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17-Esters of 17-Hydroxy-21-Desoxy-Steroids

Greenford

We, GLAXO LABORATORIES LIMITED, a British Company of Greenford, Middlesex, 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:—

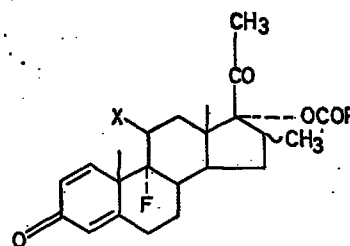
This invention is concerned with new steroid compounds having inter alia high anti-inflammatory action on topical administration.

An important use of anti-inflammatory compounds is in topical preparations for the local treatment of inflammations and considerable research has been directed to finding compounds having good local action on topical administration.

It is an object of the invention to provide new steroid compounds having particularly high anti-inflammatory action on topical application.

We have found that certain 17-esters of certain 21-desoxy steroids, hereinafter described, in general provide considerably enhanced anti-inflammatory action following topical application as compared with other closely analogous compounds. These new esters have in fact been found to possess anti-inflammatory action on topical application exceeding that of some of the best compounds hitherto especially proposed for topical purposes (as judged for example by the patch test of McKenzie et al. Arch. Derm., 1962, 86, 608).

According to the present invention therefore there are provided compounds represented by the general formula:—



where X is a hydroxyl group in the β -configuration, and R is an alkyl group containing up to three carbon atoms.

The invention further provides the new compounds, 17 α - acetoxy - 9 α - fluoro - 16 β - methylpregna - 1,4 - diene - 3,11,20 - trione and 17 α - propionyloxy - 9 α - fluoro - 16 β - methylpregna - 1,4 - diene - 3,11,20 - trione.

The invention further includes pharmaceutical preparations for use in the topical treatment of inflammations comprising one or more of the above new compounds in association with a topical vehicle therefor.

According to this invention 17 α - acetoxy - 9 α - fluoro - 11 β - hydroxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione; 17 α - propionyloxy - 9 α - fluoro - 11 β - hydroxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione; 17 α - butyryloxy - 9 α - fluoro - 11 β - hydroxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione and 17 α - isobutyryloxy - 9 α - fluoro - 11 β - hydroxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione are particularly preferred compounds. 17 α - Propionyloxy -

9 α - fluoro - 11 β - hydroxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione in particular is a compound having extremely high anti-inflammatory action on topical administration.

The active steroid may be formulated into a preparation suitable for topical administration in conventional manner in a topical vehicle with the aid of one or more carriers or excipients. Examples of various types of preparation include ointments, lotions, creams, powders, drops, suppositories, retention enemas, chewable or suckable tablets or pellets (e.g. for the treatment of aphthous ulcers) and aerosols. Ointments and creams may for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Such base may thus, for example, include water and/or an oil such as liquid paraffin or a vegetable oil such as arachis oil or castor oil. Thickening agents which may be used according to the nature of the base include soft paraffin, aluminium stearate, cetostearyl alcohol, polyethylene glycols, woolfat, hydrogenated lanolin and beeswax.

Lotions may be formulated with an aqueous or oily base and will in general also include one or more of the following namely, emulsifying agents, dispersing agents, suspending agents, thickening agents, colouring agents and perfumes.

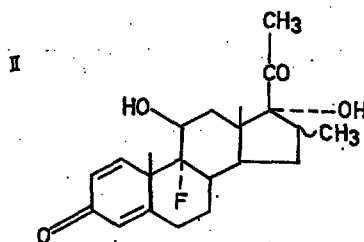
Powders may be formed with the aid of any suitable powder base e.g. talc, lactose or starch. Drops may be formulated with an aqueous base also comprising one or more dispersing agents, suspending agents or solubilising agents.

The proportion of active steroid in the topical compositions according to the invention depends on the precise type of formulations to be prepared but will generally be within the range of from 0.0001% to 5% by weight. Generally however for most types of preparations advantageously the proportion used will be within the range of from 0.001—0.5% and preferably 0.01 to 0.25%.

For topical application e.g. in the treatment of inflammations, topical compositions as above described may be applied to the affected area one or more times per day.

The compositions according to the invention may also include one or more preservatives or bacteriostatic agents e.g. methyl hydroxy benzoate, propyl hydroxy benzoate, chlorocresol or benzalkonium chloride. The compositions according to the invention may also contain other active ingredients such as antimicrobial agents, particularly antibiotics.

