TABLE I

Micro assays by C. S. Chamberlain, Research Laboratories, Parke, Davis & Co. Macro assays by the method of Cislak and Hamilton, THIS JOURNAL, **52**, 632 (1930).

	Name	Crystal form	M. p., °C.	Formula	As analyses, % Calcd.	Found
1	4-β-Methyl-β-hydroxypropoxyphenylarsonic acid	Blunt needles[a]	189–192	$C_{10}H_{15}O_5As$	25.83	25.65
2	Sodium salt of 1		>325	$C_{10}H_{14}O_5AsNa$	24.05	23.90
3	3-Nitro-4-β-methyl-β-hydroxypropoxyphenylarsonic acid	Hexagonal plates[a]	210–215	$C_{10}H_{14}O_7NAs$	22.38	22.30
4	3-Amino-4-β-methyl-β-hydroxypropoxyphenylarsonic acid	Rectangular prisms[b]	150–155	$C_{10}H_{16}O_5NAs$	24.55	24.40[c]
5	3-Amino-4-β-methyl-β-hydroxypropoxyphenylarsine oxide	Irregular bars[a]	123–124	$C_{10}H_{14}O_3NAs \cdot H_2O$	25.9	25.7[d]
6	4,4′-Di-β-methyl-β-hydroxypropoxyarsenobenzene	Yellow amorphous powder	135–140	$C_{20}H_{26}O_4As_2$	31.30	31.50
7	3,3′-Diamino-4,4′di-β-methyl-β-hydroxypropoxyarsenobenzene	Yellow amorphous powder	125–130	$C_{20}H_{28}O_4N_2As_2$	29.4	29.15

[a] By recrystallization from water. [b] With one molecule of water of crystallization, m. p. 65–70°. [c] Micro Dumas for N % calcd. 4.58, found 4.45. [d] Micro arsenic.

again 75 cc. of 6% ammonium hydroxide solution was added. The neutral solution was cooled to 0°, made slightly alkaline for fifteen minutes, then made neutral to litmus paper with acetic acid. It was then charcoaled, filtered, and cooled for three days before crystallization was complete.

4,4′-Di-β-methyl-β-hydroxypropoxyarsenobenzene and 3,3′-Diamino-4,4′-di-β-methyl-β-hydroxypropoxyarsenobenzene.—To 100 cc. of hot water was added 4 g. of 4-β-methyl-β-hydroxypropoxyphenylarsonic acid and 25 cc. of 50% hypophosphorous acid. The solution was boiled for one-half hour and the pale yellow amorphous solid which separated was filtered off, washed well with water, and finally with a little ethanol. The corresponding 3,3′-diamino-arseno derivative was obtained in a similar manner except that the reaction mixture was neutralized with sodium hydroxide before the arseno separated.

Summary

4-Hydroxyphenylarsonic acid was condensed with isobutylene oxide to form 4-β-methyl-β-hydroxypropoxyphenylarsonic acid and this was reduced to the corresponding arseno derivative with hypophosphorous acid.

3-Nitro-4-β-methyl-β-hydroxypropoxyphenylarsonic acid was obtained directly from the nitration of 4-β-methyl-β-hydroxypropoxyphenylarsonic acid.

3-Amino-4-β-methyl-β-hydroxypropoxyphenylarsonic acid was obtained by reduction of the corresponding nitro derivative with ferrous hydroxide and catalytically with Raney nickel catalyst. The corresponding arsine oxide and arseno derivatives of this amino arsenical were also prepared.

DETROIT, MICH. RECEIVED FEBRUARY 3, 1939

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

The Structure of Vitamin B_6. I

BY ERIC T. STILLER, JOHN C. KERESZTESY AND JOSEPH R. STEVENS

Since the reports by Keresztesy and Stevens[1,2] from this Laboratory on the isolation and characterization of crystalline vitamin B_6, further research work has been carried out with the object of determining the chemical constitution of this vitamin. This objective was reached and we now wish to record the evidence which led us to the structure of vitamin B_6. Recently, Kuhn and his coworkers[3–5] have announced the results of researches which led to the same structure for the vitamin.

