SPECIFICATION

Hydrocortisone derivative

Various kinds of corticosteroids have recently been used as antirheumatic, anti-inflammatory, anti-allergic and antishock agents. Further, with respect to the administration route, they have recently become widely utilized externally as well as internally. Most of these compounds have the structure of which the corticosteroid is substituted by methyl, hydroxy, halogen (bromine, chorine or fluorine), esterified hydroxy or acetonised hydroxy, or the structure of the derivative of said corticosteroid. Accordingly, they are in the forms remarkably modified or changed from naturally occurring corticosteroids, such as, for example, triamcinolone, fluorocinolone acetonide, betamethasone, dexamethasone and their derivatives. Although these compounds are clinically effective, they tend to show side effects such as systemic action, and some therapeutists have been concerned about the side effects of such halogen-substituted structures. Furthermore, since each of these prior compounds has a structure considerably modified or changed from natural occurring corticosteroid structures, their mechanisms of the metabolism and excretion in a living body are complicated. Accordingly, even if they are externally administered, they are not always safe.

With such a background we have made various tests with a view to developing a steroid having a structure similar to that of a naturally occurring cortiscosteroid, and showing an excellent anti-inflammatory action on topical administration. As a result, we have found that 17α-butyryloxy-11β-hydroxy-21-propionyloxy-4-pregnen-3,20-dione, ie: hydrocortisone 17-butyrate 21-propionate, has a much higher topical anti-inflammatory activity than other hydrcortisone derivatives and commercially available steroidal agents for external administration.

Accordingly the present invention relates to 17α-butyryloxy-11β-hydroxy-21-propionyloxy-4-pregnen-3,20-dione (I).

According to a further feature of the invention there is provided a pharmaceutical composition containing said compound.

The compound (I) of the present invention may be synthesized according to various methods, preferably according to the following method.

Hydrocortisone is reacted with the compound (II) represented by the general formula

$$CH_3CH_2CH_2C(OR)_3 \qquad (II)$$

wherein R is lower alkyl containing 1 to 5 carbon atoms, to give the corresponding 17α,21-(1'-alkoxy-1'-propylmethylenedioxy)-11β-hydroxy-4-pregnen-3,20-dione (III).

The cleaving reaction of the compound (III) with an acid such as oxalic acid or a mineral acid such as hydrochloric acid gives hydrocortisone 17-butyrate (IV). The acylation of the compound (IV) at its 21-hydroxy position gives the compound (I) of the present invention. The acylation is generally carried out by using an acylating agent such as propionic acid anhydride or halide (bromide or chloride) in a solvent such as chloroform, methylene chloride, tetrahydrofuran, toluene or benzene in the presence of a base such as pyridine or triethylamine according to the conventional method. When the acid anhydride is used, the acylation is generally completed in pyridine in 2 to 3 hours at room temperature. When the acid halide is used, the acylation is, preferably, carried out under cooling at 0 to 10°C for about 3 to 5 hours. After completion of the acylation, the reaction solution is poured into ice water and extracted with a solvent such as chloroform to give the compound (I). Alternatively, the reaction solution may be directly concentrated under reduced pressure to give the compound (I). The purification of the compound (I) obtained by each method may be carried out by the recrystallization or column chromatography.

The compound (I) of the present invention has high topical anti-inflammatory action, and may be used for treatment of skin diseases such as acute or chronic eczema, seborrhoeic eczema, atopic dermatitis, infantile eczema, contact dermatitis and psoriasis vulgaris. For these purposes the compound (I) is administered topically in a conventional dosage form such as ointments, creams, lotions, liquid coatings, plasters and powders prepared according to conventionally pharmaceutical practice. The compound (I) may be used in the range of 0.01 to 5.0 % by weight, preferably, 0.05 to 2.0 % by weight in said conventional form.

The compound (I) has excellent anti-inflammatory and percutaneous absorption effects which generally exceed those of other diesters of hydrocortisone. It is beleived that these prominent effects are due to the kinds and combination of both esters at the 17 and 21 positions of hydrocortisone. Namely, although the compound (I) has a structure which is not so far from a natural occurring steroid structure and does not contain such substituents as halogens, the compound (I) has excellent anti-inflammatory activity over other derivatives containing such substituents.

Vasoconstrictor test

Petroleum-based ointments containing 0.1 % of the compounds listed in Table 1, respectively, were prepared. These ointments were randomly applied to forearms of the healthy adult male volunteers, and then they were removed at 4 hours after application. The degrees of vasoconstriction on the applied sites were recorded at 4 hours after removal of the ointments by four degrees as H +, ± and −, which are scored as 3, 2, 1 and 0, respectively. The scores of thirty volunteers for each ointment were sumed. The total and average scores of each test compound are shown in Table 1, wherein the total score is the value of the sumed score of each ointment, and the average score is obtained by dividing the total score by the number of the volunteers.

