SYNTHESIS OF METHYL-SUBSTITUTED BENZOFURO-, BENZOTHIENO-, AND BENZOSELENOPHENO[2,3-b]PYRIDINES

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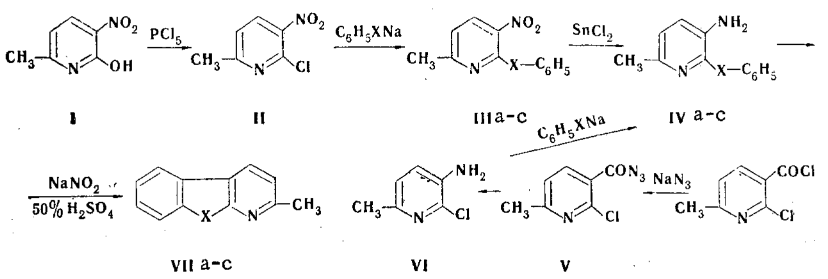
Three-ring systems with benzo[b]furan, benzo[b]selenophene, and benzo[b]thiophene rings condensed with the pyridine ring and with a methyl group in the α position of the pyridine ring were synthesized by the reaction of 2-chloro-3-nitro-6-methylpyridine with sodium phenoxide, sodium thiophenoxide, or sodium selenophenoxide, reduction of the resulting 2-phenoxy-, 2-phenylthio-, and 2-phenylseleno-3-nitro-6-methylpyridines with stannous chloride in concentrated hydrochloric acid, diazotization of the substituted 3-aminopyridines, and heating of the diazonium compounds in 25% sulfuric acid.

Heterocyclic systems with a benzo[b]furan or benzo[b]selenophene ring condensed with the pyridine ring and a methyl group in the α position relative to the nitrogen of the pyridine ring were previously unknown. We described monomethyl-substituted thionaphthenopyridines in 1965 [1]. In the present communication, we describe a general method for the synthesis of systems of this type from 2-hydroxy-3-nitro-6-methylpyridine (I):



a X=O; b X=Se; c X=S

Nitropyridine I was obtained by heating 2-hydroxy-6-methylpyridine [2] with nitric acid. The reaction of I with phosphorus pentachloride gave 2-chloro-3-nitro-6-methylpyridine (II) [3,4], the heating of which with sodium phenoxide, selenophenoxide, or thiophenoxide in anhydrous ethanol gave, respectively, 2-phenoxy-, 2-phenylseleno-, and 2-phenylthio-3-nitro-6-methylpyridines (IIIa-c). The latter were reduced with stannous chloride in concentrated hydrochloric acid to 2-phenoxy-, 2-phenylseleno-, and 2-phenylthio-3-amino-6-methylpyridines (IVa-c). Compounds IV were also obtained by reaction of 2-chloro-3-amino-6-methylpyridine (VI), synthesized from the azide of 2-chloro-6-methylpyridine-3-carboxylic acid (V), with sodium phenoxide, selenophenoxide, and thiophenoxide in heated anhydrous ethanol.

Aminopyridines IVa-c were diazotized with sodium nitrite in dilute sulfuric acid, and the diazonium compounds were converted to 2-methylbenzofuro-, 2-methylbenzoselenopheno-, and 2-methylbenzothieno-[2,3-b]pyridines (VIIa-c) by cyclization by heating in 25% sulfuric acid (see [5]).

A shift of the absorption maximum to longer wavelengths is observed in the UV spectra of the bases on passing from benzofuro- (VIIa) to thionaphtheno- (VIIc) and selenonaphtheno[2,3-b]pyridine (VIIb): λ_{max} (in ethanol), respectively, at 232, 244 (227), and 254 nm. The same phenomenon is also characteristic for the absorption spectra of the nitro (IIIa-c) and amino (IVa-c) derivatives of pyridine.

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EXPERIMENTAL

Azide (V) of 2-Chloro-6-methylpyridine-3-carboxylic Acid. A solution of 6.5 g (0.1 mole) of sodium azide in 50 ml of water was added dropwise with stirring at 0-5° to a solution of 19 g (0.1 mole) of 2-chloro-6-methylpyridine-3-carboxylic acid chloride in 50 ml of ether, and the mixture was stirred at room temperature for 1 h. The ether was removed with a fine stream of air, and the residue was removed by filtration, washed with water, and dried in vacuo over phosphorus pentoxide to give 17 g (86%) of colorless plates with mp 43-45° (dec.). Found, %: C 42.7; H 2.5; N 28.5. $C_7H_5ClN_4O$. Calculated, %: C 42.7; H 2.5; N 28.5.