Other workers[6–9] have confirmed the original findings of Keresztesy and Stevens.[1,2]

(1) Keresztesy and Stevens, *Proc. Expll. Biol. Med.*, **38**, 64 (1938).

(2) Keresztesy and Stevens, THIS JOURNAL, **60**, 1267 (1938).

(3) Kuhn and Wendt, *Ber.*, **72**, 305, 311 (1939).

(4) Kuhn, Andersag, Westphal and Wendt, *ibid.*, **72**, 309 (1939).

(5) Kuhn, Wendt and Westphal, *ibid.*, **72**, 310 (1939).

(6) Lepkovsky, *Science*, **87**, 169 (1938); *J. Biol. Chem.*, **124**, 125 (1938).

(7) Kuhn and Wendt, *Ber.*, **71**, 780, 1118 (1938).

(8) Ichiba and Michi, *Sci. Papers Inst. Phys. Chem. Research*, **34**, 623, 1014 (1938).

(9) György, THIS JOURNAL, **60**, 983 (1938).

The vitamin was isolated from rice bran[2] as the hydrochloride $C_8H_{12}O_3NCl$, m. p. 204–206° (dec.), of a base $C_8H_{11}O_3N$, m. p. 160°. The base was optically inactive, contained no alkyloxy or N-alkyl residues and gave a deep red color with aqueous ferric chloride, indicating the presence of a phenolic hydroxyl group. The vitamin is stable to acid and alkalies and does not react with nitrous acid. The vitamin contained one C-methyl residue, and estimations of active hydrogen atoms showed the presence of three in the molecule. The fact, that the base was of tertiary cyclic nature and gave a red color with ferric chloride very similar to that produced by β-hydroxypyridine, led us to a comparison of the vitamin with β-hydroxypyridine and its derivatives. Vitamin B_6 is a weak base, the pK_b for which is of the same order as that of β-hydroxypyridine (Table I).

TABLE I

*p*K (BASE) VALUES FOR VITAMIN B_6 AND HYDROXYPYRIDINES

	*p*K (base)
Vitamin B_6	6.2×10^{-10}
β-Hydroxypyridine	6.0×10^{-10}
α-Pyridone	1.7×10^{-13}

It already has been reported by Keresztesy and Stevens[2] that the vitamin shows very characteristic absorption spectra which change markedly with change of hydrogen ion concentration. The absorption spectra of 2-methyl-3-hydroxy-5-ethylpyridine,[10] 2-methyl-5-hydroxypyridine[11] and β-hydroxypyridine resemble very closely that of the vitamin and the same pronounced alterations in character are exhibited on change of *p*H.

In acid solution (*p*H 2.1) all four compounds exhibit a single band at approximately 2920 Å. of similar intensity (Fig. 1 and Table II). β-Hydroxypyridine, however, shows a shift of 100 Å. toward the ultraviolet. In alkaline solution (*p*H 10.2), the four compounds show two new bands with the complete disappearance of the "acid" band (Fig. 2, Table II).

TABLE II

ABSORPTION MAXIMA OF HYDROXYPYRIDINES

	*p*H 2.1		*p*H 10.2	
	λ	ε × 10^{-3}	λ	ε × 10^{-3}
β-Hydroxypyridine	2825	5.95	2340	8.70
			2980	4.25
2-Methyl-5-hydroxy-pyridine	2925	5.95	2390	8.1
			3075	3.4

Kuhn and Wendt,[3] in discussing the absorption spectra of the vitamin in acid and alkaline media, speak of a reversible shift of the absorption spectra by means of alkali. In our experience the absorption spectra apparently present a more complicated picture than can be explained by a mere shift toward the longer wave lengths of the type found in purely carbocyclic phenols.[12,13] They can be accounted for, however, by the amphoteric nature of the vitamin.

