

PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Novel Di-esters

We, SCHERICO LIMITED, of Winkelriedstr. 56, Lucerne, Switzerland, a body corporate constituted under the laws of Switzerland, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a class of therapeutically active steroids of the pregnane series, to processes for their manufacture and to therapeutic preparations containing them. More particularly, the invention is concerned with 17 α ,21-di-carboxylic acid ester derivatives of steroids of the pregnane series, to processes for their manufacture and to therapeutic preparations containing them.

Anti-inflammatory steroids of the pregnane series are now well known, being used in medicine for the treatment of inflammatory conditions, rheumatic conditions and other diseases. Among the first steroids of the pregnane series demonstrated to possess anti-inflammatory activity, and to be utilised in therapy especially for the alleviation of inflammatory conditions, were compounds characterized by the presence of a double bond in the 4 position or double bonds in the 1- and 4-positions, a ketonic oxygen atom in the 3- and 20-positions, a 17 α -hydroxyl group, a ketonic oxygen atom or β -hydroxyl group in the 11-position, and a hydroxyl or esterified hydroxyl group in the 21-position. Of recent years, compounds of the pregnane series having halogen attached at the 9 α - and 11 β -positions have attracted interest as anti-inflammatory agents, following upon the present Applicants' discovery that such compounds display anti-inflammatory activity.

Research and experimental investigations on the anti-inflammatory activity of steroids of the pregnane series has now led to the discovery, on which this invention is based, of

another class of anti-inflammatory steroids of the pregnane series. Specifically, it has now been found that the presence, in certain 9 α ,11 β -dihalogeno-16 α -lower-alkyl-steroids of the pregnane series, of a carboxylic acid ester group at each of the 17 α - and 21-positions confers advantageous therapeutic properties. The most significant of these properties is an enhanced anti-inflammatory activity, so that the 17 α ,21-di-carboxylic acid ester derivatives of the 9 α ,11 β -dihalogeno-16 α -lower-alkyl compounds display, as a class, superior anti-inflammatory activity to corresponding compounds with only one carboxylic acid ester group which is attached to the 17 α - or 21-position. Further, somewhat surprisingly, the 16 α -lower alkyl di-ester compounds have a superior anti-inflammatory activity to the corresponding 16 β -lower-alkyl or the 16-des-lower-alkyl analogues.

Accordingly, in one of its aspects, this invention provides as novel steroids with anti-inflammatory activity 9 α ,11 β -dihalogeno-16 α -lower - alkyl - 1,4 - pregnadiene - 17 α ,21 - diol-3,20-dione compounds having a carboxylic acid ester group attached at each of the 17 α - and 21-positions.

By "lower" throughout the specification and in the claims appended hereto, is meant containing not more than five carbon atoms. The preferred lower alkyl groups are methyl and ethyl.

Within this class of 17 α ,21-di-carboxylic acid ester compounds, particular importance is attached to the 17 α ,21-di-carboxylic acid esters of 9 α ,11 β -dihalogeno-, especially 9 α ,11 β -dichloro-, 16 α -methyl-1,4-pregnadiene-17 α ,21-diol-3,20-dione compounds which constitute a highly preferred group. The importance of these particular compounds derives from their unusual potency, as evidenced both by pharmacological and clinical tests, as anti-inflammatory agents in which

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role they display superior anti-inflammatory activity to the corresponding 9 α ,11 β -dihalo- geno compounds containing a carboxylic acid ester group only at the 17 α - or 21-position. Further, these compounds have an anti-inflammatory activity which is far greater than that of the corresponding 16 β -methyl or 16-des-methyl analogues. Preferably, the carboxylic acid ester group at the 17 α - and 21-positions is an acyl radical containing from 1 to 5 carbon atoms. These acyl radicals may, for example, be saturated or unsaturated, straight or branched chain aliphatic, or saturated or unsaturated cycloaliphatic radicals.

Examples of suitable acyl radicals include those derived from acetic, propionic, butyric, isobutyric, valeric acids and cyclopropylcarboxylic acid. Di-esters derived from such acids, therefore, would include the 17 α ,21-di-acetate, the 17 α ,21-di-propionate, the 17 α ,21-di-butyrate, the 17 α ,21-di-isobutyrate and the 17 α ,21-di-valerate. The ester groups at the 17 α - and the 21-positions need not be the same. Mixed di-esters, in which the acyl group at the 17 α -position is different from that at the 21-position, such, for example, as the 17 α -butyrate-21-acetate, the 17 α -propionate-21-acetate, the 17 α -acetate-21-butyrate, the 17 α -acetate-21-propionate, and the 17 α -butyrate-21-propionate are also provided by this invention.

