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THE 2-, 4-, AND 6-PYRIDONES RELATED TO 1-METHYL-NICOTINONITRILE*

TREVOR ROBINSON and CARL CEPURNEEK†

Chemistry Department, University of Massachusetts, Amherst, Massachusetts

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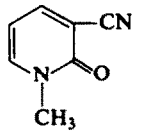
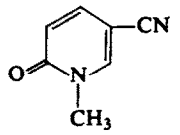
Abstract—The 2-, 4-, and 6-pyridones related to 1-methylnicotinonitrile have been synthesized and their properties compared. The 4-pyridone is a new compound and the 2-pyridone has not been obtained synthetically before. The 4- and 6-pyridones are identical to two of the products obtained from enzymatic oxidation of nicotinonitrile methiodide.

OXIDATION of nicotinonitrile methiodide by an enzyme preparation from castorbean seedlings has been found to yield two compounds believed to be pyridones.[1,2] Authentic samples of the possible pyridones were desired for comparison. 1-Methyl-3-cyano-2-pyridone (ricinidine) (I) was obtained by Späth and Koller[3] by degradation of the alkaloid ricinine. It has apparently never been made synthetically. Impure 1-methyl-5-cyano-2-pyridone (II) has perhaps been made in very low yield by alkaline ferricyanide oxidation of nicotinonitrile methiodide,[4] but Patton[5] definitely obtained it by aerial oxidation of an alkaline solution of the corresponding perchlorate. The yield by this procedure was also very low, and several other products were formed simultaneously. 1-*Methyl*-3-*cyano*-4-*pyridone* (III) has never been reported in the literature although the corresponding amide and other related compounds have been recently synthesized.[6]



(I)



(II)

We have applied the alkaline ferricyanide oxidation procedure of Pullman and Colowick[7] to nicotinonitrile methiodide and have found it a convenient method for preparing ricinidine (I) which can be extracted from the aqueous reaction mixture by chloroform and obtained

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[1] T. ROBINSON, *Fed. Proc.* **21**, 399 (1962).
[2] T. ROBINSON, In preparation.
[3] E. SPÄTH and G. KOLLER, *Ber.* **56**, 880 (1923).
[4] H. L. BRADLOW and C. A. VANDERWERF, *J. Org. Chem.* **16**, 73 (1951).
[5] J. W. PATTON, Ph.D. thesis, University of Wisconsin (1961).
[6] T. WIELAND, C. FEST and G. PFLEIDERER, *Ann.* **642**, 163 (1961).
[7] M. E. PULLMAN and S. P. COLOWICK, *J. Biol. Chem.* **206**, 121 (1954).

pure with a single recrystallization. This contrasts with the results of Bradlow and Vanderwerf[4] who found no trace of (I). Since ricinidine is only slightly soluble in water, in their procedure it was probably precipitated along with the potassium ferricyanide and was discarded before the reaction mixture was worked up. The ricinidine we obtained was identified by hydrolyzing it to 1-methyl-3-carboxamido-2-pyridone by the method of Galat.[8] The compound so obtained was identical to an authentic sample prepared by the method of Pullman and Colowick.[7] If the alkaline ferricyanide reaction mixture was made neutral, extracted with isobutyl alcohol, and the alcohol extract chromatographed on paper, six constituents were shown to be present by observation in u.v. light (Table 1); one of these (R_f 0·63) corresponded to ricinidine (I). Because of the complexity of this mixture, the method was abandoned as a means for unequivocal synthesis of the other two pyridones although, as will be shown below, both were present.

TABLE 1. PAPER CHROMATOGRAPHY OF PRODUCTS FROM ALKALINE FERRICYANIDE OXIDATION OF NICOTINONITRILE METHIODIDE

	Fluorescence under u.v. light†	
R_f value*	366 mμ	254 mμ
Origin	††	††
0·28	†	--
0·63	††	††
0·80	0	–
0·85	††	††
0·88	††	0

* Solvent was toluene:iso-propyl alcohol:acetic acid:water (10:5:1:1).

† Slight fluorescence, †; fluorescence, ††; not visible, 0; quench, –.

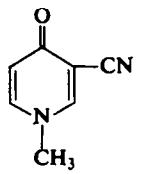
Preparation of compound (II) was carried out by the method of Patton.[5] Further identification was made by saponification to the acid by the method of Bradlow and Vanderwerf.[4] Compound (II) so prepared was found to correspond on paper chromatograms to the R_f 0·80 spot found in the ferricyanide oxidation mixture (Table 1).

