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Pyridines. III. 3-*n*-Butylpyridine and an Unusual Alkylation in its Synthesis<sup>1</sup>

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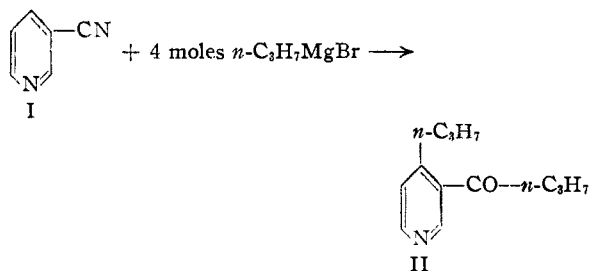
The catalytic dehydrogenation of nicotine by means of palladium<sup>2</sup> produces, in addition to 3,2'-nicotyrine, smaller amounts of a lower-boiling by-product. The elementary analysis and the melting point of the picrate of this material,<sup>3</sup> combined with the fact that methylamine is another by-product,<sup>4</sup> have suggested its structure to be that of 3-*n*-butylpyridine. This has now been established by synthesis, as reported herein.

The synthesis involved the reduction of 3-pyridyl *n*-propyl ketone. The latter was prepared in 40% yield from equimolar amounts of nicotinonitrile and *n*-propylmagnesium bromide and in 30% yield by the reaction of nicotiny chloride with di-*n*-propylcadmium.

Wolff-Kishner reduction of 3-pyridyl *n*-propyl ketone according to the improved procedure of Herr, Whitmore and Schiessler<sup>5</sup> resulted in a 60% yield of 3-*n*-butylpyridine, identical with the by-product from nicotine.

3-Pyridyl *n*-propyl ketone has previously been prepared by LaForge<sup>6</sup> from nicotinonitrile (I) and excess *n*-propylmagnesium iodide. LaForge noted, however, that the method leaves something to be desired and that the ketone so obtained is difficult to obtain pure. We, too, have found the reaction quite unusual.

Shriner and Turner<sup>7</sup> have studied the addition of Grignard reagents to nitriles and have reported optimum results with the use of four moles of reagent to one of nitrile. This procedure applied to nicotinonitrile (I) and *n*-propylmagnesium bromide formed none of the expected 3-pyridyl *n*-propyl ketone, but gave instead a 22% yield of another ketone, 4-*n*-propyl-3-pyridyl *n*-propyl ketone (II). The structure was deduced by oxidation to ciuchomeric acid.



(1) For the previous communication on pyridine chemistry, see Frank, Pelletier and Starks, *THIS JOURNAL*, **70**, 1767 (1948).

(2) Frank, Holley and Wikholm, *ibid.*, **64**, 2835 (1942).

(3) Maas and Zablinksi, *Ber.*, **47**, 1172 (1914).

(4) The presence of methylamine as suggested by the work of Clemo and Swan, *J. Chem. Soc.*, 603 (1945), on other nicotine derivatives, has been confirmed by Dr. Fred E. Woodward of this Laboratory.

(5) Herr, Whitmore and Schiessler, *THIS JOURNAL*, **67**, 2061 (1945).

(6) LaForge, *ibid.*, **50**, 2477 (1928).

(7) Shriner and Turner, *ibid.*, **52**, 1267 (1930).

The alkylation of pyridine nuclei by Grignard reagents is well-known,<sup>8</sup> but generally occurs only at comparatively high temperatures, and then introduces the alkyl group at the alpha position. Apparently the alkylation in this case is facilitated by the presence of the beta cyano group, perhaps by 1,4-addition, a supposition substantiated by the fact that under the same reaction conditions pyridine itself is not alkylated. Further experiments have not extended the reaction; *viz.*, an excess of methylmagnesium iodide with nicotinonitrile gave only 3-acetylpyridine.