In certain instances, the presence of different acyl groups inheres with an enhanced utility of the di-ester compounds, because of the increased solubility of the resulting di-ester in vegetable oils or lipid carriers with which they may be associated in therapeutic preparations.

Typical 9 α ,11 β - dihalogeno - 16 α - lower alkyl - pregnadiene - 17 α ,21 - diol - 3,20 - dione 17 α ,21-di-carboxylic acid ester compounds provided by this invention include the following: 9 α ,11 β - dichloro - 16 α - methyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione - 17 α ,21 - di - acetate; 9 α ,11 β - dichloro - 16 α - methyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione - 17 α ,21 - di - propionate; 9 α ,11 β - dichloro - 16 α - methyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione - 17 α ,21 - di - butyrate; 9 α ,11 β - dichloro - 16 α - methyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione - 17 α ,21 - di - valerate; 9 α ,11 β - dichloro - 16 α - methyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione - 17 α - acetate - 21 - propionate and the 17 α - propionate - 21 - acetate analogue; 9 α ,11 β - dichloro - 16 α - methyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione - 17 α - acetate - 21 - butyrate and the 17 α - butyrate-21-acetate analogue; 9 α ,11 β -dichloro - 16 α - methyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione - 17 α - acetate - 21-valerate and the 17 α -valerate-21-acetate analogue; 9 α ,11 β - dichloro - 16 α - methyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 -

dione - 17 α - propionate - 21 - butyrate and the 17 α - butyrate - 21 - propionate analogue; 9 α ,11 β - dichloro - 16 α - methyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione - 17 α - propionate - 21 - valerate and the 17 α - valerate - 21 - propionate analogue; 9 α ,11 β - dichloro - 16 α - methyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione - 17 α - butyrate - 21 - valerate and the 17 α - valerate - 21 - butyrate analogue; 9 α ,11 β - dichloro - 16 α - methyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione - 17 α ,21 - di - cyclopropylcarboxylate; 9 β ,11 β - difluoro analogue of the aforementioned compounds; 9 α - fluoro - 11 β - chloro analogues of the aforementioned compounds; 9 α -bromo-11 β -fluoro analogue of the aforementioned compounds; 9 α ,11 β - dichloro - 16 α - ethyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione - 17 α ,21 - di - acetate; 9 α ,11 β - dichloro - 16 α - ethyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione - 17 α ,21 - di - propionate; 9 α ,11 β - dichloro - 16 α - ethyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione - 17 α ,21 - di - butyrate; 9 α ,11 β - dichloro - 16 α - ethyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione - 17 α ,21 - di - valerate; 9 α ,11 β - dichloro - 16 α - ethyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione - 17 α - acetate - 21 - propionate and the 17 α - propionate - 21 - acetate analogue; 9 α ,11 β - dichloro - 16 α - ethyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione - 17 α - acetate - 21 - butyrate and the 17 α - butyrate - 21 - acetate analogue; 9 α ,11 β - dichloro - 16 α - ethyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione - 17 α - acetate - 21 - valerate and the 17 α - valerate - 21 - acetate analogue; 9 α ,11 β - dichloro - 16 α - ethyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione - 17 α - propionate - 21 - butyrate and the 17 α -butyrate-21-propionate analogue; 9 α ,11 β - dichloro - 16 α - ethyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione - 17 α - propionate - 21 - valerate and the 17 α - valerate - 21 - propionate analogue; 9 α ,11 β - dichloro - 16 α - ethyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione - 17 α - butyrate - 21 - valerate and the 17 α - butyrate - 21 - valerate analogue; 9 α ,11 β - dichloro - 16 α - ethyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione - 17 α ,21 - di - cyclopropylcarboxylate; 9 α ,11 β - difluoro analogues of the aforementioned compounds; 9 α - fluoro - 11 β - chloro analogues of the aforementioned compounds; 9 α - chloro - 11 β -bromo-analogues of the aforementioned compounds; 9 α -bromo-11 β -fluoro analogues of the aforementioned compounds.

