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PRODUCTION OF PYRIDINE-CARBOXYLIC ACIDS

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This invention relates to an improved process for the production of pyridine-carboxylic acids from heterocyclic nitrogen compounds containing a pyridine nucleus substituted by an oxidizable organic grouping attached to the nucleus by one or more carbon-to-carbon linkages and capable of being oxidized to a carboxylic group. The invention relates more particularly to the production of pyridine-carboxylic acids from alkyl substituted pyridine compounds. A particular aspect of the invention relates to the production of nicotinic acid from beta-substituted alkyl pyridine compounds.

It has been disclosed heretofore that pyridine-carboxylic acids are produced by the oxidation of alkyl substituted pyridines. Such processes, as disclosed heretofore, consist, for example, of the oxidation of the alkyl pyridine with the aid of aqueous permanganate solutions, nitric acid or solutions of chromic acid in sulfuric acid. These methods have, however, proven themselves highly impractical due to the relatively low yields obtained therewith and the complexity and difficulties inherent in the operative steps involved. These difficulties have been obviated to some degree by the utilization of a process involving the oxidation of the alkyl substituted pyridine in the form of its salt with the aid of a halogen. Such a process, however, still is handicapped by serious disadvantages militating against efficient large scale operation. These difficulties include relatively low yields and a complexity of operative steps. The latter difficulty is occasioned by the necessity in such processes as disclosed heretofore for the conversion of any unconverted pyridine compound, generally present in the form of its salt, to relatively pure alkyl pyridine before its return to the reaction zone. Since the conversions per pass in such a process as disclosed heretofore are low, the conversion of 3-methyl pyridine to nicotinic acid generally being of the order of only about 19%, the substantial amounts of material which must be subjected to highly complex operative steps to enable their conversion to relatively pure alkyl pyridine prior to recycling to the reaction zone, results in detracting materially from practical operation of the process.

It is an object of the present invention to provide an improved process for the more efficient production of pyridine-carboxylic acids from heterocyclic nitrogen compounds containing a pyridine nucleus substituted by an oxidizable organic grouping attached to the nucleus by one or more carbon-to-carbon linkages and capable of being oxidized to a carboxylic group enabling the at-

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tainment of a high yield of pyridine-carboxylic acid with a minimum of operative steps.

A more particular object of the invention is the provision of an improved process enabling the more efficient production of pyridine-carboxylic acids from alkyl substituted pyridine compounds enabling the obtaining of high yields with a minimum of operative steps.

Still another object of the invention is the provision of an improved process enabling the more efficient production of pyridine monocarboxylic acids from methyl substituted pyridine compounds enabling the attainment of high yields with a minimum of operative steps.

A still more particular object of the invention is the provision of an improved process for the production of nicotinic acid from beta-substituted alkyl pyridine compounds enabling the attainment of high yields with a minimum of operative steps. Other objects and advantages of the invention are apparent from the following detailed description thereof.

In accordance with the process of the invention a heterocyclic nitrogen compound containing a pyridine nucleus substituted by an oxidizable organic grouping attached to the nucleus by one or more carbon-to-carbon linkages and capable of being oxidized to a carboxylic group is subjected to an elevated temperature in an aqueous medium and in the presence of a free halogen in a reaction zone, and pyridine carboxylic acids are removed therefrom substantially as rapidly as formed. In a preferred method of executing the invention a portion of the reaction mixture is continuously withdrawn from the reaction zone, pyridine-carboxylic acids are removed from the portion thus withdrawn, and the entire remaining portion of the withdrawn reaction mixture, free of any substantial amount of carboxylic acids, is returned as such to the reaction zone. It has been found that such continuous removal of the pyridine-carboxylic acids from the reaction mixture substantially as rapidly as formed, results in the attainment of increased yields and enables the continuous recycle of substantially all of the remaining reaction mixture directly to the reaction zone, thereby obviating the complexity of operative steps heretofore resorted to in processes limited to the recycling of only relatively pure alkyl pyridines.