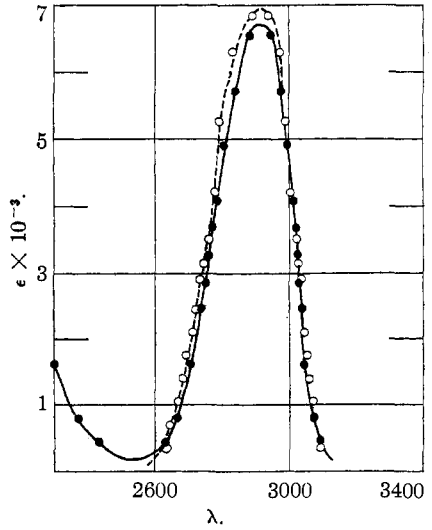


Fig. 1.—Absorption spectra in aqueous solution at *p*H 2.1 for: ●, vitamin B_6; ○, 2-methyl-3-hydroxy-5-ethylpyridine.

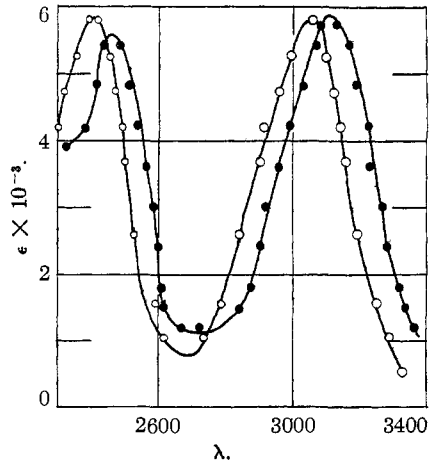


Fig. 2.—Absorption spectra in aqueous solution at *p*H 10.2 for: ●, vitamin B_6; ○, 2-methyl-3-hydroxy-5-ethylpyridine.

(10) Unpublished work from this Laboratory.
(11) Graf, *J. prakt. Chem.*, **133**, 19 (1932).
(12) Baly and Ewbank, *J. Chem. Soc.*, **87**, 1347 (1905).
(13) Ley, *Z. physik. Chem.*, **94**, 405 (1920).

The absorption spectra of the vitamin in aqueous solution between *p*H 4 and 6.75 are shown in Fig. 3. It is obvious from these curves, that, as the hydrogen ion concentration decreases, the single "acid" band at 2920 Å. gradually decreases in intensity without a shift of wave length. Between *p*H 4 and 5.1 two new bands appear at 2550 and 3260 Å. while the "acid" band is still present. At *p*H 6.75 this latter band has disappeared and the 3260 Å. band has fully developed. Between *p*H 6.75 and 10.2 the 2550 Å. band has fully developed and both "alkaline" bands exhibit a shift toward the shorter wave lengths to 2460 and 3110 Å., respectively. This shift is in the reverse direction to that shown by purely carbocyclic phenols in neutral and alkaline solution.

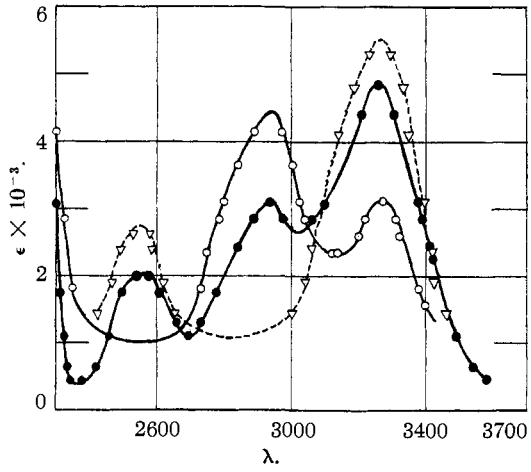


Fig. 3.—Absorption spectra of vitamin B_6 at: ○, *p*H 4; ●, *p*H 5.1; ▽, *p*H 6.75.

The three β-hydroxypyridine derivatives which were examined exhibit absorption bands which vary in an exactly analogous manner to those of the vitamin with change of hydrogen ion concentration. The absorption spectra of α- and γ-pyridone were measured in both acid and alkaline solution but were quite unlike that of the vitamin.

