SYNTHESIS OF METHYL-SUBSTITUTED PYRANO-, THIAPYRANO-, AND SELENAPYRANO[2,3-b]PYRIDINES

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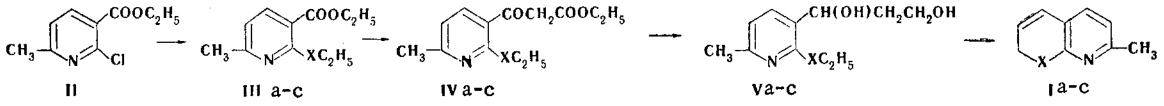
2H-Pyrano-, 2H-thiapyrano-, and 2H-selenapyrano[2,3-b]pyridines containing a methyl group in the α position of the pyridine ring were synthesized by Claisen condensation of the ethyl esters of, respectively, 2-ethoxy-, 2-ethylthio-, and 2-ethylseleno-6-methylpyridine-3-carboxylic acids with ethyl acetate, reduction of the resulting ethyl esters of 2-ethoxy-, 2-ethylthio-, and 2-ethylseleno-6-methylnicotinoylacetic acids with lithium aluminum hydride, and heating of the resulting 2-substituted 3-(α,γ-dihydroxypropyl)-6-methylpyridines with 48% hydrobromic acid.

Unsubstituted pyrano- and thiapyrano[2,3-b]pyridines were described in 1970 [1,2].

We have synthesized pyrano-, thiapyrano-, and selenapyrano[2,3-b]pyridines (I) containing an active methyl group in the α position of the pyridine ring from ethyl 2-chloro-6-methylpyridine-3-carboxylate (II):



I, III-V a X=O; b X=S; c X=Se

Bases of this sort are the starting compounds for the synthesis of polymethine dyes.

The ethyl esters of, respectively, 2-ethoxy-, 2-ethylthio-, or 2-ethylseleno-6-methylpyridine-3-carboxylic acid (IIIa-c) were obtained by the reaction of II with sodium ethoxide, sodium ethylmercaptide, or sodium ethylselenide in anhydrous ethanol by heating under nitrogen. The Claisen condensation of III with ethyl acetate gave the ethyl esters of substituted nicotinoylacetic acid (IVa-c), which were converted to the corresponding 3-(α,γ-dihydroxypropyl)-6-methylpyridines (Va-c) by reduction with lithium aluminum hydride in anhydrous ether. Heating the latter with 48% hydrobromic acid gave 7-methyl-2H-pyrano-, -thiapyrano-, and -selenapyrano[2,3-b]pyridines (Ia-c).

EXPERIMENTAL

Ethyl 2-Ethylthio-6-methylpyridine-3-carboxylate (IIIb). A 15.5-g (0.25 mole) sample of ethanethiol was added dropwise under nitrogen to an ice water-cooled solution of 17 g (0.25 mole) of sodium ethoxide in 300 ml of anhydrous ethanol, the mixture was heated to 40°, and 39.8 g (0.2 mole) of II was added in portions in the course of 30 min. The mixture was refluxed for 1.5 h, and the alcohol was removed by vacuum distillation. The residue was treated with 100 ml of water and 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 32.5 g (72%) of a light-yellow oil with bp 103-104° (0.05 mm). Found, %: C 58.5; H 6.6; S 14.1. $C_{11}H_{15}NO_2S$. Calculated, %: C 58.6; H 6.7; S 14.2.

Ethyl 2-Ethylseleno-6-methylpyridine-3-carboxylate (IIIc). This compound [58.1 g (71%)] was similarly obtained from 22.5 g (0.33 mole) of sodium ethoxide, 35.7 g (0.33 mole) of ethaneselenol, and 60 g

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(0.30 mole) of II. The light-yellow oil had bp 105-108° (0.05 mm). Found, %: C 48.4; H 5.4; N 5.0. $C_{11}H_{15}NO_2Se$. Calculated, %: C 48.5; H 5.5; N 5.1.

Ethyl 2-Ethoxy-6-methylpyridine-3-carboxylate (IIIa). This compound [17.5 g (85%)] was obtained by refluxing a mixture of 17 g (0.25 mole) of sodium ethoxide, 39.8 g (0.2 mole) of II, and 150 ml of anhydrous ethanol for 2.5 h. The colorless liquid had bp 122-124° (8 mm). Found, %: C 63.0; H 7.0; N 6.5. $C_{11}H_{15}NO_3$. Calculated, %: C 63.1; H 7.1; N 6.7.

