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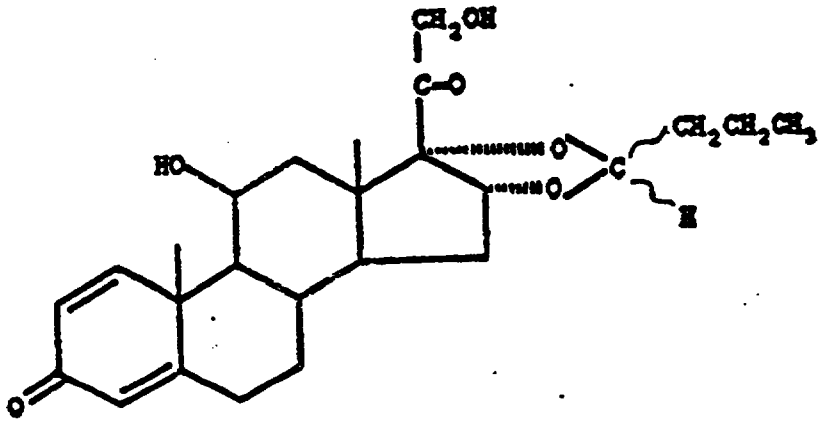
SX 1043-1 WO

Process for the manufacture of Budesonide

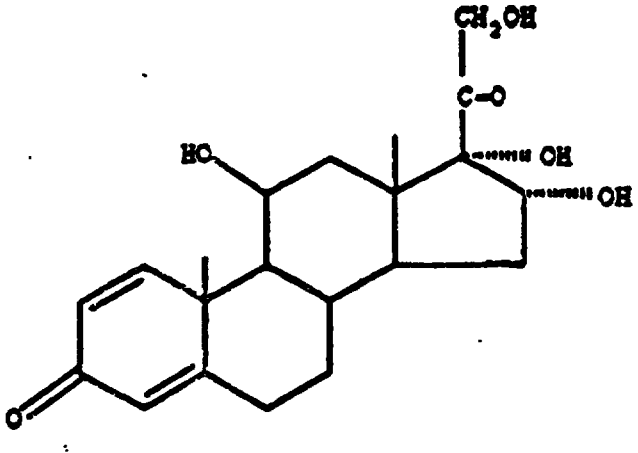
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Technical field

The present invention relates to a novel process for the manufacture of (22 R,S)-16α,17α-butylidenedioxy-11β,21-dihydroxypregna-1,4-diene-3,20-dione (budesonide)



by reacting 11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione (16α-hydroxyprednisolone)



with butanal, $CH_3CH_2CH_2CHO$, in a solvent medium in the presence of an acid catalyst.

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Prior art

According to a previously known process disclosed in GB patent no. 1 429 922 Budesonide is manufactured by reacting 16α-hydroxyprednisolone with butanal in dioxane and with perchloric acid as a catalyst. The product is recovered by diluting the reaction mixture with methylene chloride,and neutralising by washing with aqueous potassium carbonate and water, evaporating the solvent followed by crystallisation from ether/ligroine. The product was further purified by chromatography e.g. on Sephadex. The main disadvantages of dioxane are its skin penetrating and peroxide formation properties. Another disadvantage with this prior art process is perchloric acid, which is a strong oxidizing agent and the use of this catalyst results in a less selective reaction, which in turn makes the subsequent work-up and purification process complicated and expensive.

Disclosure of the invention

The object of the invention is to create a novel process, which gives a more selective reaction and a more simple and economic work-up and purification process.

This is achieved with the process according to the present invention, wherein the reaction is performed in acetonitrile with p-toluenesulphonic acid as a catalyst.

The combination of the less basic (compared to dioxane) solvent acetonitril and the weaker, i.e. non-oxidizing p-toluenesulphonic acid gives a more selective reaction, and also a more simple and exonomic work-up and purification process compared to the above discussed prior art process using dioxane and perchloric acid.

According to a preferred embodiment of the invention the reaction is stopped by the addition of water and adjustment of the pH of the reaction mixture. This might be done by the addition of sodium hydrogen carbonate in water. The product then crystallizes. The crystals are filtered off, dissolved in methylene chloride and methanol and are then crystallized by the addition

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a suitable hydrocarbon, such as ligroine, hexane, cyclohexane or heptane, giving a crude product, which is then recrystallized in methanol/water to give pure budesonide.

The process according to the invention for the manufacture of budesonide thus consists of two steps.

Step 1. Budesonide crude

16α-hydroxyprednisolone is reacted with butanal in acetonitrile. p-Toluenesulphonic acid is added as a catalyst. The reaction mixture is diluted with water and aqueous sodium hydrogen carbonate. After cooling to 5-15°C the crystallized product is filtered off and washed with water. The wet or dried substance is then dissolved in methylene chloride. If the substance used is wet the water phase formed upon dissolution is removed. Methanol is added and the resulting crude budesonide is precipitated by the addition of ligroine or another suitable hydrocarbon (e.g. hexane, heptane or cyclohexane) and is then filtered off.