2-Hydroxy-3-nitro-6-methylpyridine (I). A solution of 21.8 g (0.2 mole) of 2-hydroxy-6-methylpyridine [2] in a mixture of 600 ml of 70% nitric acid and 130 ml of water was heated to 70°, 200 ml of 70% nitric acid was added, and the temperature of the mixture was raised to 80° in the course of 15-20 min. The mixture was cooled, diluted with 1 liter of ice water, and vacuum evaporated. The residue was treated with 50 ml of ice water, and the solid reaction product was removed by filtration, washed with water, and dried to give 18.7 g (60%) of a product with mp 207-209°. Recrystallization from water gave light-yellow prisms with mp 225-226° (dec.) (mp 226-227° [3]). Found, %: N 18.0. $C_6H_6N_2O_3$. Calculated, %: N 18.2.

2-Chloro-3-amino-6-methylpyridine (VI). A. A mixture of 1.96 g (0.01 mole) of V and 6 ml of dilute (1 :1) acetic acid was refluxed for 30 min in a stream of nitrogen (until carbon dioxide evolution ceased) and was then vacuum evaporated. The residue was cooled and neutralized with dilute sodium hydroxide solution, and the solid product was removed by filtration, washed with water and ether, and dried to give 0.92 g (61%) of colorless prisms of N,N'-bis(2-chloro-6-methyl-3-pyridyl)urea with mp 286-287° (dec., from ethanol). Found, %: C 50.0; H 3.8; Cl 22.6; N 17.9. $C_{13}H_{12}Cl_2N_4O$. Calculated, %: C 50.2; H 3.8; Cl 22.8; N 18.0.

The filtrate was extracted with ether, and the ether solutions were combined, washed with water, and dried. The ether was removed by distillation to give 0.2 g (15%) of colorless plates of VI with mp 82-83° (from benzene). Found, %: Cl 24.9. $C_6H_7ClN_2$. Calculated, %: Cl 24.9.

B. A mixture of 3.9 g (0.02 mole) of V and 30 ml of anhydrous ethanol was refluxed for 3 h in a stream of nitrogen, after which the alcohol was removed by vacuum distillation. The residue was treated with 10 ml of 40% potassium hydroxide solution, and the mixture was refluxed for a few minutes to hydrolyze the urethane, cooled, and extracted with ether to give 2.1 g (75%) of VI.

2-Phenoxy-3-nitro-6-methylpyridine (IIIa). An 18.8-g (0.2 mole) sample of phenol and 34.4 g (0.2 mole) of 2-chloro-3-nitro-6-methylpyridine was added in portions with stirring to a solution of sodium ethoxide [from 4.6 g (0.2 g-atom) of sodium] in 100 ml of anhydrous ethanol under nitrogen. The mixture was refluxed for 10 h, after which it was vacuum evaporated, and the residue was treated with water. The aqueous mixture was made alkaline with 5% sodium hydroxide solution and extracted with ether. The extract was washed with 10% sodium hydroxide solution and water and dried with magnesium sulfate. The ether was removed by distillation, and the residue was dissolved in a small amount of anhydrous ether. The solution was cooled, and an ether solution of hydrogen chloride was added to it until precipitation of the hydrochloride was complete. The precipitate was removed by filtration, washed with anhydrous ether, and vacuum dried over phosphorus pentoxide to give 23.4 g (44%) of light-yellow prims (from anhydrous ethanol—anhydrous ether) of the hydrochloride of IIIa with mp 109-110° (dec.). UV spectrum: λ_{max} 304 nm, ε 1.1 · 10^4 (in ethanol). Found, %: C 53.9; H 4.0; Cl 13.2. $C_{12}H_{10}N_2O_3 \cdot HCl$. Calculated, %: C 54.0; H 4.1; Cl 13.3.

A similar procedure was used to obtain the hydrochloride of 2-phenylseleno-3-nitro-6-methylpyridine (IIIb) [40% yield, light-yellow prisms with mp 151-152° (dec.). UV spectrum: λ_{max} 344 nm, ε 1.21 · 10^4 (in ethanol). Found, %: C 43.6; H 3.2; Cl 10.6. $C_{12}H_{10}N_2O_2Se \cdot HCl$. Calculated, %: C 43.7; H 3.3; Cl 10.7] and the hydrochloride of 2-phenylthio-3-nitro-6-methylpyridine (IIIc) [40% yield, light-rose prisms with mp 148-150° (dec.). UV spectrum: λ_{max} 335 nm, ε 1.06 · 10^4 (in ethanol). Found, %: C 50.9; H 3.8; Cl 12.4. $C_{12}H_{10}N_2O_2S \cdot HCl$. Calculated, %: C 51.0; H 3.9; Cl 12.5.]

