This invention relates to the catalytic oxidation to pyridine carboxylic acids of heterocyclic aromatic nitrogen compounds having an oxidizable organic grouping attached to the nitrogen-containing aromatic nucleus by one or more carbon-to-carbon linkages; more particularly, it relates to the production of nicotinic acid from compounds of this type.

The present need of plentiful supplies of the vitamin B complex for proper nutritional requirements has greatly increased the importance of producing suitable quantities of nicotinic acid, a member of the vitamin B complex, from heterocyclic aromatic nitrogen compounds obtainable from coal tar having an oxidizable organic grouping attached to the nitrogen-containing aromatic nucleus by one or more carbon-to-carbon linkages, e.g., quinoline or 3-picoline. It is known that such heterocyclic aromatic nitrogen compounds may be oxidized to form carboxylic acids by treatment with potassium permanganate or hydrogen peroxide. These methods require relatively expensive oxidizing reagents and the reactions are usually carried out in dilute solutions, with the result that undesirably large volumes of reaction mixture must be handled.

It is an object of this invention to provide a new process for the oxidation of heterocyclic aromatic nitrogen-containing compounds having at least one oxidizable organic grouping attached to the nitrogen-containing aromatic nucleus by one or more carbon-to-carbon linkages, at least one of which groups is in the 3-, or beta position.

A more specific object of this invention is to provide a simple and practical process for the preparation of nicotinic acid from inexpensive heterocyclic aromatic nitrogen compounds such as quinoline or 3-picoline.

In accordance with this invention an N-heteroaryl compound containing a pyridine nucleus and having an oxidizable organic grouping attached to the nitrogen-containing aromatic nucleus by one or more carbon-to-carbon linkages is oxidized to a pyridine carboxylic acid by reaction with nitrogen tetroxide in a sulfuric acid medium.

Among the N-heteroaryl compounds having an oxidizable organic grouping attached to the nitrogen-containing aromatic nucleus by one or more carbon-to-carbon linkages which may be treated in accordance with this invention are beta-picoline, the lutidines, the collidines, quinoline, hydroxyquinolines, quinoline sulfonic acids, quinaldine, lepidine and nicotine. In every case it has been found that such substances upon being subjected to treatment in accordance with our invention yield pyridine carboxylic acids; an important feature of our invention is that it permits the production of the highly valuable nicotinic acid in good yields for example from readily available quinoline, 2-methyl-5-ethyl pyridine, or 3-picoline. The preferred compounds are those having an oxidizable organic group attached to the nitrogen-containing aromatic nucleus in the beta position. While it has been known that under appropriate conditions nitric acid may be used to oxidize compounds of the above type, a product of such oxidations has always been nitrogen tetroxide; it is most surprising, therefore, to discover that this reaction product of the nitric acid oxidation is itself capable of rapidly oxidizing N-heteroaryl compounds of the type described to the corresponding pyridine carboxylic acids in good yields.

The term "N-heteroaryl compounds" is employed throughout the specification and claims to denote a heterocyclic compound formed by the replacement of one group of an aromatic nucleus by a nitrogen atom.

As herelafore pointed out, our invention is applicable to the oxidation of any N-heteroaryl compound containing a pyridine nucleus and having one or more oxidizable organic groupings attached to the nitrogen-containing aromatic nucleus by one or more carbon-to-carbon linkages, at least one of the said groups being in the 3-, or beta position. The nature of the product obtained will vary, depending upon the particular compound treated. Thus, for example, the oxidation of 3-picoline, 2-methyl-5-ethyl-pyridine, 2,3-lutidine, quinoline, 8-hydroxy-quinoline, quinoline-8-sulfonic acid, or nicotine in accordance with this invention yields the highly valuable nicotinic acid, thus making possible the production of this material from a wide variety of N-heteroaryl compounds. Oxidation of quinaldine yields isocinchomerinic and nicotinic acids.

A preferred embodiment of our invention involves the oxidation of quinoline to nicotine acid since the quinoline reactant is readily available and easily oxidized and the product obtained is the most valuable of the pyridine carboxylic acids at the present time. The N-heteroaryl compounds treated may be in substantially pure condition, or in crude form such as may be recovered from coal tar by fractionation.

The nitrogen tetroxide employed may be in substantially pure state or it may be diluted with
an inert gas; for example, ammonia oxidation gas, i.e. the nitrogen tetroxide gas mixture obtained from an ammonia oxidizer after condensing out the water and allowing the nitrogen oxides to oxidize to the tetroxide, may advantageously be used.

