(CONVENTION. By one or more persons and/or a Company.) 623503 Form 4.

COMMONWEALTH OF AUSTRALIA

Patents Act 1952-1969

CONVENTION APPLICATION FOR A PATENT

(1) Here insert (in full) Name or Names of Applicant or Applicants, followed by Address(es).

I/We RICHTER GEDEON VEGYESZETI GYAR R.T.,
a company incorporated under the laws of Hungary of
19-21, Gyomroi ut, Budapest, X., Hungary.

(2) Here insert Title of Invention.

hereby apply for the grant of a Patent for an invention entitled:(2)
NOVEL STEROID DIOLS, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND PROCESS FOR PREPARING SAME

which is described in the accompanying complete specification. This applications is a Covention application and is based on the application numbered(3)
1156/89

(3) Here insert number(s) of basic application(s).

(4) Here insert Name of basic Country or Countries, and basic date or dates.

for a patent or similar protection made in(4) Hungary on 9th March, 1989.

I/~~My~~/Our address for service is WATERMARK PATENT & TRADEMARK ATTORNEYS 290 Burwood Road, Hawthorn, Victoria, Australia.

DATED this 7th day of March, 1990

FO14962 08/03/90

(5) Signature(s) of Applicant(s) or Seal of Company and Signatures of its Officers as prescribed by its Articles of Association.

By: RICHTER GEDEON VEGYESZETI GYAR R.T.

LOUIS C. GEBHARDT

Registered Patent Attorney

To: THE COMMISSIONER OF PATENTS.

(CONVENTION Company.) Form 8

COMMONWEALTH OF AUSTRALIA

Patents Act 1952-1969

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT OR PATENT OF ADDITION

(1) Here insert (in full) Name of Company.

In support of the Convention Application made by(1) RICHTER GEDEON VEGYESZETI GYAR RT.

(hereinafter referred to as the applicant) for a Patent

(2) Here insert title of Invention.

for an invention entitled:(2) NOVEL STEROID DIOLS, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND PROCESS FOR PREPARING SAME.

(3) Here insert full Name and Address, of Company official authorized to make declaration.

We ~~I~~(3) EVA FRIEDMANN and GABOR GEREB, both of 19-21, Gyomroi ut, Budapest, X., Hungary

do solemnly and sincerely declare as follows:

1. I am authorised by the applicant for the patent to make this declaration on its behalf.

2. The basic application as defined by Section 141 of the Act was made in(4) Hungary on the 9th day of March 19 89, by RICHTER GEDEON VEGYESZETI GYAR R.T.

(4) Here insert basic Country or Countries followed by date or dates and basic Applicant or Applicants.

~~xxxhc xhxxofxxxx 19xxxxxhx~~

(5) Here insert (in full) Name and Address of Actual Inventor or Inventors.

3.(5) The persons name on the reverse hereof

is/are the actual inventor sof the invention and the facts upon which the applicant is entitled to make the application are as follow:

The applicant is the assignee of the invention from the said actual inventors

4. The basic application referred to in paragraph 2 of this Declaration was the first application made in a Convention country in respect of the invention the subject of the application.

DECLARED at Budapest, Hungary

this 19th day of March 19 90

(6) Signature. (6)

To: THE COMMISSIONER OF PATENTS.

Edwd. Waters & Sons,

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(12) PATENT ABRIDGMENT (11) Document No. AU-B-51102/90
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(54) Title
16,17-DIHYDROXYPREGNANE DERIVATIVES

International Patent Classification(s)
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1156/89	**09.03.89**	**HU HUNGARY**

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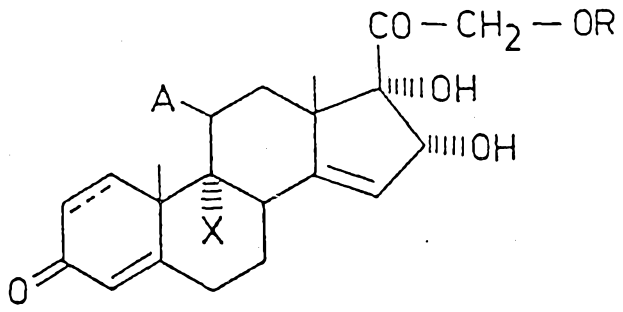
(57) Claim

1. ~~Novel~~ Δ^{14}-16α,17-dihydroxypregnane derivatives of general formula (I),



(I)

wherein

A stands for hydrogen, hydroxyl or trifluoroacetoxy group;

X stands for hydrogen or halogen with the proviso that if A is hydrogen, then X also means hydrogen;

R stands for hydrogen, benzoyl or C_{1-8}alkanoyl group; and

--- represents a single or double bond between two adjacent carbon atoms.

.../2

10. A process for the preparation of an anti-inflammatory pharmaceutical composition, which comprises mixing as active ingredient one or more novel Δ^{14}-16α,17-dihydroxypregnane derivative(s) of general formula (I), wherein A, X, R and the symbol (bond line) ---- are as defined in claim 1, with carriers, diluting, stabilizing, pH- and osmotic pressure-adjusting agents and formulating additives commonly used in the pharmaceutical industry and transforming them to a pharmaceutical composition.

