

A Catalytic Green Process for the Production of Niacin

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Abstract: A brief overview is provided of the commonly known methods for producing nicotinic acid (niacin), together with a comment on the fulfilment of the requirements for a green process. This is preceded by a short discussion on what is here understood as 'green', together with the importance of niacin. Lonza's contribution to Green Chemistry is illustrated by a new process for producing niacin, namely the direct air oxidation of picoline.

Keywords: Catalytic process · Green chemistry · Niacin · Oxidation · Picoline

Introduction and Scope of Article

The Importance of Niacin

Co-enzyme I (nicotinamide-adenine dinucleotide NAD) and co-enzyme II (nicotinamide-adenine dinucleotide phosphate NADP) are required by all living cells. They enable both the conversion of carbohydrates into energy and the metabolism of proteins and fats. Both nicotinamide and nicotinic acid are building blocks for these co-enzymes. The common name for the vitamin is niacin, and strictly speaking, refers only to nicotinic acid:



Nicotinic acid (niacin) and nicotinamide (niacinamide)

Since the human body produces neither nicotinic acid nor the amide, it is dependent on intake *via* foodstuffs. After the recognition of the importance of niacin, the number of deaths due to the vitamin deficiency disease pellagra dropped in the US from over 7500 to 70 in the years from 1929 to 1956 (E. Kodicek, *Nutr. Dieta* **1962**, 4, 109 – taken from [1]) Although niacin is found in a bound form naturally in wheat, yeast and pork and beef liver, the majority of niacin today is produced synthetically by chemical oxidation of alkyl pyridines. To demonstrate the economic significance of this, in 1995 worldwide a total of 22000 metric tonnes of niacin and niacinamide were produced [2].

The Importance of Green Processes

The industrialisation of the world is irrevocably leading to an increase in ecological problems such as pollution, global warming and possible irreversible effects the earth's stratosphere. Today, belatedly, more emphasis is being made to minimise such effects at the research and development stages of new processes. Armor [3] defines green chemistry as the design of chemical products and processes which reduce or eliminate the genera-

tion of hazardous substances. In his article a list of twelve principles is given which should characterise future approaches to new chemical processes. These principles include not only the obvious features such as avoidance of waste production, high carbon efficiency (low carbon dioxide waste!), and low energy consumption, but also rather more subtle features. Thus a feedstock which is environmentally benign may involve ecologically or energetically unfavourable processes to manufacture it in the first place. He quotes H₂O₂ and ammonia as examples of very energy-intensive feedstock, and how research should be directed at the total energy demand of a given process. A vital part of any new chemical process development will involve the design, manufacture and utilisation of catalysts, which of course themselves will be subject to the same screening as the chemical process itself.

Definition of a Green Process

We cannot agree that the acceptability of a process is governed solely by its cost. An economic process is not necessarily green, especially if waste treatment is ig-

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nored or neglected. An industrial process may contravene one or more green principles, and yet still make money, even if complex waste treatment adds to the costs and diminishes economic viability. But the cost of energy today is extremely low, considering the fact that our present utilisable energy resources are limited. Thus for a given product, the following guidelines should govern the choice of route:

- Choice of feed-stock (costs are relevant of course, but also total resources, energy, waste, etc. in the manufacture of the given feed-stock are important factors)
- Choice of reaction path (minimise energy requirements by use of selective catalysts)
- Choice of catalyst (efficiency, separation from product, recycling of catalyst)
- Downstream processing/unit operations (minimising the number of stages necessary to obtain the product in the state desired by the customer)
- Minimising not only the amount of pollutants, but also the volume of waste streams (effluent/ off-gases and solid waste)
- Recycling of auxiliary, side-, and intermediate products into the process.