According to a further feature of the invention the new compounds according to the invention are prepared by acylating a compound of the general formula



to introduce the appropriate RCOO-radical at the 17-position. For the preparation of the two new compounds in which there is a keto group at the 11-position, the 11-hydroxy group is oxidised to a keto group before or after the acylation, the compound of formula II having the methyl group at position 16 in the β -configuration.

The acylation may be carried out by treating the parent 17-hydroxy compound with the appropriate acid anhydride or acid chloride, if desired in the presence of a non-hydroxylic solvent and in the presence of a strong acid catalyst. The non-hydroxylic solvent may for example be chloroform, methylene chloride or benzene and the strong acid catalyst may for example be perchloric acid, toluene - *p* - sulphonic acid or a strongly acidic cation exchange resin e.g. Amberlite (Registered Trade Mark) IR 120. The optimum reaction conditions, particularly of acid concentration and reaction time, should be determined by pilot experiments using thin layer chromatography.

In a further method of acylation the parent 17 α -hydroxy compound may be reacted with the appropriate aliphatic acid in the presence of trifluoroacetic anhydride.

The carboxylic acid esters of 11 - dehydro - 21 - desoxy compounds can for example be prepared from the corresponding 11-hydroxy compounds (a) by oxidation of the 11 β -hydroxy group, conveniently with chromic anhydride in a tertiary organic base e.g. pyridine and subsequently acylating the 17-position as described above or (b) by reversing the procedure i.e. acylating the 17-position first as described above and subsequently oxidising the 11 β -hydroxyl position.

For a better understanding of the invention the following examples are given by way of illustration only. In the Examples all temperature are given in $^{\circ}\text{C}$.

EXAMPLE 1

17 α - Acetoxy - 9 α - fluoro - 11 β - hydroxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione

9 α - Fluoro - 11 β ,17 α - dihydroxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione (1 g.) was suspended in benzene (200 ml.) and acetic anhydride (12 ml.) containing 60% perchloric acid (0.012 ml.) was added; the solution was

- shaken at room temperature for 1½ hours, the reaction being followed by thin layer chromatography. The small amount of undissolved solid was filtered off, and the filtrate was washed with sodium bicarbonate solution and water, dried and evaporated to dryness. The white solid was triturated with benzene to remove some 11,17-diacetate, filtered and crystallised from a mixture of acetone and petroleum to give 17 α - acetoxy - 9 α - fluoro - 11 β - hydroxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione (250 mg.) with m.p. 255—259°, $[\alpha]_D^{25} + 74^\circ$ (c, 1.0 in CHCl₃) λ $\frac{\text{EtOH}}{\text{max.}}$ 238 m μ (ϵ 15,500).
- 15 (Found: C, 68.5; H, 7.1. C₂₄H₃₁FO₅ requires C, 68.8; H, 7.5%).

EXAMPLE 2

- 9 α - Fluoro - 11 β - hydroxy - 16 β - methyl - 17 α - propionyloxypregna - 1,4 - diene - 3,20 - dione
- 20 The reaction was carried out as in Example 1, propionic anhydride being substituted for acetic anhydride and the reaction time being increased to 2 hours. The crude solid was crystallised twice from a mixture of acetone and petroleum to give 9 α - fluoro - 11 β - hydroxy - 16 β - methyl - 17 α - propionyloxy - 1,4 - diene - 3,20 - dione, (19.8%), m.p. 240—245°. (Found: C, 68.9; H, 7.6. C₂₅H₃₃FO₅ requires C, 69.3; H, 7.6%).

EXAMPLE 3

- 17 α - Butyryloxy - 11 β - hydroxy - 9 α - fluoro - 16 β - methylpregna - 1,4 - diene - 3,20 - dione
- 35 The reaction was carried out as in Example 1 butyric anhydride being substituted for acetic anhydride and with a reaction time of 2 hours. The benzene was evaporated off under reduced pressure, methanol (100 ml.) and sodium bicarbonate (100 ml.) were added and the solution was stirred at room temperature for 4 hours to decompose the excess butyric anhydride. The methanol was distilled off, water was added and the steroid was isolated with chloroform. Two crystallisations from a mixture of acetone and petroleum gave 17 α - butyryloxy - 11 β - hydroxy - 9 α - fluoro - 16 β - methylpregna - 1,4 - diene - 3,20 - dione (16%), m.p. 250—255°. $[\alpha]_D^{25} + 60^\circ$ (c, 1.0 in CHCl₃) λ max 238—240 m μ , (ϵ 15,900). (Found: C, 70.2; H, 8.0; C₂₆H₃₅FO₅ requires C, 69.9; H, 7.9%).