The oxidation procedure of this invention may be carried out by dissolving the N-heteroaryl compound to be oxidized in sulfuric acid and then passing nitrogen tetroxide through the solution at elevated temperatures for a sufficient length of time to accomplish the desired oxidation. The amount of sulfuric acid employed should be sufficient to completely dissolve the N-heteroaryl compound. While about 1½ to 2 mols of sulfuric acid per mol of N-heteroaryl compound is usually sufficient to effect such solution, an excess is preferably used, for example between about 5 and about 10 mols of sulfuric acid per mol of N-heteroaryl compound. A larger excess does no harm and in certain instances may be desirable in effecting a reduction in temperature rise of the reaction mixture. The concentration of the sulfuric acid employed may vary from 90 to 100% H₂SO₄, the conventional 96% H₂SO₄ being suitable. Use of oxidation catalysts, particularly selenium dioxide, is desirable; the amount of catalyst used may vary between about 1 and 5 grams of selenium dioxide per gram mol of N-heteroaryl compound being particularly effective. The temperature at which the oxidation is carried out may vary between about 225 and about 350°C, depending to some extent upon the particular compound being oxidized; generally, oxidation may advantageously be accomplished at temperatures between 250° and 325°C, whereas oxidation of the more resistant 3-picoline is preferably effected at temperatures between 300° and 350°C.

It is desirable to commence oxidation of the N-heteroaryl compound at temperatures in the lower portion of the above ranges, e.g. 250° to 275°C for quinoline and 300° to 325°C for 3-picoline, and then, after the oxidation has proceeded substantially, to raise the temperature to the upper portion of the above ranges, e.g. 275° to 300°C for quinoline or 325° to 350°C for 3-picoline. The oxidation may suitably be carried out in a vessel equipped with a condenser to return the volatilized reactants and permit removal of water vapor and gaseous oxidation products. When reaction is complete, which requires from 30 to 120 minutes and can be determined in the case of the more easily oxidized compounds such as quinoline by substantial evolution of the free fumes of unreacted nitrogen tetroxide, the passage of nitrogen tetroxide is stopped and heating may be continued for a few minutes longer to remove the oxides of nitrogen and to insure completeness of the oxidation. In cases of more difficultly oxidized materials such as 3-picoline, some evolution of red fumes takes place throughout the oxidation process.

Pyridine carboxylic acid is the pyridine carboxylic acid that may be recovered from the reaction mass in any suitable manner in the form of the free acid or in the form of a salt or an amide thereof containing the radical of the free acid, i.e. the radical pyrCO— in which Pyr denotes the pyridine nucleus. When the acid is to be isolated in alicyclic acid, the reaction mass may be drained in water and excess acid neutralized with an alkali to a pH value between about 5 and about 7. If necessary, the drained mass may be decolorized by boiling with a small amount of charcoal and filtering. Copper sulfate is then added in slight excess and the mixture is stirred with heating and allowed to cool, whereby copper nicotinate precipitates. The copper nicotinate is filtered, slurried with water and the water slurry is treated with hydrogen sulfide to form copper sulfide, leaving an aqueous solution of nicotinic acid; this solution may then be concentrated and the nicotinic acid recovered by crystallization. The nicotinic acid may also be recovered from its copper salt by reaction of the salt with sulfuric acid. Heating the copper oxide thus formed from the aqueous sodium nicotinate solution, acidifying the solution and recovering nicotinic acid therefrom by crystallization.

The following examples are illustrative of our invention; amounts are given in parts by weight.

**Example 1.**—8 parts of quinoline were dissolved in 100 parts of 96% sulfuric acid containing 1 to 2 parts selenium dioxide. The solution was then heated to 300°C and introduction was commenced of nitrogen tetroxide until gas mixture containing 10% Na₂O₃ and being in nitrogen-tetroxide gas mixture obtained from an ammonia oxidizer after condensing out the water and allowing the nitrogen oxides to oxidize to the tetroxide. The temperature was then rapidly raised to 305°C and maintained for 30 minutes, at the end of which time flow of nitrogen tetroxide was discontinued, 25 parts having been passed through the reaction mass; heating of the mass was continued for a few minutes to remove excess nitrogen tetroxide and to complete the oxidation, and the mass was then permitted to cool. The reaction mass was then drowned in water and the pH value of the drowned mass was adjusted to 6 by addition of sodium hydroxide; the solution was then boiled with activated carbon and filtered. Copper sulfide was then added to the solution and the resulting mixture was heated to effect formation of copper nicotinate, cooled and filtered. The copper nicotinate thus recovered was slurried in water and hydrogen sulfide passed through the slurry, the copper sulfide formed being recovered by filtration. Nicotinic acid was recovered from the filtrate by evaporation. An 89.5 mole percent yield of nicotinic acid was obtained.

