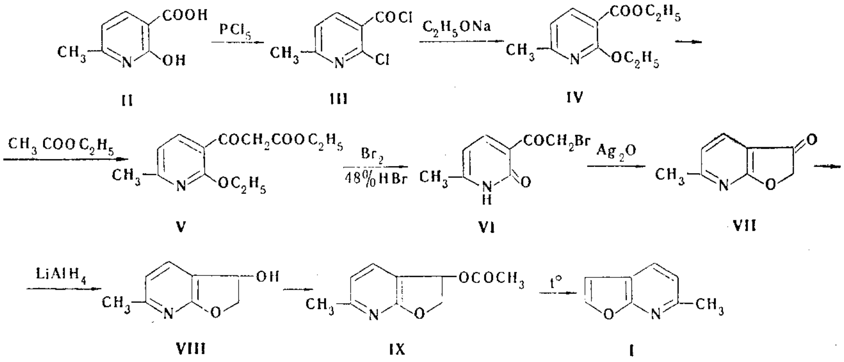
SYNTHESIS OF 6-METHYLFURO[2,3-b]PYRIDINE

P. I. Abramenko and V. G. Zhiryakov

UDC 547.722.2'821.07

The Claisen condensation of ethyl 2-ethoxy-6-methylpyridine-3-carboxylate with ethyl acetate gave ethyl 2-ethoxy-6-methylnicotinoylacetate, which was converted to 3-bromoacetyl-6-methyl-2-pyridone by heating with bromine in 48% hydrobromic acid. The cyclization of the bromoacetylpyridone by the action of silver oxide in methanol gave 3-oxo-6-methyl-2,3-dihydrofuro[2,3-b]pyridine, which was reduced to 3-hydroxy-6-methyl-2,3-dihydrofuro[2,3-b]pyridine with lithium aluminum hydride in dimethoxyethane. Acetylation of the latter gave its acetate, the pyrolysis of which in vacuo gave 6-methylfuro[2,3-b]-pyridine.

Unsubstituted furo[2,3-b]pyridine was obtained by pyrolysis of acetoxydihydrofuro[2,3-b]pyridine [1]. In the present communication we describe the synthesis of 6-methylfuro[2,3-b]pyridine (I), which contains a methyl group in the α position of the pyridine ring, from 2-hydroxy-6-methylpyridine-3-carboxylic acid (II) [2]:



Base I is the starting compound for the preparation of polymethine dyes.

2-Chloro-6-methylpyridine-3-carboxylic acid chloride (III) was obtained by heating II with phosphorus pentachloride. Ethyl 2-ethoxy-6-methylpyridine-3-carboxylate (IV) was synthesized by the reaction of III with a dimolar amount of sodium ethoxide in anhydrous ethanol. Claisen condensation of IV with ethyl acetate gave ethyl 2-ethoxy-6-methylnicotinoylacetate (V). The action of a heated mixture of bromine in 48% hydrobromic acid on V gave 3-bromoacetyl-6-methyl-2-pyridone (VI), which was converted to 3-oxo-6-methyl-2,3-dihydrofuro[2,3-b]pyridine (VII) by cyclization by means of silver oxide in methanol at room temperature. Reduction of VII with lithium aluminum hydride in dimethoxyethane gave 3-hydroxy-6-methyl-2,3-dihydrofuro[2,3-b]pyridine (VIII), which was acetylated with acetic anhydride in pyridine. Pyrolysis of IX in vacuo (140-160 mm) gave I in 86% yield.

The IR spectrum of VI contains the characteristic frequency of the C = O stretching vibrations and a band of the NH stretching vibrations at 1665 and 3440-3480 cm^{-1}, which are absent in the spectra of the other derivatives. The IR spectrum of VII contains the characteristic frequencies of the C = O stretching vibrations at 1730 cm^{-1} and ν_{C-O} at 1260 and 1102 cm^{-1}.

All-Union State Scientific-Research and Design Institute of the Photographic-Chemical Industry, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1544-1546, November, 1972. Original article submitted October 12, 1971.

Frequencies of the C—H stretching vibrations of the furan ring at 3165 and 3130 cm^{-1} and ν_{C-H} of the pyridine ring at 3080 and 3060 cm^{-1} are observed in the IR spectrum of I.

