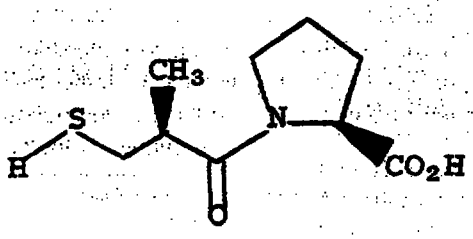
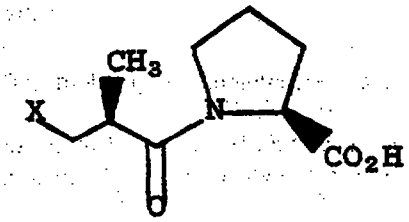
Description

This invention relates to processes for making the angiotensin converting enzyme (ACE) inhibitor captopril.

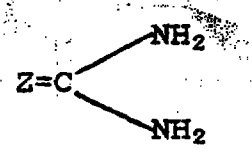
Captopril (Capoten®) is a widely marketed ACE inhibitor useful as a cardiovascular agent. Preparation of captopril is described in U.S. Patent No. 4,105,776 (issued August 8, 1978). Captopril may be described by the structure

I 

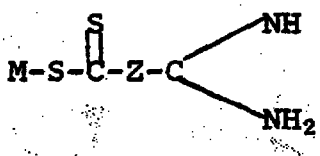
U.S. Patent No. 4,668,798 describes a process for making captopril from a substrate (i.e. starting material) of the formula

A 

wherein X is chlorine or bromine. In that process, carbon disulfide is reacted with a urea of the formula

B 

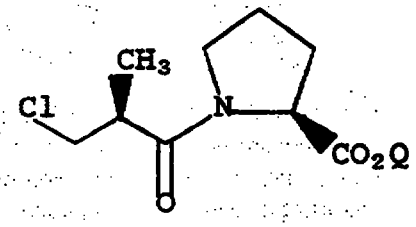
in the presence of an alkali metal base to form the compound

C 

wherein M is alkali metal and Z is oxygen or sulfur. Compound C is then reacted with Compound A, and the resulting product is hydrolyzed to form captopril in the reaction mixture. Thereafter, the reaction mixture is extracted a number of times with methylene chloride or ethyl acetate, treated with zinc powder to remove sulfide contaminants, and the resulting crude captopril is crystallized from an organic solvent.

U.S. Patent No. 4,460,780 describes a process for making captopril using the substrate

D



wherein Q is hydrogen, sodium, potassium, or ammonium. In a reaction sequence similar to the above-described process, substrate D is reacted with an alkali trithiocarbonate and then hydrolyzed with an acid. The resulting product is dissolved in sulfuric acid, treated with zinc powder to remove disulfide impurities, and crystallized from an organic solvent to remove the sulfide impurity.

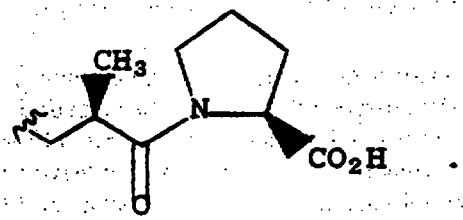
The preparation of captopril from substrates A and D requires the use of a sulfur-transfer reagent such as compound B or C. Many such reagents are prone to undergo oxidation-reduction reactions with compounds containing sulfur moieties, leading to the formation of disulfide and other impurities. A second source of disulfide impurity, however, is reaction of captopril with molecular oxygen according to the formula:

$$2R^1\text{-SH} + O_2 \longrightarrow R^1\text{-S-S-}R^1 + H_2O_2$$

$$2R^1\text{-SH} + H_2O_2 \longrightarrow R^1\text{-S-S-}R^1 + 2H_2O$$

$$4R^1\text{-SH} + O_2 \longrightarrow 2R^1\text{-S-S-}R^1 + 2H_2O$$

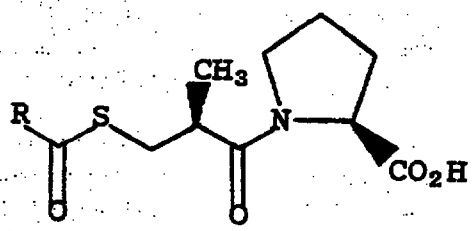
wherein R^1 is the remainder of captopril, having the structure



