THE SYNTHESIS OF ISOMERIC 4- AND 6-ETHOXY-3-ETHYLPYRIDINES

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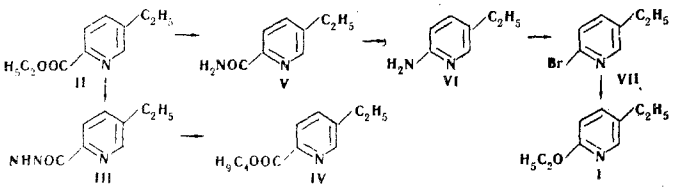
The synthesis of isomeric 4- and 6-ethoxy-3-ethylpyridines has been effected and a difference in the behavior of substituents in the α- and γ-positions of the isomeric pyridine derivatives has been observed.

During a study of various reactions of 2-chloro-3-(β-chloroethyl)-4, 6-dihydroxypyridine (which is an intermediate in the synthesis of azaindoles [8]; we shall report various reactions of this compound separately), the necessity arose for the synthesis of isomeric 2- and 4-ethoxy-5-ethylpyridines. Neither of these compounds has been described in the literature.

We carried out the synthesis of 2-ethoxy-5-ethylpyridine (I) from ethyl 5-ethylpicolinate (II). This was obtained in a known manner by the oxidation of 5-ethyl-2-methylpyridine (aldehyde collidine) with selenium dioxide [1] and the subsequent esterification of the 5-ethylpicolinic acid formed [2].

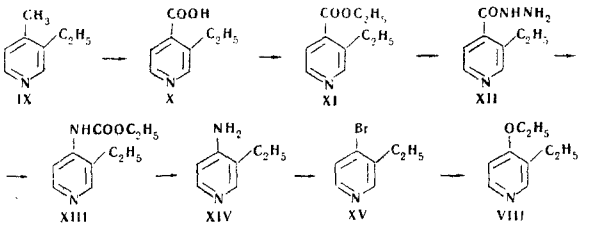
The reaction of the ester II with hydrazine hydrate in boiling ethanol gave a 96% yield of the hydrazide of 5-ethylpicolinic acid (III). However, the treatment of this hydrazide (III) with n-butyl nitrite under the conditions of the Curtius reaction led to the formation not of a 2-amino-5-ethylpyridine but of butyl 5-ethylpicolinate (IV). A similar conversion of a hydrazide into an ester in the Curtius reaction has been observed previously by one of us together with E. E. Mikhlina [3] in the 2-substituted quinuclidine series. However, while in the case of quinuclidine-2-carboxylic hydrazide the formation of the corresponding ester was a side reaction taking place with a yield of 25% and the main product was methyl-N-(2-quinuclidyl)urethane (yield 44%), in the Curtius reaction with the hydrazide III the butyl ester IV was obtained with a yield of 75.2%.

In view of this, to obtain 2-amino-5-ethylpyridine we used the Hofmann degradation. The amide of 5-ethylpicolinic acid (V) was obtained from the corresponding ethyl ester II with a yield of 83.5% and was converted by treatment with sodium hypobromite into 6-amino-3-ethylpyridine (VI) with a yield of 50%.



The passage from VI to 2-ethoxy-5-ethylpyridine (I) was effected by the method that is classical for α- and γ-substituted pyridines: by diazotization of the amino derivative VI in hydrobromic acid and then heating the substituted bromopyridine VII with sodium ethoxide. As was to be expected, both reactions took place with high yields (86.7 and 63.8%), and enabled the pyridine I with a fixed position of the ethoxy group to be obtained.

The following scheme was used for the synthesis of the isomeric 4-ethoxy-3-ethylpyridine (VIII).



