



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : C25B 3/02, C07D 213/79	A1	(11) International Publication Number: WO 92/00403 (43) International Publication Date: 9 January 1992 (09.01.92)
(21) International Application Number: PCT/US91/03807 (22) International Filing Date: 29 May 1991 (29.05.91) (30) Priority data: 534,863 28 June 1990 (28.06.90) US (71) Applicant: REILLY INDUSTRIES, INC. [US/US]; 1510 Market Square Center, Indianapolis, IN 46204 (US). (72) Inventor: TOOMEY, Joseph, E., Jr. ; 2035 Rosedale Drive, Indianapolis, IN 46227 (US). (74) Agents: REEVES, Charles, R. et al.; Woodard, Emhardt, Naughton, Moriarty & McNett, Bank One Center/Tower, Suite 3700, 111 Monument Circle, Indianapolis, IN 46204 (US).		(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent). Published <i>With international search report.</i>
(54) Title: ELECTROCHEMICAL SYNTHESIS OF NIACIN AND OTHER N-HETEROCYCLIC COMPOUNDS (57) Abstract An electrochemical oxidation of a <i>pi</i> -deficient N-heterocyclic precursor compound having an oxidizable organic group attached by a carbon-to-carbon linkage. This precursor compound is at least sparingly water soluble. The preferred electro-oxidation is conducted at an effective anode and in a medium which consists essentially of water, carboxylic acid, and the precursor compound. Preferred are electro-oxidations of substituted pyridine and quinoline bases and a particularly preferred aspect provides a convenient electrochemical synthesis of niacin from 3-methylpyridine.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland	KR	Republic of Korea	SN	Senegal
CI	Côte d'Ivoire	LI	Liechtenstein	SU	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
DE	Germany	MC	Monaco	US	United States of America
DK	Denmark				

ELECTROCHEMICAL SYNTHESIS OF NIACIN AND
OTHER N-HETEROCYCLIC COMPOUNDS

BACKGROUND OF THE INVENTION

This invention resides generally in the fields of
5 N-heterocyclic and electrochemistry, and in a preferred
aspect provides a convenient and commercially practicable
electrochemical oxidation of pyridine bases to corresponding
carboxylic acids such as niacin.

In this regard, pyridinecarboxylic acids are useful inter
10 alia as chemical intermediates and corrosion inhibitors.
Further, one such acid identified as 3-pyridinecarboxylic
acid (also known by the names Vitamin B-3, nicotinic acid and
niacin) has particular value as an essential vitamin. Its
importance in the human diet, for example, led in the 1940's
15 to niacin fortification of wheat flour and other consumer
products. The adoption and continuation of this practice has
generated steady demand for niacin and a concomitant driving
force for improved methods to produce this and other
pyridinecarboxylic acids. Moreover, recent reports that
20 niacin may help reduce cholesterol levels in the blood have
sparked an even greater demand for improved synthetic
processes in this area.

As background respecting these processes, early
oxidations of pyridine derivatives such as methylpyridines
25 were conducted using chemical oxidizing agents and
catalysts. More recent investigations have included these
chemical methodologies in addition to attempts at
electrochemical oxidations.

Accordingly, reports relating to chemical oxidizing
30 agents dating back over a hundred years disclose forming
niacin by partial oxidation of nicotine with nitric acid,
potassium permanganate or potassium dichromate. See
Woodward, Badgett and Kaufman, Ind. Eng. Chem., Vol. 36,
No. 6, (1944) p. 544 and sources cited therein. Studies

-2-

using these chemical oxidizing agents have continued, for instance, with potassium permanganate oxidations of alkylpyridine bases being reported by Black, Depp and Corson, J. Org. Chem., Vol. 14, 14 (1949); by Lovrecek, Radovi
5 Jugoslav. Akad. Znanosti i Umjetnosti 296, 65-83 (1953); and by Plattner, Keller, and Boller, Helv. Chim. Acta. 37, 1379-92 (1954). These reactions have suffered, however, in that they have generally caused excessive oxidation and resultant ring degradation, particularly with
10 polyalkylpyridines. Likewise, Bengtsson, Acta. Chem. Scand. 9, 832-36 (1955) reports nitric acid oxidations of pyridine homologs which has proven a more economic route, but nevertheless requires undesirably high temperatures and pressures which can cause decarboxylation or loss of carbon
15 dioxide from the resulting product.

Other reported chemical methodologies have included oxidation of pyridine derivatives with ozone, ozonized oxygen or ozonized air [G. B. Patent No. 17,003], and also oxidation by action of sulfuric acid in the presence of a selenium
20 compound. U.S. Patent Nos. 2,449,906 and 2,513,009. Additionally, U.S. Patent No. 2,513,251 reports oxidation of pyridine derivatives by reaction with nitrogen tetroxide in a sulfuric acid medium.

