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**3,4-Substituted Pyridines. I. Synthesis of 3-Vinyl-4-methylpyridine**

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This paper is the first of a series in the study of model compounds and possible starting materials which may prove useful for the ultimate synthesis of the quinine alkaloids.

The basic approach under consideration parallels Rabe's<sup>1</sup> synthesis of hydroquinine which started with  $\beta$ -collidine and included the intermediates: ethyl  $\beta$ -(3-ethyl-4-piperidyl)-propionate, hydroquinicine, and hydroquinone. Inasmuch as the partial synthesis of quinine from quinicine has been reported,<sup>2,3</sup> it appears that the synthesis of quinine would resolve itself into the synthesis of a 3,4-substituted pyridine capable of undergoing this series of reactions and substituted in the 3-position with a group which can be converted to a vinyl radical after reduction of the pyridine nucleus.

simple 3,4-substituted pyridines. The experimental conditions given for the synthesis of  $\beta$ -collidine<sup>4</sup> are too drastic to be used as a general method of preparation.

The first steps of this synthesis have been adapted by Robinson<sup>5,6</sup> and co-workers to prepare 2,6-dihydroxy-3-( $\beta$ -phenoxyethyl)-4-methylpyridine "in the hope that it might prove to be a suitable intermediate for the synthesis of quinine derivatives, *e. g.*, meroquinine, which contain the vinyl group as a side chain." They also reported similar compounds including the anhydride of 4-methyl-2,3-furano-2',3'-dihydro-6-hydroxypyridine (VI). However, this method of preparation of this interesting substance "could not be developed to a practical extent." We have found a simple practical method for its

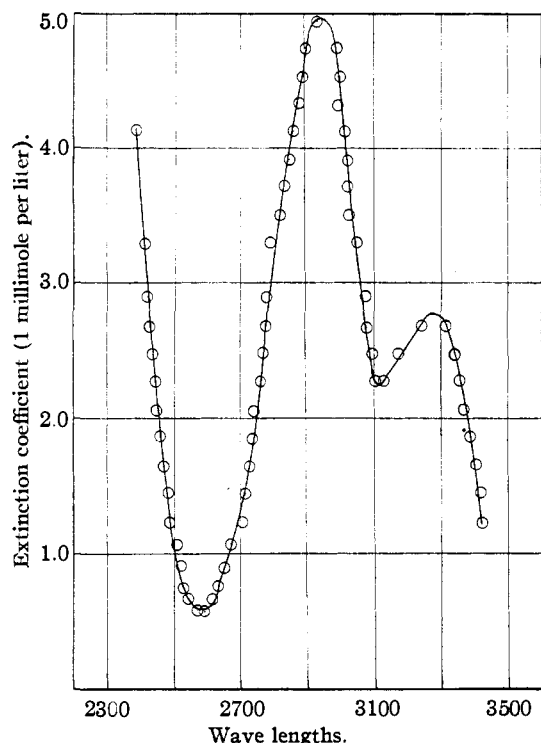


Fig. 1.—Absorption spectrum of Compound V in alcohol.

The literature contains comparatively little information on the methods of synthesis for the

(1) Rabe, Huntenburg, Schultze and Volger, *Ber.*, **64**, 2492-2500 (1931).

(2) Rabe, *ibid.*, **44**, 2088 (1911); **45**, 2163 (1912).

(3) Rabe and Kindler, *ibid.*, **51**, 466 (1918).

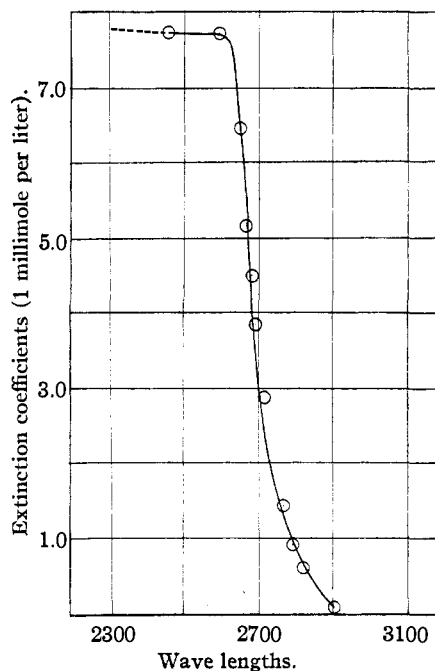


Fig. 2.—Absorption spectrum of Compound VI in alcohol.