3-Ethyl-4-methylpyridine (β-collidine, IX) was subjected to selective oxidation with selenium dioxide; this gave an almost quantitative yield of 3-ethylisonicotinic acid (X). The ethyl ester of this acid (XI) was converted quantitatively into the corresponding hydrazide (XII) which, unlike the isomer III described above, underwent the Curtius reaction on treatment with n-butyl nitrite to form ethyl-N-(3-ethyl-4-pyridyl)urethane (XIII). In this case, the yield of the normal Curtius reaction product was 51.4%. Subsequent saponification of XIII by boiling in hydrochloric acid and diazotization of the amine XIV led to 4-bromo-3-methylpyridine (XV). In contrast to the relative stability of the 2-bromo-5-ethylpyridine (VII) isomeric with it, XV is highly labile. The XV obtained in the form of a colorless mobile liquid rapidly became turbid and was gradually converted into a solid quaternary salt of polymeric nature, even at room temperature. Nevertheless, the high lability of the halogen enabled the bromine in freshly-distilled XV to be replaced by an ethoxy group with a yield of 4-ethoxy-3-ethylpyridine (VIII) of 83.4%.

The difference in the behavior of functional groups in the α and γ positions of the pyridine nucleus observed during the above-described syntheses is interesting. It has already been mentioned that the hydrazide of 3-ethylisonicotinic acid (XII) underwent a normal Curtius reaction with the formation of ethyl-N-(3-ethyl-4-pyridyl)urethane while the isomeric hydrazide of the substituted picolinic acid (III) did not undergo the Curtius reaction. As in the case of the unsubstituted α- and γ-halopyridines [6], 4-bromo-3-ethylpyridine (XV) underwent intermolecular quaternization considerably more readily than the pyridine VII isomeric with it. Finally, by analogy with the known ionization constants of the unsubstituted α- and γ-alkoxypyridines (pK_a is 3.28 for 2-methoxypyridine and 6.62

for 4-methoxypyridine [7]), VIII behaved as a considerably stronger base than I. While the hydrochloride of I is not precipitated with alcoholic hydrogen chloride from an ethereal solution of the base, under the same conditions VIII forms a highly crystalline hydrochloride stable to hydrolysis.

As in the case of other α- and γ-substituted pyridines the differences that we have observed in the behavior of the isomeric 4- and 6-substituted 3-ethylpyridines are obviously connected with the difference in the screening of the pyridine nitrogen by the substituents in the 4 and 6 positions and also with the dissimilar inductive influences of these substituents in dependence on their positions in the pyridine molecule.

EXPERIMENTAL

5-Ethylpicolinic acid hydrazide (III). A mixture of 18 g (0.1 mole) of ethyl 5-ethylpicolinate (II) [2] and 5.8 g (0.12 mole) of hydrazine hydrate was boiled in 50 ml of ethanol for 5 hr. The reaction mixture was evaporated to dryness in vacuum. This gave 15.98 g (96.2%) of III, colorless crystals, mp 58°–59° C (from ether). The substance is readily soluble in methanol and water, less soluble in benzene, ethanol, and ether, and insoluble in petroleum ether. Found, %: C 58.30; H 6.81; N 25.04. Calculated for $C_8H_{11}N_3O$, %: C 58.18; H 6.67; N 25.45.

Curtius reaction with 5-ethylpicolinic acid hydrazide (III). A solution of 5.3 g (0.032 mole) of III in 60 ml of butanol was treated with 9.1 ml of a 19% solution of hydrogen chloride (0.048 mole) in butanol. The reaction mixture was cooled to 0° C and, with stirring, 5 g (0.048 mole) of freshly distilled n-butyl nitrite was added in drops over 20 minutes. Stirring was continued at room temperature for 3 hr and then at the boil (bath temperature 125° C) for 4 hr. The reaction mixture was evaporated in vacuum and the residue was distilled. A fraction with bp 126°–128° C (1 mm) was collected. The yield of butyl 5-ethylpicolinate (IV) was 5.42 g (75.2%). Colorless oily substance, sparingly soluble in water, readily soluble in the usual organic solvents, n_D^{20} 1.4982; IR spectrum (all the IR spectra were taken on a UR-10 recording spectrophotometer): 1726 cm^{-1} ($-COOC_4H_9$). Found, %: C 69.50; H 8.22; N 6.75. Calculated for $C_{12}H_{17}NO_2$, %: C 69.50; H 8.06; N 6.75.

