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3,592,748

PREPARATION OF QUINONES

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U.S. Cl. 204-78

16 Claims

ABSTRACT OF THE DISCLOSURE

Preparation of quinones and naphthoquinones from phenols or naphthols by subjecting an aqueous solution containing the phenol or the naphthol and a hydroxylamine disulfonate to electrolysis.

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a continuation-in-part application of U.S. patent application Ser. No. 841,130, filed July 11, 1969.

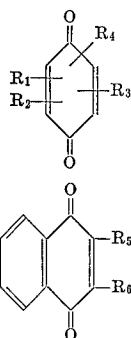
BACKGROUND OF THE INVENTION

In the past, quinones such as tri-lower alkyl quinone, an important intermediate for vitamin E and related compounds, as well as naphthoquinones which are important intermediates for vitamin K, have been commercially synthesized from phenols or naphthols through the utilization of oxidizing agents such as potassium permanganate and lead dioxide. This has proven extremely disadvantageous since these oxidizing agents in this reaction form solid metallic oxides such as lead oxides and manganese oxides which become entrained in the quinone product and consequently contaminated the quinone or naphthoquinone product. It is very important in the syntheses of vitamin E, vitamin K and related products that any product or intermediate utilized have a high degree of purity. It is with considerable difficulty and expense that the entrained solid metallic oxides are removed from the quinone or naphthoquinone. Therefore, a method whereby quinones or naphthoquinones of high purity can be produced by oxidation of phenols or naphthols has long been desired in the art.

Another method whereby phenols have been converted into quinones has been by nitrosation of the phenol and subsequent saponification to the quinone. This method also has suffered from various drawbacks since formation of tars and other byproducts occurs during this process. These tars have produced a contaminated product which has only been purified by costly and time-consuming procedures.

SUMMARY OF THE INVENTION

In accordance with this invention, it has been found that quinones and naphthoquinones having the following formulae:



I-a

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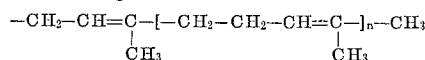
I-b

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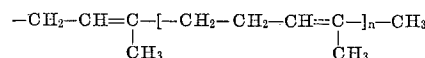
I-b

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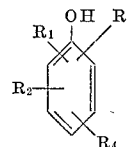
wherein R₁ and R₂ and R₄ are hydrogen, lower alkyl, lower alkoxy and halogen; R₃ is lower alkyl, hydrogen, lower alkoxy, halogen and a radical of the formula:



wherein the double bond shown by the dotted line can optionally be fully hydrogenated; n represents an integer from 0 to 9 inclusive; R₅ is hydrogen or lower alkyl; R₆ is hydrogen, lower alkyl and a radical of the formula:

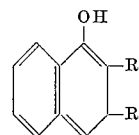


n is an integer from 0 to 9; and the double bond shown by the dotted line can optionally be fully hydrogenated; can be produced by electrolytically subjecting a phenol or a naphthol having the formulae:



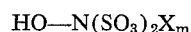
II-a

wherein R₁, R₂, R₃ and R₄ are as above; with the proviso that the position para to the hydroxy group is unsubstituted; and



II-b

wherein R₅ and R₆ are as above; to electrolysis in the presence of a hydroxylamine of the formula:



III

wherein X is an ammonium ion, alkali metal or alkaline earth metal; and m is 1 or 2, with the proviso that when X is an ammonium ion or monovalent metal, m is 2, and when X is a divalent metal, m is 1.

By this process, a quinone or naphthoquinone is produced in substantially pure form in substantially quantitative yields without any contamination from solid metal oxides. In this process only one mole of the hydroxylamine of Formula III per mole of the phenol or the naphthol having the Formulae II-a or II-b is needed to produce the quinone or naphthoquinone of Formulae I-a or I-b in substantially quantitative yields. In the past, at least two moles of an oxidizing agent per mole of the phenol of Formula II-a or naphthol of Formula II-b had to be utilized for this conversion. Therefore, the process of this invention provides a simple and economic method for producing a quinone or naphthoquinone of high purity from a phenol or from a naphthol.

