Synthesis of 3-Pyridoxyalkanoic Acids and their Derivatives (1)

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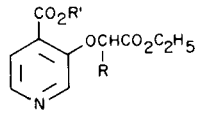
During the course of a synthetic program directed toward the synthesis of derivatives of furo[2,3-c]pyridine, we desired a facile preparation of intermediates of type I which have been previously undescribed.



Ia, R = H, R' = C_2H_5

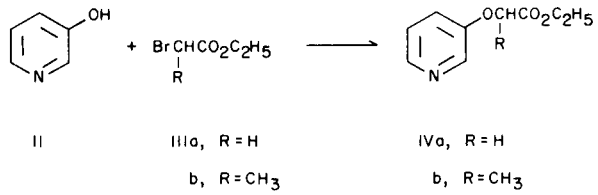
b, R = CH_3, R' = C_2H_5

c, R = R' = CH_3

The starting point chosen for the synthesis of I was through 3-hydroxyisonicotinic acid. This approach was chosen after an examination of previous attempts reported on the preparation of 2-alkoxypyridines. Shapiro (4) found that attempts to alkylate 3-hydroxypyridine (II) with various alkyl halides resulted for the most part in alkylation at the pyridine nitrogen atom. Successful syntheses of 3-alkoxypyridines include the treatment of the potassium or sodium salt of II with alkyl halides (5), the reaction of potassium or sodium alkoxides with 3-bromopyridine (6), and more recently the addition of 1,2-dialkoxyethylenes to α,β-unsaturated carbonyl compounds and treatment of the resulting dialkoxypyran derivatives with ammonia (7). Only the method of Furst and Dietz (5) appeared to be of value in our sequence. Since 3-hydroxyisonicotinic acid was not readily available it was synthesized through a long path starting with the ozonolysis of isoquinoline to cinchomeronic acid (3,4-pyridinedicarboxylic acid) (8). The acid was converted to cinchomeronimide (9) which then treated under conditions of the Hofmann hypobromite reaction (10) yielded 3-aminoisonicotinic acid. Diazotization followed by esterification gave the previously unreported ethyl ester of 3-hydroxyisonicotinic acid (Va).

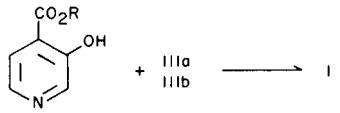
Treatment of Va with IIIb and sodium methoxide in methanol resulted only in ester exchange to form Vb with no formation of the expected condensation product. The reaction was repeated using Vb but only starting material was isolated. In an attempt to rationalize the failure to form derivatives of I under these conditions, the alkylation of 3-hydroxypyridine was studied.

Refluxing II and ethyl bromoacetate (IIIa) with sodium ethoxide in ethanol gave IVa in only 8% yield whereas II and IIIb with sodium ethoxide at room temperature gave a 37% yield of IVb. A refluxing mixture of II, IIIb and ethanolic potassium hydroxide gave only 21% of IVb. However, the yield of IVb was increased to 67% using sodium hydride in dimethylsulfoxide at room temperature. Interestingly, attempts to prepare the *N*-oxides of IVa and IVb resulted in concomittant ester hydrolysis to give the corresponding acid *N*-oxides (VIa and VIb). Hydrolysis



II IIIa, R = H IVa, R = H

b, R = CH_3 b, R = CH_3



Va, R = C_2H_5

b, R = CH_3

VIa, R = H VII

b, R = CH_3

was unexpected in view of the reported formation of the *N*-oxide of ethyl 3-pyridylacetate under the same conditions with no observed hydrolysis (11).

Attention was again turned to the synthesis of I. Treatment of Vb with IIIb gave an oil; n.m.r. data fit that expected for Ic but consistently gave a poor elemental analysis as the picrate salt. Repeating the reaction using Va and IIIa followed by chromatography yielded, in addition to the starting ester, 8% of the desired product,

Ia. Using Va and IIIb under the same conditions gave Ib but again in low yield. No other products of the reactions were isolated.

In view of the successful syntheses of 3-pyridoxyacetic acid and 2-(3-pyridoxy)propionic acid derivatives with sodium hydride and dimethylsulfoxide, the preparation of 3-allyloxypyridine (VII) under these conditions was studied. As part of a study of the Claisen rearrangement of allyloxypyridines, Moffett (12) reported the preparation of 2-, 3-, and 4-allyloxypyridine. 3-Allyloxypyridine was obtained in only 5% yield and no attempt to effect rearrangement was reported. Using sodium hydride and dimethyl sulfoxide, II and allyl bromide gave us a 45% yield of VII. An attempt to effect Claisen rearrangement of VII gave only intractable polymeric material.

The use of sodium hydride and dimethylsulfoxide in preparing other derivatives of 3-hydroxypyridine is currently under investigation.

