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PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

17 α -Monoesters of 11,17,21-Trihydroxy Steroid Compounds

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 high anti-inflammatory action on topical administration.

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

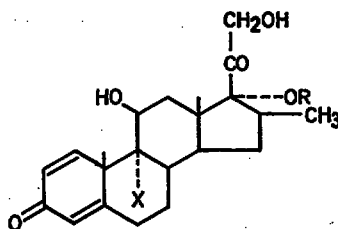
It is an object of the invention to provide new steroid compounds having particularly high anti-inflammatory action on topical application. It is a further object of the invention

to provide compositions for topical application having high anti-inflammatory action.

We have found that certain new 17 α -monoesters hereinafter described, in general provide considerably enhanced anti-inflammatory action following topical application as compared with other closely analogous compounds and/or the corresponding 17 α ,21-dihydroxy parent compounds. These new monoesters have in fact been found to possess anti-inflammatory action on topical application exceeding that 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:—

(I)



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where X is fluorine or chlorine, especially fluorine and R is an alkanoyl group containing from 2 to 6 carbon atoms. Also according to the present invention there is provided a pharmaceutical composition for use in the topical treatment of inflammation comprising a compound of formula (I) where R and X have the meanings stated above together with a topical vehicle for said steroid.

[Price 4s. 6d.]

The compounds according to this invention have in general, particularly high anti-inflammatory action on topical administration and are hence useful in the local treatment of inflammations.

The term "alkanoyl" is used herein in its broad sense to include straight and branched chained alkanoyl groups and cycloalkanoyl groups.

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The group R may for example be an acetyl, propionyl butyryl, isobutyryl, valeryl or cyclopentanecarbonyl group and X is preferably fluorine. Compounds are preferred in which the group R contains not more than 5 carbon atoms, a compound of particular interest being betamethasone 17-valerate, the anti-inflammatory activity of which (judged both by the patch test and by clinical trial) is quite outstanding.

The active steroid may be formulated into a preparation suitable for topical administration in conventional manner with the aid of one or more carriers or excipients. Examples of types of preparation include ointments, lotions, creams, powders, sprays, drops, (e.g. ear drops and eye drops) suppositories or retention enemas, (e.g. for the treatment of rectal or colonic inflammation) and 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 bases 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, stabilizing 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 or non-aqueous base also comprising one or more dispersing agents, suspending agents or solubilising agents.

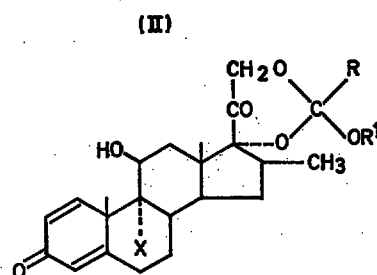
The pharmaceutical compositions according to the invention may also include one or more preservatives or bacteriostatic agents e.g. methyl hydroxy benzoate, propyl hydroxy benzoate, chlorocresol, and benzalkonium chlorides.

The compositions according to the invention may also contain other active ingredients such as antimicrobial agents, particularly antibiotics.

The proportion of active steroid in the compositions according to the invention depends on the precise type of formulation 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 to 0.5% and preferably 0.01 to 0.25%.

The new 17α -monoesters according to the

invention may be prepared by any convenient method. Such methods in principle involve hydrolysis of a corresponding 17,21-orthoester or 17,21-diester. In one such method the corresponding 17,21-orthoester (the preparation of which is described in our copending application No. 18641/63—3621/64, Serial No. 1,043,347) is subjected to hydrolysis, preferably under mild conditions to avoid any risk of the resulting 17α -monoester being rearranged to the isomeric 21-monoester. The above-mentioned orthoesters are compounds of the formula



in which R is an alkyl group containing 1—5 carbon atoms and R^1 is a lower alkyl group containing from 1 to 4 carbon atoms for example a methyl or ethyl group.

The hydrolysis of the orthoesters is preferably carried out in the presence of an acid catalyst e.g. a lower alkanolic acid e.g. acetic or propionic acid, or a strong mineral acid such as hydrochloric acid or sulphuric acid. The concentration of acid used varies according to its strength and the esters to be produced. In the case of weak acids the reaction media may consist essentially of the acid, while for strong acids and easily hydrolysed compounds a trace of acid may be sufficient. The reaction may be carried out in the presence of water and a polar solvent medium, with or without heating according to the conditions necessary for any given compound. Solvents which may be used include esters e.g. ethyl acetate and ethers such as dioxan and tetrahydrofuran. Where weak acids e.g. acetic acid or propionic acid are used for the hydrolysis these may also serve as the solvent media. The presence of some water is necessary but this may only need to be present in trace quantities.

