5-hydroxymethylpyridine (pyridoxamine) and 2-methyl-3-hydroxy-4-formyl-5-hydroxymethylpyridine (pyridoxal) have been synthesized, and their structures have been proved. These two compounds greatly exceed pyridoxine in growth promoting power for *L. casei* and *S. lactis R.*[5,8] Direct oxidation of pyridoxine yielded, in addition to pyridoxal, the lactone of 2-methyl-3-hydroxy-4-carboxy-5-hydroxymethylpyridine.

Two other closely related compounds, 2-methyl-3-hydroxy-4-hydroxymethyl-5-aminomethylpyridine and 2-methyl-3-hydroxy-4-hydroxymethyl-5-formylpyridine, have been synthesized and found to be inactive toward lactic acid bacteria.

The two amines were converted by nitrous acid to pyridoxine. The two aldehydes were catalytically hydrogenated to yield pyridoxine.

Rahway, New Jersey Received September 30, 1944

[Contribution from the Baker Laboratory of Chemistry at Cornell University]

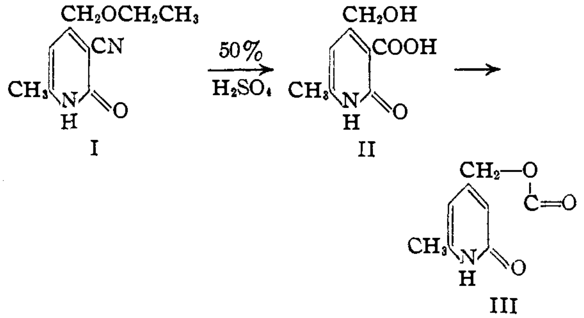
Pyridine Derivatives. I. 3-Cyano-4-ethoxymethyl-6-methyl-2-pyridone and Some Related Transformation Products

By William F. Bruce and Harry W. Coover, Jr.

The importance of certain pyridine derivatives in biologically active systems has directed our attention to the synthesis and chemical behavior of some substances containing the pyridine nucleus. Because of our interest in the lactone of 2-methyl-3-hydroxy-4-hydroxymethyl-5-carboxypyridine, as a chick antianemia factor,[1] we have studied the synthesis of this substance reported by Harris, Stiller and Folkers.[2] From this study, certain improvements in the synthesis of the starting materials, some new reactions of the intermediates, involving the behavior of the lactone ring, and a desirable variation in the synthesis have been developed.

The ethoxyacetylacetone required for the ring closure was prepared by Sommelet[3] from ethyl ethoxyacetate and acetone in 42% yield. By a variation of the conditions of reaction and method of isolation, the yield has been increased to 62%. The ethyl ethoxyacetate required for this condensation has been made by the esterification of ethoxyacetic acid in the presence of hydrogen chloride,[4] in 69–72% yield. By using a suitable amount of benzene and sulfuric acid, we have secured a yield of 88–90%.

Hydrolysis of the 3-cyano-4-ethoxymethyl-6-methyl-2-pyridone (I) secured by the method of Harris, Stiller and Folkers gave a product which melted above 320°, in agreement with their description. The initial product, however, was more soluble in water than that which resulted after crystallization from alcohol. The decomposition points, determined by the method of approaching a limit,[5] were 340 and 360°, respectively. Upon analysis, the substance of lower decomposition point had the composition of the hydroxy acid (II), the other product being the lactone (III).



Treatment of this lactone with ammonia gave a product with the same decomposition point as the lactone, but analysis showed that the product had added a molecule of ammonia. By reaction with ammonia, three other lactones also added one molecule of ammonia. In each case, the change could not be demonstrated by the decomposition point, since loss of ammonia occurred on heating, and the decomposition point observed even in a sealed tube, was that of the starting material. Analysis showed the real nature of the product. Upon reaction with phosphorus pentachloride, the lactone III was readily converted to the α-chloro derivative (IV) and by treatment with bromine to a β-bromo derivative (V). Attempts to reduce the lactone by sodium and alcohol gave only oily products.

The nitration of the α-chloropyridine derivative (IV) gave an 80% yield of the known chloronitrolactone. In our hands, the nitration of the chlorolactone gave consistently better yields than the reverse procedure. This variation, therefore, appears more desirable than the reported procedure for the preparation of the hydroxy lactone.

Reduction of the initial condensation product, I, gave 3-aminomethyl-4-ethoxymethyl-6-methyl-2-pyridone (VI) characterized as the picrate, acetyl and phenylisothiocyanate derivatives. The β-bromo and 4-bromomethyl derivatives of VI were also prepared. By nitration and reduction, I was converted to a diamine.