EXPERIMENTAL

All melting points were corrected. Elemental analyses were performed by Midwest Microlab, Indianapolis, Indiana and on an F&M Model 185 at the University of Kansas. N.m.r. spectra were obtained with a Varian A-60 spectrometer with tetramethylsilane (TMS) as an internal standard.

Cinchomeronic Acid.

The procedure described by Lindenstruth and VanderWerf (8) was followed. From 200 g. of isoquinoline there was obtained 45 g. (18%) of product, m.p. 257-259° (lit. (8) m.p. 259-260°).

Cinchomeronimide.

The procedure described by Bachman and Barker (9) was followed. From 100 g. (0.6 mole) of cinchomeronic acid, 400 g. (3.8 moles) of acetic anhydride and 92 g. (1.56 moles) of acetamide there was obtained a product which, after recrystallization from acetic acid, weighed 81.9 g. (92%); m.p. 229-231° (lit. (9) m.p. 226-227°).

3-Aminoisonicotinic Acid.

Bromine (88 g., 0.55 mole) was slowly added to a solution of 132 g. (3.3 moles) of sodium hydroxide in 200 ml. of water while maintaining the temperature at 5°. Cinchomeronimide (81.9 g., 0.55 mole) then was added in one portion. When all of the imide had dissolved, the mixture was heated to 80° for 5 minutes then allowed to cool slowly to room temperature, acidified with acetic acid, and left overnight at 5°. The resulting solid was collected, washed with water, dried and used without further purification for the subsequent diazotization procedure. There was obtained 57.5 g. (76%) of product, m.p. 290-295° (lit. (9) m.p. 297-300°).

3-Hydroxyisonicotinic Acid.

The procedure of Blanchard, *et al.*, (13) was followed. From 57.5 g. of the amine there was obtained 52.7 g. (93%) of product, m.p. 312-315°).

Ethyl 3-Hydroxyisonicotinate (Va).

A mixture of 6.3 g. (0.046 mole) of 3-hydroxyisonicotinic acid, 100 ml. of absolute ethanol, 7 ml. of concentrated sulfuric acid and 200 ml. of benzene was refluxed for 36 hours. Work-up in the normal manner followed by recrystallization from chloroform-Skelly B gave 4.9 g. (64%) of yellow needles, m.p. 43-45°; n.m.r. spectrum (deuteriochloroform) showed signals at 8.50 (1H, singlet, 2-pyridine proton), 10.0-10.5 (1H, broad, OH), 7.61 (1H, doublet, 5-pyridine proton), 8.23 (1H, doublet, 6-pyridine proton), 1.38 (3H, triplet, CH_3-C) and 4.44 p.p.m. (2H, quartet, O-CH_2-C).

Anal. Calcd. for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.71; H, 5.65; N, 8.54.

Ethyl 3-Pyridoxyacetate (IVa).

To a solution of 4.6 g. (0.2 mole) of sodium metal dissolved in 100 ml. of anhydrous ethanol was added 19 g. (0.2 mole) of 3-hydroxypyridine. The mixture was stirred for 15 minutes and 33 g. (0.2 mole) of ethyl bromoacetate was added slowly. The mixture was refluxed for 10 hours, cooled, the resulting sodium bromide removed by filtration and the filtrate evaporated. Water was added to the residue and the mixture extracted several times with chloroform. The organic extracts were combined, dried over magnesium sulfate and the solvent removed by distillation. The residue was distilled to give 2.5 g. (8%) of material boiling at 118-120° at 1 mm.; n.m.r. spectrum (deuteriochloroform) showed signals at 4.80 (2H, singlet, (O-CH_2-C=O), 1.31 (3H, triplet, CH_3-C), 4.40 (2H, quartet, O-CH_2-C) and 7.5 and 8.7 p.p.m. (4H, multiplets. pyridine protons).

3-Pyridoxyacetic Acid-*N*-Oxide (VIa).

A mixture of 2.5 g. of IVa, 10 ml. acetic acid and 10 ml. of 30% hydrogen peroxide was refluxed on a steam bath for 24 hours. The solvents were removed by distillation at reduced pressure and the residue recrystallized from ethanol to give 1.2 g. (55%) of the product, m.p. 210° dec.

Anal. Calcd. for $C_7H_7NO_4$: C, 49.70; H, 4.17; N, 8.28. Found: C, 49.60; H, 4.55; N, 8.18.

Ethyl 2-(3-Pyridoxy)propionate (IVb).