Step 2. Budesonide

The crude budesonide is dissolved in methanol at about 60°C. The solution is filtered through a closed filter and the product is crystallized by the addition of water. After cooling to 5-20°C, filtration and washing with methanol/water the budesonide is dried in vacuum at 40-45°C.

This process is simplified, more economic and less health hazardous compared to prior art processes.

Working example

The reaction is carried out in a nitrogen atmosphere. 15,4 g p-toluenesulphonic acid is dissolved into 200 ml acetonitrile. To the solution 50,0 g 16α-hydroxyprednisolone and 17.6 ml butanal are added. The temperature rises to 25°C. After 30 min most of the material is dissolved. Shortly thereafter the product starts to crystallize. After 3 hours the reaction is stopped by the addition of 75 ml aqueous saturated sodium hydrogen carbonate solution, whereupon the product crystallizes. The dried product

is dissolved in methylene chloride and methanol and is crystallized by the addition of ligroine (b.p. 40 - 65), giving crude budesonide.

5 The crude budesonide product is recrystallized from methanol/water giving pure budesonide with isomer ratio A:B $\approx$ 1:1 (HPLC), $[\alpha]_D^{25}$ 100.0° (c = 0.2; CH_2CL_2); M^+ 430 (theor. 430.5)

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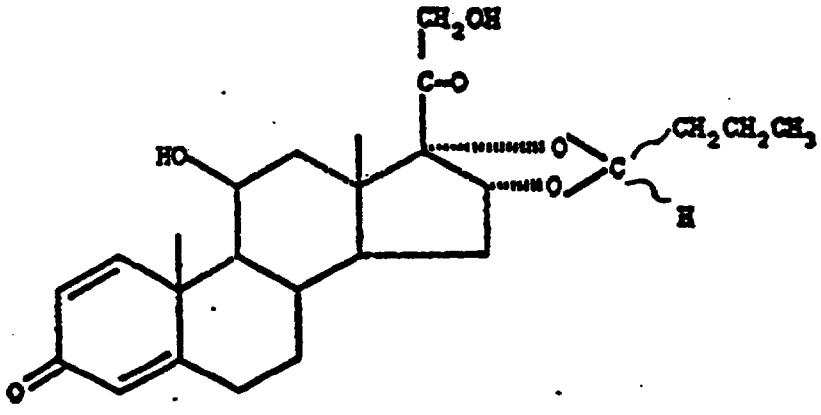


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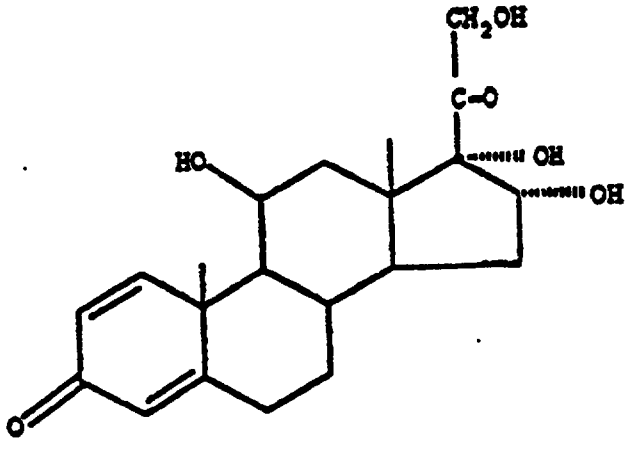
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C l a i m s

1. Process for the manufacture of (22 R,S)-16α,17α-butylidene-dioxy-11ß,21-dihydroxypregna-1,4-diene-3,20-dione



by reacting 11ß,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione



with butanal, $CH_3CH_2CH_2CHO$ in a solvent medium in the presence of a catalyst, c h a r a c t e r i s e d in that the reaction is performed in acetonitrile with p-toluenesulphonic acid as a catalyst.

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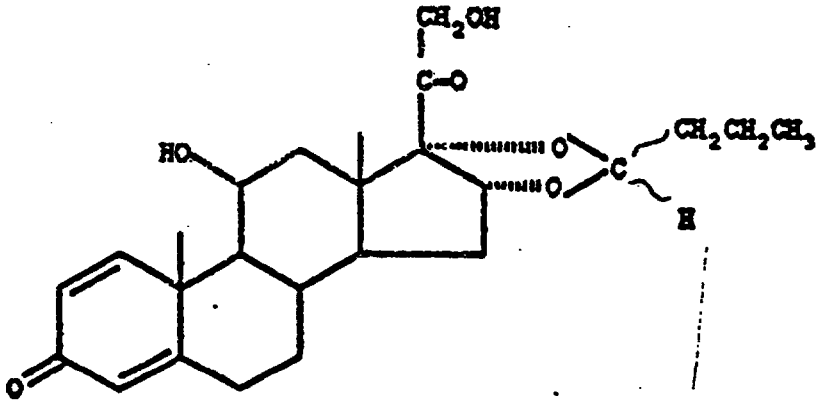
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3. Process according to claim 1 or 2, c h a r a c t e r i - z e d in that the crystals obtained upon termination of the reaction are filtered off, dissolved in methylene chloride and methanol and are then crystallized by the addition a suitable hydrocarbon, such as ligroine, hexane, cyclohexane or heptane, giving a crude product, which is then recrystallized in methanol/water to give pure budesonide.

