

PATENT SPECIFICATION

NO DRAWINGS

1047.519

Inventors: JOSEPH ELKS, PETER JOHN MAY and
NIALL GALBRAITH WEIR

Date of filing Complete Specification (under Section 3 (3) of the Patents Act 1949) June 2, 1964.

Application Date: June 11, 1963.

No. 22739/64.

Application Date: Jan. 28, 1964.

No. 22740/64.

(Divided out of No. 1,047,518.)

Complete Specification Published: Nov. 2, 1966.

© Crown Copyright 1966.



Index at acceptance:—C2 U(2, 4A2, 4B2, 4C4, 4C5, 4X); A5 B(1R2, 1S, 1Z, 2R2, 2S, 2Z)

Int. Cl.:—C 07 c 169/36 // A 61 k

COMPLETE SPECIFICATION

17 α ,21-Diesters 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.

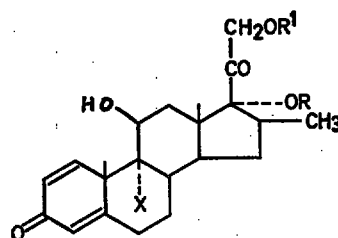
An important use of anti-inflammatory compounds is their use in topical preparations for the local treatment of inflammations and considerable research has been directed to find compounds having good local action on topical administration.

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 17,21-diesters 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 diesters 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)



where X is fluorine or chlorine, preferably fluorine, R is an alkanoyl group containing 2 to 6 carbon atoms and R¹ is an alkanoyl group containing 1 to 7 carbon atoms, the total number of carbon atoms in the groups R and R¹ together being not greater than 9. The term "alkanoyl group" is used herein in its broad sense to include straight and branched chained alkanoyl groups and cycloalkanoyl groups. 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, R¹ and X have the meanings stated above together with a topical vehicle for said steroid.

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 group R may for example be an acetyl, propionyl, butyryl, isobutyryl or valeryl group. R¹ may for example be a formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl or hexahydrobenzoyl group.

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, drops, (e.g. ear drops and eye drops), sprays, 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 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, dispersing agents, suspending agents, thickening agents, colouring agents, perfumes, and stabilizing agents.

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. Non-aqueous bases may also be used.

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 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 to 0.5% and preferably 0.01 to 0.25%.

The new 17 α ,21-diester according to the invention may be prepared by the acylation of the corresponding 17 α ,21-diols or 17 α -hydroxy-21-acyloxy compounds. This reaction is preferably effected by reaction of the steroid with the appropriate acid anhydride in the presence of a strong acid catalyst e.g. *p*-toluene sulphonic acid, perchloric acid or strongly acidic cation exchange resins. Furthermore the reaction may be carried out in the presence or absence of a solvent. Where a solvent is used it is preferably of a non-polar nature,

examples of suitable solvents being carbon tetrachloride, benzene, toluene, methylene chloride and chloroform. Heating may or may not be necessary according to the reactivity of the reaction components.

Where a compound is desired in which R and R¹ are different acyl groups one may first prepare a 21-monoester and esterify this to introduce a different acyl group in the 17 α -position.

17 α ,21-Diesters may also be prepared by the acylation of corresponding 21-hydroxy 17 α -monoesters (prepared for example by the method described in our copending application No. 23223/63—3623/64 (Serial No. 1,047,518)). This esterification is preferably carried out with the appropriate acid anhydride or acid chloride under basic conditions, preferably in the presence of a tertiary organic base e.g. pyridine, quinoline, N-methyl piperidine, N-methylmorpholine or dimethylaniline. It is convenient to work using an excess of the tertiary organic base as solvent, but other solvents e.g. benzene, toluene, dioxan or tetrahydrofuran may also be used. The reaction is carried out with or without heating as may be necessary.

It will be appreciated that this method also is suitable for the production of diesters in which R and R¹ are different acyl groups.

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

EXAMPLE 1

21 - Butyryloxy - 9 α - fluoro - 11 β - hydroxy - 17 α - isobutyryloxy - 16 β - methylpregna-1,4-diene - 3,20 - dione (Betamethasone 17 - isobutyrate 21-butyrate)

9 α - Fluoro - 11 β ,21 - dihydroxy - 17 α -isobutyryloxy - 16 β - methyl - pregna - 1,4-diene - 3,20 - dione (1.08 g.) in pyridine (10 ml.) was treated with butyric anhydride (2 ml.) at room temperature and the mixture set aside for 17 hours at 0°C. Dilution with water and extraction with ether gave the crude diester which was crystallised from ether-petroleum ether at -80°C. to afford 21 - butyryloxy-9 α - fluoro - 11 β - hydroxy - 17 α - isobutyryloxy - 16 β - methylpregna - 1,4 - diene - 3,20-dione, m.p. 149—150°C (decomp.), after previous softening [α]_D + 65.0° (c 1.0, dioxan),

λ $\frac{\text{EtOH}}{\text{max.}}$ 237—240 m μ (ϵ 15,550) (Found: C,

67.7; H, 7.95. C₃₀H₄₁FO₇ requires C, 67.7; H, 7.8%).

