1 442 925

PATENT SPECIFICATION

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(54) NOVEL TRIAMCINOLONE DERIVATIVE

(71) We, AMERICAN CYANAMID COMPANY, a corporation organised and existing under the laws of the State of Maine, United States of America, of Berdan Avenue, Township of Wayne, State of New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a new triamcinolone derivative.

The new triamcinolone derivative of this invention is 16α,17α-cyclopentylidenedioxy - 9α - fluoro - 11β,21 - dihydroxy - 1,4 - pregnadiene - 3,20-dione 21-acetate. This compound is more effective by the vasoconstriction assay than many steroids used in the past as a topical anti-inflammatory agent.

The steroid of the present invention, 16α,17α-cyclopentylidenedioxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione 21-acetate may be prepared by treating a suspension of 9α-fluoro-11β,16α,17,21-tetrahydroxy-1, 4-pregnadiene-3,20-dione (triamcinolone, a commercially available product) with perchloric acid and cyclopentanone. The suspension is stirred until solution is complete and then stored in a cold room. The product 16α,17α-cyclopentylidenedioxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione is collected, washed with n-hexane and air dried.

The above product is treated with pyridine and acetic anhydride, stirred for about 2 1/2 hours and then poured into a mixture of ice and water. The steriod acetate is collected by filtration and air dried.

The 16α,17α-cyclopentylidenedioxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione 21-acetate may be incorporated with a pharmaceutically acceptable carrier to form a variety of pharmaceutical compositions for topical application at concentrations of, for example, 0.01% to 0.5%, by weight based on the total weight of the steroid and pharmaceutical carrier.

The pharmaceutical compositions containing the steroid of this invention may take the form of any of the standard pharmaceutical topical preparations such as solutions, suspensions, lotions, ointments, creams, unguents, sprays, powders and foams. Excipients used in such preparations may include buffers such as phosphate, citrate or tartrate, surfactants such as polyoxyethylene (20) sorbitan monooleate (polysorbate 80) which is a complex mixture of polyoxyethylene ethers of mixed partial oleic esters of sorbitol anhydrides and oxylated tertiary octylphenol formaldehyde polymer, which is a surface tension reducing agent. Preservatives such as methyl and propyl parabens, which are the methyl and propyl esters of *p*-hydroxybenzoic acid, potassium sorbate and benzyl alcohol can be used. Oils, waxes and fats are useful as emollients and ointment or emulsion bases such as petroleum, wool fat (anhydrous lanolin), squalane and spermaceti can also be useful. Stabilizers such as talc, clays, vegetable colloids, carboxymethylcellulose and carboxypolymethylene, and perfumes or fragrances such as lavender, lemon and gardenia, may be found useful. Such preparations may be packaged in pressure containers and added to appropriate propellants such as trichlorofluoromethane, dichlorodifluoromethane, or 1,2-dichloro-1,1,2,2-tetrafluoroethane which are commonly used.

The compound 16α,17α-cyclopentylidenedioxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione 21-acetate was tested in comparison with a variety of

other steroids having known topical anti-inflammatory activity according to a method measuring vasoconstriction. This assay is described in the following publications: (1) "Bioassay System for Formulations of Topically Applied Glucocorticosteroids", R. B. Stoughton, Archives of Dermatology, *106*, 825—827 (1972); (2) "Topical Activities of Betamethasone Esters in Man", A. W. McKenzie and R. M. Atkinson, Archives of Dermatology, *89*, 741—746 (1964); (3) "Method for Comparing Percutaneous Absorption of Steroids", A. W. McKenzie and R. B. Stoughton, Archives of Dermatology, *86*, 608—610 (1962); (4) "Percutaneous Absorption of Steroids", A. W. McKenzie, Archives of Dermatology *86*, 611—614 (1962).

The various compounds were prepared for testing by formulating each at three different concentrations 0.005%, 0.025% and 0.125% in an ointment vehicle consisting of 10% polyethylene glycol 400 in white petrolatum. These formulations were applied to the forearm skin at a dose of 10 mg. in an area 2.0 to 2.5 cm. in diameter. Persons with normal skin were used. Two steroids (each at the above three concentrations, plus a vehicle placebo) were evaluated in a panel of 10 subjects, using four sites on each ventral forearm. The sites were randomized and a blank control on each arm was always included. The ventral forearm sites were then protected by an elevated plastic guard which allowed the dose to remain in place and ambient conditions to prevail.

The sites were thoroughly washed 20 hours after application and two sets of readings were taken, one in the A.M. and the second in the P.M. Blanching (vasoconstriction) was determined on a graded basis: 0 = no blanching; + = just detectable blanching; ++ = definite but not maximum; +++ = marked maximum blanching. This system allows 30 readings for each steroid in direct comparison with another under the same conditions, in the same subjects, at the same time.

The results appear in the following Table, wherein the number of pluses for each steroid for the A.M. and P.M. readings have been totaled.