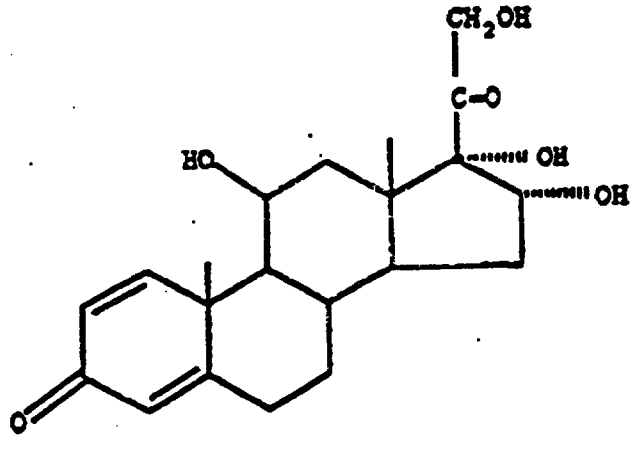
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Abstract

The present invention relates to a novel process for the manufacture of (22 R,S)-16α,17α-butylidenedioxy-11ß,21-dihydroxy-pregna-1,4-diene-3,20-dione



by reacting 11ß,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione



with butanal, $CH_3CH_2CH_2CHO$ in acetonitrile with p-toluenesulphonic acid as a catalyst.

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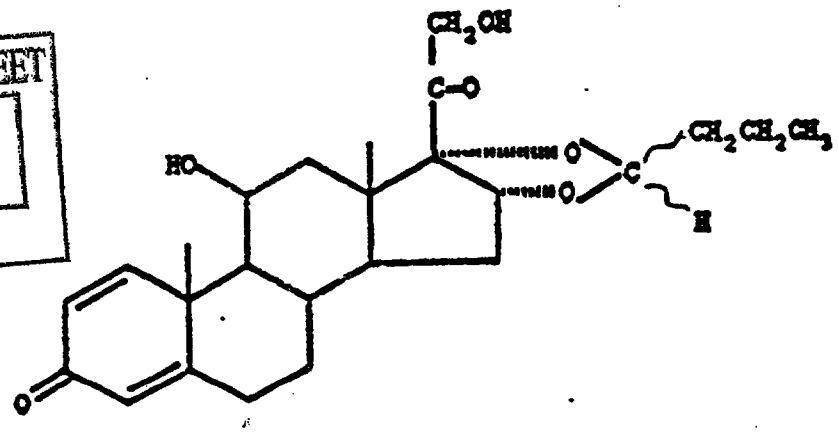
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Process for the manufacture of Budesonide

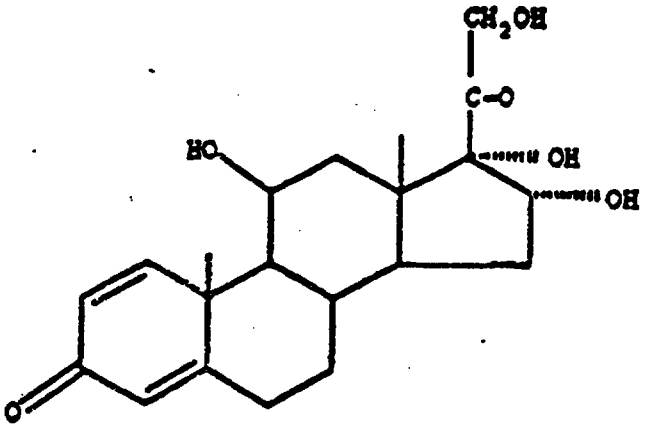
Technical field

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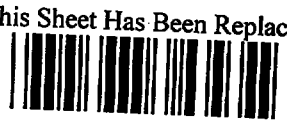


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Prior art

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Disclosure of the invention

The object of the invention is to create a novel process, which gives a more selective reaction and a more simple and economic work-up and purification process.

This is achieved with the process according to the present invention, wherein the reaction is performed in acetonitrile with p-toluenesulphonic acid as a catalyst.

The combination of the less basic (compared to dioxane) solvent acetonitril and the weaker, i.e. non-oxidizing p-toluenesulphonic acid gives a more selective reaction, and also a more simple and exonomic work-up and purification process compared to the above discussed prior art process using dioxane and perchloric acid.

According to a preferred embodiment of the invention the reaction is stopped by the addition of water and adjustment of the pH of the reaction mixture. This might be done by the addition of sodium hydrogen carbonate in water. The product then crystallizes. The crystals are filtered off, dissolved in methylene chloride and methanol and are then crystallized by the addition

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The process according to the invention for the manufacture of budesonide thus consists of two steps.

