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SEPARATION AND PURIFICATION OF THE TOCOPHEROLS

James G. Baxter and Julius D. Taylor, Rochester, N. Y., assignors to Distillation Products, Inc., Rochester, N. Y., a corporation of Delaware

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7 Claims. (Cl. 260—333)

This invention relates to improved procedure for separating tocopherols from a mixture thereof: in particular it relates to a method for resolving a mixture of alpha and at least one other tocopherol into its components.

The tocopherols are known to have vitamin E activity and also antioxidant activity. However, the vitamin E activity varies inversely with the antioxidant activity; i. e., the alpha tocopherol is highest in vitamin E and lowest in antioxidant activity while the gamma form is highest in antioxidant activity and lowest in vitamin E activity. For this and other reasons it is frequently desirable to separate the mixtures of tocopherol as they naturally occur into individual tocopherol constituents. Separation has heretofore been accomplished by fractional crystallization of mixed tocopherol allophanates; also by adsorbing the tocopherol mixture on an adsorbent column, breaking up the column and eluting appropriate sections of the column with eluting solvents. See, for instance, Emerson, "Journal of Biological Chemistry," 1937, 90, and Drummond, "Biochemical Journal," 1938, 1953. These procedures are rather costly and are not particularly suited for commercial operations due to the rather expensive and complicated steps.

This invention has for its object to provide procedure whereby the foregoing difficulties can be overcome. Another object is to provide simplified procedure for the resolution of tocopherol mixtures into individual components. Another object is to provide improved procedure whereby a mixture of alpha and at least one other tocopherol can be separated into its individual components. Other objects will appear hereinafter.

These and other objects are accomplished by our invention which includes subjecting a mixture containing alpha and at least one other tocopherol to an esterification treatment adapted to form a carboxylic acid ester, terminating the esterification reaction when the amount of tocopherol esterified corresponds to about the amount of tocopherol other than alpha present in the mixture and then treating the reaction product to separate esterified tocopherol from unesterified alpha tocopherol. It has beeen found that alpha tocopherol reacts much more slowly with esterification reagents than the beta or gamma tocopherols. Therefore, if a mixture is treated in the foregoing manner a preferential esterification of the forms other than alpha present takes place. It is then a simple matter to treat the esterification mixture to separate the esters from the non-esterified portion.

In the following description we have given several of the preferred embodiments of our invention, but it is to be understood that these are set forth for the purpose of illustration and not in limitation thereof.

Tocopherols naturally occur as mixtures in many, if not all, of the vegetable oils. Such mixtures also occur in some animal oils but to a lesser extent. Our invention is of general application to tocopherol concentrates produced from all such natural sources. It is also applicable to mixtures of alpha and other tocopherols which can be prepared synthetically. Our invention is of particular value in connection with the separation of tocopherols present in scum produced during the deodorization treatment of vegetable or animal oils. Such scum is obtained by condensing the steam or like carrier gas utilized during the vacuum deodorization of vegetable and animal oils. The steam used in the deodorization treatment carries over relatively volatile matter which contains a quite high content of tocopherols. This treatment can be directly treated in accordance with our invention, but it is preferred that it be subjected to a concentration procedure designed to increase the tocopherol content. Thus, the scum may be subjected to high vacuum unobstructed path distillation and a tocopherol fraction of high concentration separated. On the other hand, the scum may be saponified and the non-saponifiable treated in accordance with our invention. Alternatively, the starting material may be obtained by saponification of the natural oil itself, according to known manner. Regardless of the source of the mixed tocopherol starting material we prefer to operate on a tocopherol concentrate starting material which contains at least 15 per cent of mixed tocopherols. The mixture may be alpha and gamma; or alpha and beta; or alpha, beta and gamma. Reference is made to Hickman application 321,913, filed March 2, 1940, for a more detailed description of the various methods of preparing tocopherol preparations from deodorizer scum.

The starting material is treated with an esterifying agent in known manner in order to form an ester of a carboxylic acid. The esterification is preferably conducted in the presence of an accelerator such as pyridine, and it is desirable to take precautions to avoid undue contact of the esterification mixture with atmospheric oxygen. We prefer to utilize an anhydride as an esterifying agent and also prefer to use anhydrides of polybasic acids and especially of dibasic acids.

However, other esterifying agents may be used, such as acid halides. Examples of satisfactory esterification agents are succinic, glutaric, citraconic, phthalic, and palmitic acid anhydrides.