Still other chemical routes to this end have included
25 catalytic air oxidations of pyridine derivatives, [U.S. Patent No. 2,437,938 and Kucharczyk and Zvakova, Collection Czech. Chem. Commun. 28, 55-60 (1963)], as well as oxidations using electro-generated superoxide ion. Sagae, Fujihira, Lund and Osa, Heterocycles, Vol. 13 (1979), p. 13.
30 Additionally, Woodward, Badgett and Kaufman, Ind. Eng. Chem., Vol. 36, No. 6, (1944), p. 544 reports catalytic oxidation of pyridine derivatives in sulfuric acid using mercuric sulfate and bismuth trinitrate catalysts (with moderate success), and selenium, selenium dioxide, and copper selenite catalysts
35 (with greater success).

-3-

As noted above, another general area of study in this field has been that of electrochemical oxidation. This discipline had its nascence in 1932 when electrochemical oxidations of 2-methylpyridine and nicotine to 2-pyridinecarboxylic acid and nicotinic acid, respectively, were first reported. Yokoyama, Bull. Chem. Soc. Japan 7, 69-72 (1932) and Yokoyama, ibid, 7 103-S (1932). These early electrochemical oxidations occurred in a sulfuric acid medium at a lead anode. Reports have since been made through the years of electrochemical oxidations of various pyridine derivatives with varying levels of success, but these oxidations have consistently occurred in moderate or better yields only in highly acidic mediums having substantial mineral acid components.

For example, the following sources report formation of the named pyridinecarboxylic acids upon electrochemical oxidation of pyridine derivatives in mediums containing sulfuric acid and at anodes of lead or lead-dioxide, or in fewer cases platinum: (1) Nicotinic acid from nicotine, Fichter and Stenzl, Helv. Chim. Acta. 19, 1171 (1936); (2) Nicotinic acid from 3-methylpyridine, Kruglikov and Khomyakov, Tr. Mosk. Khim.-Teknol. Inst. 1961 (32), 194; (3) Quinolinic acid from quinoline, Yokoyama and Yamamoto, Bull Chem. Soc. Japan 18, 121 (1943); Khomyakov, Bakhchisarait's'yan, Tioshin, Kruglikov and Kazakova, Tr. Mosk. Khim.-Teknol. Inst. (32), 249 (1961); Khomyakov and Borkhi, Tr. Vses. Nauch.-Issled. Inst. Khim. Reaktivov Osobo Chist. Khim. Veshchestv 29, 226 (1966); Khomyakov, Bzbanovskii and Borkhi, ibid, 29, 304 (1966); Borkhi and Khomyakov, Khim. Geterotsikl Soedin 1967 (1), 167; and Tsodikov, Borkhi, Brudz, Khomutov and Khomyakov, ibid, 1967 (1) 112; (4) Nicotinic acid from 3-methylpyridine, and quinolinic acid from quinoline, Kulka, J. Am. Chem. Soc. 68, 2472 (1946); U.S. Patent No. 2,512,483; Khomyakov and Kruglikov, Trudy Moskov. Khim.-Teknol. Inst. im. D. I.

-4-

Mendeleeva (25), 178 (1957); and Khomyakov, Kruglikov and Berezovskii, Zhur. Obshchei Khim. 28, 2898 (1958); (5) Quinolinic acid from sulfonated quinoline, U.S. Patent No. 2,453,701; (6) Isonicotinic acid from the methylol
5 derivative of 4-picoline, Kruglikov and Khomyakov, Tr. Mosk. Khim.-Teknol. Inst. 1961 (32), 201; (7) Lutidinic acid from 2,4-lutidine, Khomyakov, Kruglikov, and Kazakova, Tr. Mosk. Khim.-Teknol. Inst. 1961 (32), 189; (8) Monosubstituted pyridinedicarboxylic acids from monosubstituted quinolines,
10 Cochran and Little, J. Org. Chem. 26, 808 (1961); (9) Isocinchomeric acid from 2-methyl-5-ethylpyridine, Borkhi and Khomyakov, Izobret. Prom. Obraztsy, Tovarnye Znaki 43 (20), 38 (1966); and Borkhi, Khim. Geterotsikl Soedin 1970 (10), 1362 (1970); and (10) Isonicotinic acid from
15 4-ethylpyridine, Nankov and Yankov, Elektrokhimiya 7 (12), 1865 (1971).

In addition, electrolytic oxidations of 4-methylpyridine in 20% nitric acid and 20% sulfuric acid mediums at platinum and lead dioxide anodes are reported by Ito and Kawada, Ann.
20 Rept. Takamine Lab. 5, 14 (1953), as are oxidations of 4-ethylpyridine in these two mediums at a platinum anode. These same two authors also report another experiment in which an extremely poor yield resulted from an electrolytic oxidation of 4-methylpyridine in an alkaline bath.
25 Similarly, U.S. Patent No. 4,750,978 reports low product yields resulting from electrolytic oxidations of 2-methyl-3-quinolinecarboxylic acid in 15% aqueous NaOH baths, and Ochiai and Okuda report very poor yields resulting from the electrolytic oxidation of 2-picoline in
30 alkaline (10% yield) and neutral (10% yield) baths in J Pharm. Soc. Japan, 70, 156 (1950).

Addressing generally these processes discussed above, both chemical and electrochemical, they present problems and inconveniences on a laboratory scale which are multiplied
35 greatly in commercial scale reactions. Catalytic oxidations

-5-

often require expensive catalysts and/or oxidizing agents and long reaction times, require the use of high temperatures and pressures, and present difficulties in processing and recovering reaction products. Moreover, in several of the
5 chemical processes, ring degradation and accompanying product losses result from excessive oxidation.