623503

Form 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952-69

COMPLETE SPECIFICATION

(ORIGINAL)

Class Int. Class

Application Number:
Lodged:

Complete Specification Lodged:
Accepted:
Published:

Priority :

Related Art :

Name of Applicant : RICHTER GEDEON VEGYESZETI GYAR R.T.

Address of Applicant : 19-21, Gyomroi ut, Budapest, X., Hungary.

Actual Inventor : CSABA MOLNAR, GYORGY HAJOS, LASZLO SZPORNY, JOZSEF TOTH, ARPAD KIRALY, ANNA BOOR, JANOS CSORGEI, KRISZTINA SZEKELY, LILL FORGACS, GYORGY FEKETE, BULCSU HERENYI, SANDOR HOLLY and JOZSEF SZUNYOG.

Address for Service : **WATERMARK PATENT & TRADEMARK ATTORNEYS.**
LOCKED BAG NO. 5, HAWTHORN, VICTORIA 3122, AUSTRALIA

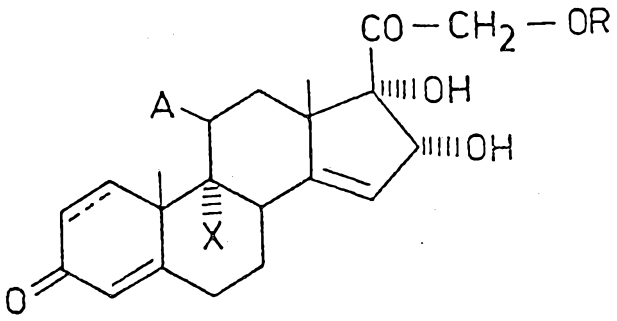
Complete Specification for the invention entitled:

NOVEL STEROID DIOLS, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND PROCESS FOR PREPARING SAME.

The following statement is a full description of this invention, including the best method of performing it known to us :-

NOVEL STEROID DIOLS, PHARMACEUTICAL COMPOSITIONS CONTAINING THEM AND PROCESS FOR PREPARING SAME

The invention relates to novel Δ^{14}-16α,17-dihydroxy-pregnane derivatives of general formula (I),



(I)

wherein

A stands for hydrogen, hydroxyl or trifluoroacetoxy group;

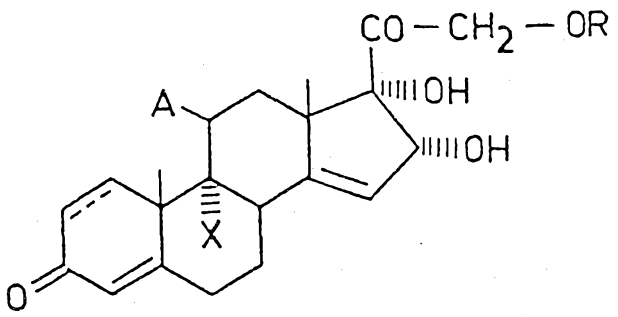
X stands for hydrogen or halogen with the proviso that if A is hydrogen, then X also means hydrogen;

R stands for hydrogen, benzoyl or C_{1-8}alkanoyl group; and

--- represents a single or double bond between two adjacent carbon atoms,

pharmaceutical compositions containing a physiologically effective dose of these compounds and process for preparing these compounds and compositions. Furthermore, the invention relates to a method of treatment, which comprises using these compounds or compositions.

The novel Δ^{14}-16α,17-dihydroxypregnane derivatives of general formula (I)



(I)

according to the invention possess valuable anti-inflammatory action and therefore they can be used as as active ingredients in pharmaceutical compositions and, on the other hand, they can be employed for the preparation of other steroid derivatives similarly possessing therapeutic effects.

Throughout this description the term halogen is meant to include fluorine, chlorine, bromine or iodine, preferably fluorine or chlorine; C_{1-8}alkanoyl means formyl, acetyl, propionyl or any of the various butiryl, valeryl, hexanoyl, heptanoyl or octanoyl groups; in addition to the above groups acyl involves benzoyl group, too. C_{2-4}alkanoic acids mean acetic, propionic, n- and isobutyric acid.

Throughout this description and in the claims alkaline metal defines lithium, sodium and potassium or their cations, respectively, as well as ammonium cation

possessing similar characteristics. Preferable alkaline metals are sodium and potassium. Alkaline earth metal defines one of magnesium, calcium, strontium and barium.