Attempts to obtain I by cyclization of (6-methyl-2-pyridyloxy)acetaldehyde dimethylacetal under various conditions (by means of phosphorous pentoxide, polyphosphoric acid, or phosphorus oxychloride in aromatic solvents, of zinc chloride or sodium acetate in acetic acid, or of hot concentrated sulfuric acid) were unsuccessful. The starting compound and considerable amounts of resinification products were isolated from the reaction mixture.

EXPERIMENTAL

(6-Methyl-2-pyridyloxy)acetaldehyde Dimethylacetal. A 10.9-g (0.1 mole) sample of 6-methyl-2-hydroxypyridine [2] was added at room temperature to a solution of 2.3 g (0.1 g-atom) of sodium in 100 ml of anhydrous ethanol, and the mixture was stirred for 30 min, after which 17.0 g (0.1 mole) of bromoacetaldehyde dimethylacetal was added to it. The mixture was then heated on a boiling-water bath for 10 h under nitrogen, and the alcohol was removed by distillation, the residue was heated at 105-110° for 5 h, cooled, and treated with water. The product was extracted with ether, and the ether solution was washed with water. The ether was removed by distillation, and the residue was vacuum distilled to give 1.2 g (6%) of a colorless oil with bp 120-125° (5 mm). Found, %: C 60.8; H 7.5; N 7.0. $C_{10}H_{15}NO_3$. Calculated,%: C 60.9; H 7.6; N 7.1.

B. A mixture of the silver salt of 2-hydroxy-6-methylpyridine (from 0.1 mole of silver carbonate and 0.1 mole of 2-hydroxy-6-methylpyridine), 42 g (0.25 mole) of bromoacetaldehyde dimethylacetal, and 150 ml of anhydrous benzene was allowed to stand in the dark at room temperature for 36 h. It was then cooled and filtered. The solid was washed with benzene, and the benzene solution was washed with 10% sodium bicarbonate, dried, and vacuum evaporated. The residue was vacuum distilled to give 10.3 g (52%) of a colorless oil with bp 121-125° (5 mm). IR spectrum (thin layer): 2945, 2870 (ν_{C-H} in the CH_3 group), 1585, 1470, 1436 (ring ν), 1240 cm^{-1} (ν_{C-O}).

2-Chloro-6-methylpyridine-3-carboxylic Acid Chloride (III). A mixture of 15.3 g (0.1 mole) of acid II [2] and 22 g (0.11 mole) of phosphorus pentachloride was heated cautiously until it liquefied and was then refluxed gently for 7-10 min. It was then cooled and treated with anhydrous benzene. The benzene solution was evaporated, and the residue was treated with anhydrous ether. The ether solution was evaporated, and the residue was vacuum distilled to give 10.4 g (55%) of a colorless liquid with bp 101-102° (4 mm). Found,%: C 44.2; H 2.1; Cl 37.2. $C_7H_5Cl_2NO$. Calculated,%: C 44.2; H 2.1; Cl 37.3.

2-Chloro-6-methylpyridine-3-carboxylic Acid. A 9.5-g (0.05 mole) sample of III was added dropwise with stirring to a water-cooled solution of 2 g (0.05 mole) of sodium hydroxide in 30 ml of water, and the mixture was stirred at room temperature for 2 h. It was then cooled, and the precipitate was removed by filtration, washed with water, and dried to give 7.3 g (86%) of a product with mp 152-154°. Recrystallization from anhydrous ethanol gave colorless prisms with mp 157-158°. Found,%: C 48.9; H 3.5; Cl 20.5. $C_7H_6ClNO_2$. Calculated,%: C 49.0; H 3.5; Cl 20.6.

Ethyl 2-Chloro-6-methylpyridine-3-carboxylate. A 19.0-g (0.1 mole) sample of III was added dropwise with stirring at room temperature to a solution of 2.3 g (0.1 g-atom) of sodium in 50 ml of anhydrous ethanol, and the mixture was stirred at room temperature for 2 h and vacuum evaporated. The residue was treated with anhydrous ether, the ether solution was evaporated, and the residue was vacuum distilled to give 15.9 g (80%) of a colorless oil with bp 124-125° (5 mm). Found,%: C 54.0; H 4.9; N 7.0. $C_9H_{10}ClNO_2$. Calculated,%: C 54.1; H 5.0; N 7.0.

