group. The protons of the CH_2N fragment are represented in the form of a split signal at 4.6 ppm because of coupling with the proton of the NH group. The signals of the AB system of protons of the pyridine ring are found at weak field (at 7.4 and 8.0 ppm).



XIII, XV, XVII, XIX R = H; XIV, XVI, XVIII, XX R = CH_3

The mass spectrum of XI contains a molecular ion peak ([M^+] 162) and peaks of fragment ions* corresponding to the assigned structure – 145 (M – OH), 134 (M – CO), 133 (M – CHO), and 119 (M – HCNO). The latter process is confirmed by the metastable ion with m/e 87.5. The peak with m/e 118 is the maximum peak (evidently M – HCNO – H), the ion responsible for which subsequently loses 27 mass units (splitting out of HCN) to give an ion with m/e 91; this is characteristic for pyridines [8].

When we heated the cis and trans isomers of acids III and IV in dilute (1: 1) or concentrated hydrochloric acid, we detected a rather complex mixture of several compounds by means of paper chromatography, but the same acid XIII (pK_a 4.12 ± 0.02), i.e., 3-carboxymethyl-1-oxo-2,3-dihydrofuro[4,3-b]pyridine, was obtained in 50-70% yields under more severe conditions – when both cis- and trans-III were heated in 73-86% sulfuric acid for 2-3 h. Thus, as we noted in the hydrolysis of o-cyanocinnamic acids [9], regardless of the stereochemical peculiarities of the starting acids, the elements of water add to the nitrile group with subsequent or simultaneous intramolecular cyclization. Similarly, cis- and trans-acids IV are converted by acid hydrolysis to lactono acid XIV [10].

*Here and subsequently, the m/e values are given for the ion peaks.

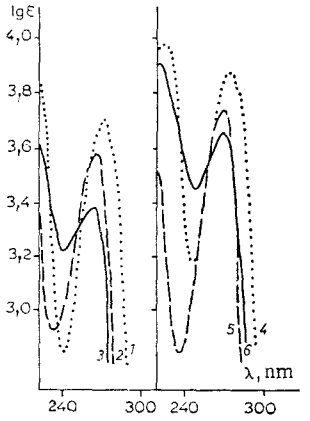


Fig. 1. UV spectra of aqueous solutions: 1) 7-oxo-5,6,8,9-tetrahydropyrid[3,2-c]azepine (XI); 2) 3-carboxymethyl-1-oxo-2,3-dihydrofuro[4,3-b]pyridine (XIII); 3) 3-carboxymethyl-1-oxo-2,3-dihydropyrrolo-[4,3-b]pyridine (XV); 4) 2-methyl-7-oxo-5,6,8,9-tetrahydropyrid[3,2-c]azepine (XII); 5) 5-methyl-3-carboxymethyl-1-oxo-2,3-dihydrofuro[4,3-b]pyridine (XIV); 6) 5-methyl-3-carboxymethyl-1-oxo-2,3-dihydropyrrolo[4,3-b]pyridine (XVI).

When cis- and trans-acids III are refluxed with aqueous sodium hydroxide, they are converted, after acidification, to a lactam with a skeleton of the II type, i.e., 3-carboxymethyl-1-oxo-2,3-dihydropyrrolo[4,3-b]-pyridine (XV). Lactam acid XVI was similarly obtained from acid IV.

The electronic absorption curves of both reduction products XI and XII and the products of lactone (XIII and XIV) or lactam (XV and XVI) ring closure are similar in character, and the absorption is similar to the absorption of derivatives of the pyridine series [11] (Fig. 1). The noted absorption maxima of lactams XV and XVI almost coincide with the absorption maxima of nicotinamide and N-substituted nicotinamides [12].

The PMR spectra of lactone XIII and lactam XV contain a multiplet of the proton of a lactone ring at 6.12-6.42 ppm and, respectively, a multiplet of the proton of a lactam ring centered at 6.13 ppm. The signal of the CH_2 group of lactone XIII lies at 3.38-3.62 ppm, and the signal of the CH_2 group of lactam XV lies at 3.63 ppm. As usual, the signals of the pyridine protons are found at weak field, but the signal of the γ-H proton is shifted to weaker field than the signal of the α-H proton under the influence of the adjacent CO group. Vibrations of the O–C=O fragment of the five-membered lactam ring are observed in the IR spectrum of XIII at 1770 cm^{-1}. The band at 2875 cm^{-1} can be assigned to the vibrations of a carboxyl group tied up in an intramolecular hydrogen bond, and the bands at 1375-1590 cm^{-1} correspond to COO^- vibrations, which indicates that the compound exists primarily in the form of an inner salt. Methyl esters XVII-XVIII (isolated in picrate form) and amides XIX and XX (without opening of the lactam ring) were obtained by esterification of XV and XVI in acidic media and subsequent ammonolysis.