Scope of Article

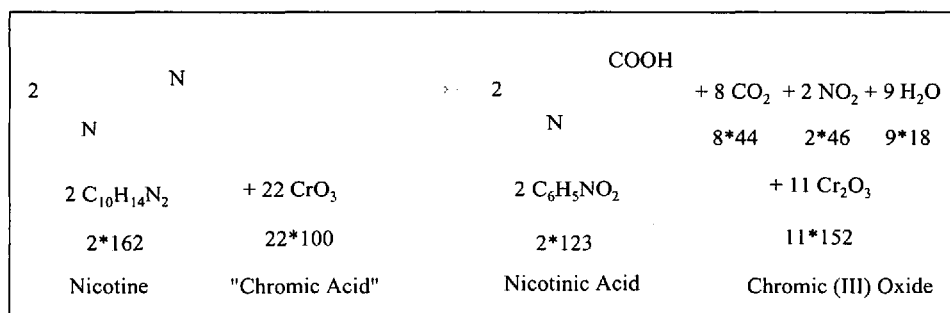
The article attempts to summarise the more well-known methods of producing niacin and assess them in relation to their 'greenness'. With the increasing awareness of ecological issues, recent methods have attempted to take some of these into account. The article looks at the latest process to produce niacin in a 'green' light.

Methods of Producing Niacin

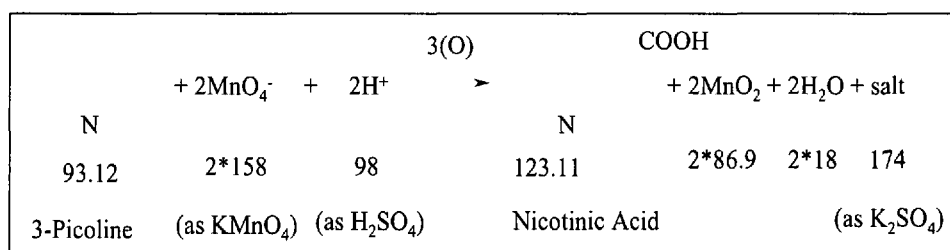
Liquid-phase Oxidation Using Permanganate, Chromic Acid or Other Metal Oxides

The classic method of preparing nicotinic acid was by oxidising nicotine with potassium dichromate. This was discovered over a hundred years ago.

This also serves as an excellent example when considering green technology. Chromic acid (CrO_3) is carcinogenic and environmentally threatening. Chromic (III) oxide, on the other hand, is extensively used in the tanning industry, and has a higher present value on the market than its precursor. Assuming an ideal chemical reaction (100% yield!), the reaction in Scheme 1 gives the following figures:



Scheme 1. The original chromic acid oxidation of nicotine to nicotinic acid



Scheme 2. The permanganate oxidation of 3-picoline

Nicotine/t nicotinic acid:	1.32 t
Chromic acid:	9.02 t
CO ₂ produced:	1.43 t
NO _x (calculated as NO ₂):	0.37 t
Chromic oxide:	6.80 t

Thus almost 9 t of side-product are produced for 1 t of desired product.

Liquid-phase Oxidation of 3-Picoline with Permanganate, Chromic Acid, or Nitric Acid

From the chemical standpoint, 3-picoline is the ideal starting-material for nicotinic acid or amide: the methyl group can be selectively and readily oxidised to the carboxyl derivative with few side-products or pollutants. High selectivity coupled with the low molecular weight compared to the end-product make picoline an attractive industrial starting-material for the production of nicotinic derivatives.

3-Picoline is obtained, typically in a 1:2 ratio along with the main product pyridine, by the gas-phase reaction of acetaldehyde, formaldehyde, and ammonia. The lack of selectivity of this reaction to either pyridine or picoline has meant that the economy of the major product (pyridine) has determined the price and availability of picoline. Thus producers of pyridine have been able to control the quantity and prices of picoline on the market. This situation has led to the search for alternative feedstock and alternative manufacturing processes for picoline.

The oxidation of picoline with permanganate or chromic acid suffers from the same drawback, albeit in a lesser form, as nicotine.

For 1 t of nicotinic acid, 2.8 t of inorganic material are produced as waste. With chromium trioxide (neglecting any inorganic acid involved to produce the required chromic acid), 1.24 t of Cr₂O₃ are produced per ton of nicotinic acid. This assumes stoichiometric quantities of permanganate and quantitative yields, both of which are unrealistic in practice. A stoichiometric excess of 50 to 100% oxidant is usual, and molar yields of 80–90% are generally not exceeded. Thus the inorganic waste for the permanganate process would probably lie around 4 t/t of niacin produced, and for chromium between 1.7 and 2.0 t/t. Clearly from an ecological standpoint, this situation is untenable. Even though chromium (III) sulphate can be utilised in the leather industry as a tanning agent [4], there are several factors which argue against this type of

process, even if the process appears on the surface to be economically attractive:

1. The combination of two economies in one process requires that both end products (here chromic oxide and nicotinic acid) can be sold. Thus the success of the process is dependent on the demand for both products being sustained. A collapse of one leg will invariably lead to the process as a whole being unsustainable. The dependence of picoline on pyridine illustrates this point.