A number of other processes are available for the preparation of captopril, but these processes inherently form disulfide and other impurities and require the additional step of removing these impurities by treatment with zinc powder at low pH or some other similar method. See Shimazaki et al., Chem. Pharm. Bull. 30 (9), 3139-3146 (1982). In addition, these processes also involve the use of organic solvents such as methylene chloride, which may carry through in trace amounts into the final products. Such organic solvents may have undesirable properties for products for human consumption and so should be avoided. Also, the extraction of captopril into an organic solvent, the separation and distillation of that solvent to isolate the crude captopril, and its subsequent crystallization are time-consuming and require valuable manufacturing equipment and capacity.

A process has now been discovered whereby captopril may be prepared without the need of treatment with zinc and sulfuric acid or other methods to remove disulfide impurities and without the use of any organic solvent for purification and crystallization. The process described in GB Patent No. 1,576,161 comprises reacting a compound of the formula

II



wherein R is lower alkyl or lower alkoxy with an aqueous solution of an alkali metal hydroxide wherein the alkali metal hydroxide has a concentration of 4 M or greater. The reaction mixture is then neutralized to give a concentrated solution of the alkali metal salt of captopril, the compound R-COO$^{\ominus}$M$^{\oplus}$ (e.g., sodium acetate) and excess alkali metal hydroxide (e.g., sodium hydroxide). Upon acidification with mineral acid captopril is produced in a concentrated solution of a salt (e.g., a sodium salt).

In accordance with the present invention, neutralization is effected by acidification to a pH of about 3.5 to 4.5. The captopril product precipitates and is collected. No further treatment is needed. Neutralization by addition of a mineral acid (such as hydrochloric acid) is preferred.

It has also been found that the solubility of oxygen, which oxidizes captopril to the undesired disulfide impurity, is much lower in concentrated salt solution than in water or dilute salt solutions. Therefore, the risk of the undesired oxygen side reaction (see above) is minimized throughout subsequent processing.

The term "lower alkyl" refers to straight and branched chain hydrocarbon groups having 1 to 4 carbon atoms Exemplary lower alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and isobutyl.

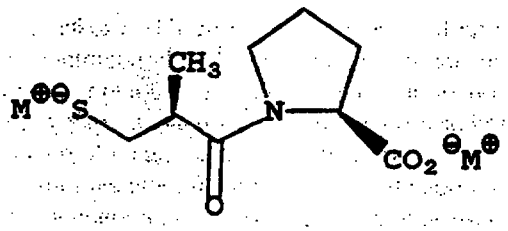
The term "lower alkoxy" refers to a lower alkyl group linked to an oxygen atom.

The term "alkali metal hydroxide" refers to NaOH, LiOH, and KOH. NaOH is the preferred alkali metal hydroxide.

A substrate of formula II may be prepared as described in U.S. Patent No. 4,105,776. Although any formula II compound is a suitable substrate for the process, a substrate wherein R is methyl is preferred.

A substrate of formula II may be treated with an alkali metal hydroxide to yield compounds of the formulas

IIIa



and

IIIb R-CO$_2^{\ominus}$M$^{\oplus}$

wherein M$^{\oplus}$ is an alkali metal ion (e.g., Na^+). An inert atmosphere (e.g., nitrogen or argon) is preferred for this part of the process. The temperature for hydrolysis is about -10 to 50 °C, with a temperature no higher than 45 °C preferred. The formula II compound is reacted with 2.5 to 5 molar equivalents, preferably about 3.3 molar equivalents, of alkali metal ions.