EXAMPLE 4

- a) 9 α - Fluoro - 17 α - hydroxy - 16 β - methylpregna - 1,4 - diene - 3,11,20 - trione
- 55 Chromium trioxide (5 g.) was added slowly to stirred pyridine (50 ml.); 9 α - fluoro - 11 β , 17 α dihydroxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione (5 g.) in pyridine (35 ml.) was added and the mixture was

allowed to stand at room temperature overnight. Chloroform was added and the solution was stirred for 30 min.; it was then filtered, and the chloroform extract was washed with 2N-hydrochloric acid, sodium bicarbonate solution and water. The solution was dried, charcoaled to remove coloured impurities, and evaporated to dryness. Crystallisation from acetone gave 9 α - fluoro - 17 α - hydroxy - 16 β - methylpregna - 1,4 - diene - 3,11,20 - trione (2.5 g.) m.p. 247—253°, $[\alpha]_D^{25} + 150^\circ$ (c, 1.0 in CHCl₃) λ $\frac{\text{EtOH}}{\text{max.}}$ 235 m μ (ϵ , 15,700). (Found: C, 70.6; H, 7.4. C₂₂H₂₇FO₄ requires C, 70.5; H, 7.3%).

- b) 17 α - Acetoxy - 9 α - fluoro - 16 β - methylpregna - 1,4 - diene - 3,11,20 - trione
- 9 α - Fluoro - 17 α - hydroxy - 16 β - methylpregna - 1,4 - diene - 3,11,20 - trione (800 mg.) was suspended in benzene (100 ml.) and acetic anhydride (8.6 ml.) containing perchloric acid (60% 0.012 ml.) was added. The solution was stirred at room temperature for 2 hours, the reaction being followed by thin layer chromatography. The benzene solution was washed with sodium bicarbonate solution and water, dried, filtered and evaporated to dryness under reduced pressure. Crystallisation from a mixture of acetone and petroleum gave 17 α - acetoxy - 9 α - fluoro - 16 β - methylpregna - 1,4 - diene - 3,11,20 - trione (500 mg.), m.p. 250—253°, $[\alpha]_D^{25} + 111^\circ$ (c, 1.0 in CHCl₃) λ $\frac{\text{EtOH}}{\text{max.}}$ 236 m μ (ϵ 15,500) (Found: C, 69.3; H, 7.2. C₂₄H₂₉FO₅ requires C, 69.3; H, 7.2%).

EXAMPLE 5

- 17 α - Acetoxy - 9 α - fluoro - 16 β - methylpregna - 1,4 - diene - 3,11,20 - trione
- Chromic anhydride (150 mg.) was carefully added to stirred pyridine (2 ml.); a solution of 17 α - acetoxy - 9 α - fluoro - 11 β - hydroxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione (45 mg.) in pyridine (3 ml.) was added and the mixture was stirred overnight at room temperature. Chloroform was added and the mixture was stirred for a further 30 minutes; it was then filtered and the chloroform layer was washed with 2N-hydrochloric acid and water, dried, charcoaled and evaporated to dryness, to give 17 α - acetoxy - 9 α - fluoro - 16 β - methylpregna - 1,4 - diene - 3,11,20 - trione (43 mg.). Crystallisation from a mixture of acetone and petroleum gave the crystalline material with m.p. 250—253°.

EXAMPLE 6

- 17 α - Isobutyryloxy - 11 β - hydroxy - 9 α - fluoro - 16 β - methylpregna - 1,4 - diene - 3,20 - dione
- 9 α - Fluoro - 11 β , 17 α - dihydroxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione (1 g.)

was suspended in benzene (200 ml.) and isobutyric anhydride (12 ml.) containing perchloric acid (60%; 0.012 ml.) was added; the solution was stirred for 6 hours at room temperature. Sodium bicarbonate solution was added and the solution was stirred overnight to decompose the excess isobutyric anhydride. The benzene layer was separated, washed with water, dried (MgSO_4) and evaporated to dryness.

Trituration with benzene gave a white solid (300 mg.) which was filtered off. Two crystallisations from acetone-petroleum gave 17 α - isobutyryloxy - 11 β - hydroxy - 9 α - fluoro - 16 β - methylpregna - 1,4 - diene - 3,20 - dione (148 mg.), m.p. 253—259°,

$[\alpha]_D + 74^\circ$ (c, 0.5 in CHCl_3), λ EtOH max.