One additional approach to 3-*n*-butylpyridine was the Wolff-Kishner reduction of nicotinylacetone. When the reduction was attempted, however, the alkaline conditions of the reaction served to cleave the 1,3-diketone, forming 3-ethylpyridine as the only product isolated.

## Experimental

**3-Pyridyl *n*-Propyl Ketone: From Nicotinonitrile.**—To the cooled Grignard reagent prepared from 33.0 g. (0.27 mole) of *n*-propyl bromide and 6.76 g. (0.28 g. atom) of magnesium in 50 ml. of dry ether was added dropwise with stirring 26.0 g. (0.25 mole) of nicotinonitrile in 200 ml. of dry ether. The mixture was then stirred for eight hours at 28–35°, followed by cooling and the addition of a cold solution of 50 g. of ammonium chloride in 200 ml. of water and 50 ml. of concentrated hydrochloric acid. The mixture was stirred for five hours, the ether layer separated, and the aqueous layer refluxed for two hours. The latter was then made just alkaline to litmus by means of aqueous sodium hydroxide and extracted with four 150-ml. portions of ether. All the ether solutions were combined, dried over anhydrous magnesium sulfate, and fractionally distilled to yield 15.0 g. (40%) of colorless liquid product, b. p. 94–98° (3 mm.),  $n_{20}^D$  1.5136.

**From Nicotiny Chloride.**—To the Grignard reagent prepared from 73.8 g. (0.60 mole) of *n*-propyl bromide in 250 ml. of dry ether in a 1-liter, three-necked, round-bottomed flask equipped with a condenser, stirrer and dropping funnel was added 55.0 g. (0.30 mole) of anhydrous cadmium chloride, followed by stirring for one-half hour. To this was added dropwise with stirring 70.0 g. (0.494 mole) of nicotiny chloride (previously prepared by the method of Meyer and Graf<sup>9</sup>) dissolved in 50 ml. of dry ether, followed by three hours of stirring and gentle refluxing. A heavy complex formed in the flask; this was treated in the same manner as described in the preparation above. The dried ether-chloroform extract of the product was fractionally distilled in a helix-packed column to give 19.0 g. (30%) of 3-pyridyl *n*-propyl ketone, b. p. 95–98° (3 mm.),  $n_{20}^D$  1.5128, sp. gr.  $_{20}^{20}$  1.043; *MR* calcd. 42.7, *MR* found 42.9.

*Anal.*<sup>10</sup> Calcd. for  $\text{C}_9\text{H}_{11}\text{NO}$ : C, 72.45; H, 7.43. Found: C, 72.33; H, 7.23.

The phenylhydrazone, recrystallized from ethyl acetate, gave white plates, m. p. 129–130° (reported,<sup>9</sup> 128–129°). The 2,4-dinitrophenylhydrazone, recrystallized from ethanol, gave orange-red needles, m. p. 153–154°.

*Anal.* Calcd. for  $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_4$ : C, 54.71; H, 4.59. Found: C, 54.70; H, 4.59.

(8) Bergstrom and McAllister, *ibid.*, **52**, 2845 (1930).

(9) Meyer and Graf, *Ber.*, **61**, 2202 (1928).

(10) Microanalyses were carried out by Misses Emily Davis, Betty Alice Snyder and Theta Spoor.

The picrate, recrystallized from ethanol, gave fluffy yellow crystals, m. p. 103–104°.

*Anal.* Calcd. for  $C_{15}H_{14}N_4O_7$ : C, 47.62; H, 3.73. Found: C, 47.90; H, 3.72.

The semicarbazone, recrystallized from water, melted at 167–167.5° (reported,<sup>6</sup> 169–170°).

*Anal.* Calcd. for  $C_{10}H_{14}N_4O$ : C, 58.23; H, 6.84. Found: C, 58.43; H, 6.75.