DETAILED DESCRIPTION OF THE INVENTION

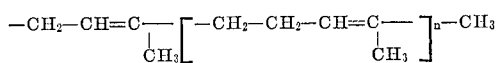
The term "lower alkyl" as used throughout this application includes both branched and straight chain alkyl groups containing from 1 to 7 carbon atoms such as methyl, ethyl, propyl, isopropyl, etc. The term "lower alkoxy" as used throughout the specification designates lower alkoxy groups containing from 1 to 7 carbon atoms such as methoxy, ethoxy, propoxy, isopropoxy, etc. The term "halogen" as used throughout this application includes all four halogens, i.e., fluorine, chlorine, bromine and iodine. The preferred halogens are fluorine and chlorine.

In the hydroxylamine of Formula III, X can be any conventional alkali metal or alkaline earth metal. Among the conventional alkali metals which X can designate are included sodium, potassium, lithium, rubidium, etc.

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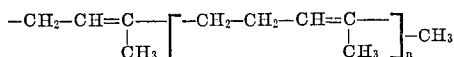
Among the alkaline earth metals which are designated by X are included calcium, magnesium, etc.

When R_3 in the compound of Formula II-a above represents the radical



wherein the double bond shown by the dotted line can optionally be fully hydrogenated; and n is as above; this radical is preferably substituted at the meta position from the hydroxy group in the compound of Formula II-a above. Among the preferred radicals are included phytyl; geranyl; farnesyl; geranyl-geranyl; farnesyl-farnesyl; 3,7,11,15,19 - pentamethyl 2,6,10,14,18 - eicosapentaenyl; 3,7,11,15,19,23,27,31 - octamethyl - 2,6,10,14,18,22,26,30-dotriacontaoctaenyl; etc.

When R_6 in the compound of Formula II-b represents the radical



wherein n is as above; and the double bond shown by the dotted line can optionally be fully hydrogenated; the preferred radicals are those where m is 3 and the dotted bond is hydrogenated and those where m is 5 and the dotted bond represents unsaturation.

The reaction of this invention is carried out by electrolytically treating a liquid aqueous reaction medium containing the phenol of Formula II-a above or the naphthol of Formula II-b above and the hydroxylamine of Formula III above. This reaction can take place by any conventional electrolytic process.

This process is carried out in a conventional electrolytic cell. In accordance with the present invention, the liquid aqueous reaction medium containing the phenol of Formula II-a above or the naphthol of Formula II-b above and the hydroxylamine of Formula III above is placed in an electrolytic cell, e.g., an electrolysis tank which may or may not be provided with a cell divider or membrane, and which is provided with an anode and cathode. The cathode and the anode can be made of any material commonly employed for making cathodes and anodes in the electro-chemical art, e.g., carbon, Monel, stainless steel, platinum, palladium, nickel, nickel-alloy, etc. The electrolytic cell can be provided with a stirrer or mechanical agitator, or the reaction medium can be circulated by means of pumps. The electrolysis can be carried out by applying voltages of from 0.5 to 50 volts to the liquid aqueous reaction medium. Generally, it is preferred to carry out the reaction utilizing from 5 to 25 volts. The electric current passed through the solution can be of a current density of up to 50 amperes per square decimeter and can be as low as 0.01 ampere per square decimeter. Generally, it is preferred to utilize a current density of from 0.02 to 25 amperes per square decimeter.

In carrying out the electrolysis reaction more efficaciously, any conventional electrolyte can, if desired, be added to the aqueous medium. Among the conventional electrolytes which can, if desired, be added to the liquid aqueous reaction medium prior to electrolysis are included sodium hydroxide, sodium bicarbonate, acetic acid, sodium carbonate, sodium acetate, sodium phosphate, sodium chloride, ammonium hydroxide, etc. Generally, it is preferred to add the electrolyte to the liquid aqueous medium in an amount of from 0.1 percent to 10 percent by weight of the liquid medium. During the electrolysis reaction, the pH of the reaction medium is maintained at 4 or above. Optionally, this reaction is carried out at a pH of from 4 to 13. The aforementioned electrolytes can be utilized to obtain the desired pH.

