2-Pyridyl Alkyl Ketones

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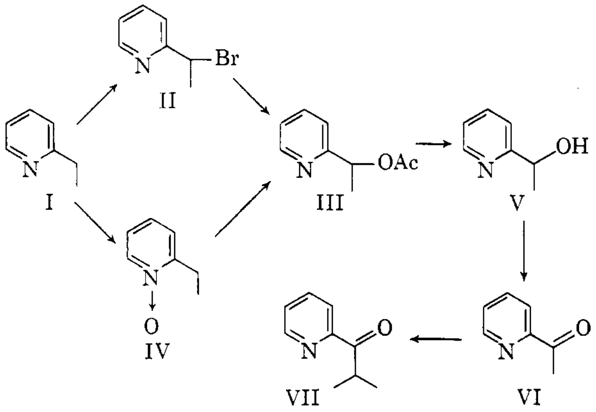
The formation of 2-pyridyl alkyl ketones from 2-alkylpyridines was of interest in the synthesis of Muscopyridine.[2] Using the scheme shown, 2-ethylpyridine (I) was transformed into 2-pyridyl methyl ketone (VI) and then to 2-pyridyl isopropyl ketone (VII).



The preparation of 2-(α-acetoxyethyl)pyridine (III) by rearrangement of 2-ethylpyridine oxide (IV) in acetic anhydride has been described.[3-5] Buu-Hoï[6] has reported that 2-picoline is brominated on the side chain, but experimental elaboration of this is lacking. We have found that radical bromination of 2-ethylpyridine produced 2-(α-bromoethyl)pyridine (II) in 75% yield. Treatment of II with silver acetate in acetic acid led to 2-(α-acetoxyethyl)pyridine (III) in 90% yield. This was shown to be identical with 2-(α-acetoxyethyl)pyridine (III) produced by rearrangement of 2-ethylpyridine oxide (IV) by comparison of their infrared spectra. Alkaline hydrolysis of III gave 2-(α-hydroxyethyl)pyridine (V) in 91% yield. The oxidation of 2-(α-hydroxyethyl)pyridine (V) to the corresponding ketone with dichromate sulfuric has been accomplished in low yield by Kuhn and Muzing.[7] Oxidation with chromium trioxide in pyridine likewise gave a low yield of the ketone.[8] A superior oxidizing agent was found in *N*-bromosuccinimide. Oxidation of 2-(α-hydroxyethyl)pyridine (V) using *N*-bromosuccinimide as the oxidizing agent was rather slow but occurred under very mild conditions, yielding 65% of pure 2-pyridyl methyl ketone.

The purpose of this study was to determine whether this sequence of reactions would be applicable to the synthesis of Muscopyridine.[2] Since this was the case, we were not interested in obtaining a specific methylation product but in obtaining a homogeneous one in reasonably good yield.

The alkylation of 2-pyridyl methyl ketone (VI) to a homogeneous substitution product was expected to be difficult due to a number of potential side reactions. Indeed, when VI was allowed to react with an equivalent amount of potassium *t*-butoxide and methyl iodide over an extended period, a 15% yield of 2-pyridyl isopropyl ketone (VII) was obtained along with a large amount of nonvolatile material. However alkylation reactions of this type are known to proceed more rapidly under the proper conditions.[9] The conditions selected, excess methyl iodide and potassium *t*-butoxide and five minute reaction time, resulted in a 48% yield of 2-pyridyl isopropyl ketone (VII).

EXPERIMENTAL[10-12]

2(α-Bromoethyl)pyridine (II). To 30.0 g. (0.28 mole) of 2-ethylpyridine in 830 ml. of carbon tetrachloride was added 50 g. (0.28 mole) of *N*-bromosuccinimide and 50 mg. of benzoyl peroxide. The solution was heated under reflux using an infrared lamp until no more *N*-bromosuccinimide remained on the bottom of the flask (2 hr.). After cooling the solution for 1 hr. in an ice bath, the succinimide was removed by filtration and washed with cold carbon tetrachloride. The filtrate was concentrated under reduced pressure and the product distilled. The yield of 2-(α-bromoethyl)pyridine was 39.22 g. (75.5%); this material was a red unstable oil, b.p. 89.5–90.5° (7 mm.) n_{D}^{25} 1.5550–1.5561.[13] The sample prepared for analysis deposited a film on the sides of the flask immediately after distillation and was therefore not analyzed.

2-(α-Acetoxyethyl)pyridine (III). In a flask covered with aluminum foil was placed 39.22 g. (0.211 mole) of 2-(α-bromoethyl)pyridine, 300 ml. of glacial acetic acid, and 38.6 g. (0.232 mole) of silver acetate. The mixture was

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[1] Present address: The Upjohn Company, Kalamazoo, Mich.