The degree of separation will be determined by the point at which the esterification is terminated. If a very sharp separation is necessary, it is best to determine the amount of tocopherol other than alpha present in the mixture and then carry out the esterification under controlled conditions with analysis of the esterification mixture at appropriate intervals, so that the esterification reaction can be closely followed and terminated at the proper point. It is best to terminate the reaction when the proportion of tocopherol which has been esterified corresponds to the proportion of gamma and/or beta tocopherol present in the mixture. It has been found by experiment that very little, if any, of the alpha tocopherol will become esterified until substantially all of the beta and gamma tocopherols are esterified. If the reaction can be followed closely and terminated at the point indicated, a very sharp separation of the tocopherols will be obtained. The rate of esterification can be controlled by varying the temperature and amount of esterifying agent, but the ratio of esterified alpha to esterified beta or gamma will remain about the same. With two mols of esterifying agent such as succinic anhydride per mol of total tocopherol present the reaction will as a general rule be completed in about 30 minutes if heated to about 60°–70° C. The "Emmerie and Engel" test for unesterified tocopherol can be used to follow the course of the reaction.

After the reaction has been carried to the desired point the esterification is terminated and the reaction mixture is treated to separate the esterified and unesterified tocopherols present therein. This separation can be accomplished by numerous methods such as solvent extraction, reaction of tocopherol esters to form derivatives, such as salts, which can then be separated quite easily due to their radically different properties from the free alpha tocopherol, high vacuum distillation to separate the lower boiling free tocopherol from the higher boiling tocopherol ester and adsorption to preferentially remove the more strongly adsorbed free tocopherol. Partitioning of the two tocopherol forms between immiscible solvents, one of which contains an alkali, is also a valuable method of separation.

Example

A 36-gram sample of commercial tocohperol concentrate containing 39 per cent mixed alpha and gamma tocopherols, in a ratio of 60 to 40 was heated at 70° C. for thirty minutes with 55 cc. of pyridine and 7 grams of succinic anhydride. A few minutes swirling served to dissolve the anhydride giving a clear solution. At the end of the heating period the reaction mixture was washed in an ether solution with 5 per cent aqueous hydrochloric acid to remove pyridine. The ether solution was then washed with water, dried, and the ether removed by distillation to leave an oil slightly darker than the commercial starting material. This oil contained 22 per cent free tocopherol. Theoretically if all of the gamma tocopherol had been esterified, the residue oil should contain 23.5 per cent free tocopherol. The residue oil was dissolved in 200 cc. of 83 per cent ethyl alcohol and treated with 1N KOH in 83 per cent ethyl alcohol until the solution was slightly alkaline to phenolphthalein. It was then extracted three times with petroleum ether. The alcohol fraction contained gamma tocopherol acid succinate which was separated by diluting the alcohol layer with water and extracting with ether in the usual way. It weighed 12.6 grams and upon saponification gave a gamma tocopherol concentrate containing 87 per cent tocopherol. An analysis of this material showed that the gamma to alpha ratio was 93 to 7, indicating that it was nearly free of the alpha form. The three petroleum ether extracts were combined and the ether removed by distillation. An alpha tocopherol fraction weighing 25.3 grams was thus obtained, containing 31 per cent of alpha tocopherol. It will thus be seen that approximately 90 per cent of the gamma tocopherol present in the original tocopherol starting material was removed. Closer control of the esterification conditions would enable quantitative separation of the two tocopherols. In this example substantially the same results would be obtained if 90 per cent aqueous methyl alcohol were used instead of 83 per cent ethyl alcohol.

It will be noted that the procedure results in a very satisfactory separation of the tocopherols contained in a mixture and that the procedure is relatively inexpensive as compared with prior art methods of separation. Another outstanding advantage of the invention is that the beta or gamma tocopherols present in the mixture are concentrated to a substantial extent; i. e., the impurities present in the starting material are rejected and remain with the alpha tocopherol.

What we claim is:

1. The process of resolving a mixture of alpha and at least one other tocopherol into its components which comprises subjecting a mixture containing alpha and at least one other tocopherol to an esterification treatment in which the esterifying agent is one which is adapted to form an ester of a carboxylic acid, terminating the esterification reaction when the amount of tocopherol esterified corresponds to about the amount of tocopherol other than alpha present in the mixture, whereby the tocopherol other than α tocopherol present in the starting mixture is largely esterified and the α tocopherol remains substantially unesterfied, and then treating the reaction product to separate esterified tochoperol from unesterified alpha tocopherol.