The concentration of the alkali metal hydroxide solution is an important factor in optimizing the yield of captopril salt (compound IIIa). It has been found that alkali metal hydroxide concentrations of greater than or equal to 4 M minimize the volume of the reactants and maximize the crystallization of captopril. At alkali metal hydroxide concentrations less than 4 M, much of the captopril will remain in solution after acidification rather than crystallize, and the crystallized captopril will be mixed with high levels of disulfide impurity due to oxidation by dissolved molecular oxygen. The present process, in contrast, employs a concentrated salt solution that minimizes the solubility of oxygen, thus protecting against oxidation to the disulfide impurity. Cf. S. D. Cramer, Ind. Eng. Chem. Process Des. Dev. 19 (1980) 300. Concentrations of about 4 to 18 M alkali metal hydroxide are suitable, but the most preferred concentration is about 9.5 M.

The captopril salt (compound IIIa) is then neutralized. It is preferred that this neutralization be effected by acidification with a mineral acid. The acidification should be carried out at a pH at which the captopril product crystallizes rather than oils out of the aqueous solution. It has been found that acidification immediately or directly to a pH of about 3 5 to 4.5 (3.9 is most preferred) ensures good crystal growth. To optimize the crystallization of captopril, the reaction mixture may be further acidified, preferably to a pH less than or equal to about 3. It has been found that such further acidification may be carried out in increments (preferably about 0.2 pH units) at regular intervals (preferably about 15 minutes). Acidification with a mineral acid such as hydrochloric acid is preferred, with concentrated aqueous hydrochloric acid (i.e., 35% hydrochloric acid or greater) most preferred.

The crystallization may also be carried out continuously, wherein the solution of captopril salt is added to a slurry of captopril while the slurry is maintained under acidic conditions. With a slow rate of addition, there is no tendency for the product to oil out of solution.

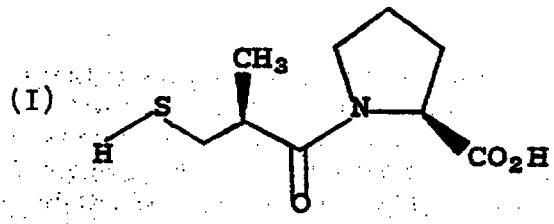
During acidification, the reaction temperature may be adjusted to aid crystal growth. Temperatures of about 20 to 45 °C are preferred. In addition, the solution may be seeded with captopril to aid crystal growth. Captopril may be further crystallized from the aqueous solution of the hydrolyzed substrate by cooling the solution. Cooling to about 0 to 4 °C is preferred.

Example

Under nitrogen atmosphere, a solution of 160 ml of 9.5 N sodium hydroxide was cooled to 0 to 2 °C, and 128 g of 1-[S-3-(acetylthio)-2-methyl-1-oxopropyl]L-proline (120 g on an anhydrous basis) was added while keeping the temperature no greater than 45 °C. After about 5 minutes at 30 to 45 °C, hydrolysis was complete as determined by HPLC, and the solution of the resulting captopril salt was acidified with 51 ml of concentrated hydrochloric acid to pH 7.3. The solution was polish-filtered at 45 °C, and the equipment was rinsed with 21 ml of distilled water. The combined filtrates were acidified at 37 to 45 °C to pH 3.90 with 49 ml of concentrated hydrochloric acid, and seeded with 0.1 g of captopril. The suspension was cooled to about 32 °C to initiate good crystal growth, and held for about one hour. The suspension was acidified with concentrated hydrochloric acid every 15 minutes in increments of about 0.2 pH units until pH 3.0 was reached. Then the suspension was acidified to pH 1.8, and kept at 30 to 34 °C for about 30 minutes. The suspension was rapidly cooled to 0 to 4 °C, and held at that temperature range for about 30 minutes. The product was filtered and washed with two-70 ml portions of cold water at about 4 °C. Vacuum-drying at 40 °C yielded 88.0 g (90.5 M%) of captopril.
Melting point: 103 to 107 °C.
Additional analytical data: 99.9% titration purity; 99.9% HPLC purity; 0.1% water. Disulfide content: 0.3%.

