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Pyridine Derivatives. II. Some 6-Methyl-4-hydroxy-2-pyridones and their Derivatives[1,2]

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In a study of pyridine derivatives related to pyridoxin, it appeared interesting to prepare and examine some theoretically possible oxidation products. "Pseudo-pyridoxin" appears to be a mixture of such oxidation products. Its activity by some tests is so much greater than that of pyridoxine that the hypothesis may be entertained that certain of these oxidation products are the real active material. The work of Snell[5] and others with pyridoxal elucidates and substantiates this hypothesis. Whether conceivable oxidation products of pyridoxin other than pyridoxal have activity is a question requiring further study. The anti-anemic activity ascribed by one group[6] to two related acids, presumably derivable by oxidation of pyridoxine has not been verified by another.[7]

Among other approaches to the synthesis of pyridine derivatives which appeared interesting for this problem, we made use of ethyl 6-methyl-4-hydroxy-2-pyridone-3-carboxylate, described by Knoevenagel,[8] and carried out the transformations shown in the accompanying flow sheet. In preparing I we were unable to approach the yields reported by Knoevenagel and found it desirable to use sodium *n*-amylate as the condensing agent, which gave the *n*-amyl ester II in reproducible if moderate yield. The use of *n*-amyl alcohol as the solvent improved the yield by more than twice the most favorable yield obtained by using sodium ethylate in a sealed tube.

The conversions shown in the flow sheet were for the most part accomplished in good yield. A few of the steps call for some comment. The melting point of *n*-amyl 6-methyl-5-amino-4-hydroxy-2-pyridone-3-carboxylate (XII), was determined to be 154° by the procedure of approaching an instantaneous decomposition point.[9] When the usual procedure beginning at room temperature was employed, a much higher decomposition point, 360°, was observed. When repeated on a larger scale, the odor of amyl alcohol was clearly evident. We, therefore, assign to product XV the polyamide structure shown and name it pyriplastin. It is a horny material insoluble in water and the common organic solvents. It is slowly soluble in hot concentrated sulfuric acid and in hot aqueous ammonia. Another example of polymerization to plastic material at the melting point which appears in this series is the amide VI, which melts with decomposition at 307–309° when inserted in the block at 305° but, if heating is begun at 295°, the substance decomposes without melting at a higher temperature.

The use of hydriodic acid as a means for reducing the nitro group in pyridines to give aminopyridines offers a very expeditious method of accomplishing such conversions. The time of re-

(1) First paper, Bruce and Coover, THIS JOURNAL, **66**, 2092 (1944).

(2) In part from a dissertation by Luiz A. Perez-Medina submitted to the faculty of the graduate school of Cornell University in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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(5) Snell, *Proc. Soc. Expil. Biol. Med.*, **51**, 324 (1942); THIS JOURNAL, **66**, 2082 (1944); **67**, 194 (1945); *J. Biol. Chem.*, **154**, 313 (1944); **157**, 491 (1945); Bellamy, Umbreit and Gunsalus, **160**, 461 (1945); Gunsalus and Bellamy, *ibid.*, **155**, 557 (1944).