Pyridine compounds oxidized to pyridine-carboxylic acids in accordance with the invention comprise as a broad class the heterocyclic nitrogen compounds containing a pyridine nucleus substituted by an oxidizable organic grouping at-

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tached to the nucleus by one or more carbon-to-carbon linkages and capable of being oxidized to a carboxylic group. Members of this class include the salts of alkyl substituted pyridines obtained, for example, by the reaction of an alkyl substituted pyridine with any acid capable of forming a salt therewith. Examples of the alkyl substituted pyridines comprise the alkyl pyridines containing one or more alkyl groups linked by carbon-to-carbon linkage to the pyridine nucleus. Particularly desirable alkyl pyridines comprise the methyl pyridines such as, for example, 2-methyl pyridine, 3-methyl pyridine, 4-methyl pyridine, 2,6-dimethyl pyridine, 2,4-dimethyl pyridine, and 2,4,6-trimethyl pyridine. Examples of salts of the alkyl pyridines comprise the hydrochlorides, the hydrobromides, sulphates, acetates, etc. Particularly preferred are the alkyl pyridine hydrohalides, such as alkyl pyridine hydrochloride, alkyl pyridine hydrobromide, etc. obtained by the interaction of an alkyl pyridine such as, for example, a methyl pyridine, with the halogen acid. The following detailed description of the invention will be made with particular reference to methylpyridine hydrochloride as the preferred pyridine compounds containing an oxidizable substituent group which are subjected to the conditions resulting in the obtaining of pyridine-carboxylic acids. It is to be understood, however, that this is done with no intent to limit the scope of the invention to the use of only these particularly referred to alkyl pyridine compounds as starting materials.

The alkyl pyridine hydrochloride such as, for example, a methylpyridine hydrochloride, is brought into contact with a free halogen at an elevated temperature in the presence of water in an oxidation zone. Suitable charge material to the oxidation zone comprises the aqueous methylpyridine hydrochloride-containing mixture obtained by the reaction of a methylpyridine with aqueous hydrochloric acid. Any of the members of the halogen group may be employed as the free halogen in oxidizing the methylpyridine hydrochloride to the corresponding pyridine carboxylic acid. Of the halogens, chlorine, bromine or iodine are preferred. The use of chlorine is particularly preferred.

Temperatures in the range of, for example, from about 50° C. to about 250° C., and preferably in the range of from about 80° to about 150° C., are employed in the oxidation of the methylpyridine salt to the corresponding pyridine-carboxylic acid. The reaction may be executed at atmospheric sub or superatmospheric pressures. The oxidation with the free halogen employed may be carried out in the presence of halogenation or oxidation catalysts and/or activating radiations such as ultraviolet light.

Under the above-defined conditions conversion of the alkyl pyridine salt to the corresponding pyridine-carboxylic acid will take place. The accumulation of substantial amounts of hydrogen halide within the reaction zone is preferably avoided. Removal of hydrogen halide may be brought about by adding to the charge, or by separately introducing into the reaction zone, a hydrogen halide accepting material, for example, an alkaline compound such as sodium carbonate, calcium carbonate or the like. Alkyl pyridine may also be comprised in the charge, or may be separately introduced into the reaction zone, to combine therein with the hydrogen halide produced, thereby forming additional alkyl pyridine hydrochloride capable of undergoing further

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conversion to the corresponding pyridine-carboxylic acid reaction product. At least a part of the alkyl pyridine thus additionally introduced into the oxidation zone of the system may be comprised in the products recycled as described more fully below, and/or may consist of unreacted alkyl pyridine contained in the alkyl pyridine hydrochloride charge to the oxidation zone.

It has now been found that the pyridine-carboxylic acid reaction product exerts a marked retarding effect upon the rate of reaction so that the presence of relatively small amounts thereof in the reaction zone will prevent its further formation. Its accumulation within the reaction zone in any substantial amounts will therefore generally prevent the obtaining of conversions per pass of a magnitude commensurate with efficient, large scale, practical operation. It has now further been found that removal of the pyridine-carboxylic acid reaction product from the reactants enables the reaction to proceed with substantially initial velocity and that, quite contrary to that held heretofore, no adverse effect is encountered by retaining in, or recycling to, the reaction zone the remaining reaction mixture, as such, in its entirety. In accordance with the invention the pyridine-carboxylic acid reaction product is therefore removed from the reaction zone substantially as rapidly as formed therein. It has been found that such method of operation results in substantially increasing the yield of the desired pyridine-carboxylic acids. The adverse effect of the accumulated pyridine-carboxylic acid upon the yield obtained, and the substantial advantage obtained by avoiding its accumulation in the reaction mixture is evidenced by the following example:

Example

Three-methylpyridine hydrochloride was prepared by adding 93 parts by weight of 3-methylpyridine (beta-picoline) to 100 parts by weight of 39% hydrochloric acid. Chlorine was introduced into the aqueous 3-methylpyridine hydrochloride thus obtained, at a temperature of about 115° C. and while subjected to ultraviolet rays. The conversion of 3-methylpyridine hydrochloride to beta-pyridine-carboxylic acid (nicotinic acid) was found to be 14.7% after a reaction time of 8 hours duration. At the end of 15 hours the conversion was still only 16.0%.