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Step 2. Budesonide

The crude budesonide is dissolved in methanol at about 60°C. The solution is filtered through a closed filter and the product is crystallized by the addition of water. After cooling to 5-20°C, filtration and washing with methanol/water the budesonide is dried in vacuum at 40-45°C.

This process is simplified, more economic and less health hazardous compared to prior art processes.

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The reaction is carried out in a nitrogen atmosphere. 15,4 g p-toluenesulphonic acid is dissolved into 200 ml acetonitrile. To the solution 50,0 g 16α-hydroxyprednisolone and 17.6 ml butanal are added. The temperature rises to 25°C. After 30 min most of the material is dissolved. Shortly thereafter the product starts to crystallize. After 3 hours the reaction is stopped by the addition of 75 ml aqueous saturated sodium hydrogen carbonate solution, whereupon the product crystallizes. The dried product

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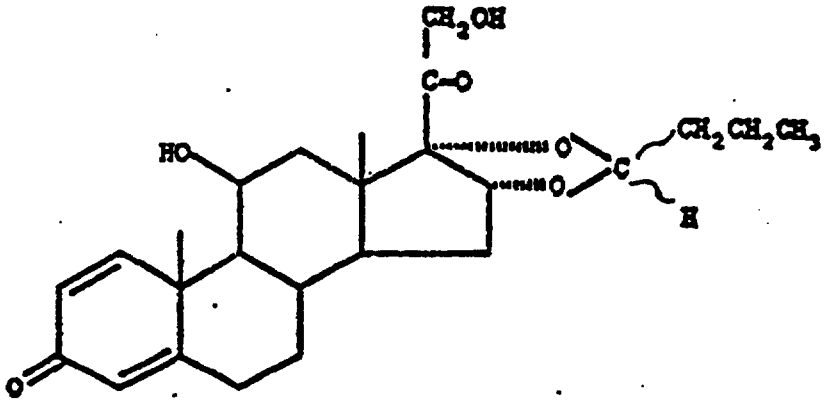


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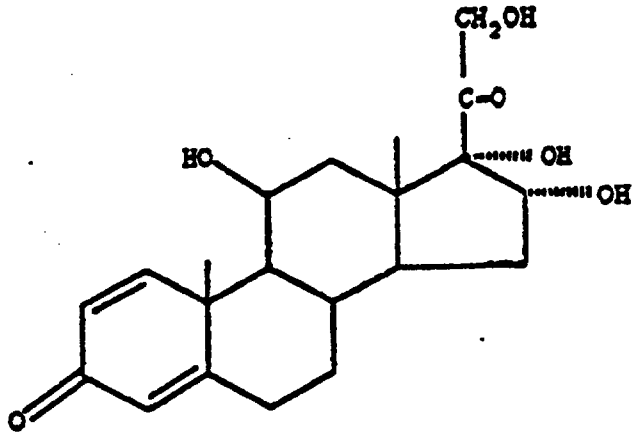
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C l a i m s

1. Process for the manufacture of (22 R,S)-16α,17α-butylidene-dioxy-11ß,21-dihydroxypregna-1,4-diene-3,20-dione



by reacting 11ß,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione



REPLACEMENT SHEET
01 MAR 1997

with butanal, $CH_3CH_2CH_2CHO$ in a solvent medium in the presence of a catalyst, c h a r a c t e r i s e d in that the reaction is performed in acetonitrile with p-toluenesulphonic acid as a catalyst.

2. Process according to claim 1, c h a r a c t e r i z e d in that the reaction is terminated by the addition of water and by adjustment of the pH of the reaction mixture.

* C L M S *

3. Process according to claim 1 or 2, c h a r a c t e r i - z e d in that the crystals obtained upon termination of the reaction are filtered off, dissolved in methylene chloride and methanol and are then crystallized by the addition a suitable hydrocarbon, such as ligroine, hexane, cyclohexane or heptane, giving a crude product, which is then recrystallized in methanol/water to give pure budesonide.