Claims

1. A process for preparing a product of the formula

(I) 

which comprises:

* C L M S *

The captopril salt (compound IIIa) is then neutralized. It is preferred that this neutralization be effected by acidification with a mineral acid. The acidification should be carried out at a pH at which the captopril product crystallizes rather than oils out of the aqueous solution. It has been found that acidification immediately or directly to a pH of about 3 5 to 4.5 (3.9 is most preferred) ensures good crystal growth. To optimize the crystallization of captopril, the reaction mixture may be further acidified, preferably to a pH less than or equal to about 3. It has been found that such further acidification may be carried out in increments (preferably about 0.2 pH units) at regular intervals (preferably about 15 minutes). Acidification with a mineral acid such as hydrochloric acid is preferred, with concentrated aqueous hydrochloric acid (i.e., 35% hydrochloric acid or greater) most preferred.

The crystallization may also be carried out continuously, wherein the solution of captopril salt is added to a slurry of captopril while the slurry is maintained under acidic conditions. With a slow rate of addition, there is no tendency for the product to oil out of solution.

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Example

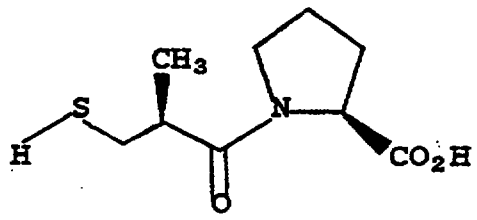
Under nitrogen atmosphere, a solution of 160 ml of 9.5 N sodium hydroxide was cooled to 0 to 2 °C, and 128 g of 1-[S-3-(acetylthio)-2-methyl-1-oxopropyl]L-proline (120 g on an anhydrous basis) was added while keeping the temperature no greater than 45 °C. After about 5 minutes at 30 to 45 °C, hydrolysis was complete as determined by HPLC, and the solution of the resulting captopril salt was acidified with 51 ml of concentrated hydrochloric acid to pH 7.3. The solution was polish-filtered at 45 °C, and the equipment was rinsed with 21 ml of distilled water. The combined filtrates were acidified at 37 to 45 °C to pH 3.90 with 49 ml of concentrated hydrochloric acid, and seeded with 0.1 g of captopril. The suspension was cooled to about 32 °C to initiate good crystal growth, and held for about one hour. The suspension was acidified with concentrated hydrochloric acid every 15 minutes in increments of about 0.2 pH units until pH 3.0 was reached. Then the suspension was acidified to pH 1.8, and kept at 30 to 34 °C for about 30 minutes. The suspension was rapidly cooled to 0 to 4 °C, and held at that temperature range for about 30 minutes. The product was filtered and washed with two-70 ml portions of cold water at about 4 °C. Vacuum-drying at 40 °C yielded 88.0 g (90.5 M%) of captopril.

Melting point: 103 to 107 °C.

Additional analytical data: 99.9% titration purity; 99.9% HPLC purity; 0.1% water. Disulfide content: 0.3%.

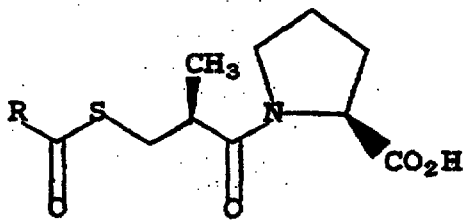
Claims

1. A process for preparing a product of the formula

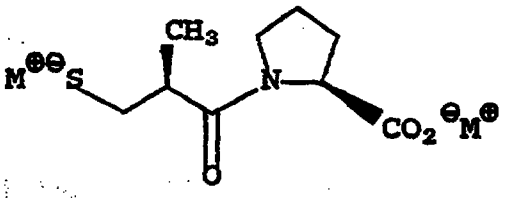
(I) 

which comprises:

(a) reacting a compound of the formula

(II) 

wherein R is C_1-C_4 alkyl or C_1-C_4 alkoxy with an aqueous solution of about 4 M or greater of sodium hydroxide, lithium hydroxide or potassium hydroxide to form a reaction mixture comprising

(IIIa) 

and

(IIIb) $R\text{-}CO_2^{\ominus}M^{\oplus}$

wherein $M^{\oplus}$ is a sodium, lithium or potassium ion; and
(b) neutralizing the reaction mixture to form the product,
characterised in that the neutralization is effected by acidification to a pH of 3.5 to 4.5.

2. The process of claim 1, wherein the neutralization is effected by acidification with a mineral acid.

3. The process of claim 2, wherein the acidification is effected with hydrochloric acid.

4. The process of claim 3, wherein the acidification is effected with an aqueous solution having a hydrochloric acid concentration of 35% or greater.

5. The process of any preceding claim, wherein R is methyl.

6. The process of any preceding claim, wherein the process is carried out under an inert atmosphere.

7. The process of any preceding claim, wherein the sodium, lithium or potassium hydroxide solution has a concentration of 4 M to 18 M.

8. The process of claim 7, wherein the sodium, lithium or potassium hydroxide solution has a concentration of 9.5 M.

9. The process of any preceding claim, wherein the aqueous solution of the sodium, lithium or potassium hydroxide is present in such an amount as to provide 2.5 to 5 molar equivalents of sodium, lithium or potassium ions, per equivalent of (II).

10. The process of claim 9, wherein the aqueous solution of the sodium, lithium or potassium hydroxide is present in such an amount as to provided 3.3 molar equivalents of sodium, lithium or potassium ions, per equivalent of (II).

11. The process of any preceding claim, wherein the aqueous solution comprises sodium hydroxide.

12. The process of any preceding claim, wherein the process step (a) is carried out at a temperature of -10 to 50 °C.

13. The process of any preceding claim, further comprising adjusting the neutralized product to a reaction temperature of 20 to 45 °C.

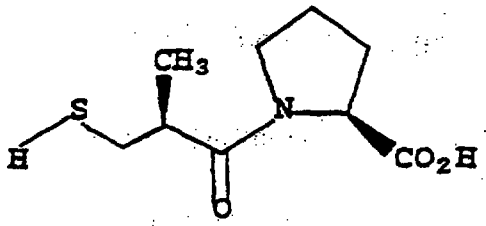
14. The process of any preceding claim, wherein said pH is 3.9.

15. The process of any preceding claim, wherein the reaction mixture is incrementally further acidified to a pH less than or equal to 3.

16. The process of claim 15, wherein the further acidification is effected in increments of 0.2 pH units at 15-minute intervals.

Patentansprüche

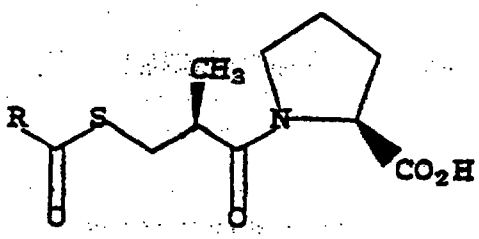
1. Verfahren zur Herstellung eine Produkte der Formel I



(I)

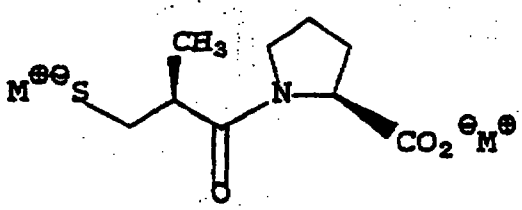
welches umfaßt:

(a) Umsetzen einer Verbindung der Formel II



(II)

in der R für einen C_1-C_4-Alkyl- oder C_1-C_4-Alkoxyrest steht, mit einer wässerigen Lösung von etwa 4 M oder mehr an Natriumhydroxid, Lithiumhydroxid oder Kaliumhydroxid, zu einem Reaktionsgemisch, umfassend