EXAMPLE 2

21-Acetoxy - 9 α - fluoro - 11 β - hydroxy-16 β - methyl - 17 α - valeryloxypregna-1,4 - diene - 3,20 - dione (betamethasone 17 - valerate 21 - acetate)

Betamethasone 17-valerate (300 mg) was dissolved in pyridine (3 ml.) and treated with acetic anhydride (0.08 ml.) and kept at 0°C

overnight. The mixture was treated with water (50 ml.), extracted with chloroform and the extracts washed with N-hydrochloric acid and water, dried and evaporated. Crystallisation of the residue from ethyl acetate-petroleum gave betamethasone 17-valerate 21-acetate (132 mg.) as fine needles, m.p. 202°C (cap.),

[α]_D + 50.5° (c 1.1 dioxan), λ _{max}^{EtOH} 238 m μ (ε 15,510), (Found: C, 66.95; H, 7.65. C₂₉H₃₉FO₇ requires C, 67.15; H, 7.6%).

EXAMPLE 3

17 α ,21 - Diacetox - 9 α - fluoro - 11 β - hydroxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione (betamethasone 17,21 - diacetate)

Betamethasone 17-acetate (1.2 g.) in ice cold dry pyridine (15 ml.) was treated with acetic anhydride (6 ml.) at room temperature for 1½ hours. The mixture was poured into ice water (ca. 1 litre) and the solid material isolated by filtration, dissolved in chloroform and dried over magnesium sulphate. The residue left after evaporation of the chloroform was crystallised from acetone-petroleum to give betamethasone 17,21-diacetate (830 mg.) as prisms, m.p. ca 130° (dec.), [α]_D + 66° (c 1.4 dioxan), λ _{max}^{EtOH} 239 m μ (ε 14,870) (Found: C, 65.65; H, 7.35. C₂₈H₃₃FO₇ requires C, 65.5; H, 7.0%).

EXAMPLE 4

17 α - Acetoxy - 9 α - fluoro - 11 β - hydroxy - 16 β - methyl - 21 - valeryloxy - 1,4 - diene - 3,20 - dione. (Betamethasone 17 - acetate 21 - valerate)

Betamethasone 17-acetate (500 mg.) in pyridine (10 ml.) was treated with valeryl chloride (0.1 ml.) at room temperature for 40 minutes. The mixture was diluted with water and extracted with ether. The extracts were washed with water, dried, and evaporated *in vacuo*. Recrystallisation of the residue from ether-acetone-petroleum gave betamethasone 17-acetate 21-valerate (300 mg.), m.p. 124—125°C. decomp., [α]_D + 64° (c 1.09 Dioxan),

λ _{max}^{EtOH} 238 m μ (ε 16,230). (Found: C, 67.5; H, 81. C₂₉H₃₉FO₇ requires C, 67.2; H, 7.6%).

EXAMPLE 5

17 α - Acetoxy - 9 α - fluoro - 21 - hexahydrobenzoyloxy - 11 β - hydroxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione (Betamethasone 17 - acetate 21 - hexahydrobenzoate).

Betamethasone 17-acetate (500 mg.) was treated with hexahydrobenzoyl chloride (0.1 ml.) and the product isolated as in Example 4. Crystallisation of the crude product from ether-acetone-petroleum afforded betamethasone 17-acetate 21-hexahydrobenzoate (408

mg.), m.p. 228—229°C. (decomp.), [α]_D + 75.7° (c 1.95 Dioxan), λ _{max}^{EtOH} 238—239 m μ (ε 16,390). (Found: C, 68.6; H, 7.6. C₃₁H₄₁FO₇ requires C, 68.4; H, 7.6%).

EXAMPLE 6

17 α - Acetoxy - 9 α - fluoro - 11 β - hydroxy - 21 - isobutyryl - oxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione (Betamethasone 17 - acetate 21 - isobutyrate)

Betamethasone 17-acetate (500 mg.) was treated with isobutyryl chloride (0.1 ml.) and the product isolated as in Example 4. Recrystallisation of the crude product from ether-acetone-petroleum gave betamethasone 17-acetate 21-isobutyrate (366 mg.), m.p. 211—212°C. (decomp.), [α]_D + 70° (c 1.7 (Dioxan),

λ _{max}^{EtOH} 238 m μ (ε 16,290). (Found: C, 66.5; H, 7.35. C₂₈H₃₇FO₇ requires C, 66.65; H, 7.4%).

EXAMPLE 7

9 α - Fluoro - 11 β - hydroxy - 17 α ,21 - diisobutyryloxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione (Betamethasone 17,21 - diisobutyrate).

Betamethasone 17-isobutyrate (500 mg.) was treated with isobutyryl chloride (0.135 ml.) and the product isolated as in Example 4. Filtration of the crude product through magnesium silicate (30 g.) in benzene-chloroform (9:1) and crystallisation from benzene-petroleum yielded betamethasone 17,21-diisobutyrate (414 mg.), m.p. 121—124°C., [α]_D + 67.2 (c 0.9 Dioxan), λ _{max}^{EtOH} 238—239 m μ (ε 15,650). (Found: C, 67.5; H, 7.65; C₃₀H₄₁FO₇ requires C, 67.65; H, 7.8%).