The electrochemical processes, on the other hand, generally avoid use of expensive chemical catalysts and oxidants and thus hold greater promise in these respects for
10 providing economical routes to pyridinecarboxylic acids. Nevertheless, commercial and technical development of economic electrochemical processes in this area has seriously lagged to date, with most reports being largely the result of qualitative study. The applicant's own earlier U.S. Patent
15 No. 4,482,439 discloses a commercially-viable electrochemical oxidation of pyridine bases performed in a flow cell having either an anion- or cation-selective ion-exchange membrane divider at a lead dioxide anode and in an aqueous medium comprising sulfuric acid in at least a 1:1 equivalent ratio
20 with the pyridine base in solution. This flow cell process provides excellent yields and constitutes a significant improvement over the prior art at the time. As in the many other reported electro-oxidations achieving notable yields, however, this process too is performed in a medium containing
25 a substantial mineral acid (sulfuric acid) component. This presents disadvantages in that effective recovery of the carboxylic acid product from such mediums requires pH neutralization which can particularly cumbersome and expensive on a commercial scale.

30 Further, simple workups of electrolysis products are essential in commercial settings as in many cases more than half of the total synthesis investment is devoted to this procedure. Auxilliary salts which serve as electrolytes but complicate the workup procedure can thus lead to pronounced
35 increases in manufacturing costs. See generally, Techniques

-6-

of Chemistry, (N. L. Weinberg and B. V. Tilak ed.), p. 279,
John Wiley & Sons (1982). Accordingly, an electrochemical
process which would allow one to eliminate or at least
substantially reduce the use of such auxilliary salts would
5 provide great advantage in commercial settings.

It is in light of this extensive background that the
applicant began his work to discover a convenient and
effective commercial process to satisfy the continuing and
increasing demand for these carboxylic acids, including of
10 particular interest niacin for the reasons stated above. By
this work the applicant has now succeeded in providing with
this invention a commercially and technically important
electrochemical process for oxidizing pyridine and other
N-heterocyclic compounds.

-7-

Summary of the Invention

Accordingly, one preferred embodiment of this invention relates to an improved electrochemical oxidation of a pi-deficient N-heterocyclic precursor compound (e.g. a
5 pyridine or quinoline derivative). The precursor compound has an oxidizable organic group attached by a carbon-to-carbon linkage, and is at least sparingly water soluble. The preferred oxidation is conducted at an effective anode and in a medium consisting essentially of water, a carboxylic acid,
10 and the precursor compound.

In another preferred aspect of the invention, the medium in which the electrochemical oxidation occurs is also substantially free from mineral acid while achieving good yields. Additionally, in the applicant's preferred work to
15 date, the precursor compound has been oxidized to a corresponding carboxylic acid or ketone product, and substituted pyridine and quinoline bases have been preferred precursor compounds. A particularly preferred aspect provides an electrochemical synthesis of niacin from
20 3-methylpyridine. Importantly, and in contrast to the prior art electrochemical processes in this area, the applicant's preferred oxidations have occurred in these simplified mediums while achieving high current efficiencies, reactant solubility, and electrolyte conductivities without the need
25 of adding mineral acid or other conductive salts.

Without restricting the invention, it is believed that these advantages may result from salt formation between the precursor compounds and the carboxylic acid in the medium thereby providing excellent water solubility of both and as
30 well a salt which acts beneficially as an electrolyte in the medium. Additionally, this salt acts as a buffer, thus stabilizing the pH of the medium during the reaction. In any case, the applicant's preferred electro-oxidations carry significant advantages over prior art processes. For
35 instance, they require no pH neutralization of the

-8-

electrolytic medium to effectively recover carboxylic acid product and also provide for simplified electrolyte mediums not requiring auxilliary salts other than the salt formed between the carboxylic acid and precursor compound.

- 5 Consequently, use of such auxilliary salts can be eliminated or, if used, their concentrations can be substantially reduced which simplifies workup procedures.

Other preferred embodiments of this invention relate to additional processes and electrochemical baths capitalizing
10 on the applicant's preferred electrochemical mediums and other discoveries as set forth herein. Additional objects and advantages of this invention will become apparent upon reading the description that follows.

-9-

DESCRIPTION OF THE PREFERRED EMBODIMENT

As stated above, one preferred embodiment of this invention relates to an electrochemical oxidation of a pi-deficient N-heterocyclic precursor compound such as, for example, a pyridine or quinoline derivative. The precursor compound has an oxidizable organic group attached by a carbon-to-carbon linkage. This precursor compound also is at least sparingly water soluble. Additionally, the electro-oxidation occurs at an effective anode and in a medium consisting essentially of water, a carboxylic acid, and the precursor compound.

As used herein, the phrase "electrochemical oxidation" is meant to include all possible variations as to reaction conditions and the like which are known to those of ordinary skill in the art to which this invention pertains. For instance, the electrochemical oxidation of the invention can occur in all possible electrochemical cell configurations including divided or undivided, mixed or unmixed, and also flow cells in addition to "tank" or "beaker" type cells. The only exceptions to this relate to any specific conditions or features which have shown to be required from applicant's testing to date which are further detailed herein. Additionally, the term "sparingly water soluble" is commonly used and well known in the art, and as used herein connotes compounds which are preferably at least about 0.01 weight percent soluble in water.