For comparison with some of the ethoxy de-

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[1] Scott, Norris, Heuser, Bruce, Coover, Bellamy and Gunsalus, *J. Biol. Chem.*, **154**, 713 (1944).

[2] Harris, Stiller and Folkers, This Journal, **61**, 1242 (1939).

[3] Sommelet, *Bull. soc. chim.*, [4] **1**, 382 (1907).

[4] Fuson and Wojcik, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons Co., Inc., New York, N. Y., 1943, p. 260.

[5] Bruce, *ibid.*, p. 14.

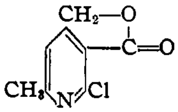
TABLE I

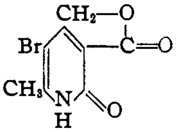
PROPERTIES OF SOME 3-CARBOXAMIDO-4-HYDROXYMETHYL-2-PYRIDONES AND -PYRIDINES

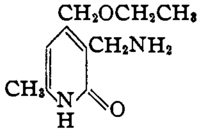
VII 3-carboxy-4-hydroxymethyl-5-nitro-6-methyl-2-pyridone lactone.[2] VIII 3-carboxy-4-hydroxymethyl-5-amino-6-methylpyridine lactone.[2]

Substance	Yield, %	M. p., °C. dec.	M. p. lactone, °C., dec.	Analyses, % Calcd. C	Analyses, % Calcd. H	Analyses, % Found C	Analyses, % Found H
$C_8H_{10}N_2O_3$ (II)	85	350	360	52.74	5.33	53.01	5.62
$C_8H_9N_3O_5$ (VII)	88	280	280	42.29	3.99	42.50	4.10
$C_8H_{10}ClN_3O_2$ (IV)	..	179	179	44.55	4.67	44.41	4.51
$C_8H_{11}N_3O_2$ (VIII)	67	219-220	225-226	53.03	6.12	52.90	6.23

rivatives above described, a condensation with methoxyacetylacetone was undertaken, and the hydrolysis, nitration, chlorination and reduction of the product were studied. Although Morii and Makino[6] have reported some of these compounds, practically no experimental details are given, and such physical constants as are reported do not agree with those we have found.


IV


V


VI

Experimental

Ethyl Ethoxyacetate.—In a 1-liter round-bottom flask was put 125 g. of ethoxyacetic acid, 230 ml. of absolute alcohol, 250 ml. of benzene and 10 ml. of concentrated sulfuric acid. The flask was provided with a reflux condenser and after refluxing for an hour, the condenser was arranged for distillation and 200 ml. of distillate collected. After cooling, the acid was neutralized by cautious addition of saturated sodium carbonate solution. The product was extracted by ether, and on distillation the fraction boiling from 153–154° amounted to 143 g., a yield of 90%.

Ethoxyacetylacetone.—In a 2-liter three-necked flask with a stirrer and dropping funnel were placed 25 g. of sodium wire and 300 ml. of dry xylene. The liquid was cooled to −5 to −7° and 120 g. of ethyl ethoxyacetate was added with stirring. Then 60 g. of anhydrous acetone (distilled over phosphorus pentoxide) was added slowly over a period of three hours with stirring, which was continued for two hours more. The mixture became viscous and reddish-brown. After twelve hours at room temperature, 300 ml. of ether was added to the mixture and the sodium salt which precipitated was collected on a funnel. After solution in 200 ml. of 20% sulfuric acid, extraction with 400 ml. of ether and drying over magnesium sulfate, the sodium salt yielded 88 g. of product boiling from 83–84° at 13 mm., a yield of 62%.

Hydrolysis of 3-Cyano-4-ethoxymethyl-6-methyl-2-pyridone.—A solution of 93 g. of the cyanopyridone (2) in 1120 ml. of 50% sulfuric acid was refluxed for three hours and then poured into 3.5 liters of water. After standing overnight in the icebox, the large faintly yellow needles which formed were washed with water, alcohol and ether. After drying for three hours at 55–60°, the substance melted at 340° with decomposition.

Anal. Calcd. for $C_8H_9NO_4$: C, 52.45; H, 4.95. Found: C, 52.18; H, 4.73.

On crystallization from alcohol, fine matted needles of the anhydrous form appeared, melting at 360° with decomposition.

Chlorination of 3-Carboxy-4-hydroxymethyl-6-methyl-2-pyridone Lactone.—To a suspension of 3.3 g. of the pyridone in 20 ml. of pure phosphorus oxychloride was added 6 g. of phosphorus pentachloride, and the mixture was refluxed for thirty minutes. The phosphorus oxychloride was removed under vacuum, and the residue was extracted with three 10-ml. portions of benzene. The product crystallized on cooling and on concentration of the mother liquor in a yield of 3 g. (80%), melting at 129–130°.