2-Phenoxy-3-amino-6-methylpyridine (IVa). A. A 9.4-g (0.1 mole) sample of phenol and 14.2 g (0.1 mole) of VI were added in small portions with stirring to a solution of sodium ethoxide [from 2.3 g (0.12 g-atom) of sodium] in 50 ml of anhydrous ethanol under nitrogen, and the mixture was refluxed for 10 h under nitrogen and vacuum evaporated. The residue was treated with water, and the mixture was made alkaline with 5% sodium hydroxide solution and extracted with chloroform. The extract was washed with 10% sodium hydroxide solution and water and dried with potassium carbonate. The chloroform was removed by distillation to give 7.8 g (39%) of colorless needles with mp 105-106°. UV spectrum: λ_{max} 243 nm, ε $1.45 \cdot 10^4$ (in ethanol). Found, %: C 71.9; H 5.9; N 13.9. $C_{12}H_{12}N_2O$. Calculated, %: C 72.0; H 6.0; N 14.0.

B. A 27.0-g sample of stannous chloride was added with vigorous stirring at 45-47° to a solution of 53.2 g (0.2 mole) of the hydrochloride of IIIa in 80 ml of concentrated hydrochloric acid, and the mixture was stirred at 48-50° for 2 h and at 70-75° for 30 min. It was then cooled with ice water, neutralized with sodium carbonate solution, made alkaline with 5% sodium hydroxide solution, and extracted with chloroform. The extract was washed with 5% sodium hydroxide solution and water and dried with potassium carbonate. The chloroform was removed by distillation to give 37.2 g (93%) of IVa.

A similar procedure was used to obtain 2-phenylseleno-3-amino-6-methylpyridine (IVb) [41 and 94% yields via methods A and B, respectively, light-yellow needles with mp 93-94°. UV spectrum: λ_{max} 263 nm, ε $1.3 \cdot 10^4$ (in ethanol). Found, %: C 51.6; H 4.2; N 10.0. $C_{12}H_{12}N_2Se$. Calculated, %: C 51.6; H 4.3; N 10.0] and 2-phenylthio-3-amino-6-methylpyridine (IVc) [43 and 86% yields via methods A and B, respectively, light-rose needles with mp 84-85°. UV spectrum: λ_{max} 262 nm, ε $1.85 \cdot 10^4$ (in ethanol). Found, %: C 66.5; H 4.3; N 12.8. $C_{12}H_{12}N_2S$. Calculated, %: C 66.6; H 4.4; N 12.9.]

2-Methylbenzofuro[2,3-b]pyridine (VIIa). A solution of 4.6 g (0.066 mole) of sodium nitrite in 20 ml of water was added dropwise with vigorous stirring at 0-5° in the course of 10 min to a solution of 6.0 g (0.03 mole) of IVa in 120 ml of 25% sulfuric acid, and the mixture was held at 0-5° for 1 h. It was then filtered, and 1.8 g of urea and 6 g of copper powder were added with vigorous stirring under nitrogen in the course of 3-5 min. The mixture was stirred at room temperature for 4 h, heated to the boiling point, cooled, and made slightly alkaline with dilute sodium hydroxide solution while cooling with ice water. The product was extracted with ether, and the extract was washed with 5% sodium hydroxide solution and water and dried with potassium carbonate. The ether was removed by distillation, and the residue was vacuum distilled to give 1.7 g (31%) of VIIa as a light-yellow oil with bp 135-138° (2 mm). UV spectrum: λ_{max} 232 nm, ε $2.46 \cdot 10^4$ (in ethanol). Found, %: C 78.5; H 4.8; N 7.5. $C_{12}H_9NO$. Calculated, %: C 78.7; H 4.9; N 7.6.

A similar procedure was used to obtain 2-methylbenzoselenopheno[2,3-b]pyridine (VIIb) [30% yield, colorless needles with mp 79-80° (from petroleum ether). UV spectrum: λ_{max} 254 nm, ε $2.34 \cdot 10^4$ (in ethanol). Found: C 58.4; H 3.5; N 4.6. $C_{12}H_9NSe$. Calculated, %: C 58.5; H 3.6; N 5.7] and 2-methylbenzothieno[2,3-b]pyridine (VIIc) [18% yield, light-yellow oil with bp 155-158° (4 mm) [1]. UV spectrum: λ_{max} 224 (244) nm, ε 2.80 (2.40) $\cdot 10^4$ (in ethanol). Found, %: N 6.9. $C_{12}H_9NS$. Calculated, %: N 7.02.]

LITERATURE CITED

1. V. G. Zhiryakov and P. I. Abramenko, Khim. Geterotsikl. Soedin., 334 (1965).
2. N. K. Kochetkov, Dokl. Akad. Nauk SSSR, 84, 289 (1952).
3. E. D. Parker and W. Shive, J. Am. Chem. Soc., 69, 63 (1947).
4. H. E. Baumgarten, H. Chien-Fan Su, J. Am. Chem. Soc., 74, 3828 (1952).
5. H. Gilman, M. Weston, Van Ess, and D. M. Hayes, J. Am. Chem. Soc., 61, 643 (1939).