The reaction is readily followed by thin layer or paper chromatography of samples of the reaction mixture as the reaction proceeds.

The 17α -monoesters may also be prepared by the hydrolysis of $17\alpha,21$ -diesters, this method of preparation being in general more suited to the production of esters having larger acyl radicals than those with smaller acyl radicals.

This reaction is preferably carried out under acidic conditions, e.g. using a strong acid e.g.

hydrochloric acid or perchloric acid in a polar solvent e.g. a lower alkanol such as methanol or ethanol.

The 17,21-diesters used as starting material in the process may have alkanoyl, aroyl or aralkanoyl groups at the 21-position but preferably a lower alkanoyl group containing 2—5 carbon atoms. These diesters may be prepared by any convenient method e.g. by the methods described in our copending application No. 22739/64—22740/64 (Serial No. 1,047,519).

For the better understanding of the invention the following examples are given only as illustration:—

EXAMPLE 1

17 α - Acetoxy - 9 α - fluoro - 11 β ,21 - dihydroxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione (Betamethasone 17 - acetate)
9 α - Fluoro - 11 β - hydroxy - 16 β - methyl - 17 α ,21 - (1' - ethoxy - 1' - methylmethylenedioxy)pregna - 1,4 - diene - 3,20 - dione (2 g.) was dissolved in acetic acid (22 ml.), and water (2 ml.) was added. After the solution had been kept for 30 minutes at room temperature water was added and the crystalline solid collected. Two crystallisations from acetone-petroleum ether afforded betamethasone 17-acetate (1.49 g.), m.p. 240—241°C (decomp.), $[\alpha]_D^{25} + 85.6^\circ$ (c 1.26, dioxan), $\lambda_{\text{EtOH}}^{\text{max}}$ 239 m μ (ϵ 15,910) (Found: C, 66.7; H, 7.3. C₂₄H₃₁FO₆ requires C, 66.3; H, 7.2%).

EXAMPLE 2

9 α - Fluoro - 11 β ,21 - dihydroxy - 16 β - methyl - 17 α - propionyloxy - pregna - 1,4 - diene - 3,20 - dione (Betamethasone 17-propionate)
A solution of 9 α - fluoro - 11 β - hydroxy - 16 β - methyl - 17 α ,21 - (1' - ethyl - 1' - ethoxymethylenedioxy)pregna - 1,4 - diene - 3,20-dione (538 mg.) in acetic acid (20 ml.), containing 2 drops of water, was allowed to stand at room temperature for 5 hr. Dilution of the mixture with water gave a white solid (457 mg.) which, after being filtered off and dried, was recrystallized from acetone to afford 9 α - fluoro - 11 β ,21 - dihydroxy - 16 β - methyl - 17 α - propionyloxy - pregna - 1,4 - diene - 3,20-dione (361 mg.) m.p. 230—235°C. $[\alpha]_D^{25} + 82.0^\circ$ (c, 1.0, dioxan), $\lambda_{\text{EtOH}}^{\text{max}}$ 238 m μ (ϵ 15,400). (Found: C, 66.8; H, 7.2; F, 4.1 C₂₄H₃₃FO₆ requires C, 66.9; H, 7.4; F, 4.2%).

EXAMPLE 3

17 α - Butyryloxy - 9 α - fluoro - 11 β ,21 - dihydroxy - 16 β - methyl - pregna - 1,4 - diene - 3,20 - dione (Betamethasone 17-butyrate)
A solution of 9 α - fluoro - 11 β - hydroxy - 16 β - methyl - 17 α ,21 - (1' - propyl - 1' - methoxymethylenedioxy)pregna - 1,4 - diene -

3,20 - dione (587 mg.) in acetic acid (5 ml.) containing water (0.2 ml.) was allowed to stand at room temperature for 2 hr. and then diluted with iced water. The white solid material (523 mg.) which was precipitated was removed by filtration, dried, and recrystallized from acetone-petroleum ether to give 17 α - butyryloxy - 9 α - fluoro - 11 β ,21 - dihydroxy - 16 β - methyl - pregna - 1,4 - diene - 3,20 - dione (455 mg.) m.p. 195°C. $[\alpha]_D^{25} + 79^\circ$ (c 1.0, dioxan), $\lambda_{\text{EtOH}}^{\text{max}}$ 238—239 m μ (ϵ 16,050). (Found: C, 67.4; H, 7.5; F, 4.0 C₂₆H₃₅FO₆ requires C, 67.5; H, 7.6; F, 4.1%).