On treatment with diazomethane the vitamin forms a monomethyl ether $C_9H_{13}O_3N$, m. p. 101–102° (*cf.* Kuhn and Wendt,[14] m. p. 89.5–90°), which gives a hydrochloride $C_9H_{14}O_3NCl$, m. p. 147–148°. The absorption spectrum of the methyl ether shows a single band at 2800 Å., $\epsilon \times 10^{-3}$, 5.80 which does not vary with change of *p*H.

The methyl ether of vitamin B_6 is oxidized readily with barium permanganate at room temperature. By using 4.4 atoms of oxygen in the oxidation, two products were obtained. One was a lactone, $C_9H_9O_3N$, m. p. 108.5–109.5°. The main product was a dibasic acid, $C_9H_9O_5N$, m. p. 208–209° (dec.) which crystallized from water with one molecule of water of crystallization. Electrometric titrations showed the acid to be dibasic having K_1, 1.36×10^{-3}; K_2, 5.6×10^{-6}; 2,6-dimethylcinchomeronic acid had K_1 1.2×10^{-3}; K_2 3.3×10^{-7}. The absorption spectrum of the acid was closely related to that exhibited by 2,6-dimethylcinchomeronic acid (Fig. 4).

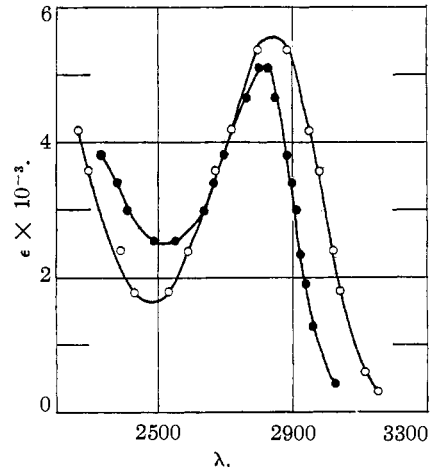


Fig. 4.—Absorption spectra in aqueous solution for: ●, dibasic acid $C_9H_9O_5N$; ○, 2,6-dimethylcinchomeronic acid.

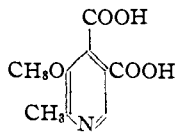
The acid $C_9H_9O_5N$ gave no color with aqueous ferrous sulfate. Therefore, neither of the carboxylic acid residues is in the α-position of the pyridine ring. Upon fusing with resorcinol, a phthalein having a greenish-yellow fluorescence was produced, indicating that the two carboxyl groups are vicinal. Thus, since the acid is a derivative of β-hydroxypyridine, the two carboxyl groups must be attached to the pyridine nucleus at positions 4 and 5.

The dibasic acid was decarboxylated by heating the sodium salt with calcium hydroxide. The product, isolated as its picrate, was not obtained quite pure, owing to the small quantity available. The analytical figures approximated those of a hydroxypicoline. The absence of the original methoxyl group was confirmed by the following evidence: a negative methoxyl estimation; production of a red color with aqueous ferric chloride after freeing the product from picric acid; the coupling of the product with diazotized

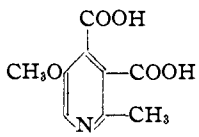
(14) Kuhn and Wendt, *Ber.*, **71**, 1534 (1938).

p-bromoaniline; the production of the two characteristic bands of a β-hydroxypyridine at 2400 and 3000 Å. at *p*H 10.5. The picrate melted at 147–148°. It was not identical with 3-hydroxy-5-methylpyridine picrate, m. p. 201–202°, and therefore was, in all probability, the picrate of 2-methyl-3-hydroxypyridine which thus far has not yielded to synthesis.

The dibasic acid $C_9H_9O_5N$ contains the original C-methyl residue present in the vitamin and must therefore be represented by either structure I or II.

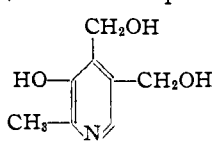


I

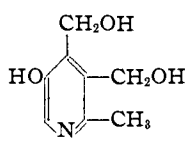


II

The dibasic acid is formed from the methoxyvitamin by the addition of two oxygen atoms with the loss of four hydrogen atoms and since the vitamin has three active hydrogen atoms in its molecule, it must be represented by either III or IV.



