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OXIDATION OF HETEROCYCLIC AROMATIC
NITROGEN COMPOUNDS

Max B. Mueller, Dumont, N. J., assignor to Allied
Chemical & Dye Corporation, New York, N. Y.,
a corporation of New York

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1 This invention relates to the production of pyridine carboxylic acids by catalytic oxidation 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 the type described.

This application is a continuation-in-part of my copending application Serial No. 564,553, filed November 21, 1944, now Patent 2,449,906, September 21, 1948.

Copending application Serial No. 454,121, filed in the name of G. W. Curtis August 8, 1942, discloses oxidation of such heterocyclic nitrogen compounds by reacting the compounds with sulfuric acid in the presence of a relatively small amount of a dissolved mercury compound, preferably in the presence of a small amount of a mixture of mercury and copper compounds.

My present invention is in the nature of an improvement upon the process described in the above identified copending Curtis application, which improvement permits a substantial reduction in the optimum temperature ranges employed in the oxidation of the heterocyclic aromatic nitrogen compounds.

The object of this invention is, therefore, to provide a new and improved process for the oxidation 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.

In accordance with my invention an N-heteroaryl compound 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 reacting a solution of the compound in sulfuric acid, said solution containing a relatively small amount of a dissolved compound, soluble in sulfuric acid, of at least one of a non-noble metal of groups I-B and II-B of the periodic table of the elements, which form two series of compounds corresponding to MO and M₂O, where M signifies a metal, that is, of mercury, compounds of mercury soluble in sulfuric acid, copper and compounds of copper soluble in sulfuric acid, preferably a small amount of a mixture of mercury and copper compounds, which catalyzes oxidation of the N-heteroaryl compound to a pyridine carboxylic acid, with nitric acid.

Oxidation of the N-heteroaryl compounds

2 above described in accordance with this invention produces highly valuable pyridine carboxylic acids in excellent yields. Furthermore, the optimum temperature ranges for the oxidation are substantially lower than those employed in oxidizing the same compound with sulfuric acid in the presence of the same catalyst. For example, production of nicotinic acid by oxidation of quinoline with sulfuric acid in the presence of a mercury or mercury-copper catalyst as described in the Curtis application is preferably accomplished at temperatures between 260° and 290° C., whereas oxidation of quinoline to nicotinic acid in the presence of a mercury or copper or mercury-copper catalyst in accordance with this invention may be most advantageously carried out at 215° to 225° C.; while oxidation of 3-picoline in the presence of such catalysts in accordance with this invention is most advantageously done at 250° to 260° C. Accordingly, my invention permits production of the desired pyridine carboxylic acids at considerably lower cost.

The term "N-heteroaryl compound" is employed throughout the specification and claims to denote those heterocyclic compounds which contain in their structure a nucleus formed by the replacement of one



group of an aromatic nucleus by a nitrogen atom.

My invention is applicable to the oxidation of any N-heteroaryl compound having an oxidizable organic grouping attached to the nitrogen-containing aromatic nucleus by one or more carbon-to-carbon linkages. Thus, the picolines, lutidines, collidines, quinoline, hydroxy-quinolines, quinoline sulfonic acids, quinaldine, isoquinoline, lepidine and nicotine may be treated in accordance with this invention. The nature of the product obtained depends upon the N-heteroaryl compound oxidized and, in some cases, upon the temperature at which the oxidation is carried out. Thus, oxidation of 3-picoline or nicotine yields nicotinic acid. Oxidation of quinoline or 8-hydroxy-quinoline at temperatures above 190° C. yields chiefly nicotinic acid, but at temperatures substantially below this value, quinaldic acid is the principal product. Oxidation of 2-picoline yields picolinic acid, and oxidation of 4-picoline yields isonicotinic acid; oxidation of isoquinoline yields cinchomeronic acid. Oxidation of quinaldine at temperatures above about 190° C. yields chiefly pyridine-2, 5-dicarboxylic acid, but oxidation of quinaldine at tem-

peratures substantially below this value yields 2-methyl pyridine-5, 6-dicarboxylic acid. A preferred embodiment of my invention involves the oxidation of quinoline or 3-picoline to nicotinic acid since the quinoline and 3-picoline reactants are available or potentially available in large amounts 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 as recovered from coal tar by conventional procedures.