EXAMPLE 8

9 α - Fluoro - 11 β - hydroxy - 16 β - methyl - 17 α ,21 - dipropionyloxy - 1,4 - diene - 3,20 - dione. (Betamethasone 17,21 - dipropionate)

Betamethasone 17-propionate (812 mg.) in pyridine (10 ml.) was treated with propionyl chloride (0.21 ml.) at 0°C for 1 hour. Dilution with water and acidification with dilute hydrochloric acid gave the crude diester. Recrystallisation from acetone-petroleum ether afforded betamethasone 17,21-dipropionate (649 mg.), m.p. 117°C (decomp.), [α]_D + 62.2° (c 0.96 Dioxan), λ _{max}^{EtOH} 238—239 m μ (ε 15,100)

(Found: C, 66.4; H, 7.4. C₂₈H₃₇FO₇ requires C, 66.65; H, 7.4%).

EXAMPLE 9

21 - Acetoxy - 9 α - fluoro - 11 β - hydroxy - 16 β - methyl - 17 α - propionyloxy - 1,4 - diene - 3,20 - dione. (Betamethasone 17 - propionate 21 - acetate).

Betamethasone 17-propionate (902 mg.) in

- pyridine (10 ml.) was treated with acetic anhydride (0.25 ml.) as in Example 8 for 18 hours. Crystallization of the crude product from ether afforded betamethasone 17-propionate 21-acetate (474 mg.), m.p. 134°C (decomp.), $[\alpha]_D + 64.1^\circ$ (c 0.92 Dioxan), $\lambda_{\text{EtOH}}^{\text{max.}}$ 238 m μ (ϵ 15,750) (Found: C, 66.1; H, 7.3. $\text{C}_{27}\text{H}_{35}\text{FO}_7$, requires C, 66.1; H, 7.2%).

EXAMPLE 10

- 10 17 α - Acetoxy - 9 α - fluoro - 21 - formyloxy-
11 β - hydroxy - 16 β - methylpregna-
1,4 - diene - 3,20 - dione. (Betamethasone
17 - acetate - 21 - formate)
15 17 α - Acetoxy - 9 α - fluoro - 11 β ,21-
dihydroxy - 16 β - methyl - pregna - 1,4-
diene - 3,20 - dione (500 mg.) in formic acid
(98—100%; 2 ml.) containing *p*-toluene-
sulphonic acid (50 mg.) was allowed to stand
at room temperature. After five hours the
20 solution was poured into ice water (100 ml.),
the precipitated solid was removed by filtra-
tion, washed with dilute sodium bicarbonate
solution and water, dried and recrystallised
from ether-petroleum ether to afford beta-
25 methasone 17-acetate 21-formate (333 mg.),
m.p. 225°C, $[\alpha]_D + 62.5^\circ$ (c 1.0, dioxan)
 $\lambda_{\text{EtOH}}^{\text{max.}}$ 237—240 m μ (ϵ 14,750) (Found: C,
64.9; H, 6.8. $\text{C}_{25}\text{H}_{31}\text{FO}_7$, requires C, 64.9;
H, 6.8%).

EXAMPLE 11

- 30 17 α - Acetoxy - 9 α - fluoro - 11 β - hydroxy-
16 β - methyl - 21 - propionyloxypregna-
1,4 - diene - 3,20 - dione (Betamethasone
17 - acetate 21 - propionate)
35 17 α - Acetoxy - 9 α - fluoro - 11 β ,21-
dihydroxy - 16 β - methyl - pregna - 1,4-
diene - 3,20 - dione (500 mg.) was dissolved
in dry pyridine (10 ml.) at 0°C and treated
with propionyl chloride (0.15 ml.). After 1
40 hour the mixture was diluted with iced water
and the precipitated solid was removed by
filtration, dissolved in ether and the solution
filtered through alumina (20 g.). Crystallisation
of the eluted material from ether-acetone-
45 petroleum ether and then ether-petroleum ether
gave betamethasone 17-acetate 21-propionate
(160 mg.), m.p. 122°C (decomp.), $[\alpha]_D +$
65.5° (c 1.0 dioxan), $\lambda_{\text{EtOH}}^{\text{max.}}$ 236—240 m μ
(ϵ 14,600) (Found: C, 66.4; H, 7.65.
50 $\text{C}_{27}\text{H}_{35}\text{FO}_7$, requires C, 66.1; H, 7.2%).

EXAMPLE 12

- 21 - Butyryloxy - 9 α - fluoro - 11 β - hydroxy-
16 β - methyl - 17 α - propionyloxypregna-
1,4 - diene - 3,20 - dione (Betamethasone
17 - propionate 21 - butyrate).
55 9 α - Fluoro - 11 β ,21 - dihydroxy - 16 β -
methyl - 17 α - propionyl - oxypregna - 1,4-
diene - 3,20 - dione (517 mg.) in dry pyridine
(10 ml.) was cooled to 0°C and treated with

butyric anhydride (0.24 ml.). After 2 days the
solution was diluted with water, acidified with
dilute hydrochloric acid and the white crystal-
line material was removed by filtration. Re-
crystallisation from ether gave betamethasone
17 - propionate 21-butyrate (439 mg.), m.p. 65
161—163°C (decomp.), $[\alpha]_D + 67.5^\circ$ (c
0.95, dioxan), $\lambda_{\text{EtOH}}^{\text{max.}}$ 238—239 m μ (ϵ 15,900)
(Found: C, 67.45; H, 7.9. $\text{C}_{29}\text{H}_{39}\text{FO}_7$, requires
C, 67.2; H, 7.6%).