The liquid aqueous medium that is subjected to electrolysis in accordance with this invention contains an inert liquid organic solvent in which the phenol is dissolved. Any conventional inert organic solvent can be utilized in accordance with this invention. Among the conventional

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inert organic solvents are included xylene, toluene, hexane, heptane, benzene, halogenated aliphatic hydrocarbons such as chlorobenzene, methylene chloride, carbon tetrachloride, etc. Generally, from about 1 mole of the hydroxylamine of Formula III above is present per mole of the phenol of Formula II-a above or the naphthol of Formula II-b above. In accordance with this invention, conversion of the phenol of Formula II-a or naphthol of Formula II-b in yields of approximately 100 percent can be carried out by utilizing only 1 mole of the hydroxylamine of Formula III per mole of the phenol or naphthol. However, if lower yields are desired, approximately 0.5 mole of the hydroxylamine of Formula III per mole of the phenol or naphthol can be utilized. On the other hand, large excesses of this hydroxylamine can, if desired, be utilized. No additional beneficial results are achieved by utilizing large excesses of hydroxylamine. However, if desired, the hydroxylamine of Formula III can be present in an amount of about 10 moles per mole of the phenol of Formula II-a or the naphthol of Formula II-b or greater. The electrolysis reaction can be carried out at any temperature of from -15°C . to 50°C . Generally, it is preferred to carry out this reaction at a temperature of -10°C . to $+10^\circ\text{C}$.

The reaction medium that is subjected to electrolysis consists of two phases, i.e., an aqueous phase and an organic phase. The aqueous phase contains the hydroxylamine of Formula III and the organic solvent phase contains the phenol of the Formula II-a above or naphthol of Formula II-b above. The electrolysis reaction can be carried out for a period of at least $\frac{1}{2}$ hour or longer. Generally, it is preferred to carry out the electrolysis for a period of from 1 to 10 hours. If desired, electrolysis can be carried out for periods longer than 10 hours. However, since the use of electrolysis times of greater than 10 hours produce no additional beneficial results, these prolonged reaction times are seldom employed.

The quinone or naphthoquinone that is formed in accordance with this invention can be easily recovered in pure form from the two-phase reaction medium since it is present in the organic solvent phase, and the other constituents of the reaction medium are in the aqueous phase. By means of phase separation, the quinone or naphthoquinone is obtained in the organic phase free of contaminants. The quinone or naphthoquinone can be easily obtained from the organic phase by evaporation of the organic solvent. Therefore, there is no need to subject the quinone or naphthoquinone obtained by the process of this invention to purification techniques such as distillation which may cause decomposition and deterioration of the quinone or naphthoquinone product.

In accordance with an embodiment of this invention, the hydroxylamine of Formula III above can be prepared by reacting ammonium, an alkali metal or alkaline earth metal nitrite with sulfur dioxide in an aqueous medium. In carrying out this reaction, the sulfur dioxide can be bubbled in as a gas into the aqueous reaction medium. Alternatively, the reaction medium can contain any source capable of liberating sulfur dioxide such as a mixture of an organic acid such as acetic acid and an alkali metal, ammonium or alkaline earth metal sulfite or bisulfite. The nitrite salt and SO_2 or SO_2 liberating source are reacted together at a temperature of from -10°C . to 50°C . to produce the hydroxylamine of Formula III above. This reaction is carried out by reacting 1 mole of the nitrite salt with 2 moles of the sulfur dioxide which can be either bubbled or liberated from the sulfur dioxide liberating source in water. Furthermore, this reaction is carried out at a pH of at least 2, preferably from 2 to 4. This pH is obtained by the addition of acetic acid or other lower alkanic acids to the reaction medium when the acids are utilized as a component of the sulfur dioxide liberating material. However, this pH can be obtained by the addition of weakly basic inorganic salts such as sodium phosphates, sodium carbonates, sodium bicarbonates, etc.