III



IV

On treatment in alkaline solution with a suspension of 2,6-dichloroquinonechloroimide, vitamin B_6 gave an immediate blue color fading to reddish-brown. According to Gibbs[15] para-substituted phenols do not give a blue color with this reagent. Thus, since the vitamin is a 3-hydroxypyridine derivative, position 6 in the ring must be unsubstituted. Confirmation of this view was obtained, since 2-methyl-5-hydroxypyridine gave no color with the same reagent while β-hydroxypyridine and 2-methyl-3-hydroxy-5-ethylpyridine produced the characteristic blue color. Therefore, structure III represents the vitamin.

Conclusive proof of structure III was obtained by the syntheses of the acid $C_9H_9O_5N$ and the lactone $C_9H_9O_3N$ which are described in the following paper.[16]

Experimental Part

Vitamin B_6 Base.—A solution of 96.6 mg. of the vitamin hydrochloride in 2.5 cc. of water was neutralized exactly with 0.1 *N* sodium hydroxide. It was evaporated to dryness at 55° in a stream of dry air. The base was eluted from the solid residue by extracting five times with 2-cc. portions of methyl alcohol and the salts precipitated by adding 6 volumes of ether. The mother liquors were evaporated to dryness and the residue was sublimed at 140–145° (10^{-4} mm.). The colorless crystalline sublimate melted at 159–160°, yield 60 mg.

Anal. Calcd. for $C_8H_{11}O_3N$: C, 56.80; H, 6.56. Found: C, 56.77; H, 6.53. C-methyl determinations gave 8.34% CH_3. Calcd. for $C_8H_{11}O_3N$: 8.87% CH_3.

The active hydrogen determination data[17] are summarized in Table III.

TABLE III

DETERMINATION OF ACTIVE HYDROGEN ATOMS

	Substance, mg.	Methane, cc. 25°	Methane, cc. 100°	Active hydrogen atoms	
(1)	1.380	0.57	0.59	2.85	2.95
(2)	1.666	.66	.65	2.74	2.70
(3)	1.321	.63	.61	3.30	3.19
(4)	1.178	.61	.55	3.58	3.23

The vitamin gave a deep red color with ferric chloride. Five-tenths mg. of the base was dissolved in 10 cc. of water and the *p*H of the solution adjusted to 9.2–9.4. On treatment of this solution with a fine suspension of 2,6-dichloroquinonechloroimide[15a] an immediate blue color was produced, which gradually faded after a few minutes to reddish-brown. Addition of a further quantity of the reagent produced a further blue coloration. β-Hydroxypyridine and 2-methyl-3-hydroxy-5-ethylpyridine also gave a blue coloration under similar conditions but 2-methyl-5-hydroxypyridine, 2-pyridone and 6-methyl-2-pyridone gave no color.

Methylation of Vitamin B_6.—A well-cooled solution of 388 mg. of the vitamin base in 10 cc. of absolute methyl alcohol was treated with an excess of diazomethane in 75 cc. of absolute ether. Nitrogen was evolved and the color of the solution changed from yellow to emerald green and then slowly to yellow-brown. After standing at room temperature for sixteen hours, the solvents and excess diazomethane were removed by distillation. The residual brown oil was taken up in 5 cc. of methyl alcohol and treated with 6 volumes of ether. The resultant precipitate was again treated in a similar manner. The combined methyl alcohol–ether liquors were evaporated to dryness and the residue transferred to a sublimation apparatus and heated at 110–120° at 10^{-4} mm. The first crop of colorless crystalline sublimate was removed and on further heating at 120–128° (10^{-4} mm.) some gas was evolved and a second crop was obtained. The total yield of the methyl ether of vitamin B_6 was 233 mg. After recrystallization from chloroform–petroleum ether, it was obtained as clusters of colorless plates, m. p. 101–102°.

Anal. Calcd. for $C_9H_{13}O_3N$: C, 58.98; H, 7.16; N, 7.65. Found: C, 58.80; H, 7.22; N, 7.59.