EXPERIMENTAL

Chromatography on a loose layer of activity II Al_2O_3 or on Leningrad B paper (by the ascending method) was used to evaluate the course of the reactions and the individuality of the compounds. The chromatograms were developed with iodine vapors (the chromatograms of XIII and XIV were developed with a 0.05% solution of Bromphenol blue).

Potentiometric titration of 0.1 mole/liter solutions of XI-XVI was accomplished with an LPU-01 pH-meter with a carbonate-free solution of sodium hydroxide at 20°C with a glass electrode–calomel electrode couple. The pK_a values were assumed to be equal to the pH values at the half-neutralization point.

The UV spectra of 10^{-4} mole/liter solutions of the compounds were recorded with SF-4A and SF-16 spectrophotometers. The PMR spectra of trifluoroacetic acid solutions of the compounds were recorded with an RS-60 spectrometer with hexamethyldisiloxane as the external standard. The IR spectra of mineral oil suspensions of the compounds were recorded with an IKS-22 spectrometer. The mass spectrum was recorded with an MKh-1303 spectrometer with introduction of the sample into the ion source.

α,β-Dibromo-β-(3-cyano-2-pyridyl)propionic Acid (V). A watch glass containing 0.17 g (0.001 mole) of trans-acid III was placed in a beaker with a ground glass cover, and 0.2 ml (0.0037 mole) of bromine was poured into the bottom of the beaker below the watch glass. The cover was placed on the beaker, and it was allowed to stand at room temperature for 2-3 days. The product was then allowed to stand in the air for 0.5-1 h, after which it was dried in a vacuum desiccator. This procedure gave 0.3 g (76%) of a yellowish powder that was soluble in ethanol, dioxane, ether, and hot benzene but only slightly soluble in carbon tetrachloride. The product had mp 140-141°C (dec.) and R_f 0.56 [propanol–5% ammonium hydroxide (4:1), Al_2O_3]. UV spectrum in water, λ_{max} (log ε): 264 nm (3.67). PMR spectrum: two doublets of aliphatic protons at δ 5.28 and 5.85 ppm (J = 10.6 Hz). Found: Br 47.8; N 8.2%. $C_9H_6Br_2N_2O_2$. Calculated: Br 47.9; N 8.3%.

Addition of Bromine to cis-Acid III. A similar procedure was used to obtain V from 0.17 g (0.001 mole) of cis-acid III and 0.2 ml (0.0037 mole) of bromine. The bromine vapors vanished after 2-3 h, and the resulting powder was converted to a brown liquid mass, which was allowed to stand overnight. It was then treated with 10-15 ml of acetone, and the mixture was refluxed on a water bath for 15-20 min. The acetone was removed by evaporation until the volume of the concentrate was one-third of the original volume, 10-15 ml of benzene was added, and the mixture was stirred vigorously until a precipitate formed. The precipitate was removed by filtration, washed with carbon tetrachloride, and dried in a vacuum desiccator to give 0.21-0.22 g (63-66%) of a product with mp 125-127°C (dec.) and R_f 0.36 and 0.54 (in the same system as in the preceding experiment).

3-Carbomethoxy-4-(3-cyano-2-pyridyl)-Δ^2-pyrazoline (VI). A 0.22-g (0.0012 mole) sample of cis- or trans-III was dissolved by heating in 15 ml of anhydrous dioxane, the solution was cooled to room temperature, and a solution of diazomethane [from 1.67 g (0.016 mole) of nitrosomethylthiourea and 5 ml of 40% potassium hydroxide solution in 17 ml of ether] was added in portions with stirring in the course of ~0.5-1 h. The mixture was then allowed to stand at room temperature, after which it was evaporated at room temperature, and the yellow precipitate was removed by filtration and washed with 5% sodium bicarbonate. Two recrystallizations from benzene gave 0.15-0.2 g (55-74%) of a yellow crystalline powder, with mp 164-165°C (successively from benzene and water) and R_f 0.58 [benzene–absolute ethanol (20:1), Al_2O_3], that was soluble in ethanol, dioxane, acetone, hot benzene, and hot water but only slightly soluble in carbon tetrachloride. UV spectrum in water, λ_{max} (log ε): 303 nm (4.02). PMR spectrum in trifluoroacetic acid, δ: s, 3.85 ($COOCH_3$); m, 4.16-4.93 ($NHCH_2CH$); pyridine protons 7.6 (β-H), 8.3 (γ-H), and 8.57 ppm (α-H). IR spectrum: 1740 (unconjugated CO group), 2235 (CN), and 3340 cm^{-1} (NH). Found: N 24.2%. $C_{11}H_{10}N_4O_2$. Calculated: N 24.3%. No melting-point depression was observed for a mixture of individual substances obtained from the cis and trans isomers of acid III.

