[CONTRIBUTION FROM THE RESEARCH LABORATORY OF MERCK & CO., INC.]

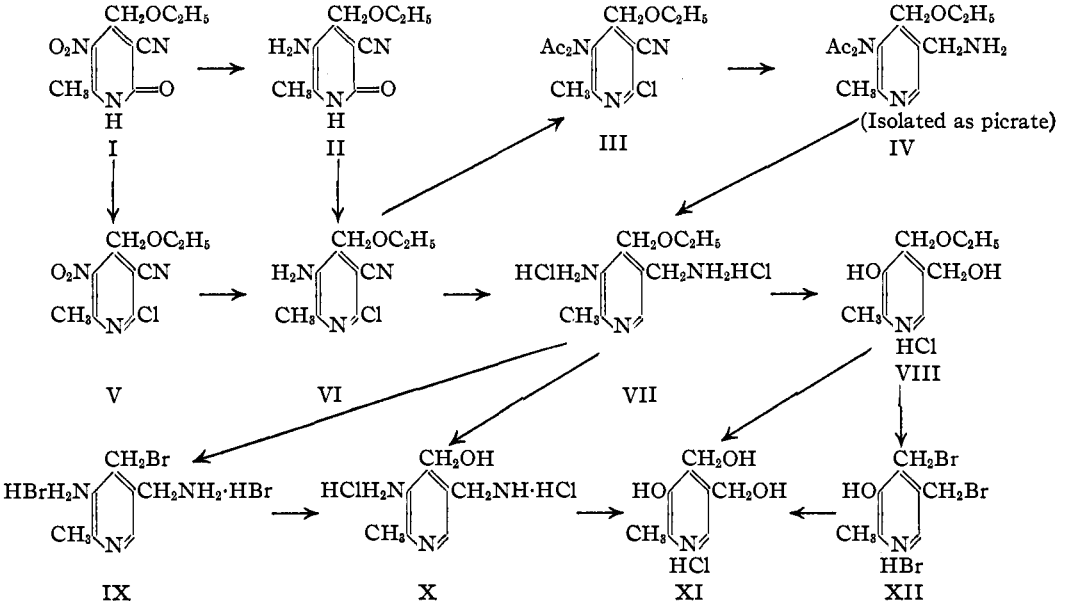
Synthesis of Vitamin B_6. II[1]

BY STANTON A. HARRIS AND KARL FOLKERS

In a previous article[2] a complete synthesis of vitamin B_6 was described. The present paper describes some variations and improvements in this synthesis, along with new derivatives of some of the intermediate compounds. These variations are shown in the set of reactions, I–XII.

The original synthesis is represented by the reactions I → V → VI → VII → VIII → XII → XI. The nitropyridone, I, was prepared by the nitration of 3-cyano-4-ethoxymethyl-6-methyl-2-pyridone, which in turn was prepared by the condensation of ethoxyacetylacetone and cyanacetamide.

The ethoxy-diamine, VII, is the key compound in all these syntheses. This compound was prepared by two new variations of these reactions: I → II → VI → VII and I → II → VI → III → IV → VII. These variations are limited by the low yield in reaction II → VI. Compounds III and IV are not essential to the success of the synthesis of the ethoxy-diamine, VII.



Acetylation of the aminopyridone, II, and the chloroaminopyridine, VI, gave a mono and a diacetate in each case. The question of the position of the second acetyl group in the diacetate of the aminopyridone, II, was settled only by analogy. Since the chloro-aminopyridine, VI, also formed a diacetate and the original pyridone, namely, 3-cyano-4-ethoxymethyl-6-methyl-2-pyridone, did not form an acetate when boiled with acetic anhydride, it was deduced that the diacetate of II had both acetyl radicals attached to the amino group.