The sulfuric acid employed is preferably concentrated sulfuric acid such as 66° Bé. acid, but more dilute acid such as 60° Bé. acid may be used, or, less desirably, fuming sulfuric acid. The amount of sulfuric acid employed may vary considerably but should be sufficient to both combine with the basic nitrogen atom of the N-heteroaryl compound and maintain the compound in solution at the temperature of oxidation; generally between about 5 and about 8 mols of sulfuric acid per mol of N-heteroaryl compound to be treated is suitable.

The catalyst employed in accordance with this invention may be the catalyst described in the co-pending Curtis application hereinabove referred to or it may be copper or a copper compound. The mercury catalyst of the Curtis application may be incorporated in the reaction mixture by dissolving metallic mercury, mercuric oxide, or salts of mercury such as mercuric or mercurous sulfate, mercuric acetate, or mercuric nitrate in the sulfuric or nitric acid reactants and the copper catalyst if used alone may be similarly incorporated. The addition of a soluble copper compound, such as copper sulfate to the mercury catalyst promotes the catalytic activity of the mercury and hence the use of a mixed mercury-copper catalyst, in which the amount of copper present in the mixture may vary between about 0.01% and 100% by weight of the mercury, is preferred. The amount of mercury catalyst employed may vary but generally between about 0.04 and about 0.1 gram atom of mercury per mol of N-heteroaryl compound is suitable.

In general the catalysts above mentioned may be used for the oxidation of any N-heteroaryl compound having an oxidizable organic grouping attached to the nitrogen-containing aromatic nucleus by one or more carbon-to-carbon linkages. However, I have found that the combined mercury-copper catalyst is particularly suitable for oxidation of polynuclear N-heteroaryl compounds such as quinoline.

In carrying out the process of my invention, the N-heteroaryl compound to be oxidized may be dissolved in the sulfuric acid, the catalyst added, and the mixture then heated to reaction temperature; gradual addition of the nitric acid is then commenced and the addition of nitric acid continued until oxidation is substantially complete, which may be determined by analysis of a portion of the reaction mass or by a marked increase in the evolution of brown oxides of nitrogen. Nitric acid containing from about 50% to about 75% HNO₃ is preferably employed although acid of other concentrations may be used if desired.

The temperature at which the oxidation is carried out may vary considerably, depending upon the N-heteroaryl compound treated, upon the catalyst employed and, in some cases, upon the desired pyridine carboxylic acid. The following table indicates optimum temperature ranges

for carrying out various oxidations in accordance with preferred embodiments of my invention:

5	Compound Oxidized with Hg Catalyst	Product	Optimum Temperature Range
			° C.
10	Quinoline.....	Nicotinic Acid.....	215 to 225
	Do.....	Quinolinic Acid.....	150 to 160
	Quinaldine.....	Pyridine-2, 5-Dicarboxylic Acid.....	215 to 225
10	Do.....	2-Methyl-Pyridine-5,6-Dicarboxylic Acid.....	150 to 160
	Methyl Pyridines.....	Corresponding acid.....	250 to 260

In general it may be said that when employing a mercury catalyst for the oxidation of polynuclear N-heteroaryl compounds in accordance with a preferred embodiment of my invention temperatures between 215° and 225° C. are preferred, unless quinoline is to be oxidized to quinolinic acid or quinaldine to 2-methyl-pyridine-5,6-dicarboxylic acid, in which cases temperatures between 150° and 160° C. are preferred. Oxidation of methyl pyridines is preferably carried out at 250° to 260° C. Broadly, temperatures anywhere between 100° and 300° C. will effect oxidation of the N-heteroaryl compounds in accordance with my invention.

While the method of carrying out the oxidation above described represents the preferred embodiment of my invention, the oxidation may also be carried out by gradually adding to sulfuric acid maintained at reaction temperature a solution containing the N-heteroaryl compound to be oxidized dissolved in the nitric acid, the catalyst being in solution, either in the nitric acid or in the sulfuric acid.