EXAMPLE 13

9 α - Fluoro - 11 β - hydroxy - 21 - isobutyryl-
oxy - 16 β - methyl - 17 α - propionyl-
oxypregna - 1,4 - diene - 3,20 - dione
(Betamethasone 17 - propionate 21 - iso-
butyrate)
75 9 α - Fluoro - 11 β ,21 - dihydroxy - 16 β -
methyl - 17 α - propionyloxy - pregna - 1,4-
diene - 3,20 - dione (364 mg.) in dry pyridine
(5 ml.) was treated with isobutyryl chloride
(0.12 ml.) for 1 hour at 0°C and worked up
as described in Example 12. Crystallisation
80 from ether gave betamethasone 17 - propionate
21 - isobutyrate (216 mg.), m.p. 153°C
(decomp.), $[\alpha]_D + 66.0^\circ$ (c 1.0 dioxan),
 $\lambda_{\text{EtOH}}^{\text{max.}}$ 236—239 m μ (ϵ 15,750) (Found:
85 C, 67.3; H, 7.8. $\text{C}_{29}\text{H}_{39}\text{FO}_7$, requires C, 67.2;
H, 7.6%).

EXAMPLE 14

9 α - Fluoro - 11 β - hydroxy - 16 β - methyl-
17 α - propionyloxy - 21 - valeryloxy-
pregna - 1,4 - diene - 3,20 - dione (Beta-
methasone 17 - propionate 21 - valerate)
95 9 α - Fluoro - 11 β ,21 - dihydroxy - 16 β -
methyl - 17 α - propionyl - oxypregna - 1,4-
diene - 3,20 - dione (328 mg.) in pyridine
(5 ml.) was treated with valeryl chloride (0.12
ml.) for 1 hour at 0°C and worked up as
described in Example 12. The crude product
was filtered through magnesium silicate (10
g.) in ethyl acetate-benzene (1:9) and the
100 eluted material recrystallised twice from ether-
petroleum ether to afford betamethasone 17-
propionate 21-valerate, m.p. 112—113°C
(decomp.), $\lambda_{\text{EtOH}}^{\text{max.}}$ 238—240 m μ (ϵ 16,400)
(Found: C, 67.7; H, 7.9 $\text{C}_{30}\text{H}_{41}\text{FO}_7$, requires
105 C, 67.7; H, 7.8%).

EXAMPLE 15

9 α - Fluoro - 11 β - hydroxy - 16 β - methyl-
21 - pivalyloxy - 17 α - propionyloxy-
pregna - 1,4 - diene - 3,20 - dione (Beta-
methasone 17 - propionate 21 - pivalate).
110 9 α - Fluoro - 11 β ,21 - dihydroxy - 16 β -
methyl - 17 α - propionyl - oxypregna - 1,4-
diene - 3,20 - dione (990 mg.) in dry pyridine
(10 ml.) was treated with pivalyl chloride (0.35
ml.) for 1 hour at 0°C and worked up as
described in Example 12. Recrystallisation of
the crude product from benzene gave beta-
115

methasone 17-propionate 21-pivalate (800 mg.), m.p. 214—215°C (decomp.) $[\alpha]_D + 64.1^\circ$ (c 0.91, dioxan), $\lambda_{\text{max}}^{\text{EtOH}}$ 239 m μ (ϵ 15,250) (Found: C, 67.5; H, 7.55. $\text{C}_{30}\text{H}_{41}\text{FO}_7$ requires C, 67.7; H, 7.8%).

EXAMPLE 16

21 - Acetoxy - 17 α - butyryloxy - 9 α - fluoro - 11 β - hydroxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione (Betamethasone 17 - butyrate 21 - acetate)

17 α - Butyryloxy - 9 α - fluoro - 11 β ,21-dihydroxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione (700 mg.) in dry pyridine (10 ml.) was treated with acetyl chloride (0.14 ml.) for 1 hour at 0°C and worked up as described in Example 12. Crystallisation of the crude product from ether-petroleum ether gave betamethasone 17-butyrate 21-acetate (420 mg.), m.p. 168°C, $[\alpha]_D + 71^\circ$ (c 1.1, dioxan), $\lambda_{\text{max}}^{\text{EtOH}}$ 237—239 m μ (ϵ 15,250) (Found: C, 66.8; H, 7.4. $\text{C}_{28}\text{H}_{37}\text{FO}_7$ requires C, 66.65; H, 7.4%).

EXAMPLE 17

17 α - Butyryloxy - 9 α - fluoro - 11 β - hydroxy - 16 β - methyl - 21 - propionyloxy - 1,4 - diene - 3,20 - dione (Betamethasone 17 - butyrate 21 - propionate).