**3-*n*-Butylpyridine.**—To 30 ml. of triethylene glycol was added 2.93 g. (0.0196 mole) of 3-pyridyl *n*-propyl ketone, 2.25 g. (0.040 mole) of potassium hydroxide and 2.70 g. (0.046 mole) of 85% hydrazine hydrate. The mixture was heated for one hour at 110–125°, cooled, and gradually reheated with a take-off condenser to a bath temperature of 185–190°. Over a period of two hours there was collected 15 ml. of liquid. This was extracted with two 15-ml. portions of ether; the residue was extracted with five 25-ml. portions of ether. All the extracts were combined, dried over anhydrous magnesium sulfate, and fractionally distilled to give 1.6 g. (60%) of 3-*n*-butylpyridine, b. p. 38–39° (0.5 mm.),  $n_D^{20}$  1.4909, sp. gr.  $^{20}_4$  0.924; *MR* calcd. 42.5, *MR* found 42.4.

*Anal.* Calcd. for  $C_9H_{13}N$ : C, 79.94; H, 9.69. Found: C, 79.57; H, 9.78.

The picrate, recrystallized from ethanol, gave yellow needles, m. p. 90–90.5°.

*Anal.* Calcd. for  $C_{15}H_{16}N_4O_7$ : C, 49.45; H, 4.42. Found: C, 49.78; H, 4.28.

The hydrochloride, recrystallized from dry dioxane, melted at 123–124°.

*Anal.* Calcd. for  $C_9H_{14}NCl$ : Cl, 20.65. Found: Cl, 20.61.

The by-product from the dehydrogenation of nicotine, kindly characterized by Mr. Sol Wexler, has b. p. 70–71° (7 mm.),  $n_D^{20}$  1.4909, sp. gr.  $^{20}_4$  0.933; *MR* calcd. 42.5, *MR* found 41.8; m. p. of picrate 91° (*Anal.* Calcd. for  $C_{15}H_{16}N_4O_7$ : C, 49.45; H, 4.42. Found: C, 49.05; H, 4.63); m. p. of hydrochloride 123–124°. Mixed m. p.'s of these derivatives with those of synthetic 3-*n*-butylpyridine were not depressed.

**4-*n*-Propyl-3-pyridyl *n*-Propyl Ketone (II).**—The Grignard reagent prepared from 221 g. (1.80 moles) of *n*-propyl bromide and 44.2 g. (1.82 g. atoms) of magnesium in 150 ml. of dry ether in a 2-liter, three-necked, round-bottomed flask equipped with a stirrer, condenser and dropping funnel was cooled in an ice-bath. To the stirred solution was added over a period of twenty minutes 46.8 g. (0.45 mole) of nicotinonitrile dissolved in 375 ml. of dry ether and 75 ml. of dry benzene. This resulted in the formation of a dark orange precipitate which dissolved after continuous stirring for ten hours at 35°. The flask was cooled to 5°, 350 ml. of dilute hydrochloric acid was added with stirring over a period of three hours, and the mixture then gently refluxed for twelve hours, until nearly all the solid material had dissolved. It was then made just alkaline to litmus by the addition of 20% aqueous sodium hydroxide, cooled, and extracted with four 200-ml. portions of chloroform and a similar amount of ether. All the extracts were combined and dried over anhydrous magnesium sulfate. Fractional distillation in a helix-packed column gave 18.6 g. (22%) of colorless liquid, 4-*n*-propyl-3-pyridyl *n*-propyl ketone, b. p. 108–111° (3 mm.),  $n_D^{20}$  1.5058, sp. gr.  $^{20}_4$  0.982; *MR* calcd. 56.5, *MR* found 57.8. Active hydrogen determination by means of lithium aluminum hydride,<sup>11</sup> kindly run by Mr. Richard Meikle, gave a value of 0.03. Infrared absorption spectra, carried out by Mrs. J. L. Johnson using a Perkin-Elmer Model 12B spectrometer with rock salt

optics, showed the presence of a carbonyl group (strong max. at 1691  $cm^{-1}$ ).

