Reinvestigation of the Synthesis of 5-Arylamino-2-picolines

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Reaction of 5-bromo- or 3-bromo-2-methylpyridine with *o*-nitroaniline gave the corresponding *N*-[2-methyl-5(or 3)pyridyl]-*o*-nitroanilines. Reduction to the corresponding amino derivatives and ring closure to 1-[2-methyl-5(or 3)pyridyl]benzotriazole allowed the structures to be confirmed and an earlier literature report to be corrected. Displacement of bromide by anthranilic acid from 5-bromo-2-methylpyridine and decarboxylation gave *N*-(2-methyl-5-pyridyl)aniline.

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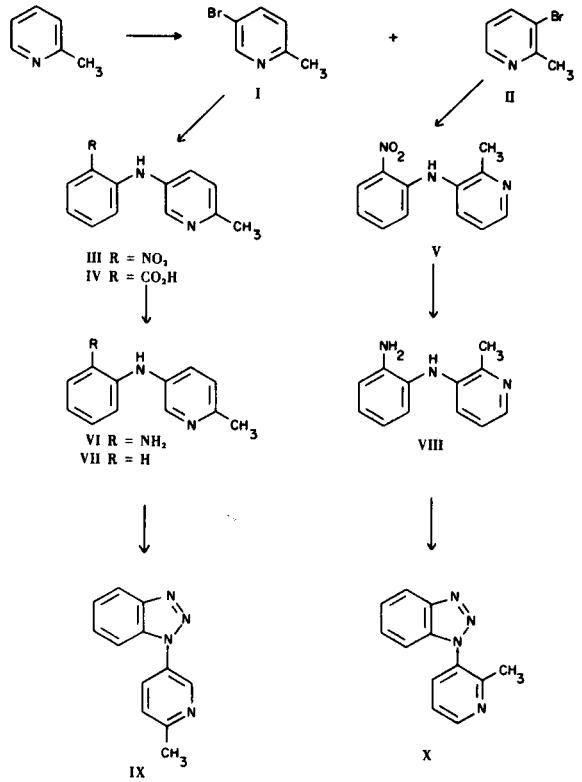
Pursuant to our interest in 5-arylamino-2-picolines [(2-methyl-5-pyridyl)anilines] as synthetic intermediates, it was found by a survey of the literature that amino-substituted picolines could be prepared *via* the Hofmann or Curtius rearrangements of 6-methylnicotinic acid derivatives (1). These reactions were, however, not readily extendable to the synthesis of arylamino analogs. Tsaranova (2) has described the synthesis of several (2-aminoarylamino)picolines by nucleophilic displacement of appropriately substituted halogenopicolines by the method devised by Späth (3) and Petrow (4) for 3- and 4-halogenopyridines; specifically, "III" was claimed to be prepared by halide displacement from "5-iodo-2-picoline" with 2-nitroaniline.

Bromination of 2-picoline with bromine and fuming sulfuric acid (5) in a sealed tube or with bromine and aluminum chloride (6) and excess picoline to neutralize the acid formed gave mixtures of 5-bromo- (I) and 3-bromo-2-methylpyridine (II). The second procedure was preferred because of technical convenience, but both methods gave comparable yields. The Friedel-Crafts-catalyzed reaction product, however, required fractional distillation to separate the bromopicolines from picoline and other contaminants. 5-Bromo-2-methylpyridine (I) crystallized well from a mixture of I and II stored at 0° for several days. Recrystallization from hexane gave colorless crystals, m.p. 36.5-37.5° [lit (1) m.p. 32°]. Treatment of I with *o*-nitroaniline in nitrobenzene at 190° containing potassium carbonate and copper powder gave a good yield of *N*-(2-methyl-5-pyridyl)-2-nitroaniline (III) which was confirmed by analysis and tentatively by nmr analysis. The orange crystals of III, m.p. 102.5-103°, did not agree in color or m.p. with those reported by Tsaranova (2) for this same compound (yellow and 123-125°). Reduction of III with 5% palladium on carbon