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This aqueous reaction medium containing the hydroxylamine disulfonate of Formula III can be utilized to convert the phenol of Formula II-a or the naphthol of Formula II-b above to the quinone or naphthoquinone of Formula I-a or Formula I-b above without isolating the hydroxylamine disulfonate. After forming the hydroxylamine in the aqueous solution, the organic solvent and phenol or naphthol of Formula II-a or Formula II-b are added. The pH can be adjusted to 4 or above, if necessary, by the addition of the electrolyte. The resulting two-phase mixture can then be subjected under agitation to electrolysis in the aforementioned manner to produce the quinone or naphthoquinone of Formulae I-a or I-b.

The invention will be more fully understood from the specific examples which follow. These examples are intended to illustrate the invention and are not to be construed as limitative thereof. The temperatures utilized in these examples are in degrees centigrade.

EXAMPLE 1

Preparation of trimethyl-para-benzoquinone from 2,3,6-trimethylphenol

15.0 g. (0.217 m.) of sodium nitrite, 250 g. of ice and 41.6 g. (0.4 m.) of sodium bisulfite were weighed into an ice cooled 1 liter resin flask. Under manual stirring 22.5 cc. (23.6 g.) (0.4 m.) of acetic acid was added at once. Most of the ice dissolved and the temperature dropped to -3°C . The clear solution was kept at this temperature and stirred mechanically for 90 minutes to produce an aqueous solution containing hydroxylamine-disodium sulfonate. At the end of the stirring period, 250 cc. of a saturated aqueous solution of sodium carbonate was added to this solution of hydroxylaminedisodium sulfonate. After the addition of sodium carbonate, 20.0 g. (0.147 m.) of 2,3,6-trimethylphenol (M.P. 63.4°) and 100 cc. of heptane were added to this aqueous solution forming a heterogeneous system.

A stainless steel anode (ca. 16 mesh/cm.) was immersed into the heterogeneous system. The cathode in the form of a stainless steel coil, was placed into a porous pot, filled with water plus 2 cc. of a saturated sodium carbonate aqueous solution, and immersed to about $\frac{3}{4}$ of its length into the reaction mixture. The cold system was now stirred mechanically and electrolyzed for five hours at 7 to 8 v./3 a. at $0-5^{\circ}\text{C}$. The current density was 0.05 ampere per square decimeter. The trimethylphenol slowly dissolved and the hexane layer changed color to yellow, then to orange and again to lemon yellow at the end. The course of the reaction was conveniently followed by thin layer chromatography. Only trace amounts of phenol could be detected at the end of the electrolysis. The water layer was violet in color and some inorganic material crystallized. The whole mixture was transferred into a 1 liter separatory funnel. The yellow heptane layer was separated and washed three times with 50 cc. of 4 N sodium hydroxide and with saturated sodium chloride solution until the washes were neutral. The water layers were twice washed with heptane. The heptane extracts were combined, dried over magnesium sulfate, filtered and evaporated to dryness (rotavap, 40°C . bath temperature). The residue, a lemon yellow oil, crystallized under running cold water. The last traces of solvent were subsequently removed under high vacuum. This procedure gave 20.8 g. (94 percent) of crystalline, yellow trimethyl-para-benzoquinone, M.P. $29.6-31^{\circ}\text{C}$. Examination of this material by thin layer chromatography revealed only one spot which indicated that no contaminants were present in this product.

EXAMPLE 2

Utilizing the procedure of Example 1, 2,3,5-trimethylphenol was converted to trimethyl-para-benzoquinone in approximately the same yield and purity as in Example 1.

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EXAMPLE 3

Utilizing the procedure of Example 1, phenol was converted to 1,4-benzoquinone.

EXAMPLE 4

Utilizing the procedure of Example 1, o-cresol was converted to 2-methyl-1,4-benzoquinone.

