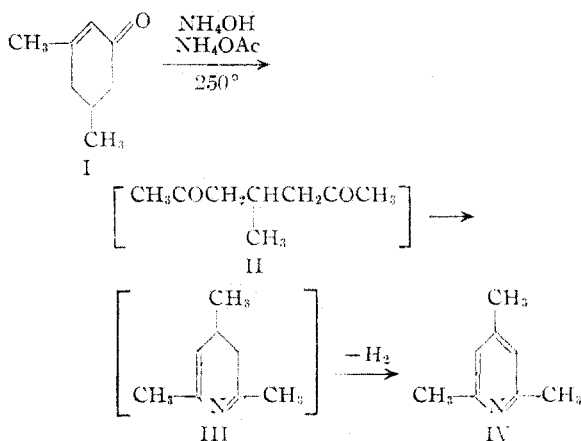


[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Pyridines. VII. Conversion of 2-Cyclohexenones to Pyridines¹

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A recent study² has shown that optimum conditions for the Chichibabin synthesis of pyridines are such that reversible aldol condensations also occur. It has further been shown that 1,5-diketones are likely intermediates in many of these reactions. We have therefore wondered whether substituted 2-cyclohexenones, which can give rise to 1,5-dicarbonyl compounds by retrograde aldol condensation, might be converted to pyridines under the conditions of the Chichibabin synthesis. Cyclohexenones are more stable and generally more available than are the dicarbonyl compounds.



Study of this reaction with 3,5-dimethyl-2-cyclohexenone (I) under numerous conditions described in the Experimental Part has indeed resulted in the formation of *sym*-collidine (IV), but only in yields up to 37%.

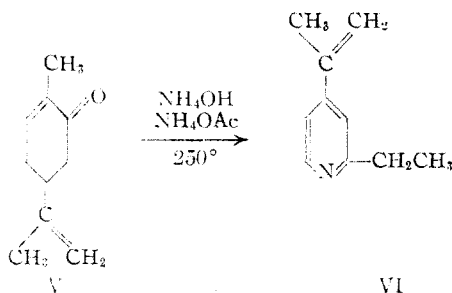
One expected reason for low yields is that the pyridines from cyclohexenones are always 2-picoline derivatives, which might be expected to undergo further condensation with cyclohexenones. A test of this possibility, however, by heating a mixture of *sym*-collidine and 3,5-dimethyl-2-cyclohexenone with ammonium acetate at 250°, resulted in a quantitative recovery of the collidine and a 30% recovery of the ketone.

If the over-all reaction occurs in the steps indicated (I-IV), then it becomes of interest to study each step. The intermediate II, 4-methyl-2,6-heptanedione, is too unstable for preparation as such, but a cyclic analog, 2,4,6-trimethylpyrilium perchlorate,³ was treated with ammonium hydroxide and ammonium acetate. This gave a 77% yield of *sym*-collidine, thus indicating that loss of yield in the synthesis I-IV occurs in the retrograde aldol condensation (I-II). Further evidence is

the fact that 3,5-dimethyl-2-cyclohexenone (I) is only 30% recovered when heated at 250° in aqueous ammonium acetate.

Evidence for the last stage of the reaction, loss of hydrogen from the dihydropyridine III, has been obtained with 3-phenyl-2-cyclohexenone, which yielded 19% of 2-methyl-6-phenylpyridine and 3.8% of 3-phenylcyclohexanol. The latter is to be expected if the starting material acts as a hydrogen acceptor in the dehydrogenation step. Addition of hydrogen acceptors, nitrobenzene and cyclohexene, however, had a deleterious effect on the yields.

Two further cyclohexenones, 3-methyl-5-phenyl-2-cyclohexenone and carvone (V), gave low yields of 2,6-dimethyl-4-phenylpyridine (4.1%) and 2-ethyl-4-isopropenylpyridine (VI) (6.4%), respectively. Formation of the latter compound, rather than the corresponding isopropyl derivative, points to the tendency of the intermediate dihydropyridine to aromatize by dehydrogenation under these conditions rather than by double bond migration. The latter would have yielded the 4-isopropyl derivative.