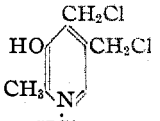
The important variations in the synthesis start with the ethoxy-diamine, VII. The first variation is represented by the reactions VII → VIII → XI. It was found that the ethoxy group of VIII could be split with dilute hydrochloric acid in a bomb tube reaction at 150°. This reaction eliminated the use of constant boiling hydrobromic acid and the necessity for the subsequent hydrolysis of the intermediate dibromide, XII. A second variation is shown by the steps VII → IX → X → XI. These steps also were shortened by another bomb tube reaction to give the third and most practical series of reactions, VII → X → XI. The hydroxy-diamine, X, was more easily isolated and recrystallized than was the 4-ethoxymethyl derivative, VIII, of vitamin B_6.

The 4-ethoxymethyl derivative, VIII, also was deëthylated with concentrated hydrochloric acid

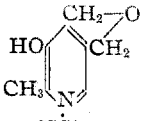
(1) The material in this paper was presented to the Organic Division of the American Chemical Society at Boston, Mass., on September 11, 1939.

(2) Harris and Folkers, THIS JOURNAL, 61, 1245 (1939).

in a bomb tube at 132° to form 2-methyl-3-hydroxy-4,5-*bis*-(chloromethyl)-pyridine hydrochloride, XIII, which was, in turn, hydrolyzed to vitamin B_6 hydrochloride, XI.



XIII



XIV

In the original synthesis,[2] vitamin B_6 hydrochloride, XI, was obtained by hydrolyzing the dibromide, XII, with hot water and removing the bromide ions with silver chloride. On recrystallizing the product from alcohol, a by-product was found in the mother liquors which proved to be an inner ether of the vitamin. This ether, 2-methyl-3-hydroxy-4,5-(epoxydimethyl)-pyridine hydrochloride, XIV, was also obtained by treating both vitamin B_6, XI, and its ethyl ether, VIII, with 50% sulfuric acid. Unlike the ethyl ether, VIII, this new ether was stable toward hydrolysis with dilute hydrochloric acid at 175°. However, it was reconverted to the dibromide, XII, by boiling with 48% hydrobromic acid, which can, in turn, be converted to vitamin B_6 hydrochloride, XI.

Experimental Part

Reduction of 3-Cyano-4-ethoxymethyl-5-nitro-6-methyl-2-pyridone, I.—The reduction was carried out with hydrogen in the presence of Adams catalyst, both in ethyl alcohol and acetic acid. From 22.5 g. of I, the yield of 3-cyano-4-ethoxymethyl-5-amino-6-methyl-2-pyridone, II, was 12.5 g. (63.6%); m. p. 250–255° with decomposition after recrystallization from ethyl alcohol.

Anal. Calcd. for $C_{10}H_{15}N_3O_2$: C, 57.96; H, 6.32; N, 20.28. Found: C, 58.15; H, 6.19; N, 20.67, 20.61.

The reduction of the nitropyridone, I, also was carried out in acetic anhydride and yielded the monoacetate of II. From 23.5 g. of I, dissolved in 200 cc. of acetic anhydride, the yield of 3-cyano-4-ethoxymethyl-5-acetylamino-6-methyl-2-pyridone was 13.3 g. (53.4%); m. p. 260° after recrystallization. An additional 8–9 g. of crude material was obtained from the mother liquor. It was difficultly soluble in acetic anhydride and ethyl alcohol, from which latter it was recrystallized.

Anal. Calcd. for $C_{12}H_{15}O_3N_3$: C, 57.82; H, 6.07; N, 16.85. Found: C, 57.80; H, 6.11; N, 16.99.

The aminopyridone, II, also was acetylated by boiling in an excess of acetic anhydride. In one experiment a small amount of the monoacetate was obtained in addition to a larger quantity of a more soluble product which proved to be a diacetate. After the removal of the acetic anhydride under reduced pressure the residue was oily but, on standing, it gradually crystallized to a solid mass. After three recrystallizations from ethyl alcohol, the diacetate of 3-cyano-4-ethoxymethyl-5-amino-6-methyl-2-pyridone melted at 176°.