2. The energy required for the production of chromic acid (or permanganate) is considerable. (Chromite ore is roasted with sodium carbonate at temperatures around 1000 °C to produce the common starting-material for most chromium compounds, namely sodium chromate)

3. The environmental problems in the leather industry due to chromium pollution can be solved, but are expensive and the alternatives are not without their own problems [4].

4. Niacin is used as a feed and food additive. The presence of even small quantities of chromium, however beneficial this may be in practice (chromium is an essential trace metal in the human metabolism), is not likely to be accepted by either today's stringent legislation, nor by buyers who are geared to high-quality supplies. Removal of last traces of impurity is possible by recrystallisation, but this increases the number of unit operations and is therefore expensive and energy consuming, and the problem remains as to what to do with the chromium-containing mother liquors.

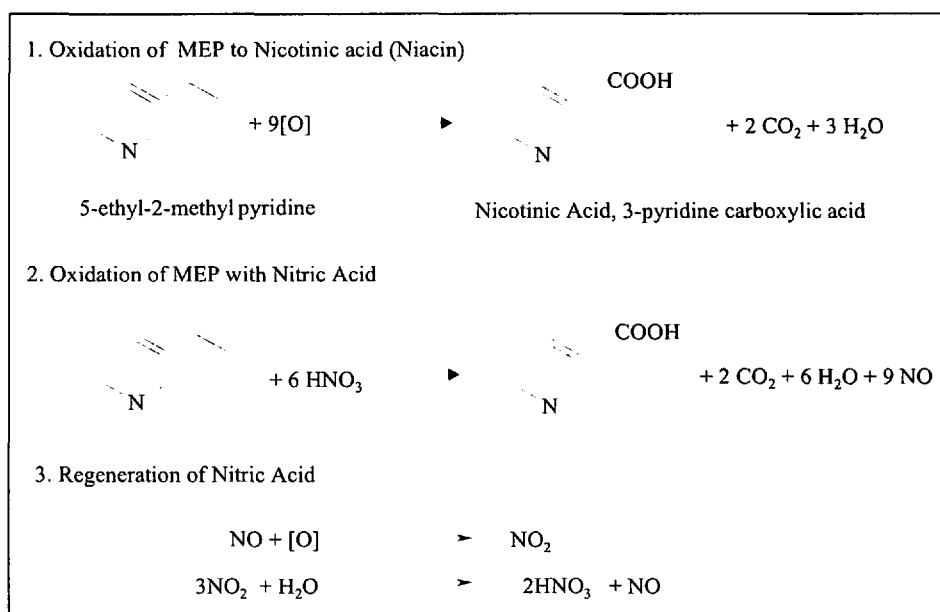
Liquid-phase Oxidation of Picoline with Nitric Acid

The liquid-phase oxidation of picoline with nitric acid at atmospheric pressures (usually with sulphuric acid to ensure sufficiently high temperatures) has been the basis of some back-yard processes, but again has many disadvantages:

1. **Safety:** Batch processes with large quantities of nitric acid and organic material are intrinsically hazardous and corrosive, and stringent precautions are necessary to avoid runaway reactions and explosions.

2. **Quality:** Nitric acid is not only an oxidant, but is also a nitrating agent. Depending on reaction conditions, considerable quantities of nitrated pyridines can be produced, which can only be separated with expensive crystallisation techniques.

3. **Ecology:** The inevitable generation of large quantities of toxic NO_x fumes re-



Scheme 3. Oxidation of 5-ethyl-2-methyl pyridine with nitric acid

quires a well-planned containment and recuperation system. This is expensive, and unless great care and considerable expense is undertaken, NO_x waste-gas will be released to the atmosphere, causing potential pollution problems. The problem of nitrated organic waste products has also to be solved.

Liquid-phase Oxidation of MEP with Nitric Acid

To avoid the above problem of picoline sourcing, non-pyridine producers have used methyl-ethyl-pyridine as an alternative for niacin. The liquid-phase oxidation with nitric acid is surprisingly selective, and has been used since 1965 by Lonza to produce up to 15000 t/year of niacin. The reaction can be approximately represented as in Scheme 3.

