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NEW PROCESS FOR THE PREPARATION OF AMINES

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This invention relates to a new process for the preparation of isoindolines. More particularly, it relates to a process for the electrolytic reduction of phthalimides to isoindolines, wherein the reduction is carried out at a cathodic reference potential of at least —1.0 volt vs. a saturated calomel electrode using a mixture of water, a lower aliphatic carboxylic acid and a strong inorganic acid as catholyte and a cathode of high overvoltage.

Several phthalimides have been reduced electrolytically in the past, but the efficiency of these processes is very low [cf. Cook and France, G. Phys. Chem. 36, 2383–89 (1932)].

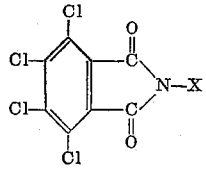
I have now found that the efficiency achievable in such reductions can be considerably improved by carrying out the reduction at the above specified cathodic reference potential, using the above stated catholyte and cathode.

Cathodes of high overvoltage are those having an overvoltage equal to or higher than lead, such as lead, lead or zinc amalgam, but preferably mercury. It is especially advantageous to work at a cathodic reference potential of —1 to —5 volts vs. a saturated calomel electrode depending on the relative percentages of components comprising the background medium.

As a lower aliphatic carboxylic acid, for example propionic or n-butyric acid, but advantageously acetic acid may be used; as a strong inorganic acid, there is used an acid, which ionizes readily, and does not decompose at the current density employed, for example phosphoric acid or a hydrohalic acid such as hydrochloric acid, or preferably sulfuric acid. Any appropriate anode, such as platinum, carbon, lead or stainless steel, and any appropriate anolyte may be employed, as for example dilute sulfuric acid or dilute hydrochloric acid. A platinum anode and a dilute sulfuric acid anolyte are preferred.

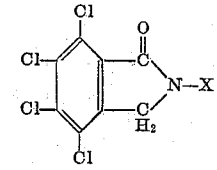
Depending on the period of time over which the reduction is carried on, there can be isolated partially reduced compounds, such as phthalimidines, which can be further reduced according to the invention yielding the final products, the isoindolines. The invention comprises also a process wherein a product obtainable as an intermediate in the above described process is used as starting material and the reduction according to the invention is carried out. Thus, it is possible to start, for example with a phthalimidine and to reduce it to the corresponding isoindoline. Isoindolines are used widely as intermediates in the chemical industry.

An important feature of my invention is that the new process gives favorable results not only with simple phthalimides, such as phthalimide itself or N-methylphthalimide, but surprisingly enough, also with more complex phthalimides, such as the new phthalimides of the formula:

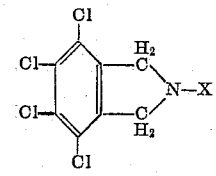


wherein X stands for an amino-alkyl such as an amino-lower alkyl group and especially for a di-lower alkyl-amino-ethyl group or an amino-ethyl group, the nitrogen atom of which is part of a saturated ring, such as a pyrrolidinoethyl, piperidino-ethyl or morpholino-ethyl group. These tetrachlorophthalimides cannot be reduced to a practical extent under the conditions used heretofore for the electrilytical reduction of phthalimides.

Moreover, the reduction of these compounds by commonly used reducing agents such as lithium aluminum hydride has been found to give only moderate yields of impure reduction products, whereas according to the invention, the new isoindolines are obtained in a pure state and excellent yield. Thus, 3,4,5,6-tetrachlorophthalimides of the above given formula can be easily reduced depending on the period of time over which the reduction is carried on, for example to 3,4,5,6-tetrachlorophthalimidines of the formula:



or to 4,5,6,7-tetrachloro-isoindolines of the formula:



wherein X has the same meaning as hereinabove. The last named compounds can also be obtained according to the invention by reduction of the aforesaid partially reduced compounds. The reduction of the amino-alkyl compounds is preferably carried out at a reference potential of —1 to —5 volts vs. a saturated calomel electrode depending on the relative percentages of the various components comprising the background medium.

The obtained N-amino-alkyl-tetrachlorophthalimidines and isoindolines are new. Depending on the working conditions, they are obtained in the form of their salts or as free bases. From the free amines, salts can be made by reacting them with acids such as hydrohalic acids, sulfuric acid, nitric acid, phosphoric acids or other inorganic or organic acids suitable for salt formation. These N-amino-alkyl compounds are important intermediates for the preparation of medicaments, such as those described and claimed in the copending application Serial No. 448,123, filed August 5, 1954, by Charles F. Huebner. Thus 2-(disubstituted amino-alkyl)-4,5,6,7-tetrachloro-isoindolines can be converted into their lower alkyl di-quaternary ammonium compounds by treatment with appropriate quaternizing agents e. g. lower alkyl halides. The thus obtained quaternary compounds, such as 2-(2′-dimethylamino-ethyl)-4,5,6,7-tetrachloro-isoindoline dimethochloride, are valuable ganglionic blocking agents.