An attempt was made to prepare the 4-pyridone (III) by dehydration of the corresponding amide (obtained from Prof. Theodor Wieland), with acetic anhydride. A product was isolated in good yield and found to be neither unchanged starting material nor (III). The u.v. spectrum was almost identical to that of the starting material, and it seems likely that the product represented acetylation rather than dehydration of the amide; it was not characterized further.

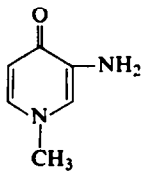
A successful synthesis of (III), from 4-hydroxypyridine via the 3-nitro-derivative and its corresponding methiodide and reduction to (IV), was achieved using previously published procedures.[9,10] The final step to (III) was accomplished using the Sandmeyer reaction in neutral solution (the reaction was unsuccessful in acidic solution). The identity of (III) was

[8] A. GALAT, *J. Am. Chem. Soc.* **70**, 3945 (1948).
[9] S. KRUGER and F. G. MANN, *J. Chem. Soc.* 2755 (1955).
[10] Y. AHMAD and D. H. HEY, *J. Chem. Soc.* 4516 (1954).

established by converting it to the corresponding amide in quantitative yield. Comparison with an authentic sample (mixed melting point, i.r. spectra) established the structure of this amide, and therefore of (III). When chromatographed on paper, synthetic (III) gave a spot coinciding with the R_f 0·28 spot of the ferricyanide reaction mixture (Table 1).



(III)



(IV)

Details of the enzymatic oxidation reaction and comparison of enzymatic and synthetic products will be published elsewhere. Two products of enzymatic oxidation of nicotinonitrile methiodide are the 4- and 6-pyridones [(II) and (III)]. Enzymatic oxidation is therefore more selective than chemical oxidation since no ricinidine (I) is formed.

EXPERIMENTAL

Elemental analyses were performed by the Schwarzkopf Microanalytical Laboratory. Ultraviolet spectra were taken with the Cary 14 spectrophotometer and infrared spectra with the Beckman IR-5.

Preparation of Ricinidine (I)

To a solution of 450 mg of nicotinonitrile methiodide in 10 ml of water was added a solution of 2 g potassium ferricyanide dissolved in 10 ml of N sodium hydroxide. The reaction mixture was kept at room temperature for 30 min and then extracted ten times with 10-ml portions of chloroform. The solvent was distilled from this extract and the residue crystallized from iso-propyl alcohol after treatment with charcoal. The product consisted of 77 mg white needles, m.p. 145–146° (lit. 140°). The i.r. spectrum showed absorption at 2200 (C≡N) and 1650 cm^{-1} (C=O). In the u.v. spectrum maxima in water were at 234 mμ (log ε, 3·74) and 327 mμ (log ε, 3·97). (Found: C, 62·69; H, 4·39; N, 21·15. Calc. for $C_7H_6N_2O$: C, 62·6; H, 4·5; N, 20·9%.)

Conversion of Ricinidine to 1-Methyl-3-carboxamido-2-pyridone (IV)

The procedure was scaled down from that described by Galat[10] using 44 mg ricinidine, 1 g Amberlite IRA-400 resin-OH, and 2·5 ml water. It was also found necessary to reflux for 2 hr rather than 1. The product was obtained in quantitative yield and crystallized from 95% ethanol, m.p. 219–220° (lit. 218–221°). Mixed melting point with an authentic sample[7] of amide showed no depression. The u.v. absorption spectrum was also identical to that of authentic amide.

Other Products of Alkaline Ferricyanide Oxidation

The alkaline ferricyanide reaction mixture as described above instead of being extracted with chloroform was made just neutral with hydrochloric acid, saturated with solid sodium chloride and extracted with five portions of isobutyl alcohol. The combined extracts were heated on the steam bath, treated with charcoal and concentrated *in vacuo* to about one-

tenth the starting volume. On cooling this solution crystals separated out and were found to be almost pure ricinidine (I). The supernatant solution was spotted on paper for chromatography. Chromatograms were developed by the ascending method in toluene:iso-propyl alcohol:acetic acid:water (10:5:1:1). After development and drying of the paper, spots were detected by examination in u.v. light. Six components were found (Table 1).