Anal. Calcd. for $C_{14}H_{17}O_4N_3$: N, 14.43; CH_3CO, 29.5. Found: N, 14.6; CH_3CO, 28.92, after refluxing in strong alkali for 25.5 hours.

Chlorination of 3-Cyano-4-ethoxymethyl-5-amino-6-methyl-2-pyridone, II.—Two grams of the aminopyridone, II, was treated with 15–20 cc. of phosphorus oxychloride and 4 g. of phosphorus pentachloride and allowed to stand overnight at 30°. The phosphorus oxychloride was removed under reduced pressure and the residue decomposed with ice water. On neutralization with ammonia, a substance crystallized which, after three recrystallizations from alcohol, melted at 146–147° and showed no depression of melting point with a pure sample of 2-methyl-3-amino-4-ethoxymethyl-5-cyano-6-chloropyridine, VI.[2] The yield of crude material was 0.38 g. (16.5%). A large proportion of unchanged starting material was obtained by extracting the aqueous mother liquor with chloroform.

Acetylation of 2-Methyl-3-amino-4-ethoxymethyl-5-cyano-6-chloropyridine, VI.—Two grams of the chloro-aminopyridine, VI, was dissolved in 10 cc. of warm acetic anhydride and then allowed to crystallize. One gram of starting material was recovered. The acetic anhydride solution was decomposed with cold water from which the acetylation product was extracted with chloroform. After washing the solution with sodium bicarbonate and with water and drying over calcium chloride, the chloroform was evaporated. The residue was recrystallized from alcohol and yielded 2-methyl-3-acetylamino-4-ethoxymethyl-5-cyano-6-chloropyridine; m. p. 134–136°.

Anal. Calcd. for $C_{12}H_{14}O_2N_3Cl$: C, 53.83; H, 5.27; N, 15.70. Found: C, 53.65; H, 5.40; N, 15.90.

In a second experiment, 3.8 g. of the chloro-aminopyridine was acetylated by boiling with 25 cc. of acetic anhydride for thirty minutes. The acetic anhydride was removed by distillation under reduced pressure and the residue was treated with 20 cc. of alcohol and 10 cc. of water. After a few minutes, crystallization took place. The crystals were recrystallized by dissolving them in the least possible amount of alcohol and adding water until the solution was slightly cloudy. The yield was 4.3 g. (82.5%) of 2-methyl-3-diacetylamino-4-ethoxymethyl-5-cyano-6-chloropyridine, III; m. p. 90–92°.

Anal. Calcd. for $C_{14}H_{16}O_3N_3Cl$: C, 54.28; H, 5.20; N, 13.57. Found: C, 53.98; H, 4.92; N, 13.34.

Reduction of 2-Methyl-3-diacetylamino-4-ethoxymethyl-5-cyano-6-chloropyridine, III.—A solution of 100 cc. of glacial acetic acid containing 3.09 g. of the chlorodiacetylaminopyridine, III, and 0.82 g. of sodium acetate was shaken with hydrogen in the presence of 10 g. of palladium charcoal and 0.5 g. of Adams catalyst until three moles of hydrogen had been absorbed. The solution was filtered, concentrated, taken up in absolute alcohol, and filtered from the separated sodium chloride. A solution of 2.5 g. of picric acid in hot alcohol was then added and after several minutes crystallization took place. The product was twice recrystallized from alcohol. The yield of the monopicrate of 2-methyl-3-diacetylamino-4-ethoxymethyl-5-aminomethylpyridine, IV, was 1.85 g. (36.4%); m. p. 190–191°.

Anal. Calcd. for $C_{20}H_{24}N_6O_{10}$: C, 47.24; H, 4.75; N, 16.53. Found: C, 47.04; H, 4.72; N, 16.64.