5-Ethylpicolinamide (V). Seven grams (0.039 mole) of the ester II and 8 ml of 20% aqueous ammonia (0.046 mole) were stirred at room temperature for 5 hr. After 2 hr, a white crystalline precipitate began to appear and its amount increased as the reaction proceeded. The reaction mixture was left to stand at room temperature for another 24 hr. The precipitate of V that had deposited was filtered off and dried in a vacuum desiccator. Yield 4.88 g (83.5%). Colorless crystals, mp 141°–142° C (from benzene). The substance is readily soluble in alcohols, acetone, chloroform, and ethyl acetate, sparingly soluble in benzene and water, and insoluble in ether and petroleum ether. IR spectrum: 1663, 3430 cm^{-1} ($-CONH_2$). Found, %: C 63.75; H 6.91; N 19.13. Calculated for $C_8H_{10}N_1O$, C 64.00; H 6.67; N 18.70.

6-Amino-3-ethylpyridine (VI). In drops, 4.7 g (0.03 mole) of bromine was added to a solution of 26.2 g (0.66 mole) of caustic soda in 210 ml of water cooled to −7° C. Then, to the solution of sodium hypobromite so formed, was added 4.5 g (0.03 mole) of the amide V. The reaction mixture was heated with stirring at 70° C for 1.5 hr. (The process was monitored by the acidification of samples of the mixture. At the end of the reaction, acidification of such a sample with hydrochloric acid did not liberate bromine). Then the reaction mixture was cooled to room temperature and the VI was extracted with ether. The ethereal extract was dried with potassium carbonate and evaporated in vacuum. The residue was distilled at 90°–92° C (3 mm). This gave 1.16 g (50%) of VI. Colorless oily substance, soluble in the usual organic solvents, sparingly soluble in water, n_D^{20} 1.5618. Found, %: C 68.85; H 8.48; N 22.71. Calculated for $C_7H_{10}N_2$, %: C 68.85; H 8.20; N 22.95.

6-Bromo-3-ethylpyridine (VII). By its addition in small portions, 1 g (0.0082 mole) of 6-amino-3-ethylpyridine (VI) was dissolved in 3 ml of 40% hydrobromic acid with cooling to −5° C. To the resulting solution at −5° C were added in drops 0.87 ml (0.017 mole) of bromine and 1 ml of concentrated hydrochloric acid and then, again in drops, a solution of 1.26 g (0.018 mole) of sodium nitrite in 2 ml of water cooled to −5° C. The reaction mixture was stirred at −5° C for another 30 min, after which it was treated with 4.5 ml of 40% aqueous sodium hydroxide, and the VII was extracted with ether. Vacuum distillation gave 1.32 g (86.7%) of VII with bp 120°–122° C (23 mm). Colorless oily substance, readily soluble in the usual organic solvents, practically insoluble in water, n_D^{20} 1.5298. Found, %: C 45.28; H 4.52; N 7.13; Br 42.91. Calculated for C_7H_8BrN, %: C 45.17; H 4.30; N 7.53; Br 43.00.

6-Ethoxy-3-ethylpyridine (I). A mixture of sodium ethoxide (from 0.17 g, 0.0074 g-atom, of sodium and 3.6 ml of absolute ethanol) and 1.03 g (0.0061 mole) of 6-bromo-3-ethylpyridine (VII) was heated in a sealed tube at 140° C for 6 hr. Then the reaction mixture was evaporated in vacuum. The residue was treated with 3 ml of 50% potassium carbonate solution and the I was extracted with ether. Vacuum distillation gave 0.53 g (63.8%) of I with bp 98° C (22 mm). Colorless oily substance, readily soluble in the usual organic solvents and sparingly soluble in water, n_D^{20} 1.4928. Found, %: C 71.14; H 8.58; N 9.14. Calculated for $C_9H_{13}NO$, %: C 71.51; H 8.60; N 9.28.