238 m μ , (ϵ 16,060) (Found: C, 70.3; H, 8.2. $\text{C}_{28}\text{H}_{38}\text{FO}_5$ requires C, 69.9; H, 7.9%).

EXAMPLE 7

17 α - Propionyloxy - 9 α - fluoro - 16 β - methylpregna - 1,4 - diene - 3,11,20 - trione 9 α - Fluoro - 17 α - hydroxy - 16 β - methylpregna - 1,4 - diene - 3,11,20 - trione (500 mg.) was dissolved in methylene chloride (40 ml.) and propionic anhydride (20 ml.) containing 60% perchloric acid (0.04 ml.) was added. After 4 hours the solution was washed with sodium bicarbonate and water and the methylene chloride was distilled off. Methanol and sodium bicarbonate solution were added and the solution was stirred for 1 hour. The methanol was distilled off and the residual solid was filtered off, dried and crystallised from acetone-petrol, with addition of charcoal, to yield 200 mg of 17 α - propionyloxy - 9 α - fluoro - 16 β - methylpregna - 1,4 - diene - 3,11,20 - trione m.p. 183—185°, $[\alpha]_D + 111^\circ$

(c, 0.5 in CHCl_3) λ EtOH max. 234—235 m μ

(ϵ 15,500).

EXAMPLE 8

17 α - Propionyloxy - 9 α - fluoro - 11 β - hydroxy - 16 β - methylpregna - 1,4 - diene 3,20 - dione

9 α - Fluoro - 11 β ,17 α - dihydroxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione (20 g.) and *p*-toluenesulphonic acid (20 g.) were dissolved in methylene chloride (2000 ml.), propionic anhydride (200 ml.) was added and the solution was allowed to stand at room temperature for 18 hours. The solution was washed with aqueous sodium bicarbonate and water and the solvent was distilled off; ethanol and sodium bicarbonate solution were added and the solution was stirred at room temperature for 30 mins. to decompose excess propionic anhydride. The solution was re-extracted with chloroform and worked up in the usual way. Trituration with benzene gave

a white solid (12.7 g.) which, on crystallisation from acetone-hexane, gave 17 α - propionyloxy - 9 α - fluoro - 11 β - hydroxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione (9.9 g.); m.p. 241—246°, $[\alpha]_D + 76^\circ$ (c,

1.0 in CHCl_3), λ EtOH max. 238 m μ , (ϵ 16,300).

(Found: C, 69.3; H, 7.7. $\text{C}_{28}\text{H}_{38}\text{FO}_5$ requires C, 69.3; H, 7.6%).

EXAMPLE 9

17 α - Propionyloxy - 9 α - fluoro - 11 β - hydroxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione

9 α - Fluoro - 11 β ,17 α - dihydroxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione (25 mg.), propionic acid (2 ml.) and trifluoroacetic anhydride (0.5 ml.) were mixed and left to stand at room temperature for 16 hours. The solution was poured into water, the product was extracted with chloroform and the extract was washed with aqueous sodium bicarbonate and evaporated to dryness. Examination of the residue by thin-layer chromatography showed the presence, as major component, of material with the same R_F as the required 17-propionate, together with two minor components.

EXAMPLE 10

17 α - Propionyloxy - 9 α - fluoro - 11 β - hydroxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione

A mixture of 9 α - fluoro - 11 β ,17 α - dihydroxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione (100 mg.), propionyl chloride (1 ml.), 60% perchloric acid (10 mg.), and methylene chloride (10 ml.) was stirred until clear, and was then left at room temperature. After 5 hours, thin-layer chromatography indicated the presence of the 17-propionate as major product, together with some 11,17-dipropionate.

EXAMPLE 11

17 α - Acetoxy - 9 α - fluoro - 11 β - hydroxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione

9 α - Fluoro - 11 β ,17 α - dihydroxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione (25 mg.) in acetic anhydride (5 ml.) was stirred overnight with Amberlite IR 120 (a cross-linked polystyrene resin bearing sulphonic acid groups; H^+ form: 50 mg.). Chloroform was added, the resin was filtered off, and the filtrate was washed with aqueous sodium bicarbonate and water, dried and evaporated. Thin-layer chromatography showed the residue to consist essentially of the 17 - mono - acetate, with traces of starting material and 11,17 - di - acetate.