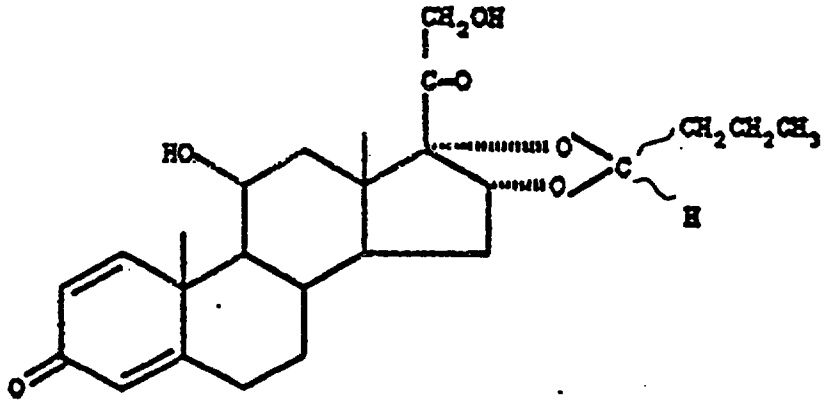
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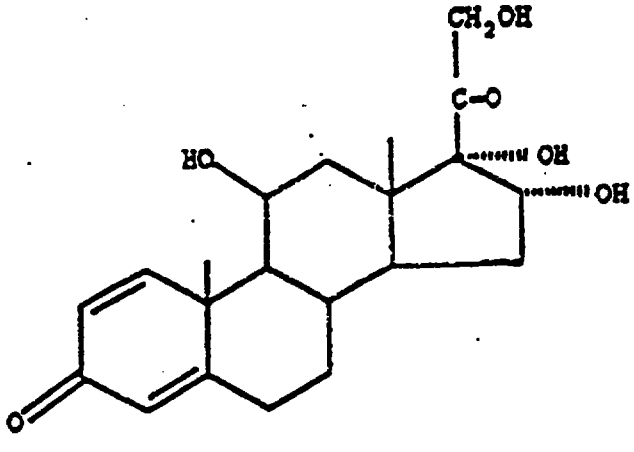
PROCESS FOR THE MANUFACTURE OF BUDESONIDE

Abstract

The present invention relates to a novel process for the manufacture of (22 R,S)-16α,17α-butylidenedioxy-11ß,21-dihydroxypregna-1,4-diene-3,20-dione



by reacting 11ß,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione



with butanal, $CH_3CH_2CH_2CHO$ in acetonitrile with p-toluenesulphonic acid as a catalyst.

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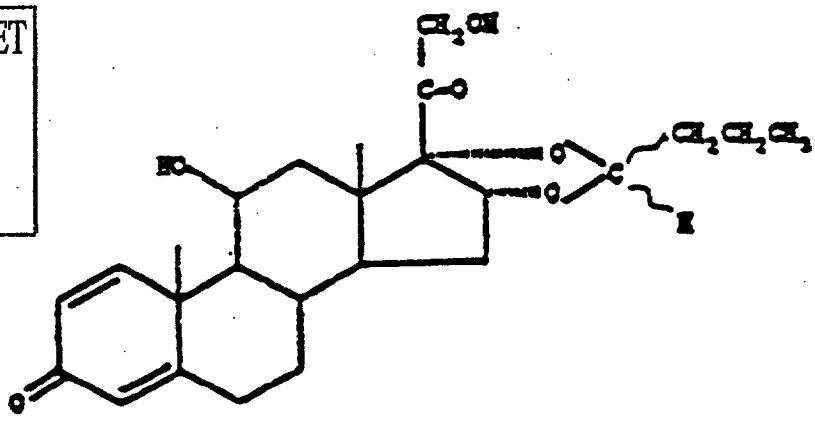
PROCESS FOR THE MANUFACTURE OF BUDESONIDE

Description

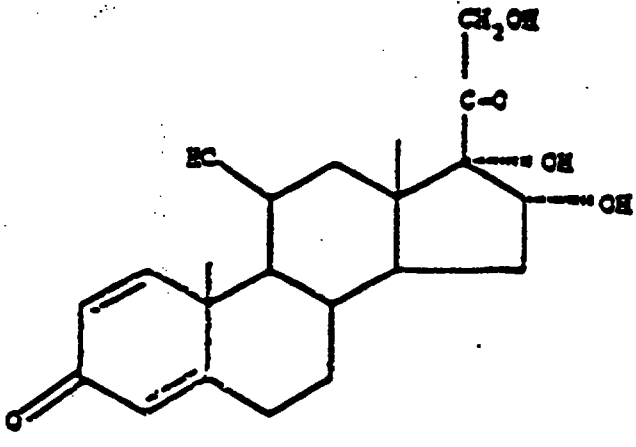
Technical field

The present invention relates to a novel process for the manufacture of (22 R,S)-16α,17α-butylidenedioxy-11β,21-dihydroxypregna-1,4-diene-3,20-dione (budesonide)

REPLACEMENT SHEET
22 JUL 1997



by reacting 11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione (16α-hydroxyprednisolone)



with butanal, $CH_3CH_2CH_2CHO$, in a solvent medium in the presence of an acid catalyst.

Prior art

According to a previously known process disclosed in GB patent no. 1 429 922 Budesonide is manufactured by reacting 16α-hydroxyprednisolone with butanal in dioxane and with perchloric acid as a catalyst. The product is recovered by diluting the reaction mixture with methylene chloride, and neutralising by washing with aqueous potassium carbonate and water, evaporating the solvent followed by crystallisation from ether/ligroine. The product was further purified by chromatography e.g. an Sephadex. The main disadvantages of dioxane are its skin penetrating and peroxide formation properties. Another disadvantage with this prior art process is perchloric acid, which is a strong oxidizing agent and the use of this catalyst results in 3 less selective reaction, which in turn makes the subsequent work-up and purification process complicated and expensive.