In a repetition of the experiment under substantially identical conditions a conversion of 3-methylpyridine hydrochloride to beta-pyridine-carboxylic acid of 14.5% was obtained after a reaction time of 7 hours. The reaction mixture was then cooled to 0° C. to crystallize the beta-pyridine-carboxylic acid produced. The beta-pyridine-carboxylic acid was separated from the cooled reaction mixture by filtration and the filtrate again subjected to substantially the identical oxidation reaction conditions employed in the preceding operation for an additional 6 hours. It was found that an additional conversion of 3-methylpyridine hydrochloride to beta-pyridine-carboxylic acid of 14.3% had been obtained.

It is thus seen that in the operation wherein removal of beta-pyridine-carboxylic acid reaction product was not resorted to a conversion in excess of 16.0% could not be obtained, whereas in the second operation wherein intermediate removal of the beta-pyridine-carboxylic acid from the reactants was resorted to a total conversion

to beta-pyridine-carboxylic acid of as high as 28.8% was obtained in a period of 13 hours.

A particular advantage of the invention resides in the ability to recycle to the reaction zone substantially all of the reaction products remaining after separating the pyridine-carboxylic acid therefrom. The process of the invention therefore enables the substantially complete conversion of the alkyl pyridine salt charged to the system to the desired pyridine-carboxylic acid without need to resort to the complex operative procedure heretofore resorted to involving the separation of unconverted alkyl pyridine salt from the remaining complex reaction mixture in the form of relatively pure alkyl pyridine before recycling. The invention thus enables the efficient conversion of alkyl pyridines to the corresponding pyridine-carboxylic acids not only with substantial increase in yield but with a minimum of operative steps.

In a preferred method of carrying out continuously the process of the invention, an alkyl pyridine such as, for example, a methylpyridine, is contacted with aqueous hydrochloric acid to result in the formation of aqueous methylpyridine hydrochloride. The resulting aqueous methylpyridine hydrochloride is brought into contact with a free halogen such as chlorine, at the reaction temperature in a reaction zone. A portion of the reaction mixture is continuously withdrawn from the reaction zone. The portion thus withdrawn is freed of pyridine-carboxylic acid reaction product, which generally will be present therein to at least a substantial degree in the form of the salt, such as pyridine-carboxylic acid hydrochloride.

Separation of the pyridine-carboxylic acid reaction product from the portion of reaction mixture withdrawn from the reaction zone is effected by any suitable means. Thus the separation may be effected by cooling the portion withdrawn from the reaction zone to a sufficiently low temperature to effect the crystallization of the pyridine-carboxylic acid reaction product. Thus in the preparation of nicotinic acid from 3-methylpyridine hydrochloride a temperature of about 0° C. has been found satisfactory. The solidified pyridine-carboxylic acid reaction product is separated from the cooled reaction mixture by such means as filtration, centrifuging or the like. The remaining portion of the reaction mixture, now free of any substantial amount of pyridine-carboxylic acid reaction product, is returned as such, without further separation of products therefrom, to the reaction zone. Withdrawal of reactants from the reaction zone and its passage to the pyridine-carboxylic acid removal step is effected at a sufficiently rapid rate to avoid the accumulation to any substantial degree of pyridine-carboxylic acid reaction product in the reaction zone.

A single reactor, provided with two consecutive zones, may be employed. In the first of said zones the alkyl pyridine, such as, for example a methylpyridine, and aqueous hydrochloric acid are introduced and converted therein to methylpyridine hydrochloride. Products comprising methylpyridine hydrochloride are passed from the first of the zones into the second zone of the reactor wherein they are subjected to the oxidation reaction temperatures in the presence of free chlorine separately introduced therein. A portion of the methylpyridine charge may be passed directly to the second zone of the reactor to function therein as the acceptor for the hy-

drogen chloride liberated during the reaction. Hydrogen chloride formed in the second or oxidation zone of the reactor may be recycled directly to the first zone of the reactor wherein the methylpyridine hydrochloride is formed. The invention is, however, in no wise limited to the use of any specific type of reactor or reactors as the reaction zone. Thus separate reactors in communication with one another may be employed and the alkyl pyridine salt formation executed in one of the reactors and the alkyl pyridine salt oxidation in the other.