EXAMPLE 12

9 α - Fluoro - 11 β - hydroxy - 16 α - methyl -

- 17 α - propionyloxypregna - 1,4 - diene - 3,20 - dione (21 - Desoxydexamehasone 17-propionate)
- 21-Desoxydexamehasone (0.5 g.) and *p*-toluenesulphonic acid (0.5 g.) were added to benzene (40 ml.) and propionic anhydride (4 ml.), and the solution was boiled under reflux for 45 minutes. The benzene was evaporated off, ethanol and sodium bicarbonate solution were added and the mixture was then stirred for 30 minutes to decompose the excess propionic anhydride. The solution was extracted with chloroform and the extract was washed with water, dried (MgSO₄) and evaporated.
- The crude product contained a trace of 21-desoxydexamehasone, *ca.* 55% of the 17-propionate and *ca.* 40% of the 11,17-dipropionate as judged by thin layer chromatography. The 17-propionate was separated by preparative layer chromatography on Kieselgel G with benzene-ethyl acetate (3:1) as developing solvent. Crystallisation from acetone-hexane gave 21-desoxydexamehasone 17-propionate (90 mg.), mp. 213–218°.
- (Found: C, 69.4; H, 7.5. C₂₅H₃₃FO₅ requires C, 69.3; H, 7.7%).
- The following examples (a) to (m) illustrate topical formulations prepared in accordance with the invention. In each Example the active ingredient used is 17 α - acetoxy - 9 α - fluoro - 11 β - hydroxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione, but it will be appreciated that this substance may be replaced by other active compounds used in accordance with the invention.
- The following examples (a) — (d) illustrate the preparation of ointments.
- EXAMPLE (a)**
- | | |
|--------------------------------|---------------------|
| Active ingredient | 0.1% w/w |
| Liquid paraffin B.P. | 10.0% w/w |
| White soft paraffin to produce | 100 parts by weight |
- Ball-mill the steroid with a little of the liquid paraffin until the particle size is reduced to 95% by number below 5 μ . Dilute the paste and rinse out the mill with the remaining liquid paraffin, mix and add the suspension to the melted white soft paraffin at 50°C. Stir until cold to give a homogeneous ointment.
- EXAMPLE (b)**
- | | |
|-------------------------|-----------|
| Active ingredient | 0.25% w/w |
| Aluminium stearate | 3.2% w/w |
| Liquid paraffin B.P. to | 100 parts |
- Disperse the aluminium stearate in the liquid paraffin by vortex stirring and heat the suspension with continued stirring, at a temperature rise rate of 2°C per minute until 90°C is reached. Maintain the temperature at 90–95°C for 30 minutes until solution is complete and a gel is formed. Cool quickly, preferably by the use of cooling coils or concentric cooling rings to produce a transparent solid gel. Mill the active ingredient to produce
- microfine particles of which not less than 90% by number are below 5 μ . Triturate with a small portion of the gel and incorporate the remaining gel to give a homogeneous mix.
- EXAMPLE (c)**
- | | |
|----------------------------|---------------|
| Active ingredient | 0.1% w/w |
| Woolfat | 12.0% w/w |
| Cetostearyl alcohol B.P.C. | 20.0% w/w |
| Liquid paraffin B.P. | 25.0% w/w |
| White soft paraffin to | 100 parts w/w |
- Ball-mill the steroid with a little of the liquid paraffin as in Example (a) and add the resulting paste, diluted with the remaining liquid paraffin, to a mixture of cetostearyl alcohol, woolfat and white soft paraffin, melted together by gentle warming. Stir until cold to give a homogeneous mix.
- EXAMPLE (d)**
- | | |
|---|---------------|
| Active ingredient | 0.5% w/w |
| Hydrogenated lanolin e.g. Lanocera sold by Croda Ltd. of London, W.C.2, England | 20.0% w/w |
| Liquid paraffin B.P. | 15.0% w/w |
| White soft paraffin to | 100 parts w/w |
- Ball-mill the steroid with liquid paraffin as in Example (a), and add the resulting paste, diluted with the remaining liquid paraffin to the mixture of hydrogenated lanolin and white soft paraffin, melted together by generally warming. Stir until cold to give a homogeneous mix.
- The following examples (e) and (f) illustrate the preparation of water-miscible creams:—
- EXAMPLE (e)**
- | | |
|----------------------------|----------------------|
| Active ingredient | 0.1% w/w |
| Beeswax (White) | 15.0% w/w |
| Cetostearyl alcohol B.P.C. | 7.0% w/w |
| Cetomacrogel 1000 B.P.C. | 3.0% w/w |
| Liquid paraffin B.P. | 5.0% w/w |
| Chlorocresol | 0.1% w/w |
| Distilled water to produce | 100 parts by weight. |
- Ball-mill the steroid with a little liquid paraffin as described in Example (a). Heat the available water to 100°C, add the chlorocresol, stir to dissolve and cool to 60°C. Melt together the beeswax, cetostearyl alcohol and cetomacrogel and maintain at 65°C. Add the steroid suspension using the remaining liquid paraffin for rinsing. Add the steroid oily phase at 60°C to the chlorocresol aqueous phase at 65°C and stir rapidly while the emulsion cools over the gelling point (40–45°C). Continue to stir at slow speed until the cream sets.
- EXAMPLE (f)**
- | | |
|----------------------------|----------|
| Active ingredient | 0.1% w/w |
| Cetostearyl alcohol B.P.C. | 7.2% w/w |
| Cetomacrogel 1000 B.P.C. | 1.8% w/w |
| Liquid paraffin B.P. | 6.0% w/w |