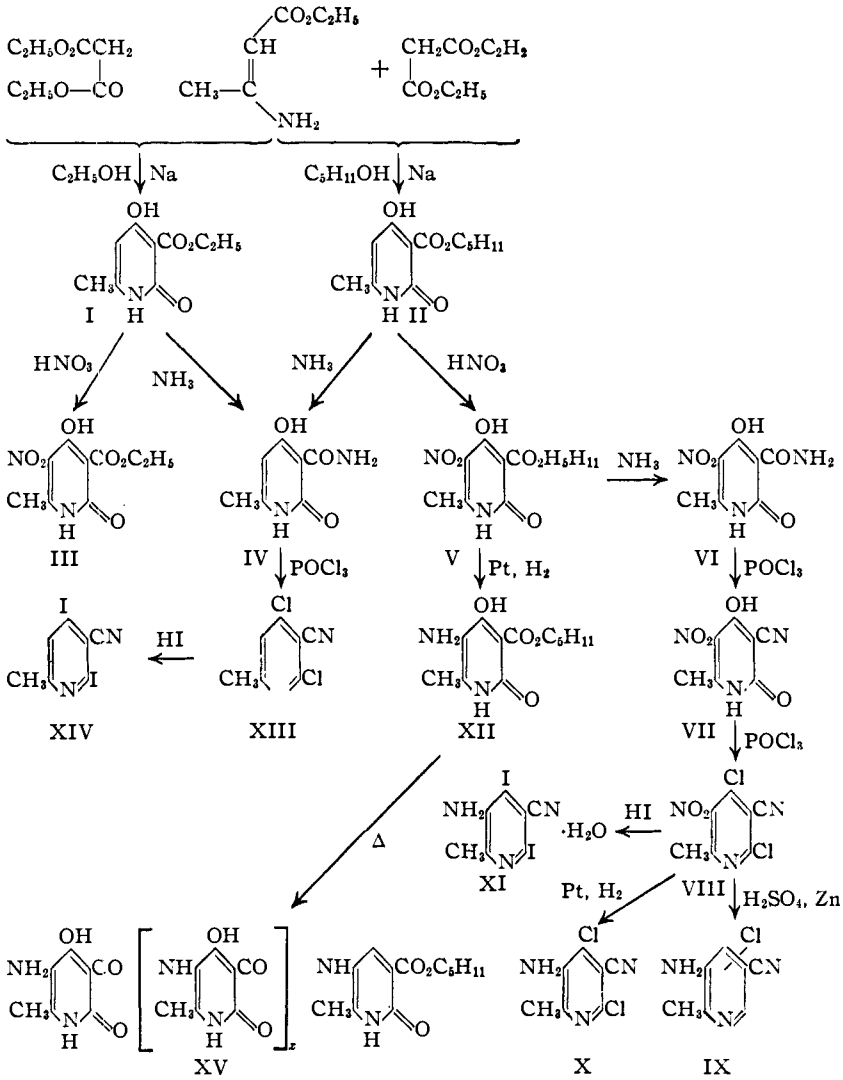
(6) Scott, Norris, Heuser and Bruce, *ibid.*, **158**, 291 (1945); Daniel, Scott, Norris and Heuser, *ibid.*, **160**, 265 (1945).

(7) Campbell, Brown, Bird and Emmett, *J. Nutrition*, **32**, 423 (1946).

(8) Knoevenagel and Fries, *Ber.*, **31**, 767 (1898)

(9) W. F. Bruce, "Organic Syntheses," Coll. Vol. II, John Wiley and Co., Inc., New York, N. Y., 1943, p. 14

FLOW SHEET



action is short and the yields are generally good. Dilution with water after most of the excess hydriodic acid has been boiled off has sufficed to give the free aminopyridine. The conversion of VIII to XI exemplifies this reaction, as well as the replacement of chlorine by iodine. Since compounds of this type are useful in X-ray work, other examples are found in the experimental part and will be offered in a subsequent paper.

The reduction by zinc and sulfuric acid of the dichloropyridine VIII to the monochloropyridine IX gave a product for which a definitive structure could not be written without further study. Reduction by hydrogen and platinum gave the dichloroamine. Attempts to replace the halogen in these compounds by groups which might lead to products related more closely to pyridoxin were without success. Upon heating with cuprous cyanide in pyridine, compounds XIII, VIII and X gave either unchanged material or at higher temperatures a black tarry material from which no discrete product was isolated.

Experimental

***n*-Amyl and Ethyl 6-Methyl-4-hydroxy-2-pyridone-3-carboxylate** (I and II).—A solution of 0.7 g. of sodium in 10 g. of absolute alcohol with 4.3 g. of aminocrotonic ester and 5.3 g. of diethyl malonate was heated on the steam-bath for seventeen hours. The yield of pure ethyl ester (I) was 860 mg., 13.1%. In a sealed tube, a solution of 2.1 g. of sodium in 27 g. of absolute alcohol with 12 g. of aminocrotonic ester and 15 g. of diethyl malonate was heated at 140–150° for five hours followed by distillation of 30 g. of solvent. The yield of I was 3.1 g. or 17%.

