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(54) **PRODUCTION D'.ALPHA.-TOCOPHEROL**
(54) **MANUFACTURE OF .ALPHA.-TOCOPHEROL**

(57) Divulgation d'un procédé de conversion de tocophérols non .alpha. en .alpha.-tocophérol par perméthylation catalytique d'au moins un tocophérol non .alpha., comprenant l'utilisation, comme agent méthylant, de méthanol à une température et à une pression près du point critique ou supercritiques, ou d'un mélange équivalent au méthanol et comprenant de l'hydrogène et du monoxyde de carbone ou du dioxyde de carbone, ou les deux, et comme catalyseur, un catalyseur d'oxydes mélangés produit à partir d'hydrotalcites, comprenant au moins de l'oxyde de cuivre et de l'oxyde de magnésium, ainsi qu'au moins un oxyde de métal trivalent, p. ex. l'oxyde d'aluminium, l'oxyde de fer (III), l'oxyde de vanadium, l'oxyde de chrome et/ou l'oxyde de gallium. Le tocophérol non .alpha. ou le mélange de tocophérols non .alpha., pouvant être présent dans une matière brute, devant être converti en .alpha.-tocophérol, est préférablement dissous dans un solvant inerte, p. ex. un alcane moyen, un alcane cyclique ou un hydrocarbure aromatique. Le produit obtenu par ce procédé a un taux d'.alpha.-tocophérol très élevé, ce dernier étant le composé le plus utile biologiquement.

(57) A process for the conversion of non-.alpha.-tocopherols into .alpha.-tocopherol by the catalytic permethylation of at least one non-.alpha.-tocopherol comprises using as the methylating agent methanol in the near-critical or super-critical pressure and temperature region or a mixture which is equivalent to methanol and which consists of hydrogen and carbon monoxide and/or carbon dioxide, and as the catalyst a mixed oxide catalyst which is produced from hydrotalcites and which has at least copper and magnesium oxide as well as at least one oxide of a trivalent metal, e.g. aluminium oxide, iron(III) oxide, vanadium oxide, chromium oxide and/or gallium oxide. The non-.alpha.-tocopherol or non-.alpha.-tocopherol mixture, optionally present in a raw material, to be converted into .alpha.-tocopherol is preferably dissolved in an inert solvent, e.g. an alkane of medium molecular weight, a cyclic alkane or an aromatic hydrocarbon. The product of this process has a very high content of .alpha.-tocopherol, which is the biologically most valuable tocopherol.

Ref. 13'538

Abstract

A process for the conversion of non-α-tocopherols into α-tocopherol by the catalytic permethylation of at least one non-α-tocopherol comprises using as the methylating agent methanol in the near-critical or super-critical pressure and temperature region or a mixture which is equivalent to methanol and which consists of hydrogen and carbon monoxide and/or carbon dioxide, and as the catalyst a mixed oxide catalyst which is produced from hydrotalcites and which has at least copper and magnesium oxide as well as at least one oxide of a trivalent metal, e.g. aluminium oxide, iron(III) oxide, vanadium oxide, chromium oxide and/or gallium oxide. The non-α-tocopherol or non-α- tocopherol mixture, optionally present in a raw material, to be converted into α-tocopherol is preferably dissolved in an inert solvent, e.g. an alkane of medium molecular weight, a cyclic alkane or an aromatic hydrocarbon.

The product of this process has a very high content of α-tocopherol, which is the biologically most valuable tocopherol.

Ref. 13'538

The present invention is concerned with a process for the permethylation of so-called "non-α-tocopherols" to α-tocopherol using methanol or an equivalent gaseous mixture under near-critical or super-critical conditions and using a particular catalyst.

As is known, the naturally occurring non-α-tocopherols β-, γ- and δ-tocopherol differ from α-tocopherol, which has the highest vitamin E activity and which is accordingly the biologically most valuable tocopherol, by the absence of one or two methyl groups in the 5- and/or 7-position of the chromane part of the molecule. Accordingly, there is a need to convert such non-α-tocopherols into α-tocopherol chemically, the main problem lying in the efficient, completing mono- or, respectively, dimethylation of the benzene ring of the substituted chromanyl group.

Since synthetic processes for the manufacture of nature-identical α-tocopherol have hitherto been found to be uneconomical and natural, especially plant, sources of tocopherols usually contain predominantly non-α-tocopherols in addition to a relatively low content of α-tocopherol, which is why the isolation of α-tocopherol from such natural materials (raw materials) is also uneconomical, the object of the present invention is to provide a process for the conversion of non-α-tocopherols, which may be present in appropriate raw materials or obtained from these, into α-tocopherol, which is in many different respects more economical than previous processes for this purpose.