2. The process of resolving a mixture of alpha and gamma tocopherol into its components which comprises subjecting a concentrate containing a mixture of alpha and gamma tocopherol to an esterification treatment in which the esterifying agent is one which is adapted to form an ester of a polybasic carboxylic acid, terminating the esterification reaction when the amount of tacopherol esterified corresponds to about the amount of gamma tocopherol present in the mixture whereby the γ tocopherol present in the starting mixture is largely esterified and the α tocopherol remains substantially unesterified and then treating the reaction product to separate gamma tocopherol ester from unesterified alpha tocopherol.

3. The process of resloving a mixture of alpha and at least one other tocopherol into its components which comprises subjecting a mixture containing alpha and at least one other tocopherol to an esterification treatment with a dibasic carboxylic acid anhydride, terminating the esterification reaction when the amount of tocopherol esterified corresponds to about the amount of to-

copherol other than alpha present in the mixture whereby the tocopherol other than α tocopherol present in the starting mixture is largely esterified and the α tocopherol remains substantially unesterified and then treating the reaction product to separate esterfied tocopherol other than α from unesterified alpha tocopherol.

4. The process of resolving a mixture of alpha and at least one other tocopherol into its components which comprises subjecting a mixture of tocopherols containing at least 15 per cent alpha and other tocopherol isomer to an esterification treatment in which the esterifying agent is one which is adapted to form an ester of a carboxylic polybasic acid, terminating the esterification reaction when the amount of tocopherol esterified corresponds to about the amount of tocopherol other than alpha present in the mixture and then treating the reaction mixture whereby the tocopherol other than α tocopherol present in the starting mixture is largely esterified and the α tocopherol remains substantially unesterified to separate esterified tocopherol other than α from unesterified alpha tocopherol.

5. The process of resolving a mixture of alpha and gamma tocopherol which comprises subjecting a mixture which contains at least 15 per cent tocopherol in the form of alpha and gamma to an esterification treatment in which the esterifying agent is a dibasic carboxylic acid anhydride, terminating the esterification reaction when the amount of tocopherol esterified corresponds to about the amount of gamma tocopherol present in the mixture whereby the γ tocopherol present in the starting mixture is largely esterified and the α tocopherol remains substantially unesterified and then treating the reaction mixture to separate esterified γ tocopherol from unesterified alpha tocopherol.

6. The process of separating a mixture of alpha and gamma tocopherol which comprises subjecting a mixture having a tocopherol concentration of at least 15 per cent and containing alpha and gamma tocopherol to an esterification treatment in which the esterifying agent is one which is adapted to form an ester of a polybasic carboxylic acid, terminating the esterification reaction when the amount of tocopherol esterified corresponds to about the amount of gamma tocopherol present in the mixture whereby the γ tocopherol present in the starting mixture is largely esterified and the α tocopherol remains substantially unesterified, neutralizing the gamma tocopheral acid ester thus formed, and extracting the mixture with a preferential solvent for one of the forms of tocopherol present therein.

7. The process of resolving a mixture of alpha and gamma tocopherol into its components which comprises subjecting a concentrate containing at least 15 per cent alpha and gamma tocopherols to an esterification treatment with a dibasic carboxylic acid anhydride, terminating the esterification reaction when the amount of tocohperol esterified corresponds to the amount of gamma tocopherol present in the mixture whereby the γ tocopherol present in the starting mixture is largely esterified and the α tocopherol remains substantially unesterified, dissolving the mixture of free alpha and esterified gamma tocopherol in a lower aliphatic alcohol containing a small amount of water, neutralizing the gamma tocopherol acid ester, extracting the alcohol solution with petroleum ether and recovering the tocopherol from the petroleum ether extract and from the alcoholic solution.

JAMES G. BAXTER.
JULIUS D. TAYLOR.

CERTIFICATE OF CORRECTION.

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JAMES G. BAXTER, ET AL.

It is hereby certified that error appears in the printed specification of the above numbered patent requiring correction as follows: Page 3, first column, lines 18 and 19, claim 4, strike out the words "and then treating the reaction mixture" and insert the same before "to" in line 23, same claim; and that the said Letters Patent should be read with this correction therein that the same may conform to the record of the case in the Patent Office.

Signed and sealed this 29th day of August, A. D. 1944.

Leslie Frazer

(Seal) Acting Commissioner of Patents.