3-Ethylisonicotinic acid (X). In portions, 18 g (0.16 mole) of freshly-prepared selenium dioxide was added over 30 min to 13 g (0.11 mole) of 3-ethyl-4-methylpyridine (IX) [4] heated to the boil. The boiling point of the reaction mixture first fell from 190° C to 150° C and then rose again to 200° C. Stirring at 200° C was continued for another 30 minutes. Then the reaction mixture was cooled to room temperature and treated with 25 ml of water, and the selenium was filtered off. The filtrate was evaporated in vacuum. This gave 15.87 g (98.7%) of 3-ethylisonicotinic acid, colorless crystals, mp 212°–213° C (from ethanol).*

3-Ethylisonicotinamide was obtained by the reaction of the chloride of the acid X with ammonia. Colorless crystals, mp 139°–140° C (from ethyl acetate). The substance is readily soluble in ethanol and chloroform, sparingly soluble in ethyl acetate and acetone, and insoluble in ether, benzene, and petroleum ether. Found, %: C 63.75; H 6.47; N 18.72. Calculated for $C_8H_{10}N_2O$, %: C 64.00; H 6.67; N 18.67.

Ethyl 3-ethylisonicotinate (XI). A mixture of 2.2 g (0.15 mole) of 3-ethylisonicotinic acid and 30 ml of saturated alcoholic hydrogen chloride was left at room temperature overnight. Then it was boiled for 3 hr and the alcohol was distilled off. The residue was made alkaline with 50% potassium carbonate solution and the XI was extracted with ether. The ethereal solution was dried with magnesium sulfate and distilled in vacuum. This gave 2.05 g (79.4%) of XI with bp 134°–136° C (20 mm). Colorless oily substance, readily soluble in the usual organic solvents and sparingly soluble in water, n_D^{20} 1.4994, IR spectrum: 1729 cm^{-1} ($-COOC_2H_5$). Found, %: C 66.62; H 7.30; N 7.93. Calculated for $C_{10}H_{13}NO_2$, %: C 67.01; H 7.28; N 7.83.

3-Ethylisonicotinic acid hydrazide (XII). A mixture of 5 g (0.028 mole) of ethyl 3-ethylisonicotinate (XI) and 3 ml (0.06 mole) of hydrazine hydrate was heated in a sealed tube at 180° C for 7 hr (preliminary experiments had shown that boiling XI with hydrazine hydrate in ethanol did not lead to the formation of XII, the initial ester XI being recovered). The residue from the evaporation of the reaction mixture (4.6 g) was converted into the dihydrochloride by the addition of an alcoholic solution of hydrogen chloride. This gave 5.86 g (87.4%) of 3-ethylisonicotinic acid hydrazide dihydrochloride monohydrate. Colorless crystals, mp 174°–175° C (from ethanol). The substance is readily soluble in water, sparingly soluble in ethanol, and insoluble

*The synthesis of 3-ethylisonicotinic acid (X) from 3-ethyl-4-methylpyridine by condensation with formalin and oxidation of the dimethylol derivative so formed with chromic acid has been described previously [5]. The yield of X by this method was 33.3%.

in benzene and ethyl acetate. Found, %: N 16.72; Cl 27.91. Calculated for $C_8H_{11}N_3 \cdot 2HCl \cdot H_2O$, %: N 16.42; Cl 27.75. After drying for a day in the vacuum pistol at 100° C. Found, %: N 17.84. Calculated for $C_8H_{11}N_3 \cdot 2HCl$, %: N 17.67.