As to specific materials, conditions and processing steps, the applicant's preferred oxidations to date have been performed at effective anodes which, under the further conditions of the invention, have oxidized the precursor compounds, preferably to their corresponding carboxylic acids or ketones. Thus, where the product is carboxylic acid, effective anodes will result in an observed increase in the total carboxylic acid component in the medium. To date, preferred effective anode materials have included graphite,

-10-

carbon, or a metal or metal oxide of palladium, platinum, irridium, ruthenium, chromium, molybdenum, tin, cerium or manganese. Of course, anode materials containing mixtures of these substances with each other or with other suitable materials are also appropriate. Further, it is contemplated that other effective anode materials also performing in this manner are acceptable for and within the scope of this invention.

Additionally, the physical and morphological characteristics of the electrodes, while having somewhat influenced results, have not to date shown to be critical. Accordingly, all physical and morphological electrode forms including, for instance, polymer coated or metal or metal oxide surface coated electrodes, are similarly contemplated as being within the scope of the invention. Also, in the case of noble metals or metal-oxides they are preferably supported on inert conductive supports. Further, the addition of metals, metal oxides or metal salts to the electrolyte as soluble species is also acceptable for catalyzing the intended chemistry or for providing mediators for electron transfer. These may be chosen to include the metals or metal oxides listed above as possible anode materials as well as others as known in the art.

Although the composition of the cathode used in the cell has not proven to be critical to date, the particular cathode materials used have to some extent influenced results. The preferred cathode materials have thus far exhibited hydrogen overpotentials not substantially exceeding those which would be predicted by the accepted Nernst equation (i.e. not high-hydrogen-overpotential cathodes), with cathodes comprising graphite, platinum, iron, steel or titanium having been found more preferred to this point.

Similarly, electrochemical cell configuration has not shown to be critical to date; however, preferred electrochemical oxidations are conducted in cells preferably

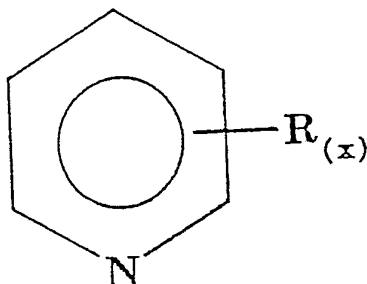
-11-

divided using porous dividers such as ceramic, glass frit, and porous plastics, or ion-exchange membranes (either anion or cation selective). Additionally, in this vein, cell voltages up to about 20V have proven appropriate for the applicant's preferred oxidations, with about 4-10V cells being preferred up to this point.

As to precursor compounds, the applicant's preferred processes have involved electro-oxidation of pi-deficient N-heterocyclic compounds which are at least sparingly water soluble. In a preferred aspect, these compounds also have a pKa of at least about 4. The term "pi-deficient N-heterocyclic compound" describes a cyclic compound which contains one or more nitrogen atoms in the ring where the lone pair of electrons on at least one of those nitrogen atoms is available to undergo reactions typical of organic nitrogen bases. Pi-deficiency has been found to be necessary in the compounds oxidized by applicant's preferred electrochemical processes, and it is believed that this is because this ensures that the substrates are basic enough to form salts with the carboxylic acid in the medium and to form conductive salts. Pi-deficient N-heterocyclic compounds include pyridines, pyrimidines and quinolines, as well as other perhaps less common chemical compounds which possess substantially the same properties as pyridine and quinoline compounds and are equivalents thereof such as diazines and triazines. Although many pi-deficient N-heterocycles are six-membered cyclic compounds, five-membered cyclic compounds with two or more nitrogen atoms are also pi-deficient, such as imidazoles or other diazoles or triazoles.

In another aspect, preferred electro-oxidations involve pi-deficient N-heterocyclic precursor compounds according to the general formula:

-12-



wherein, $x = 1-3$; and

$R = \text{---CH}^3$,

a primary or secondary alkyl group having about 2-6 carbon atoms,

5 a cycloalkyl group having about 3-6 carbon atoms,

an aralkyl group of the formula $[\text{---}(\text{CH}_2)_n\text{---aryl}]$

where $n = 1-3$,

$\text{---}(\text{CH}_2)_m\text{COR}'$ or $\text{---}(\text{CH}_2)_m\text{CHOHR}'$ where $m = 0-5$ and

$R' = \text{H}$ or an alkyl group having about 1-6 carbon atoms, or a
10 cycloalkyl, aryl or aralkyl group having about 3-10 carbon atoms;

and wherein two adjacent R groups on the ring taken together may be a fused cycloalkyl or fused aryl group.

More preferred precursor compounds have been mono- and
15 di- alkylpyridine bases, wherein the alkyl group is preferably lower alkyl, such as methyl, ethyl, propyl, butyl, etc., with a particularly preferred aspect of the invention being an electro-oxidation of 3-methylpyridine to niacin.