Appertaining to this object of the invention, some processes for the conversion of non-α-tocopherols into α-tocopherol are already known from the state of the art. For example, European Patent Publication (EP) 176 690 (Henkel Corporation) discloses a process for the methylation of non-α-tocopherols using a methylating agent in the gas/liquid phase and in the presence of a metal oxide catalyst; this is a direct, one-stage methylation of the chromane ring, which is to be seen as a complete tocopherol methylation, i.e. a permethylation.

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The catalyst used for this purpose is "functionally" defined in EP 176 690 in the sense that any catalyst which is capable of inducing an alkylating reaction can be used; typically it can be a metal oxide or a mixture of several metal oxides in which the metal atom(s) is/are selected from Groups IIA, IIB, IIIA, IVA, IVB, VB, VIB, VIIB and VIII of the Periodic Table. The oxides of Be, Mg, Ca, Ti, Zr, V, Mo, Cr, Mn, Tc, Fe, Co, Ni, Zn, Cd, In, Sn, Si, Al, La, Ce, Pr and Nd are indicated to be preferred metal oxides. Such catalysts can be used as such ("neat") or on an inert carrier material and can be produced in any suitable manner, even in situ. In the case of the in situ production method, for example, a metal salt is introduced into the reactor and subsequently reacted or decomposed to the corresponding metal oxide. The methylation can be effected after removal of byproducts and any unreacted reactants. According to an example of the "external" production of such a catalyst, dry tin hydroxide is added to a solution of ammonium vanadate in aqueous oxalic acid and treated with a solution, likewise added in activated form, of partially polymerized silicon hydroxide to give a precipitate. This is dried, calcinated and shaped by pressing. In a further example of EP 176 690 solid titanium dioxide is added to an aqueous mixture of ammonium vanadate and oxalic acid and the new mixture is heated and dried, then calcinated and shaped by pressing. In both cases there are obtained oxide mixtures which however cannot be designated crystallographically as mixed oxides; rather they are vanadium oxide on a tin oxide/silicon dioxide or, respectively, titanium dioxide carrier. In EP 176 690 there is no teaching of hydrotalcites or hydrotalcite-like metal hydroxycarbonates as possible metal-containing materials from which the metal oxide or mixed oxide catalysts could be produced, not to mention catalysts containing copper oxide (copper belongs to Group Ib of the Periodic Table).

Further, in EP 176 690 a temperature range of about 390 to about 470°C is mentioned as the especially favourable temperature range and the ambient (normal) pressure is mentioned as the most preferred pressure. Moreover, the use of excess methylating agent or an inert carrier gas, e.g. nitrogen, but not of an (additional) solvent, is foreseen.

It has now surprisingly been found that this known process of the Henkel Corporation can be improved decisively by a particular choice of catalyst and of the other reaction conditions. The object of the present invention is a process of the conversion of non-α-tocopherols into α-

tocopherol by the catalyzed permethylation of at least one non-α-tocopherol using a methylating agent, which process comprises using as the methylating agent methanol which is in the near-critical or super-critical pressure and temperature range or a mixture equivalent to methanol consisting of hydrogen and carbon monoxide and/or carbon dioxide, and using as the catalyst a mixed oxide catalyst which is produced from hydrotalcites and which contains at least copper and magnesium oxide as well as at least one oxide of a trivalent metal.

As indicated above, the educt used in the process in accordance with the invention can in principle be a raw material which contains at least one non-α-tocopherol, e.g. β-, γ- or δ-tocopherol, or a tocopherol mixture which is produced or otherwise obtained from such a raw material and which likewise contains at least one non-α-tocopherol. The tocopherol mixture is produced or otherwise obtained according to methods which have been known for a long time. Since, as is known, vegetable oils and fats, such as, for example, soya oil, rape oil, cottonseed oil, groundnut oil, wheatgerm oil, corn oil, barley oil, rye oil, thistle oil and the like, are valuable natural sources of tocopherols (inter alia α- and non-α-tocopherols), such oils or preferably their distillates, concentrates and other products, which have a higher content of tocopherols and contain fewer undesired other components, e.g. sterols, free and esterified fatty acids, waxes and glycerides, can be used as the educt in the process in accordance with the invention. However, the presence of sterols and the other named components does not significantly impair the process in accordance with the invention. Thistle oil and soya oil in particular have been found to be valuable sources of tocopherols, inter alia α-tocopherol and the non-α-tocopherols to be converted into this in accordance with the invention. It is, of course, irrelevant whether or not, inter alia, α-tocopherol itself is present in the educt, since the α-tocopherol does not prevent the conversion of the non-α-tocopherols into α-tocopherol and itself remains unreacted in the product of the process.

The methanol in the near-critical or super-critical region, which is used in the process in accordance with the invention, is methanol which is heated and which is under pressure, namely methanol which has a pressure of at least about 50 bar (5 MPa) and a temperature of at least about 240°C. In the case of this minimum temperature the super-critical range starts with a pressure of about 77.5 bar (7.75 MPa). Of course, these physical

data also correspond simultaneously to the pressures or temperatures at which the process in accordance with the invention is carried out as a whole (under "near-critical or super-critical conditions"). An addition of up to about 20 volume percent of water to the methanol can increase the selectivity of the methylation, but reduces its velocity.