Ethyl 2-Ethylthio-6-methylnicotinoylacetate (IVb). A 4.6-g (0.2 g-atom) sample of sodium and 17.6 g (0.2 mole) of ethyl acetate were added to 74.5 g (0.33 mole) of IIIb at 85-90°, and the mixture was heated at 90° for 1.5 h, after which 2.3 g (0.1 g-atom) of sodium and 8.8 g (0.1 mole) of ethyl acetate were added at intervals of 30 min [a total of 23 g (1 g-atom) of sodium and 88 g (1 mole) of ethyl acetate were added]. The mixture was diluted with 200 ml of anhydrous benzene, heated at 90-93° for 5-6 h, cooled, and treated with a mixture of 72 g of acetic acid and 200 ml of water while cooling. The pH of the mixture was brought to 7.0 by the addition of potassium carbonate, and the reaction product 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 fractionally distilled in vacuo to give 17.6 g (20%) of IVb as a light-yellow oil with bp 146-149° (1 mm). Found, %: C 58.3; H 6.2; S 11.8. $C_{13}H_{17}NO_3S$. Calculated, %: C 58.4; H 6.3; S 12.0.

A similar method was used to obtain ethyl 2-ethoxy-6-methylnicotinoylacetate (IVa) [70% yield, colorless oil with bp 127-130° (3 mm). Found, %: C 62.0; H 6.7; N 6.7. $C_{13}H_{17}NO_4$. Calculated, %: C 62.14; H 6.8; N 6.8] and ethyl 2-ethylseleno-6-methylnicotinoylacetate (IVc) [18% yield, bp 153-156° (1 mm). Found, %: C 49.5; H 4.9; N 4.4. $C_{13}H_{17}NO_3Se$. Calculated, %: C 49.7; H 5.0; N 4.5.]

2-Ethylthio-6-methyl-3-(α,γ-dihydroxypropyl)pyridine (Vb). A solution of 26.7 g (0.1 mole) of IVb in 100 ml of anhydrous ether was added dropwise to an ice water-cooled suspension of 6 g (0.16 mole) of lithium aluminum hydride in 300 ml of anhydrous ether, and the mixture was stirred at room temperature for 2 h, refluxed for 30 min, cooled, and hydrolyzed by the addition of saturated ammonium chloride solution. The reaction product was extracted with ether, and the ether extract was washed with water and dried with sodium sulfate. The ether was removed by distillation, and the residue was vacuum distilled to give 9.9 g (44%) of a light-yellow oil with bp 163-166° (1 mm). Found, %: C 58.1; H 7.4; S 14.0. $C_{11}H_{17}NO_2S$. Calculated, %: C 58.1; H 7.5; S 14.1.

A similar method was used to obtain 2-ethoxy-6-methyl-3-(α,γ-dihydroxypropyl)pyridine (Va) [51% yield, light-yellow oil with bp 138-141° (1 mm). Found, %: C 62.4; H 8.0; N 6.5. $C_{11}H_{17}NO_3$. Calculated,%: C 62.5; H 8.1; N 6.6] and 2-ethylseleno-6-methyl-3-(α,γ-dihydroxypropyl)pyridine (Vc) [41% yield, light-yellow oil with bp 168-170° (1 mm). Found, %: C 48.0; H 6.1; N 5.1. $C_{11}H_{17}NO_2Se$. Calculated, %: C 48.1; H 6.2; N 5.1.]

7-Methyl-2H-thiapyrano[2,3-b]pyridine (Ib). A solution of 4.59 g (0.02 mole) of Vb in 60 ml of 48% hydrobromic acid was heated at 115-120° for 30 min and vacuum evaporated. A solution of the residue in 50-60 ml of methanol was treated with hydrated silver oxide until it was neutralized, and the mixture was stirred at room temperature and filtered. The filtrate was vacuum evaporated, and the residue was dissolved in ether. The ether solution was dried with sodium sulfate, and the ether was removed by distillation. The residue was vacuum distilled to give 1.7 g (52%) of a light-yellow oil with bp 94-96° (1 mm). Found, %: C 66.1; H 5.4; S 19.5. C_9H_9NS. Calculated, %: C 66.2; H 5.5; S 19.6.

A similar procedure was used to obtain 7-methyl-2H-pyrano[2,3-b]pyridine (Ia) [63% yield, colorless oil with bp 78-79° (1 mm). Found, %: C 73.3; H 6.1; N 9.4. C_9H_9NO. Calculated, %: C 73.5; H 6.1; N 9.5. The hydrobromide was obtained as light-yellow prisms with mp 152° (from ethanol). Found, %: Br 35.0. $C_9H_9NO \cdot HBr$. Calculated, %: Br 35.1], and 7-methyl-2H-selenapyrano[2,3-b]pyridine (Ic) [54% yield, light-yellow oil with bp 99-101° (1 mm). Found,%: C 51.3; H 4.3; N 6.6. C_9H_9NSe. Calculated, %: C 51.4; H 4.3; N 6.6.]

LITERATURE CITED

1. H. Sliva, Bull. Soc. Chim. France, 631 (1970).
2. H. Sliva, Bull. Soc. Chim. France, 642 (1970).