Ethyl-N-(3-ethyl-4-pyridyl)urethane (XIII). Forty milliliters of absolute ethanol was added to 5.5 g (0.0222 mole) of the monohydrate of the dihydrochloride of XII. The reaction mixture was cooled to 0° C, and 4.6 g (0.045 mole) of freshly-distilled n-butyl nitrite was added to it dropwise over 20 minutes. The reaction mixture was stirred at room temperature for 3 hr and at the boil for 6 hr. Then the ethanol was distilled off in vacuum and the residue was triturated with acetone. This gave 2.55 g (51.4%) of the hydrochloride of XIII. Colorless crystals, mp 170°-171.5° C. The substance is readily soluble in water and ethanol and insoluble in ether and acetone. IR spectrum: 1738 cm^{-1} ($-NHCOC_2H_5$). Found, %: N 12.66; Cl 15.92. Calculated for $C_9H_{14}N_2O_2 \cdot HCl$, %: N 12.80; Cl 16.25.

4-Amino-3-ethylpyridine (XIV) was obtained by the saponification of 0.11 g (0.00048 mole) of the hydrochloride (XIII) by boiling it with 7 ml of concentrated hydrochloric acid for 10 hr. After the evaporation of the reaction mixture, the residue was recrystallized from a mixture of ethanol and ethyl acetate. The yield of the hydrochloride of XIV was 0.08 g (86.2%), mp 209°-210° C. The substance is readily soluble in water and ethanol and insoluble in ether, acetone, and ethyl acetate. Found, %: C 52.96; H 7.30; Cl 22.64. Calculated for $C_7H_{10}N_2 \cdot HCl$, %: C 53.00; H 6.95; Cl 22.40.

4-Bromo-ethylpyridine (XV). In drops at −5° C, 1.1 ml (0.022 mole) of bromine was added to a solution of 1.6 g (0.01 mole) of 4-amino-3-ethylpyridine hydrochloride in 4 ml of 40% hydrochloric acid, and this was followed by a solution of 1.54 g (0.015 mole) of sodium nitrite in 3 ml of water cooled to −5° C. After the mixture had been kept at −5° C for half an hour, 6 ml of 40% sodium hydroxide solution was added with stirring (temperature not above 20° C), and the XV was extracted with ether. The ethereal extract was dried with magnesium sulfate and evaporated, and the residue (0.98 g) was distilled in vacuum. This gave 0.66 g (34.1%) of XV with bp 104° C (28 mm). The substance, isolated in the form of a colorless transparent liquid, is readily soluble in the usual organic solvents and very rapidly becomes yellow with the separation of a solid quaternary salt of polymeric nature. The ease of quaternization of XV explains its low yield after distillation. This property of 4-bromo-3-ethylpyridine also explains the necessity for carrying out all operations rapidly and with freshly-distilled samples of XV.

Found, %: C 44.92; H 4.50; N 7.57; Br 42.70. Calculated for C_7H_8BrN, %: C 45.17; H 4.30; N 7.53; Br 43.00.

4-Ethoxy-3-ethylpyridine (VIII). A mixture of 0.4 g (0.00215 mole) of 4-bromo-3-ethylpyridine (XV) and the sodium ethoxide obtained from 0.08 g (0.0035 g-atom) of sodium and 2 ml of absolute ethanol was heated in a sealed tube at 140° C for 6 hr. Then the reaction mixture was evaporated in vacuum 5 ml of 50% potassium carbonate solution was added to the residue, and the VIII was extracted with ether. The ethereal extract was dried with potassium carbonate and distilled in vacuum. This gave 0.27 g (83.4%) of VIII with bp 100° C (30 mm). Colorless oily substance, readily soluble in the usual organic solvents and sparingly soluble in water. Found, %: N 9.00; 9.47. Calculated for $C_9H_{13}NO$, %: N 9.14.

Hydrochloride, colorless crystals, mp 140°-141.5° C (from ethyl acetate). The substance is readily soluble in water, chloroform, and isopropanol, sparingly soluble in ethyl acetate, methanol, ethanol, benzene, and toluene, and insoluble in ether, petroleum ether, and acetone. Found, %: C 57.24; H 7.36; N 7.45; Cl 18.98. Calculated for $C_9H_{13}NO \cdot HCl$, %: C 57.60; H 7.47; N 7.47; Cl 18.93.

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3 March 1966

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