As an alternative to the methanol in the near-critical or super-critical state, there can be used in the process in accordance with the invention either a mixture of hydrogen and carbon monoxide which is equivalent to methanol or the equivalent mixture of hydrogen and carbon dioxide. The first-named mixture is conveniently a mixture which is basically suitable for the synthesis of methanol. Accordingly this mixture contains hydrogen and carbon monoxide in the molar ratio of about 2:1 or greater; it is used under the same pressure and temperature conditions as methanol. The second-named "equivalent mixture" is also conveniently one which is basically suitable for the synthesis of methanol. In this case the molar ratio hydrogen:carbon dioxide is about 3:1 or greater and the mixture is also used under the same pressure and temperature conditions as methanol. With respect to the synthesis of methanol from such "equivalent mixtures", reference is made, for example, to Catalysis Today, Vol. 11, No. 2, pages 173-291, especially pages 230-235 (1991).

An especially suitable equivalent mixture is one which contains both carbon monoxide and carbon dioxide and which accordingly can be regarded as a combination of both of the aforementioned gas mixtures.

The so-called hydrotalcites, from which the mixed oxide catalyst used in accordance with the invention is produced, are a known class of isomorphic minerals which occur in nature and which in each case are mixed hydroxycarbonates of different metals, e.g. magnesium and aluminium or magnesium and iron. "Hydrotalcite" itself has the chemical formula $Mg_6Al_2(OH)_{16}CO_3 \cdot 4H_2O$ and other minerals having a similar structure are present in nature or have been synthesized, such as sjögrenite and pyroaurite. The latter minerals are conventional hydrotalcite-like compounds; in the scope of the present invention hydrotalcite and hydrotalcite-like compounds - of the recognized general formula $[M(II)_{1-x}M(III)_x(OH)_2]^{x+}(A^{n-}x/n).mH_2O$, wherein M(II) and M(III) signify divalent and trivalent metal ions, respectively, A^{n-} signifies an exchangeable anion and x signifies 0.1-0.33 - are all to be understood under

the abbreviation "hydrotalcites". For relevant literature concerning hydrotalcites and their production, primarily by coprecipitation, and their use as catalysts, partly as such or after calcination to mixed metal oxides, see, inter alia, Catalysis Today, Vol. 11, No. 2, 173-291 (1991) and the literature references cited therein, Appl. Catalysis A: General 119, 241-252 (1994), and ibid., 145, 141-153 and 225-230 (1996).

The mixed oxide catalyst produced from hydrotalcites and used in accordance with the invention contains at least copper oxide and magnesium oxide (both copper and magnesium are divalent metals) as well as at least one oxide of a trivalent metal [denoted hereinafter as "metal (III) oxide"]. The respective metal(III) oxides are preferably oxides of aluminium and iron(III). However, oxides of other divalent and/or trivalent metals can also be present. Examples of other divalent (II) and trivalent (III) metals are beryllium(II), calcium(II), vanadium(III), chromium(III), manganese(II), iron(II), cobalt(II), nickel(II), zinc(II), gallium(III) and cadmium(II). Preferably, the mixed oxide catalyst only contains aluminium oxide and iron(III) oxide in addition to copper oxide and magnesium oxide.

In the mixed oxide catalyst which is produced from hydrotalcites and which is used in accordance with the invention the atomic ratio of the (total) divalent metals to the trivalent metal or - where several metal (III) oxides are present - to the total trivalent metals conveniently amounts to about 2:1 to about 10:1, preferably about 3:1 to about 4:1. With respect to the atomic ratio between the divalent metals present (inter alia essentially copper and magnesium), then the atomic ratio of copper to magnesium or of copper to magnesium and other divalent metals present conveniently amounts to about 5:95 to about 60:40, preferably about 25:75 to about 50:50. The atomic ratio between the preferably present aluminium and the likewise preferably present iron or the totality of the other trivalent metals [Al:other metals (III)] preferably amounts to about 2:1 to about 1:2, especially about 2:1.

In addition to the essentially present copper oxide, magnesium oxide and metal (III) oxide(s), there can be present in the mixed oxide catalyst used in accordance with the invention, inter alia, oxides of lithium, sodium and/or potassium in an amount which is conveniently up to about 2% of the total weight of the mixed oxide catalyst. These alkali metals are normally

present because alkali metal bases are required for the production or working up of the mixed oxide catalyst and are not washed out completely.