17 α - Butyryloxy - 9 α - fluoro - 11 β ,21-dihydroxy - 16 β - methyl - pregna - 1,4 - diene - 3,20 - dione (700 mg.) in dry pyridine (10 ml.) was treated with propionyl chloride (0.17 ml.) at 0°C for 1.5 hours and worked up as described in Example 12. The crude product was dissolved in benzene and the solution filtered through alumina (25 g.). The eluted material was recrystallised from ether-petroleum ether to give betamethasone 17-butyrate 21-propionate, m.p. 145°C, $[\alpha]_D + 68.5^\circ$ (c 0.98, dioxan), $\lambda_{\text{max}}^{\text{EtOH}}$ 238 m μ (ϵ 15,700) (Found: C, 67.2; H, 7.5. $\text{C}_{29}\text{H}_{39}\text{FO}_7$ requires C, 67.1; H, 7.6%).

EXAMPLE 18

17 α ,21 - Dibutyryloxy - 9 α - fluoro - 11 β - hydroxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione (Betamethasone 17,21 - dibutyrate)

17 α - Butyryloxy - 9 α - fluoro - 11 β ,21-dihydroxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione (700 mg.) in dry pyridine (10 ml.) was treated with butyric anhydride (0.32 ml.) and the solution kept for 5 hours at room temperature and then overnight at 0°C. The mixture was diluted with iced water and the solid which separated was collected and chromatographed on alumina (25 g.). Recrystallisation of the eluted material from ether-petroleum ether afforded betamethasone 17,20-dibutyrate, m.p. 125°C, $[\alpha]_D + 64^\circ$

(c 1.0, dioxan), $\lambda_{\text{max}}^{\text{EtOH}}$ 238 m μ (ϵ 15,900) (Found: C, 67.3; H, 7.5. $\text{C}_{30}\text{H}_{41}\text{FO}_7$ requires C, 67.7; H, 7.8%).

EXAMPLE 19

17 α - Butyryloxy - 9 α - fluoro - 11 β - hydroxy - 16 β - methyl - 21 - valeryloxy - 1,4 - diene - 3,20 - dione (Betamethasone 17 - butyrate 21 - valerate)

17 α - Butyryloxy - 9 α - fluoro - 11 β ,21-dihydroxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione (700 mg.) in dry pyridine (10 ml.) was treated with valeryl chloride (0.23 ml.) at 0°C for 40 minutes and worked up as described in Example 12. The product was crystallised from ether-petroleum ether to afford betamethasone 17-butyrate 21-valerate, m.p. 106—107°C, $[\alpha]_D + 62^\circ$ (c 0.8, dioxan), $\lambda_{\text{max}}^{\text{EtOH}}$ 237—238 m μ (ϵ 15,600) (Found: C, 68.2; H, 7.9. $\text{C}_{31}\text{H}_{43}\text{FO}_7$ requires C, 68.1; H, 7.9%).

EXAMPLE 20

21 - Acetoxy - 9 α - fluoro - 11 β - hydroxy - 17 α - isobutyryloxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione (Betamethasone 17 - isobutyrate 21 - acetate)

9 α - Fluoro - 11 β ,21 - dihydroxy - 17 α - isobutyryloxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione (1 g.) in dry pyridine (12 ml.) containing acetyl chloride (0.3 ml.) was kept at 0°C for 5 hours and then worked up as described in Example 12. Crystallisation from ether-petroleum ether at -80°C gave betamethasone 17-isobutyrate 21-acetate (929 mg.), m.p. 131°C (decomp.), $[\alpha]_D + 56.6^\circ$ (c 1.0, dioxan), $\lambda_{\text{max}}^{\text{EtOH}}$ 238—239 m μ (ϵ 14,900) (Found: C, 66.5; H, 7.7. $\text{C}_{28}\text{H}_{37}\text{FO}_7$ requires C, 66.65; H, 7.4%).

EXAMPLE 21

9 α - Fluoro - 11 β - hydroxy - 17 α - isobutyryloxy - 16 β - methyl - 21 - propionyloxy - 1,4 - diene - 3,20 - dione (Betamethasone 17 - isobutyrate 21 - propionate).

9 α - Fluoro - 11 β ,21 - dihydroxy - 17 α - isobutyryloxy - 16 β - methylpregna - 1,4 - diene - 3,20 - dione (1 g.) in dry pyridine (12 ml.) containing propionyl chloride (0.24 ml.) was kept at 0°C for 1 hour. The solid which was precipitated by the addition of water was recrystallised from ether-petroleum ether at -80°C to afford betamethasone 17-isobutyrate 21-propionate (663 mg.), m.p. 93°C (decomp.), $[\alpha]_D + 61.5^\circ$ (c 1.0, dioxan),

$\lambda_{\text{max}}^{\text{EtOH}}$ 237—238 m μ (ϵ 15,600) (Found: C, 67.0; H, 7.3. $\text{C}_{29}\text{H}_{39}\text{FO}_7$ requires C, 67.1; H, 7.6%)

EXAMPLE 22

5 9α - Fluoro - 11β - hydroxy - 17α - isobutyryloxy - 16β - methyl - 21 - valeryl-oxypregna - $1,4$ - diene - $3,20$ - dione (Betamethasone 17 - isobutyrate 21 -valerate)