Experimental

sym-Collidine (IV).—The Chichibabin-type syntheses were carried out in a 500-ml. steel autoclave as previously described.² The 3,5-dimethyl-2-cyclohexenone⁴ (0.08–0.24 mole) and ammonium acetate were mixed in the autoclave; the ammonia was added as 28% ammonium hydroxide in amounts from eight to ten times the theoretical, based on a quantitative yield of *sym*-collidine. Temperatures were mainly in the range 250–300°, and pressures generated ranged from 1000 to 1500 pounds per square inch. Reaction times were varied from one to seven hours; three hours was found to be sufficient for maximum yields.

Purification of *sym*-collidine from these reactions was accomplished by separation of the aqueous and non-aqueous phases of the reaction mixtures, saturation of the aqueous phase with potassium carbonate, and thorough extraction of this solution with chloroform. The extracts were combined with the original organic layer, dried over Drierite, and fractionally distilled in an eight-inch helix-packed column, b. p. 36–37° (2 mm.), 60–63° (11 mm.); *n*_D²⁰ 1.4939; m. p. of picrate 155–156° (lit.,³ 155–156°). In experiments in which 3,5-dimethyl-2-cyclohexenone was recovered the reaction mixtures were first acidified

(1) For the previous communication on pyridine chemistry see Frank and Riener, *THIS JOURNAL*, **72**, 4182 (1950).

(2) Frank and Seven, *ibid.*, **71**, 2629 (1949).

(3) Baeyer and Piccard, *Ann.*, **384**, 208 (1911).

(4) Horning, Denekas and Field, "Organic Syntheses," Vol. 27, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 24.

and extracted with chloroform; then made alkaline with potassium carbonate and extracted again. The extracts were dried separately over Drierite and fractionally distilled.

In comparison with the typical Chichibabin reactions involving aldehydes and ketones,² which begin to occur exothermically at temperatures around 200°, the use of 3,5-dimethyl-2-cyclohexenone appears to require somewhat higher temperatures, 250–300°. Poor yields were obtained at temperatures below 250°.

Use of ammonium acetate is necessary for maximum yields. For example, yields of 35–37% *sym*-collidine were obtained with the use of 1.0–1.2 moles of ammonium acetate per mole of 3,5-dimethyl-2-cyclohexenone. Decreasing the ammonium acetate to 0.5 mole lowered the yields to 13.7–15.3%; elimination of the ammonium acetate entirely gave a yield of 5.6%. On the other hand, the use of ammonium acetate in place of ammonium hydroxide gave poor results.

Other experiments were as follows: heating 0.081 mole of 3,5-dimethyl-2-cyclohexenone with 0.088 mole of ammonium carbonate monohydrate for seven hours at 150°, an experiment reported by Knoevenagel and Erler,⁵ yielded a trace of *sym*-collidine, isolated as its picrate. Similar reaction with ammonium sulfate gave a quantitative recovery of the cyclohexenone. Use of sodium hydroxide rather than ammonium acetate as a catalyst gave much tar, no collidine, and a 13% recovery of the cyclohexenone. Refluxing of 3,5-dimethyl-2-cyclohexenone with hydroxylamine hydrochloride, 20% ethanolic sodium hydroxide and ethylene glycol at 140° gave only a 22% recovery of the cyclohexenone. Replacement of the ketone by its oxime in the autoclave runs gave a 23% yield of *sym*-collidine, as compared with 35–37% with the ketone itself.

Refluxing of 5.0 g. (0.023 mole) of 2,4,6-trimethylpyrylium perchlorate,³ 62 ml. (0.896 mole) of 28% aqueous ammonia and 1.76 g. (0.022 mole) of ammonium acetate for two hours, extraction of the mixture with chloroform, and distillation of the extracts gave 2.1 g. (77%) of *sym*-collidine, b. p. 48° (6 mm.); n_D^{20} 1.4977.

In the experiment designed to test the possibility of condensation between 3,5-dimethyl-2-cyclohexenone and *sym*-collidine, 0.024 mole of the cyclohexenone and 0.058 mole of *sym*-collidine were heated with 0.082 mole of ammonium acetate for six hours at 250°. Essentially all the collidine was recovered, b. p. 40–41° (1.8 mm.); n_D^{20} 1.4987; m. p. of picrate 155–156°⁸, and 30% of the cyclohexenone, b. p. 62–64° (3 mm.); n_D^{20} 1.4806; m. p. of 2,4-dinitrophenylhydrazone 149–150° (lit.,⁶ 150°).