In principle, the process in accordance with the invention is carried out by conducting the non-α-tocopherol, the mixture of several non-α-tocopherols or the raw material containing at least one non-α-tocopherol, in each case optionally dissolved in an inert solvent, together with methanol or the equivalent mixture explained in more detail above under (with respect to pressure and temperature) near-critical or super-critical conditions through a reactor loaded with the mixed oxide catalyst, e.g. a heated tube loaded with the catalyst. The crude product which flows from the reactor then only needs to be separated, e.g. by distillation, from the gases which result in the methylation, primarily hydrogen and carbon monoxide, as well as from excess methanol and any residual inert solvents used. After the methylation and any separation of gases, excess methanol, solvents etc. the product enriched in α-tocopherol can, if desired, be subjected repeatedly to the process in accordance with the invention in order each time to obtain a product which is more strongly enriched in α-tocopherol, if the intended purpose of use makes this necessary, i.e. in order to achieve the required degree of conversion to α-tocopherol. The nature of a catalytic process is such that the desired degree of conversion can also be achieved by lengthening the contact time of the non-α-tocopherol or of the mixture or raw material containing this on the catalyst, by increasing the amount of catalyst in the reactor or lowering the flow rate of the non-α-tocopherol, mixture or raw material used in the reactor. No significant decomposition of the tocopherols normally occurs during the reaction.

As the aforementioned inert solvent there comes into consideration conveniently a non-polar organic solvent, preferably an alkane of medium molecular weight, primarily a C_{5-10}-alkane, e.g. pentane, hexane or heptane, or mixtures thereof, e.g. a petroleum ether having a boiling range between about 40°C and about 120°C; a cyclic alkane, e.g. cyclohexane; or an aromatic hydrocarbon, e.g. toluene.

When the non-α-tocopherol, mixture of several non-α-tocopherols or raw material containing at least one non-tocopherol to be methylated is dissolved in an inert solvent - and is thus diluted - , the concentration of the non-α-tocopherol, the non-α-tocopherols or the non-α-tocopherol content in

the solvent conveniently amounts to about 10 g/l to about 500 g/l, preferably about 100 g/l to about 500 g/l.

The amount of methanol used as the methylating agent relative to the non-α-tocopherol(s) generally corresponds to at least one equivalent of (estimated) methylatable positions in the non-α-tocopherol (mixture), conveniently about 10 to about 1000 equivalents, preferably about 25 to about 250 equivalents.

If an equivalent mixture of hydrogen and carbon monoxide and/or carbon dioxide is used as the methylating agent in place of methanol, then the amount of carbon monoxide and/or carbon dioxide likewise corresponds to at least one equivalent of the (estimated) methylatable positions in the non-α-tocopherol (mixture). Also in this case the amount is conveniently about 10 to about 1000 equivalents, preferably about 25 to about 250 equivalents.

The rate at which the optionally diluted non-α-tocopherol, the non-α-tocopherol mixture or the raw material containing at least one non-α-tocopherol is passed over the mixed oxide catalyst and also the corresponding flow rate of the methylating agent can be adjusted and correlated with respect to each other, to the amount of catalyst, to the catalyst activity, to the reaction temperature and to the reaction pressure such that the methylation proceeds as efficiently as possible having regard to conversion and reaction duration. In this case, the optimal contact times lie in the range of about 1 to about 100 minutes.

As already mentioned several times, the process in accordance with the invention is carried out under near-critical or super-critical conditions with respect to the methanol or the equivalent methylating agent. The critical pressure itself amount to about 77.5 bar (about 7.75 MPa) and the critical reaction temperature to about 240°C. The permethylation is conveniently carried out at pressures between about 50 bar and about 120 bar (about 5 to about 12 MPa), preferably at pressures between about 70 bar and about 90 bar (about 7 to about 9 MPa), particularly at about 80-85 bar (8-8.5 MPa) (at pressures below about 77.5 bar, i.e. in the "near-critical range", a more rapid reaction takes place, but dark impurities contained in the crude product are not separated from the reactor and can adversely influence the activity of the catalyst). Moreover, an especially high reaction velocity is

achieved, for example, at about 50 bar (5 MPa), but to the detriment of catalyst stability. Pressures of more than about 120 bar (12 MPa) reduce the reaction velocity and necessitate the use of expensive equipment without bringing any compensating advantages.

The reaction temperature conveniently lies in the range of about 240°C to about 350°C, preferably in the range of about 280°C to about 320°C.

An advantage of the process in accordance with the invention is that no recognizable racemization of the optically active centres of the non-α-tocopherols to be permethylated takes place. When a tocopherol mixture from natural sources is used as the educt, there is typically obtained as the product RRR-α-tocopherol having an optical purity of at least 99.5%. Also, no other decomposition of the educt or of the product which is worthy of note takes place during the permethylation.

A further advantage resides in the fact that the catalyst can be used many times, so that, for example, in the case of an undesirably low methylation the product obtained can again be reacted using the catalyst without the activity of the repeatedly used catalyst being noticeably reduced. In this connection, in general a large amount of non-α-tocopherol(s) can be methylated on one catalyst without a noticeable deactivation of the catalyst taking place.