Deacetylation of 2-Methyl-3-diacetylamino-4-ethoxymethyl-5-aminomethylpyridine, IV.—The picrate of IV was decomposed with hydrochloric acid (1:1) and the picric acid was extracted first with nitrobenzene and finally with ether. An attempt was then made to diazotize the free amino group by the addition of one mole of sodium nitrite. The solution was then hydrolyzed by boiling for one and one-half hours with 15% hydrochloric acid, after which it was concentrated to dryness, taken up in absolute alcohol, and treated with acetone. The only product which was isolated was the dihydrochloride of 2-methyl-3-amino-4-ethoxymethyl-5-aminomethylpyridine, VII; m. p. 193–195°.[2] Dr. J. van de Kamp of this Laboratory reported that drying of this compound at 100° under a vacuum from an oil pump raised the m. p. to 204–205°. Recrystallization of the ethoxy-diamine, VII, from 95% alcohol yielded a monohydrate; m. p. 127–129°.

Anal. Calcd. for $C_{10}H_{21}O_2N_2Cl_2$: C, 41.97; H, 7.39; N, 14.68. Found: C, 42.02; H, 7.41; N, 14.93.

Deëthylation of the Dihydrochloride of 2-Methyl-3-amino-4-ethoxymethyl-5-aminomethylpyridine, VII.—The ethoxydiamine, VII (1.55 g.), was treated in a distillation flask with 20 cc. of boiling 48% hydrobromic acid until about one-half of the acid had been distilled. On cooling and scratching the concentrated solution, crystallization took place. The product was recrystallized by dissolving it in a small amount of water and adding 8–10 volumes of alcohol, which yielded the dihydrobromide of 2-methyl-3-amino-4-bromomethyl-5-aminomethylpyridine, IX; m. p. 260–265° with decomposition.

Anal. Calcd. for $C_8H_{14}N_3Br_3$: C, 24.51; H, 3.60; N, 10.72. Found: C, 24.97, 24.90; H, 3.71, 3.62; N, 10.66.

This bromomethyl-diamine, IX, was heated with hot water and then stirred with silver chloride until the bromide ions were completely removed. The solution was concentrated to dryness under reduced pressure and the residue was recrystallized from 95% alcohol. The product was the dihydrochloride of 2-methyl-3-amino-4-hydroxymethyl-5-aminomethylpyridine, X; m. p. 235–237°.

Anal. Calcd. for $C_8H_{16}N_3OCl_2$: C, 40.01; H, 6.30; N, 17.50. Found: C, 39.81; H, 6.14; N, 17.48.

It was found later that the ethoxy-diamine, VII, could be hydrolyzed directly to the hydroxy-diamine, X. A solution of 2.24 g. of VII in 34 cc. of 2.5 *N* hydrochloric acid was heated in a bomb tube for four hours at 175–180°. The slightly colored solution was filtered with charcoal and concentrated to dryness under reduced pressure. The product was recrystallized from water and alcohol. The yield of the hydroxy-diamine, X, was 1.44 g. (76.7%); m. p. 235–237°. There was no depression of mixed melting point with a sample of X obtained above.

Diazotization of the Dihydrochloride of 2-Methyl-3-amino-4-hydroxymethyl-5-aminomethylpyridine, X, to form Vitamin B_6, XI.—A solution of 1.28 g. of the hydroxy-diamine, X, in 22 cc. of water was added simultaneously with a solution of 2.24 g. of sodium nitrite to 45 cc. of hot (90–95°) 2.5 *N* hydrochloric acid. The yellow solution was concentrated to dryness under reduced pressure and the residue washed with acetone, which removed some of the color. The vitamin hydrochloride was extracted from the sodium chloride with hot absolute alcohol. This solution was filtered with charcoal and concentrated to a small volume. On addition of acetone the vitamin B_6 hydrochloride crystallized; m. p. 208°. The yield was 0.5 g. (45.4%).

Anal. Calcd. for $C_8H_{11}NO_3Cl$: C, 46.72; H, 5.88. Found: C, 46.51; H, 5.70.