Anal. Calcd. for $C_8H_6ClNO_2$: C, 52.3; H, 3.29. Found: C, 52.37; H, 3.33.

Ammonolysis of the Pyridone Lactones.—A solution of 2 g. of a pyridone lactone in 20 ml. of hot water was saturated with ammonia while cooling to room temperature. After standing overnight, the solution was evaporated to dryness *in vacuo* and the product was crystallized from water or 50% alcohol. The results for the following lactones are presented in Table I.

Nitration of 2-Chloro-3-carboxy-4-hydroxymethyl-5-amino-6-methylpyridine Lactone.—Nine and two-tenths g. (0.05 mole) of the lactone of 2-chloro-3-carboxy-4-hydroxymethyl-6-methylpyridine was dissolved in 20 ml. of concentrated sulfuric acid. This solution was added slowly to an ice-cold solution of 40 ml. of concentrated sulfuric acid and 17 ml. of fuming nitric acid (sp. gr. 1.5). The mixture warmed spontaneously to a temperature of 35°. The solution was then cooled to 15° and at once poured on crushed ice. The final volume was 300 ml. A yellow solid formed at once, and was filtered and dried without delay. The yield was 9.1 g. (80%). After recrystallization from benzene, the substance melted at 178–179°. On treatment of this substance with alkali, a red color appeared.

Reduction of 3-Cyano-4-ethoxymethyl-6-methyl-2-pyridone (I).—In a 200-ml. round-bottom flask containing 50 ml. of absolute alcohol and 0.2 g. of Raney nickel was put 6.9 g. (0.05 mole) of 3-cyano-4-ethoxymethyl-6-methyl-2-pyridone (I). Hydrogen was passed into the flask with shaking. In a period of three hours, 0.1 mole of hydrogen was absorbed. After filtering the catalyst and concentrating the solution to 30 ml., the product (VI) crystallized on cooling. After recrystallization from alcohol, the substance melted at 193–194°; yield, 9.6 g. (85%).

Anal. Calcd. for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22. Found: C, 60.93; H, 7.99.

The picrate, formed by adding benzene solutions of the aminopyridone and picric acid, is a light yellow fluffy crystalline solid, soluble in alcohol and melting at 178–179°.

Anal. Calcd. for $C_{16}H_{19}N_5O_9$: C, 45.18; H, 4.50. Found: C, 45.00; H, 4.20.

The phenyl isothiocyanate derivative, formed by adding the aminopyridone to excess phenyl isothiocyanate and concentrating *in vacuo*, was recrystallized from alcohol. It gave white fluffy crystals melting at 171–172°.

Anal. Calcd. for $C_{17}H_{21}N_3O_2S$: C, 61.60; H, 6.39. Found: C, 61.31; H, 6.08.

The acetyl derivative, formed by adding the aminopyridone to acetic anhydride, was recrystallized from alcohol. It appeared microcrystalline, melting at 270–271°.

Anal. Calcd. for $C_{12}H_{18}N_2O_3$: C, 60.48; H, 7.61. Found: C, 60.40; H, 7.51.

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(6) Morii and Makino, *Enzymologia*, 7, 385–386 (1939).

Bromination of 3-Aminomethyl-4-ethoxymethyl-6-methyl-2-pyridone.—To a solution of 2.3 g. (0.01 mole) of 3-aminomethyl-4-ethoxymethyl-6-methyl-2-pyridone in 10 ml. of glacial acetic acid was added a slight excess of bromine. The solution was added to 25 ml. of cold water and 5 ml. of concentrated ammonium hydroxide. The bromo compound was collected on a filter and recrystallized from alcohol. The product appeared microcrystalline and melted at 223°. The yield was 2.4 g. or 80%.

Anal. Calcd. for $C_{10}H_{15}BrN_2O_2$: C, 43.64; H, 5.49. Found: C, 44.85; H, 5.07.

Bromination of 3-Carboxy-4-hydroxymethyl-6-methyl-2-pyridone Lactone (I).—A solution of 1.7 g. (0.01 mole) of the lactone in 20 ml. of glacial acetic acid was heated to 70°, and a slight excess of bromine was added. The solution was poured into 30 ml. of cold water and decolorized by ammonium hydroxide. The product was collected on a filter and recrystallized from 50% alcohol. The substance appeared as nearly white microcrystalline needles melting with decomposition at 315°; the yield was 2.1 g. or 84%.

Anal. Calcd. for $C_8H_6BrNO_3$: C, 39.37; H, 2.48. Found: C, 39.52; H, 2.71.