The simplicity of the process and of the working up as well as the high selectivity which can be achieved make the process in accordance with the invention especially suitable for the large scale manufacture of α-tocopherol.

The present invention is illustrated by the following Examples:

Example 1

Production of a typical catalyst used in accordance with the invention, and a typical reactor (laboratory scale)

Production:

8 g (20 mmol) of aluminium nitrate, 4 g (10 mmol) of iron(III) nitrate, 14 g (60 mmol) of copper(II) nitrate and 15 g (60 mmol) of magnesium nitrate

(all as hydrates, i.e. as the nitrate $\bullet 9H_2O$, $\bullet 9H_2O$, $\bullet 3H_2O$ and respectively, $\bullet 6H_2O$) were dissolved in 240 ml of water. The resulting solution was stirred at 90°C during 30 minutes into a solution of 30 g (360 mmol) of sodium bicarbonate in 240 ml of water. The mixture was stirred at 90°C for a further 2 hours. The precipitate was filtered off and washed with water until the filtrate reacted neutral. This pulp-like precipitate was either dried directly at about 120°C or previously formed using a hand syringe into "rope-like extrudates" having a diameter of about 1.5 mm. The dried catalyst precursor (as fragments or as "rope-like extrudates") was calcinated at 250-400°C for about 4 hours with access to air. The fragments were ground in a mortar, while the "rope-like extrudates" were broken into pieces 2-5 mm in length. The thus-produced catalyst was filled into a reactor.

Reactor:

The reactor consisted of an upright high-pressure tube which was heated via a thermostatically controlled oil heating jacket. The tube had an internal diameter of 7.8 mm, a heated length of 25 cm and an overall length of about 40 cm.

A tube closed on one side and having an external diameter of 3.2 mm was present in the reactor and over the entire length and served as a housing for a thermoelement with which the temperature in the longitudinal axis of the entire reactor could be measured.

The outlet, which was covered with a filter, was situated at the lower end of the reactor. The space between filter and the beginning of the heating zone was filled with sea sand. The catalyst was placed above this, giving different catalyst bed depths according to amount and bulk density. The space above the catalyst bed was empty.

The pressure monitor, a breakable disk and the inlet for the educt were situated at the upper end of the reactor. Two high pressure pumps supplied methanol and the additional solvent (e.g. toluene, hexane or additional methanol) to the reactor. One liquid stream - usually the larger - was pre-heated. The non-α-tocopherol was admixed as the educt with the non-heated stream, so that the adjustment could be made from pure solvent to educt solution.

The outlet was connected to a pressure-tight valve with which the pressure in the reactor could be adjusted. From there the product solution was conducted into a receiver.

Example 2

A catalyst powder, calcinated at 350°C and still containing about 0.5% sodium, was prepared from a solution of the nitrates of iron(III) (10 mmol), aluminium (20 mmol), magnesium (60 mmol) and copper(II) (60 mmol). 1.8 g (3.5 ml) of this catalyst were filled into the reactor. At 320°C there were pumped into the reactor 1.25 ml/min. of pre-heated hexane with the first pump and 0.625 ml/min. of methanol with the second. The pressure was adjusted to 100 bar (10 MPa).

Then, 3 ml of a methanolic solution containing 1 g of RRR-γ-tocopherol in place of methanol were pumped in with the second pump. Subsequently, further methanol was pumped in during 40 minutes in order to flush the product from the reactor. The total product solution was collected in the receiver, evaporated and analyzed by gas chromatography (GC). The evaporation residue contained 86.0 GC area-% α- and 3.9 GC area-% γ-tocopherol. Further investigation indicated that the optical activity of the educt had been retained and that at the most 1 weight-% of 2S-isomers was obtained.

In a further experiment on the same catalyst packing using the same conditions (temperature, pressure and flow velocities) as above, 3 ml of a methanolic solution containing 1 g of RRR-δ-tocopherol were pumped in. The evaporated product solution contained 53.85 GC area-% α- and 21.94 GC area-% β/γ-tocopherol.

Example 3

"Rope-like extrudates", calcinated at 350°C, were produced as the catalyst from a solution of the nitrates of iron(III) (10 mmol), aluminium (20 mmol), magnesium (60 mmol) and copper(II) (60 mmol).

3.0 g (6 ml) of this catalyst were filled into the reactor. At 300°C there were pumped into the reactor 2.25 ml/min. of hexane with the first pump

and 0.75 ml/min. of pre-heated methanol/water (9/1 v/v) with the second. The pressure was adjusted to 90 bar (9 MPa). Then, 9 ml of a solution containing 1 g of RRR-δ-tocopherol in hexane were pumped in in place of hexane with the first pump. Subsequently, hexane was again pumped in during about 60 minutes in order to flush the product from the reactor. The entire product solution was collected in the receiver, evaporated and analyzed by GC.

