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# ALIEN PROPERTY CUSTODIAN

## COMPOUNDS HAVING VITAMIN $B_6$ ACTIVITY

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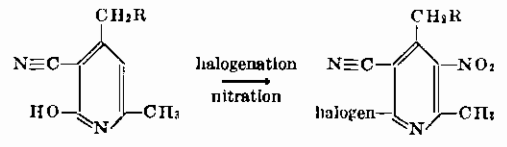
This invention relates to compounds having vitamin $B_6$ activity, intermediates used in their production, and to processes for such production.

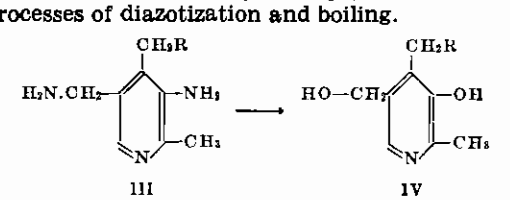
Synthetic substances having the properties of vitamin $B_6$ in biological tests have not been heretofore known. Vitamin $B_6$ is obtained in small amounts from natural material by means of very troublesome procedures. It has not previously been obtained synthetically.

According to this invention, compounds with the activity of vitamin $B_6$ may be prepared from 2-methyl-3-nitro-5-cyano-6-halogen pyridines having in position 4 the group $CH_2R$, where R is hydrogen, hydroxyl or a group which may be converted into OH. These substances are easily prepared from acetyl acetone or its derivatives of the formula $CH_3—CO—CH_2—CO—CH_2R_1$, where $R_1$ is OH or a group which may be converted into OH, ammonia, and a suitable derivative of malonic acid or cyano acetic acid (such as malonic amide, permitting the subsequent conversion of the acid amide into the nitrile group; or cyanoacetic ester or its amide) which is adapted to permit formation of a pyridine nucleus. The stated reaction components may be allowed to react simultaneously, or the mono-imine may be first prepared from acetyl-acetone (or its derivatives) and ammonia, and then condensed with the malonic acid derivative. Compounds of formula I are thus obtained in good yields, which are converted into the desired starting material of formula II by nitration and halogenation.




I II

The invention consists in reducing these compounds under such conditions that a substitution of the halogen by hydrogen and a reduction of the cyano- and nitro groups to aminomethyl and amino groups takes place, for which end catalytical reduction is particularly suited. Both amino groups of the compound III thus obtained may be substituted by hydroxyl groups, by the usual processes of diazotization and boiling.




III IV

The synthesis may be very easily and simply carried out as follows:

2,4-dimethyl-5-cyano-6-hydroxypyridine, easily obtainable from the imino compound of the acetyl acetone and cyano acetic ester, is nitrated, for example, with a mixture of concentrated sulfuric and nitric acid or with nitric acid and acetic anhydride. The nitrated compound is then chlorinated, for example, with thionyl chloride, phosgene, or $POCl_3$ and $PCl_5$, whereby 2,4-dimethyl-3-nitro-5-cyano-6-chloropyridine is obtained.

Surprisingly, this substance may be reduced catalytically in one operation to 2,4-dimethyl-3-amino-5-aminomethylpyridine. The catalytic reduction of a cyano group in the pyridine series has not been heretofore carried out, the reduction having been always carried out, in a troublesome way, by reducing chemicals, and with very poor results. Finally, both the aliphatic and the pyridine amino groups are transformed into hydroxyl groups in one operation by diazotization and boiling in an acid solution.

2,4-dimethyl-3-hydroxy-5-hydroxymethylpyridine thus obtained melts at 254° C. and, surprisingly, shows the biological activity of vitamin $B_6$.

We have also discovered that an alkoxyacetylacetone may be reacted with a cyanacetic acid ester to form 2-methyl-4-methoxymethyl-5-cyano-6-hydroxypyridine, and that upon nitration and chlorination of the latter compound, 2-methyl-3-nitro-4-alkoxymethyl-5-cyano-6-chloropyridine is obtained. The latter compound is hydrogenated to 2-methyl-3-amino-4-alkoxymethyl-5-aminomethylpyridine, which is diazotized to form 2-methyl-3-hydroxy-4-alkoxymethyl-5-hydroxymethylpyridine. The latter compound, upon treatment with hydrobromic acid, forms 2-methyl-3-hydroxy-4,5-di-(bromomethyl)-pyridine, which, upon hydrolysis, forms vitamin $B_6$.

The following examples illustrate methods of carrying out the present invention, but it is to be understood that these examples are given by way of illustration, and not of limitation.

*Example I*

2,4-dimethyl-5-cyano-6-hydroxypyridine is nitrated with concentrated sulfuric and nitric acid to the 2,4-dimethyl-3-nitro-5-cyano-6-hydroxypyridine. The 3-nitro derivative thus obtained is chlorinated with a mixture of $POCl_3$ and $PCl_5$. 2,4-dimethyl-3-nitro-5-cyano -6- chloropyridine, melting at 112° C., is obtained.