Conversion of 2-Methyl-3-hydroxy-4-ethoxymethyl-5-hydroxymethylpyridine, VIII, to Vitamin B_6 Hydrochloride.—This ethyl ether of vitamin B_6, VIII, has now been obtained in a purer form with a slightly higher melting point than was reported in a previous paper.[3] It was most easily purified as the free base in acetone solution by the addition of ether and filtration with charcoal. The nearly colorless solution was then treated with dry hydrogen chloride. The precipitated salt was recrystallized from alcohol by the addition of an equal volume of acetone. Washing with acetone gave colorless crystals of 2-methyl-3-hydroxy-4-ethoxymethyl-5-hydroxymethylpyridine hydrochloride, VIII; m. p. 135–136°.

Anal. Calcd. for $C_{10}H_{14}NO_3Cl$: C, 51.38; H, 6.90; N, 6.00. Found: C, 51.20; H, 6.81; N, 6.25, 6.20.

A solution of 4 g. of the ethyl ether, VIII, in 20 cc. of water and 1 cc. of 2.5 *N* hydrochloric acid was heated in a bomb tube at 155–160° for six hours. The slightly colored solution was treated with charcoal, filtered, and concentrated to dryness under reduced pressure. The yield of slightly yellow crystals was 2.92 g. (83%). After recrystallization from absolute alcohol, with the use of charcoal for decolorization, pure white vitamin B_6 hydrochloride was obtained; m. p. and mixed m. p. 208–209°.

The cleavage of the ethoxy group of VIII also was accomplished by dissolving 0.2 g. of this substance in 6 cc. of concentrated hydrochloric acid and heating in a bomb tube at 132° for one hour. On cooling in ice water, crystals separated and were recrystallized from a little concentrated hydrochloric acid. The yield of 2-methyl-3-hydroxy-4,5-*bis*-(chloromethyl)-pyridine hydrochloride, XIII, was 0.09 g. (45%), m. p. 206° with preliminary darkening around 200°.

Anal. Calcd. for $C_8H_{10}NOCl_3$: C, 39.62; H, 4.16; N, 5.78. Found: C, 39.48; H, 3.98; N, 5.94.

This dichloride, XIII (50 mg.), was converted to vitamin B_6 hydrochloride by heating in 10 cc. of water on the steam-bath for one hour. The water was evaporated and the material recrystallized from alcohol and acetone. The first crop of vitamin B_6 hydrochloride (10 mg.) melted at 202–203° and showed no depression of melting point with a pure specimen of the vitamin.

2-Methyl-3-hydroxy-4,5-(epoxydimethyl)-pyridine Hydrochloride, XIV.—In recrystallizing vitamin B_6 prepared by the hydrolysis of 2-methyl-3-hydroxy-4,5-*bis*-(bromomethyl)-pyridine hydrobromide, XII, a by-product was found in the mother liquors. After the pure vitamin hydrochloride crystallized out, a mixture of substances melting at about 195° was obtained. When acetone was added to the final mother liquor a substance melting above 230° was formed. Recrystallization from alcohol yielded 2-methyl-3-hydroxy-4,5-(epoxydimethyl)-pyridine hydrochloride; m. p. 239–240° with decomposition.

Anal. Calcd. for $C_8H_{10}O_2NCl$: C, 51.21; H, 5.37; N, 7.47. Found: C, 51.13; H, 5.21; N, 7.62.

This epoxy compound, XIV, was obtained in small yields when 1-g. quantities of vitamin B_6, XI, and its ethyl ether, VIII, were treated with 15 cc. of 50% sulfuric acid for one hour on the steam-bath. The sulfuric acid was neutralized with sodium hydroxide, the water was evaporated, and the product was extracted with acetone as the free base. The addition of dry hydrogen chloride gave a product which, after crystallization from alcohol, was identical with the by-product described above.