10 9α - Fluoro - $11\beta,21$ - dihydroxy - 17α - isobutyryloxy - 16β - methylpregna - $1,4$ - diene - $3,20$ - dione (1 g.) in dry pyridine (12 ml.) containing valeryl chloride (0.34 ml.) was kept for 30 minutes at 0°C . and then diluted with water. The precipitated solid was crystallised from ether-petroleum ether at -80°C . to afford betamethasone 17 -isobutyrate 21 -valerate (935 mg.), m.p. 98°C . (decomp.), $[\alpha]_D + 68.5^\circ$ (c 1.0 dioxan),

$\lambda_{\text{EtOH}}^{\text{max}}$ 238—239 $m\mu$ (ϵ 15,600) (Found: C,

68.1; H, 7.8. $\text{C}_{31}\text{H}_{43}\text{FO}_7$, requires C, 68.1; H, 7.9%).

EXAMPLE 23

20 21 - Acetoxy - 9α - chloro - 11β - hydroxy - 16β - methyl - 17α - propionyloxypregna - $1,4$ - diene - $3,20$ - dione

25 9α - Chloro - $11\beta,21$ - dihydroxy - 16β - methyl - 17α - propionyloxy - pregna - $1,4$ - diene - $3,20$ - dione (400 mg.) in dry pyridine (1.6 ml.) containing acetic anhydride (1.6 ml.) was kept at room temperature for 50 minutes and the solution was then diluted with water.

30 Recrystallisation of the precipitated material from acetone-petroleum ether gave 21 -acetoxy - 9α - chloro - 11β - hydroxy - 16β - methyl - 17α - propionyloxypregna - $1,4$ - diene - $3,20$ - dione (290 mg.), m.p. 217 — 219°C . after previous sintering, $[\alpha]_D + 94^\circ$

35 (c 0.96, CHCl_3), $\lambda_{\text{EtOH}}^{\text{max}}$ 238—239 $m\mu$ (ϵ 15,100) (Found: C, 63.75; H, 7.1; Cl, 7.0. $\text{C}_{27}\text{H}_{35}\text{ClO}_7$, requires C, 63.95; H, 7.0; Cl, 7.0%).

EXAMPLE 24

40 9α - Chloro - 11β - hydroxy - 16β - methyl - $17\alpha,21$ - dipropionyloxypregna - $1,4$ - diene - $3,20$ - dione

45 9α - Chloro - $11\beta,21$ - dihydroxy - 16β - methyl - 17α - propionyloxypregna - $1,4$ -

diene - $3,20$ - dione (1.4 g.) in dry pyridine (17 ml.) containing propionyl chloride (0.5 ml.) was kept at 0°C . for 1 hour and then at room temperature for 30 minutes. Dilution with water afforded a solid which, on crystallisation from acetone-ether at -80°C ., gave 9α - chloro - 11β - hydroxy - 16β - methyl - $17\alpha,21$ - dipropionyloxypregna - $1,4$ - diene - $3,20$ - dione (1.2 g.), m.p. 117 — 120°C . (decomp.), $[\alpha]_D + 98.0^\circ$ (c 1.0, dioxan),

$\lambda_{\text{EtOH}}^{\text{max}}$ 238 $m\mu$ (ϵ 15,990) (Found: C, 64.8;

H, 7.0; Cl, 6.75. $\text{C}_{28}\text{H}_{37}\text{ClO}_7$, requires C, 64.55; H, 7.15; Cl, 6.8%).

EXAMPLE 25

17 $\alpha,21$ - Diacetoxy - 9α - fluoro - 11β - hydroxy - 16β - methylpregna - $1,4$ - diene - $3,20$ - dione (Betamethasone $17,21$ -diacetate

60 Betamethasone 21 -acetate (780 mg.) was suspended in benzene (200 ml.) and acetic anhydride (24 ml.) containing perchloric acid (60%; 0.024 ml.) was added. The solution was stirred at room temperature for 55 minutes, the reaction being followed by thin-layer chromatography. The solution was

70 washed with sodium bicarbonate solution and water, dried (MgSO_4) and evaporated to dryness. The residual froth was dissolved in benzene and chromatographed on neutral alumina (Grade III). Elution with benzene and benzene/ether gave, first, betamethasone $11,17,21$ -triacetate, and then a fraction which was shown by thin-layer chromatography to be a mixture of betamethasone $11,21$ -diacetate and betamethasone $17,21$ -diacetate.

80 The following examples illustrate topical formulations prepared in accordance with the invention. In each example the active ingredient may for example be betamethasone $17,21$ -dipropionate, but it will be appreciated that this substance may be replaced by other active compounds used in accordance with the invention.

85 The following examples a)—d) illustrate the preparation of ointments.

Example a)

Active ingredient

Liquid paraffin B.P.

White soft paraffin to produce

0.1% w/w

10.0% w/w

100 parts by weight

95 Ball-mill the steroid with a little of the liquid paraffin until the particle size is reduced to 95% by number below 2μ . 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

Aluminium stearate

Liquid paraffin B.P.

to

0.25% w/w

3.2% w/w

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 micro-fine 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.

