

1

2,702,802

**PROCESS OF MAKING ISOCINCHOMERONIC ACID
AND DECARBOXYLATION OF SAME TO NIACIN**

Robert S. Aries, New York, N. Y.

No Drawing. Application December 27, 1951,
Serial No. 263,709

5 Claims. (Cl. 260—295.5)

This invention relates to an improved process for making niacin from 2,5-dialkyl pyridines, and more particularly from the readily available 2-methyl-5-ethyl-pyridine by oxidation with nitric acid to isocinchomeronic acid followed by decarboxylation to niacin.

Niacin, more commonly termed nicotinic acid, is one of the B-complex vitamins essential for growth and the prevention and cure of pellagra, and as such it is in demand as an additive to the human diet and as a general animal feed supplement.

The principal object of the present invention is to improve existing methods for making niacin involving the oxidation of the 2,5-dialkyl pyridines by nitric acid.

Heretofore a common method of making niacin has been to cause a 2,5-dialkyl pyridine, and particularly 2-methyl-5-ethyl-pyridine, to react with nitric acid under conditions of superatmospheric pressures and elevated temperatures, e. g., 185° C. and above, to yield niacin in a single operation, even though essentially two reactions are involved, namely, oxidation of the 2,5-dialkyl pyridine to isocinchomeronic acid, followed by decarboxylation of the latter to niacin. Optimum conditions for the decarboxylation reaction involve a temperature range of 185–190° C. or higher. The oxidation reaction, on the other hand, proceeds at a lower temperature, e. g., from 155° to 188° C., with satisfactory results to be had at the lower temperature range. However, when the oxidation reaction is carried out at the higher temperatures best suited for the decarboxylation reaction, it is found that the nitric acid mixture present is extremely corrosive to stainless steel, the only structural material readily available for a reaction chamber within which to carry out the reaction. Thus, in the prior art costly tantalum or platinum lined equipment has been recommended for the combined oxidation-decarboxylation reactions.

Investigation of the effect of corrosion of the above-mentioned oxidation reaction products at temperatures 185–190° C. on stainless steel has yielded the following data:

Stainless Steel Type	Liquid	Vapor
304.....	0.031	0.063
316.....	0.039	0.071
309.....	0.028	0.054

Local corrosion rates may far exceed the overall corrosion rates shown above. This may be attributed to unavoidable differences in metallurgy at various points in the stainless steel. These differences are to be ascribed to variations in the manufacture of the steel, the fabrication of the vessel, and the heat treatment process. In addition, I have found that the decarboxylation reaction, especially at the lower temperatures, is slower than the oxidation reaction and is responsible for a long holdup in the time required to effect substantially complete conversion of the isocinchomeronic acid to niacin. Because of this, large equipment is required, thereby increasing the total corrosion involved.

It is therefore a more specific object of my invention to provide an improved process in which the oxidation reaction to isocinchomeronic acid is carried out separately from the decarboxylation reaction to niacin under conditions best suited for each, with the consequent saving of equipment life and with other substantial advantages to be mentioned.

2

A further object is to provide an improved process of converting isocinchomeronic acid to niacin.

A still further object is to devise an improved process of recovering the produced niacin in the form of a niacin ester.

In carrying out my invention I therefore preferably react 2-methyl-5-ethyl-pyridine with nitric acid at temperatures from 155 to 180° C. to form principally isocinchomeronic acid. I then separate the isocinchomeronic acid from the reaction products and convert it to niacin, preferably in absence of nitric acid and employing temperatures best suited for this reaction in the range of 180–190° C. or higher, whereby the reaction is carried out under conditions which are not corrosive and which in some instances, if desired, do not require the use of pressure equipment. Furthermore, by using a concentrated solution or slurry of isocinchomeronic acid as compared to that normally present in the reactor, the decarboxylation to niacin may be carried out in small compact, relatively inexpensive equipment.

I have found that the isocinchomeronic acid may be separated from the reaction mixture by adjusting its pH to 1.0–2.0, preferably 1.5. Normally, by proper choice of feed rate, feed composition, temperature and pressure, this range of pH may be automatically had. Then the reaction mixture is cooled to 25° C. and the precipitate filtered off and washed or reslurried with a small amount of water to remove traces of nitric acid, thereby yielding a product which is essentially isocinchomeronic acid. It is then slurried in a solvent medium or vehicle hereinafter disclosed, and therein subjected to temperatures from 180 to 190° C. or higher. If desired, the medium can be so chosen that no pressure is required to reach the desired temperature or, in any event, one that is no higher than that of the vapor pressure of the medium at the temperature used. Among the non-reactive media which I prefer may be mentioned the following: water, commercial heat transfer oil (consisting of high boiling hydrocarbons) sulfuric acid and various organic solvents such as cyclohexanone.

Especially when sulfuric acid has been used as the vehicle, I may advantageously recover the produced niacin in the form of an ester by adding to the acid mixture a slight excess of a lower, saturated, aliphatic alcohol, then heating the mixture with agitation and under reflux until esterification is complete, then cooling, neutralizing and extracting with a suitable solvent. After removal of the extract by distillation, the niacin ester may then be refined by subjecting it to distillation and recovering the pure niacin ester as the distillate.