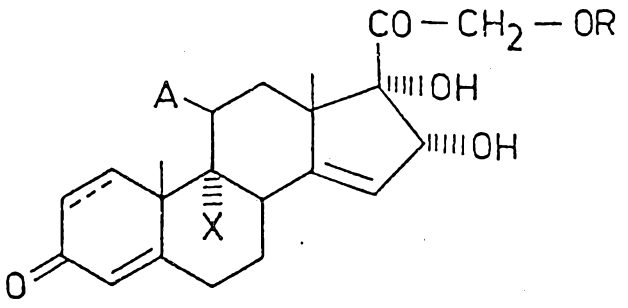
It is known (L. Fieser and M. Fieser: Steroids, Reinhold Publ. Co., page 650, 1967) that patients suffering from rheumatoid arthritis have successfully been cured with cortisone as early as 1949. However, treatments widely carried out with cortisone or hydrocortisone, respectively, have soon shown that native corticosteroids induced a number of undesired (unwanted) side effects in addition to the aimed antiinflammatory effect. (Such harmful side effects were: salt and water household disorders, water retention, osteoporosis, recrudescence of healed gastric ulcers and the like.)

Several modifications were made on the structure of cortisone and hydrocortisone to eliminate these side effects and increase the desired antiinflammatory action.

These research works resulted e.g. in the discovery of prednisolone, triamcinolone, dexamethasone, fluocinolone acetonide as well as novel 3-chloropregnane derivatives (see the Hungarian patent specification No. 182,775). The role of these drugs has not been diminished in the modern therapy up to the present.

In the course of our synthetic work aimed at derivatives having more favourable effects in comparison with those of the known ones it has been found that the novel Δ^{14}-16α,17-dihydroxypregnane derivatives of

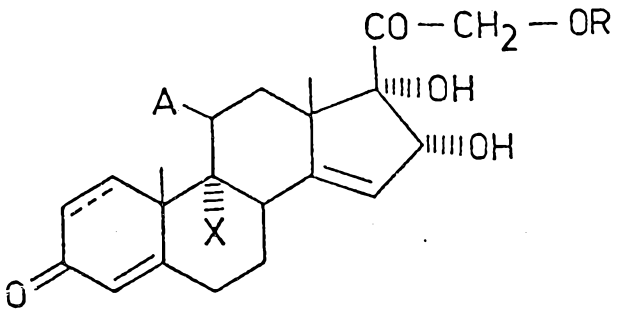
general formula (I)



(I)

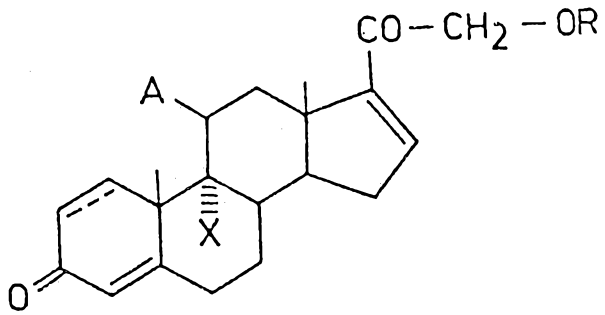
exert a favourable antiinflammatory action and/or they can be used as starting substances for the preparation of other highly effective antiinflammatory corticoids.

According to an other aspect of the invention, there is provided a process for the preparation of the new compounds of general formula (I)



(I)

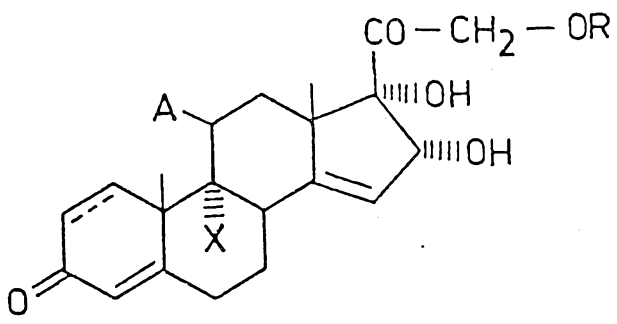
which comprises oxydizing a pregnane derivative of general formula (II)



(II)

wherein A, X and the symbol (bond line) ---- are as defined above and R is as defined above except hydrogen, with an alkaline metal permanganate or alkaline earth metal permanganate in a C_{2-4}alkanoic acid medium in the presence of water and optionally acetone; then,

if desired, hydrolyzing a thus obtained Δ^{14}-16α,17--dihydroxypregnane derivative of general formula (I) wherein A, X and the symbol (bond line) ---- are as defined above and R stands for an acyl group to obtain a compound of general formula (I)



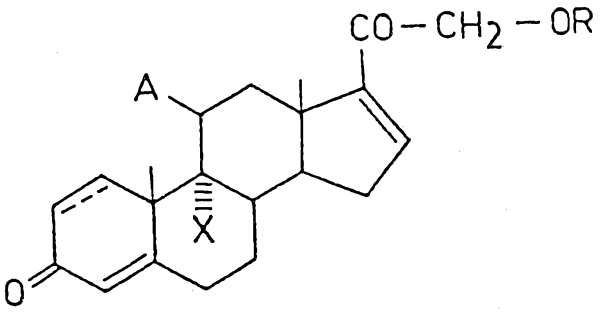
(I)

wherein R stands for hydrogen.