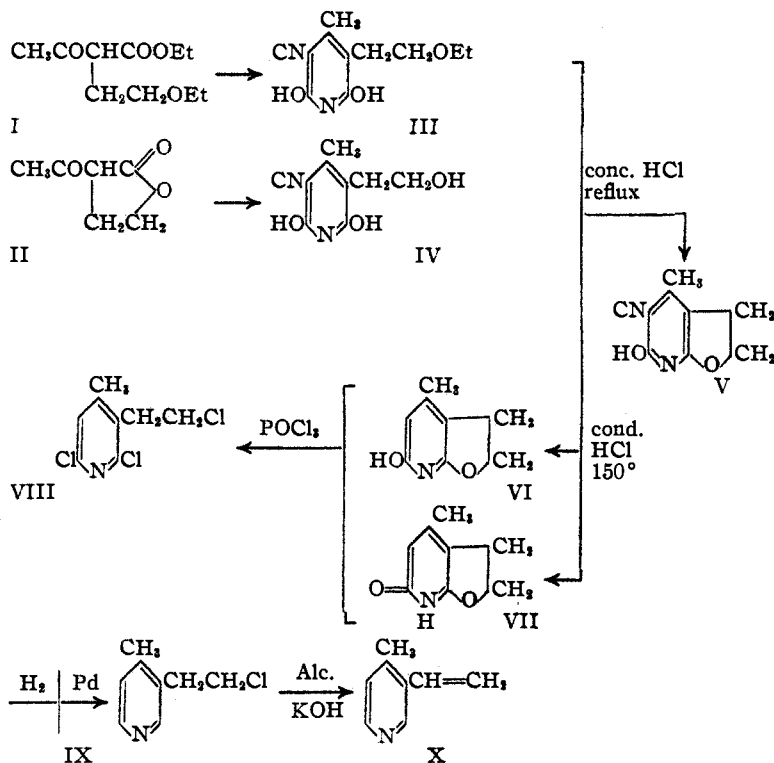
synthesis by condensing acetobutyrolactone<sup>7</sup> with cyanoacetamide to give 2,6-dihydroxy-3-( $\beta$ -hydroxyethyl)-4-methyl-5-cyanopyridine (IV) which

(4) Ruzicka and Fornasir, *Helv. Chim. Acta*, **2**, 338 (1919).

(5) Matejka, Robinson and Watt, *J. Chem. Soc.*, 2019 (1932).

(6) Robinson and Watt, *ibid.*, 1536-43 (1934).

(7) Knunyanaty, Chelintzer and Osetrova, *C. A.*, **28**, 4382<sup>o</sup> (1934).



dine (VIII). The nuclear halogens of the trichloro compound were eliminated by reductive cleavage to give a  $\beta$ -chloroethylpyridine (IX) which was easily converted to 3-vinyl-4-methylpyridine (X).

### Experimental Part

Ethyl  $\alpha$ -( $\beta$ -ethoxyethyl)-acetoacetate (I) was prepared according to the method of Clarke and Gurin.<sup>8</sup>

The product boiled at  $115^\circ$  (10 mm.) whereas the literature records the boiling point as  $85\text{--}90^\circ$  (10 mm.).

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_{15}\text{O}_4$ : C, 59.38; H, 8.98. Found: C, 59.10; H, 8.90.

**2,6-Dihydroxy-3-( $\beta$ -ethoxyethyl)-4-methyl-5-cyano-pyridine [Ammonium Salt], III.**—A mixture of 40.4 g. of (I), 16.8 g. of cyanoacetamide, and 75 g. of concentrated ammonia was allowed to stand for four days. The precipitate was filtered off, washed with absolute alcohol, then with ether, and dried; yield, 16.5 g. (34.6%).