TABLE

Compound	Total Pluses
16α,17α-cyclopentylidenedioxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione 21-acetate	103
16α,17α-cyclopentylidenedioxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione	61
9α-fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxy-1,4-pregnadiene-3,20-dione 21-acetate	65
16α,17α-(1-ethylpropylidenedioxy)-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione	60
2α,9α-difluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxy-progesterone 21-acetate	55
9α-fluoro-11β,21-dihydroxy-16α,17α-isopropylidenedioxy-4-pregnene-3,20-dione 21-valerate	62

The compound of the present invention is far superior to other related steroids tested.

The following Examples will serve to illustrate the invention and show the preparation of the compound of the invention and formulations using the present compound. Example 1 relates to an intermediate.

Example 1.

Preparation of 16α,17α-Cyclopentylidenedioxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione

A 15 gm. (38.1 mmole) portion of 9α-fluoro-11β,16α,17,21-tetrahydroxy-1,4-

pregnadiene-3,20-dione is placed in a 500 ml. round bottom flask equipped with a magnetic stirrer bar and stopper. A 200 ml. (2.26 moles) portion of cyclopentanone and 30 drops of perchloric acid are added and the suspension is stirred at room temperature for about 1 1/2 hours. A pale yellow solution results. This solution is stored in a cold room for about 1 hour. A precipitate forms which is recovered by filtration, washed with n-hexane and air dried yielding 3.6 gm. of product. The filtrate is concentrated under reduced pressure to about 25 ml. A solution of sodium bicarbonate is added until the concentrate is alkaline. A 25 ml. portion of chloroform is added and after mixing the concentrate is stored in a cold room overnight. A precipitate forms which is collected by filtration, washed with water until the washings are neutral to pH paper and air dried yielding an additional 8.4 gm. of product. The second filtrate is evaporated under reduced pressure to an oil. Acetone and activated charcoal are added, the mixture is filtered through diatomaceous earth and the filtrate is concentrated on a steam bath while adding n-hexane to the point of incipient crystallization. The mixture is allowed to stand overnight. The precipitate is collected by filtration, washed with acetone:n-hexane (1:9) and air dried yielding 2.7 gm. of product. The total yield for the subject product is 14.7 gm.

Example 2.

Preparation of 16α,17α-Cyclopentylidenedioxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione 21-acetate

An 11.1 gm. (24.1 mmole) portion of the product of Example 1 is placed in a 250 ml. round bottom flask. A 100 ml. portion of pyridine is added and the mixture is stirred to a complete solution. A 5.5 ml. (54.6 mmole) portion of acetic anhydride is added dropwise and the mixture is stirred for 2 1/2 hours. An 11 ml. portion of methanol is added and the mixture is stirred an additional hour. This mixture is concentrated under reduced pressure to about 10—15 ml. and then poured slowly into a mixture of ice, water and dilute hydrochloric acid. This mixture is stirred and the solid which forms is collected by filtration, washed with water to a neutral pH and air dried yielding 11.5 gm. This solid is taken up in hot acetone, treated with activated charcoal and filtered while hot through diatomaceous earth. The filtrate is concentrated on a steam bath while adding n-hexane to the point of incipient crystallization. This mixture is allowed to cool to room temperature. The solid which forms is collected by filtration, washed with acetone:n-hexane (1:14) and air dried yielding 7.0 gm. of the desired product.

Example 3.

Topical Cream Formulations Containing Variable Percentages of 16α,17α-Cyclopentylidenedioxy - 9α - fluoro - 11β,21 - dihydroxy - 1,4 - pregnadiene - 3,20-dione 21-acetate

Ingredient	Percent Range (w/w)
Steroid	0.01—0.5
Glyceryl monostearate N.F.	1—5
Squalane*	1—5
Polysorbate 60**	1—5
Polysorbate 80 U.S.P.***	1—5
Spermaceti	5—20
Stearyl alcohol U.S.P.	5—20
Sorbitol solution U.S.P.	1—10
Preservatives	3—5
Distilled water qs ad	100

* Squalane = 2,6,10,15,19,23-Hexamethyltetracosane
** Polysorbate 60 = Polyoxyethylene sorbitan monostearate
*** Polysorbate 80 = Polyoxyethylene sorbitan monooleate

The ingredients are mixed in a conventional manner for preparing a pharmaceutical topical cream providing a white cream which may contain, for example, depending upon selected percentage of ingredients, such steroid percentages as 0.01, 0.025, 0.1 or 0.5%.

Example 4.

Topical Ointment Formulations Containing Variable Percentages of 16α,17α-Cyclopentylidenedioxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione 21-acetate

Ingredient		Percent Range (w/w)
Steroid		0.01—0.5
Polyethylene glycol 400 U.S.P.		5—20
White Petrolatum U.S.P.	qs ad	100

The ingredients are blended in a conventional manner providing a colorless topical ointment, which may provide, for example, such steroid percentages as 0.01, 0.025, 0.10 or 0.50%.