The amyl ester (II) was made by refluxing a solution of 1.4 g. of sodium in 25 cc. of *n*-amyl alcohol with 8 g. of aminocrotonic ester and 10 g. of diethyl malonate for four hours. The semi-solid jelly-like residue was dissolved in 120 cc. of water and extracted with two 50-cc. portions of ether. When the aqueous layer was slightly acidified the amyl ester precipitated. Upon crystallization from alcohol it melted at 146–147°; yield, 6.4 g. (43%).

Anal. Calcd. for $C_{12}H_{17}NO_4$: C, 60.34; H, 7.16; N, 5.86. Found[10]: C, 60.01; H, 7.06; N, 6.09.

In order to prove the structure of the amyl ester, a hot concentrated solution in alcohol was treated with excess aqueous ammonia, boiled for several minutes to remove excess ammonia and cooled to give 6-methyl-4-hydroxy-3-carboxamido-2-pyridone identical with the compound (IV) reported by Späth[11] and made for comparison from the ethyl ester (I).

***n*-Amyl 6-Methyl-5-nitro-4-hydroxy-2-pyridone-3-carboxylate** (V).—An ice-cold solution of 30 g. of the amyl ester (II) in 60 cc. of concentrated sulfuric acid was treated with 15 cc. of fuming nitric acid (d. 1.5). In twenty minutes the temperature rose to 50°, and was held between 40 and 50° by cooling with water until the reaction was over. The solution was poured on 600 g. of crushed ice. The product (V) was collected on a filter, washed with water and dried. The yield was 32 g. (90%). After crystallization from 80% methanol, the melting point was 201–202°. The compound was insoluble in water, soluble in methanol, ethanol, *n*-propanol and acetone. It gave a red color with ferric chloride.

Anal. Calcd. for $C_{12}H_{16}N_2O_6$: C, 50.69; H, 5.68; N, 9.86. Found[10]: C, 50.93; H, 5.70; N, 9.57.

When 500 mg. of this ester was boiled with 10 cc. of 56% hydriodic acid and the solution concentrated, a crystalline product resulted melting with decomposition

(10) Analysis by Dr. C. Tiedcke.

(11) Späth and Koller, *Ber.*, **58**, 2124 (1925).

at 260°. It was readily soluble in water, absolute alcohol, acetone and pyridine; insoluble in acetic acid, ethyl acetate, benzene and chloroform. The aqueous solution gave a red color with ferric chloride and on treatment with barium carbonate precipitated a white solid which gave a negative Beilstein test and decomposed above 350°. By analysis the original precipitate appears to be the dihydriodic acid salt of 6-methyl-5-amino-4-hydroxy-3-carboxy-2-pyridone. Further work with the iodine-free base is desirable to establish the structure of this substance, since stable salts of pyridones are unusual.

Anal. Calcd. for $C_7H_{10}I_2N_2O_4$: C, 19.10; H, 2.28. Found[12]: C, 18.63; H, 2.69.

6-Methyl-5-nitro-4-hydroxy-3-carboxamido-2-pyridone (VI).—A suspension of 9 g. of the nitro ester (V) in 50 cc. of alcoholic ammonia containing 0.14 g. of ammonia per gram of solution was heated under pressure in a steam-bath for twelve hours. After filtration, washing with alcohol and drying, 6.5 g. (96.5%) of product was secured. It was crystallized from hot water to which a few drops of ammonium hydroxide solution was added. Filtration of the hot solution into a large volume of water containing enough acetic acid to neutralize the ammonium hydroxide gave the amide, which crystallized in white needles melting with decomposition at 307–309° provided heating began at 305°. When heating was begun at 295°, the substance decomposed much higher without melting.

Anal. Calcd. for $C_7H_7N_3O_5$: C, 39.42; H, 3.31. Found[12]: C, 40.18; H, 3.38.

