Published Apr. 20, 1943

Serial No. 346,569

ALIEN PROPERTY CUSTODIAN

PROCESS FOR THE MANUFACTURE OF DERIVATIVES OF PYRIDINE

Otto Zima and Fritz Jung, Darmstadt, Germany; vested in the Alien Property Custodian

No Drawing. Application filed July 20, 1940

This invention relates to a process for the manufacture of derivatives of pyridine.

The reduction of cyanopyridines to the corresponding aminomethylpyridines is a reaction on which much work has been done at various times, since considerable difficulties are encountered in that the usual reduction process for aliphatic or aromatic cyano groups is not effective with the cyano group attached to the pyridine nucleus. Thus, although aminomethyl compounds were early prepared by the reduction of aromatic or aliphatic cyano compounds, aminomethylpyridines were unknown until 1933. Camps [Arch. Pharm., 240, 370 (1902)] first tried to prepare these chemotherapeutically interesting substances by the reduction of cyanopyridine, using sodium amalgam as a reducing agent. However, instead of the hoped for compound, cleavage of hydrocyanic acid took place, together with saponification of the compound to the acid amide and then to the acid. With aluminum amalgam no better results were obtained.

Wibaut and Overhoff [Rec. trav. chim., 52, 55–6 (1933)] were the first to carry out the desired reaction although unintentionally. In attempting to convert the cyano group of 2,6-dichloro-4-cyanopyridine into the aldehyde group according to the method of Stephen, by treatment with stannous chloride and hydrochloric acid, and subsequent hydrolysis, they obtained surprisingly enough a straightforward reduction of the cyano group to the aminomethyl group. This process, however, can not be applied to other cyanopyridines. In an attempt to reduce 2-cyanopyridine according to this method, most of the starting material was recovered, and a small portion of it was hydrolyzed.

Graf [J. prakt. Chem. 140, 39 ff, (1934); 146 88 ff, (1936)] was the first to finally describe a process for the reduction of cyanopyridines, which has shown itself to be of general application up to the present time. In this process, chromium salts in an alkaline solution are used as reducing agents. This procedure is extremely troublesome and tedious, since it is dependent on the exact amount of the chromium salts used. With excess of salt, ammonia is split off, giving methylpyridines and, moreover, the yields are often less than 50%.

According to the present invention, the reduction of cyanopyridines to the corresponding aminomethyl compound occurs with 90% yields, and the elimination of the reducing agent and the working up of the mixture are quite simple. We have discovered that the reduction of a cyanopyridine with hydrogen in the presence of hydrogen carrying catalysts, particularly noble metal catalysts, procedes surprisingly smoothly. although undesired results, such as the formation of secondary amines, nitrogen free substances or heterocyclic substances, have been observed with this reaction in other cyano compounds.

This new reduction process gives excellent results even with cyanopyridines having relatively complicated substituents. The reduction of the cyano group is not hindered, even though the compound to be reduced contains other groups such as halogen or nitro, which are also liable to catalytical reduction.

The catalytical hydrogenation of the cyano group can be carried out in solution with or without the addition of acid. The lower aliphatic alcohols, glacial acetic acid, diluted acids, etc., are suitable solvents. When the reduction is carried out at atmospheric pressure at room temperature, it ceases on the absorption of the theoretical amount of hydrogen (4 atoms hydrogen for each cyano group).

The compounds obtained according to the invention are used as medicinals or as intermediate products for the manufacture of medicinals.

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

7.1 g. 2,4-dimethyl-3-nitro-5-cyano-6-chloropyridine (m. p. 112° C.) is dissolved in 200 cc. methanol with the addition of 15.7 cc. 2 N hydrochloric acid in the presence of 10 g. of 10% Pd-charcoal, and shaken with hydrogen at room temperature. On the absorption of 6 mol. of hydrogen, the hydrogenation ceases. The solution, filtered off from the catalyst, is evaporated almost completely and treated then with ether, 2,4 - dimethyl - 3 - amino-5-aminomethylpyridine crystallizes out as the dihydrochloride in white shiny platelets, melting at 310° C. Yield, 95% of theory.

Crystalline 2,4-dimethyl -3 - amino - 5 -aminoethylpyridine is isolated by extraction of a concentrated alkaline solution of the dihydrochloride with chloroform. On recrystallization from methanol and ether it melts at 132° C.

Example II

7.4 g. of 2,4-dimethyl-5-cyano-6-hydroxy-pyridine, (m. p. 291° C.) in 400 cc. of methanol and 5 cc. of concentrated hydrochloric acid (d=1.19)

is hydrogenated in the presence of 10 g. Pd-charcoal at 60° C. After 10 hours, 2 mol. of H are absorbed, and the hydrogenation ceases. After filtration of the catalyst, the solvent is evaporated almost completely, and the 2,4-dimethyl-5-aminomethyl-6-hydroxypyridine crystallizes out on the addition of ether as the hydrochloride in shiny platelets. On recrystallization from methanol and ether it melts at 320° C. Yield, 92% of theory.

Example III

1.7 g. of 2,4-dimethyl-3-amino-5-cyano-6-chloropyridine, m. p. 140° C. (obtained by the discontinuation of the hydrogenation described in Example I after the absorption of 3 mol. H) is shaken with hydrogen in methanol with the addition of 1 cc. of concentrated hydrochloric acid (d=1.19) at 60° C. in the presence of 0.5 g. of Pd-charcoal. Upon the absorption of 3 mol. of H, the hydrogenation ceases. The catalyst is filtered off with suction, the solvent is evaporated, and the residue is treated with ether. 2,4-dimethyl-3-amino-5-aminoethylpyridine separates out as the dihydrochloride. On recrystallization from methanol and ether it melts at 310° C. Yield, 1.5 g.

Example IV

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.

OTTO ZIMA.
FRITZ JUNG.