(IIIa)

und

$R\text{-}CO_2^{\ominus}M^{\oplus}$ (IIIb)

* C L M S *

wobei $M^{\oplus}$ ein Natrium-, Lithium- oder Kalium-Ion ist; und

(b) Neutralisieren des Reaktionsgemisches unter Herstellung des Produktes,

dadurch gekennzeichnet, daß das Neutralisieren durch Ansäuern auf einen pH-Wert von 3,5 bis 4,5 bewirkt wird.

2. Verfahren nach Anspruch 1, wobei das Neutralisieren durch Ansäuern mit einer Mineralsäure bewirkt wird.

3. Verfahren nach Anspruch 2, wobei das Ansäuern mit Salzsäure herbeigeführt wird.

4. Verfahren nach Anspruch 3, wobei das Ansäuern mit einer wässerigen Lösung mit einer Salzsäurekonzentration von 35% oder höher bewirkt wird.

5. Verfahren nach einem der vorangehenden Ansprüche, wobei R eine Methylgruppe ist.

6. Verfahren nach einem der vorangehenden Ansprüche, wobei das Verfahren unter einer Inertatmosphäre durchgeführt wird.

7. Verfahren nach einem der vorangehenden Ansprüche, wobei die Natrium-, Lithium- oder Kaliumhydroxidlösung eine Konzentration von 4 M bis 18 M hat.

8. Verfahren nach Anspruch 7, wobei die Natrium-, Lithium- oder Kaliumhydroxidlösung eine Konzentration von 9,5 M hat.

9. Verfahren nach einem der vorangehenden Ansprüche, wobei die wässerige Lösung des Natrium-, Lithium- oder Kaliumhydroxids in einer solchen Menge vorliegt, daß 2,5 bis 5 Mol-Äquivalente an Natrium-, Lithium- oder Kalium-Ionen pro Äquivalent (II) bereitgestellt werden.

10. Verfahren nach Anspruch 9, wobei die wässerige Lösung des Natrium-, Lithium- oder Kaliumhydroxids in einer solchen Menge vorliegt, daß 3,3 Mol-Äquivalente an Natrium-, Lithium- oder Kalium-Ionen pro Äquivalent (II) bereitgestellt werden.

11. Verfahren nach einem der vorangehenden Ansprüche, wobei die wässerige Lösung Natriumhydroxid umfaßt.

12. Verfahren nach einem der vorangehenden Ansprüche, wobei der Verfahrensschritt (a) bei einer Temperatur von -10 bis 50 °C durchgeführt wird.

13. Verfahren nach einem der vorangehenden Ansprüche, welches außerdem das Einstellen des neutralisierten Produktes auf eine Reaktionstemperatur von 20 bis 45 °C umfaßt.

14. Verfahren nach einem der vorangehenden Ansprüche, wobei der pH-Wert 3,9 ist.

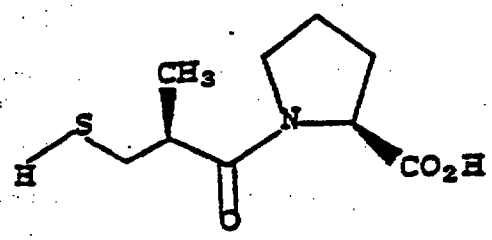
15. Verfahren nach einem der vorangehenden Ansprüche, wobei das Reaktionsgemisch schrittweise weiter angesäuert wird bis zu einem pH-Wert von 3 oder geringer.

16. Verfahren nach Anspruch 15, wobei das weitere Ansäuern in Schritten von 0,2 pH-Einheiten mit Intervallen von 15 Minuten herbeigeführt wird.