[2] K. Bieman, G. Büchi, and B. H. Walker, *J. Am. Chem. Soc.*, **79**, 5558 (1957).

[3] G. Kobayashi and S. Furukawa, *Pharm. Bull.*, **1**, 347 (1953).

[4] V. Boekelheide and W. J. Linn, *J. Am. Chem. Soc.*, **76**, 1286 (1954).

[5] O. H. Bullitt and J. T. Maynard, *J. Am. Chem. Soc.*, **76**, 1370 (1954).

[6] N. P. Buu-Hoï, *Ann.*, **556**, 1 (1944).

[7] E. Kuhn and W. Muzing, *Ber.*, **85**, 29 (1952).

[8] G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 422 (1953).

[9] R. M. Lukes, G. I. Poos, R. E. Beyler, W. F. Johns, and L. H. Sarett, *J. Am. Chem. Soc.*, **75**, 1707 (1953).

[10] Boiling points and melting points are uncorrected.

[11] All of the distillations were performed through a modified Podbielniak column constructed according to J. Cason and H. Rapoport, in *Laboratory Text in Organic Chemistry*, Prentice-Hall, Inc., New York, N. Y. 1950, p. 232.

[12] We are indebted to Dr. S. M. Nagy and his associates for analyses and for the infrared spectra, which were determined in 10% solution or 1% in potassium bromide, unless otherwise indicated, with a Baird Double Beam Infrared Recording Spectrometer, Model B, fitted with a sodium chloride prism.

[13] It was noticed that all of the pyridines reported here tended to react with carbon dioxide and/or water during the measurement of the index of refraction. The value always became lower as a consequence of this. In one case the value for the index of refraction dropped by 0.0042 on opening the refractometer for one minute.

immediately placed in an ice bath and cooled until the acetic acid commenced to crystallize. The cooling bath was then removed and the solution stirred (magnetically) for 9 hr. at room temperature, heated to reflux and left at room temperature overnight. The silver bromide was separated by filtration of the cooled solution and the filtrate was distilled under reduced pressure. After distillation of the acetic acid there was obtained 31.5 g. (90.5%) of 2-(α-acetoxyethyl)pyridine, b.p. 112–113° (12 mm.), [reported[4] b.p. 109–111° (16 mm.)].[14]

The infrared spectrum (pure liquid) of the acetate prepared by this route was identical with the infrared spectrum of the acetate prepared by rearrangement of 2-ethylpyridine oxide (IV).

2-(α-Hydroxyethyl)pyridine (V). To 9.0 g. (0.225 mole) of sodium hydroxide, 83 ml. of water and 57 ml. of methanol under a nitrogen atmosphere was added 31.5 g. (0.191 mole) of 2-(α-acetoxyethyl)pyridine. The solution was heated under reflux for 11.5 hr., transferred to a continuous extractor, diluted with 300 ml. of saturated sodium chloride solution and continuously extracted with benzene for 25 hr. Distillation of the extract yielded 21.37 g. (91%) of 2-(α-hydroxyethyl)pyridine, b.p. 93.5–94.0° (7 mm.) n_{D}^{25} 1.5223 (reported[5] b.p. 85–89° (5 mm.) n_{D}^{25} 1.5253).[15] The picrolonate, recrystallized from ethanol, melted at 184–186° dec.[15]

2-Pyridyl methyl ketone (VI). To a solution of 105 g. of *N*-bromosuccinimide, 1200 ml. of acetone, and 120 ml. of water was added 31.64 g. (0.257 mole) of 2-(α-hydroxyethyl)-pyridine and 2 ml. of glacial acetic acid. The pale yellow solution turned red within 12 hr. and pale yellow again after a total of 20.5 hr.[16] The reaction mixture was allowed to stand for a total of 48 hr. before being neutralized with solid sodium carbonate. A sodium thiosulfate solution was added to the lacrimatory mixture until a drop of the mixture failed to produce a blue color when placed on a piece of acidified starch iodide paper. The lacrimatory properties of the two phase system disappeared at this time. The cooled solution was filtered and the filtrate made acidic with hydrochloric acid (*p*H 1). After removal of the acetone by distillation, the residue was made basic (*p*H 9) and the aqueous solution distilled. The 1.0 l. of distillate was continuously extracted with benzene for 36 hr. Distillation of the extract yielded 20.00 g. (65%) of 2-pyridyl methyl ketone, b.p. 82–83.5° (13–15 mm.) n_{D}^{25} 1.5153 [reported[17] b.p. 78° (12 mm.)].