- White soft paraffin 15.0% w/w
Chlorocresol 0.1% w/w
Distilled water to produce 100 parts by weight.
- 5 Prepare as described in Example (e), replacing the beeswax with white soft paraffin in the oily phase.
The following examples (g) and (h) illustrate the preparation of lotions:
- 10 **EXAMPLE (g)**
Active ingredient 0.25% w/v
Lanbritol (Registered Trade Mark) wax* 0.93% w/v
Diethylene glycol monostearate 0.65% w/v
15 Cetostearyl alcohol B.P.C. 0.65% w/v
Liquid paraffin B.P. 1.95% w/v
Glycerin 5.0% w/v
Isopropyl alcohol 6.5% v/v
Methyl *p*-hydroxy benzoate 0.15 w/v
20 Distilled water to produce 100 volumes
Ball-mill the steroid with half the glycerin, as in Example (a), and use the isopropyl alcohol for dilution and rinsing purposes.
Melt together the lanbritol wax, diethylene glycol monostearate, cetostearyl alcohol and liquid paraffin and maintain at 60°C. Heat the available water and remaining glycerin to 95°C. Add the methyl parahydroxy benzoate and stir until dissolved. Cool to 65°C. Add the oily mix at 60°C to the aqueous phase at 65°C and allow to cool while stirred rapidly until the emulsion gels at 40–45°C, thereafter stir slowly. Add the well mixed steroid suspension slowly to the lotion base and stir to
35 obtain a homogeneous mix.
- EXAMPLE (h)**
Active ingredient 0.05% w/v
Tween (Registered Trade Mark) 80 (Polyoxyethylene sorbitan mono-oleate 0.01% w/v
40 Carbopol (Registered Trade Mark) 934 (carboxy vinyl polymers 0.3% w/v
Diethanolamine 0.5% w/v (approx.)
45 Distilled water to produce 100 vols.
Ball-mill the steroid with a little water and the Tween 80 as in Example (a). Disperse the Carbopol 934 in the available
50 water by vortex stirring. Add the diethanolamine slowly with stirring until the clear thickened mix has a pH of 7.0. Incorporate the steroid slurry into the lotion base and mix well.
- EXAMPLE (i)**
55 **Aerosol Spray Lotion**
Active ingredient (microfine) 2.5 mgm.
*Lanbritol wax is a non-ionic wax for stabilizing emulsions consisting of a mixture of fatty alcohols with polyethylene glycol ethers of fatty alcohols sold by Ronsheim Moore of London, W.C.1, England.
- Fractionated coconut oil to 1.20 g
Dichlorodifluoromethane 16.32 g
Trichlorofluoromethane 24.48 g 60
Dry the steroid overnight at 60°C under vacuum and over phosphorus pentoxide. Ball-mill the dried powder for at least 4 hours with a little of the dried filtered oil. Rinse out the mill with more dried filtered oil and pass the suspension through a 325 mesh B.S. sieve. Assay the suspension and dilute with more dried filtered oil to the required concentration. Incorporate the suspension into the pressure container with the propellants in a conventional manner. 70
- EXAMPLE (j)**
Aphthous Ulcer Pellets
Active ingredient (microfine) 0.25 mg.
Lactose 69.90 mg. 75
Acacia 3.00 mg.
Magnesium stearate 0.75 mg.
Pass the steroid, lactose and acacia, separately through a No. 60 B.S. mesh sieve. Blend the powders and granulate with 50% ethanol in water. Pass the mass through a No. 12 mesh B.S. sieve and dry the granules at 50°C. Pass the dried granules through a No. 20 mesh B.S. sieve and blend in the magnesium stearate, previously passed through a No. 100 mesh B.S. sieve. Compress in a conventional manner on 7/32 inch diameter punches, to give a pellet that will dissolve slowly in the mouth. 80
- EXAMPLE (k)** 90
Retention Enema
Active ingredient (microfine) 0.0005% w/v
Tween 80 0.05% w/v
Ethanol 0.015% v/v 95
Methyl *p*-hydroxy benzoate 0.08% w/v
Propyl *p*-hydroxy benzoate 0.02% w/v
Distilled water to 100 vols.
Heat the available water to 95°C, add the methyl and propyl *p*-hydroxy benzoates and stir to dissolve. Cool the vehicle to room temperature. Disperse the steroid in the ethanol and add to the Tween 80; warm the mixture to 50°C and stir until the steroid is in solution. Add the steroid solution to the vehicle, stirring vigorously to avoid precipitation, and make up to volume with water if required. Distribute the enema into plastic bags e.g. P.V.C. bags for self-administration or into other containers suitable for use. 110
- EXAMPLE (l)**
Eye Drops
Active ingredient 0.025% w/v
Tween 80 2.5% w/v
Ethanol 0.75% v/v 115
Benzalkonium chloride 0.02% w/v
Phenyl ethanol 0.25% v/v
Sodium chloride 0.60% w/v
Water for injection to 100 vols.