EXAMPLE 4

9 α - Fluoro - 11 β ,21 - dihydroxy - 16 β - methyl - 17 α - valeryloxy - pregna - 1,4 - diene - 3,20 - dione (Betamethasone 17-valerate)
1) 9 α - Fluoro - 11 β - hydroxy - 16 β - methyl - 17 α ,21 - (1' - butyl - 1' - methoxymethylenedioxy)pregna - 1,4 - diene - 3,20-dione (1 g.) was dissolved in acetic acid (20 ml.) containing a few drops of water and the mixture was left overnight at room temperature. Dilution of the solution with water (100 ml.) afforded a solid which was removed by filtration. The aqueous filtrate was extracted with ether, the ether extract washed with dilute sodium carbonate solution and water, dried over magnesium sulphate and evaporated to give a crystalline solid which was combined with the solid removed earlier. Recrystallization from acetone-petroleum ether produced 9 α - fluoro - 11 β ,21 - dihydroxy - 16 β - methyl - 17 α - valeryloxy - pregna - 1,4 - diene - 3,20-dione (529 mg.) as needles m.p. 183—184°C, $[\alpha]_D^{25} + 77^\circ$ (c, 1.0 dioxan) $\lambda_{\text{EtOH}}^{\text{max}}$ 239 m μ (ϵ 15,920) (Found: C, 67.7; H, 7.8; F, 3.5. C₂₇H₃₇FO₆ requires C, 68.05; H, 7.8; F, 4.0%).

2) A suspension of 9 α - fluoro - 11 β ,17 α ,21-trihydroxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione (2 g.) in sodium dried benzene (500 ml.) was distilled vigorously for a few minutes, toluene - *p* - sulphonic acid monohydrate (30 mg.) and methyl orthovalerate (5 ml.) were added and distillation was continued for 10 mins. The mixture was then boiled under reflux for 1.5 hr. after which time unreacted betamethasone alcohol (400 mg.) was removed by filtration. The benzene solution was treated with solid sodium bicarbonate and a few drops of pyridine, filtered and evaporated to dryness at about 50°C. The residue, in ether, was filtered through grade III basic alumina (20 g.) to remove traces of unreacted betamethasone alcohol, the ether removed *in vacuo* and the residue of crude betamethasone 17,21-methyl orthovalerate was treated with acetic acid (20 ml.)

and a few drops of water and left overnight at room temperature. The acetic acid solution was poured into water (100 ml.) and extracted with chloroform. The chloroform extracts were washed in turn with water, saturated sodium bicarbonate solution and water, dried and evaporated *in vacuo*. The residual gum was triturated with ether and a white crystalline solid (1.16 g.) isolated by filtration. Recrystallization from ether (containing a small amount of acetone)—petroleum ether gave 9 α - fluoro - 11 β ,21 - dihydroxy - 16 β - methyl - 17 α - valeryloxy - 1,4 - diene - 3,20 - dione (871 mg.) as fine needles.

EXAMPLE 5

9 α - Fluoro - 11 β ,21 - dihydroxy - 17 α - isobutyryloxy - 16 β - methyl - pregna - 1,4 - diene - 3,20 - dione (Betamethasone 17-isobutyrate)

A solution of betamethasone (1 g.) in dioxan (40 ml.) was treated with toluene-*p*-sulphonic acid monohydrate (50 mg.) and methyl orthoisobutyrate (2.0 ml.) at room temperature for 10 minutes. The reaction mixture was poured into dilute sodium bicarbonate (400 ml.) and the precipitated betamethasone orthoisobutyrate isolated by filtration. This material was treated with acetic acid (20 ml.) containing a few drops of water at room temperature for 10 minutes and then poured into water (400 ml.). The precipitated material was filtered off, dissolved in ether, and dried over magnesium sulphate. The residue left after removal of the ether, was crystallised twice from a mixture of ether, containing a small amount of acetone, and petroleum to give betamethasone 17-isobutyrate (186 mg.) as rods, m.p. 248°C. (dec.), $[\alpha]_D + 79.7^\circ$ (c 1.0 dioxan), λ EtOH max.

