Oxidation of Pyridine Bases to Pyridine Carboxylic Acids with Dilute Nitric Acid at High Temperature and Pressure

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Pyridine homologues were oxidized in a stainless steel autoclave using dilute nitric acid at temperatures of about 200° C and pressures of about 30–40 kg/cm². Beta-picoline gave nicotinic acid in 50–60 % yield and gamma-picoline was oxidized to *isonicotinic* acid in an average yield of about 93 %. Gamma-ethylpyridine also gave a very good yield (90 %) of *isonicotinic* acid. The yield from 2,4-lutidine was 45 % and from 2,4,6-collidine 40 %.

Isonicotinic acid was also prepared from mixtures of 2,4- and 2,6-lutidines as well as from commercial mixtures of higher pyridine homologues. A product of good purity was obtained in satisfactory yield. It is thus possible to produce *isonicotinic* acid in a convenient way from cheap "by-product" pyridines.

Formerly the industrial oxidation of pyridine homologues and of quinoline and its derivatives was mainly carried out using expensive oxidizing agents such as potassium permanganate and there are still plants operating in this way. Nitric acid has been used for the oxidation of nicotine to nicotinic acid and there are several patents claiming the oxidation of different pyridine bases with nitric acid or nitrogen tetroxide in the presence of sulphuric acid at temperatures of about 300° C. Small quantities of selenium are used as catalyst¹. Other patent specifications describe the oxidation of quinoline derivatives, *e. g.* oxiquinoline, with nitric acid in the presence of HCl² and methods have been given of oxidizing sulphates and phosphates of quinoline, *isoquinoline*, alkyl quinolines and picolines with nitric acid³. A characteristic feature of these methods is that they operate at atmospheric pressure. There are examples, however, of the process being conducted at higher pressures.

Thus, 2,5-dialkylpyridines have been oxidized with nitric acid of 60 % concentration at 160–200° C under pressure to give pyridine-2,5-dicarboxylic acid⁴. Using such comparatively concentrated nitric acid under pressure can be expected to cause explosions and such have been reported. Oxidation

of 2-methyl-5-ethylpyridine with air under pressure in the presence of HNO_3 was recently reported in a patent⁵, and the oxidation of this compound and beta-picoline with nitric acid at 150—180° C in the presence of catalysts was recently claimed⁶. The oxidation of 2-methyl-5-ethylpyridine with dilute nitric acid under pressure was originally carried out by Krzikalla⁷ and nicotinic acid is now made on an industrial scale at 185° C and about 20 atm. pressure⁸. No details are, however, given as to the method of carrying out this process and nothing has been published concerning the possibility of using high pressure oxidation with dilute nitric acid for the industrial manufacture of isonicotinic acid and nicotinic acid from other pyridine bases. This paper gives a concentrated survey of experimental work which had the purpose of studying technical methods of making nicotinic acid and isonicotinic acid out of various raw materials by high pressure oxidation with dilute nitric acid.

Nicotinic acid can be made from beta-picoline in fairly good yield by oxidizing with 10 % HNO_3 at 230° C and 35—40 atm. Higher yield but lower conversion was obtained at 200° C.

Isonicotinic acid was made from various raw materials. Gamma-picoline gave a 93.5 % yield with HNO_3 of 10 % concentration at 230° C and 40 atm. and gamma-ethylpyridine was oxidized at 200° C and 30—40 atm. in a 90 % yield. 2,4-Lutidine gave a 45 % yield and 2,4,6-collidine gave a 40 % yield under similar conditions.

It is however rather expensive to use these pure compounds as raw materials for the production of isonicotinic acid and, also they have sometimes been in very short supply. Therefore a method has been developed, which uses low-priced mixtures of pyridine bases instead of pure isomers. Such mixtures have been oxidized with dilute nitric acid at about 200° C and 30—40 atm. to give isonicotinic acid of good purity in satisfactory yield. This makes it possible to produce this new pharmaceutical intermediate at low cost using readily available "by-product" pyridines.

Most of the processes reported in this paper have also been run successfully on a semi-technical scale. The technical performance of the methods towards semi-continuous and continuous methods has also been studied.

EXPERIMENTAL

The oxidations were carried out in a stainless steel autoclave according to a procedure described in a previous paper⁹. Some experiments were run in the presence of phosphoric acid which was shown to prevent corrosion and sometimes also to improve the yield.