Hydrochloride.—To a solution of 56 mg. of the methyl ether in 0.15 cc. of methyl alcohol, 1.2 cc. of ether was added. After the addition of a few drops of methyl alcohol saturated with hydrogen chloride, the hydrochloride crystallized rapidly as clusters of colorless needles; yield

(15) (a) Gibbs, *J. Biol. Chem.*, **72**, 649 (1927); see also (b) Theriault, *Ind. Eng. Chem.*, **21**, 343 (1929).

(16) Harris, Stiller and Folkers, THIS JOURNAL, **61**, 1242 (1939).

(17) We wish to express our indebtedness to Professor J. B. Niederl of New York University who very kindly arranged to have the active hydrogen determinations carried out.

50 mg. After recrystallization from methyl alcohol–ether, it had m. p. 147–148°.

Anal. Calcd. for $C_9H_{14}O_3NCl$: C, 49.18; H, 6.42. Found: C, 49.23; H, 6.61.

Oxidation of the Methyl Ether of Vitamin B_6.—To a solution of 323 mg. of the vitamin methyl ether in 15 cc. of water, 0.1 *M* barium permanganate (equivalent to 4.4 oxygen atoms) was added in small amounts. The equivalent of two oxygen atoms was used up rapidly. Thereafter, the oxidation proceeded more slowly and to complete the oxidation it was allowed to stand at room temperature for sixteen hours. The slight excess of permanganate was destroyed and the manganese dioxide was centrifuged off and washed repeatedly with hot water. The combined aqueous liquors were concentrated to about 50 cc. at 40° under reduced pressure and the greater part of the barium removed by treatment with 0.1 *N* sulfuric acid. The precipitated barium sulfate was washed thoroughly with warm water and the combined aqueous liquors further concentrated at 40° under reduced pressure to 15 cc. The residual barium was removed quantitatively with 0.01 *N* sulfuric acid. The resultant barium-free solution (*p*H 3.6) was then concentrated to 1.5 cc. and set in the refrigerator overnight. The faintly yellow crystalline material was collected and washed with a small quantity of ice water; yield 210 mg.

Fractional crystallization of this material proved to be ineffective in affording a separation into its constituents. Extraction with ether or benzene gave 6 mg. of more soluble material which after recrystallization from water was obtained as colorless needles, m. p. 108.5–109.5°.

Anal. Calcd. for $C_9H_9O_3N$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.49; H, 4.94; N, 7.93.

The substance contained no free carboxyl group but on heating with alkali it consumed one equivalent, due to the saponification of a lactone group. Thus: (a) 0.416 mg. required 0.245 cc. 0.01 *N* NaOH; (b) 0.401 mg. required 0.265 cc. 0.01 *N* NaOH. Calcd. for $C_9H_9O_3N$: (a) 0.232 cc.; (b) 0.224 cc. 0.01 *N* NaOH.

A further quantity of the lactone was isolated by heating the crude oxidation product in a sublimation apparatus under high vacuum (100–105° at 10^{-4} mm.). The unsublimed residue was taken up in the minimum amount of hot water and after cooling an acid was obtained as clusters of colorless flattened needles, m. p. 209–210° (dec.). The melting point varied somewhat, depending on the rate of heating. The compound crystallized with one molecule of water of crystallization as determined by drying *in vacuo* at 67° for two hours. The analysis was performed upon this dried material.

Anal. Calcd. for $C_9H_9O_5N \cdot H_2O$: H_2O, 7.87. Found: H_2O, 7.20. Calcd. for $C_9H_9O_5N$: C, 51.16; H, 4.30; N, 6.63; neut. equiv., 211. Found: C, 51.07; H, 4.48; N, 6.46; neut. equiv., 213.

The acid gave no color with aqueous ferrous sulfate. A small amount of the oxidation product was heated at 130° for a few minutes with resorcinol and a few drops of concentrated sulfuric acid. Upon rendering the resultant melt alkaline with dilute sodium hydroxide, a yellow solution was produced having a greenish-yellow fluorescence. 2,6-Dimethylcinchomeronic acid and quinolinic acid when treated in the same manner gave a similar greenish-yellow fluorescence.