5-Ethyl-2-methyl-pyridine (MEP) is itself produced by the liquid-phase condensation of paraldehyde and ammonia. Again this complex reaction proceeds surprisingly selectively (>70%) and is the main reason why this material offers itself as an alternative to the simpler molecule picoline. Continuous development and improvement of this process over the years have led to a high-quality product, and to Lonza's ability to maintain its position as the world leader in niacin manufacture.

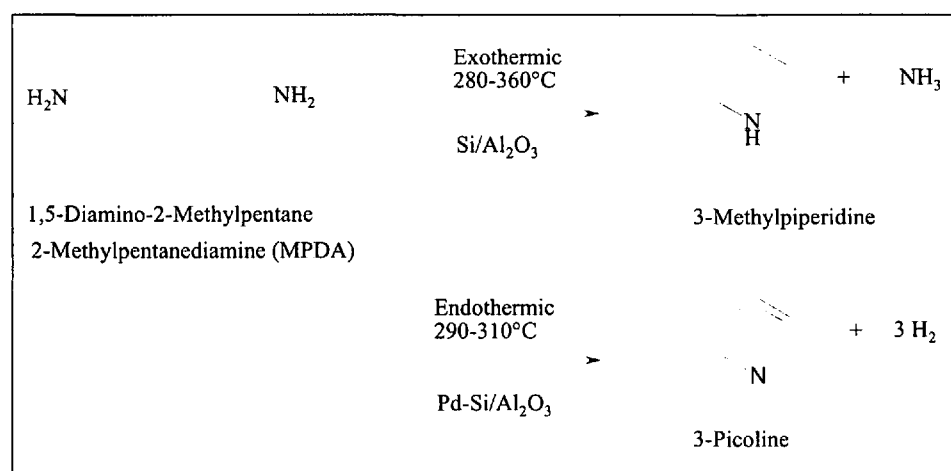
But however many improvements and developments have been made to this process, it intrinsically holds some disadvantages, when considered from the 'green' stand-point:

1. **Safety:** Using nitric acid at high temperatures and pressures requires a well-conceived and continually executed safety concept, using advanced reaction technology.

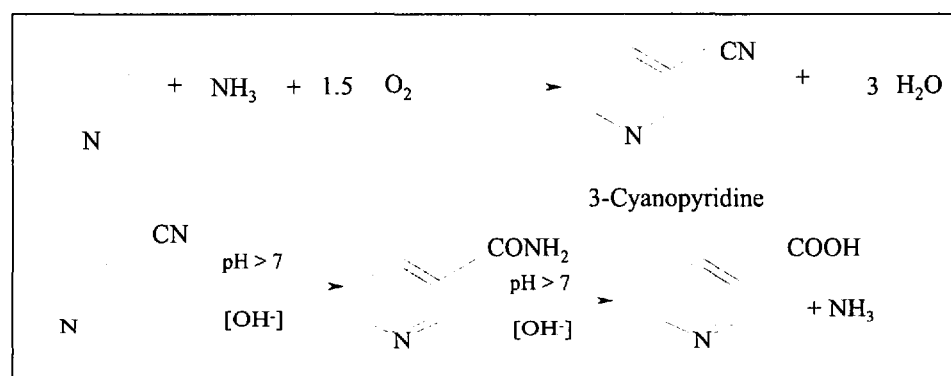
2. **Ecology** (carbon dioxide and nitric oxides): Although nitric oxide fumes can be largely regenerated to nitric acid, some nitric oxide (NO) is invariably present in the off-gases, which then has to be catalytically treated to remove the last traces of NO_x. Carbon dioxide, however, cannot readily be recycled, and this is vented to the atmosphere. In today's process (including deep oxidation of the starting material), as can be readily calculated from the reaction equation, over 1 t of CO₂ is produced per tonne of niacin.

3. **Downstream processing:** In order to produce a product quality acceptable to today's standards, extensive processing in the form of recrystallisation and decolourising is necessary. As mentioned above, recrystallisation is an energy and labour intensive process.