The evaporation residue was again made up to 9 ml with hexane and, as above, pumped through the reactor and analyzed.

In this manner the tocopherol was pumped through the reactor a total of eleven times. The analytical results of the individual methylation steps are compiled in Table 1 hereinafter.

Table 1

Methylation Passage	α-Tocopherol GC area-%	γ-Tocopherol GC area-%	β-Tocopherol GC area-%	δ-Tocopherol GC area-%
1	23.7%	4.6%	46.5%	19.6%
2	43.3%	2.3%	44.8%	4.4%
3	56.9%	1.3%	36.6%	1.2%
4	65.0%	0.8%	29.1%	0.4%
5	71.4%	0.6%	22.0%	*
6	73.8%	0.7%	19.1%	*
7	72.5%	0.9%	19.9%	*
8	79.5%	0.9%	12.7%	*
9	82.4%	0.8%	9.8%	*
10	85.2%	0.8%	7.3%	*
11	85.9%	0.9%	6.1%	*

*: no longer detectable

Example 4

"Rope-like extrudates", calcinated at 350°C, were produced as the catalyst from a solution of the nitrates of iron(III) (10 mmol), aluminium (20 mmol), magnesium (90 mmol) and copper(II) (30 mmol).

3.0 g (7 ml) of this catalyst were filled into the reactor. At 300°C there were pumped into the reactor 3 ml/min. of hexane with the first pump and 0.75 ml/min. of pre-heated methanol/water (8/2 v/v) with the second. The pressure was adjusted to 90 bar (9 MPa).

Then, 9 ml of a solution containing 1 g of RRR-δ-tocopherol in hexane were pumped in in place of hexane with the first pump. Subsequently, further hexane was pumped in during 60 minutes in order to flush the product from the reactor. The entire product solution was collected in the receiver, evaporated and analyzed by GC.

The evaporation residue was again made up to 9 ml with hexane and, as above, pumped through the reactor and analyzed.

In this manner the tocopherol was pumped through the reactor a total of six times. The analytical results of the individual methylation steps are compiled in Table 2 hereinafter:

Table 2

Methylation-passage	α-Tocopherol GC area-%	γ-Tocopherol GC area-%	β-Tocopherol GC area-%	δ-Tocopherol GC area-%
1	27.0%	4.1%	39.2%	26.7%
2	57.4%	1.5%	33.5%	3.3%
3	71.7%	1.2%	21.1%	0.5%
4	77.3%	1.3%	15.2%	*
5	80.9%	1.5%	11.6%	*
6	83.7%	1.7%	7.9%	*

*: no longer detectable

Example 5

A catalyst powder, calcinated at 400°C, was produced from a solution of the nitrates of iron(III) (10 mmol), aluminium (20 mmol), magnesium (60 mmol) and copper(II) (60 mmol).

3.95 g (9 ml) of this catalyst were filled into the reactor. At 320°C there were pumped into the reactor 9 ml/min. of pre-heated hexane with the first pump and 2.8 ml/min. of methanol with the second. The pressure was adjusted to 90 bar (9 MPa).

Then 10 ml of a methanolic solution containing 2.5 g of a non-α-tocopherol concentrate (educt) of which only about a half consisted of tocopherols, was pumped in instead of methanol with the second pump. Subsequently, further methanol was pumped in during about 60 minutes with the second pump in order to flush the product from the reactor. The collected product solution was evaporated and analyzed by GC (product 1).

In a second experiment (as above) 10 ml of a methanolic solution containing 1 g of the non-α-tocopherol concentrate (educt) described above were pumped in instead of methanol with the second pump. Subsequently, further methanol was pumped in during about 60 minutes with the second pump in order to flush the product from the reactor. The collected product solution was evaporated and analyzed by GC (product 2). The results are compiled in Table 3 hereinafter:

Table 3

	α-Tocopherol	γ-Tocopherol	δ-Tocopherol	β-Tocopherol	Sterols	Remainder
Educt (weight-%)	3%	27%	13%	*	5.6%	50%
Product 1 (GC area-%)	25.8%	17.5%	4.6%	7.3%	**	**
Product 2 (GC-area-%)	39.4%	8.7%	1.2%	6.3%	**	**

* : non detectable

**: not measured

In another experiment on this catalyst, 5 ml/min. of pre-heated hexane at 320°C were pumped into the reactor with the first pump and 2 ml/min. of methanol with the second. The pressure was adjusted to 90 bar (9 MPa).