Table 1

compound	total score	average score
compound (I)	74	2.47
hydrocortisone 17,21-diacetate	47	1.57
hydrocortisone 17-acetate 21-propionate	50	1.67
hydrocortisone 17-acetate 21-butyrate	10	0.33
hydrocortisone 17-propionate 21-acetate	54	1.80
hydrocortisone 17,21-dipropionate	61	2.03
hydrocortisone 17-propionate 21-butyrate	58	1.93
hydrocortisone 17-butyrate 21-acetate	55	1.83
hydrocortisone 17,21-dibutyrate	47	1.57
hydrocortisone 17-valerate 21-acetate	58	1.93
hydrocortisone 17-valerate 21-propionate	49	1.63
hydrocortisone 17-valerate 21-butyrate	38	1.27
hydrocortisone 17-butyrate	51	1.70
betamethasone 17-valerate	60	2.00
placebo ointment	2	0.07

Percutaneous absorption test

Percutaneous absorption of the compound (I) was examined using normal rat skin, and compared with those of hydrocirtosine and hydrocortisone 17-butyrate.

1.0 ml of an aqueous solution containing 5 μg of the test compound was charged into a short glass tube fixed at an area on the rat abdominal surface (4 cm^2) where the hair had been cut off. After a predetermined time, the recovered amount of the test compound in the residual aqueous solution was determined by high pressure liquid chromatography.

Percentaneous absorption (%) of the test compound is calculated by the following expression

$$\frac{5\ \mu g - \text{Recovered amount } (\mu g)}{5\ \mu g} \times 100$$

and results are shown in Table 2, wherein the mean and its standard error are given for each set of experiments.

Table 2

Steroid	Time (hours) 1.0	3.0	5.0	7.0
hydrocortisone	1.8 ± 1.4	4.6 ± 2.2	5.6 ± 2.5	6.5 ± 3.1
hydrocortisone 17-butyrate	4.5 ± 1.8	7.5 ± 2.3	11.4 ± 3.8	14.1 ± 4.2
compound (I)	10.8 ± 4.2	14.7 ± 3.1	28.0 ± 4.7	43.4 ± 5.7

Subacute toxicity test

The subacute toxicity of the compound (I) when it was administered to Wistar strain rats by

the subcutaneous route consecutively for 30 days was investigated in contrast with hydrocortisone 17-butyrate and betamethasone 17-valerate, under the same experimental conditions. The test compounds were suspended in 5% gum arabic in appropriate concentrations. Animals were given the doses of 0.08, 0.4, 2.0, 10 and 50 mg/kg of the compound (I), 0.08, 0.4 and 2.0 mg/kg of hydrocortisone 17-butyrate, and 0.08, 0.4 and 2.0 mg/kg of betamethasone once daily, respectively. The animals serving control were administered 5% gum arabic for the same period. There were fatal cases in the males and females given 50 mg/kg of the compound (I). In all animals treated by any test compound, as the dose level increased, such changes as depression of body weight gains, decreases in WBC count, increases in total cholesterol amount, and decreases in the thymus, adrenal, spleen and mesenteric lymphonodi weight were evident. Further the atrophy of the thymus, adrenal, spleen and mesenteric lymphonodi were remarkable when examined histopathologically. At the same dosage level, changes produced by betamethasone 17-valerate were the most severe. In the urinalysis, no changes were seen in the treated groups as compared with the control group. In the recovery test performed 30 days after the termination of the drum administration, changes of the organs were almost restored to normal.

It was concluded that the substrate toxicity of steroids by subcutaneous administration was in the following order: betamethason 17-valerate > hydrocortisone 17-butyrate ≧ the compound (I).

The present invention is further illustrated by the following detailed example.

Example

(1) A solution of hydrocortisone (5 g) in dimethylformamide (5 ml) containing ethyl orthobutyrate (5 ml) and p-toluenesulfonic acid (200 mg) was heated with stirring at 110°C for 3 hours. To the reaction mixture pyridine (3 ml) was added. After evaporation of the solvent the residue was purified by column chromatography over silica gel and recrystallization from acetone-n-hexane to yield hydrocortisone 17, 21-cyclic ethyl orthobutyrate (3 g). m.p. 166–167°C.

(2) A solution of hydrocortisone 17, 21-cyclic ethyl orthobutyrate (2.5 g) in methanol (200 ml) containing saturated aqueous oxalic acid (2.5 ml) was allowed to stand at room temperature overnight. After the reaction was complete, the mixture was purified by column chromatography on silica gel with chloroform and recrystallization from acetone-n-hexane to give hydrocortisone 17-butyrate (1.2 g). m.p. 208–210°C.