6-Methyl-5-nitro-4-hydroxy-3-cyano-2-pyridone (VII).—A suspension of 4 g. of 6-methyl-5-nitro-4-hydroxy-3-carboxamido-2-pyridone in 40 cc. of phosphorus oxychloride was heated on the steam-bath under pressure until solution took place, or about fifty minutes. The pink solution which resulted was cooled in ice and gave a precipitate. Recrystallization of this precipitate from methanol gave a white substance melting with decomposition at 253°.

Anal. Calcd. for $C_7H_5N_3O_4$: C, 43.1; H, 2.56. Found[12]: C, 43.31; H, 2.60.

2-Methyl-3-nitro-4,6-dichloro-5-cyanopyridine (VIII).—By continuing the reaction above described for a period of twenty hours, and removing the solvent *in vacuo*, a brown oil which soon solidified was obtained. Recrystallization of this material from 35 cc. of 50% methanol gave 3.4 g. (78%) of white needles melting at 199–200°. The product was soluble in ethyl acetate, benzene, acetone and alcohol; insoluble in water.

Anal. Calcd. for $C_7H_3Cl_2N_3O_2$: C, 36.21; H, 1.30; N, 18.12; Cl, 30.57. Found[12]: C, 35.00; H, 1.24; N, 17.31; Cl, 31.25.

2-Methyl-3-nitro-4,6-di-iodo-5-cyanopyridine.—By digesting 3.5 g. of the dichloro compound (VIII) with 30 cc. of 56% hydriodic acid somewhat below the boiling point, a heavy yellow precipitate was present within fifteen minutes. After cooling and diluting with an equal volume of 50% methanol 4.3 g. (92.5%) of the di-iodo pyridine resulted. Recrystallization from methanol gave almost white needles melting at 209–211°.

Anal. Calcd. for $C_7H_3I_2N_3O_2$: N, 10.12. Found[12]: N, 9.81.

2-Methyl-3-amino-4,6-di-iodo-5-cyanopyridine Hydrate (XI).—By boiling the suspension of 2.6 g. of the dichloro compound (VIII) in 30 cc. of hydriodic acid, solution occurred and a considerable amount of iodine was liberated, which was removed by adding more hydriodic acid containing hypophosphorus acid as preservative. After concentration and crystallization from 50% methanol, 3.5 g. of pale yellow crystals soluble in water and insoluble in alcohol or acetic acid resulted.

Anal. Calcd. for $C_7H_5I_2N_3 \cdot H_2O$: C, 20.9; H, 1.74. Found[12]: C, 20.97; H, 2.42.

Reduction of 2-Methyl-3-nitro-4,6-dichloro-5-cyanopyridine (VIII) by Zinc and Sulfuric Acid.—A suspension of 1 g. of VIII and 2.5 g. of zinc dust in 5 cc. of methanol was boiled for a few minutes, after which 13 cc. of 2 *N* sulfuric acid was added. The mixture was refluxed for forty minutes when complete solution took place. On cooling a precipitate appeared which was collected on a filter and extracted with hot methanol. On concentration a substance crystallized in yellow scales melting at 226°. Upon recrystallization from methanol, the substance (IX) melted at 227°.

Anal. Calcd. for $C_7H_6ClN_3$: Cl, 21.19. Found[12]: Cl, 21.30.

Reduction of 2-Methyl-3-nitro-4,6-dichloro-5-cyanopyridine (VIII) by Hydrogen and Platinum.—A solution of 1.6 g. of 2-methyl-3-nitro-4,6-dichloro-5-cyanopyridine (VIII) in 70 cc. of 95% alcohol with 0.2 g. of platinum oxide[13] was shaken with hydrogen at about 2 atm. until no more absorption occurred, or about three quarters of an hour. The solution was filtered with charcoal, and the filtrate concentrated to a small volume. After standing in the refrigerator overnight, this solution deposited crystals which were recrystallized from 50% methanol to give 2-methyl-3-amino-4,6-dichloro-5-cyanopyridine (X), white needles melting at 179–180°, insoluble in water, soluble in alcohol, acetone, ethyl acetate, ether and acetic acid.