If desired, an antibacterial component such as neomycin may be added to the formulation in amounts ranging from 0.1% to 3% (w/w), as the sulfate in a micronized form.

Example 5.

Topical Foam Formulation Containing 16α,17α-Cyclopentylidenedioxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione 21-acetate

Ingredient	Weight Range/ Container
Steroid	0.5—50 mg.
"Arlace" 60*	20—50 mg.
"Myrj" 59**	300—500 mg.
Glyceryl monostearate	100—300 mg.
Cetyl alcohol	70—100 mg.
Sorbitol 70%	300—400 mg.
Propylparaben	3—5 mg.
Methylparaben	10—15 mg.
Veegum Neutral	15—20 mg.
Distilled water	6—10 mg.
"Freon" 12/114 (40/60)***	1.3—2.0 gm.

* "Arlace" = Sorbitan monostearate ("Arlace" is a registered Trade Mark)
** "Myrj" = Polyoxyethylene derivative of fat forming fatty acids ("Myrj" is a registered Trade Mark)
*** "Freon" = Dichlorodifluoromethane/1,2 - dichloro - 1,1,2,2 - tetrafluoroethane ("Freon" is a registered Trade Mark)

The ingredients are blended in a conventional manner, filled in containers and then pressurized with "Freon".

Example 6.

Ophthalmic Ointment Containing Variable Percentages of 16α,17α-Cyclopentylidenedioxy-9α-fluoro-11β,21-dihydroxy-1,4-pregnadiene-3,20-dione 21-acetate

Ingredient		Percent Range (w/w)
Steroid		0.01—0.50
Mineral Oil, Light N.F.		1—5
White Petrolatum U.S.P.	qs ad	100

The ingredients are blended in a conventional manner providing an off-white ophthalmic or otic preparation. Neomycin may be added as the micronized sulfate salt if an antibacterial ingredient is desired.

Example 7.

Topical Lotion Formulation Containing Variable Percentages of 16α,17α-Cyclopentylidenedioxy - 9α - fluoro - 11β,21 - dihydroxy - 1,4 - pregnadiene - 3,20-dione 21-acetate

Ingredient	Percent Range (w/w)
Steroid	0.01—0.5
Polawax PD 34*	3—5
"Volpo" 20**	0.5—2
Oleyl alcohol	1—5
Methylparaben	0.12—0.2
Propylparaben	0.02—0.06
Squalane	1—5
Potassium sorbate	0.05—0.25
Sorbitol 70% solution	5—10
Distilled water qs ad	100

* Polawax = Higher fatty alcohols and ethylene oxide reaction products
** "Volpo" 20 = Polyoxyethylene ether of oleyl alcohol ("Volpo" is a registered Trade Mark)

The ingredients are blended in a conventional manner to provide an opaque creamy lotion.

WHAT WE CLAIM IS:—

1. 16α,17α - Cyclopentylidenedioxy - 9α - fluoro - 11β,21 - dihydroxy - 1,4-pregnadiene - 3,20 - dione 21 - acetate.

2. A process for preparing the compound of Claim 1, comprising treating 16α,17α - cyclopentylidenedioxy - 9α - fluoro - 11β,21 - dihydroxy - 1,4 - pregnadiene-3,20-dione with pyridine and acetic acid, stirring the reaction mixture for about 2½ hours, pouring the reaction mixture into a mixture of ice and water, and recovering the resulting 21-acetate compound by filtration.

3. A pharmaceutical composition comprising the compound of Claim 1 and a pharmaceutically acceptable carrier.

4. A pharmaceutical composition according to Claim 3, wherein the compound of Claim 1 is present in a concentration of from 0.01% to 0.50% by weight, based on the total weight of said compound and said carrier.

5. A pharmaceutical composition according to Claim 3 and substantially as described in any one of Examples 3—7 herein.

6. A process for preparing the compound of Claim 1, substantially as described in Examples 1 and 2 herein.

7. The compound of Claim 1 when prepared by a process according to Claim 2 or Claim 6.

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Methylparaben	0.12—0.2
Propylparaben	0.02—0.06
Squalane	1—5
Potassium sorbate	0.05—0.25
Sorbitol 70% solution	5—10
Distilled water qs ad	100

* Polawax = Higher fatty alcohols and ethylene oxide reaction products
** "Volpo" 20 = Polyoxyethylene ether of oleyl alcohol ("Volpo" is a registered Trade Mark)

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3. A pharmaceutical composition comprising the compound of Claim 1 and a pharmaceutically acceptable carrier.

4. A pharmaceutical composition according to Claim 3, wherein the compound of Claim 1 is present in a concentration of from 0.01% to 0.50% by weight, based on the total weight of said compound and said carrier.

5. A pharmaceutical composition according to Claim 3 and substantially as described in any one of Examples 3—7 herein.

6. A process for preparing the compound of Claim 1, substantially as described in Examples 1 and 2 herein.

7. The compound of Claim 1 when prepared by a process according to Claim 2 or Claim 6.

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