catalyst gave 2-amino-*N*-(2-methyl-5-pyridyl)aniline (VI), which also melted differently than reported in the literature (2). When the same sequence of reactions was repeated with 3-bromo-2-methylpyridine (II) containing some isomeric (I), the halide displacement gave *N*-(2-methyl-3-pyridyl)-2-nitroaniline (V) after column chromatography on silica gel to separate the isomers, and 2-amino-*N*-(2-methyl-3-pyridyl)aniline (VIII) as the product of the catalytic reduction. The physical characteristics of the 2,3-substituted pyridine derivatives V and VIII

agreed well with those reported by Tsaranova (2) for their 2,5-substituted counterparts. Further confirmation for the structures of the literature compounds as 2,3 isomers instead of 2,5 isomers was obtained from FT100 nmr spectral comparisons of III to V and VI to VIII. The α-pyridyl proton of III and VI appeared as a doublet or quartet with 2-3 Hz couplings indicating the absence of an adjacent β-proton. The nmr spectra of V and VIII, however, revealed the α-pyridyl proton as a quartet with 2 Hz and 5 Hz coupling, confirming the presence of an adjacent proton. Derivatization of the substituted phenylene diamines (VI and VIII) by diazotization and ring closure to the corresponding pyridyl benzotriazoles (IX and X, respectively) went smoothly. Nmr spectral analysis of the benzotriazole derivatives was consistent with the other data presented (see Experimental).

Further examination of the copper-catalyzed displacement reactions of I and II showed that the displacement went well when the arylamine nucleophile possessed an adjacent electron-withdrawing group. Reactions with aniline and *p*-bromoaniline gave no significant amounts of product, but the use of potassium anthranilate (*in situ*) under these reaction conditions with I gave a fair yield of *N*-(2-methyl-5-pyridyl)-anthranilic acid (IV) which could be decarboxylated in refluxing quinoline to give *N*-(2-methyl-5-pyridyl)aniline (VII).

EXPERIMENTAL

Melting points were determined on a Kofler hot stage and are uncorrected. Nmr spectra were determined on a Varian T60 unless otherwise noted in an appropriate solvent with tetramethylsilane as an internal reference; chemical shifts are reported in ppm. All new compounds were chromatographically homogeneous (tlc) on silica gel with dichloromethane-methanol mixtures (9:1, 19:1, or 99:1) as developers.

N-(2-Methyl-5-pyridyl)-2-nitroaniline (III).

A mixture of 5-bromo-2-picoline (I, 8.6 g., 50 mmoles), *o*-nitroaniline (6.2 g., 45 mmoles), anhydrous potassium carbonate (12.4 g., 90 mmoles), copper powder (500 mg.) and a few drops of Aliquat 336 (7) in nitrobenzene (50 ml.) were heated in an oil bath. Foaming occurred at 150° and a small amount of water and nitrobenzene were removed by distillation. The temperature was then taken to 195-200° for 2.5 hours to complete the reaction [a small amount of starting material remained by tlc (99:1)]. The mixture was poured into water (the flask was rinsed with dichloromethane) and steam-distilled until all nitrobenzene and bromopicoline had been removed and only colored water was coming over (bromopicoline can be recovered by dilute hydrochloric acid extraction of a dichloromethane extract of the distillate). The distillation residue was extracted with dichloromethane and the dried solution was evaporated *in vacuo* to a small volume and chromatographed on silica gel (500 g.). Elution with dichloromethane removed nitroaniline from the the column and dichloromethane-methanol (97:3) removed the product which was recrystallized from dichloromethane-hexane to give orange crystals, 3.1 g. (30%), m.p. 102-5-103°; nmr (deuteriochloroform, 100 MHz): 8.47 [1H, d, $J_{4',6'}$ = 2.4 Hz, (Py) H-6'], 8.21 (1H, pair of doublets, $J_{3,4}$ = 8.4 Hz, $J_{3,5}$ = 1.6 Hz, H-3), 7.50 [1H, pair of doublets, $J_{3',4'}$ = 8.0 Hz, (Py) H-4'], 7.38 (1H, pair of quartets, $J_{4,5}$ = 8.4 Hz, $J_{4,6}$ = 1.6 Hz, H-4), 7.20 [1H, doublet, (Py) H-3], 7.06 (1H, pair of doublets, $J_{5,6}$ = 8.4 Hz, H-6), 6.80 (1H, pair of quartets, H-5), 2.60 (3H, s, CH_3).