In the course of the process according to the invention, the introduction of hydroxyl groups into 16α- and 17-positions as well as the Δ^{14} double bond formation proceed in a single-step reaction in the compounds of general formula (II) containing the Δ^{16} double bond. This transformation is surprising since no transformation of this kind has been described in the theoretical literature discussing the oxidation of unsaturated bonds with permanganate. A similar

transformation has only been reported in a single literature reference (J. Chem. Soc. 1955, 4383) where the oxidation of 3β-acetoxypregna-5,16-dien-20-one was discussed; it has been stated that in the course of the oxidation, besides 3β-acetoxy-16α,17α-dihydroxypregn-5-en-20-one, its 14,15-dehydro derivative was also formed as a result of a side reaction. The yield of the side product was low and not discussed in detail in the above paper.

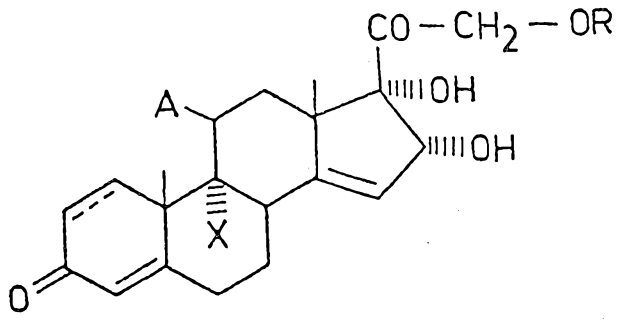
According to a preferred embodiment of the process of the invention the pregnane derivative of general formula (II)



(II)

used as starting substance is conveniently dissolved either in a mixture of acetic acid and acetone or in glacial acetic acid; then an aqueous potassium permanganate solution is portionwise added to the above solution at a temperature below 0 °C (suitably at a temperature between -10 to -30°C, preferably between -20 °C and -25 °C) in case of using a mixture of acetic acid and acetone or at a temperature between 0 to 20°C, about 10 °C in case of using glacial acetic acid. The aqueous potassium permanganate solution is used in an excess of 0.8 to 1.0

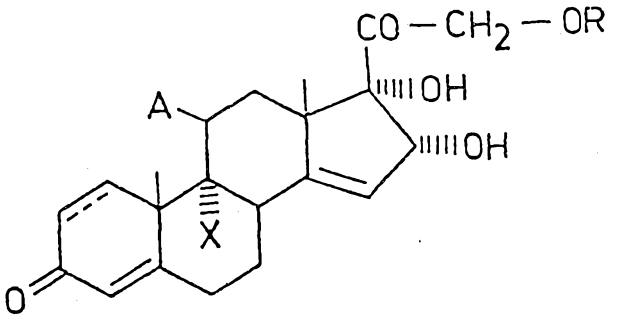
mole calculated for the steroid compound. This reaction proceeds within a period of 5 to 30 minutes depending on the starting substance used. During this period the temperature of the mixture is kept constantly. After termination of the reaction the mixture is poured into water to precipitate the Δ^{14}-16α,17-dihydroxypregnane derivatives of general formula (I)



(I)

wherein R stands for C_{1-8}alkanoyl group or benzoyl group.

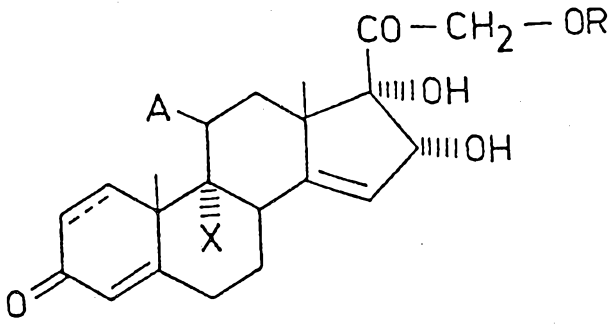
The thus obtained products of general formula (I)



(I)

wherein R is C_{1-8}alkanoyl or benzoyl group can be hydrolyzed by dissolving in a protic solvent, e.g. methanol and treating with an aqueous alkaline metal carbonate or, suitably, with aqueous perchloric acid solution.

The Δ^{14}-16α,17-dihydroxypregnane derivatives of general formula (I)



(I)

according to the invention possess valuable glucocorticoid effects.

Two principal (essential) demands are set up against topically used steroid antiinflammatory drugs: a) they should be as active as possible in various animal experiments used for investigating the antiinflammatory action; and b) they should induce the lowest harmful systemic side effect. This latter effect can be well characterized by the thymus weight-decreasing action (involution).

The tests used for investigation of the anti-inflammatory action of the compounds according to the invention are described hereinafter. Prednisolone (11β,17α,21-trihydroxypregna-1,4-dien-3,20-dione) was used as reference drug in these tests.

1) The oxazolone-induced contact dermatitis model

[Br. J. Pharmac. 43, 403 (1971)]

Male CFLP mice weighing 20 to 24 g each were used in this test. The abdominal skin of the animals was

shaved and 0.1 ml of a 2% oxazolone solution in olive oil was applied onto the skin. Seven days following this treatment an inflammation response was elicited by applying 10 µl of a 2% oxazolone solution in acetone onto the left ears of the animals. The right ears were used as control. After 24 hours the ears of the animals were cut off and weighed. On investigation of the test compounds, the substance under test was added in various concentrations to the acetone solution containing oxazolone. For evaluation the diminution of the ear weight increase was expressed as "percentage of inhibition" in comparison to the control treated with no active agent. Ten mice were used in each group.