Preparation of 1-*Methyl-5-cyano-2-pyridone* (II)

The procedure used was essentially that described in a thesis by Patton,[5] but the product was purified by chromatography on alumina rather than Florisil. The product was obtained as colorless crystals melting at 160–161° (lit. 157–159°) and gave an i.r. spectrum similar to that recorded by Patton.[5] The u.v. spectrum in water showed the same maxima reported by Patton but somewhat different values for ϵ (253 mμ, logϵ = 4·23 and 297 mμ, logϵ = 3·69). Since our crystals were colorless rather than the yellow reported by Patton, and because of our slightly higher melting point, his preparation may have been contaminated by an impurity absorbing strongly in the same region of the u.v. spectrum as the desired product. (Found: C, 62·72; H, 4·55; N, 21·05. Calc. for $C_7H_6N_2O$: C, 62·6; H, 4·5; N, 20·9%).

Saponification of 1-*Methyl-5-cyano-2-pyridone*

The same procedure was used as described previously.[4] The product melted at 240–241·5° (lit. for 1-methyl-2-pyridone-5-carboxylic acid 239·5–240·8°). The i.r. spectrum was consistent with that of the expected product.

Attempted Conversion of 1-*methyl-3-carboxamido-4-pyridone to the Corresponding Nitrile*

The amide (13·6 mg) was refluxed with acetic anhydride (1 ml) for 4·5 hr and residual acetic anhydride removed by distillation under reduced pressure. The residue was dissolved in hot absolute ethanol, treated with charcoal, and the solution on cooling deposited white crystals, m.p. 218–220°. The i.r. spectrum of these crystals showed no nitrile bands.

Synthesis of 1-*Methyl*-3-*cyano*-4-*pyridone* (III)

Commercial 4-hydroxypyridine (Aldrich Chemical Co.) was converted to (IV) by published procedures.[9,10] To a solution of 1·25 g of crude (IV) in 15 ml 2 N HCl was added 20% sodium nitrite solution until excess nitrous acid was detected with starch–iodide paper. During the addition the reaction mixture was kept at 0°. The solution was allowed to stand in an ice–salt bath 1 hr and filtered. The filtered solution was neutralized with potassium carbonate and added to a solution of 2·4 g cuprous cyanide and 3·4 g potassium cyanide at 30°. The mixture was heated gradually on the steam bath until gas evolution ceased. The deep red solution was washed with two 20-ml portions of ethyl ether, evaporated to dryness and the residue extracted with acetone. The acetone extract was mixed 6:1 with petroleum ether and passed through an alumina column, washing the column with additional acetone–petroleum ether solvent. Paper chromatography of fractions from the column indicated the presence of only one substance, so the combined effluents were evaporated to dryness yielding 0·55 g of product, m.p. 173–179°. The crude product was redissolved in acetone, treated with charcoal and recrystallized to yield a colorless product melting at 179–181°. The i.r. spectrum showed bands at 2230 (C≡N) and 1650 cm^{-1} (C=O). The u.v. spectrum in water gave maxima at 256 mμ (logϵ, 4·12) and 282 mμ (shoulder; log ϵ, 3·69). (Found: C, 62·81; H, 4·53; N, 21·0. Calc. for $C_7H_6N_2O$: C, 62·6; H, 4·5; N, 20·9%).

Conversion of 1-*Methyl*-3-*cyano*-4-*pyridone* (III) *to the Corresponding Amide*

The procedure was as described above for saponification of ricinidine using 14 mg (III), 2 g resin, 2 ml water. Yield of product was quantitative. It did not depress the melting point (179–181°) of an authentic sample, and the two i.r. spectra were identical. (179–181° is the correct m.p. both for (III) and the amide which therefore cannot be distinguished by melting point alone.)

Note added in proof. Recently Mukherjee and Chatterjee[11] have synthesized 1-methyl-5-cyano-2-pyridone by a different procedure from ours and have shown it to be identical with the alkaloid nudiflorine of *Trewia nudiflora*.

Acknowledgement—We wish to express our thanks to Professor Theodor Wieland for providing a sample of 1-methyl-3-carboxamido-4-pyridone.

[11] R. MUKHERJEE and A. CHATTERJEE, *Chem. & Ind. (London)* 1524 (1964).