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_{15}\text{O}_3\text{N}_3$ : N, 17.56. Found: N, 17.16.

**2,6-Dihydroxy-3-( $\beta$ -hydroxyethyl)-4-methyl-5-cyanopyridine [Ammonium Salt], IV.**—To a mixture of 835 g. of ethyl cyanoacetate and 945 g. of  $\alpha$ -acetobutyro lactone (II) was added 2220 ml. of 28% ammonia with stirring. Heat was evolved and a solid separated which redissolved as the addition of ammonia was continued. Upon standing overnight a precipitate formed which was filtered off and washed with alcohol; yield, 812 g. (52%).

A portion of the yield was recrystallized from alcohol for analysis; the melting point was indefinite.

*Anal.* Calcd. for  $\text{C}_9\text{H}_{13}\text{O}_3\text{N}_3$ : C, 51.40; H, 5.72; N, 19.9. Found: C, 51.13; H, 6.02; N, 19.8.

**2,3-(2',3'-Dihydrofuran)-4-methyl-5-cyano-6-hydroxypyridine, V.**—A mixture of 20 g. of IV and 100 ml. of concentrated hydrochloric acid was refluxed for one-half hour. At first, a solution was obtained but after refluxing for about fifteen minutes, a precipitate suddenly separated. The mixture was cooled, diluted with 1 volume of water, filtered and washed with water; yield, 17 g. A sample was recrystallized from water several times for analysis. It is only slightly soluble in boiling water or alcohol. The compound gives no ferric chloride test; the melting point is indefinite.

*Anal.* Calcd. for  $\text{C}_9\text{H}_{13}\text{O}_2\text{N}_3$ : C, 61.35; H, 4.58; N, 15.9. Found: C, 61.55; H, 4.83; N, 15.7.

**2,3-(2',3'-Dihydrofuran)-4-methyl-6-hydroxypyridine, VI.**—A mixture of 87.2 g. of IV and 400 ml. of concentrated hydrochloric acid was heated for eight hours at  $150^\circ$  in sealed tubes. Two volumes of water was added, the solution was cooled in ice, made slightly alkaline with ammonia

is readily converted to the furan with the removal of the cyano group by treating with concentrated hydrochloric acid at  $150^\circ$ . This substance was also prepared by starting with  $\beta$ -ethoxyethyl bromide, the intermediate in this case being the ethyl ether of (IV); these reactions are shown below.

Robinson reported only one form of the furan; however, it was observed that it exists in two stable isomeric forms (a) m. p.  $177.5\text{--}179^\circ$  and (b)  $250^\circ$ , either of which can be converted to an equilibrium mixture by heating with concentrated hydrochloric acid at  $150^\circ$  for four hours or by dissolving in 10% alkali and allowing to stand for a short time. The lower melting form gives no color with ferric chloride and is very soluble in ethyl acetate. Its isomer gives a strong ferric chloride test and is much less soluble in ethyl acetate. Their absorption spectra are quite different (Figs. 1 and 2). It is evident the substances are desmotropes; the higher melting compound is the pyridine form (VI) and the lower melting, the pyridone (VII) form. Samples of the pure isomers showed no conversion to the other form after one year's storage. Mild treatment with phosphorus oxychloride yields a dichloro compound while more vigorous conditions give a 2,6-dichloro-3-( $\beta$ -chloroethyl)-pyri-

(8) H. T. Clarke and S. Gurin, *This Journal*, **57**, 1876 (1935).

and then neutralized with acetic acid. After standing for several hours it was filtered, washed with water and dried; yield, 55 g. (87.5%).

The yield thus obtained is a mixture of the two isomers and may be used directly for the chlorination. They may be separated by treating the mixture with hot ethyl acetate in which the low-melting isomer is soluble. After repeated recrystallization this isomer A is obtained in pure form, as shown by a negative ferric chloride test, m. p. 177.5–179°, and amounts to roughly 10–30% of the total yield. The high melting isomer B is obtained readily by recrystallizing the ethyl acetate insoluble portion from methanol; m. p. 250°; mixed m. p. 9 pts. A and 1 pt. B, 160–167°.