- Dissolve the sodium chloride, benzalkonium chloride and phenyl ethanol in the water for injection. Suspend the steroid in the alcohol and add to the Tween 80. Warm the mixture to 50°C and stir until dissolved. Add the steroid solution to the eye-drop vehicle with rapid stirring to obtain a clear solution. Sterilise the bulk by filtration through a sintered glass filter and distribute into sterile small well filled, neutral glass eye-drop containers.

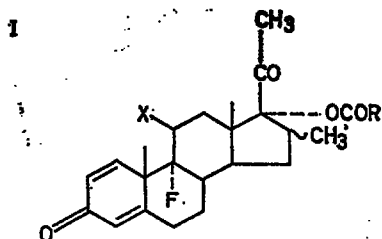
EXAMPLE (m)

Nasal Drops			
Active ingredient	0.005%	w/v	
15 Tween 80	0.05%	w/v	
Alcohol 95%	0.15%	v/v	
Methyl paraben (<i>p</i> -hydroxy benzoate)	0.04%	w/v	
20 Propyl paraben (<i>p</i> -hydroxy benzoate)	0.02%	w/v	
Sodium chloride	0.70%	w/v	
Distilled water to	100	vols.	

- Dissolve the sodium chloride and the parabens in the distilled water heated to 95°C, and allow the solution to cool. Disperse the steroid in the alcohol and add to the Tween 80. Warm the mixture to 50°C and stir until solution of the steroid is effected. Add the steroid solution to the vehicle with rapid stirring to obtain a clear solution. Filter the solution free from particulate matter through a sintered glass filter and distribute into small, well filled containers.

WHAT WE CLAIM IS:—

1. Compounds of the general formula



in which X is a hydroxyl group in the β -configuration, and R is an alkyl group containing up to three carbon atoms.

2. 17α - Acetoxy - 9α - fluoro - 11β - hydroxy - 16β - methylpregna - $1,4$ - diene - $3,20$ - dione.
 3. 17α - Acetoxy - 9α - fluoro - 16β - methylpregna - $1,4$ - diene - $3,11,20$ - trione.
 45 4. 17α - Propionyloxy - 9α - fluoro - 11β - hydroxy - 16β - methylpregna - $1,4$ - diene - $3,20$ - dione.
 5. 17α - Propionyloxy - 9α - fluoro - 16β - methylpregna - $1,4$ - diene - $3,11,20$ - trione.
 50 6. 17α - Butyryloxy - 9α - fluoro - 11β - hydroxy - 16β - methylpregna - $1,4$ - diene - $3,20$ - dione.

7. 17α - Isobutyryloxy - 9α - fluoro - 11β - hydroxy - 16β - methylpregna - $1,4$ - diene - $3,20$ - dione.

8. A pharmaceutical preparation for use in the topical treatment of inflammations comprising a compound as claimed in any of claims 1 to 7 in association with a topical vehicle for said compound.

9. A composition as claimed in claim 8 in the form of a lotion, powder, drops, suppository, retention enema, chewable or suckable tablet or pellet, aerosol, ointment or cream.