The invention is described in greater details in the examples that follow, which are presented by way of illustration and not of limitation. Temperatures are expressed in degrees centigrade. The instrument used in these examples for the controlled-potential-reduction is described by me in Anal. Chem. 229, 804 (1950).

This application is a continuation-in-part of my copending applications Serial No. 457,282, filed September 20, 1954, and now abandoned, and Serial No. 498,772, filed April 1, 1955, and now abandoned.

Example 1

5 g. of N-(2'-dimethylamino-ethyl)-3,4,5,6-tetrachlorophthalimide are dissolved in a mixture of 20 ml. of concentrated hydrochloric acid and 105 ml. of glacial acetic acid. This solution is put in the cathode chamber having a mercury cathode. The cathode chamber is separated from the anode chamber by a permeable diaphragm; as such there is used a regenerated cellulose foil sold to the trade as "Visking" sausage skin. A platinum anode is used. The anolyte is a mixture of 20 ml. of concentrated hydrochloric acid and 105 ml. of water. At a cathodic reference potential of —4.0 volts vs. a standard calomel electrode and at a temperature of 45–50° the current density is 0.086 amp./cm.². After 282 minutes the electrolysis is discontinued and the catholyte made basic with dilute sodium hydroxide. The basic solution is then extracted with ether, the ethereal solution washed with water and dried. On evaporation of the solvent 2-(2'-dimethylamino-ethyl)-isoindoline crystallizes. It can be recrystallized from pentane and melts at 69–71°. The thus obtained tertiary amine can be converted into the 2-(2'-dimethylamino-ethyl)-4,5,6,7-tetrachloro-isoindoline dimethochloride which is a valuable ganglionic blocking agent by the following procedure:

3.8 g. of 2-(2'-dimethylamino-ethyl)-4,5,6,7-tetrachloro-isoindoline are dissolved in 25 ml. of 90 percent ethanol and refluxed 2 hours with 6 ml. of methyliodide. The corresponding dimethiodide separates during the reaction. It is collected by filtration and recrystallized from a mixture of ethanol and water; M. P. 244–246°. It can be converted into the dimethochloride by shaking its aqueous solution with an excess of freshly prepared silver chloride and evaporating to dryness the aqueous solution after removal of the silver salts. 2-(2'-dimethylamino - ethyl) - 4,5,6,7 - tetrachloro - isoindoline dimethochloride is recrystallized from ethanol-ethylacetate; M. P. 276–280°.

The N-(2'-dimethylamino-ethyl) - 3,4,5,6 - tetrachlorophthalimide used as starting material can be prepared as follows:

50 g. of 3,4,5,6-tetrachlorophthalic anhydride is added with stirring and cooling to 30 ml. of 2-dimethylamino-ethyl amine. The mixture is heated at 170° for 45 minutes and the oily residue then dissolved in 200 ml. of hot ethanol. On cooling, N-(2'-dimethylamino-ethyl)-3,4,5,6-tetrachlorophthalimide separates. It crystallizes from ethanol; M. P. 184–186°.

Example 2

5 g. of N-(2'-dimethylamino-ethyl)-3,4,5,6-tetrachlorophthalimide is dissolved in a mixture of 105 ml. of glacial acetic acid, 13.3 ml. of water and 6.7 ml. concentrated sulfuric acid. This solution is placed in the cathode chamber having a mercury cathode. The cathode chamber is separated from the anode chamber as indicated in Example 1 and the same anode is used. The anolyte is a 1.95 N aqueous sulfuric acid solution and a platinum anode is used. At a cathodic reference potential of —4.0 volts vs. a standard calomel electrode and at an average temperature of 45° the current density is 0.114 amp./cm.². After 100 minutes the reaction is complete. The catholyte is then made basic, extracted with ether, the ether washed with water and evaporated, whereupon the 2-(2'-dimethylamino-ethyl)-4,5,6,7-tetrachloro-isoindoline described in Example 1 is obtained in crystalline form.

Example 3

5 g. of N-(2'-dimethylamino-ethyl)-3,4,5,6-tetrachlorophthalimide is submitted to electrolytic reduction in exactly the same manner as described in Example 1. After 120 minutes the catholyte is made basic with a sodium hydroxide solution. The aqueous solution is then extracted with ether and the residue remaining in the aqueous phase filtered off and dried. Thus, crystalline N-(2'-dimethylamino - ethyl) - 3,4,5,6 - tetrachlorophthalimidine is obtained, which after recrystallization from ethanol forms white needles; M. P. 166–167°.

Example 4

5 g. of N-(2'-dimethylamino-ethyl)-3,4,5,6-tetrachlorophthalimide is subjected to electrolysis under the same conditions as shown in Example 1. After 120 minutes the catholyte is worked up in the same manner as in Example 1. There is obtained the 2-(2'-dimethylamino-ethyl)-4,5,6,7-tetrachloro-isoindoline described in Example 1.