* C L M S *

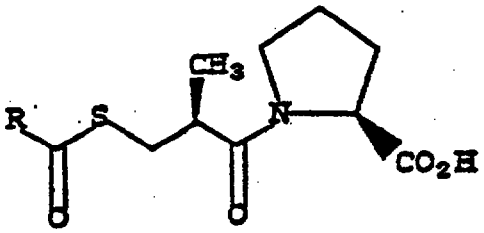
Revendications

1. Procédé de préparation d'un produit de formule

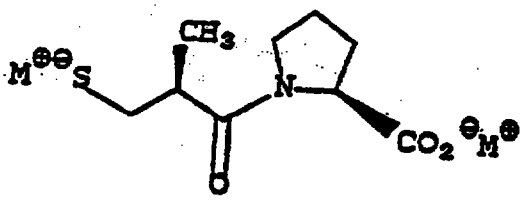
(I) 

qui consiste:

(a) à faire réagir un composé de formule

(II) 

dans laquelle R est un groupe alkyle en C_1-C_4 ou alcoxy en C_1-C_4, avec une solution aqueuse d'hydroxyde de sodium, d'hydroxyde de lithium ou d'hydroxyde de potassium environ 4 M ou plus, pour former un mélange réactionnel comprenant

(IIIa) 

et

(IIIb) $R\text{-}CO_2^{\ominus}M^{\oplus}$

où $M^{\oplus}$ est un ion sodium, lithium ou potassium; et

(b) à neutraliser le mélange réactionnel pour former le produit,

caractérisé en ce qu'on réalise la neutralisation par acidification à un pH de 3,5 à 4,5.

2. Procédé selon la revendication 1, dans lequel on réalise la neutralisation par acidification avec un acide minéral.

3. Procédé selon la revendication 2, dans lequel on réalise l'acidification avec de l'acide chlorhydrique.

4. Procédé selon la revendication 3, dans lequel on réalise l'acidification avec une solution aqueuse dont la concentration en acide chlorhydrique est de 35% ou plus.

5. Procédé selon l'une quelconque des revendications précédentes, dans lequel R est le groupe méthyle.

6. Procédé selon l'une quelconque des revendications précédentes, dans lequel le procédé est mis en oeuvre sous atmosphère inerte.

* C L M S *

7. Procédé selon l'une quelconque des revendications précédentes, dans lequel la solution d'hydroxyde de sodium, de lithium ou de potassium a une concentration de 4 M à 18 M.

8. Procédé selon la revendication 7, dans lequel la solution d'hydroxyde de sodium, de lithium ou de potassium a une concentration de 9,5 M.

9. Procédé selon l'une quelconque des revendications précédentes, dans lequel la solution aqueuse de l'hydroxyde de sodium, de lithium ou de potassium est présente en quantité telle qu'elle fournit 2,5 à 5 équivalents molaires d'ions sodium, lithium ou potassium par équivalent de (II).

10. Procédé selon la revendication 9, dans lequel la solution aqueuse de l'hydroxyde de sodium, de lithium ou de potassium est présente en quantité telle qu'elle fournit 3,3 équivalents molaires d'ions sodium, lithium ou potassium par équivalent de (II).

11. Procédé selon l'une quelconque des revendications précédentes, dans lequel la solution aqueuse comprend de l'hydroxyde de sodium.

12. Procédé selon l'une quelconque des revendications précédentes, dans lequel l'étape (a) du procédé est mise en oeuvre à une température de -10 à 50 °C.

13. Procédé selon l'une quelconque des revendications précédentes, comprenant en outre un réglage du produit neutralisé à une température de réaction de 20 à 45 °C.

14. Procédé selon l'une quelconque des revendications précédentes, dans lequel ledit pH est égal à 3,9.

15. Procédé selon l'une' quelconque des revendications précédentes, dans lequel on augmente encore l'acidité du mélange réactionnel, par paliers, jusqu'à un pH inférieur ou égal à 3.

16. Procédé selon la revendication 15, dans lequel on réalise l'augmentation d'acidité par paliers de 0,2 unité de pH, à intervalles de 15 minutes.