237—239 m μ (ϵ 15,950), (Found: C, 67.75; H, 7.4. C₂₆H₃₅FO₆ requires C, 67.55; H, 7.65%).

EXAMPLE 6

9 α - Fluoro - 11 β ,21 - dihydroxy - 17 α - isovaleryloxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione (Betamethasone 17-isovalerate).

Betamethasone (2 g.) was treated with methyl orthoisovalerate (4.0 ml.) and the intermediate betamethasone orthoisovalerate rearranged with aqueous acetic acid as described in Example 5 to afford betamethasone 17-iso-valerate (361 mg.) as needles, m.p. 220°C, $[\alpha]_D + 76.0^\circ$ (c 0.93 dioxan), λ EtOH max. 238—239 m μ (ϵ 15,680). Found C, 68.3; H, 8.2, C₂₇H₃₇FO₆ requires C, 68.05; H, 7.8%.

EXAMPLE 7

9 α - Fluoro - 17 α - hexanoyloxy - 11 β ,21 - dihydroxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione (Betamethasone 17-hexanoate)

Methyl orthohexanoate (0.6 ml.) was added to a solution of betamethasone (500 mg.) in dioxan (20 ml.) containing toluene-*p*-sulphonic acid (5 mg.). After 20 minutes at room temperature the mixture was poured into dilute sodium bicarbonate solution and the precipitated solid was filtered off and washed thoroughly with water. Recrystallisation from acetone-petroleum ether afforded betamethasone 17,21 - methyl orthohexanoate (424 mg.), m.p. 147—149°C, $[\alpha]_D + 68.1^\circ$ (c 0.93 Dioxan), λ EtOH max. 237—238 m μ (ϵ 16,340).

(Found: C, 68.75; H, 8.45. C₂₉H₄₁FO₆ requires C, 69.05; H, 8.2%).

The above orthoester (295 mg.) was dissolved in acetic acid (5 ml.) containing water (0.11 ml.) and the solution was kept at room temperature for 30 minutes. Dilution with water and recrystallisation of the precipitated solid from acetone-petroleum ether gave betamethasone 17-hexanoate (193 mg.), m.p. 166—169°C, $[\alpha]_D + 69.2^\circ$ (c 0.9 Dioxan), λ EtOH max. 236—239 m μ (ϵ 16,000). (Found: C, 68.25; H, 7.95. C₂₈H₃₈FO₆ requires C, 68.55; H, 8.0%).

EXAMPLE 8

17 α - Cyclopentanecarbonyloxy - 9 α - fluoro - 11 β ,21 - dihydroxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione (Betamethasone 17-cyclopentanecarboxylate)

Betamethasone 17,21-methyl orthocyclopentanecarboxylate (400 mg.) was dissolved in acetic acid (5 ml.) containing water (0.1 ml.) and the solution was left at room temperature for 25 minutes. Dilution with water and recrystallisation of the precipitated solid from acetone-petroleum ether afforded betamethasone 17-cyclopentane-carboxylate (233 mg.), m.p. 227.5—229.5°C, $[\alpha]_D + 72.3^\circ$ (c 0.95 in Dioxan), λ EtOH max. 237—238 m μ (ϵ 16,100).

(Found: C, 68.75; H, 7.7, C₂₈H₃₇FO₆ requires C, 68.85; H, 7.65%).

EXAMPLE 9

9 α - Fluoro - 11 β ,21 - dihydroxy - 16 β - methyl - 17 α - valeryloxy - pregna - 1,4 - diene - 3,20 - dione (Betamethasone 17-valerate)

Betamethasone alcohol (12.1 g.) was suspended with stirring in ethyl acetate (242 ml.). Toluene - *p* - sulphonic acid monohydrate (0.66 g.) and methyl orthovalerate (11 ml.) were added. Complete solution occurred on

slight warming. The solution was then treated with 2N-aqueous sulphuric acid (2.5 ml.) at room temperature for 15 minutes before washing with saturated sodium bicarbonate solution (150ml.) and water (150 ml.). The organic phase was dried over anhydrous magnesium sulphate, filtered and evaporated to dryness under reduced pressure.