The pyridine carboxylic acid product obtained as a result of the oxidation may be recovered in any suitable manner. In the case of nicotinic acid, produced in accordance with the preferred embodiment of this invention, the acid reaction mixture containing sulfuric acid, nicotinic acid sulfate and the catalyst may be cooled to room temperature and poured into water or ice; the sulfuric acid may then be partially neutralized with an alkaline material such as ammonia and any precipitate which forms removed by filtration. The pH value of the solution may then be raised to between about 5 and about 7 by adding sufficient alkali, or by adding an excess of ammonia thereto and boiling until the solution becomes acid to litmus, and the nicotinate converted into copper nicotinate by reaction with copper sulfate; the copper nicotinate precipitate may be recovered by filtration and converted by reaction with sodium hydroxide into sodium nicotinate. Nicotinic acid is preferably recovered from the sodium nicotinate by the addition of an acid such as hydrochloric or sulfuric acid to the sodium nicotinate solution until the pH value thereof is between about 3 and about 4, preferably between about 3.4 and about 3.6, and cooling, since I have found maximum yields of nicotinic acid may thereby be obtained; a Brom Phenol Blue indicator may be used in adjusting the pH value since the neutral point of this indicator to nicotinic acid, i. e. the point at which the indicator just turns yellow, is within the ranges above mentioned. The nicotinic acid may also be recovered by decomposing the copper nicotinate with hydrogen sulfide, filtering off the copper sulfide thus formed and recovering nicotinic acid from the filtrate. Cinchomeronic acid may be advantageously recovered from the reaction mixture resulting from oxidation of isoquinoline by

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cooling the mixture, partially neutralizing, adjusting the pH value of the solution to between 1 and 2, preferably between 1.4 and 1.6, and crystallizing the acid. Isonicotinic acid may be recovered from the reaction mixture resulting from oxidation of 4-picoline by substantially the same manner that cinchomeric acid is recovered except that the pH value of the partially neutralized solution should be adjusted to between 3 and 4, preferably between 3.4 and 3.6.

The following examples are illustrative of my invention. Amounts are given in parts by weight.

Example 1

735 parts by weight of 93% sulfuric acid, 10 parts of mercuric nitrate monohydrate and 176.5 parts of quinoline were mixed and the mixture heated to between 215° and 225° C. Addition of 70% nitric acid to the mixture was then commenced, and the addition continued gradually over a period of about 4 hours during which time 470 parts of nitric acid were introduced, the reaction mixture being maintained at a temperature between 215 and 225° C. throughout the addition. At the end of this time the reaction mixture was poured onto ice and sufficient 35% sodium hydroxide solution was added to bring the solution to a pH of about 10. The alkaline solution was agitated with activated carbon for ½ hour, filtered, and acid added until the pH value of the solution had been lowered to 5; the solution was then again treated with activated carbon, filtered and the pH of the filtrate adjusted to between 6 and 7. The filtrate was then heated to between 85° and 90° C. and a solution of copper sulfate was slowly added thereto, after which the mixture was heated at 85° to 90° C. for about ½ hour. Copper nicotinate thus formed was recovered by filtration.

Example 2

735 parts of 93% sulfuric acid, 4.66 parts of copper sulfate and 179 parts of quinoline were mixed and the mixture heated to between 215° and 225° C. Addition of 70% nitric acid to the mixture was then commenced; the nitric acid was gradually added over a period of 5½ hours, during which time 670 parts of nitric acid were introduced, the reaction mixture being maintained between 215° and 225° C. At the end of this time copper nicotinate was formed and recovered as described in Example 1.