Example 5

10 g. of N-(2'-dimethylamino-ethyl)-3,4,5,6-tetrachlorophthalimide are reduced in the manner indicated in Example 1, using as catholyte a mixture of 50 ml. acetic acid, 15 ml. concentrated sulfuric acid and 60 ml. water. As cathode, mercury is used, and a platinum anode in 4.5 N aqueous sulfuric acid serves as anode. At a cathodic reference potential of —2.6 volts vs. a standard calomel electrode and at an average temperature of 50–60°, the current density is 0.354 amp./cm.². The reduction is completed after 75 minutes. The cathode is then made basic, extracted with ether, the ether washed with water and evaporated whereupon the 2-(2'-dimethylamino-ethyl)-4,5,6,7-tetrachloroisoindoline described in Example 1 is obtained in crystalline form.

Example 6

10 g. of N-(2'-dimethylamino-ethyl)-3,4,5,6-tetrachlorophthalimide are reduced electrolytically in the manner indicated in Example 1 using a mercury cathode and as catholyte a mixture of 15 ml. concentrated sulfuric acid, 60 ml. of water and 50 ml. of acetic acid. A platinum anode is used and the anolyte consists of 4.5 N aqueous sulfuric acid. At a cathodic reference potential of —1.6 volts vs. a standard calomel electrode and at an average temperature of 50–60°, the current density is 0.086 amp./cm.² and the reaction is completed after 310 minutes. The catholyte is then made basic, extracted with ether, the ether washed with water and evaporated whereupon the 2-(2'-dimethylamino-ethyl)-4,5,6,7-tetrachloro-isoindoline described in Example 1 is obtained in crystalline form.

Example 7

4 g. of N-methyl-3,4,5,6-tetrachlorophthalimide are reduced electrolytically in the manner indicated in Example 1. As cathode mercury is used and the catholyte consists of a mixture of 108 ml. acetic acid, 9 ml. concentrated sulfuric acid and 8 ml. water. Platinum in 2.7 N aqueous sulfuric acid is used as anode. At a cathodic reference potential of —5.0 volts vs. a standard calomel electrode and at an average temperature of 40–50° the current density is 0.08 amp./cm.² and the reaction is completed after 125 minutes. The catholyte is then made basic with an aqueous solution of sodium hydroxide and the precipitate which forms washed with water and dried. After recrystallization from ethanol the thus obtained 2 - methyl - 4,5,6,7 - tetrachloroisoindoline melts at 150–152°.

Example 8

6.8 g. of N-(2'-dimethylamino-ethyl)-3,4,5,6-tetrachlorophthalimide are dissolved in a mixture of 30 ml. acetic acid, 9 ml. concentrated sulfuric acid and 36 ml. distilled water. This solution is placed in the cathode chamber having a lead cathode. The cathode chamber is separated from the anode chamber by an ion-exchange resin membrane such as "Amberplex C–1" (Roehm and Haas Co., Philadelphia). The anolyte consists of a solution of 9 ml. sulfuric acid in 66 ml. distilled water, and a platinum anode is used. The reduction is performed at a current density of 0.0423 amp./cm.². The temperature is maintained at 55° C. The reference potential

obtained under these conditions is —1.04 volts vs. a saturated calomel electrode. After twice the theoretical amount of current has passed, the catholyte is made basic, extracted with ether, the ether washed with water, and evaporated whereupon 2-(2'-dimethylamino-ethyl)-4,5,6,7-tetrachloro-isoindoline described in Example 1 is obtained in crystalline form.

What is claimed is:

1. A process for the preparation of N-aminoalkyl-3,4,5,6-tetrachloroisoindolines, which comprises electrolytically reducing N-aminoalkyl-3,4,5,6-tetrachlorophthalimides at a cathodic reference potential of at least —1.0 volt vs. a saturated calomel electrode, using an aqueous catholyte consisting essentially of water, a lower aliphatic carboxylic acid selected from the group consisting of acetic acid ,propionic acid and n-butyric acid and a strong inorganic acid selected from the group consisting of phosphoric acid, hydrochloric acid and sulfuric acid and a cathode of high overvoltage.

2. A process according to claim 1 wherein a N-(2'-di-lower alkyl-amino-ethyl)-3,4,5,6-tetrachlorophthalimide is used as starting material.

3. A process according to claim 1 wherein water, acetic acid and sulfuric acid is used as the aqueous catholyte.

4. A process according to claim 1, wherein a lead cathode is used.

5. A process according to claim 1, wherein a mercury cathode is used.

6. A process for the preparation of 2-(2'-dimethylamino-ethyl)-4,5,6,7-tetrachloro-isoindoline which comprises electrolytically reducing N-(2'-dimethylamino-ethyl)-3,4,5,6-tetrachlorophthalimide at a cathodic reference potential of at least —1.0 volt vs. a saturated calomel electrode employing a mercury cathode and an aqueoue catholyte consisting essentially of water, acetic acid and sulfuric acid.

7. A process for the preparation of 2-(2'-dimethylamino-ethyl)-4,5,6,7-tetrachloro-isoindoline which comprises electrolytically reducing N-(2'-dimethylamino-ethyl)-3,4,5,6-tetrachlorophthalimide at a cathodic reference potential of at least —1.0 volt vs. a saturated calomel electrode employing a lead cathode and an aqueous catholyte consisting essentially of water, acetic acid and sulfuric acid.

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