The crude betamethasone 17-valerate was dissolved by stirring at reflux temperature in acetone (30 ml.); 80—100 petroleum ether (100 ml.) was slowly added before the mixture was allowed to cool to room temperature when the product was collected by filtration, washed by displacement with 10% acetone-petrol (25 ml.) and dried *in vacuo* at 40°C. to yield a white crystalline solid, 12.1 g. (81.5%), m.p. 180—182°C, $[\alpha]_D + 75.8^\circ$ (c, 1.0 acetone).

EXAMPLE 10

9 α - Fluoro - 11 β ,21 - dihydroxy - 16 β -methyl - 17 α - valeryloxy - pregna - 1,4 - diene - 3,20 - dione (Betamethasone 17-valerate)

Betamethasone 17,21-orthovalerate prepared from betamethasone alcohol (200 g.) was dissolved in acetone (1.0 l.) and water (300 ml.) added, followed by 2N-aqueous sulphuric acid (30 ml.) and stirred at room temperature for 15 minutes. Water (1.0 l.) was added and the mixture stirred until crystallisation occurred when more water (5.0 l.) was added. The mixture was stirred at room temperature for 20 minutes before the product was collected by filtration and washed with water.

The damp cake was dissolved in acetone (1.5 l.) and stirred with charcoal (10 g.) at room temperature for 1 hour. The charcoal was removed by filtration through a kieselguhr bed and washed with acetone (50 ml). To the stirred filtrate was slowly added distilled water (5.0 l.) was added. The mixture was stirred for 30 minutes before the product was collected by filtration, washed with distilled water (1.5 l.) and dried *in vacuo* at 40°C. to yield betamethasone 17-valerate as an off-white crystalline solid 222 g. (91.4%), m.p. 188—190°C, $[\alpha]_D + 78.6^\circ$ (c, 1.0 acetone).

EXAMPLE 11

9 α - Fluoro - 11 β ,21 - dihydroxy - 16 β -Methyl - 17 α - valeryloxy - pregna - 1,4 - diene - 3,30 - dione (Betamethasone 17-valerate)

9 α - Fluoro - 11 β - hydroxy - 16 β - methyl - 17 α ,21 - divaleryloxy - pregna - 1,4 - diene - 3,20-dione (514 mg.) was dissolved in methanol (30 ml.) and aqueous perchloric acid (72%; 2 ml.) was added. The solution was allowed to stand at room temperature for 5 hours and was then poured into cold water. The precipitated mixture (415 mg.) of 17-mono- and 17,21- di-ester was collected and chromatographed on alumina (12 g.) Elution with ethyl acetate-benzene (1:9 and 1:3) afforded, after crystallisation from ether,

9 α - fluoro - 11 β ,21 - dihydroxy - 16 β -methyl - 17 α - valeryloxypregna - 1,4 - diene - 3,20-dione (111 mg.), m.p. 177—178°C (decomp.), $[\alpha]_D + 76.4^\circ$ (c 1.1 dioxan).

EXAMPLE 12

9 α - Chloro - 11 β ,21 - dihydroxy - 16 β -methyl - 17 α - propionyloxy - pregna - 1,4-diene-3,20-dione

9 α - Chloro - 11 β - hydroxy - 16 β -methyl - 17 α ,21 - (1' - ethoxy - 1' - ethyl-methylenedioxy) - pregna - 1,4 - diene - 3,20-dione (300 mg) in acetone (35 ml.) was stirred and treated with water (1 ml.) and 2N-sulphuric acid (0.1 ml.). After 50 minutes the solution was diluted with water and the precipitated solid was collected and recrystallised from acetone-petroleum ether to afford 9 α - chloro - 11 β ,21 - dihydroxy - 16 β -methyl - 17 α - propionyloxypregna - 1,4-diene-3,20-dione, m.p. 196—198°C (decomp),

$[\alpha]_D + 107.5^\circ$ (c 0.78, chloroform), $\lambda_{\text{max}}^{\text{EtOH}}$ 237—239 m μ (ϵ 15,500) (Found: C, 64.2; H, 6.9; Cl, 7.7. C₂₅H₃₃ClO₆ requires C, 64.55; H, 7.15; Cl, 7.6%).

The following examples illustrate topical formulations prepared in accordance with the invention. In each example the active ingredient may for example be betamethasone 17-monovalerate, 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 2 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 w/w

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
10	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	0.05% w/w
	Hydrogenated lanolin e.g. Lanocera sold by Croda Ltd. of London, W.C.2, England	20.0% w/w
25	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 gently warming. Stir until cold to give a homogeneous mix.