Example 3

735 parts of 93% sulfuric acid, 10 parts of mercuric nitrate monohydrate, 4.6 parts of copper sulfate and 178 parts of quinoline were mixed and the mixture heated to between 215° and 225° C. Addition of 70% nitric acid to the mixture was then commenced; the nitric acid was gradually added over a period of 3¼ hours, during which time 670 parts of nitric acid were introduced, the reaction mixture being maintained at a temperature between 215° and 225° C. At the end of this time the reaction mixture was poured onto ice and sufficient 35% sodium hydroxide solution was added to bring the solution to a pH of about 10. The alkaline solution was agitated with activated carbon for ½ hour, filtered, and acid added until the pH value of the solution had been lowered to 5; the solution was then again treated with activated carbon, filtered and the pH of the filtrate adjusted to between 6 and 7. The filtrate was then heated to between 85° and 90° C. and a solution of copper sulfate was slowly added thereto, after which the mixture was heated at

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85° to 90° C. for about ½ hour. Copper nicotinate thus formed was recovered by filtration.

Example 4

735 parts of 93% sulfuric acid, 10 parts of mercuric nitrate monohydrate, 4.7 parts of copper sulfate, and 173.5 parts of isoquinoline were mixed and the mixture heated to between 215° and 225° C. Addition of 70% nitric acid to the mixture was then commenced; the nitric acid was added gradually over a period of 4¼ hours, during which time 670 parts of the acid were added, the temperature being maintained between 215° and 225° C. The reaction mixture was then poured onto ice and permitted to stand until the ice had melted. The cooled mixture was then brought to a pH of 1.7 by addition of ammonium hydroxide and cooled to 10° C.; crude cinchomeric acid was removed by filtration. The cinchomeric acid was purified by dissolving the acid in sodium hydroxide, treating the solution with activated carbon, adjusting the pH of the solution to between 1.2 and 1.3 and crystallizing the pure acid.

Example 5

A mixture of 735 parts of 93% sulfuric acid, 10 parts of mercuric nitrate monohydrate, 4.66 parts of copper sulfate and 96.5 parts of quinaldine was heated to a temperature between 215° and 225° C. Addition of 70% nitric acid to the mixture was then commenced; the nitric acid was added gradually over a period of 4¾ hours during which time 715 parts of nitric acid were introduced, the temperature being maintained between 215° and 225° C. Upon completion of the oxidation the reaction mixture was treated as described in Example 1 to recover the copper salt. 25 parts of copper salt thus obtained were reacted with 8 parts of sodium hydroxide in 100 parts of water to form the sodium salt, the copper oxide produced being removed by filtration. The solution of the sodium salt was treated with activated carbon, filtered, the filtrate brought to a pH of about 5 with hydrochloric acid and again treated with activated carbon and filtered. Sufficient hydrochloric acid was then added to bring the pH value of the solution to between 3 and 3.5, the solution was cooled and the product which crystallized removed by filtration. The carboxylic acid thus obtained melted with decomposition at 250° to 251° C. and had a neutral equivalent of 83.7 (determined as specified on pages 116 et seq. of "The Systematic Identification of Organic Compounds" by Shriner and Fuson—1940): its methyl ester melted at 161° to 162° C. The calculated neutral equivalent for pyridine-2,5-dicarboxylic acid is 83.5 and the methyl ester of this acid melts at 164° C. so that the product obtained as above described was clearly the copper salt of pyridine-2,5-dicarboxylic acid.

Example 6

735 parts of 93% sulfuric acid, 12.66 parts of mercuric oxide, 9.32 parts of copper sulfate and 144 parts of quinaldine were mixed and the mixture heated to a temperature between 150° and 155° C. Addition of 70% nitric acid to the mixture was then commenced; the nitric acid was added gradually over a period of 18 hours during which time 1430 parts of acid were introduced. A copper salt was recovered from this reaction mixture as described in Example 1. 28.5 parts of copper salt were slurried with 60 parts of water, a solution of 17 parts of sodium hydroxide in 30 parts of water added thereto and the resulting mixture heated on a steam bath for ½

hour. Copper oxide precipitate was removed by filtration and the filtrate treated with activated carbon and filtered. The resulting solution was adjusted to a pH value of about 5 by addition of nitric acid and the solution again treated with activated carbon and filtered; the filtrate was brought to a pH value of 1.6 by the addition of nitric acid, cooled and the crystals which formed recovered by filtration. The product was then recrystallized from 100 parts of water. The recrystallized product upon drying was found to decompose with evolution of carbon dioxide at 168.5° C. to yield a product which solidified and melted again at 202° to 206° C.; the melting point of 2-methylpyridine-5-carboxylic acid is 207° C. The neutral equivalent of the recrystallized product was 90.3; the calculated neutral equivalent of 2-methyl pyridine-5,6-dicarboxylic acid is 90.5. From these facts it is clear that the recrystallized product was 2-methyl-pyridine-5,6-dicarboxylic acid.