2) The local granuloma sac model

[Recent Progr. Hormone Res. 8, 117 (1953); Arzneim.-Forsch. 27, 11 (1977)].

This method was used to investigate the anti--exudative action of the topically administered glucocorticoids. The systemic side effect (thymus involution) was observed on the same experimental animals.

Groups consisting of 10 female RG Hann Wistar rats each weighing 130 to 150 g were used. After shaving the back of the animals 25 ml of air were injected beneath the back skin and 1 ml of 2% croton oil inducing inflammation was introduced to the air sac. After 5 days the content of the sac was sucked off and once 3 doses each of the glucocorticoids to be tested or prednisolone,

respectively, in a volume of 0.5 ml suspension in Tween 80 were administered by an injection syringe. On the 10th day following the start of the experiment the animals were sacrificed and the exudate liquid of the sac (expressed as ml) was measured. The percentage of the antiinflammatory effect was calculated based on the decrease in the volume of exudate related to that of the control.

Then, the thymi of the animals were excised and the harmful systemic side effect of the test compounds was calculated as percentage based on the comparison of the thymus weight of animals treated with the test compounds to that of the untreated control group.

The above investigations gave the following results.

Antiinflammatory effect on the oxazolone-induced contact dermatitis model

Compound	Dose (µg/ear)	Ear weight increase (%)	Inhibition (%)
Control	0	108.8	0
Prednisolone	0.3	86.1	20.8
Prednisolone	1.0	76.9	29.3
Prednisolone	3.0	68.6	36.9
Example No. 3	0.3	86.2	20.8
Example No. 3	1.0	75.5	30.6
Example No. 3	3.0	58.1	46.6
Example No. 4	0.3	77.2	29.1
Example No. 4	1.0	68.8	36.8
Example No. 4	3.0	60.4	44.5

2) Antiinflammatory effect on the local granuloma sac model

Compound	Dose (mg/sac)	Exudate (ml)	Inhibition (%)	Thymus involution (%)
Control	0	15.3	0	0
Prednisolone	1	11.7	23.6	27.2
Prednisolone	3	9.2	39.9	44.1
Prednisolone	9	5.8	62.2	55.5
Example No. 3	1	10.3	32.7	28.7
Example No. 3	3	9.2	39.9	33.1
Example No. 3	9	3.8	74.9	37.7
Example No. 4	1	10.4	32.1	21.1
Example No. 4	3	7.5	50.8	23.8
Example No. 4	9	5.8	62.3	33.9

It is unambiguously evident from the results of the above investigations that the novel Δ^{14}-16α,17-dihydroxy-pregnane derivatives of general formula (I) according to the invention exert on both models a highly significant local (topical) antiinflammatory activity exceeding that of the reference substance and their harmful systemic effect (thymus involution) is lower than that of prednisolone.

The invention is illustrated in detail by the following non limiting Examples.

Example 1

Preparation of 11β,16α,17,21-tetrahydroxypregna-4,14-dien-3,20-dion-21-acetate

A solution containing 1 g (2.588 mmol) of 11β,21-dihydroxypregna-4,16-dien-3,20-dion-21-acetate in 40 ml of glacial acetic acid is cooled to 13 to 15 °C and 0.45 g (2.847 mol) of potassium permanganate dissolved in 40 ml of water is portionwise added at the same temperature during 5 to 10 minutes. After the addition, the excess of the oxidizing agent is decomposed by adding 0.6 g of sodium pyrosulfite dissolved in 4.0 ml of water to the reaction mixture. After stirring for 15 minutes the reaction mixture is poured into 500 ml of deionized water, stirred for 1 hour, filtered and the precipitate is washed with water up to neutral. After drying the product is recrystallized from ethyl acetate to give 0.48 g (44.3%) of the title compound, m.p.: 220-225 °C.

Example 2

Preparation of 11β,16α,17,21-tetrahydroxypregna-1,4,14-trien-3,20-dion-21-acetate

10 g (26.0 mmol) of 11β,21-dihydroxypregna-1,4,16-trien-3,20-dion-21-acetate are dissolved in 400 ml of glacial acetic acid at 15 °C, then 4.52 g (28.6 mmol) of potassium permanganate dissolved in 400 ml of water are portionwise added at the same temperature during 5 to 10 minutes. Thereafter, the excess of permanganate

is decomposed by adding 5.94 g of sodium pyrosulfite dissolved in 40 ml of water. After stirring for 20 minutes the reaction mixture is poured into 10 litres of water. After stirring for 1 hour the suspension is filtered, washed up to neutral and dried. The crude product obtained is recrystallized from ethyl acetate to give 5.11 g (47.2%) of the title substance, m.p.: 238-243 °C.

