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A Synthesis of Vitamin B_6

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In the synthesis herewith reported, dehydration of the amide of 2-methyl-4-carboxy-5-cyanopyridone-6 to 2-methyl-4,5-dicyanopyridone-6 was followed by transformation, through nitration and chlorination, to 2-methyl-3-nitro-4,5-dicyano-6-chloropyridine and, by a stepwise catalytic reduction process, to 2-methyl-3-amino-4,5-di-aminomethylpyridine which, as a salt, was converted to vitamin B_6.

Conversion of 2-methyl-4-carbethoxy-5-cyanopyridone-6[1] to the amide, by the action of either alcoholic or liquid ammonia, was essentially quantitative. The amide was dehydrated with phosphorus oxychloride, without solvent or in toluene solution, to the dinitrile which readily crystallized from acetone, glacial acetic acid or aqueous alcohol. Purification, however, was not essential and the crude product, after mere separation from unchanged amide, could be nitrated directly. Chlorination of the crude nitro derivative gave a satisfactory product and the chlorinated pyridine, after crystallization from an ether–petroleum ether solution or sublimation in high vacuum, was rapidly reduced catalytically in acetic anhydride solution. The resulting 2-methyl-3-amino-4,5-dicyano-6-chloropyridine, which crystallized as the free base from acetic acid containing hydrogen chloride, was dissolved in 90% methanol, treated with hydrochloric acid[2] in excess of that required to neutralize the anticipated triamine, and the solution was added slowly, in an atmosphere of hydrogen, to an agitated suspension of palladium in methanol. Addition of ether to the filtered, aqueous methanol solution of the reduced product precipitated the trihydrochloride of 2-methyl-3-amino-4,5-di-aminomethylpyridine. In the final transformation aqueous solutions of the trihydrochloride and of sodium nitrite were added simultaneously to hot aqueous hydrochloric, or better sulfuric, acid and the vitamin was isolated by appropriate concentration and extraction.

(1) Prepared according to the method of Bardhan, *J. Chem. Soc.*, 2223 (1929).

(2) Sulfuric acid was also used in this reduction. A solution of the substituted dinitrile (0.25 g.) in 50 cc. of 95% methanol containing 0.3 cc. of concentrated sulfuric acid was added slowly, in an atmosphere of hydrogen, to a suspension of palladium (prepared by reducing 1 g. of the chloride) in 50 cc. of 95% methanol, water was added to dissolve the precipitated product, the filtered solution was concentrated *in vacuo* to a volume of 2 cc., ethanol was added, the precipitated, crude sulfate was redissolved in 2 cc. of water, the solution was decolorized with active carbon and the sulfate was crystallized by the addition of glacial acetic acid. *Anal.* Calcd. for $C_8H_{14}N_4 \cdot 2H_2SO_4$: C, 26.50; H, 4.97; N, 15.46; SO_4, 53.0. Found: C, 26.85; H, 5.33; N, 15.0; SO_4, 52.4

Experimental

The Amide of 2-Methyl-4-carboxy-5-cyanopyridone-6.—The corresponding ethyl ester (200 g.) was added to 3.5 l. of absolute methanol saturated at 0° with ammonia and, after one week at 0°, the filtered solution, concentrated *in vacuo* to a small volume, gave the amide (m. p. above 300° with decomposition; yield 95–98%). *Anal.* Calcd. for $C_8H_7O_2N_2$: C, 54.2; H, 3.96; N, 23.76. Found: C (1) 54.44, (2) 54.48; H (1) 4.38, (2) 4.70; N (1) 22.77, (2) 22.81. On further concentration, the mother liquor yielded a small amount of slightly impure, yellowish amide.

2-Methyl-4,5-dicyanopyridone-6.—The amide of 2-methyl-4-carboxy-5-cyanopyridone-6 (2 g.) was heated with 25 cc. of phosphorus oxychloride at 145–150° for fifty minutes, the unchanged oxychloride was distilled *in vacuo*, the residue was treated with 50 g. of cracked ice and the crude product, after crystallization from aqueous alcohol, gave 0.4 g. of the pure dinitrile, m. p. 241–243°. *Anal.* Calcd. for $C_7H_5N_3O$: C, 60.3; H, 3.14; N, 26.4. Found: C (1) 60.25, (2) 60.55; H (1) 3.05, (2) 2.86; N (1) 26.15, (2) 26.02.

In a larger preparation, a mechanically stirred mixture of 50 g. of the amide, 250 cc. of toluene and 250 cc. of phosphorus oxychloride was heated at 130–135° for nine and one-half hours. After fifteen hours at room temperature, the undissolved material was filtered off, extracted successively with toluene, ether and acetone and yielded 8.9 g. of unchanged amide. The toluene filtrate and the combined toluene and ether extracts were evaporated *in vacuo*, the residue was treated with 20 cc. of ice-water, the resulting mixture was diluted with 800 cc. of hot acetone, the insoluble material was filtered off and, after two extractions with 300 cc. of hot acetone, yielded 11.3 g. of unchanged amide. Concentration of the combined acetone extracts *in vacuo* yielded 13.4 g. of crude diritrile, m. p. 239–243°, which, combined with that obtained in similar preparations, was recrystallized and gave the pure product, m. p. 241–243°.

2-Methyl-3-nitro-4,5-dicyanopyridone-6.—A suspension of the dinitrile (3.8 g.) in 20 cc. of acetic anhydride was treated at 45–52° with a solution prepared from 3 cc. of fuming nitric acid, 3 cc. of acetic anhydride and a few crystals of urea. The resulting solution, poured onto cracked ice, yielded 2.6 g. of the crude nitro compound which was dissolved in 75 cc. of acetone, the solution was treated with active charcoal, the filtrate was concentrated *in vacuo* to a small volume, ether was added and the precipitated nitropyridone, after recrystallization from an acetone–ether solution, gave 1.6 g. of the pure product, m. p. 242–244° *Anal.* Calcd. for $C_8H_4N_4O_3$: C, 47.01,

H, 1.96; N, 27.42. Found: C (1) 47.22, (2) 47.32; H (1) 2.11, (2) 2.06; N (1) 27.53, (2) 27.42.