**Example 2.**—27 parts quinoline were dissolved in 370 parts of 96% sulfuric acid containing 1 to 2 parts of selenium dioxide. The solution was heated to 200°C and introduction of pure nitrogen tetroxide was started. The temperature was rapidly raised to 300°C and maintained at this point for a period of 35 minutes, at the end of which time flow of nitrogen tetroxide was discontinued, 35 parts of nitrogen tetroxide having been passed into the reaction mixture. The solution was then heated a few more minutes to remove excess nitrogen tetroxide and to complete the oxidation. Nicotinic acid was recovered as described in Example 1; a yield of 83 mole percent was obtained.

**Example 3.**—27 parts of quinoline were dissolved in 280 parts of 96% sulfuric acid. The solution was then heated to 200°C and introduction of nitrogen tetroxide was started. The temperature was rapidly raised to 300°C, and maintained at this value for 35 minutes, at the end of which time flow of nitrogen tetroxide was discontinued, 36 parts thereof having been passed into the reaction mixture. Heating of the mixture was continued a few more minutes to remove the excess nitrogen tetroxide and to complete the oxidati-
tion. Nicotinic acid was recovered as described in Example 1, a 63 mol percent yield being obtained.

Example 4.—25 parts of 3-picoline were dissolved in 370 parts of 96% sulfuric acid containing 1 to 2 parts of selenium dioxide. The solution was then heated to 315° C. and maintained between 315° and 330° C. for 45 minutes while passing 20 parts of nitrogen tetroxide thereinto. At the end of this time nicotinic acid was recovered from the reaction mixture as described in Example 1. A 58% attack on the 3-picoline, with a 75 mol percent yield of nicotinic acid (based on 3-picoline attacked) was obtained.

Example 5.—25 parts of quinoline were dissolved in 370 parts of 96% sulfuric acid containing 1 to 2 parts of selenium dioxide. 45 parts of nitrogen tetroxide were passed into the reaction mixture over a period of 40 minutes while maintaining the temperature between 260° and 300° C. A 70 mol percent yield of a mixture of pyridine-2,5, dicarboxylic acid and nicotinic acid was obtained.

The process of our invention may be carried out as a batch operation or as a continuous process. When operating on a continuous basis, suitable arrangements for continuously contacting the reactants are provided, for example, for the passage of liquid sulfuric acid and nitrogen tetroxide-containing gas co-current or counter-current through a tube or tower, which may be supplied with plates, packing or other devices for enhancing contact.

Since certain changes may be made in carrying out the above process without departing from the scope of the invention, it is intended that all matter contained in the above description shall be interpreted as illustrative and not in a limiting sense.

We claim:

1. A process for the production of nicotine acid, which comprises reacting quinoline in a sulfuric acid medium with gaseous nitrogen tetroxide and recovering a compound containing the nicotine acid radical.

2. A process for the production of nicotine acid, which comprises reacting quinoline with gaseous nitrogen tetroxide in a sulfuric acid medium containing a small amount of a selenium compound at a temperature between 250° and 325° C. and recovering nicotine acid.

3. A process for the production of nicotine acid, which comprises reacting 3-picoline with gaseous nitrogen tetroxide in a sulfuric acid medium containing a small amount of a dissolved selenium compound at a temperature between about 300° and about 350° C. and recovering nicotine acid.

4. A process for the production of nicotine acid, which comprises reacting quinoline in a sulfuric acid medium with gaseous nitrogen tetroxide and recovering a compound containing the nicotinic acid radical.

5. A process for the production of nicotinic acid, which comprises reacting quinoline with gaseous nitrogen tetroxide in a sulfuric acid medium containing a small amount of a selenium compound at a temperature between 250° and 325° C. and recovering nicotinic acid.

6. A process for the production of nicotine acid, which comprises reacting 3-picoline with gaseous nitrogen tetroxide in a sulfuric acid medium containing a small amount of a dissolved selenium compound at a temperature between about 300° and about 350° C. and recovering nicotinic acid.

7. A process for the production of nicotine acid, which comprises reacting quinoline in a sulfuric acid medium containing a small amount of a selenium compound at a temperature between about 225° and about 250° C. and recovering nicotine acid.

8. A process for the production of nicotine acid, which comprises reacting quinoline in a sulfuric acid medium with gaseous nitrogen tetroxide and recovering a compound containing the nicotine acid radical.

9. A process for the production of nicotine acid, which comprises reacting quinoline in a sulfuric acid medium with gaseous nitrogen tetroxide and recovering a compound containing the nicotine acid radical.

10. A process for the production of nicotine acid, which comprises reacting quinoline in a sulfuric acid medium with gaseous nitrogen tetroxide and recovering a compound containing the nicotine acid radical.