*Anal.* Calcd. for  $C_{12}H_{17}ON$ : C, 75.35; H, 8.96. Found: C, 75.63; H, 9.15.

The picrate, recrystallized from ethanol as yellow flakes, melted at 126°.

*Anal.* Calcd. for  $C_{18}H_{23}O_8N_4$ : C, 51.43; H, 4.79; N, 13.33. Found: C, 51.64; H, 4.89; N, 13.51.

The compound did not form a 2,4-dinitrophenylhydrazones, probably because of steric hindrance around the carbonyl group.

**Oxidation of 4-*n*-Propyl-3-pyridyl *n*-Propyl Ketone (II).**—To a solution of 20 g. (0.127 mole) of potassium permanganate in 200 ml. of water was added 2.0 g. (0.010 mole) of 4-*n*-propyl-3-pyridyl *n*-propyl ketone, and the mixture was heated at 80–90° for five hours. Excess permanganate was destroyed by addition of a few drops of methanol, and manganese dioxide was removed by filtration. To the filtrate was added 20 g. of copper sulfate (pentahydrate) in 100 ml. of water. The light blue precipitate was collected on a filter, washed with cold water, and added to 50 ml. of 10% hydrochloric acid which had previously been saturated with hydrogen sulfide. The cupric sulfide which precipitated was removed by filtration and the filtrate evaporated, leaving a light blue solid. This treatment with hydrogen sulfide was repeated, whereupon the solid on evaporation was crude cinchomeronic acid, a cream-colored solid, 1.25 g., m. p. 223–228°. After two recrystallizations from water, the m. p. was 260° (dec.).

*Anal.* Calcd. for  $C_7H_9NO_4$ : C, 50.31; H, 3.01. Found: C, 49.87, 49.68; H, 3.21, 3.25.

Similar oxidation of isoquinoline gave the same acid, m. p. 260° (dec.). A mixed m. p. was not depressed.

**Other Reactions with Grignard Reagents.**—The experiment described above for 4-*n*-propyl-3-pyridyl *n*-propyl ketone (II) was repeated with the same molar quantities using pyridine instead of nicotinonitrile. Distillation of the final product yielded only pyridine, 22.1 g. (61% recovery), b. p. 90–113°, m. p. of picrate 165–166°.

The same procedure using one-half-molar quantities of nicotinonitrile and two-molar amounts of methylmagnesium iodide gave only 3-acetylpyridine (0.13 mole), b. p. 215–217°,  $n_D^{20}$  1.5308.

**Wolff-Kishner Reduction of Nicotinylacetone.**—A mixture of 4.89 g. (0.030 mole) of nicotinylacetone, previously prepared by the method of Kuick and Adkins,<sup>12</sup> 3.36 g. (0.060 mole) of potassium hydroxide, 40 ml. of triethylene glycol and 7.0 g. (0.12 mole) of 85% hydrazine hydrate was treated in the same manner as the materials in the above-described preparation of 3-*n*-butylpyridine. The product on distillation was 1.43 g. of nearly colorless liquid, b. p. 58–60° (10 mm.),  $n_D^{20}$  1.4968, characterized as 3-ethylpyridine by means of its picrate, m. p. 127–128° (reported,<sup>13</sup> 128–130°).

*Anal.* Calcd. for  $C_{13}H_{12}N_4O_7$ : C, 46.43; H, 3.58. Found: C, 46.41; H, 3.63.

### Summary

3-*n*-Butylpyridine has been synthesized and found identical with one of the products of dehydrogenation of nicotine.

The addition of a large excess of *n*-propylmagnesium bromide to nicotinonitrile results in the formation of 4-*n*-propyl-3-pyridyl *n*-propyl ketone.

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(11) Krynitsky, Johnson and Carhart, *THIS JOURNAL*, **70**, 486 (1948).

(12) Kuick and Adkins, *ibid.*, **57**, 143 (1935).

(13) Stoehr, *J. prakt. Chem.*, [2] **45**, 38 (1892).