The oxidation reaction may be executed in the liquid or vapor phase. When operating in the liquid phase the oxidation zone may comprise a column wherein the chlorine and methylpyridine hydrochloride are brought into counter-current contact. Liquid, comprising unconverted reactants and pyridine-carboxylic acid, is continuously drawn from the lower part of the column. Pyridine-carboxylic acid is removed from the liquid thus drawn from the base of the column and the remaining reactants, substantially free of pyridine-carboxylic acid, are recycled in their entirety to the top of the column. Such continuous operation involving the continuous recycle of liquid from the base of the column to the top thereof, with removal of pyridine-carboxylic acid reaction product from the recycle stream, assures the continuous contact of reactants comprising methylpyridine free of any substantial amount of pyridine-carboxylic acid reaction product with the free halogen. Thereby assuring the obtaining of high yields of the desired pyridine-carboxylic acid with a minimum of operative steps.

A particular advantage of the invention resides in its ability to enable the production, with substantially improved efficiency, of valuable nicotinic acid from beta-substituted alkyl pyridines such as 3-methylpyridine, by the oxidation of the alkyl pyridines in the form of their salts under the conditions set forth herein. The product obtained will of course vary with the specific charge material employed. Thus the alkyl pyridine charged will be oxidized under the conditions set forth herein to the corresponding pyridine-carboxylic acid. Thus 2-methylpyridine, 3-methylpyridine and 4-methylpyridine are oxidized, in the form of their salts to picoline acid, nicotinic acid, and isonicotinic acid, respectively. Utilization of a di-substituted alkyl pyridine will result in the production of pyridinedicarboxylic acid. Thus utilization of a charge comprising 2,3-methylpyridine will result in the obtaining of a product comprising quinolinic acid.

We claim as our invention:

1. The process for the production of nicotinic acid which comprises heating an admixture of 3-methylpyridine hydrochloride, chlorine and water at a temperature of about 115° C., thereby converting said admixture to reaction products comprising nicotinic acid and unconverted 3-methylpyridine hydrochloride, continuing said heating until a conversion of 3-methylpyridine hydrochloride to nicotinic acid of about 14% has been obtained, thereafter separating nicotinic acid from said reaction products, and further heating said remaining reaction products in the presence of added chlorine at a temperature of about 115° C., thereby effecting the further conversion of at least a substantial amount of said unconverted 3-methylpyridine hydrochloride to nicotinic acid.

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2. The process for the production of nicotinic acid which comprises heating an admixture of 3-methylpyridine-hydrochloride, chlorine and water at a temperature of from about 80° C. to about 150° C., thereby converting said admixture to reaction products comprising nicotinic acid and unconverted 3-methylpyridine-hydrochloride, continuing said heating until a conversion of 3-methylpyridine-hydrochloride to nicotinic acid of about 14% has been obtained, thereafter separating nicotinic acid from said reaction products, and further heating the remaining reaction products in the presence of added chlorine at a temperature of from about 80° C. to about 150° C. thereby effecting the further conversion of at least a substantial amount of said unconverted 3-methylpyridine-hydrochloride to nicotinic acid.

3. The process for the production of nicotinic acid which comprises heating an admixture of 3-methylpyridine-hydrochloride, chlorine and water at a temperature of from about 50° C. to about 250° C., thereby converting said admixture to reaction products comprising nicotinic acid and unconverted 3-methylpyridine-hydrochloride, continuing said heating until a conversion of 3-methylpyridine-hydrochloride to nicotinic acid of about 14% has been obtained, thereafter separating nicotinic acid from said reaction products, and further heating the remaining reaction products in the presence of added chlorine at a temperature of about 50° C. to about 250° C. thereby effecting the further conversion of at least a substantial amount of said unconverted 3-methylpyridine-hydrochloride to nicotinic acid.

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ride, continuing said heating until a conversion of 3-methylpyridine-hydrochloride to nicotinic acid of about 14% has been obtained, thereafter separating nicotinic acid from said reaction products, and further heating the remaining reaction products in the presence of added chlorine at a temperature of about 50° C. to about 250° C. thereby effecting the further conversion of at least a substantial amount of said unconverted 3-methylpyridine-hydrochloride to nicotinic acid.

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