The following example e) and f) illustrate the preparation of water-miscible creams:—

EXAMPLE e)

	Active ingredient	0.1% w/w
	Beeswax	15.0% w/w
	Cetostearyl alcohol B.P.C.	7.0% w/w
40	Cetomacrogol 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 65°C. Melt together the beeswax, cetostearyl alcohol and cetomacrogol 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
	Cetomacrogol 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

Prepared 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:

EXAMPLE g)

	Active ingredient	0.25% w/v
	'Lanbritol' wax*	0.93% w/v
	Diethylene glycol monostearate	0.65% w/v
	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
	Distilled water to produce	100 volumes

* '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. (Lanbritol is a registered Trade Mark).

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 stirring 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 obtain a homogeneous mix.

EXAMPLE h)

	Active ingredient	0.05% w/v
	Tween 80 (Polyoxyethylene sorbitan mono-oleate sold by Atlas Powder Co.)	0.01% w/v
	Carbopol 934 (carboxy vinyl polymers sold by B. F. Goodrich Chemical Co., Cleveland, Ohio)	0.3% w/v
	Diethanolamine	0.5% w/v (approx)
	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 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. (Tween and Carbopol are registered Trade Marks).

EXAMPLE i)

Aerosol Spray Lotion

Active ingredient	2.5 mgm.
Fractionated coconut oil	to 1.20 G.
Dichlorodifluoromethane	16.32 G.
Trichlorofluoromethane	24.48 G.

Dry the active ingredient 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.

EXAMPLE j)

Aphthous Ulcer Pellets

Active ingredient	0.25 mgm.
Lactose	69.90 mg.
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.

EXAMPLE k)

Retention Enema

Active ingredient	0.0005% w/v
Tween 80	0.05% w/v
Ethanol	0.015% v/v
Methyl <i>p</i> -hydroxy benzoate	0.08% w/v
Propyl <i>p</i> -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 precipita-

tion, and make up to volume with water if required. Distribute the enema into suitable plastic bags e.g. P.V.C. bags for self-administration or into other containers suitable for use.

EXAMPLE l)

Eye Drops

Active ingredient	0.025% w/v
Tween 80	2.5% w/v
Ethanol	0.75% v/v
Benzalkonium chloride	0.02% w/v
Phenyl ethanol	0.25% v/v
Sodium chloride	0.60% w/v
Water for injection	to 100 volumes

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 5/3 sintered glass filter and distribute into sterile small well filled, neutral glass eye-drop containers.

EXAMPLE m)

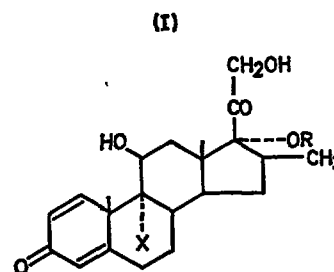
Nasal drops

Active ingredient	0.005% w/v
Tween 80	0.05% w/v
Alcohol 95%	0.15% v/v
Methyl <i>p</i> -hydroxy benzoate	0.04% w/v
Propyl <i>p</i> -hydroxy benzoate	0.02% w/v
Sodium chloride	0.70% w/v
Distilled water	to 100 volumes.

Dissolve the sodium chloride and the methyl and propyl *p*-hydroxy benzoates 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. A steroid compound of the formula



where X is fluorine or chlorine and R is an alkanoyl group containing 2—6 carbon atoms.



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Ball-mill the steroid with a little water and the Tween 80 as in Example a). Disperse the Carbopol 934 in the available 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. (Tween and Carbopol are registered Trade Marks).

EXAMPLE i)

Aerosol Spray Lotion

Active ingredient	2.5 mgm.
Fractionated coconut oil	to 1.20 G.
Dichlorodifluoromethane	16.32 G.
Trichlorofluoromethane	24.48 G.

Dry the active ingredient 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.

EXAMPLE j)

Apthous Ulcer Pellets

Active ingredient	0.25 mgm.
Lactose	69.90 mg.
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.