EXAMPLE 5

Utilizing the procedure of Example 1, 1-hydroxy-2-methoxybenzene was converted to 2-methoxy-1,4-benzoquinone.

EXAMPLE 6

Utilizing the procedure of Example 1, 1-hydroxy-2-chlorobenzene was converted to 2-chloro-1,4-benzoquinone.

EXAMPLE 7

Utilizing the procedure of Example 1, 2,5-dimethoxyphenol was converted to 2,5-dimethoxy-1,4-benzoquinone.

EXAMPLE 8

Utilizing the procedure of Example 1, 2-methyl-1-hydroxy-naphthalene was converted to 2-methyl-1,4-naphthoquinone.

EXAMPLE 9

Utilizing the procedure of Example 1, 2-methyl-3-difarnesyl-1-hydroxy-naphthalene is converted to 2-methyl-3-difarnesyl-1,4-naphthoquinone (vitamin K_2).

EXAMPLE 10

By the procedure of Example 1, 2-methyl-3-phytyl-1-hydroxy-naphthalene is converted to 2-methyl-3-phytyl-1,4-naphthoquinone.

EXAMPLE 11

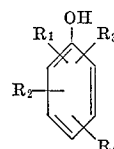
By the procedure of Example 1, 2,3-dimethoxy-5-methyl 6 all trans farnesyl-phenol is converted to 2,3-dimethoxy-5-methyl 6 all trans farnesyl-farnesyl-1,4-benzoquinone.

EXAMPLE 12

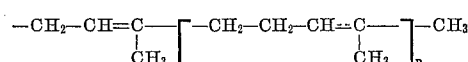
By the procedure of Example 1, 2,3-dimethoxy-5-methyl-6-phytyl phenol is converted to 2,3-dimethoxy-5-methyl-6-phytyl-1,4-benzoquinone.

I claim:

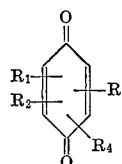
1. A process for converting a phenol of the formula



wherein R_1 , R_2 and R_4 are hydrogen, lower alkyl, lower alkoxy and halogen and R_3 is hydrogen, lower alkoxy, halogen, lower alkyl and a radical of the formula



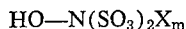
wherein the double bond shown by the dotted line can optionally be fully hydrogenated and n is an integer from 0 to 9 inclusive, with the proviso that the position para to the hydroxy group is unsubstituted to a quinone of the formula



wherein R_1 , R_2 , R_3 and R_4 are as above comprising subjecting an aqueous medium containing said phenol to electrolysis, in an electrolytic cell having an anode and a

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cathode, in the presence of a hydroxylamine disulfonate of the formula



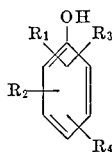
wherein X is an ammonium ion, alkali metal or alkaline earth metal and m is 1 or 2 with the proviso that when X is an ammonium ion or monovalent metal, m is 2, and when X is a divalent metal, m is 1 to form said quinone at said anode.

2. The process of claim 1 wherein said phenol is 2,3,6-trimethylphenol.

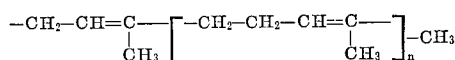
3. The process of claim 1 wherein said phenol is 2,3,5-trimethylphenol.

4. The process of claim 1 wherein said electrolysis is carried out at a voltage of from 0.5 to 50 volts.

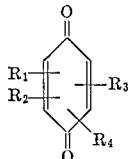
5. A process for converting a phenol of the formula



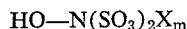
wherein R_1 , R_2 and R_4 are hydrogen, lower alkyl, lower alkoxy and halogen and R_3 is hydrogen, lower alkoxy, halogen, lower alkyl and a radical of the formula



wherein the double bond shown by the dotted line can optionally be fully hydrogenated and n is an integer from 0 to 9, inclusive, with the proviso that the position para to the hydroxy group is unsubstituted to quinone of the formula



wherein R_1 , R_2 , R_3 and R_4 are as above comprising reacting an alkali metal or alkaline earth metal nitrite with sulfur dioxide in an aqueous medium to produce an aqueous solution containing a hydroxylamine of the formula



wherein X is an ammonium ion, alkali metal or alkaline earth metal and m is 1 or 2, with the proviso that when X is an ammonium ion or monovalent metal, m is 2, and when X is a divalent metal, m is 1 adding said phenol to said aqueous solution and subjecting said aqueous solution containing said phenol to electrolysis, in an electrolytic cell having an anode and a cathode, to produce said quinone at said anode.