Example 3

Preparation of 11β,16α,17,21-tetrahydroxypregna-1,4,14-trien-3,20-dion-21-acetate

After dissolving 55 g (143.1 mmol) of 11β,21-dihydroxypregna-1,4,16-trien-3,20-dion-21-acetate in 1100 ml of glacial acetic acid, 1650 ml of acetone are added and the solution is cooled between -20 °C and -25 °C.

20.35 g (128.8 mmol) of potassium permanganate are dissolved in 440 ml of water, cooled to 0 °C and portionwise added to the above solution of the steroid maintained at -25 °C during 10 to 15 minutes. After 5 minutes the reaction mixture is examined by thin layer chromatography [DC Alufolien Kieselgel 60 F_{254} (Merck) by using a developing system containing chloroform/ether/methanol in 70:30:2 volume ratio and detecting with phosphoric acid]. After about 15 minutes no starting material can be detected in the reaction mixture. The mixture is poured into a solution

containing 27 g of sodium pyrosulfite in 27.5 litres of ice-water under stirring. The suspension obtained is stirred at 0 °C for 1 hour, then filtered. The precipitate is washed up to neutral, dried and recrystallized from ethyl acetate to give 36.14 g (60.7%) of the title compound, m.p.: 240-243 °C.

Example 4

Preparation of 11β,16α,17,21-tetrahydroxypregna-1,4,14-trien-3,20-dione

0,40 g (2.87 mmol) of potassium carbonate dissolved in 6 ml of water is added to a solution of 2 g (4.78 mmol) of 11β,16α,17,21-tetrahydroxypregna-1,4,14-trien-3,20-dion-21-acetate in 400 ml of methanol under nitrogen. After 15 minutes the pH value of the solution is adjusted to 6.5 by adding acetic acid, the mixture is evaporated to a volume of 15 to 20 ml under reduced pressure and the residue is poured into 500 ml of ice-water. After stirring for 30 minutes the suspension is filtered and the precipitate is dried. The crude product obtained is recrystallized from an 1:3 (volume ratio) mixture of chloroform/methanol to obtain 1.2 g (66.7%) of the title compound, m.p.: 240-242 °C.

Example 5

Preparation of 16α,17,21-trihydroxypregna-4,14-dien-3,20-dion-21-acetate

0.53 g (3.373 mmol) of potassium permanganate dissolved in 5 ml of water is portionwise added at

20 °C during 5 minutes to a solution containing 1 g (2.699 mmol) of 21-hydroxypregna-4,16-dien-3,20-dion-21-acetate dissolved in 10 ml of glacial acetic acid at room temperature. After addition, the excess of permanganate is decomposed by adding a solution of 0.72 g of sodium pyrosulfite in 5 ml of water to the reaction mixture, then the mixture is poured into 500 ml of water containing 16.7 g of potassium hydrogen carbonate. After stirring for 1 hour the suspension is filtered, the precipitate is washed with water and dried to give 0.50 g (46.0%) of the title product, m.p.: 215-220 °C.

Example 6

Preparation of 16α,17,21-trihydroxypregna-1,4,14-trien-3,20-dion-21-acetate

11 ml of acetone are added to a solution containing 0.35 g (0.95 mmol) of 21-hydroxypregna-1,4,16-trien-3,20-dion-21-acetate in 7 ml of glacial acetic acid and the solution is cooled to a temperature between -20 °C and -25 °C. Thereafter, 0.23 g (1.45 mmol) of potassium permanganate dissolved in 2 ml of water is portionwise added at the same temperature. After 15 minutes the reaction mixture is poured into 200 ml of ice-water containing 0.3 g of sodium pyrosulfite. After stirring for 45 minutes the suspension is filtered, the precipitate is washed and dried to obtain 0.20 g (52.6%) of the title compound, m.p.: 220-223 °C.

Example 7

Preparation of 9α-fluoro-11β,16α,17,21-tetrahydroxy-pregna-1,4,14-trien-3,20-dion-21-acetate

1.0 g (2.48 mmol) of 9α-fluoro-11β,21-dihydroxypregna-1,4,16-trien-3,20-diol-21-acetate is dissolved in 20 ml of glacial acetic acid, 30 ml of acetone are added, then the solution is cooled to a temperature between -20 °C and -25 °C. A solution containing 0.36 g (2.28 mmol) of potassium permanganate in 10 ml of water is portionwise added at the same temperature. After 20 minutes the reaction mixture is poured into 500 ml of ice-water containing 0.5 g of sodium pyrosulfite. After stirring for 1 hour the suspension is filtered, the precipitate is washed with cold water and dried to give 0.79 g (73.2%) of the title compound, m.p.: 242-247 °C.