The phenylhydrazone recrystallized from methanol-water melted at 156–158° (reported[17] m.p. 155.5–156°).

2-Pyridyl isopropyl ketone[18] (VII). To a solution prepared from 4.5 g. (0.116 mole) of potassium and 230 ml. of *t*-butyl alcohol (distilled from 3 g. of sodium), 300 ml. of sodium-dried benzene was added. To the stirred refluxing solution under a nitrogen atmosphere was added, as fast as possible, 7.0 g. (0.058 mole) of 2-pyridyl methyl ketone. This addition was followed immediately by the addition, during 1 min., of 24.6 g. (0.174 mole) of methyl iodide in 5 ml. of dry benzene. The solution was maintained at reflux for an additional 4 min., then quenched with 50 ml. of ice water. After the addition of 25 ml. of concd. hydrochloric acid, the solution was concentrated under reduced pressure. The residue was made basic by the addition of 20 g. of potassium hydroxide (*p*H 11). After saturating the solution with solid sodium chloride, it was extracted with eight portions of ether. The combined ether solutions were filtered through and dried over sodium sulfate, concentrated under reduced pressure, and distilled. There was obtained a forerun of 1.37 g., b.p. 73.5–87.5° (7 mm.) n_{D}^{25} 1.5084–1.5053, followed by 4.15 g. (48%) of 2-pyridyl isopropyl ketone, b.p. 87.5–88.5° (7 mm.) n_{D}^{25} 1.5000–1.4989 (reported[19] 107–108° (25 mm.) n_{D}^{25} 1.5028). The pot residue amounted to 1.0 g.

Anal. Calcd. for $C_9H_{11}NO$: C, 72.45; H 7.43. Found: C, 72.56; H 7.69.

The 2,4-dinitrophenylhydrazone after one recrystallization from ethyl acetate melted at 180.0–181.6°. The analytical sample melted at 181.0–181.4° (reported[19] m.p. 181.0–181.5°).

Anal. Calcd. for $C_{15}H_{15}N_5O_4$: C, 54.61; H, 4.59. Found: C, 54.46; H, 4.70.

When equimolar quantities of potassium, methyl iodide, and methyl 2-pyridyl ketone were used, the same product was obtained in 15% yield. The infrared spectrum was identical with that of the ketone prepared above, and a mixture melting point of the 2,4-dinitrophenylhydrazones was undepressed.

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(14) We have repeated the preparation of 2-(α-acetoxyethyl)pyridine using the procedure of Boekelheide and Linn[4] and obtained a 67% yield of the acetate. b.p. 105–110° (9–10 mm.) n_{D}^{25} 1.4893– 1.4923 (reported[5] n_{D}^{25} 1.4913).

(15) Hydrolysis of the acetate produced *via* the *N*-oxide route[4] yielded the alcohol in 75% yield, b.p. 93.5–94.5° (7 mm.) n_{D}^{25} 1.5220–1.5230.

Anal. Calcd. for C_7H_9ON: C, 68.27; H, 7.37. Found: C, 68.49; H, 7.65.

The ultraviolet absorption spectrum in ethanol showed: $\lambda_{\max.}$ 256 mμ log ε 3.48, $\lambda_{\max.}$ 261 mμ log ε 3.55, $\lambda_{\max.}$ 267.5 mμ log ε 3.23.

The picrolonate prepared from this material was recrystallized from ethanol and melted at 183.0–185.6° dec.

Anal. Calcd. for $C_{17}H_{17}N_5O_6$: C, 52.71; H, 4.42. Found: C, 52.93; H, 4.79.

(16) B. C. Anderson, Ph.D. thesis, Massachusetts Institute of Technology, 1955.

(17) P. C. Teague, A. R. Ballentine, and G. L. Rushton, *J. Am. Chem. Soc.*, **75**, 3429 (1953).

(18) S. Bertucat, *Compt. Rend.*, **232**, 1758 (1951), has claimed the synthesis of this compound and three of its derivatives; however, no physical properties were reported for the compound and we have been unable to prepare any of the recorded derivatives.

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Cyclizations Leading to 2-Acylpyrroles and 2-Pyrrolecarboxylic Esters[1,2]

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Prior to the outset of this investigation, the reductive condensation of certain β-diketones and β-ketoaldehydes with ethyl α-oximinoacetoacetate[3–5]

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(1) Studies in the Pyrrole Series, XXIX. Paper XXVIII, B. Harrell and A. H. Corwin, *J. Am. Chem. Soc.*, **78**, 3135 (1956).

(2) This work was supported by a research grant (NSF-G 1195) from the National Science Foundation.

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