Cleavage of the Epoxydimethyl Group.—2-Methyl-3-hydroxy-4,5-(epoxydimethyl)-pyridine resisted hydrolysis on heating with 2.5 *N* hydrochloric acid at 175° for four hours. However, the ether group was split when 3.7 g. of the epoxydimethyl derivative, XIV, was distilled with 60 cc. of 48% hydrobromic acid until the volume was reduced to 30 cc. After cooling and filtering, the yield of 2-methyl-3-hydroxy-4,5-*bis*-(bromomethyl)-pyridine hydrobromide, XII, was 6.42 g. (86.5%); m. p. 228.5°. This melting point was 5° higher than previously reported.[2]

Anal. Calcd. for $C_8H_{10}NOBr_3$: C, 25.53; H, 2.66; N, 3.72. Found: C, 25.71; H, 2.89; N, 3.73.

Acknowledgment.—The authors are indebted to Messrs. D. F. Hayman and W. Reiss for the microanalyses and to Mr. A. N. Wilson for technical assistance.

Summary

Variations and improvements in the synthesis of vitamin B_6 have been made. The compounds 2-methyl-3-hydroxy-4-ethoxymethyl-5-hydroxymethylpyridine and 2-methyl-3-amino-4-ethoxymethyl-5-aminomethylpyridine have been hydrolyzed directly to the corresponding hydroxy derivatives by heating with dilute hydrochloric acid at 150–175° under pressure. Derivatives of some of the intermediates and a new inner ether of vitamin B_6 have been described.

RAHWAY, N. J. RECEIVED OCTOBER 10, 1939

[CONTRIBUTION FROM THE SANDERS LABORATORY OF CHEMISTRY, VASSAR COLLEGE, AND THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

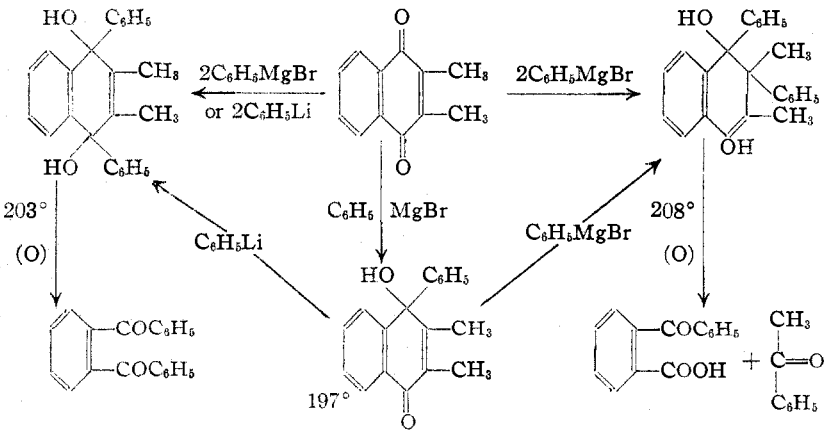
The Reaction between 2,3-Dimethyl-1,4-naphthoquinone and Phenylmagnesium Bromide. II[1]

BY H. MARJORIE CRAWFORD

In an earlier paper[2] it was shown that phenylmagnesium bromide reacts with 2,3-dimethyl-1,4-naphthoquinone to give all of the expected reduction and addition products. These solids accounted for about 30% of the starting material, the other product being a dark, thick oil. No amorphous materials were encountered. Four addition products were described, two resulting from the 1,2- and 1,4-addition of one molecule of phenylmagnesium bromide to one molecule of the quinone, and two resulting from the 1,2-1,2- and 1,2-1,4-addition of two molecules of phenylmagnesium bromide to one molecule of the quinone.

Further reactions of the two di-addition products are described in this paper.

The structures of the two di-addition products were established as shown by the following equations.



In the Grignard machine, both di-addition compounds showed two active hydrogens. Oxidation of both compounds gave known products which served to locate the phenyl groups. The 203° compound gave *o*-dibenzoylbenzene and the 208° compound gave acetophenone and *o*-benzoyl-

(1) Reported at the fall meeting of the American Chemical Society at Boston, Mass., September, 1939.

(2) Crawford, THIS JOURNAL, 57, 2000 (1935).