Example 7

735 parts of 93% sulfuric acid, 6.33 parts of mercuric oxide, 4.66 parts of copper sulfate, and 72.5 parts of 8-hydroxy quinoline were mixed and the mixture heated to a temperature between 150° and 155° C. Addition of 70% nitric acid to the mixture was then commenced; the nitric acid was added gradually over a period of 3½ hours, during which time 710 parts of acid were added, the reaction mixture being maintained at 150° to 155° C. Upon completion of the reaction, the mixture was treated as described in Example 1 to recover the copper salt. Upon treating the copper salt with sodium hydroxide, a solution of a sodium salt was produced which was acidified to a pH value of 1.4 and cooled; quinolinic acid was recovered as product.

Example 8

735 parts of 93% sulfuric acid, 10 parts of mercuric nitrate monohydrate, 4.66 parts of copper sulfate, and 55 parts of nicotine were mixed and the mixture heated to between 215° and 225° C. Addition of 70% nitric acid was then commenced; the nitric acid was added gradually over a period of 2½ hours, during which time 755 parts of acid were introduced, the reaction mixture being maintained at between 215° and 225° C. Upon completion of the reaction copper nicotinate was recovered as described in Example 1.

Example 9

735 parts of sulfuric acid, 10 parts of mercuric nitrate monohydrate, 4.66 parts of copper sulfate and 93 parts of 4-picoline were mixed and the mixture heated to 250° to 255° C. Addition of 70% nitric acid to the mixture was then commenced; the acid was added gradually over a period of 5 hours, during which time 710 parts of acid were added, the temperature being maintained between 250° and 255° C. Upon completion of the oxidation the crude reaction mixture was made strongly alkaline with sodium hydroxide and steam distilled to remove unreacted 4-picoline. The residue was brought to a pH of 8 with sulfuric acid, treated with activated carbon, filtered, the filtrate brought to a pH of 5 with sulfuric acid and then again treated with activated carbon and filtered. The resulting filtrate was acidified to a pH value of 3.5 and isonicotinic acid crystallized therefrom.

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 mat-

ter contained in the above description shall be interpreted as illustrative and not in a limiting sense.

I claim:

1. In the catalytic oxidation to a pyridine carboxylic acid of an N-heteroaryl compound containing a pyridine nucleus and containing an oxidizable organic grouping attached to the nitrogen-containing aromatic nucleus by at least one carbon-to-carbon linkage, the improvement which comprises conducting the oxidation by reacting nitric acid with a solution containing the N-heteroaryl compound and a relatively small amount, dissolved in sulfuric acid, of a compound of at least one of the metals selected from the group consisting of mercury and copper, and recovering a compound containing the pyridine carboxylic acid radical.

2. In the catalytic oxidation to a pyridine carboxylic acid of an N-heteroaryl compound containing a pyridine nucleus and containing an oxidizable organic grouping attached to the nitrogen-containing aromatic nucleus by at least one carbon-to-carbon linkage, the improvement which comprises conducting the oxidation by reacting nitric acid with a solution containing the N-heteroaryl compound and a relatively small amount, dissolved in sulfuric acid, of a compound of at least one of the metals selected from the group consisting of mercury and copper, while maintaining the solution at a temperature between about 100° and 300° C., and recovering a compound containing the pyridine carboxylic acid radical.

3. In the catalytic oxidation to a pyridine carboxylic acid of an N-heteroaryl compound containing a pyridine nucleus and containing an oxidizable organic grouping attached to the nitrogen-containing aromatic nucleus by at least one carbon-to-carbon linkage, the improvement which comprises conducting the oxidation by reacting nitric acid with a solution containing the N-heteroaryl compound and a relatively small amount of a mercury compound dissolved in sulfuric acid, and recovering a compound containing the pyridine carboxylic acid radical.