Decarboxylation of the Acid $C_9H_9O_5N$.—A solution of 21.3 mg. of the dicarboxylic acid in 2 cc. of water was neutralized to phenolphthalein with 0.1 *N* sodium hydroxide. The solution was evaporated to dryness and the resulting sodium salt was dried over sulfuric acid *in vacuo*. The finely ground salt, which weighed 27.4 mg., was mixed thoroughly with 250 mg. of calcium hydroxide and placed in a 6-mm. Pyrex tube. The products of the pyrolysis were collected in a U-tube cooled in ice and the escaping gases were passed into dilute hydrochloric acid. A slow stream of hydrogen was passed through the apparatus and the mixture was gradually heated in a sodium nitrate–potassium nitrate bath to 360–370° and held there for fifteen minutes. The temperature was then gradually raised to 480° during twenty minutes. After cooling, the U-tube, which contained a small drop of water and a little yellow oil, was cut out and extracted with ether. The drop of water, after it had been extracted several times with ether, gave a deep red color with aqueous ferric chloride. The ethereal extracts were dried with anhydrous sodium sulfate and concentrated to 2 cc.; 24.4 mg. of picric acid dissolved in 2 cc. ether was then added. On concentration to 2 cc. and cooling at 0° the solution deposited yellowish-brown crystals. On further concentration of the mother liquor a second crop was obtained. The total yield was 13.1 mg. The product was twice recrystallized from alcohol–ether and obtained as greenish-yellow prisms, m. p. 147–148°.

Anal. Calcd. for $C_{13}H_{12}O_8N_4$: C, 44.33; H, 3.44. Calcd. for $C_{12}H_{10}O_8N_4$: C, 42.60; H, 2.98. Found: C, 43.42; H, 3.44.

A micro-methoxyl determination gave no methyl iodide even when carried out under conditions for determining $N\text{-}CH_3$ residues. When similar determinations were carried out on the picrates of 2-methyl-5-methoxypyridine[10] and 2-methyl-3-methoxy-5-ethylpyridine,[10] they gave no methyl iodide under normal conditions but gave the theoretical amount of methyl iodide when run under the conditions for an $N\text{-}CH_3$ determination.

The remaining crystalline picrate and the picrate recovered from the mother liquors of the recrystallizations were treated with dilute hydrochloric acid and the picric acid removed by extraction with ether. The aqueous acid solution was evaporated to dryness leaving about 2 mg. of an oil. This material showed absorption maxima at 2400 and 3000 Å. at *p*H 10.5 characteristic of a β-hydroxypicoline. A portion of the remaining material gave a deep red color with ferric chloride and coupled with diazotized *p*-bromoaniline to give a red solution. β-Hydroxypyridine coupled with the same reagent to give a very similar red color.

The authors wish to express their appreciation to Dr. R. T. Major and Dr. K. Folkers for much helpful advice, to Dr. T. J. Webb and Mr. W. A. Bastedo, Jr., for carrying out the physical measurements, to Mr. J. Finkelstein for preparing the β-hydroxypyridines and to Messrs. Hayman and Reiss for carrying out the microanalyses. They are also indebted to Messrs. E. Rickes and H.

Koones for their assistance in the preparation of the vitamin B_6 used in this work.

Summary

1. The methyl ether of vitamin B_6 was oxidized to give a lactone $C_9H_9O_3N$ and a dibasic acid $C_9H_9O_5N$.

2. The acid was shown to be 2-methyl-3-methoxypyridine-4,5-dicarboxylic acid.

3. Vitamin B_6 was shown to be 2-methyl-3-hydroxy-4,5-di-(hydroxymethyl)-pyridine.

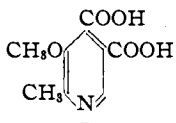
RAHWAY, NEW JERSEY RECEIVED MARCH 15, 1939