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.62; H, 4.73; N, 18.32.

N-(2-Methyl-5-pyridyl)anthranilic Acid (IV) and *N*-(2-Methyl-5-pyridyl)aniline (VII).

A mixture of anthranilic acid (2.74 g., 20 mmoles), anhydrous potassium carbonate (2.76 g., 20 mmoles), copper powder (1.27 g., 20 mmoles), and nitrobenzene (25 ml.) were heated to 160° in an oil bath. The small amount of water formed was removed by distillation and rinsing of the distillation head. The mixture was cooled to ~100° as 5-bromo-2-picoline (I, 3.44 g., 20 mmoles) was added and the reaction mixture was heated to 195° for 15 minutes, when the reaction could be shown to be complete by tlc. The mixture was cooled and diluted with cold water and ether. A small amount of decomposition product was filtered and the water phase was separated and washed again with ether and filtered. Acidification with acetic acid caused the product to precipitate as a relatively pure but dark solid (IV, 1.5 g., 30%). This material was taken on directly to the decarboxylation which was effected by refluxing quinoline (15 ml., 230-240°). After one-half hour, carbon dioxide evolution appeared to have ceased and the mixture was steam distilled to remove solvent, the residue was diluted with ethyl acetate and filtered. The ethyl acetate layer was separated, washed with saturated sodium chloride solution, dried, and evaporated to a residue which crystallized. The product was recrystallized with charcoal treatment from hot hexane to give VII (330 mg., 27%), m.p. 98.5-99°; nmr (deuteriochloroform): 8.32 [1H, doublet, $J_{4',6'}$ = 3 Hz, (Py) H-6'], 7.2 (7H, multiplet, H-4',5', aromatic H of anilino), 5.85 (1H, broad s, NH), 2.47 (3H, s, CH_3).

Anal. Calcd. for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.21. Found: C, 78.22; H, 6.69; N, 15.01.

N-(2-Methyl-3-pyridyl)-2-nitroaniline (V).

The reaction was run as in the preparation of III using a mixture of I and II containing a small amount of picoline (33.8 g., 200 mmoles), *o*-nitroaniline (20 g., 145 mmoles), anhydrous potassium carbonate (20 g., 145 mmoles), 9.2 g. of copper powder (145 mmoles) and nitrobenzene (100 ml.). After partial chromatographic resolution of III and V, the yellow isomer (III) could be fractionally crystallized from boiling ether and recrystallized from dichloromethane-hexane. The yield of III by fractional crystallization (4.5 g., 14%, m.p. 127-128.5°), additional quantities of III and V were obtained by further chromatographic resolution of mixtures on silica gel by ethyl acetate; nmr (deuteriochloroform, 100 MHz): 8.45 [1H, pair of doublets, $J_{4',6'}$ = 1.6 Hz, $J_{5',6'}$ = 4.8 Hz, (Py) H-6'], 8.23 (1H, pair of doublets, $J_{3,5}$ = 1.6 Hz, $J_{3,4}$ = 8.4 Hz, H-3), 7.60 [1H, pair of doublets, $J_{4',5'}$ = 8.0 Hz, (Py) H-4'], 7.38 (1H, pair of quartets, $J_{4,5}$ = 8 Hz, $J_{4,6}$ = 20, H-4), 7.22 [1H, quartet, (Py) H-5'], 6.83 (1H, pair of quartets, $J_{5,6}$ = 8 Hz, H-5), 6.77 (1H, pair of doublets, H-6), 2.55 (3H, s, CH_3).