My invention will be best understood by reference to the following illustrative examples:

Example 1

12.0 grams of 2-methyl-5-ethyl-pyridine were weighed out and added to enough concentrated nitric acid and distilled water such that the final mixture was 20 percent nitric acid and the mole ratio of acid to base was 7 to 1. The mixture was placed in a standard 250 cc. stainless steel rocker bomb and heated to 175° C. for a period of one hour.

On cooling to 25° C. a precipitate was obtained which was filtered off. This precipitate was reslurried with 100 cc. of distilled water and it was then filtered. Sufficient wash water was used to make all transfers of precipitates quantitative. The wet precipitate was charged into the rocker bomb with 50 cc. of distilled water. The mixture was heated as described in Example 2. On completion of the reaction, the reaction product was found to contain 3.0 grams of niacin and no isocinchomeronic acid.

The reaction between 2-methyl-5-ethyl-pyridine and nitric acid was repeated using the quantities and conditions as described above. The reaction mixture was found to contain 27 mole percent isocinchomeronic acid based on the 2-methyl-5-ethyl-pyridine charged.

Example 2

10 grams of isocinchomeronic acid and 100 grams of water were charged to 250 cc. rocker bomb. The mixture was heated to 205° C. and maintained at this temperature for 2 hours. An analysis of the reaction prod-

3

uct showed that 94 mole percent of the isocinchomeric acid was converted to niacin and only a slight trace of isocinchomeric acid could be detected.

Example 3

10 grams of isocinchomeric acid were heated in a glass beaker with 50 ml. of heat transfer oil. The temperature was maintained at 235° C. for 2 hours with agitation. On cooling, niacin came out of solution and was filtered off. On analysis, a 92 mole percent of the isocinchomeric acid was found to have been converted to niacin and no trace of the original dicarboxylic acid could be detected.

Example 4

10 grams of isocinchomeric acid were heated in a glass beaker with 50 ml. of concentrated sulfuric acid with agitation until the evolution of carbon dioxide was complete. On cooling and neutralizing, analysis showed that 96 mole percent of the dicarboxylic acid had been converted to niacin.

Example 5

Example 4 was repeated except that to the cooled reaction product was added 50 grams of denatured alcohol and the mixture was refluxed for eight hours. The reaction product was neutralized with ammonium hydroxide over cracked ice. The cold alkaline solution was extracted three times with ether. The combined ether extracts were dried over anhydrous sodium sulfate and distilled under vacuum after the ether was removed. Ethyl nicotinate was obtained as the reaction product.

I claim:

1. The method of making niacin from isocinchomeric acid by the decarboxylation thereof by heat with recovery of the niacin produced, characterized by mixing isocinchomeric acid in a non-reactive, substantially non-corrosive liquid vehicle selected from the group consisting of water, high temperature heat transfer oil, concentrated sulfuric acid and cyclohexanone, and heating the mixture to a decarboxylating temperature range above 180° C. and maintaining such temperature range until the decarboxylation is substantially complete.

2. The method of making niacin from isocinchomeric acid by the decarboxylation thereof by heat with

4

recovery of the niacin produced, characterized by mixing isocinchomeric acid in water, and heating the mixture to a decarboxylating temperature range above 180° C. and maintaining such temperature range until the decarboxylation is substantially complete.

3. The method of making niacin from isocinchomeric acid by the decarboxylation thereof by heat with recovery of the niacin produced, characterized by mixing isocinchomeric acid in heat transfer oil, and heating the mixture to a decarboxylating temperature range above 180° C. and maintaining such temperature range until the decarboxylation is substantially complete.

4. The method of making niacin from isocinchomeric acid by the decarboxylation thereof by heat with recovery of the niacin produced, characterized by mixing isocinchomeric acid in concentrated sulfuric acid, and heating the mixture to a decarboxylating temperature range above 180° C. and maintaining such temperature range until the decarboxylation is substantially complete.

5. The method of making niacin from isocinchomeric acid by the decarboxylation thereof by heat with recovery of the niacin produced, characterized by mixing isocinchomeric acid in cyclohexanone, and heating the mixture to a decarboxylating temperature range above 180° C. and maintaining such temperature range until the decarboxylation is substantially complete.

References Cited in the file of this patent

UNITED STATES PATENTS

2,280,040	Seibert et al.	Apr. 14, 1942
2,389,065	Lee et al.	Nov. 13, 1945
2,524,957	Burrows et al.	Oct. 10, 1950

FOREIGN PATENTS

234,588	Switzerland	Feb. 1, 1945
---------	-------------------	--------------

OTHER REFERENCES

- 40 Elderfield, "Heterocyclic Compounds" (1950), vol. 1, pp. 568-71.
Maier-Bode et al., "Pyridin Und Seine Derivate" (1934), p. 236.