Example 8

Preparation of 11β,16α,17,21-tetrahydroxypregna-1,4,14-trien-3,20-dion-11-trifluoroacetate-21-acetate

After dissolving 5 g (10.41 mmol) of 11β-trifluoro-acetoxy-21-acetoxypregna-1,4,16-trien-3,20-dione in a mixture comprising 100 ml of glacial acetic acid and 150 ml of acetone the solution is cooled to a temperature between -20 °C and -25 °C, then 1.48 g (9.37 mmol) of potassium permanganate dissolved in 25 ml of water are added at the same temperature. The excess of the oxidizing agent is decomposed by adding 2.0 g of sodium hydrogen sulfite dissolved in 10 ml of water, then the

mixture is poured into 2500 ml of ice-water. After stirring for 1 hour the suspension is filtered, the precipitate is washed with a little volume of cold water and dried to give 3.20 g (60.0%) of the title product, m.p.: 119-124 °C.

Example 9

Preparation of 11β,16α,17,21-tetrahydroxypregna-1,4,14-trien-3,20-dion-21-benzoate

150 ml of acetone are added to a solution containing 5 g of 11β,21-dihydroxypregna-1,4,16-trien-3,20-dion-21-benzoate in 100 ml of glacial acetic acid, the solution is cooled to a temperature between -20 °C and -25 °C and 1.59 g of potassium permanganate dissolved in 25 ml of water are added at the same temperature. The excess of the oxidizing agent is decomposed by adding 2.5 g of sodium hydrogen sulfite dissolved in 10 ml of water, then the mixture is poured into 2500 ml of ice-water. After stirring for 1 hour the suspension is filtered, the precipitate is washed with a little volume of cold acetone-water mixture and dried to obtain 3.83 g (71.5%) of the title compound, m.p.: 155-158 °C.

The following Δ^{14}-16α,17-dihydroxypregnane derivative of general formula (I) were also prepared as described in Examples 1 to 9:

11β,16α,17,21-tetrahydroxypregna-1,4,14-trien-3,20-dion-21-butyrate; and

11β, 16∝, 17, 21-tetrahydroxypregna-1, 4, 14-trien-3, 20-dion-21-caproate.

Example 10

Preparation of ointment

Components:

Δ^{14}-16∝-hydroxyprednisolone-21-acetate	0.5 g
methyl p-hydroxybenzoate	0.1 g
Polysorbate 60	6.0 g
isopropyl myristate	6.0 g
1,2-propylene glycol	11.0 g
liquid paraffin	14.0 g
cetyl stearyl alcohol	6.0 g
desalted water	ad 100.0 g

Isopropyl myristate, liquid paraffin and cetyl stearyl alcohol are molded (fatty phase). Methyl p-hydroxybenzoate is dissolved in 20 ml of desalted water while heating. The active agent is dissolved in 1,2-propylene glycol. To the molded fatty phase Polysorbate 60 and the half of the necessary amount of water are added, mixed up, the mixture is cooled to 40°C and the solutions of the active agent and methyl p-hydroxybenzoate are added thereto. The mixture is stirred until it is cooled, the mass thereof given above is completed with water and after homogenization the ointment is filled into tubes.

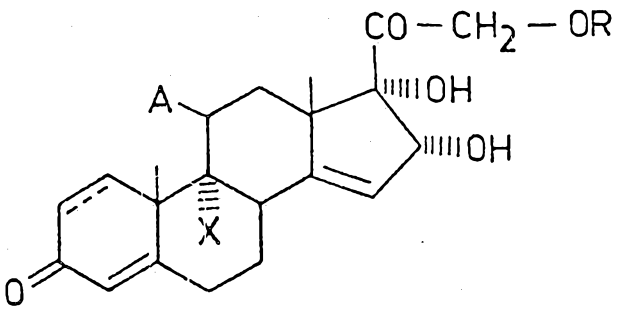
The composition is administered externally onto the inflamed skin.

The used concentration may be about 0.25 to 1.0% by wt. when administered topically.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

~~Claims~~

1. ~~Novel~~ Δ^{14}-16α,17-dihydroxypregnane derivatives of general formula (I),



(I)

wherein

A stands for hydrogen, hydroxyl or trifluoroacetoxy group;

X stands for hydrogen or halogen with the proviso that if A is hydrogen, then X also means hydrogen;

R stands for hydrogen, benzoyl or C_{1-8}alkanoyl group; and

--- represents a single or double bond between two adjacent carbon atoms.

2. A compound selected from the group consisting of 11β,16α,17,21-tetrahydroxypregna-4,14-dien-3,20-dion-21-acetate,

11β,16α,17,21-tetrahydroxypregna-1,4,14-trien-3,20-dion-21-acetate,

16α,17,21-trihydroxypregna-4,14-dien-3,20-dion-21-acetate,

16α,17,21-trihydroxypregna-4,14-dien-3,20-dione,

16α,17,21-trihydroxypregna-1,4,14,-trien-3,20-dion-21-acetate,

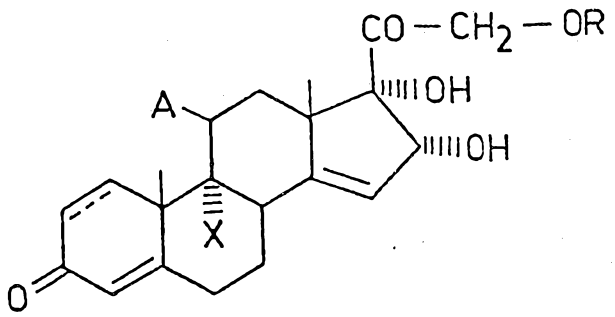
9α-fluoro-11β,16α,17,21-tetrahydroxypregna-1,4,14-trien-3,20-dion-21-acetate,

11β,16α,17,21-tetrahydroxypregna-1,4,14-trien-3,20-dion-11-trifluoroacetate-21-acetate, and

11β,16α,17,21-tetrahydroxypregna-1,4,14-trien-3,20-dion-21-benzoate.