15	<i>Example c)</i>	
	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
20	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.

30	<i>Example d)</i>	
	Active ingredient	0.05% w/w
	Hydrogenated lanolin e.g. Lanocerina 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 gently warming. Stir until cold to give a homogeneous mix. The following example e) and f) illustrate the preparation of water-miscible creams:—

45	<i>Example e)</i>	
	Active ingredient	0.1% w/w
	Beeswax	15.0% w/w
	Cetostearyl alcohol B.P.C.	7.0% w/w
	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.

65	<i>Example f)</i>	
	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 preparations of lotions:

	<i>Example g)</i>	
	Active ingredient	0.25% w/v
	Lanbritol wax*	0.93% w/v
	Diethylene glycol monostearate	0.65% w/v
5	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 <i>p</i> -hydroxy benzoate	0.15% w/v
10	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).

- 15 Ball-mill the steroid with half the glycerin, as in Example a) and use the isopropyl alcohol for dilution and rinsing purposes. 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 25 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.
- 20 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

30	<i>Example h)</i>	
	Active ingredient	0.05% w/v
	Tween 80	
	(Polyoxyethylene sorbitan mono-oleate sold by Atlas Powder Co.)	0.01% w/v
35	Carbopol 934	
	(carboxy vinyl polymers sold by B. F. Goodrich Chemical Co., Cleveland, Ohio)	0.3% w/v
	Diethanolamine	0.5% w/v (approx)
40	Distilled water	to produce 100 vols.

- 45 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).

50	<i>Example i)</i>	
	<i>Aerosol Spray Lotion</i>	
	Active ingredient	2.5 mgm.
	Fractionated coconut oil	1.20 G.
	Dichlorodifluoromethane	16.32 G.
55	Trichlorofluoromethane	24.48 G.

- 60 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.

	<i>Example j)</i>	
	<i>Aphthous Ulcer Pellets</i>	
	Active ingredient	0.25 mgm.
	Lactose	69.90 mg.
	Acacia	3.00 mg.
	Magnesium stearate	0.75 mg.

75 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

10	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
15	Propyl <i>p</i> -hydroxy benzoate	0.02% w/v
	Distilled water to	100 vols

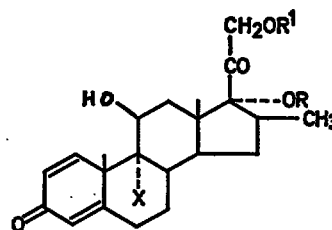
Heat the available water to 95°C, add the methyl and propyl *p*-hydroxy benzoates and stir to dissolve. Cool the vehicle to room temperature. Disperse the steroid in the ethanol and add to the Tween 80; warm the mixture to 50°C and stir until the steroid is in solution. Add the steroid solution to the vehicle, stirring vigorously to avoid precipitation, 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.

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 compound of the formula

(I)



30	<i>Example l)</i> <i>Eye Drops</i>	
	Active ingredient	0.025% w/v
	Tween 80	2.5% w/v
	Ethanol	0.75% v/v
	Benzalkonium chloride	0.02% w/v
35	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.

in which X is fluorine or chlorine, R is an alkanoyl group containing 2 to 6 carbon atoms and R¹ is an alkanoyl group containing 1 to 7 carbon atoms, the total number of carbon atoms in the groups R and R¹ together being not greater than 9.

2. Compounds as claimed in claim 1 in which X is fluorine.

3. Compounds as claimed in claim 1 in which X is chlorine.

4. Compounds as claimed in any of the preceding claims in which R is an acetyl, propionyl, butyryl, isobutyryl or valeryl group.

5. Compounds as claimed in any of the preceding claims in which R¹ is a formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, or hexahydrobenzoyl group.

6. Betamethasone 17 - acetate 21 - formate.

7. Betamethasone 17,21 - diacetate.

8. Betamethasone 17 - acetate 21 - propionate.

9. Betamethasone 17 - acetate 21 - isobutyrate.

10. Betamethasone 17 - acetate 21 - valerate.

50	<i>Example m)</i> <i>Nasal Drops</i>	
	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
55	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



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 peller that will dissolve slowly in the mouth.

5

Example k)

Retention Enema

10	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
15	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 precipitation, 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.

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.

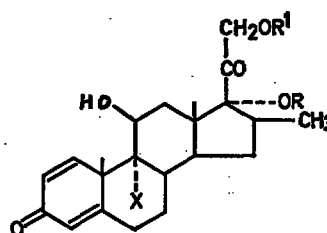
65

WHAT WE CLAIM IS:—

1. A compound of the formula

70

(I)



Example l)

Eye Drops

30	Active ingredient	0.025% w/v
	Tween 80	2.5% w/v
	Ethanol	0.75% v/v
	Benzalkonium chloride	0.02% w/v
35	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.

in which X is fluorine or chlorine, R is an alkanoyl group containing 2 to 6 carbon atoms and R¹ is an alkanoyl group containing 1 to 7 carbon atoms, the total number of carbon atoms in the groups R and R¹ together being not greater than 9.