Then, 100 ml of a methanolic solution containing 1 g of δ-tocopherol were pumped in instead of methanol with the second pump. The product solution was collected separately every 6.5 minutes (corresponding to 12.5 ml of educt solution), evaporated and analyzed by GC. The results are compiled in Table 4 hereinafter:

Table 4

Sample (GC area-%)	α-Tocopherol	γ-Tocopherol	δ-Tocopherol	β-Tocopherol
1	94.8%	3.4%	0%	0.5%
2	92.8%	3.8%	0%	0.4%
3	91.7%	3.7%	0%	0.6%
4	91.8%	3.6%	0%	0.8%
5	91.1%	3.4%	0%	0.9%
6	91.5%	3.4%	0%	1.0%
7	90.7%	3.5%	0%	1.1%

Example 6

"Rope-like extrudates", calcinated at 350°C, were produced as the catalyst from a solution of the nitrates of iron(III) (10 mmol), aluminium (20 mmol), magnesium (60 mmol) and copper(II) (60 mmol).

3.0 g (7 ml) of this catalyst were filled into the reactor. At 300°C there were pumped into the reactor 1 ml/min. of hexane with the first pump and 3 ml/min. of pre-heated methanol/water (9/1 v/v) with the second. The pressure was adjusted to 85 bar (8.5 MPa).

Then, 3 ml of a solution containing 0.5 g of RRR-δ-tocopherol (educt) in hexane were pumped in instead of hexane with the first pump. Subsequently, further hexane was pumped in during about 60 minutes in

order to flush the product from the reactor. The entire product solution was collected in the receiver, evaporated and analyzed by GC (area-% method).

The evaporation residue was again made up to 3 ml with hexane and, as above, pumped through the reactor and analyzed.

In this manner the tocopherol was pumped through the reactor a total of eleven times. After the last passage 0.4 g of product was still present, since eleven analytical samples each of 5-10 mg had to be removed from the reaction mixture. The analytical results of the individual methylation steps are compiled in Table 5 hereinafter:

Table 5

Methylation passage	α-Tocopherol	γ-Tocopherol	β-Tocopherol	δ-Tocopherol
Educt	0.8%	4.5%	0.1%	94.0%
1	30.7%	3.8%	48.2%	11.1%
2	57.3%	1.3%	34.2%	1.2%
3	72.8%	0.7%	20.3%	0.3%
4	81.7%	0.6%	11.7%	*
5	86.4%	0.7%	6.9%	*
6	89.3%	0.6%	3.9%	*
7	90.8%	0.6%	2.2%	*
8	91.2%	0.7%	1.4%	*
9	91.6%	0.7%	0.8%	*
10	91.3%	0.8%	0.5%	*
11	91.8%	0.8%	0.3%	*

* : no longer detectable

In a further experiment on this catalyst, 2.5 ml/min. of pre-heated methanol/toluene mixture (4/1 v/v) at 320°C were pumped into the reactor with the first pump and 0.5 ml/min. of toluene with the second. The pressure was adjusted to 85 bar (8.5 MPa).

Then, 210 ml of a solution containing 7.089 g of a non-α-tocopherol concentrate in toluene were pumped in instead of toluene with the second

pump. After this educt solution had been pumped in it was again replaced by toluene for about 1 hour in order to flush the product completely from the reactor. The collected product solution was evaporated.

Educt and product were accurately weighed and analyzed. The following compilation (Table 6) confirms that practically all tocopherol had been converted into RRR-α-tocopherol without the appearance of any significant decomposition.

Table 6

Batch and yield calculation of the quantitative experiment

Educt	α-Tocopherol	γ-Tocopherol	β-Tocopherol	δ-Tocopherol	Remainder
Molecular weight	430.720	416.693	416.693	402.666	15.2%
Composition (weight %)	3.67%	48.51%	1.28%	31.30%	
Batch weight (total = 7.089 g)	0.260 g (0.603 mmol)	3.439 g (8.252 mmol)	0.091 g (0.218 mmol)	2.218 g (5.509 mmol)	1.08 g
Theoretical yield of α-tocopherol after methylation	0.260 g	3.554 g	0.094 g	2.373 g	
Total α-tocopherol according to theory:	6.281 g				
Product Yield calculation Found yield = 7.136 g					
Tocopherol content (weight %)	83.66%	0.81%	1.08%		
Tocopherol weight	5.970 g				
Chemical yield (% of theory)	95.05%	0.95%	1.23%		
Analysis of the methyl ether for optical activity	RRR-α 93.41%	2S-α 0.44%	RRR-β 1.24%		

A further packing of the above catalyst of 3 g (6 ml) was filled into the reactor. At 270°C 1 ml/min. of toluene was pumped into the reactor with the first pump and 2 ml/min. of pre-heated methanol with the second. The pressure was adjusted to 85 bar (8.5 MPa).

Then 5 solutions, each of 30 ml and each containing 0.5 to 8 g (see Table) of non-α-tocopherol concentrate in toluene, were pumped in successively in place of toluene with the first pump. Further toluene was pumped in between the tocopherol solutions during about 30 minutes in order to flush the product from the reactor. After the individual tocopherol solutions had been pumped in a product sample was withdrawn and analyzed by GC (area-% method). The results listed in Table 7 hereinafter show a clear conversion into α-tocopherol, which depends on the loading of the reactor and thus on the residence time.