10. A composition as claimed in either of claims 8 or 9 containing from 0.0001 to 5% by weight of said compound.

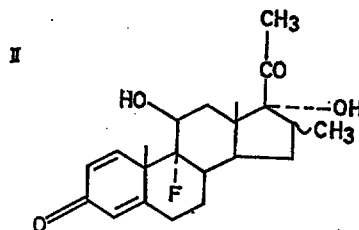
11. A composition as claimed in claim 10 containing from 0.001 to 0.5% by weight of said compound.

12. A composition as claimed in claim 10 containing from 0.01 to 0.25% by weight of said compound.

13. A composition as claimed in any of claims 8—12 also including an antimicrobial agent.

14. Pharmaceutical compositions substantially as herein described with reference to the examples (a) to (m).

15. A process for the preparation of compounds as claimed in any of claims 1 to 7 in which a compound of the general formula



is acylated to introduce the appropriate RCOO-radical at the 17-position, and, where it is desired to produce a compound as claimed in either of claims 3 or 5, the 11β -hydroxy group is oxidised to a keto group before or after the acylation, said compound of formula II in this case having the methyl group at position 16 in the β -configuration.

16. A process as claimed in claim 15 in which the acylation is effected by reacting the parent 17-hydroxy compound with the appropriate acid anhydride or acid chloride in the presence of a strong acid catalyst.

17. A process as claimed in claim 15 in which the reaction is carried out in the presence of a non-hydroxylic solvent.

18. A process as claimed in claim 17 in which the solvent is chloroform, methylene chloride or benzene.

19. A process as claimed in any one of claims 16 to 18 in which the strong acid catalyst is perchloric acid, *p*-toluene sulphonic acid or a strongly acidic cation exchange resin.

- Dissolve the sodium chloride, benzalkonium chloride and phenyl ethanol in the water for injection. Suspend the steroid in the alcohol and add to the Tween 80. Warm the mixture to 50°C and stir until dissolved. Add the steroid solution to the eye-drop vehicle with rapid stirring to obtain a clear solution. Sterilise the bulk by filtration through a sintered glass filter and distribute into sterile small well filled, neutral glass eye-drop containers.

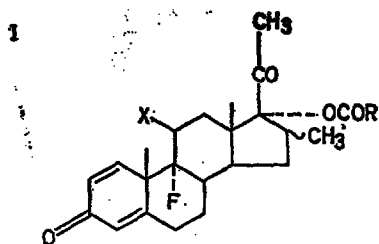
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Sodium chloride	0.70% w/v
Distilled water to	100 vols.

- Dissolve the sodium chloride and the parabens in the distilled water heated to 95°C, and allow the solution to cool. Disperse the steroid in the alcohol and add to the Tween 80. Warm the mixture to 50°C and stir until solution of the steroid is effected. Add the steroid solution to the vehicle with rapid stirring to obtain a clear solution. Filter the solution free from particulate matter through a sintered glass filter and distribute into small, well filled containers.

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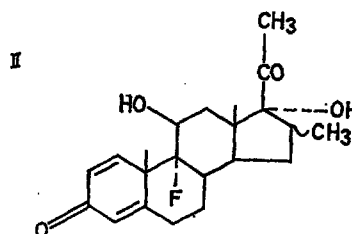
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17. A process as claimed in claim 15 in which the reaction is carried out in the presence of a non-hydroxylic solvent.

18. A process as claimed in claim 17 in which the solvent is chloroform, methylene chloride or benzene.

19. A process as claimed in any one of claims 16 to 18 in which the strong acid catalyst is perchloric acid, *p*-toluene sulphonic acid or a strongly acidic cation exchange resin.



20. A process as claimed in claim 15 in which the acylation is effected by reacting the parent 17-hydroxy compound with the appropriate aliphatic acid in the presence of trifluoroacetic anhydride.
- 5 21. A process as claimed in any of the claims 15 to 20 for the preparation of the new 11-keto compounds in which the 11 β -hydroxy group is oxidised to a keto group before or
- 10 after acylation of the 17 α -hydroxy group by reaction with chromic anhydride in the presence of a tertiary organic base.
22. A process as claimed in claim 21 in which the tertiary organic base is pyridine.
23. A process for the preparation of compounds as claimed in any of claims 1 to 7 substantially as herein described with reference to Examples 1 to 12.
24. Compounds as claimed in any of claims 1 to 7 when prepared by a process as claimed in any of claims 15 to 23.
- 15 20

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