Ethyl 2-Ethoxy-6-methylpyridine-3-carboxylate (IV). A 19-g (0.1 mole) sample of III was added dropwise with stirring at room temperature to a solution of 13.6 g (0.2 mole) of sodium ethoxide in 100 ml of anhydrous ethanol, and the mixture was refluxed for 2 h. The alcohol was removed by distillation, 100 ml of water was added to the residue, and the mixture was extracted with ether. The extract was washed with water and dried with sodium sulfate. The ether was removed by distillation, and the residue was vacuum distilled to give 17.4 g (83%) of a colorless liquid with bp 122-125° (8 mm) [3]. IR spectrum (thin layer): 2998 (pyridine ν_{C-H}), 2885-2950 (ν_{CH_2} and ν_{CH_3}), 1740, 1710 (conjugated ester $\nu_{C=O}$), 1600, 1582 (ring ν), 1470, 1423 (ring ν and δ_{CH_2}), 1283, 1140, and 1040 cm^{-1} (ν_{C-O}).

Ethyl 2-Ethoxy-6-methylnicotinoylacetate (V). This compound was obtained via the method in [3]. IR spectrum (thin layer): 3000 (pyridine ν_{C-H}), 2950, 2925, 2885 (ν_{CH_2} and ν_{CH_3}), 1748 (ester $\nu_{C=O}$), 1680 (conjugated ketone $\nu_{C=O}$), 1290, 1225, 1038 cm^{-1} (ν_{C-O}).

3-Bromoacetyl-6-methyl-2-pyridone (VI). A 50-g (0.2 mole) sample of V and 10.7 ml of bromine were added slowly with stirring and ice-cooling to 120 ml of 48% hydrobromic acid. Toward the end of the addition, the bromine was decolorized more slowly, and the hydrobromide precipitated from the reaction mixture. To dissolve it, the mixture was warmed on a water bath, and the addition of the bromine was completed at room temperature. After all of the bromine had been added, the mixture was heated to 45°, and the temperature was raised to 60° in the course of 30 min (carbon dioxide evolution was observed). The mixture was heated to 80°, and the ethyl bromide was removed by distillation at 80-90° in the course of 1 h. The mixture was cooled and poured over 200 g of ice, and the aqueous mixture was stirred for 15 min. The precipitate was removed by filtration, suspended in 100 ml of ice water, and neutralized to pH 6-7 by the addition of sodium carbonate. The solid reaction product was removed by filtration, washed with ice water, and recrystallized from alcohol in the presence of activated charcoal to give 25.7 g (56%) of light-yellow crystals with mp 160-161° (dec.). IR spectrum (KBr): 3450-3480 (ν_{NH}), 2980 ($\nu_{\mathrm{C-H}}$), 1665 (pyridone $\nu_{\mathrm{C=O}}$), 1620, 1562 cm^{-1} (ring $\nu_{\mathrm{C=C}}$). Found,%: C 41.7; H 3.1; Br 34.7. $C_2H_8BrNO_2$. Calculated,%: C 41.9; H 3.1; Br 34.9.

3-Oxo-6-methyl-2,3-dihydrofuro[2,3-b]pyridine (VII). A 19.7-g (0.085 mole) sample of freshly prepared silver oxide was added in portions with stirring under nitrogen to a suspension of 18.3 g (0.08 mole) of VI in 250 ml of methanol, and the mixture was stirred at room temperature for 1 h and filtered. The precipitate was washed with methanol, and the methanol solution was decolorized with activated charcoal and evaporated. The residue was recrystallized from alcohol to give 8.95 g (75%) of light-yellow crystals with mp 99-101°. IR spectrum (KBr): 3110, 3050, 2982, 2945 ($\nu_{\mathrm{C-H}}$ and $\nu_{\mathrm{CH_2}}$), 1730 ($\nu_{\mathrm{C=O}}$), 1618, 1477, 1442 (ring ν), 1260, 1102 cm^{-1} ($\nu_{\mathrm{C-O}}$). Found,%: C 64.3; H 4.7; N 9.3. $C_8H_7NO_2$. Calculated: C 64.4; H 4.7; N 9.4.