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22 JUL 1997

Disclosure of the invention

The object of the invention is to create a novel process, which gives a more selective reaction and a more simple and economic work-up and purification process.

This is achieved with the process according to the present invention, wherein the reaction is performed in acetonitrile with p-toluenesulphonic acid as a catalyst.

The combination of the less basic (compared to dioxane) solvent acetonitril and the weaker, i.e. non-oxidizing p-toluenesulphonic acid gives a more selective reaction, and also a more simple and exonomic work-up and purification process compared to the above discussed prior art process using dioxane and perchloric acid.

According to a preferred embodiment of the invention the reaction is stopped by the addition of water and adjustment of the pH of the reaction mixture. This might be done by the addition of sodium hydrogen carbonate in water. The product then crystallizes. The crystals are filtered off, dissolved in methylene chloride and methanol and are then crystallized by the addition a suitable hydrocarbon, such as ligroine, hexane, cyclohexane or heptane, giving a crude product, which is then recrystallized in methanol/water to give pure budesonide.

The process according to the invention for the manufacture of budesonide thus consists of two steps.

Step 1. Budesonide crude

16α-hydroxyprednisolone is reacted with butanal in acetonitrile. p-Toluenesulphonic acid is added as a catalyst. The reaction mixture is diluted with water and aqueous sodium hydrogen carbonate. After cooling to 5-15 °C the crystallized product is filtered off and washed with water. The wet or dried substance is then dissolved in methylene chloride. If the substance used is wet the water phase formed upon dissolution is removed. Methanol is added and the resulting crude budesonide is precipitated by the addition of ligroine or another suitable hydrocarbon (e.g. hexane, heptane or cyclohexane) and is then filtered off.

Step 2. Budesonide

The crude budesonide is dissolved in methanol at about 60 °C. The solution is filtered through a cloned filter and the product is crystallized by the addition of water. After cooling to 5-20 °C, filtration and washing with methanol/water the budesonide is dried in vacuum at 40-45 °C.

This process is simplified, more economic and less health hazardous compared to prior art processes.

Working example

The reaction is carried out in a nitrogen atmosphere. 15,4 g p-toluenesulphonic acid is dissolved into 200 ml acetonitrile. To the solution 50,0 g 16α-hydroxyprednisolone and 17.6 ml butanal are added. The temperature rises to 25 °C. After 30 min most of the material is dissolved. Shortly thereafter the product starts to crystallize. After 3 hours the reaction is stopped by the addition of 75 ml aqueous saturated sodium hydrogen carbonate solution, whereupon the product crystallizes. The dried product is dissolved in methylene chloride and methanol and is crystallized by the addition of ligroine (b.p. 40 - 65), giving crude budesonide.

The crude budesonide product is recrystallized from methanol/water giving pure budesonide with isomer ratio A:B = 1:1 (HPLC), $[\alpha]_D^{25}$ 100.0 ° (c = 0.2; CH_2CL_2); M^+ 430 (theor. 430.5)

Claims

1. Process for the manufacture of (22 R,S)-16α,17α-butylidenedioxy-11β,21-dihydroxypregna-1,4-diene-3,20-dione

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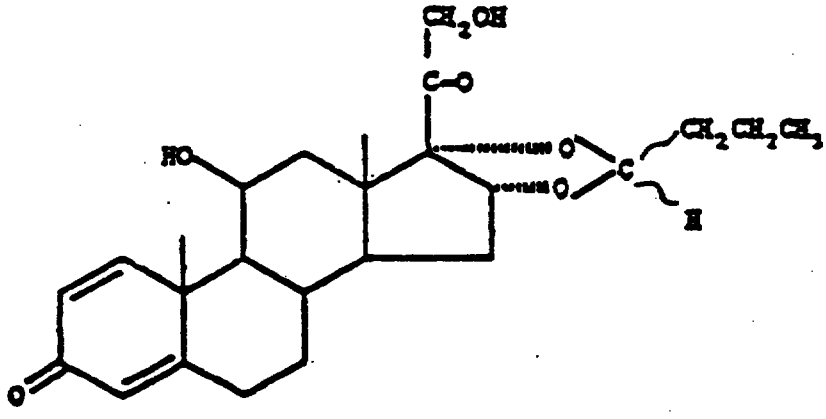
Claims