As to the rate of charge passed through the cell,
20 optimization of current densities will depend on the particular medium and cell configurations selected, and is well within the skill of those working in this area. However, in the applicant's preferred oxidations, current has preferably been passed in amounts sufficient to achieve
25 current densities ranging from about 1 to about 400 mA/cm^2 . Further, in the particularly preferred oxidations of 3-methylpyridine to niacin, current has been passed in amounts sufficient to achieve current densities of about 10 to about 100 mA/cm^2 .

-13-

In addition, the total amount of charge passed through the cell will, of course, depend upon the efficiency of electron transfer for the intended chemistry. Generally, however, the applicant's studies have shown that the charge
5 passed should be limited to that just necessary to achieve maximum conversion of the precursor compound. Similarly, temperatures have not proven critical in the applicant's studies with temperatures of about minus 20°C up to the reflux temperatures of the electrolytes having proven
10 appropriate to date.

Respecting the electrochemical medium of this preferred embodiment, in addition to the other requirements set forth herein, it has to date preferably exhibited a pH above about 2 and up to about 8, with a more preferred pH range being
15 about 4-7. Additionally, the water, precursor compound, and carboxylic acid are preferably included in amounts whereby the particular precursor compound and carboxylic acid used each constitute at least about 5 weight % of the medium. More preferred systems include the precursor compound and
20 carboxylic acid each constituting about 10% by weight or greater of the medium. Additionally, the most preferred oxidations of precursor compounds to carboxylic acids have been conducted in mediums having levels of carboxylic acid approaching or even exceeding saturation point. In this
25 manner, as charge is passed through the cell, corresponding carboxylic acid has been formed in amounts whereby carboxylic acid precipitates from the medium as its saturation point therein is exceeded. This enables an extraordinarily convenient recovery of the corresponding carboxylic acid
30 product from the medium.

In a further aspect, preferred oxidations to carboxylic acids have been conducted in mediums wherein the corresponding carboxylic acid of the precursor compound constitutes all or at least a substantial component of the
35 total carboxylic acid in the medium. In this way, a

-14-

precipitate of corresponding carboxylic acid of increased purity has been obtained.

In the case of the applicant's particularly preferred electrochemical synthesis of niacin, the medium has
5 preferably contained water and 3-methylpyridine in a weight ratio from about 1:0.01 to about 1:4. It has additionally been preferred that these mediums be saturated in niacin.

In other facets of the invention, preferred mediums are substantially free from the mineral acids predominantly used
10 in the prior art. Additionally, preferred mediums have demonstrated conductivities of at least about 500 micro-Seimens (reciprocal millionths of an ohm) per centimeter (cm) as reported further hereinbelow.

As stated above, other preferred embodiments of this
15 invention relate to additional electrochemical processes as well as electrochemical baths which provide significant advantages corresponding to those discussed hereinabove. In this regard, one preferred embodiment of the invention relates to a process for electrochemically oxidizing a
20 precursor compound as described herein wherein the oxidation is conducted in an aqueous electrolyte. In accordance with this embodiment significant improvements and advantages are provided by the step of initially charging the electrolyte with an effective amount of a carboxylic acid to
25 significantly enhance water solubility of the precursor compound. What constitutes an effective amount in this respect varies according to the particular chemistries involved. However, the applicant's studies to date have shown that the addition of about 2% by weight of the
30 precursor's corresponding carboxylic acid is more than enough to significantly enhance water solubility of the precursor compound. Additional preferred aspects of this preferred embodiment correspond to those discussed in the embodiment above.

35 Another preferred embodiment, as stated, involves an

-15-

improved electrochemical bath capitalizing on the applicant's preferred electrochemical mediums described herein and thereby providing significant advantages and advancements over the prior art.

5 Reference will now be made to specific examples for the purpose of further describing and understanding the features of the applicant's preferred embodiments and in addition their advantages and improvements over the art. It is understood, however, that these examples are representative
10 only, and that such additional embodiments and improvements of the same are within the contemplation and scope of the applicant's invention as would occur to one of ordinary skill in this art.

EXAMPLE 1

15 Electrochemical Oxidation of Beta-Picoline

An electrolyte medium was prepared containing 87 parts water by weight, 8 parts beta-picoline, and 5 parts niacin. The solution was charged into an undivided cell and electrolyzed using an anodized tin anode with a platinum
20 cathode at a constant current between 0.1 and 1.0 A (10-100 mA/sq. cm). Analysis of the electrolyte indicated an increase in niacin corresponding to a 75% current efficiency. An analogous oxidation was also performed except current was continuously passed until niacin precipitated
25 from the medium as it was formed, and as its saturation point was exceeded.

EXAMPLE 2

Electrochemical Oxidation of Beta-Picoline

In this Example a carboxylic acid other than the
30 corresponding carboxylic acid was used in the medium. Accordingly, an electrolyte medium was prepared and electrolyzed as initially in Example 1 except acetic acid was

-16-

used in the place of niacin. The electrolyte was analyzed and indicated an increase in niacin corresponding to a 61% current efficiency.

EXAMPLE 3

5 Electrochemical Oxidation of Alpha-Picoline

An electrolyte was prepared containing 85 parts by weight water, 10 parts alpha-picoline, and 5 parts picolinic acid. The solution was electrolyzed as initially in Example 1 above to give an increase in picolinic acid corresponding to 83%
10 current efficiency.