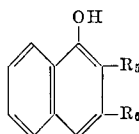
6. The process of claim 5 wherein said sulfur dioxide is produced in said aqueous medium by the reaction of alkali or alkaline earth metal sulfite or bisulfite and acetic acid.

7. The process of claim 5 wherein said phenol is 2,3,5-trimethylphenol.

7. The process of claim 5 wherein said phenol is 2,3,6-trimethylphenol.

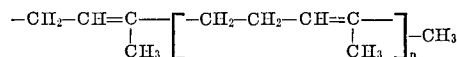
9. The process of claim 6 wherein said electrolysis is carried out at a voltage of from 0.5 to 50 volts.

10. A process for converting a naphthol of the formula:

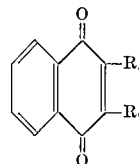


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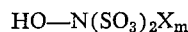
wherein R_5 is lower alkyl or hydrogen; R_6 is hydrogen, lower alkyl and a radical of the formula:



wherein the double bond shown by the dotted line can optionally be fully hydrogenated; and n is an integer from 0 to 9 inclusive; to a naphthoquinone of the formula:



wherein R_5 and R_6 are as above; comprising subjecting an aqueous medium containing said phenol to electrolysis, in an electrolytic cell having an anode and a cathode, in the presence of a hydroxylamine disulfonate of the formula:



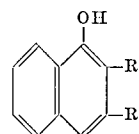
wherein X is an ammonium ion, alkali metal or alkaline earth metal and m is 1 or 2 with the proviso that when X is an ammonium ion or monovalent metal, m is 2, and when X is a divalent metal, m is 1 to form said naphthoquinone at said anode.

11. The process of claim 10 wherein said naphthol is 2-methyl-3-difarnesyl-hydroxynaphthalene.

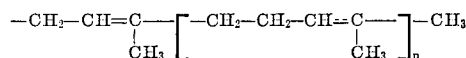
12. The process of claim 10 wherein said naphthol is 2-methyl-3-phytyl-hydroxynaphthalene.

13. The process of claim 10 wherein said electrolysis is carried out at a voltage of from 0.5 to 50 volts.

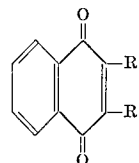
14. A process for converting a naphthol of the formula:



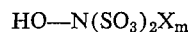
wherein R_5 is lower alkyl or hydrogen, R_6 is hydrogen, lower alkyl and a radical of the formula:



wherein the double bond shown by the dotted line can optionally be fully hydrogenated; and n is an integer from 0 to 9 inclusive; to naphthoquinone of the formula:



wherein R_5 and R_6 are as above; comprising reacting an alkali metal or alkaline earth metal nitrite with sulfur dioxide in an aqueous medium to produce an aqueous solution containing a hydroxylamine of the formula:



wherein X is an ammonium ion, alkali metal or alkaline earth metal and m is 1 or 2, with the proviso that when X is an ammonium ion or monovalent metal, m is 2, and when X is a divalent metal, m is 1 adding said naphthol to said aqueous solution and subjecting said aqueous solu-

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tion containing said naphthol to electrolysis, in an electrolytic cell having an anode and a cathode, to produce said naphthoquinone at said anode.

15. The process of claim 14 wherein said sulfur dioxide is produced in said aqueous medium by the reaction of alkali or alkaline earth metal sulfite or bisulfite and acetic acid.

16. The process of claim 14 wherein said electrolysis is carried out at a voltage of from 0.5 to 50 volts.

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