3-Hydroxy-6-methyl-2,3-dihydrofuro[2,3-b]pyridine (VIII). A solution of 5.96 g (0.04 mole) of VII in 30 ml of dimethoxyethane was added in the course of 20 min to a cooled (ice–salt mixture) suspension of 0.76 g (0.02 mole) of lithium aluminum hydride in 50 ml of anhydrous dimethoxyethane, and the mixture was stirred at room temperature for 2 h, cooled with ice, and hydrolyzed by the addition of a solution of 1.4 g of ammonium chloride in 4.5 ml of water. The precipitate was removed by filtration and washed with dimethoxyethane. The solution was dried with potassium carbonate and evaporated, and the residue was recrystallized from dimethoxyethane to give 4.72 g (78%) of light-yellow crystals with mp 92° [bp 139° (0.1 mm)]. IR spectrum (3% solution in $CHCl_3$): 3160-3310 ($\nu_{\mathrm{O-H}}$), 3050 ($\nu_{\mathrm{C-H}}$), 1472 (ring ν), 1100 cm^{-1} ($\nu_{\mathrm{C-O}}$). Found,%: C 63.7; H 5.9; N 9.3. $C_8H_9NO_2$. Calculated,%: C 63.5; H 6.0; N 9.3.

3-Acetoxy-6-methyl-2,3-dihydrofuro[2,3-b]pyridine (IX). A 10-ml sample of acetic anhydride was added dropwise to a solution of 4.53 g (0.03 mole) of VIII in 12 ml of pyridine, and the mixture was held at room temperature overnight. It was then vacuum evaporated to give 4.93 g (85%) of a light-yellow oil with bp 93° (0.8 mm). Found,%: C 62.2; H 5.6; N 7.3. $C_{10}H_{11}NO_3$. Calculated,%: C 62.1; H 5.7; N 7.2.

6-Methylfuro[2,3-b]pyridine (I). A 5.8-g (0.03 mole) sample of IX was slowly vacuum distilled at 140-160 mm and up to 150° (in the vapors) in the presence of pumice granules. The distillate was treated with 50 ml of ether, dried with potassium carbonate, and filtered. The ether was removed from the filtrate by distillation, and the residue was vacuum distilled to give 3.4 g (86%) of a colorless liquid with bp 90-92° (13 mm). IR spectrum (thin layer): 3165, 3130 (furan $\nu_{\mathrm{C-H}}$), 3080, 3060 (pyridine $\nu_{\mathrm{C-H}}$), 1610 (furan $\nu_{\mathrm{C=C}}$ and pyridine ring ν), 1535, 1475, 1450, 1410 (pyridine ring ν), 1342, 1272, 1220 cm^{-1} ($\nu_{\mathrm{C-O}}$). PMR spectrum (CCl_4): δ 2.63 (singlet, CH_3), 6.64 (doublet, 3-H, J = 2.5 Hz), 7.03 (doublet, 5-H, J = 8 Hz), 7.59 (doublet, 2-H), 7.70 (doublet, 4-H). Mass spectrum: m/e 133 (100%, $[M]^{+}$), 132 (27.2%, $[M-1]^{+}$), 104 (35.9%, $[M-28]^{+}$). Found,%: C 72.1; H 5.2; N 10.4. C_8H_7NO. Calculated,%: C 72.2; H 5.2; N 10.5. The picrate was obtained as light-yellow needles (from ethanol) with mp 138-140°. Found,%: N 15.4. $C_8H_7NO \cdot C_6H_3N_3O_7$. Calculated,%: N 15.5. The ethiodide was obtained as colorless prisms (from ethanol) with mp 184-186°. Found,%: C 41.4; H 4.5; I 43.8. $C_{10}H_{12}INO$. Calculated,%: C 41.5; H 4.6; I 43.9.

LITERATURE CITED

1. H. Sliva, Bull. Soc. Chim. France, 646 (1970).
2. N. K. Kochetkov, Dokl. Akad. Nauk SSSR, 84, 289 (1952).
3. P. I. Abramenko and V. G. Zhiryakov, Khim. Geterotsikl. Soedin., 1539 (1972).