EXAMPLE 4

Electrochemical Oxidation of 3,5-Lutidine

The experiment was performed as initially in Example 1 above, except 3,5-lutidine was substituted for the
15 beta-picoline and dinicotinic acid was substituted for the niacin used to prepare the initial electrolyte medium. The medium was electrolyzed and thereafter contained dinicotinic acid in increased amounts indicating a 68% current efficiency.

EXAMPLE 5

20 Electrochemical Oxidation of 2,3-Lutidine

2,3-Lutidine and quinolinic acid were used according to the general initial procedure of Example 1 above. Increased quinolinic acid concentration after electrolysis corresponded to an 87% efficiency.

25

EXAMPLE 6

Electrochemical Oxidation of 2-Methylquinoline

An electrolyte medium was prepared containing 89 parts water by weight, 5 parts 2-methylquinoline, and 6 parts quinoline-2-carboxylic acid. The medium was charged into an
30 undivided cell and electrolyzed using a molybdenum anode and a platinum cathode at a constant current between 0.05 and 1.5 A ($5-150 \text{ mA/cm}^2$). Analysis of the electrolyte indicated a

-17-

93% current efficiency in the production of quinoline-2-carboxylic acid.

EXAMPLES 7 and 8

Electrochemical Oxidations of5 2-Methylquinoline in Divided Cells

In two parallel experiments, either an anion-exchange membrane or a cation-exchange membrane was used to divide the electrochemical cell. The anolyte solution was prepared as described in Example 6 above. The catholyte solution
10 consisted of dilute sodium sulfate and a small amount of added sulfuric acid. When the anion-exchange membrane was used, additional sulfuric acid had to be added to the catholyte to compensate for the sulfate anions transferred through the membrane to the anolyte compartment.

15 Analysis of the reacted electrolytes indicated current efficiencies greater than 85% in the production of quinoline-2-carboxylic acid. While cation-exchange membranes are generally preferred, the choice between anion- and cation-exchange membranes depends on the composition of the
20 catholyte. For example, anion-exchange membranes are sometimes preferred including in some processes wherein hydroxide anion is transferred from the catholyte to the anolyte.

EXAMPLE 9

25 Electrochemical Oxidation of 4-Acetylpyridine

An electrolyte medium was prepared containing 90 parts water by weight, 7 parts 4-acetylpyridine, and 3 parts isonicotinic acid. The solution was charged into an undivided cell and electrolyzed using a palladium anode and a
30 platinum cathode at a constant current density. Analysis of the electrolyte indicated a 98% current efficiency. Isolation of the acid by precipitation at the isoelectric point (pH approx. 3.0 to 3.5) gave an 89% yield of

-18-

isonicotinic acid (the weight of the isonicotinic acid present at the start of the electrolysis was subtracted out of the total weight yield to determine the chemical yield efficiency).

5

EXAMPLE 10

Electrochemical Oxidation of 2-Benzylpyridine

An electrolyte medium was prepared containing 85 parts water by weight, 5 parts 2-benzylpyridine, and 10 parts picolinic acid. The solution was charged into an undivided
10 cell and electrolyzed at a molybdenum anode with a graphite cathode at a constant current density between 0.1 and 1.0 A (10-100 mA² cm.). Analysis of the electrolyte indicated an 88% current efficiency for the production of 2-benzoylpyridine.

15

EXAMPLE 11

Water/Beta-Picoline/Niacin Mediums

To study the physical and electrochemical properties of various medium compositions, mixtures of beta-picoline and water were prepared and then saturated with added niacin by
20 stirring at 25°C for at least 17 hours. The mixtures were thereafter thermostated in a water bath for one day. Conductivity was then determined with a Yellow Springs Instrument's Model 31 Conductivity Bridge, and the amount of niacin in the solution was analyzed by titration with sodium
25 hydroxide. The results are given in Table 1 below in which all percentages are expressed as weight-to-weight percent in the final saturated solution, and conductivity is expressed as micro-Seimens (reciprocal millionths of an ohm) per centimeter.

-19-

TABLE 1

	Medium	Water (%)	Picoline (%)	Niacin (%)	Conductivity (microS/cm)
	a	98.45	0.00	1.55	300
5	b	80.36	8.92	10.72	12000
	c	67.37	16.84	15.79	15000
	d	57.20	24.52	18.28	13000
	e	48.43	32.29	19.28	10000
	f	40.67	40.67	18.66	8000
10	g	32.88	49.32	17.80	5000
	h	25.33	59.11	15.56	3000
	i	17.34	69.35	13.31	1200
	j	8.83	79.49	11.68	210
	k	0.00	89.21	10.79	12

15 The results presented in Table I demonstrate the significance of the applicant's discovery and highlight the magnitude of its advantages over the prior art processes in achieving commercially practicable electrochemical syntheses of N-heterocyclic compounds. Excellent conductivities and

20 reactant solubilities were exhibited in simple carboxylic acid, precursor, and water mediums. For example, medium "b" containing water, niacin and a moderate amount (8.92 weight %) of picoline demonstrated a conductivity of 12000 microS/cm. This represents a forty fold increase over

25 the 300 microS/cm conductivity of medium "a" containing only niacin and water. In addition, mediums "c" and "d" appear particularly favorable in that they provide excellent conductivity as well as solubility of the precursor compound. In this regard, the selection and optimization of

30 electrolyte mediums will depend upon a balancing of these and other factors as will be apparent to those experienced in this field.