1. Process for the manufacture of (22 R,S)-16α,17α-butylidenedioxy-11β,21-dihydroxypregna-1,4-diene-3,20-dione

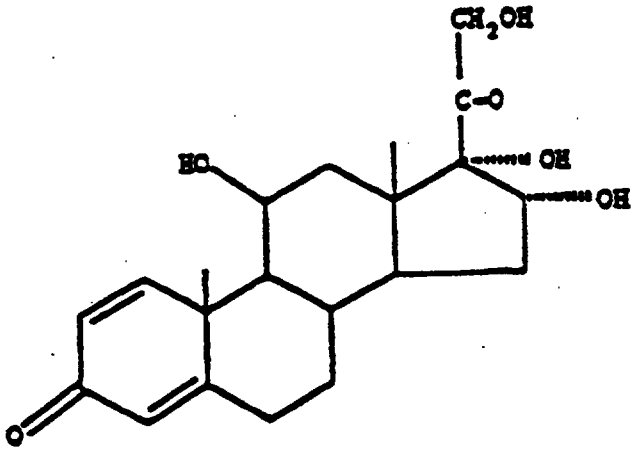
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by reacting 11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione



with butanal, $CH_3CH_2CH_2CHO$ in a solvent medium in the presence of a catalyst, **characterised** in that the reaction is performed in acetonitrile with p-toluenesulphonic acid as a catalyst.

2. Process according to claim 1, **characterized** in that the reaction is terminated by the addition of water and by adjustment of the pH of the reaction mixture.

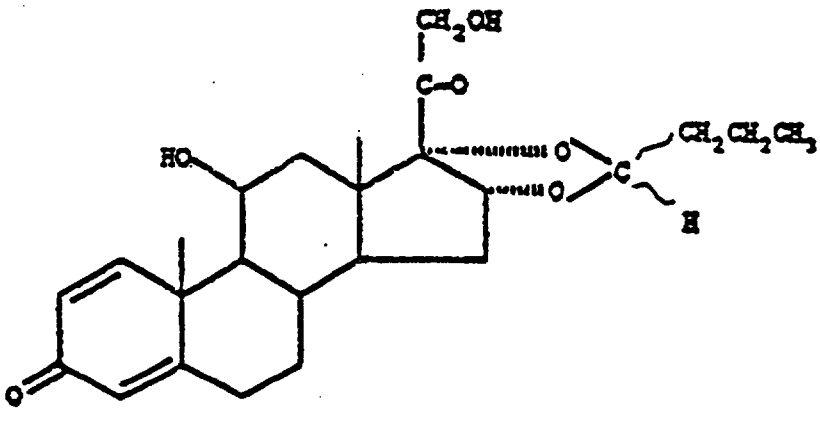
3. Process according to claim 1 or 2, **characterized** in that the crystals obtained upon termination of the reaction are filtered off, dissolved in methylene chloride and methanol and are then crystallized by the addition a suitable hydrocarbon, such as ligroine, hexane, cyclohexane or heptane, giving a crude product, which is then recrystallized in methanol/water to give pure budesonide.

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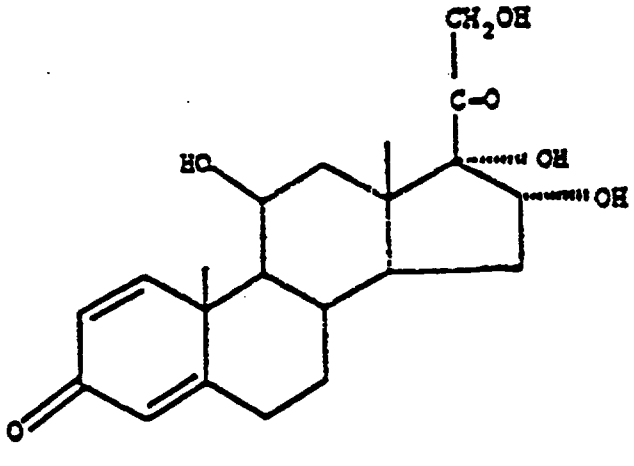
PROCESS FOR THE MANUFACTURE OF BUDESONIDE

Abstract

The present invention relates to a novel process for the manufacture of (22 R,S)-16α,17α-butylidenedioxy-11ß,21-dihydroxy-pregna-1,4-diene-3,20-dione



by reacting 11ß,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione



with butanal, $CH_3CH_2CH_2CHO$ in acetonitrile with p-toluenesulphonic acid as a catalyst.

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☐ Abstract : paged ... to paged ...

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Disclosure of the invention

The object of the invention is to create a novel process, which gives a more selective reaction and a more simple and economic work-up and purification process.

This is achieved with the process according to the present invention, wherein the reaction is performed in acetonitrile with p-toluenesulphonic acid as a catalyst.

The combination of the less basic (compared to dioxane) solvent acetonitril and the weaker, i.e. non-oxidizing p-toluenesulphonic acid gives a more selective reaction, and also a more simple and exonomic work-up and purification process compared to the above discussed prior art process using dioxane and perchloric acid.

According to a preferred embodiment of the invention the reaction is stopped by the addition of water and adjustment of the pH of the reaction mixture. This might be done by the addition of sodium hydrogen carbonate in water. The product then crystallizes. The crystals are filtered off, dissolved in methylene chloride and methanol and are then crystallized by the addition a suitable hydrocarbon, such as ligroine, hexane, cyclohexane or heptane, giving a crude product, which is then recrystallized in methanol/water to give pure budesonide.