2-Methyl-3-nitro-4,5-dicyano-6-chloropyridine.—The nitropyridone (5.9 g.), 7.5 g. of phosphorus pentachloride and 50 cc. of chlorobenzene were heated at 135° for two hours, solvent was distilled *in vacuo*, the residue was extracted with ether, the solution was treated with active charcoal, the filtrate was concentrated *in vacuo* to a small volume, petroleum ether was added and the precipitated, crude chloro compound (5.4 g.) gave 4.3 g. of the pure product, m. p. 86–86.5°, after recrystallization. *Anal.* Calcd. for $C_8H_3N_4O_2Cl$: C, 43.15; H, 1.35; N, 25.15; Cl, 15.95. Found: C, (1) 43.56, (2) 43.31; H (1) 1.63, (2) 1.58; N (1) 24.2, (2) 24.23; Cl (1) 15.60, (2) 15.33.

2-Methyl-3-amino-4,5-dicyano-6-chloropyridine.—A solution of 1 g. of the corresponding nitro derivative in 75 cc. of acetic anhydride was reduced catalytically in the usual manner (with 0.1 g. of platinum oxide catalyst, 390 cc. of hydrogen was absorbed during one hundred and sixty minutes), catalyst was filtered off and solvent was distilled *in vacuo*. The residue was washed with acetone, recrystallized successively from aqueous acetone and from acetic acid containing hydrogen chloride and yielded the amine (0.455 g., m. p. 221–221.5°). *Anal.* Calcd. for $C_8H_5N_4Cl$: C, 49.8; H, 2.60; N, 29.1; Cl, 18.45. Found: C, 49.96; H, 3.04; N, 29.22; Cl, 19.08.

2-Methyl-3-amino-4,5-di-aminomethyl-pyridine Trihydrochloride.—A solution of 2-methyl-3-amino-4,5-dicyano-6-chloropyridine (0.75 g.) and 0.75 g. of hydrogen chloride in 112.5 cc. of methanol containing 10% of water was added, during sixteen and one-half hours, to a mechanically agitated suspension of 3 g. of palladium chloride in 75 cc. of 90% methanol and absorbed 550 cc. of hydrogen at 30°. Sufficient water was added to dissolve the precipitated product, the filtered solution was diluted with an equal volume of ether, the deposited salt was washed with absolute methanol and yielded 0.78 g. of the trihydrochloride. *Anal.* Calcd. for $C_8H_{17}N_4Cl_3$: C, 34.83; H, 6.21; N, 20.33; Cl, 38.65. Found: C, 34.71; H, 6.30; N, 20.14; Cl (1) 38.87, (2) 38.48.

During twenty-four hours, the methanol filtrates deposited 0.095 g. of slightly impure salt of the triamine.

2-Methyl-3-hydroxy-4,5-di-hydroxymethyl-pyridine Hydrochloride.—A solution of 2-methyl-3-amino-4,5-di-aminomethylpyridine trihydrochloride (0.3 g.) in 5 cc. of water was added simultaneously with a solution of 0.68 g. of sodium nitrite in 5 cc. of water to 50 cc. of hot 2.5 *N* hydrochloric acid. When the evolution of gas ceased the product was evaporated to dryness *in vacuo*, the residue was extracted three times with acetone and repeatedly with hot ethanol, the combined alcohol extracts were concentrated *in vacuo* to a small volume and the solution, diluted with acetone, yielded, during fifteen hours at 5°, the crystalline hydrochloride of the vitamin, m. p. 208–209°, which did not depress the melting point of an authentic specimen. In a similar preparation [the solutions of the trihydrochloride (0.4 g. in 7 cc. of water) and of sodium nitrite (0.33 g. in 7 cc. of water) were added to 20 cc. of hot 2.5 *N* hydrochloric acid], the hydrochloride of the vitamin was purified by crystallization from hot butanol, m. p. 208–209°. *Anal.* Calcd. for $C_8H_{12}O_3NCl$: C, 46.72; H, 5.88; Cl, 17.27. Found: C, 46.40; H, 6.02; Cl, 17.30.

Solutions prepared from 1.33 g. of the triamine trihydrochloride in 10 cc. of water and from 2 g. of sodium nitrite in 10 cc. of water were added simultaneously to a hot solution of 2.5 cc. of concentrated sulfuric acid in 22.5 cc. of water and, after twenty minutes, 11.75 g. of barium chloride dissolved in 45 cc. of water was added. The filtrate was evaporated to dryness *in vacuo*, the residue was washed with acetone, extracted repeatedly with hot ethanol, solvent was distilled *in vacuo* from the combined and decolorized extracts, a solution of the residue in dilute hydrochloric acid was filtered through active charcoal, solvent was distilled *in vacuo* and the residue, crystallized from hot butanol, yielded 0.2055 g. of the hydrochloride of the vitamin. The filtrate deposited 0.1565 g. more of the hydrochloride.

Summary

A synthesis of vitamin B_6 is described which involves dehydration of the amide of 2-methyl-4-carboxy-5-cyanopyridone-6 to 2-methyl-4,5-dicyanopyridone-6 and, by a process of nitration, chlorination and appropriate stepwise catalytic reductions, transformation to the trihydrochloride of 2-methyl-3-amino-4,5-di-aminomethyl-pyridine which is converted to the vitamin.

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