75

2. Compounds as claimed in claim 1 in which X is fluorine.

80

3. Compounds as claimed in claim 1 in which X is chlorine.

4. Compounds as claimed in any of the preceding claims in which R is an acetyl, propionyl, butyryl, isobutyryl or valeryl group.

85

5. Compounds as claimed in any of the preceding claims in which R¹ is a formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, or hexahydrobenzoyl group.

6. Betamethasone 17 - acetate 21 - formate.

90

7. Betamethasone 17,21 - diacetate.

8. Betamethasone 17 - acetate 21 - propionate.

9. Betamethasone 17 - acetate 21 - isobutyrate.

95

10. Betamethasone 17 - acetate 21 - valerate.

Example m)

Nasal Drops

50	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
55	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

60



* C L M S *

10.

1,047,519

11. Betamethasone 17 - acetate 21 - hexa-
hydrobenzoate.
12. Betamethasone 17 - propionate 21-
acetate.
- 5 13. Betamethasone 17 - propionate 21-
butyrate.
14. Betamethasone 17 - propionate 21-
isobutyrate.
- 10 15. Betamethasone 17,21 - dipropionate.
16. Betamethasone 17 - propionate 21-
valerate.
17. Betamethasone 17 - propionate 21-
pivalate.
18. Betamethasone 17 - butyrate 21-
acetate.
- 15 19. Betamethasone 17 - butyrate 21-
propionate.
20. Betamethasone 17,21 - dibutyrate.
21. Betamethasone 17 - butyrate 21-
valerate.
- 20 22. Betamethasone 17,21 - di - isobutyrate.
23. Betamethasone 17 - valerate 21-
acetate.
24. Betamethasone 17 - isobutyrate 21-
acetate.
- 25 25. Betamethasone 17 - isobutyrate 21-
propionate.
26. Betamethasone 17 - isobutyrate 21-
valerate.
- 30 27. Betamethasone 17 - isobutyrate 21-
butyrate.
28. 17α - propionyloxy - 21 - acetoxy - 9α -
chloro - 11β - hydroxy - 16β - methylpregna-
1,4 - diene - 3,20 - dione.
- 35 29. $17\alpha,21$ - dipropionyloxy - 9α - chloro-
 11β - hydroxy - 16β - methylpregna - 1,4-
diene - 3,20 - dione.
30. A pharmaceutical composition for use
in the topical treatment of inflammation com-
prising a steroid compound as claimed in any
one of the preceding claims in association with
a topical vehicle for said steroid.
- 40 31. A composition as claimed in claim 30
in the form of a lotion, powder, drops, sup-
pository, retention enema, chewable or suck-
able tablets or pellets, aerosol, ointment or
cream.
- 45 32. A composition as claimed in claim 30
or claim 31 containing from 0.0001% to 5%
by weight of the steroid compound.
- 50 33. A composition as claimed in claim 32
containing from 0.001% to 0.5% by weight
of the steroid compound.
34. A composition as claimed in claim 33
containing from 0.01% to 0.25% by weight of
the steroid compound.
- 55 35. A composition as claimed in claim 30
substantially as herein described.
36. A composition as claimed in claim 30
substantially as herein described with reference
to any of Examples a) to m).
- 60 37. A process for the preparation of com-
pounds as defined in claim 1 in which a
corresponding $17\alpha,21$ -diol, a 17α -hydroxy-21-
acyloxy compound or a 17α -acyloxy-21-
hydroxy compound is subjected to acylation
with an appropriate acylating agent.
- 65 38. A process as claimed in claim 37 in
which the acylating agent is an acid anhydride.
39. A process as claimed in claim 37 in
which the acylating agent is an acid chloride.
- 70 40. A process as claimed in claim 38 or
claim 39 in which the starting material is a
 $17\alpha,21$ -diol or a 17α -hydroxy-21-acyloxy com-
pound and the reaction is carried out in the
presence of a strong acid catalyst.
- 75 41. A process as claimed in claim 40 in
which the catalyst is *p*-toluene-sulphonic acid
or perchloric acid.
42. A process as claimed in either of claims
40 or 41 in which the reaction is carried out
in the presence of a non-polar solvent.
- 80 43. A process as claimed in claim 38 or
claim 39 in which the starting material is a
 17α -acyloxy-21-hydroxy compound and the
reaction is effected under basic conditions.
- 85 44. A process as claimed in claim 43 in
which the reaction is carried out in the pre-
sence of a tertiary organic base.
45. A process as claimed in claim 44 in
which the tertiary organic base is pyridine,
quinoline, N-methyl piperidine, N-methyl-
morpholine or dimethylaniline.
- 90 46. A process as claimed in any of claims
43 to 45 in which the reaction is carried out
in the presence of a solvent which may be an
excess of a tertiary organic base.
- 95 47. A process for the preparation of com-
pounds as defined in claim 1 substantially as
described with reference to the foregoing pre-
parative examples Nos. 1 to 25.
- 100 48. Compounds as defined in claim 1 when
prepared by a process as claimed in any of
claims 37 to 47.

For the Applicants:
FRANK B. DEHN & CO.,
Chartered Patent Agents,
Imperial House,
15—19, Kingsway, London, W.C.2.

F. B. Dehn