Anal. Calcd. for $C_7H_5Cl_2N_3$: C, 41.6; H, 2.47. Found[12]: C, 41.90; H, 2.63.

Reduction of *n*-Amyl 6-Methyl-5-nitro-4-hydroxy-2-pyridone-3-carboxylate (V) by Hydrogen and Platinum.—A suspension of 2 g. of *n*-amyl 6-methyl-5-nitro-4-hydroxy-2-pyridone-3-carboxylate (V) in 80 cc. of absolute alcohol, with 0.2 g. of platinum oxide catalyst (13), was shaken with hydrogen at 2 atm. The solid gradually dissolved and absorption of hydrogen stopped after one hour. The solution was filtered, concentrated to a small volume and kept in the refrigerator overnight. The white crystals were collected on a filter and washed with ether.

After crystallization from absolute alcohol, the pale yellow needles (XII) melted at 154° by the method of approaching an instantaneous decomposition point.[9] The substance was readily soluble in alcohol, acetic acid, acetone and ethyl acetate; it was very slightly soluble in water and insoluble in ether.

Anal. Calcd. for $C_{12}H_{18}N_2O_4$: C, 56.66; H, 7.14. Found[12]: C, 56.15; H, 6.80.

While the substance gave on heating at 154° a melt which soon solidified, when heating began at 145°, no melting at 154° was observed. Transformation to a product of much higher decomposition point occurred gradually. When done with several grams, the odor of amyl alcohol was clearly apparent. The product (XV) was clear and horny. It decomposed above 360° and was insoluble in water and the common organic solvents. Concentrated sulfuric acid had no effect at room temperature but dissolved the material hot. The same was true of aqueous ammonia. The number of molecules joined in pyriplastin, as we have named this material, has not been studied, but by determination of alkoxyl groups as was done by Pacsu in the similar problem of the polycondensation of glycine esters[14] information concerning the degree of condensation could be obtained.

Proof of Structure of II by Conversion to the Amide (IV).—A hot concentrated alcoholic solution of II was treated dropwise with aqueous ammonia to incipient cloudiness. The solution was boiled to remove excess ammonia and on cooling gave the known amide (IV) decomposing at 280° in agreement with Späth and Koller.[11] Treatment of this amide with phosphorus oxychloride gave 2-methyl-4,6-dichloro-5-cyanopyridine (XIII) melting at 101°.[11] A solution of 500 mg. of this compound in 10 cc. of 56% hydriodic acid was boiled for five minutes, which resulted in the formation of a heavy precipitate. The mixture was cooled and diluted with an equal volume of water. The solid was collected and washed with water

(12) Analysis by J. Rigas.

(13) Bruce, THIS JOURNAL, **58**, 687 (1936).

(14) Pacsu and Wilson, *J. Org. Chem.*, **7**, 117 (1942).

and methanol. The yield was 900 mg. (91%). After two crystallizations from 80% acetic acid the product formed pale yellow needles melting at 211–212°, slightly soluble in water, acetone, and alcohol, soluble in acetic acid and very soluble in pyridine (XIV).

Anal. Calcd. for $C_7H_4I_2N_2$: N, 7.53. Found[10]: N, 7.50.

Nitration of Ethyl 6-Methyl-4-hydroxy-2-pyridone-3-carboxylate (I).—A solution of 2 g. of I in 4 cc. of concentrated sulfuric acid was cooled in ice and treated with 2 cc. of fuming nitric acid (d. 1.5). The temperature of the reaction mixture, which was removed from the ice-bath, slowly rose above room temperature. When it was again at room temperature, the solution was added to 30 g. of ice. The yellow product which precipitated was collected on a filter and washed with water. The ethyl 6-methyl-5-nitro-4-hydroxy-2-pyridone-3-carboxylate (III) weighed 2.1 g. (86%) and melted at 253° with decomposition after recrystallization from alcohol.

Anal. Calcd. for $C_9H_{10}N_2O_6$: C, 44.61; H, 4.16; N, 11.57. Found[10]: C, 44.95; H, 3.94; N, 11.46.