Sample	Educt amount (g)/30 ml	α-Tocopherol	γ-Tocopherol	β-Tocopherol	δ-Tocopherol
Educt		4.17%	56.03%	1.31%	36.17%
1	8.01	6.68%	51.47%	2.59%	33.19%
2	4.02	8.29%	50.71%	3.72%	31.99%
3	2.02	11.38%	48.47%	6.04%	29.08%
4	1.09	18.49%	42.41%	10.17%	23.15%
5	0.51	28.46%	34.89%	13.89%	17.05%

In a further series of experiments, 1 ml/min. of toluene at 300°C was pumped into the reactor with the first pump and 2 ml/min. of pre-heated methanol with the second. The pressure was again adjusted to 85 bar (8.5 MPa).

Then, a further 5 solutions, each of 30 ml and each containing 0.5 to 8 g (see Table) of non-α-tocopherol concentrate in toluene, were pumped in instead of toluene with the first pump. Further toluene was pumped in between the tocopherol solutions during about 30 minutes in order to flush the product from the reactor. After the individual tocopherol solutions had been pumped in a product sample was withdrawn and analyzed by GC (area

% method). The results listed in Table 8 hereinafter show once again a clear conversion into α-tocopherol which depends on the loading of the reactor and thus on the residence time. Also, this series shows in comparison to the above series that at higher temperature a greater conversion takes place with otherwise equal conditions.

Table 8

Sample	Educt amount (g)/30ml	α-Tocopherol	γ-Tocopherol	β-Tocopherol	δ-Tocopherol
Educt		4.17%	56.03%	1.31%	36.17%
1	8.02	16.51%	44.22%	8.58%	25.03%
2	4.00	27.99%	35.25%	14.20%	16.60%
3	2.00	49.66%	19.82%	18.39%	6.24%
4	1.02	58.07%	6.62%	11.65%	1.46%
5	0.52	80.71%	4.60%	6.71%	0.46%

Claims

1. A process for the conversion of non-α-tocopherols into α-tocopherol by the catalytic permethylation of at least one non-α-tocopherol with a methylating agent, which process comprises using as the methylating agent methanol in the near-critical or super-critical pressure and temperature region or a mixture which is equivalent to methanol and which consists of hydrogen and carbon monoxide and/or carbon dioxide, and as the catalyst a mixed oxide catalyst which is produced from hydrotalcites and which contains at least copper and magnesium oxide as well as at least one oxide of a trivalent metal.

2. A process according to claim 1, wherein aluminium oxide, iron(III) oxide, vanadium oxide, chromium oxide and/or gallium oxide, preferably aluminium oxide and/or iron(III) oxide, is/are used as the oxide(s) of a trivalent metal.

3. A process according to claim 1 or claim 2, wherein in the mixed oxide catalyst the atomic ratio of the (total) divalent metals to the total trivalent metal(s) amounts to about 2:1 to about 10:1, preferably about 3:1 to about 4:1, and the atomic ratio of copper to magnesium or of copper to magnesium and further divalent metals present amounts to about 5:95 to about 60:40, preferably about 25:75 to about 50:50.

4. A process according to any one of claims 1 to 3, wherein aluminium oxide, iron oxide and optionally oxides of other trivalent metals are present in the mixed oxide catalyst and the atomic ratio between aluminium and iron or between aluminium and the totality of the other trivalent metals amounts to about 2:1 to about 1:2, especially about 2:1.

5. A process according to any one of claims 1 to 4, wherein the non-α-tocopherols to be converted into α-tocopherol, optionally present in a raw material, are dissolved in an inert solvent, said inert solvent being an alkane of medium molecular weight, preferably a C_{5-10}-alkane, e.g. pentane, hexane or heptane, a C_{5-10}-alkane mixture, e.g. petroleum ether having a boiling range between about 40°C and about 120°C; a cyclic alkane, e.g. cyclohexane; or an aromatic hydrocarbon, e.g. toluene.

6. A process according to any one of claims 1 to 5, wherein the amount of methanol or the amount of carbon monoxide and/or carbon dioxide in a mixture, equivalent to methanol, of hydrogen and carbon monoxide and/or carbon dioxide used as the methylating agent relative to the non-α-tocopherol(s) corresponds to about 10 to about 1000 equivalents, preferably about 25 to about 250 equivalents, of the methylatable positions in the non-α-tocopherol (mixture).

7. A process according to any one of claims 1 to 6, wherein the permethylation is carried out at a pressure between about 50 bar and about 120 bar (about 5 to about 12 MPa), preferably between about 70 bar and about 90 bar (about 7 to about 9 MPa), particularly at about 80-85 bar (about 8-8.5 MPa) and at a reaction temperature in the range of about 240°C to about 350°C, preferably in the region of about 280°C to about 320°C.

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