4. In the catalytic oxidation to a pyridine carboxylic acid of an N-heteroaryl compound containing a pyridine nucleus and containing an oxidizable organic grouping attached to the nitrogen-containing aromatic nucleus by at least one carbon-to-carbon linkage, the improvement which comprises conducting the oxidation by reacting nitric acid with a solution containing the N-heteroaryl compound and a relatively small amount of a copper compound dissolved in sulfuric acid, and recovering a compound containing the pyridine carboxylic acid radical.

5. In a catalytic oxidation to a pyridine carboxylic acid of an N-heteroaryl compound containing a pyridine nucleus and containing an oxidizable organic grouping attached to the nitrogen-containing aromatic nucleus by at least one carbon-to-carbon linkage, the improvement which comprises conducting the oxidation by reacting nitric acid with a solution containing the N-heteroaryl compound and a relatively small amount of a mixture of mercury and copper compounds dissolved in sulfuric acid, and recovering a compound containing the pyridine carboxylic acid radical.

6. In the catalytic oxidation of quinoline to nicotinic acid, the improvement which comprises conducting the oxidation by adding nitric acid containing between about 50% and about 75%

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HNO₃ to a solution of quinoline in concentrated sulfuric acid containing a relatively small amount of a mixture of mercury and copper compounds while maintaining the solution at a temperature between about 215° and about 225° C., and recovering a compound containing the nicotinic acid radical.

7. In the catalytic oxidation of quinoline to quinolinic acid, the improvement which comprises conducting the oxidation by adding nitric acid containing between about 50% and about 75% HNO₃ to a solution of quinoline in concentrated sulfuric acid containing a relatively small amount of a mixture of mercury and copper compounds while maintaining the solution at a temperature between about 150° and about 160° C., and recovering a compound containing the quinolinic acid radical.

8. In the catalytic oxidation of a methyl pyridine to the corresponding pyridine carboxylic acid, the improvement which comprises conducting the oxidation by adding nitric acid containing between about 50% and about 75% HNO₃ to a solution of a methyl pyridine in sulfuric acid containing a relatively small amount of a mixture of mercury and copper compounds while maintaining the solution at a temperature between about 250° and 260° C., and recovering a compound containing the pyridine carboxylic acid radical.

9. In the catalytic oxidation of quinoline to nicotinic acid, the improvement which comprises conducting the oxidation by adding nitric acid containing between about 50% and about 75% HNO₃ to a solution of quinoline in between about 5 mols and about 8 mols of concentrated sulfuric

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acid per mol of quinoline, said solution also containing a relatively small amount of a compound of at least one of the metals, mercury and copper, while maintaining the solution at a temperature of between about 215° C. and about 225° C., and recovering a compound containing the nicotinic acid radical.

10. In the catalytic oxidation of quinoline to nicotinic acid, the improvement which comprises conducting the oxidation by adding nitric acid containing between about 50% and about 75% HNO₃ to a solution of quinoline in between about 5 mols and about 8 mols of concentrated sulfuric acid per mol of quinoline, said solution also containing between about 0.04 and about 0.1 gram atom of mercury per mol of quinoline, while maintaining the solution at a temperature of between about 215° C. and about 225° C., and recovering a compound containing the nicotinic acid radical.

11. In the catalytic oxidation of quinoline to nicotinic acid, the improvement which comprises conducting the oxidation by adding nitric acid containing between about 50% and about 75% HNO₃ to a solution of quinoline in between about 5 mols and about 8 mols of concentrated sulfuric acid per mol of quinoline, said solution also containing between about 0.04 and about 0.1 gram atom of mercury per mol of quinoline and between about 0.01% and 100% by weight of the mercury of copper while maintaining the solution at a temperature of between about 215° C. and about 225° C., and recovering a compound containing the nicotinic acid radical.

MAX B. MUELLER.

No references cited.