To a solution of 19 g. (0.2 mole) of II in 120 ml. of DMSO was added 10.5 g. (0.22 mole) of a 50% mineral oil dispersion of sodium hydride. The resulting solution was stirred at room temperature followed by the dropwise addition of 36.2 g. (0.2 mole) of ethyl 2-bromopropionate. After 10 minutes the mixture solidified. The solid mass was dissolved in water and the resulting mixture extracted with chloroform. After drying and evaporating the organic extracts, the residue was distilled to give 26 g. (67%) of the product, b.p. 86-88° at 0.2 mm.; n.m.r. spectrum (deuteriochloroform) showed signals at 1.65 (3H, doublet, propionyl CH_3), 1.25 (3H, triplet, ester CH_3), 4.27 (2H, quartet, O-CH_2), 4.87 (1H, quartet, O-CH-C), and 7.2-7.38 and 8.24-8.50 p.p.m. (4H, multiplets, pyridine protons).

Anal. Calcd. for $C_{16}H_{16}N_4O_{10}$ (as picrate): C, 45.29; H, 3.80; N, 13.20. Found: C, 45.56; H, 4.00; N, 13.37.

2-(3-Pyridoxy)propionic Acid-*N*-Oxide (VIb).

A mixture of 14.2 g. (0.073 mole) of IVb, 15 ml. of acetic acid and 25 ml. of 30% hydrogen peroxide was heated at 70° for 24 hours. The solvents were removed by distillation at reduced pressure. The residual oil was dissolved in methanol and the mixture stored at 5° overnight. There was obtained 3.0 g. (24%) of product, m.p. 136-139°.

Anal. Calcd. for $C_8H_9NO_4$: C, 52.46; H, 4.92; N, 7.65. Found: C, 52.29; H, 5.25; N, 7.72.

Ethyl 4-Carbethoxy-3-pyridoxyacetate (Ia).

The procedure described for the preparation of IVb was essentially followed using 10 g. (0.06 mole) of ethyl 3-hydroxy-

isonicotinate, 2.9 g. (0.06 mole) of sodium hydride dispersion and 10 g. (0.06 mole) of ethyl bromoacetate. The mixture was poured onto ice and extracted several times with ether. The ether extracts were combined, washed with water, dried over magnesium sulfate and evaporated. The residue was chromatographed on a silicic acid column; cyclohexane-ethyl acetate (19:1) gave starting material and Skelly B-ethyl acetate (2:1) eluted 1.3 g. of the product as a non-crystallizable oil; n.m.r. spectrum (deuteriochloroform) showed signals at 4.80 (2H, singlet, $O-CH_2-C=O$), 1.08-1.58 (6H, multiplet, ester CH_3-C), 4.1-4.6 (4H, multiplet, ester $O-CH_2$), 7.60 (1H, doublet, 5-pyridine proton) and 8.4 p.p.m. (2H, distorted doublet, 2- and 6- pyridine protons).

Anal. Calcd. for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 57.04; H, 5.97; N, 5.47.

Ethyl 2-(4-Carbethoxy-3-pyridoxy)propionate (Ib).

The procedure described for the preparation of IVb was followed using 10 g. (0.06 mole) of ethyl 3-hydroxyisonicotinate, 5.8 g. (0.12 mole) of sodium hydride dispersion and 10.9 g. (0.6 mole) of ethyl 2-bromopropionate. The residue obtained from extraction was chromatographed on a silicic acid column; Skelly B-ethyl acetate (19.1) eluted starting material and Skelly B-ethyl acetate (3:1) gave 1.3 g. of the product as a non-crystallizable oil; n.m.r. spectrum (deuteriochloroform) showed signals at 1.2-1.5 (6H, multiplet, ester CH_3), 4.1-4.6 (4H, multiplet, ester CH_2), 1.68 (3H, doublet, propionyl CH_3), 4.93 (1H, quartet, O-CH-C), 7.60 (1H, doublet, 5-pyridine proton) and 8.47 p.p.m. (2H, distorted doublet, 2- and 6-pyridine protons).

Anal. Calcd. for $C_{13}H_{17}NO_5$: C, 58.41; H, 6.41; N, 5.24. Found: C, 58.25; H, 6.51; N, 5.13.

3-Allyloxypyridine (VII).

The procedure described for the preparation of IVb was followed using 19 g. (0.2 mole) of 3-hydroxypyridine, 10.5 g. (0.22 mole) of sodium hydride dispersion and 29 g. (0.2 mole) of allyl bromide. The residue obtained from ether extraction was distilled to give 12.1 g. (45%) of the product, b.p. 90-92° at 10 mm. (lit. (12) b.p. 96° at 12 mm.); n.m.r. spectrum (deuteriochloroform) showed signals at 3.7-3.8 (2H, multiplet, $O-CH_2$), 5.1-6.4 (3H, multiplet, $CH=CH_2$), and 7.1-7.3 and 8.2-8.5 p.p.m. (4H, multiplets, pyridine protons).

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(3) National Science Foundation Undergraduate Research Participant, 1965-1967.

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