EXAMPLE 12

Water/Gamma-Picoline/Isonicotinic Acid Mediums

35 Solubility of the isonicotinic acid in pure water was measured as less than 1 wt %. Impressively, isonicotinic acid formed a saturated solution at 21 wt% acid, 35 wt% water, and 39 wt% gamma-picoline.

-20-

EXAMPLE 13

Water/Alpha-Picoline/Picolinic Acid Mediums

Conductivity of alpha-picoline/water solutions having more than 10 wt% water was less than 150 micro-Seimens/cm.

- 5 To the contrary, a conductivity of 24500 micro-Seimens/cm was measured for a 3-component system in which picolinic acid was miscible in mixtures of water/alpha-picoline having more than 10 wt% water.

EXAMPLE 14

10 Water/2,4-Lutidine/Lutidinic Acid Mediums

A medium of 66 wt% water and 33 wt% 2,4-lutidine was prepared and found largely heterogeneous. Surprisingly, an addition of only 2 wt% lutidinic acid caused the medium to become homogeneous. Further lutidinic acid was added to form
15 a solution of 26 wt% diacid, 25 wt% 2,4-lutidine, and 49 wt% water, which demonstrated a conductivity of 13000 micro-Seimens/cm.

EXAMPLE 15

Water/2,3-Lutidine/Quinolinic Acid Mediums

- 20 A medium of 66 wt% water and 33 wt% 2,3-lutidine was prepared and also found substantially heterogeneous, whereafter addition of only 2 wt% quinolinic acid caused considerable solublization of the 2,3-lutidine. Additional quinolinic acid was added to form solutions of greater than
25 25 wt% diacid, 25 wt% 2,3-lutidine, and 50 wt% water (conductivity 11000 micro-Seimens/cm). Additionally, it was noted that the presence of 2,3-lutidine significantly increased the solubility of quinolinic acid in water.

-21-

EXAMPLE 16

Comparative Study of a Non-N-Heterocyclic Compound

ortho-Toluidine was found essentially insoluble in water. Addition of anthranilic acid did not increase water
5 solubility of either component, thus demonstrating the necessity of an N-heterocyclic precursor compound to achieve the significant advantages of the invention.

-22-

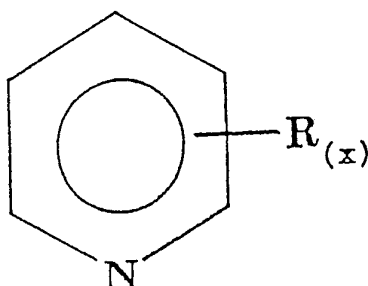
CLAIMS

I CLAIM:

1. In an electrochemical oxidation of a pi-deficient N-heterocyclic compound, said compound having an oxidizable organic group attached by a carbon-to-carbon linkage and being at least sparingly water soluble, the improvement comprising conducting said oxidation at an effective anode and in a medium consisting essentially of water, carboxylic acid, and said compound.
2. The electrochemical oxidation of claim 1 wherein during said conducting said medium is at least substantially free from mineral acid.
3. The electrochemical oxidation of claim 1 wherein during said conducting said medium has a pH of about 2 to about 8.
4. The electrochemical oxidation of claim 3 wherein said compound is a pyridine or quinoline derivative and wherein during said conducting said medium has a pH of about 4 to about 7.
5. The electrochemical oxidation of claim 1, 2, 3 or 4 wherein during said conducting said anode comprises graphite, carbon, or a metal or metal oxide of palladium, platinum, irridium, ruthenium, molybdenum, tin, cerium, chromium or manganese.
6. The electrochemical oxidation of claim 5 wherein during said conducting the counter electrode to said anode is a cathode comprising graphite, platinum, or titanium.

-23-

7. The electrochemical oxidation of claim 1 wherein during said conducting said compound has the general formula:



wherein, $x = 1-3$; and

$R = \text{---CH}_3$,

5 a primary or secondary alkyl group having about 2-6 carbon atoms,

a cycloalkyl group having about 3-6 carbon atoms,

an aralkyl group of the formula $[\text{---}(\text{CH}_2)_n\text{---aryl}]$

where $n = 1-3$,

10 $\text{---}(\text{CH}_2)_m\text{COR}'$ or $\text{---}(\text{CH}_2)_m\text{CHOHR}'$ where $m = 0-5$ and

$R' = \text{H}$ or an alkyl group having about 1-6 carbon atoms, or a cycloalkyl, aryl or aralkyl group having about 3-10 carbon atoms;

and wherein two adjacent R groups on the ring taken together
15 may be a fused cycloalkyl or fused aryl group.

8. The electrochemical oxidation of claim 7 wherein during said conducting said medium is at least substantially free from mineral acid.

9. The electrochemical oxidation of claim 7 wherein
20 during said conducting said medium has a pH of about 2 to about 8.

