

UNITED STATES PATENT OFFICE

2,389,065

PROCESS FOR THE MANUFACTURE OF
NICOTINIC ACID

John Lee, Nutley, N. J., and Stephen D. Heineman,
New York, N. Y., assignors to Hoffmann-La
Roche Inc., Nutley, N. J., a corporation of New
Jersey

No Drawing. Application September 24, 1941,
Serial No. 412,157

4 Claims. (Cl. 260—295.5)

This invention relates to a method for the man-
ufacture of nicotinic acid from quinolinic acid
by decarboxylation of the latter. It will be ap-
parent that an improved method of this type is
highly desirable, since the quinolinic acid is now
a readily available source for the production of
the technically important nicotinic acid.

It has been known that pyridine carboxylic
acids, such as quinolinic acid, when heated to
their melting point, suffer decarboxylation.
Thus, quinolinic acid when heated to 195° C. loses
1 mol of carbon dioxide and gradually forms a
solid mass of nicotinic acid which melts at 230°
C. This method is useless for technical purposes,
since it yields an inhomogeneous fusion mass
which, moreover, is discolored and still contains
all the impurities inherent in the crude quinolinic
acid.

It was found by S. Hoogewerff and others (Ber.
14, 974, 1884) that decarboxylation can be effected
by boiling the pyridine carboxylic acid, such as
quinolinic acid, in glacial acetic acid at its boil-
ing point of 118° C. Quinolinic acid is soluble in
the glacial acetic acid, but in order to effect com-
plete decarboxylation it is necessary to reflux the
solution for a considerable period of time, and in
order to recover the nicotinic acid, the solution
must be evaporated. It is apparent, therefore,
that this method is expensive since it requires
considerable time and heating costs. Moreover,
the glacial acetic acid used is extremely corrosive
to the usual types of chemical manufacturing
equipment.

It is, thus, an object of the present invention to
provide a decarboxylation method which operates
at high velocity and effects the reaction in a com-
paratively short period of time, thus increasing
the efficiency of a given piece of equipment and
cutting the overhead and the heating costs. It
is a further object to provide a means for decar-
boxylating at comparatively low temperatures,
such as are readily accessible by use of low pres-
sure steam, and thus, economizing in construction
and heat costs.

A further object is to provide a method which
can operate in the usual manufacturing labora-
tory equipment without any special precautions
and without corrosion of the vessel occurring and
without any contamination of nicotinic acid oc-
curring, due to the metallic impurities.

Another object is to avoid tedious evaporations
of liquor to crystallize out the nicotinic acid
formed and to obtain high yields of the acid.

A further object is to remove colored impurities
from the crude quinolinic acid so as to obtain in
one operation substantially pure nicotinic acid.

We have now found that the disadvantages of
prior methods can be avoided and the objects of
our invention be satisfied if decarboxylation is
effected by heat treatment in glycerine, glycols
or ethylene glycols alone or more preferably in
the presence of an indifferent organic liquid in
which both nicotinic acid and quinolinic acid are
substantially insoluble or in which at least the
nicotinic acid is substantially insoluble at room
temperature.

We have found that such indifferent liquids, i. e.
liquids which do not react chemically with quin-
olinic or nicotinic acid, are suitably hydrocarbons
of the benzenoid and naphthenoid series and the
esters of acids containing benzenoid or naph-
thenoid nucleus.

In most of these solvents the most effective de-
carboxylation occurs between 125° and 140° C.,
but may start slowly as low as 110° C., slightly
higher temperatures being necessary with the hy-
drocarbon materials other than xylene to effect a
satisfactory decarboxylation rate.

In particular, we have found that a mixture of
the hydrocarbon solvent and of the glycol miscible
therewith, offers several advantages over the hy-
drocarbon solvent alone.

Decarboxylation in that case occurs at a rather
low temperature, the velocity of reaction is higher
than that obtained with hydrocarbon alone, and
the retention of the impurities is improved. Fur-
thermore, the mixture retains practically no nico-
tinic acid in solution, and no difficulties in filter-
ing the decarboxylated reaction mixture are en-
countered if the solution is filtered at a tem-
perature at which the components are miscible.

Thus, we have discovered that a mixture of
xylene and nona-ethylene glycol at the tempera-
ture of about 130° C. develops an exceptionally
good decarboxylating effect, and that the yields
of nicotinic acid are quantitative. This is dis-
tinctly surprising, since it was to be expected that
decarboxylation in a material in which quinolinic
acid is particularly insoluble, would require tem-
peratures approaching the melting point of quin-
olinic acid at 195° C. on the theory that the liquid
would surely act as a heat transfer agent. That
this is not so, contrary to expectation, is indi-
cated by the fact that on heating the quinolinic
acid at 160° C. with liquid petrolatum no decar-
boxylation occurs. Moreover, when heating in
direct heat transfer agents like liquid petrolatum,
even as low as 160° C., extensive carbonization
occurs.

Other solvents containing the benzene nucleus
which have this decarboxylating effect were found
to be esters of phthalic acid, and the like. These

offer the advantage that they can be mixed in various proportions with the glycols which have a considerably greater decarboxylating effect to give solvent mixtures in which the nicotinic acid is comparatively insoluble, which, nevertheless, decarboxylate rapidly at about 130° to 140° C. The range of glycols that may be used with the esters is rather extensive since the class of glycols generally is more soluble in the esters than in the hydrocarbons.