Methoxyacetylacetone.—The ester required for the preparation of this diketone was prepared in 70% yield by the esterification of methoxyacetic acid by alcohol and sulfuric acid. The observed boiling point at 740 mm. was 142°, d^{20} 1.0073, $n^{20}\text{D}$ 1.4050. To a 1-liter three-necked flask containing 300 ml. of dry xylene and 25 g. of sodium wire, cooled to −5°, was added with stirring 106 g. (1 mole) of ethyl methoxyacetate. Then over a three-hour period 58 g. (1 mole) of anhydrous acetone was added with thorough stirring. The mixture became brown and viscous. After twelve hours at room temperature, 300 ml. of ether was added to precipitate the sodium salt of methoxyacetylacetone. After collection on a filter and washing with ether, the sodium salt was dissolved in 200 ml. of 20% sulfuric acid and the product was extracted with 400 ml. of ether. On distillation at 13 mm., the product, boiling from 80–82°, was obtained in a 40% yield (52 g.).

Anal. Calcd. for $C_6H_{10}O_3$: C, 55.37; H, 7.75. Found: C, 55.16; H, 7.82.

3-Cyano-4-methoxymethyl-6-methyl-2-pyridone.—To 4.3 g. (0.05 mole) of cyanoacetamide in 25 ml. of hot alcohol, 6.5 g. (0.01 mole) of methoxyacetylacetone and 2 ml. of piperidine was added slowly with stirring. The solution became warm, and after cooling to room temperature was placed in the icebox for twelve hours. The product, recrystallized from alcohol, was obtained in a yield of 7.6 g. or 85%, and melted at 241–2° (Morii and Makino[6] report 226°).

Anal. Calcd. for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66. Found: C, 60.37; H, 5.51.

Since the condensation could take place in more than one way, proof of the structure of this product was secured by hydrolysis to the known lactone, as in the study of the ethoxy analog.

3-Cyano-4-methoxymethyl-5-nitro-6-methyl-2-pyridone. Five and three-tenths grams (0.03 mole) of 3-cyano-4-methoxymethyl-6-methyl-2-pyridone was added to 20 ml. of acetic anhydride which had been cooled in an ice-bath, the mixture being treated with a cold solution of 2 ml. of acetic anhydride and 2.4 ml. of fuming nitric acid. The solid gradually dissolved as the mixture evolved heat. When the temperature had increased to 40–45°, but not 50°, the solution was cooled to 25° and allowed to stand. When it was poured on ice, a solid formed which on crystallization from alcohol amounted to 5 g. or 75%, melting at 212°.

Anal. Calcd. for $C_9H_9N_3O_4$: C, 48.43; H, 4.06. Found: C, 48.21; H, 4.23.

2-Chloro-3-cyano-4-methoxymethyl-5-nitro-6-methylpyridine.—A suspension of 2.2 g. (0.01 mole) of 3-cyano-4-methoxymethyl-5-nitro-6-methyl-2-pyridone in 20 ml. of reagent grade phosphorus oxychloride was treated with 3.1 g. of phosphorus pentachloride. After refluxing for three hours, the solvent was removed in a vacuum. The oily residue was dissolved in 10 ml. of hot benzene and, after the container was cooled and scratched, finally crystallized. The total yield amounted to 0.79 g. or 30%, melting at 71–73°.

Anal. Calcd. for $C_9H_8ClN_3O_3$: C, 44.73; H, 3.34. Found: C, 44.55; H, 3.45.

2-Methyl-3-amino-4-methoxymethyl-5-aminomethylpyridine.—Reduction of 1.2 g. (0.005 mole) of 2-methyl-3-nitro-4-methoxymethyl-5-cyano-6-chloropyridine dissolved in 30 ml. of alcohol, with 0.2 g. of platinum oxide and 3 g. of 5% palladium on charcoal in the presence of hydrogen, gave 0.5 g. (45%) of 2-methyl-3-amino-4-methoxymethyl-5-aminomethylpyridine hydrochloride, melting at 149°.

Anal. Calcd. for $C_9H_{16}ClN_3O$: C, 49.65; H, 7.41. Found: C, 49.36; H, 7.62.

Summary

The preparation of 3-carboxy-4-hydroxymethyl-6-methyl-2-pyridone, a highly potent antianemia factor for chicks, has been improved. The lactone ring in this and related pyridine and pyridones can be opened by ammonia, but the hydroxy amides thus formed readily lose ammonia. The substance can also exist in the open hydroxy acid form. β-Bromination, α-chlorination, and nitration of this lactone give good yields. The lactone ring is resistant to reduction. The preparation of the lactone by way of the methoxy, rather than the ethoxy diketone gives somewhat better yields on ring closure and α-chlorination and a much better yield on nitration than the corresponding ethoxy series.

Philadelphia, Pa. Received September 11, 1944