10. The electrochemical oxidation of claim 9 wherein during said conducting said medium has a pH of about 4 to about 7.

-24-

11. The electrochemical oxidation of claim 7 wherein during said conducting said anode comprises graphite, carbon, or a metal or metal oxide of palladium, platinum, irridium, ruthenium, molybdenum, tin, cerium, chromium or
5 manganese.

12. The electrochemical oxidation of claim 11 wherein during said conducting said anode comprises molybdenum.

13. The electrochemical oxidation of claim 11 wherein during said conducting said anode comprises palladium.

10 14. The electrochemical oxidation of claim 11 wherein during said conducting said anode comprises tin.

15. The electrochemical oxidation of claim 11 wherein during said conducting said anode comprises chromium.

16. The electrochemical oxidation of claim 11 wherein
15 during said conducting the counter electrode to said anode is a cathode comprising graphite, platinum, or titanium.

17. The electrochemical oxidation of claim 16 wherein during said conducting said medium has a pH of about 4 to about 7.

20 18. The electrochemical oxidation of claim 17 wherein during said conducting said medium has a conductivity of at least about 500 micro-seimens per centimeter.

19. The electrochemical oxidation of claim 18 wherein during said conducting current densities of about 1 mA/cm^2
25 to about 400 mA/cm^2 are applied to said cell.

-25-

20. The electrochemical oxidation of claim 19 wherein said compound is oxidized to a corresponding ketone.

21 The electrochemical oxidation of claim 19 wherein said compound is oxidized to a corresponding carboxylic acid.

5 22. The electrochemical oxidation of claim 21 wherein said medium contains said corresponding carboxylic acid at levels at least approaching saturation point.

23. The electrochemical oxidation of claim 22 wherein during said conducting a current efficiency approaching 60%
10 or above is achieved.

24. The electrochemical oxidation of claim 23 wherein during said conducting said compound is a mono- or di-methylpyridine.

25. The electrochemical oxidation of claim 24 wherein
15 during said conducting said methylpyridine is 3-methylpyridine and said corresponding carboxylic acid is niacin.

26. The electrochemical oxidation of claim 25 wherein during said conducting current densities of about 10 to about
20 100 mA/cm² are applied to said cell.

27. The electrochemical oxidation of claim 26 wherein during said conducting a current efficiency approaching 70% or above is achieved.

28. The electrochemical oxidation of claim 27 wherein
25 during said conducting niacin is formed in amounts whereby it precipitates from the medium as its saturation point therein is exceeded.

-26-

29. The electrochemical oxidation of claim 28 wherein during said conducting said medium is substantially free from mineral acid.

30. In an electrochemical oxidation of a pi-deficient
5 N-heterocyclic precursor compound having an oxidizable organic group attached by a carbon-to-carbon linkage, said compound being at least sparingly water soluble, and said oxidation being conducted in an aqueous electrolyte, the improvement comprising the step of:
10 initially charging said electrolyte with an effective amount of a carboxylic acid to significantly enhance water solubility of said compound.

31. The electrochemical oxidation of claim 30 wherein during said charging said compound is a mono- or di-
15 methylpyridine and said acid is a pyridinecarboxylic acid.

32. The electrochemical oxidation of claim 31 wherein during said charging said methylpyridine is 3-methylpyridine and said pyridinecarboxylic acid is niacin.

33. An improved electrochemical bath consisting
20 essentially of:

a pi-deficient N-heterocyclic compound having an oxidizable organic group attached by a carbon-to-carbon linkage, said compound being at least sparingly water soluble;

25 water; and

carboxylic acid;

wherein said compound, water, and carboxylic acid are present in amounts whereby said compound and acid each constitute at least about 2 weight % of said bath.

-27-

34. The electrochemical bath of claim 33 wherein said compound is a pyridine or quinoline derivative.

35. The electrochemical bath of claim 34 wherein said compound is a mono- or di- methylpyridine.

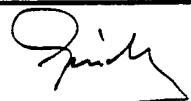
5 36. The electrochemical bath of claim 35 wherein said carboxylic acid is a pyridinecarboxylic acid.

37. The electrochemical bath of claim 36 wherein said methylpyridine is 3-methylpyridine and said pyridinecarboxylic acid is niacin.

INTERNATIONAL SEARCH REPORT

PCT/US 91/03807

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 C25B3/02 ; C07D213/79		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C25B ; C07D	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP,A,217 439 (STAMICARBON B.V.) April 8, 1987 see claims 1-9 ---	1
A	EP,A,253 439 (STAMICARBON B.V.) January 20, 1988 see claims 1-11 ---	1
¹⁰ Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent-family		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
17 SEPTEMBER 1991	16. 10. 91	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	GROSEILLER P.A. 	

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9103807
SA 49743

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

17/09/91

Patent document cited in search report	Publication date	Patent family member(s)	Publication date

EP-A-217439	08-04-87	NL-A- 8502485	01-04-87
		NL-A- 8502486	01-04-87
		JP-A- 62124287	05-06-87
		US-A- 4693793	15-09-87

EP-A-253439	20-01-88	NL-A- 8601826	01-02-88
		JP-A- 63028894	06-02-88
		US-A- 4759834	26-07-88