EXAMPLE k)

Retention Enema

Active ingredient	0.0005% w/v
Tween 80	0.05% w/v
Ethanol	0.015% v/v
Methyl <i>p</i> -hydroxy benzoate	0.08% w/v
Propyl <i>p</i> -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 of 50°C and stir until the steroid is in solution. Add the steroid solution to the vehicle, stirring vigorously to avoid precipita-

tion, and make up to volume with water if required. Distribute the enema into suitable plastic bags e.g. P.V.C. bags for self-administration or into other containers suitable for use.

EXAMPLE l)

Eye Drops

Active ingredient	0.025% w/v
Tween 80	2.5% w/v
Ethanol	0.75% v/v
Benzalkonium chloride	0.02% w/v
Phenyl ethanol	0.25% v/v
Sodium chloride	0.60% w/v
Water for injection	to 100 volumes

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 5/3 sintered glass filter and distribute into sterile small well filled, neutral glass eye-drop containers.

EXAMPLE m)

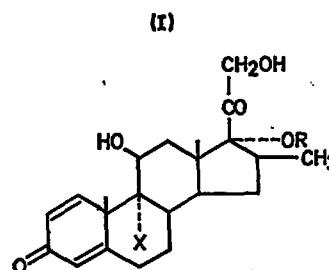
Nasal drops

Active ingredient	0.005% w/v
Tween 80	0.05% w/v
Alcohol 95%	0.15% v/v
Methyl <i>p</i> -hydroxy benzoate	0.04% w/v
Propyl <i>p</i> -hydroxy benzoate	0.02% w/v
Sodium chloride	0.70% w/v
Distilled water	to 100 volumes.

Dissolve the sodium chloride and the methyl and propyl *p*-hydroxy benzoates 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. A steroid compound of the formula



where X is fluorine or chlorine and R is an alkanoyl group containing 2—6 carbon atoms.



2. A compound as claimed in claim 1 in which X is fluorine.
3. A compound as claimed in either of the preceding claims in which R is an acetyl, propionyl, butyryl or valeryl group.
4. A compound as claimed in either of claims 1 or 2 in which R is an isobutyryl, isovaleryl or cyclopentane-carbonyl group.
5. Betamethasone 17-acetate.
6. Betamethasone 17-propionate.
7. Betamethasone 17-butyrate.
8. Betamethasone 17-isobutyrate.
9. Betamethasone 17-valerate.
10. Betamethasone 17-isovalerate.
11. Betamethasone 17-cyclopentanecarboxylate.
12. Betamethasone 17-hexanoate.
13. 17α - propionyloxy - 9α - chloro - $11\beta,21$ - dihydroxy - 16β - methylpregna- 14 ,-diene- $3,20$ -dione.
14. A pharmaceutical composition for use in the topical treatment of inflammation comprising a steroid compound as claimed in any one of the preceding claims in association with a topical vehicle for said steroid.
15. A composition as claimed in claim 14 in the form of a lotion, powder, drops, suppository, retention enema, chewable or suckable tablets or pellets, spray, aerosol, ointment or cream.
16. A composition as claimed in claim 15 containing from 0.0001% to 5% by weight of the steroid compound.
17. A composition as claimed in claim 16 containing from 0.001% to 0.5% by weight of the steroid compound.
18. A composition as claimed in claim 17 containing from 0.01% to 0.25% by weight of the steroid compound.
19. A composition as claimed in claim 14 substantially as herein described.
20. A composition as claimed in claim 14 substantially as herein described with reference to any of Examples a) to m).
21. A process for the preparation of the compounds defined in claim 1 in which a corresponding $17\alpha,21$ - ortho - ester or $17\alpha,21$ -diester is subjected to hydrolysis.
22. A process as claimed in claim 21 in which the hydrolysis is carried out in the presence of an acid catalyst.
23. A process as claimed in claim 22 in which the starting material is an orthoester and the acid catalyst is a lower alkanolic acid or a strong mineral acid.
24. A process as claimed in claim 23 in which the acid catalyst is acetic acid, propionic acid, hydrochloric acid or sulphuric acid.
25. A process as claimed in claim 22 in which the starting material is a $17,21$ -diester and the acid catalyst is a strong mineral acid.
26. A process as claimed in claim 25 in which the acid catalyst is perchloric or hydrochloric acid.
27. A process as claimed in any of claims 21—26 in which the hydrolysis is carried out in the presence of water and a polar solvent medium.
28. A process for the preparation of the compounds defined in claim 1 substantially as described with reference to Examples 1—12.
29. Compounds as defined in claim 1 when prepared by a process as claimed in any of claims 21—28.

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