3. An antiinflammatory pharmaceutical composition, which comprises as active ingredient a therapeutically effective dose of one or more Δ^{14}-16α,17-dihydroxypregnane derivative(s) of general formula (I), wherein A, X, R and the symbol (bond line) ---- are as defined in claim 1, in admixture with carriers and/or diluting, stabilizing, pH- and osmotic pressure-adjusting agents and formulating additives commonly used in the pharmaceutical industry.

4. A process for the preparation of the ~~novel~~ Δ^{14}-16α,17-dihydroxypregnane derivatives of general formula (I),



(I)

wherein

A stands for hydrogen, hydroxyl or trifluoroacetoxy group;

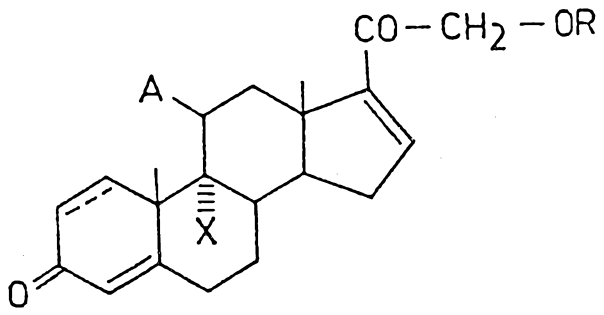
X stands for hydrogen or halogen with the proviso that if A is hydrogen, then X also means hydrogen;

R stands for hydrogen, benzoyl or C_{1-8}alkanoyl group; and

--- represents a single or double bond between two adjacent carbon atoms,

which comprises

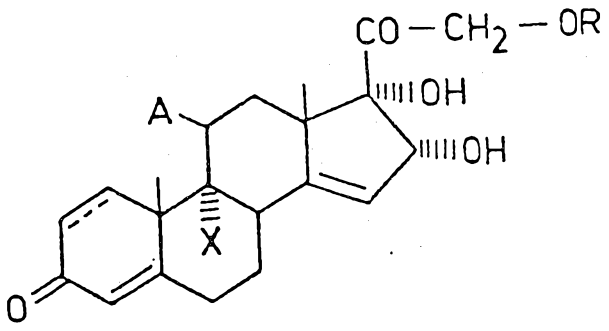
oxidizing a pregnane derivative of general formula (II),



(II)

wherein A, X and the symbol (bond line) ---- are as defined above and R is as defined above except hydrogen, with an alkaline metal permanganate or alkaline earth metal permanganate in a C_{2-4}alkanoic acid medium in the presence of water and optionally acetone; then,

if desired, hydrolyzing a thus obtained Δ^{14}-16α,17-dihydroxypregnane derivative of general formula (I), wherein A, X and the symbol (bond line) ---- are as defined above and R stands for an acyl group, to obtain a compound of general formula (I)



(I)

wherein R stands for hydrogen.

5. A process as claimed in claim 4, which comprises carrying out the oxidation by using an aqueous alkaline metal permanganate or alkaline earth metal permanganate solution in glacial acetic acid medium.

6. A process as claimed in claim 4, which comprises carrying out the oxidation by using an aqueous alkaline metal permanganate or alkaline earth metal permanganate solution in glacial acetic acid medium in the presence of acetone.

7. A process as claimed in any of the claims 4 to 6, which comprises using potassium permanganate as an alkaline metal permanganate.

8. A process as claimed in claim 5, which comprises carrying out the oxidation at a temperature between 0 ^{o}C and 20 ^{o}C.

9. A process as claimed in claim 6, which comprises carrying out the oxidation at a temperature between -10 ^{o}C and -30 ^{o}C.

10. A process for the preparation of an anti-inflammatory pharmaceutical composition, which

comprises mixing as active ingredient one or more novel Δ^{14}-16α,17-dihydroxypregnane derivative(s) of general formula (I), wherein A, X, R and the symbol (bond line) ---- are as defined in claim 1, with carriers, diluting, stabilizing, pH- and osmotic pressure-adjusting agents and formulating additives commonly used in the pharmaceutical industry and transforming them to a pharmaceutical composition.

11. Method for treating mammals including human suffering from an inflammantory disease, characterized by using a therapeutically effective amount of a novel Δ^{14}-16α,17-dihydroxypregnane derivative of general formula (I) wherein A, X, R and the symbol (bond line) ---- are as defined in claim 1, alone or in form of a pharmaceutical composition.

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