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

Structure of Vitamin B_6. II

BY STANTON A. HARRIS, ERIC T. STILLER AND KARL FOLKERS

This paper deals with the syntheses of the dibasic acid $C_9H_9O_5N$, I, and the lactone $C_9H_9O_3N$, II, which were obtained by Stiller, Keresztesy and Stevens[1] by the oxidation of the methyl ether of vitamin B_6. The synthetic lactone and acid were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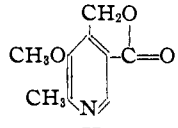
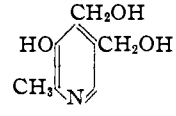
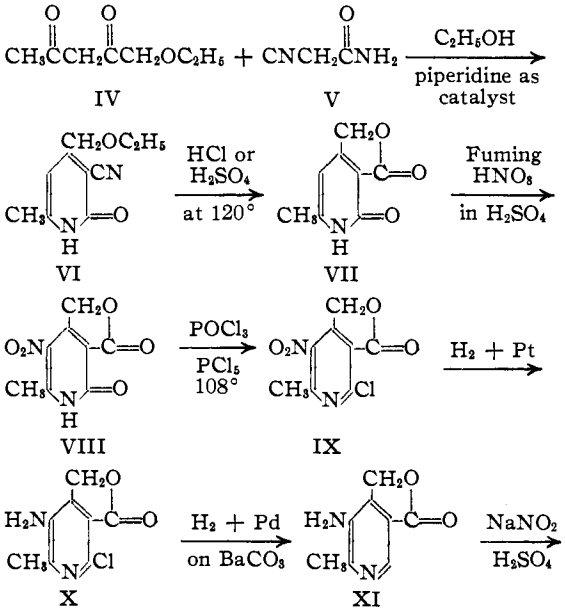
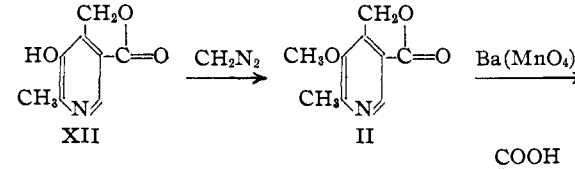

II

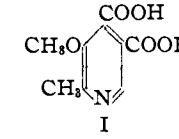

III

found to be identical with the corresponding compounds obtained from vitamin B_6. Thus, conclusive proof is furnished that vitamin B_6 is 2-methyl-3-hydroxy-4,5-di-(hydroxymethyl)-pyridine, III. The syntheses may be represented graphically in the following manner.

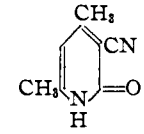


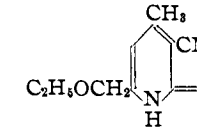
(1) Stiller, Keresztesy and Stevens, THIS JOURNAL, 61, 1237 (1939).




I

The synthesis of VI is similar to the synthesis of 3-cyano-4,6-dimethyl-2-pyridone, XIII, which was obtained by the condensation of acetylacetone and cyanacetamide as previously described by Bardhan,[2] and also Simonsen and Nyak.[3]


XIII


XIV

The condensation of IV and V might have led to the alternative 3-cyano-4-methyl-6-ethoxymethyl-2-pyridone, XIV. The proof that the condensation product had structure VI, instead of IV, was shown by its conversion on hydrolysis to the lactone VII, which was obtained in 85% yield. It is obvious that the pyridone derivative, XIV, would be incapable of giving a lactone on hydrolysis. The pyridone derivative, VI, was obtained pure in better than 80% yield with no evidence of any other product being formed.

Experimental Part

3-Cyano-4-ethoxymethyl-6-methyl-2-pyridone, VI.—To 65.3 g. of cyanoacetamide,[4] V, dissolved in 500 cc. of hot 95% alcohol, 93.1 g. of ethoxyacetylacetone[5] and ca. 8.5 cc.

(2) Bardhan, *J. Chem. Soc.*, 2223 (1929).

(3) Simonsen and Nyak, *ibid.*, 792 (1915).

(4) Corson, Scott, and Vose, "Org. Syntheses," Coll. Vol. I, John Wiley & Sons Co., Inc., New York, N. Y., 1932, p. 173.

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