We have found that a lower boiling hydrocarbon, such as toluol, B. P. 111° C., which alone has no significant decarboxylating effect, can, at the temperature at which it normally boils, be made to decarboxylate quinolinic acid at an appreciable rate by the addition of a suitable amount of a glycol. A 1:1 mixture of nonaethylene glycol and toluene is such.

Furthermore, we have found that we may advantageously use a mixture of glycol, an ester and a hydrocarbon. In this case a miscible decarboxylating liquid can be obtained containing a higher proportion of a glycol than would be possible using a mixture of a glycol and a hydrocarbon alone. For example, a mixture of 2 parts nona-ethylene glycol and 8 parts xylol are not completely miscible at room temperature but the addition of 1 part of butylphthalate gives a completely miscible mixture. Such a mixture has a rapid decarboxylating action, a solvent capacity for impurities and filters with ease.

In the foregoing description of our invention, by a liquid hydrocarbon we mean a cyclic hydrocarbon of the class of benzene homologs with 8 or more carbon atoms such as the xylols, diethylbenzenes and other substituted benzenes such as those commercially known as the alkanzenes, liquid hydrogenated naphthalene hydrocarbons such as tetralin and decalin.

By an ester we mean aliphatic esters of acids containing a benzenoid or naphthenoid nucleus such as benzoic acid, phthalic acid, naphthalene carboxylic acid and the like, as for example, methyl benzoate, isopropyl benzoate, dimethyl phthalate, dibutyl phthalate, ethyl- α -naphthalene monocarboxylate.

By a glycol we mean glycol and its homologs such as propylene glycol and also diethylene glycol and its homologs such as triethylene glycol, tetraethylene glycol and nonaethylene glycol.

By a miscible glycol we mean a glycol miscible with the above mentioned hydrocarbon solvents at least at temperatures above 60° C.

By a glycerin we mean glycerin and its monoesters which are liquid above 115° C., such as glycerin monochlorhydrin, glyceryl monoacetate.

The following examples illustrate our invention:

Example 1

5 parts by weight of quinolinic acid and 7 parts by volume diethylene glycol are heated at 135 to 140° until CO₂ evolution ceases after about 30 minutes. The mixture can be filtered directly or diluted with a small amount of cold ethylacetate and filtered. Nicotinic acid is obtained in a yield of 84%.

Example 2

5 parts by weight of quinolinic acid and 4 parts by volume triethylene glycol are heated to 125° for 35 minutes, cooled, diluted with 5 parts by volume cold ethylacetate and filtered. The yield of nicotinic acid is 88%.

Example 3

5 parts by weight of quinolinic acid and 6 parts by volume nonaethylene glycol are heated to 145° for 15 minutes, cooled, diluted with benzol and filtered. A yield of nicotinic acid of 94% is obtained as colorless or faintly buff tinted crystals.

Example 4

6 parts of quinolinic acid and 8 parts dipropylene glycol are heated to 130° C. When the evolution of CO₂ is completed in 30 minutes, 10 parts of cold ethylacetate are added and the mixture filtered and the nicotinic acid washed with ethyl acetate. Yield 96%.

Example 5

A mixture of 2 parts nonaethylene glycol, 8 parts technical xylol, 1 part butyl phthalate and 5 parts quinolinic acid are heated under reflux with stirring to 115-135° C. Decarboxylation begins at about 110° and is brisk at 115° C. At 135° it is very rapid. After decarboxylation is complete, which required from 15 minutes to 2 hours according to the temperature and size of the batch, the liquid is cooled and the nicotinic acid filtered off under suction. The nicotinic acid is washed on the filter with a little benzol and then dried. The yield is quantitative.

Example 6

5 parts of quinolinic acid are suspended in a mixture of 2½ parts of toluol and 2½ parts nonaethylene glycol. This mixture is refluxed until CO₂ evolution ceases, cooled and the nicotinic acid filtered off.

What we claim is:

1. In a process for the manufacture of nicotinic acid, the steps of heating quinolinic acid in an indifferent liquid medium selected from the group consisting of nonaethylene glycol and a mixture of toluol with a substantial amount of nonaethylene glycol, in which medium nicotinic acid is substantially insoluble at room temperature, within the temperature range of from 110 to 135° C. until the evolution of carbon dioxide ceases, cooling the medium, and recovering the nicotinic acid thus produced.

2. In a process for the manufacture of nicotinic acid, the steps of heating quinolinic acid in a mixture of toluol and nonaethylene glycol, containing a substantial quantity of the latter, within the temperature range of from 110 to 135° C. until the evolution of carbon dioxide ceases, cooling the mixture, and recovering the nicotinic acid thus produced.

3. In the process of decarboxylating quinolinic acid into nicotinic acid by heating in a decarboxylating medium, the step which comprises heating the initial material in nonaethylene glycol to 135° C. until the evolution of carbon dioxide ceases, cooling the mixture, diluting it with benzol and filtering the precipitate.

4. In the process of decarboxylating quinolinic acid into nicotinic acid in a decarboxylating medium, the step which comprises heating the quinolinic acid within a temperature range between 110° and 140° C. in a composition comprising a polyhydroxy aliphatic alcohol admixed with a substance selected from the group consisting of benzenoid and naphthenoid hydrocarbons, and continuing the heating in said temperature range until the evolution of carbon dioxide ceases, and recovering the nicotinic acid thus produced.

JOHN LEE.

STEPHEN D. HEINEMAN.