4. **Starting material:** Although MEP is produced from cheap starting-materials (ammonia and paraldehyde), the process itself produces considerable quantities of side-products and/or waste material, which have to be separated and suitably treated to avoid environmental pollution. Additionally, the carbon efficiency of the MEP conversion to niacin is at best only 0.75 (two carbon atoms are burnt off during oxidation), so that from the green standpoint, MEP is not the ideal starting material.



Scheme 4. Alternative process for picoline manufacture



Scheme 5. Ammoxidation of 3-picoline and hydrolysis of cyanopyridine to niacinamide and niacin

Modern Approaches

Over the last 10 to 15 years, green aspects have increasingly gained recognition, and several approaches have been made in an attempt to at least partially overcome such problems.

Alternative Technology for Picoline Manufacture

As mentioned above, the bulk of picoline is produced today by the condensation of acetaldehyde, formaldehyde and ammonia in the gas-phase, which simultaneously produces large quantities of pyridine. A selective and suitable alternative method starting from these or similar simple molecules has yet to be developed. Given the thermodynamic properties of the molecules and reactions involved, it does not seem likely to expect a selective process for 3-picoline following this strategy.

Nevertheless, a viable alternative has been found; namely the condensation of the molecule 2-methyl-pentanediamine (MPDA) to methyl piperidine, followed

by the dehydrogenation to 3-picoline [5]. 2-methyl-glutaronitrile is the major side-product in the adiponitrile process and, as such, a readily available starting material (~10⁵ mtpa). It is readily hydrogenated to MPDA (Scheme 4).

Although this route has the same fundamental weakness of being coupled to another product (adiponitrile), the foreseeable future of nylon 6,6 and the route to its manufacture (hydrogen cyanide addition to butadiene) seem assured for the next 10 to 20 years or so. Several advantages are apparent in this route:

1. The 3-picoline produced has a very high isomeric purity
2. Picoline is produced in a two-stage catalytic process which is practically energetically neutral: an endothermic (ring closure) and an exothermic (dehydrogenation) reaction.
3. Ammonia is liberated during the ring closure which can be utilised in a following process (ammoxidation or solubilising nicotinic acid)
4. Utilisation of a waste-product (2-methyl-glutaronitrile can be used as a co-

monomer in the production of other polyamides, but the end-product niacin has an intrinsically much higher value).

Liquid-phase Oxidation of 3-Picoline with Oxygen

Picoline can be selectively oxidised with air in the liquid phase to niacin (see e.g. [6]). A catalyst combination such as cobalt and manganese acetate and/or bromide is usually used in an acetic acid medium, and the air oxidation takes place under elevated temperatures and pressures. The disadvantages of this process are the following:

1. The product must be efficiently and cleanly separated from the reaction solution. In practice the two goals run contrary to each other; if the product is clean, then non-negligible quantities remain in solution and *vice-versa*.
2. In practice, additional cleaning steps are necessary to ensure purity of product.
3. The mother liquor contains metallic catalysts which must be recycled if the process is to be efficient. Re-cycling the reaction solution (mother-liquor) usually entails considerable effort in working up and cleaning (the spent solution contains water, tars and/or high boilers and of course the metal catalyst salts in addition to acetic acid).

Electrochemical Oxidation

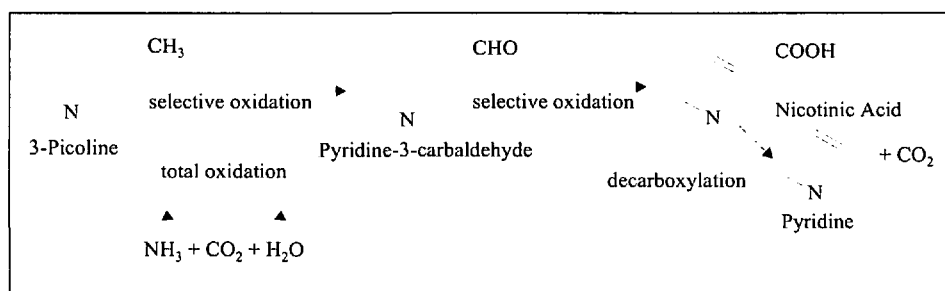
A description of the anodic oxidation of picoline to niacin falls outside the scope of this article, since the industrial realisation appears unlikely. Quite good selectivity has been achieved in the laboratory, but both the direct anodic oxidation as well as the indirect method using manganese oxide are presently solely of academic interest.