11. A process for the production of nicotine acid, which comprises reacting quinoline in a sulfuric acid medium with gaseous nitrogen tetroxide and recovering a compound containing the nicotine acid radical.
to a temperature of at least about 200° C., passing nitrogen tetroxide in the vapor state therethrough while maintaining the temperature of the solution between about 225° C. and about 350° C. until the reaction is substantially complete, and recovering a compound containing the nicotinic acid radical.

12. In a process for the oxidation of N-heteroaryl compounds containing a pyridine nucleus and having at least one oxidizable organic grouping attached to the nitrogen-containing aromatic nucleus by at least one carbon-to-carbon linkage at least one of which is in the beta position to the nitrogen, the steps which comprise dissolving the N-heteroaryl compound in a mixture of about 5 mols and about 10 mols of sulfuric acid per mol of N-heteroaryl compound, heating the mixture to a temperature of at least about 200° C. passing nitrogen tetroxide in the vapor state therethrough while maintaining the temperature of the solution between about 225° C. and about 350° C. and while removing water of reaction and gaseous reaction products substantially as formed, until the reaction is substantially complete, discontinuing the passage of nitrogen tetroxide, while continuing to maintain the temperature in the range above defined for an additional period sufficient to evolve substantially all unreacted oxides of nitrogen, and recovering a compound containing the nicotinic acid radical.

13. In a process for the oxidation of N-heteroaryl compounds containing a pyridine nucleus and having at least one oxidizable organic grouping attached to the nitrogen-containing aromatic nucleus by at least one carbon-to-carbon linkage at least one of which is in the beta position to the nitrogen, the steps which comprise dissolving the N-heteroaryl compound in a mixture of a quantity of concentrated sulfuric acid in excess of that theoretically necessary completely to dissolve the N-heteroaryl compound and between about 1 gram and about 5 grams of selenium dioxide per gram mol of N-heteroaryl compound, heating the mixture to a temperature of at least about 200° C., passing nitrogen tetroxide in the vapor state therethrough while maintaining the temperature of the solution between about 225° C. and about 350° C. until the reaction is substantially complete, and recovering a compound containing the nicotinic acid radical.

14. In a process for the oxidation of N-heteroaryl compounds containing a pyridine nucleus and having at least one oxidizable organic grouping attached to the nitrogen-containing aromatic nucleus by at least one carbon-to-carbon linkage at least one of which is in the beta position to the nitrogen, the steps which comprise dissolving the N-heteroaryl compound in a mixture of a quantity of concentrated sulfuric acid in excess of that theoretically necessary completely to dissolve the N-heteroaryl compound and between about 1 gram and about 5 grams of selenium dioxide per gram mol of N-heteroaryl compound, heating the mixture to a temperature of at least about 200° C., passing nitrogen tetroxide in the vapor state therethrough while maintaining the temperature of the solution between about 225° C. and about 350° C. and about 90% nitrogen, while maintaining the temperature of the solution between about 225° C. and about 350° C. until the reaction is substantially complete, and recovering a compound containing the nicotinic acid radical.

15. In a process for the oxidation of quinoline to nicotinic acid, the steps which comprise dissolving quinoline in between about 1/4 mols and about 10 mols of sulfuric acid per mol of quinoline, heating the mixture to a temperature of at least about 200° C., passing therethrough a gaseous mixture consisting of about 10% NaO₂ and about 90% nitrogen, while maintaining the temperature of the solution between about 250° C. and about 325° C., and while removing water of reaction and gaseous reaction products substantially as formed for a period of not more than about 120 minutes until the reaction is substantially complete, discontinuing the passage of nitrogen tetroxide while continuing to maintain the temperature in the range above defined for an additional few minutes to complete the reaction and to evolve substantially all unreacted oxides of nitrogen.

16. In a process for the oxidation of quinoline to nicotinic acid, the steps which comprise dissolving quinoline in a mixture of a quantity of concentrated sulfuric acid in excess of that theoretically necessary completely to dissolve the quinoline and between about 1 gram and about 5 grams of selenium dioxide per gram mol of quinoline, heating the mixture to a temperature of at least about 200° C., passing nitrogen tetroxide in the vapor state therethrough while maintaining the temperature of the solution between about 250° C. and about 325° C. until the reaction is substantially complete.

17. In a process for the oxidation of 3-picoline to nicotinic acid, the steps which comprise dissolving 3-picoline in a mixture of a quantity of concentrated sulfuric acid in excess of that theoretically necessary completely to dissolve 3-picoline and between about 1 gram and about 5 grams of selenium dioxide per gram mol of 3-picoline, heating the mixture to a temperature of at least about 200° C., passing nitrogen tetroxide in the vapor state therethrough while maintaining the temperature of the solution between about 300° C. and about 350° C. until the reaction is substantially complete.

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