Oxidation of beta-picoline. β -Picoline (50 g) was oxidized with an equivalent quantity of 10 % nitric acid in the presence of 60 g of 89 % orthophosphoric acid at 230° and 35—40 atm. pressure. The nitric acid was added in 2 portions and the total reaction time was 2 hours. The volume of the autoclave was 2.5 litres. Since a homogeneous solution was formed no stirring was necessary.

The autoclave was then discharged through a riser by means of the pressure in the autoclave. By evaporation of the reaction product, removing the rest of the nitric acid by heating with ethyl alcohol and esterification with ethyl alcohol, the nicotinic acid formed was converted to the ethyl ester. In a series of experiments this was obtained in a 50—60 % yield (calculated on converted picoline) and had a satisfactory degree of purity. (Saponification value 365—376). About 40 % of the picoline was unchanged and

was recovered. The corrosion of stainless steel proved to be as low as 0.1–0.2 g per m² per hour.

The process can also be conducted continuously, by pumping in the reactants using high pressure pumps and discharging the contents of the autoclave continuously through a riser. The acid can also be added portionwise (all the organic compound being added at the start of the reaction) so that excess of acid is present only towards the end of the reaction.

In another series of experiments the oxidation was carried out as above but the nicotinic acid was obtained by evaporation of the acid solution and adjusting the pH value to 3.5. A further amount of nicotinic acid could be obtained *via* the copper salt (unconverted picoline being removed by distillation), after raising the pH value.

When the picoline was oxidized as above but at 200° C, the reaction was slower, necessitating a longer reaction time, but the yield was higher.

β -Picoline was also oxidized in the same way without the addition of phosphoric acid. The yield was somewhat lower and the corrosion was more serious.

Oxidation of gamma-picoline. Gamma-picoline (90 g), an equivalent quantity of 10 % nitric acid and 89 % orthophosphoric acid (108 g) were heated in an autoclave at 230° C and a pressure of 40 kg per cm². The reaction was allowed to proceed for one hour after the temperature had reached 230° C. While still warm the batch was discharged and concentrated to one-half the original volume.

After cooling, part of the product precipitated. After adjusting the pH value to 3.5, the isonicotinic acid was filtered off and washed with water. To the mother liquor, which contained a small amount of isonicotinic acid, alkali was added until the pH value was 7, and unconverted picoline was then distilled with steam.

The steam distillation was discontinued when the distillate no longer smelt of picoline and in this way approximately 15 % of the original amount of picoline was recovered. The picoline solution was used for a new run. After having precipitated the phosphoric acid with CaCl₂, the isonicotinic acid remaining in the mother liquor was precipitated as the copper salt. After boiling it with NaOH, isonicotinic acid could be obtained.

In a series of such oxidations the average yield was 93.5 %. The equivalent weights of the crude product varied from 122.4 to 123.3 against the theoretical 123.1. The tertiary nitrogen content was in very good agreement. The crude product could be converted directly to pure isonicotinic acid hydrazide, in high yield.

Other experiments were carried out as above, except that initially a smaller quantity of the components was run in and then a solution of gamma-picoline in nitric acid and phosphoric acid was gradually added in portions as each preceding addition had reacted. For the first charging a 10 % acid was used, and then 30 % nitric acid. In this way a higher capacity was attained. The portionwise addition can also be accomplished by means of high-pressure pumps, and the procedure can be made continuous by continuous discharge *via* a riser.

Oxidations were also carried out without the addition of phosphoric acid. The yield was of the same order of magnitude but the corrosive attack was more severe.

Oxidation of gamma-ethylpyridine. Gamma-ethylpyridine was oxidized with 30 % HNO₃ in 10 % excess, at 180–200° C and 30–40 kg per cm². The reaction time was one hour after the temperature had reached 180° C. The main part of the isonicotinic acid was obtained on adjusting the pH value to 3.5 and a further small quantity was isolated *via* the copper salt. The yield was about 90 %. Oxidations were also carried out in the same way with 10 % HNO₃ and in the presence of phosphoric acid. The yield was about the same.

In preparing gamma-ethylpyridine by treating pyridine with acetic anhydride and zinc there was obtained, after the ethyl pyridine fraction had been steam-distilled, a fraction boiling at 175–210° C (760 mm Hg). This was oxidized with HNO₃ as above and isonicotinic acid in 60 % yield was obtained.

Isonicotinic acid from 2,4-lutidine and 2,4,6-collidine. 2,4-Lutidine, technical grade, was oxidized with 20 % HNO₃ in equivalent amount in the presence of phosphoric acid. The temperature was 230° C, the pressure 40 kg per cm² and the reaction time at 230° C one hour. Isonicotinic acid was then obtained in 45 % yield, not taking into account the unconverted lutidine. The product was obtained partly by direct precipitation at pH 3 and partly *via* the copper salt.