Gas-phase Oxidation of Picoline to Cyanopyridine

The gas-phase ammoxidation to cyanopyridine followed by a hydrolysis either to nicotinamide [7] or nicotinic acid [8] are commercial processes, and for the production of nicotinamide, represents the most logical and direct route *via* 3-picoline (Scheme 5).

Gas-phase Oxidation of Picoline to Nicotinic Acid

Employing the cyanopyridine route for the production of nicotinic acid involves the fixation of a nitrogen atom in the ammoxidation step, followed by its



Scheme 6. Reactions in the gas-phase oxidation of picoline to nicotinic acid

removal in the ultimate hydrolysis. This is a contradiction to the principles of a green process, and in the last ten years, efforts have been made to oxidise picoline in the gas phase directly to nicotinic acid [9][10]. It is this process that, in terms of green chemistry, represents the state of the art today. The reactions are represented in Scheme 6.

Both the Boreskov Institute and Lonza have developed pilot processes for the manufacture of niacin based on the catalytic gas-phase oxidation of picoline. They differ predominantly in the method of removing niacin from the process. Whereas Boreskov rely on a de-sublimation procedure, Lonza's patented technology is based on spray drying of a highly concentrated solution of ammonium nicotinate. This method takes advantage of the fact that, under Lonza's reaction conditions, ammonia is produced as a side product in the total or deep oxidation.

The green advantages of the process can be summarised as follows:

1. Use of air as oxidant instead of stoichiometric quantities of chemical oxidising agents
2. Use of catalysts to promote reaction
3. Reaction carried out at atmospheric pressure
4. Gas-phase reaction means that catalyst does not have to be recovered from solution
5. Energy from exothermic reaction can be recovered
6. Few unit operations
7. The only solvent used is water
8. Ammonia is recycled
9. Waste is minimised by a highly selective reaction
10. Conversion is high, leading to an efficient use of equipment, energy and material
11. Throughput is acceptable for a commercial process

Development and Description of Lonza's Direct Oxidation Process

Search for and Identification of the Catalyst

It has been known for several years that transition metal oxides are good oxidising catalysts for alkyl pyridines. This is due to their ability to exist in several stable oxidation states and their favourable redox properties. Whereas classical oxidising agents such as chromium or manganese lose one or more oxygen atoms to effect the oxidation of an organic material, a catalyst component such as molybdenum, vanadium or niobium is reduced by the organic material, and is practically simultaneously re-oxidised by oxygen in the air (Mars-van Krevelen mechanism).

Lonza has investigated various representatives of this type of catalyst for both niacin feed stocks, MEP and 3-picoline, but recently, based on the arguments presented above, Lonza has concentrated on the latter as a feed stock.

The search for a catalyst for this oxidation has proceeded in several laboratories including Lonza's [9-12], and has led to the identification of vanadium oxide as one of the most suitable. This material is normally used with a support, typically an oxide of titanium, aluminium or silicon, or a mixture of these. The accessibility for the substrate to enter and react on the catalyst surface, and for the product to be removed, are governed by factors such as physical form, pore size, pore distribution, and surface area. These and other factors must be considered when designing a catalyst, and its chemical composition is only the starting-point. Lonza has developed catalysts on a pilot scale which satisfy the criteria for niacin production: they are selective, active, and have a long life (turnover) time. Apart from small quantities of side-products