trans-β-(3-cyano-2-pyridyl)acrylamide (IX). A 10-ml sample of 25% ammonium hydroxide was added to a cooled (to room temperature) solution of 1.88 g (0.01 mole) of VII in 105 ml of methanol (the solution was obtained by heating), and the mixture was allowed to stand at room temperature for 8-10 days [the end of the reaction was determined by chromatography with a benzene–ethanol system (4:1) and Al_2O_3]. The solution was then evaporated to a small volume on a water bath, and the resulting precipitate was removed by filtration, washed on the filter with 10 ml of water, and dried to give 0.51-0.6 g (30-37%) of a product with R_f 0.55 [benzene–ethanol (5:1), Al_2O_3] and mp 246-247°C (from ethanol). The white crystalline powder was soluble in ethanol, hot dioxane, and hot water but only slightly soluble in carbon tetrachloride. The PMR spectrum contained two doublets of olefinic protons at 7.53 and 7.98 ppm (J = 16 Hz) and signals of pyridine protons at 8.08 (β-H), 8.82 (γ-H), and 8.98 ppm (α-H). Found: N 24.3%. $C_9H_7N_3O$. Calculated: N 24.3%.

trans-β-(6-Methyl-3-cyano-2-pyridyl)acrylamide (X). As in the preceding experiment, 3 g (0.015 mole) of ester VIII was dissolved by heating in 150 ml of methanol, the solution was cooled, 30 ml of 25% ammonium hydroxide was added, and the mixture was allowed to stand at room temperature for 14 days (the end of the reaction was determined by chromatography). Workup gave 0.7 g (24%) of a white crystalline powder with mp 266-267°C (from ethanol) and R_f 0.62 (in the same system as in the preceding experiment) and solubilities similar to the solubilities of amide IX. UV spectrum in water, λ_{max} (log ε): 268 nm (4.35). Found: N 22.4%. $C_{10}H_9N_3O$. Calculated: N 22.45%.

7-Oxo-5,6,8,9-tetrahydropyrid[3,2-c]azepine (XI). A solution of 4.7 g (0.025 mole) of VII in 100 ml of methanol and 25 ml of ethyl acetate was added to a Raney nickel catalyst (obtained from 20 g of Raney alloy),

and hydrogen was passed through the mixture at normal pressure until 1.67 liters had been absorbed. The resulting solution was decanted, and the precipitate was washed twice with 25-ml portions of methanol. The solutions were collected and filtered, and the filtrates were evaporated on a water bath. Ethyl acetate was added to the residue, and the mixture was stirred. It was then cooled, and the precipitate was removed by filtration and washed with benzene to give 1.8 g (44%) of a product with mp 163.5-165°C (from water). The light-colored crystalline powder was soluble in hot water and hot benzene and had Rf 0.63 [benzene–ethanol (4:1), Al_2O_3]. UV spectrum in water, λ_{max} (log ε): 263 nm (3.59). Found: C 68.0; H 6.9; N 17.3%. $C_9H_{10}N_2O$. Calculated: C 67.5; H 6.7; N 17.3%.

2-Methyl-7-oxo-5,6,8,9-tetrahydropyrid[3,2-c]azepine (XII). The procedure in the preceding experiment was used to obtain 2.5 g (46.5%) of a substance with mp 174.5-176°C (from butyl acetate) from 5.05 g (0.025 mole) of ester VIII. The light-colored crystalline powder was soluble in hot benzene, hot water, and dioxane and had Rf 0.67 (in the system used for azepine XI). UV spectrum in water, λ_{max} (log ε): 269 nm (3.73). PMR spectrum: two triplets at 3.0-3.6 (CH_2CH_2), a split signal at 4.67 (CH_2N), a singlet at 2.63 (CH_3), and signals of pyridine protons at 8.0 (γ-H) and 7.4 ppm (β-H). Found: N 15.9%. $C_{10}H_{12}N_2O$. Calculated: N 15.8%.