The reduction of this substance and its conversion to a product resembling pyriplastin has not yet been completed.

Summary

A series of pyridones derived from *n*-amyl 6-methyl-4-hydroxy-2-pyridone-3-carboxylate has been prepared. Nitration of the ester and conversion of the nitro derivative to an amide gave a product containing both the amide group and two replaceable hydroxyl groups or their equivalent. Treatment with phosphorus oxychloride affected the amide group first. The intermediate cyano pyridone was isolated and characterized. Further treatment with phosphorus oxychloride replaced the hydroxyls by chlorine. The amine-ester, *n*-amyl 6-methyl-5-amino-4-hydroxy-2-pyridone-3-carboxylate, gave on heating a polycondensation to a polyamide, pyriplastin. Conversion of the dichloro compounds to di-iodo compounds and reduction of the nitro group by hydriodic acid preserved with hypophosphorous acid has been found convenient and rapid. Conversion of the dihalogenated compounds to substances more closely related to pyridoxin has not been successful.

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The Preparation and Reactions of Some Polysubstituted Pyridines. 2-Methyl-3-hydroxy-5-hydroxymethylpyridine (4-Deshydroxymethylpyridoxin)

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The well-known reactivity of 2- and 4-halogen substituents in the pyridine nucleus prompted a study of the replacement of one or both of the halogens of 2-methyl-3-nitro-4,6-dichloro-5-cyanopyridine[3] (VI) and of the corresponding amino compound (IX) by the cyano group. Although attempts to bring about such a replacement using a variety of conditions and reagents were uniformly unsuccessful, the behaviors of these and other halogenated pyridines in certain reactions seem of sufficient interest to report. In connection with this work a related series of tetrasubstituted pyridine derivatives, prepared from the cyanopyridone (I), was developed. The transformations and interrelationships of the various pyridine derivatives that are the subject of this paper are illustrated in the accompanying flow sheet.

The reduction of the nitro group of VI over Adams platinum oxide catalyst or with stannous chloride produced IX, but reduction of this nitro group with zinc and sulfuric acid simultaneously removed the 4-chloro substituent to yield X, which was also obtained from VII. Both IX and X, as would be expected, were converted by hydrogenation over a palladium catalyst to the diamine XIII, which was isolated as the dihydrochloride.

It was not possible to replace any of the halogen substituents of VI, IX or XV by the cyano group using either sodium, cuprous, mercuric or silver cyanide in a variety of solvents and at reaction temperatures of 80–200°. In most cases the halogen compound was recovered unchanged, but when a solution of IX and sodium cyanide in 80% methanol was refluxed for forty-eight hours one of the chlorine substituents was replaced by a methoxyl group. The fact that the corresponding 4-bromo compound (XV) yielded the same product, establishes XII as the structure of this methoxy compound. The preferential replacement of the 4-halogen substituents of IX and XV by a methoxyl instead of the cyano group in an alcoholic solution of sodium cyanide was quite unexpected and remains difficult to rationalize.[4]

A noteworthy difference in behavior was observed with the amines IX and X. Both of these amines were readily diazotized and the diazonium chloride of the former was hydrolyzed to the corresponding 2-methyl-3-hydroxy-4,6-dichloro-5-cyanopyridine. However, a similar attempt to convert the diazonium chloride prepared from X

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(3) Bruce and Perez-Medina, THIS JOURNAL, **69**, 2571 (1947).

(4) A similar but not exactly analogous inertness of halogen to replacement by a cyano group is shown by bromoacetal, which reacts very slowly (forty hours) and incompletely (14%) with a refluxing solution of sodium cyanide and catalytic amounts of sodium iodide in ethyl alcohol to form cyanoacetal (Uhle and Jacobs, *J. Org. Chem.*, **10**, 81 (1945)). However, the halogen of either chloro-, bromo- or iodoacetal is readily replaced by a hydroxyl group in an alcoholic solution of sodium hydroxide (Beyerstedt and McElvain, THIS JOURNAL, **58**, 529 (1936)).