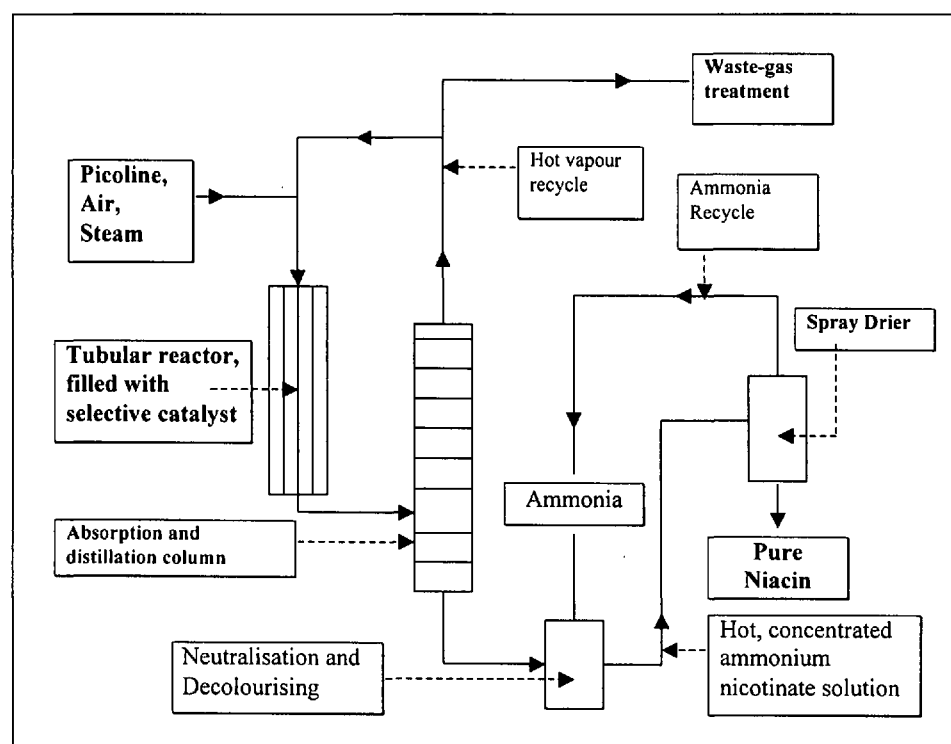
ammonia, carbon dioxide and pyridine, and of the carboxaldehyde intermediate (see Scheme 6), practically no other products have been detected.

Process Development

In order to have a viable process, one must be able to efficiently remove the product in a pure state and as completely as possible from the system. The particle form (crystal size, shape, uniformity) and flow characteristics of the niacin are additional criteria often determined by the customer, which must be also taken into consideration during development.

Picoline vapour is selectively and almost quantitatively converted into nicotinic acid in the reactor. Nicotinic acid is transported from the reactor by the hot air and water vapour. These vapours are partially condensed in an absorption and distillation column. Niacin and water condense to form a solution, whereas unconverted picoline, pyridine carboxaldehyde, water vapour and gases leave the top of the column still in the vapour phase. Most of these vapours can be recycled. A small purge is necessary to remove the waste products formed in the reaction. This waste stream can either be condensed and the liquid subsequently incinerated, or the hot vapours can be catalytically oxidised and de-nitrified by standard procedures.

The solubility of niacin in water, even at 100 °C, is fairly low, so that large quantities of water are necessary for total dissolution. This is a disadvantage in a green process, since large amounts of energy are required to remove excess water in an evaporation or crystallisation process. Additionally the presence of the ammonium ion from the total oxidation (see Scheme 6) reduces the amount of niacin that can be separated by crystallisation, because in contrast to niacin, ammonium nicotinate is very soluble. This constitutes a potential problem for an economic green process. In solution, ammonium nicotinate is highly stable and can be refluxed without decomposition. However, Lonza utilises the fact that ammonium nicotinate decomposes into its separate constituents when water is removed at temperatures above 160 °C. This provided the key to the process: the solubility and thus the concentration of niacin is raised by converting the majority of the acid to the ammonium salt and spray-drying the concentrated solution [10]. Thus the following advantages are simultaneously incorporated:



Scheme 7. Schematic layout of the Lonza Niacin Air Oxidation Process

- The amount of water to be removed is drastically reduced, thus saving energy
- The physical form of the spray-dried product is very uniform
- The niacin obtained is very pure
- Ammonia liberated from the spray-drier can be recycled into the process
- No mother liquor is produced, avoiding additional work-up, recycling or possible waste.

A schematic overview of the process is shown in Scheme 7.

The essential steps, including catalyst and reaction technology, neutralisation with ammonia and the spray-drying step, have all been successfully demonstrated on a pilot and/or semi technical scale.

Conclusions

The new process fulfils many of the criteria of green chemistry for the next generation of chemical processes. The reaction is efficient both in carbon efficiency and in selectivity, the oxidant is air and the solvent is water. Picoline may be produced from a waste-product, and ammonia is recycled. The reaction is exothermic, and heat generated may be recovered and utilised elsewhere in the process. No toxic, corrosive or hazardous oxidising agents are employed, and the oxidation catalyst is stable, long-lived

and environmentally benign. We feel this process demonstrates Lonza's commitment to combine economic and ecological principles in process development.

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