3-Carboxymethyl-1-oxo-2,3-dihydrofuro[4,3-b]pyridine (XIII). Concentrated H_2SO_4 (1 ml) was added to 0.87 g (0.005 mole) of cis- or trans-acid III, and the mixture was heated to 60-70°C to dissolve the solid. The solution was allowed to stand overnight, after which 0.15-0.46 ml of water was added, and the mixture was heated at 90-100°C for 3-4 h. It was then neutralized to pH 3.5-4, and the precipitate was removed by filtration, washed with 10 ml of water, squeezed, and dried to give 0.65 g (67%) of a product with mp 163-164° (from ethanol). The light-colored crystalline powder was soluble in aqueous bicarbonate solutions, acids, and water but only slightly soluble in benzene and carbon tetrachloride and has Rf 0.63 [methanol–25% ammonium hydroxide (4:1), paper] and pK_a 4.07 ± 0.02. UV spectrum [10] in water, λ_{max} (log ε): 270 nm (3.60) [10]. PMR spectrum: 6.12-6.42 ppm, t (lactone ring CH); 3.38-3.62 ppm, q (CH_2 group); pyridine ring protons at 9.13 (γ-H), 8.19 (β-H), and 9.0 ppm (α-H). IR spectrum: 2875 (hydrogen bond), 1770 (five-membered lactone ring OCO); 1715 (COOH); 1590, 1455, 1400, and 1375 cm^{-1} (COO^-). Found: C 55.8; H 3.6; N 7.1%. $C_9H_7NO_4$. Calculated: C 55.9; H 3.6; N 7.2%.

5-Methyl-3-carboxymethyl-1-oxo-2,3-dihydrofuro[4,3-b]pyridine (XIV). Concentrated H_2SO_4 (1 ml) was added to 0.47 g (0.0025 mole) of cis- or trans-acid IV, and the solid was dissolved by heating to 60-70°C. Water (0.15-0.46 ml) was added, and the mixture was heated at 90°C for 2.5-3 h. It was then neutralized to pH 3.5-4, and the precipitate was removed by filtration, washed with 10 ml of water, squeezed, and dried to give 0.3-0.35 g (58-68%) of a white crystalline powder with mp 186.5-188°C (from ethanol) and Rf 0.67 (in the system used for XIII). The solubilities of the product were similar to the solubilities of XIII. UV spectrum [10] in water, λ_{max} (log ε): 225 (3.97), 275 nm (3.87). Found: N 6.7%. $C_{10}H_9NO_4$. Calculated: N 6.8%. pK_a 4.12 ± 0.02.

3-Carboxymethyl-1-oxo-2,3-dihydropyrrolo[4,3-b]pyridine (XV). A mixture of 1.74 g (0.01 mole) of cis- or trans-acid III and a solution of 1.2 g of sodium hydroxide in 11 ml of water was heated at 120°C for 4.5 h, after which it was cooled to room temperature, acidified successively with concentrated hydrochloric acid and 12% hydrochloric acid to pH 3.5-4, and allowed to stand overnight in a refrigerator. The resulting precipitate was removed by filtration, washed with water, and dried to give 0.9-1.1 g (47-57%) of a white crystalline substance that was soluble in aqueous solutions of acids, alkalis, and bicarbonates but only slightly soluble in nonpolar solvents. The product had mp 182-183°C (dec., from water). Two recrystallizations from 50% ethanol gave a product with mp 184-185°C (dec.), Rf 0.68 [ethanol–25% ammonium hydroxide–water (2:1:2), Al_2O_3], and pK_a 4.07 ± 0.02. UV spectrum in water, λ_{max} (log ε): 262 nm (3.38). PMR spectrum in trifluoroacetic acid (at 63-65°C): 3.63, d (CH_2) (J = 7.7 Hz coupling with the CH proton); 6.13, t (lactam ring proton); pyridine ring protons at 9.3 (γ-H), 8.23 (β-H), and 9.16 ppm (α-H). Found: N 14.3%. $C_9H_8N_2O_3$. Calculated: N 14.6%.