45 g of 2,4,6-collidine and 30 % nitric acid in 10 % excess were placed in a laboratory autoclave together with phosphoric acid and heated without stirring to about 180° C when the reaction started. This first batch having reacted, a total amount of 90 g of collidine and a corresponding quantity of 30 % acid in 10 % excess were fed into the autoclave in several portions. The temperature was maintained at 190–200° C and the pressure at 30–40 kg per cm² for the whole period. Nitrogen oxides were expelled from time to time. After the last addition, the autoclave was allowed to stand at 200° C and 40 kg pressure for one hour.

The acid solution was evaporated to give, on cooling, 21 g of *isonicotinic* acid. After further evaporation and adjustment of the pH value to 3.5, an additional 34 g were isolated. Thereafter 15 g of copper *isonicotinate* and a portion of unconverted collidine were obtained.

Isonicotinic acid from mixtures of pyridine bases. 80 g of a synthetic mixture of ca. 42 % gamma-picoline, 34 % beta-picoline and 24 % 2,6-lutidine were placed in an autoclave together with 1 275 g of 10 % HNO₃, and the batch was heated to 190° C. The temperature rose to a maximum of 235° C, and the pressure to a maximum of 40 kg per cm². The reaction time at 220–230° C and 30–40 kg per cm² was approximately one hour. The reaction mixture was then evaporated to a volume of about 450 ml at which point 25 g of a product precipitated which, judging by the melting point and equivalent weight, consisted of *isonicotinic* acid. Without being subjected to any purification process, this crude product was used for preparing the hydrazide. The compound obtained was, according to the analyses, pure *isonicotinic* hydrazide. The yield from the hydrazide synthesis was quite as good as when pure *isonicotinic* acid was used as the raw material. From the mother liquor from the oxidation an additional amount of *isonicotinic* acid could be obtained by precipitation of the copper salt.

In the same way 45 g of a commercial mixture of pyridine bases with a boiling range of 164–181° C at 760 mm Hg were oxidized with 10 % HNO₃ in 10 % excess (the mixture being considered as collidine) at 200–210° C and 35–40 kg per cm². After evaporation, 10 g of a product was obtained having an equivalent weight of 124.5. This product was converted, without further purification, to the hydrazide in the usual way and a product was obtained which, on the basis of the analyses, was pure *isonicotinic* hydrazide. An additional amount of *isonicotinic* acid could be obtained from the mother liquor.

Other experiments were run as above except that the autoclave was charged with the mixture of pyridine homologues and 30 % nitric acid in 10 % excess. When this batch had reacted, a further amount of the homogenous mixture in 40 % HNO₃ was successively run in *via* pressure cylinders. The reaction took place at 200–210° C, and 40 kg per cm². The reaction time, after all the reactants had been added, was one hour at the temperature and pressure stated.

When the reaction was completed, the batch was discharged while boiling off the water, and the pH value was adjusted to 3.5 without further evaporation. After cooling, *isonicotinic* acid precipitated and this was converted, without purification, to the pure hydrazide in good yield. In applying this procedure, the capacity of the apparatus turned out to be very high. In a 2.5 litre autoclave approximately 200 g of pyridine homologues could be oxidized per batch. The yield in such tests has been 40 g of *isonicotinic* acid per 100 g of mixture of pyridine homologues. A stronger acid, *e. g.* 50 %, can also be added to the autoclave, and the oxidation can be carried out continuously in the autoclave as well as in tubes.

Further oxidations were run as follows:

Into an autoclave was pumped a solution of 4.5 parts by weight of the homogenous mixture, just referred to, in an amount of 40 % nitric acid corresponding to 10 % excess, the mixture of pyridine homologues being calculated as collidine. Meanwhile the autoclave was heated to 180–190° C. The reaction started when the temperature had reached this value and proceeded at 190–195° C and 30 kg per cm² for 2 hours. The autoclave was filled to 70 % of its volume. The solution was blown out through a riser and evaporated in vacuum to approximately one third of its original volume. After adjusting the pH value to 3.5, and centrifuging, washing and drying, 1.5 parts by weight of a yellow product were obtained. By recrystallizing from water a white product was obtained which, on analysis, proved to be pure *isonicotinic* acid. The yield on recrystallization was over 90 %. The crude *isonicotinic* acid was used directly and with excellent results for preparation of the hydrazide.

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