The process according to the invention for the manufacture of budesonide thus consists of two steps.

Step 1. Budesonide crude

16α-hydroxyprednisolone is reacted with butanal in acetonitrile. p-Toluenesulphonic acid is added as a catalyst. The reaction mixture is diluted with water and aqueous sodium hydrogen carbonate. After cooling to 5-15 °C the crystallized product is filtered off and washed with water. The wet or dried substance is then dissolved in methylene chloride. If the substance used is wet the water phase formed upon dissolution is removed. Methanol is added and the resulting crude budesonide is precipitated by the addition of ligroine or another suitable hydrocarbon (e.g. hexane, heptane or cyclohexane) and is then filtered off.

Step 2. Budesonide

The crude budesonide is dissolved in methanol at about 60 °C. The solution is filtered through a cloned filter and the product is crystallized by the addition of water. After cooling to 5-20 °C, filtration and washing with methanol/water the budesonide is dried in vacuum at 40-45 °C.

This process is simplified, more economic and less health hazardous compared to prior art processes.

Working example

The reaction is carried out in a nitrogen atmosphere. 15.4 g p-toluenesulphonic acid is dissolved into 200 ml acetonitrile. To the solution 50.0 g 16α-hydroxyprednisolone and 17.6 ml butanal are added. The temperature rises to 25 °C. After 30 min most of the material is dissolved. Shortly thereafter the product starts to crystallize. After 3 hours the reaction is stopped by the addition of 75 ml aqueous saturated sodium hydrogen carbonate solution, whereupon the product crystallizes. The dried product is dissolved in methylene chloride and methanol and is crystallized by the addition of ligroine (b.p. 40 - 65), giving crude budesonide.

The crude budesonide product is recrystallized from methanol/water giving pure budesonide with isomer ratio A:B = 1:1 (HPLC), $[\alpha]_D^{25}$ 100.0 ° (c = 0.2; CH_2CL_2); M^+ 430 (theor. 430.5)

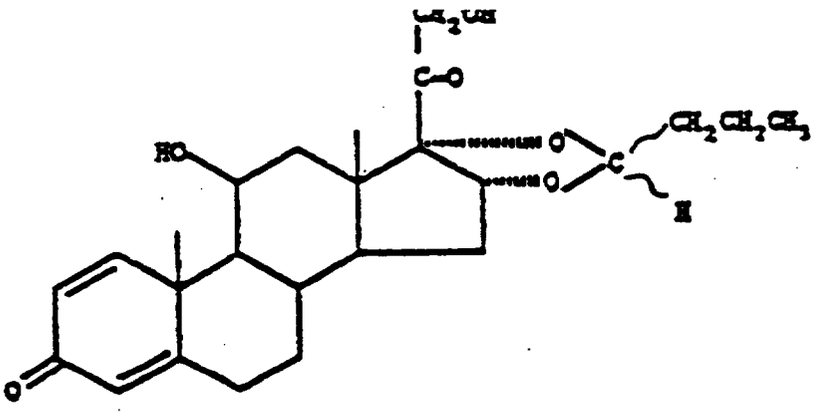
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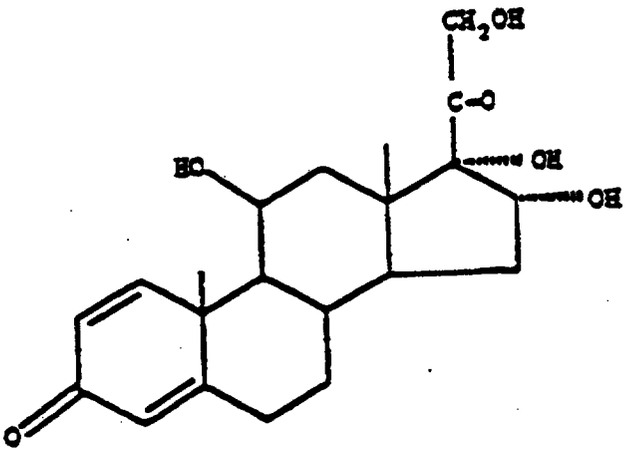
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Claims

1. Process for the manufacture of (22 R,S)-16α,17α-butylidenedioxy-11β,21-dihydroxypregna-1,4-diene-3,20-dione



by reacting 11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione



with butanal, $CH_3CH_2CH_2CHO$ in a solvent medium in the presence of a catalyst, characterised in that the reaction is performed in acetonitrile with p-toluenesulphonic acid as a catalyst.

2. Process according to claim 1, characterized in that the reaction is terminated by the addition of water and by adjustment of the pH of the reaction mixture.

3. Process according to claim 1 or 2, characterized in that the crystals obtained upon termination of the reaction are filtered off, dissolved in methylene chloride and methanol and are then crystallized by the addition a suitable hydrocarbon, such as ligroine, hexane, cyclohexane or heptane, giving a crude product, which is then recrystallized in methanol/water to give pure budesonide.