5-Methyl-3-carboxymethyl-1-oxo-2,3-dihydropyrrolo[4,3-b]pyridine (XVI). The procedure for the synthesis of XV was used to obtain 1.2-1.3 g (29-32%) of XVI from 3.76 g (0.02 mole) of cis- or trans-acid IV, 2.4 g (0.06 mole) of sodium hydroxide, and 22 ml of water after heating at 120°C for 4.5 h. The white crystalline powder, the solubilities of which were similar to the solubilities of XV, had mp 143-144°C (dec.). Two recrystallizations from 50% ethanol gave a product with mp 146-147°C (dec.) and Rf 0.69 (in the system used for XV). UV spectrum in water, λ_{max} (log ε): 270 nm (3.65). The product had pK_a 4.12 ± 0.02. IR spectrum: 2875 (hydrogen bond), 1684 and 1650 (secondary amide), and 1370-1600 cm^{-1} (inner bond). Found: N 13.3%. $C_{10}H_{10}N_2O_3$. Calculated: N 13.6%.

3-Carbomethoxymethyl-1-oxo-2,3-dihydropyrrolo[4,3-b]pyridine (XVII). A 0.96 g (0.005 mole) sample of XV was heated in 10 ml of methanol in the presence of 1 ml of concentrated H_2SO_4, after which the methanol was removed by evaporation on a water bath, and the residual solution was neutralized with potassium bicarbon-

ate to pH 8 and extracted with ethyl acetate. A hot solution of 1.48 g (0.005 mole) of picric acid in 20 ml of ethyl acetate was added to the extract. The ethyl acetate was removed by evaporation to a small volume, and the resulting precipitate was removed by filtration to give 1.2 g of a yellow crystalline picrate that was soluble in hot ethanol and hot water and had mp 163-164°C (from water) and Rf 0.72 [benzene–ethanol (20:3), Al_2O_3]. Found: N 16.2%. $C_{10}H_{10}N_2O_3 \cdot C_6H_3N_3O_7$. Calculated: N 16.1%.

5-Methyl-3-carbomethoxymethyl-1-oxo-2,3-dihydropyrrolo[4,3-b]pyridine (XVIII). The procedure for the synthesis of XVII was used to obtain the picrate of XVIII from 1.03 g (0.005 mole) of XVI by heating in 30 ml of methanol in the presence of 1 ml of concentrated H_2SO_4 and subsequent reaction with picric acid. The product was a yellow crystalline powder with mp 152-153°C (from water) and Rf 0.66 (in the system used for XVII). The picrate was soluble in hot water and hot ethanol. Found: N 15.7%. $C_{11}H_{12}N_2O_3 \cdot C_6H_3N_3O_7$. Calculated: N 15.5%.

3-Carboxamidomethyl-1-oxo-2,3-dihydropyrrolo[4,3-b]pyridine (XIX). Crude XVII was treated with excess (11 ml) 25% ammonium hydroxide immediately after it was prepared by esterification of XV, and the mixture was allowed to stand at room temperature for ~14 h. It was then evaporated to 10-15 ml, and the concentrate was cooled. The resulting precipitate was removed by filtration and washed on the filter with 5 ml of water to give 0.5-0.6 g (63% based on the starting acid) of the amide as a white crystalline powder with mp 245-246.5° (dec., from ethanol) and Rf 0.36 [benzene–ethanol (2:1), Al_2O_3]. UV spectrum in water, λ_{max} (log ε): 214 (4.03) and 269 nm (3.75). Found: N 21.9%. $C_9H_9N_3O_2$. Calculated: N 22.0%.

5-Methyl-3-carboxamidomethyl-1-oxo-2,3-dihydropyrrolo[4,3-b]pyridine (XX). A 10-ml sample of 25% ammonium hydroxide was added to XVIII (immediately after its preparation by esterification of XVI), and the mixture was allowed to stand at room temperature for 10-15 h (the end of the reaction was determined by chromatography). The solution was evaporated on a water bath to 10 ml, and the concentrate was cooled. The resulting precipitate was removed by filtration, washed on the filter with 5 ml of water, squeezed, and dried to give 0.6 g (59% based on the starting acid) of the amide as a white crystalline powder with mp 256.5-257°C (dec., from ethanol) and Rf 0.46 (in the system used for XIX). The product was soluble in hot water and hot ethanol but only slightly soluble in benzene. UV spectrum in water, λ_{max} (log ε): 219 (4.01) and 275 nm (3.81). Found: N 20.6%. $C_{10}H_{11}N_3O_2$. Calculated: N 20.5%.

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