2-Methyl-6-phenylpyridine and 3-Phenylcyclohexanol, 2,6-Dimethyl-4-phenylpyridine, and 2-Ethyl-4-isopropenylpyridine (VI).—These compounds were prepared in the manner described above for *sym*-collidine at 250°, with reaction times of three hours, and using 10 moles of 28% ammonium hydroxide and 1 mole of ammonium acetate per mole of cyclohexenone.

From 33.0 g. (0.192 mole) of 3-phenyl-2-cyclohexenone⁷ was obtained by chloroform extraction and fractional

distillation 1.3 g. (3.8%) of 3-phenylcyclohexanol, b. p. 105° (23 mm.), which crystallized in the receiver, m. p. 78–79° (lit.,⁸ 79.5–80.5°); m. p. of benzoate 66–67° (lit.,⁸ 68°), and 6.0 g. (18.6%) of 2-methyl-6-phenylpyridine, b. p. 97–100° (1.5 mm.); n_D^{20} 1.6065; m. p. of picrate 135° (lit.,⁹ 135°).

From 37.2 g. (0.20 mole) of 3-methyl-5-phenyl-2-cyclohexenone¹⁰ was similarly obtained a tar which was distilled at 2 mm. pressure to yield colorless needles of 2,6-dimethyl-4-phenylpyridine, 1.5 g. (4.1%) after crystallization from methanol-benzene, m. p. 58–59° (lit.,³ 58–59°); m. p. of picrate 229–230° (lit.,³ 230°).

The reaction mixture from 19.2 g. (0.128 mole) of carvone (obtained from Magnus, Mabee and Reynard, Inc., New York) was acidified with concentrated hydrochloric acid, extracted with chloroform, made alkaline with potassium carbonate, and again extracted with chloroform to give a solution which yielded on distillation 1.2 g. (6.4%) of 2-ethyl-4-isopropenylpyridine, b. p. 60–62° (1.3 mm.); n_D^{20} 1.5260; sp. gr. $^{20}_4$ 0.964; *MR* calcd.: 46.48; *MR* found: 46.85.

Anal. Calcd. for C₁₀H₁₃N: C, 81.68; H, 8.90; N, 9.51. Found: C, 81.41; H, 9.21; N, 9.51.

A picrate, yellow platelets from ethanol, melted at 170–171°.

Anal. Calcd. for C₁₆H₁₆O₇N₄: C, 51.07; H, 4.29; N, 14.89. Found: C, 51.14; H, 4.27; N, 14.97.

Evidence that this product was a 4-isopropenyl derivative rather than a 4-isopropyl derivative was obtained by the fact that it decolorized 2% potassium permanganate solution and by comparison of its ultraviolet absorption spectrum with the spectra of 4-vinyl- and 4-ethylpyridines. The spectra, kindly determined by Mr. John Gardner using a Beckmann Model D spectrophotometer, had absorption maxima at 245 m μ (log ϵ 3.96; 0.58 g./liter of 95% ethanol), 242.5 m μ (log ϵ 4.12; 0.72 g./liter of 95% ethanol) and 256 m μ (log ϵ 3.28; 0.46 g./liter of 95% ethanol), respectively. Intensities of the absorption of 2-ethyl-4-isopropenylpyridine and 4-vinylpyridine were higher than that for the ethyl derivative in the whole range from 210–300 m μ .

Summary

The reaction of substituted 2-cyclohexenones with excess ammonium hydroxide in the presence of ammonium acetate at 250° results in the formation of substituted 2-picolines, presumably by a retrograde aldol condensation followed by ring closure with the ammonia. The preparations of *sym*-collidine, 2-methyl-6-phenylpyridine, 2,6-dimethyl-4-phenylpyridine and 2-ethyl-4-isopropenylpyridine have been studied.

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(6) Dane and Schmitt, *Ann.*, **536**, 202 (1938).

(7) Woods and Tucker, *THIS JOURNAL*, **70**, 2174 (1948).

(8) Boyd, Clifford and Probert, *J. Chem. Soc.*, **117**, 1383 (1920).

(9) Scholtz, *Ber.*, **28**, 1726 (1895).

(10) Henze, Wilson and Townley, *THIS JOURNAL*, **65**, 963 (1943).