7.1 g. of 2,4-dimethyl-3-nitro-5-cyano-6-chloropyridine is dissolved in 200 cc. methanol and shaken with $H_2$ with the addition of 15.6 cc. 2NHCl in the presence of 5 g. of Pd-charcoal at room temperature. After 40 hours, 6 mol. of $H_2$ is absorbed, and the hydrogenation ceases. After filtering off the catalyst, the solvent is evaporated and the residue recrystallized from methanol and ether. The 2,4-dimethyl-3-amino-5-methyl-

aminopyridine crystallizes in the form of its dihydrochloride in white glistening platelets with a decomposition point of 310° C. Yield: 95% that of theory. The free base may be isolated by extraction of a concentrated alkaline solution of the dihydrochloride with chloroform, and melts at 132° C. after recrystallization from methanol and ether.

2.24 g. of 2,4-dimethyl-3-amino-5-methylaminopyridine dihydrochloride is dissolved in 10 cc. of water and treated with a solution of 1.5 g. sodium nitrite in 10 cc. water. 15 cc. of 1 N hydrochloric acid is added to this mixture while stirring. The reaction solution is kept for approximately 1 hour at 60° C. until no more nitrite can be determined with starch paper impregnated with potassium iodide. Then the solution is evaporated in vacuo and the well-dried residue is extracted several times with absolute alcohol. The residue remaining on the evaporation of the alcohol is recrystallized from methanol and ether, whereby 2,4-dimethyl-3-hydroxy-5-hydroxymethylpyridine in the form of the hydrochloride, melting at 254° C., is crystallized out.

In the vitamin $B_6$ test as a growth substance for lactic acid bacteria according to Möller [Zeitschrift für physiol. Chemie, 254, 285 (1938)] this substance shows indisputably positive activity from which the optimal concentration is placed around 1γ/cc.

Heretofore, no substance has shown activity in this test, other than the natural vitamin $B_6$.

*Example II*

2-methyl-3-nitro-4-methoxymethyl-5-cyano-6-chloropyridine is prepared by condensation of methoxyacetylacetone with cyanoacetic acid ester in 25% ammonia at 60° C., 2-methyl-4-methoxymethyl-5-cyano-6-hydroxypyridine being obtained. This compound is first nitrated by means of 86% nitric acid in acetic anhydride at a temperature not higher than 60° C. to form 2-methyl-3-nitro-4-methoxymethyl-5-cyano-6-hydroxypyridine, and the latter compound is chlorinated with phosphorus pentachloride and phosphorus oxychloride by heating under reflux.

15 g. of 2-methyl-3-nitro-4-methoxymethyl-5-cyano-6-chloropyridine is shaken with hydrogen at room temperature in 600 cc. methanol with the addition of 31.5 cc. 2 N hydrochloric acid in the presence of 10 g. of 10% palladium charcoal. The absorption of 3 mol. of hydrogen proceeds rapidly with evolution of heat. In 15 hours the hydrogenation ceases after absorption of 6 moles of hydrogen. The catalyst is filtered off, the solvent is distilled off, and ether is added, whereupon 2-methyl-3-amino-4-methoxymethyl-5-aminomethylpyridine separates out in white needles. On recrystallization from methanol it melts at 236° C. The yield amounts to 90% of theory.

To a solution of 7.3 g. of 2-methyl-3-amino-4-methoxymethyl-5-methylaminopyridine-dihydrochloride in 50 cc. of water is added dopwise and while stirring a solution of 4.4 g. sodium nitrite in 50 cc. water and 29 cc. 2 N hydrochloric acid. The solution is kept at 60–70° for 30 minutes longer and finally is evaporated to dryness at 40° C. in vacuo. It is separated from the sodium chloride by extraction of the well-dried residues with absolute alcohol, and the solution obtained is evaporated in vacuo. The residue is recrystallized from absolute alcohol and acetone. Thus 2-methyl-3-hydroxy-4-methoxymethyl-5-hydroxymethylpyridine, as the monohydrochloride salt melting at 182° C., is obtained. Yield, 5 g.

The 4-methoxymethyl group of this compound may be easily converted by boiling with 66% hydrobromic acid. Since the hydrobromic acid attacks also the aliphatic hydroxyl group, 2-methyl-3-hydroxy-4,5-di-(bromomethyl)-pyridine is obtained, which may be converted into 2-methyl-3-hydroxy-4,5-di-(hydroxymethyl)-pyridine by treating it with boiling water, and then with silver chloride.

Other 4-alkoxymethylpyridines may be used in the process. For example, when employing ethoxyacetylacetone as a starting material, the corresponding 4-ethoxymethyl-pyridine will be obtained.

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