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C, 62.87; H, 4.84; N, 18.33. Found: C, 62.68; H, 4.90; N, 18.08.

2-Amino-*N*-(2-methyl-5-pyridyl)aniline (VI).

A solution of the nitro compound (III, 7.57 g., 33 mmoles) in methanol (300 ml.) was hydrogenated over a 5% palladium on

charcoal catalyst (0.25 g.) until hydrogen uptake ceased (5 hours). After filtering and washing the catalyst (methanol), the filtrate was evaporated *in vacuo* to an oil. Addition of petroleum ether (b.p. 30-60) and scratching induced crystallization. The product was filtered and washed with petroleum ether (6.51 g., 99%), m.p. 109-110°; nmr (deuteriochloroform): 8.13 (1H, t, $J_{6',3'}$, $J_{6',4'}$ = 2 Hz, H-6'), 7.05 (6H multiplet), 5.40 (1H broad, NH), 3.80 (2H broad, NH_2), 2.54 (3H, s, CH_3).

Anal. Calcd. for $C_{12}H_{13}N_3$: C, 72.33; H, 6.57; N, 21.09. Found: C, 72.55; H, 6.39; N, 21.07.

2-Amino-*N*-(2-methyl-3-pyridyl)aniline (VIII).

The reaction was run exactly as in the synthesis of VI using V (1.15 g., 5 mmoles) in methanol (50 ml.) and 0.06 g. of 5% palladium/carbon. The oily residue was taken up in ether, charcoaled, and diluted with hexane to afford crystalline product in two crops (0.7 g., 70%), m.p. 109-110°: nmr (deuteriochloroform): 8.07 (1H, q, $J_{6',5'}$ = 5 Hz, $J_{6',4'}$ = 2.5 Hz, H-6'), 6.95 (6H multiplet), 5.12 (1H broad, NH), 3.74 (2H broad, NH_2), 2.51 (3H, s, CH_3).

Anal. Calcd. for $C_{12}H_{13}N_3$: C, 72.33; H, 6.57; N, 21.09. Found: C, 72.17; H, 6.39; N, 21.01.

1-(2-Methyl-5-pyridyl)benzotriazole (IX).

A solution of VI (6.5 g., 33 mmoles) in water (115 ml.) and 2.5*N* hydrochloric acid (26.4 ml., 66 mmoles) was cooled in an ice bath with stirring as a solution of sodium nitrite (2.28 g., 33 mmoles) in water (17 ml.) was added dropwise over 30 minutes. Stirring was continued for another 30 minutes before 10% sodium bicarbonate solution was added to neutralize the reaction mixture. Extraction of the mixture with ethyl acetate removed the product. The organic layer was washed with saturated sodium chloride solution, dried, charcoaled, and evaporated *in vacuo* to a residue. Addition of petroleum ether caused crystallization. The product (two crops) could be recrystallized from dichloromethane (5.85 g., 84%), m.p. 119-120°; nmr (deuteriochloroform, 100 MHz): 8.91 [1H, d, $J_{4',6'}$ = 2.5 Hz, (Py) H-6'], 9.2-7.4 (6H multiplet), 2.71 (3H, s, CH_3).

Anal. Calcd. for $C_{12}H_{10}N_4$: C, 68.55; H, 4.79; N, 26.65. Found: C, 68.31; H, 4.61; N, 26.70.

1-(2-Methyl-3-pyridyl)benzotriazole (X).

The product was prepared from VIII by the procedure for the synthesis of IX to furnish X in 53% yield after column chromatography on silica gel, m.p. 67.5-68; nmr (deuteriochloroform, 100 MHz): 8.72 [1H, q, $J_{5',6'}$ = 4.8 Hz, $J_{4',6'}$ = 2.0 Hz, (Py) H-6], 8.2-7.4 (6H multiplet), 2.26 (3H, s, CH_3).

Anal. Calcd. for $C_{12}H_{10}N_4$: C, 68.55; H, 4.79; N, 26.65. Found: C, 68.81; H, 4.68; N, 26.89.

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