*Anal.* Calcd. for  $C_8H_9O_2N$ : C, 63.70; H, 5.98; N, 9.24. Found: A, C, 63.42; H, 6.16; N, 9.17; B, C, 63.58; H, 6.19; N, 9.22.

Both isomers gave the same chloro compound in the next step.

**2,6-Dichloro-3-( $\beta$ -chloroethyl)-4-methylpyridine, VIII.**—Fifty grams of VI and 150 g. of phosphorus oxychloride were heated in sealed tubes at 180° for five hours. The solution was poured onto ice and, after standing for several hours, the crystals were filtered off, washed with water and dried. They were taken up in ether and the solution was decolorized with charcoal. After concentration the residue was crystallized from isopropanol; yield, 42 g. (57%). A sample was recrystallized from isopropanol for analysis; m. p. 68.9°.

*Anal.* Calcd. for  $C_8H_8NCl_2$ : C, 42.80; H, 3.59; N, 6.24. Found: C, 42.95; H, 3.57; N, 5.99.

Under milder conditions a dichloro compound was obtained. Five grams of VI and 15 g. of phosphorus oxychloride were heated at 120° for seven hours. The solution was poured onto ice and allowed to stand for several hours. The supernatant liquors were decanted from the semi-crystalline precipitate. The precipitate was dissolved in chloroform, the solution was washed with water, dried, treated with charcoal and concentrated. The residue crystallized on cooling. The yield was crystallized once from isopropanol and again from 50% isopropanol; yield, 1 g.; m. p. 132.8°.

*Anal.* Calcd. for  $C_8H_9ONCl_2$ : C, 46.62; H, 4.40. Found: C, 46.89; H, 4.81.

**3-( $\beta$ -Chloroethyl)-4-methylpyridine, IX.**—To a solution of 0.3 g. of palladium chloride in 10 ml. of hot 2.5 N hydrochloric acid were added 50 ml. of methanol and 3 g.

of acid-washed charcoal. The mixture was reduced with hydrogen and 6.73 g. of VIII in 100 ml. of methanol was added. The reduction was complete in two hours at room temperature and 30 lb. pressure. The catalyst was filtered off and the alcohol was removed under vacuum. The residue was taken down several times with absolute alcohol to get rid of the water. Finally the crystalline residue was dissolved in a small amount of absolute alcohol and precipitated with ether; yield, 5 g. (85.5%).

A portion was recrystallized twice from alcohol-ether and once from acetone for analysis; m. p. 170–171° (hydrochloride).

*Anal.* Calcd. for  $C_8H_{11}NCl_2$ : C, 50.01; H, 5.77; N, 7.29. Found: C, 49.84; H, 5.85; N, 7.02.

**3-Vinyl-4-methylpyridine, X.**—To a concentrated solution of 3.84 g. of IX in hot methanol was added a hot solution of 2.80 g. of potassium hydroxide in a small amount of methanol. The mixture was refluxed for three hours and allowed to stand overnight. Water was added and the mixture was extracted with ether. After drying the ether extract over Drierite, the hydrochloride was prepared by saturating the solution with hydrogen chloride. The ether was decanted from the semi-crystalline mass and the residue was crystallized from acetone; yield, 1.5 g. (50%). The yield was recrystallized twice from methanol-ether. The compound readily takes up bromine; yield, 1.2 g.; m. p. 164–166°.

*Anal.* Calcd. for  $C_8H_{10}NCl$ : C, 61.75; H, 6.48; N, 9.00. Found: C, 61.62; H, 6.84; N, 8.81.

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### Summary

A new practical synthesis of 4-methyl-2,3-furano-2',3'-dihydro-6-hydroxypyridine has been found. This substance exists in two desmotropic forms which have been isolated and characterized.

The synthesis of 3-methyl-4-vinylpyridine is reported.

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