(3) To a solution of hydrocortisone 17-butyrate (1.0 g) in pyridine (5 ml) propionic acid anhydride (2 ml) was added at 0°C, and the mixture was allowed to stand at room temperature overnight. The reaction mixture was poured into ice-water (100 ml) and extracted with chloroform. The chloroform solution was washed with dil. HCl and water and dried over anhydrous sodium sulfate. Evaporation of the chloroform and recrystallization of the residue from benzene-n-hexane gave colorless crystals (1 g), m.p. 79–84°C. Moreover, a solution of these crystals in ethanol was added dropwise to water with stirring, and the precipitate formed was filtrated and dried over phosphorus pentoxide in vacuo at room temperature to give hydrocortisone 17-butyrate 21-propionate as colorless crystalline powders, m.p. 117–117.5°C (decomp. at 265–268°C).

NMR: (in C_5D_5N); 1.00 (3H, s), 1.00–1.30 (6H, m), 1.43 (3H, s), 4.48 (1H, m), 4,74 (2H, d.d., J = 18 Hz, 6 Hz), 5,65 (1H, s).

CLAIMS

1. 17α-butyryloxy-11-hydroxy-21-propionyloxy-4-pregnen-3, 20-dione.
2. A process for the production of the compound of claim 1 which comprises acylating hydrocortisone 17-butyrate at its 21-hydroxy position.
3. A process according to claim 2 wherein acylation is effected by an acylation agent selected from a propionic acid anhydride or a propionic acid halide.
4. A process according to claim 3 wherein the acylation is effected in a solvent selected from chloroform, methylene chloride, tetrahydrofuran, toluene or benzene, in the presence of a base.
5. A process according to claim 4 wherein the base is pyridine or triethylamine.
6. A process according to any one of claims 2 to 5 wherein the compound of claim 1 is isolated either by extraction with a solvent from iced water or by reduced pressure concentration.
7. A process according to any one of claims 2 to 6 wherein the compound of claim 1 is purified by recrystallization or column chromatography.
8. A process according to any one of claims 2 to 7 wherein the hydrocortisone 17-butyrate is formed by a reacting hydrocortisone with a compound of the general formula:

$CH_3CH_2CH_2C(OR)_3$

wherein R is C1 to 5 alkyl to form the corresponding 17α-21-(1′-alkoxy-1′-propylmethylene-

the subcutaneous route consecutively for 30 days was investigated in contrast with hydrocortisone 17-butyrate and betamethasone 17-valerate, under the same experimental conditions. The test compounds were suspended in 5% gum arabic in appropriate concentrations. Animals were given the doses of 0.08, 0.4, 2.0, 10 and 50 mg/kg of the compound (I), 0.08, 0.4 and 2.0 mg/kg of hydrocortisone 17-butyrate, and 0.08, 0.4 and 2.0 mg/kg of betamethasone once daily, respectively. The animals serving control were administered 5% gum arabic for the same period. There were fatal cases in the males and females given 50 mg/kg of the compound (I). In all animals treated by any test compound, as the dose level increased, such changes as depression of body weight gains, decreases in WBC count, increases in total cholesterol amount, and decreases in the thymus, adrenal, spleen and mesenteric lymphonodi weight were evident. Further the atrophy of the thymus, adrenal, spleen and mesenteric lymphonodi were remarkable when examined histopathologically. At the same dosage level, changes produced by betamethasone 17-valerate were the most severe. In the urinalysis, no changes were seen in the treated groups as compared with the control group. In the recovery test performed 30 days after the termination of the drum administration, changes of the organs were almost restored to normal.

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8. A process according to any one of claims 2 to 7 wherein the hydrocortisone 17-butyrate is formed by a reacting hydrocortisone with a compound of the general formula:

$CH_3CH_2CH_2C(OR)_3$

wherein R is C1 to 5 alkyl to form the corresponding 17α-21-(1′-alkoxy-1′-propylmethylene-

dioxy)-11β-hydroxy-4-pregnen-3,20-dione (Compound III), and cleaving said compound (III) with an acid to form the hydrocortisone 17-butyrate.

9. A pharmaceutical composition comprising the compound of claim 1 and a pharmaceutically acceptable diluent or carrier.

10. A pharmaceutical composition according to claim 9 wherein the compound of claim 1 is present in the composition in an amount of 0.01% to 5.0% by weight.

11. A pharmaceutical composition according to claim 9 wherein the compound of claim 1 is present in the composition in an amount of 0.05 to 2.0% by weight.

12. A pharmaceutical composition for the treatment of skin conditions comprising the compound of claim 1.

13. A process for the production of the compound of claim 1 substantially as hereinbefore set forth with reference to the example.

14. A pharmaceutical composition according to claim 9 and substantially as hereinbefore set forth.

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