As indicated hereinbefore, the 17 α ,21-di-carboxylic acid esters of the 9 α ,11 β -dihalo- geno steroids, especially the di-esters of the 9 α ,11 β -dihalo- geno-, say 9 α ,11 β -dichloro-, 16 α -methyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20-dione compounds, display superior anti-

inflammatory activity to the corresponding 9 α ,11 β -dihalogeno compounds having an ester group only at the 17 α - or 21-position and a hydroxy group at the other position. Accordingly, an important therapeutic advantage of these compounds when employed as anti-inflammatory agents, is that the average doses can be lower than the average doses of the aforementioned mono-ester compounds and also the 16 β -lower alkyl and 16-des-lower alkyl analogues. Further, despite the smaller dose the novel di-esters attain a higher maximum level of action and preserve their action for a greater length of time.

The anti-inflammatory activity of the novel di-ester compounds has been confirmed *in vivo* in rats employing standard pharmacological tests such as the intracutaneous pouch assay and clinically, in topical application, by the McKenzie test (see McKenzie and Atkinson, Topical Activities of Betamethasone Esters in Man. Arch. Derm. 1964, Vol. 89, 741-746).

This invention also provides, in another of its aspects, processes for manufacturing the 17 α ,21-di-carboxylic acid ester derivatives of the 9 α ,11 β -dihalogeno-16 α -lower alkyl compounds, the features of which depend upon the starting compound utilised.

For instance, the starting compound may be a 9 α ,11 β -dihalogeno-16 α -lower-alkyl-1,4-pregnadiene - 17 α ,21 - diol - 3,20 - dione compound, which is readily available, in which event, the process involves esterification, using a known procedure, to introduce the desired acyl groups at the 17 α - and 21-positions. Again, the starting compound may be a 16 α -lower alkyl - 1,4,9(11) - pregnatriene - 17 α , - 21-diol-3,20-dione compound, in which event, the process involves, as an initial step, esterification by a known procedure, followed by the halogenation of the 17 α ,21-di-ester compound so obtained in a known manner to give the 9 α ,11 β -dihalogeno compound. Clearly, when the starting compound is the appropriate 17 α ,21-di-ester of the aforementioned 1,4,9(11)-pregnatriene compounds, then the process need involve only the halogenation step. In another possible process, the starting compound, whether a 9 α ,11 β -dihalogeno-16 α -lower - alkyl - 1,4 - pregnadiene - 17 α ,21-diol-3,20-dione compound or a 16 α -lower - alkyl - 1,4,9(11) - pregnatriene - 17 α ,21-diol-3,20-dione compound, includes an ester group at either the 17 α - or the 21-position, and this monoester compound is esterified to introduce the desired acyl group at whichever of the 17 α - or 21-positions does not already contain an acyl substituent and, when appropriate, halogenated to give the desired di-ester-dihalogeno compound.

The word "known" as used in the specification and the claiming clauses appended hereto, in relation to the esterification and halogenation procedures involved in the processes

according to the invention, designates procedures in actual use or described in the literature on the subjects.

The starting compounds may contain suitable additional substituents in other parts of the steroid molecule.

The esterification to obtain a di-ester with the same ester group at the 17 α - and the 21-position is effected by conventional procedures using, for instance, an appropriate carboxylic acid, or its halide or anhydride.

The 17 α ,21-di-propionate of 9 α ,11 β -dichloro - 16 α - methyl - 1,4 - pregnadiene - 17 α ,21-diol-3,20-dione as a typical di-ester having the same ester groups at the 17 α - and the 21-positions, may be prepared, for example, by reacting the diol with a mixture of trifluoroacetic anhydride and propionic acid at a temperature of about 80° to about 100° for about 30 to about 90 minutes. The 9 α ,11 β - dichloro - 16 α - methyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione 17 α ,21-di-propionate so produced is conveniently precipitated from the reaction mixture by addition of water thereto. The precipitate may then be separated by filtration and purified by recrystallization from an inert organic solvent or solvent mixture, such as, for example, methanol, ethanol, acetone, ethyl acetate, acetone-hexane, ether-in-hexane, or by chromatography using an adsorbent such as silica gel or magnesium silicates. Reaction with other aliphatic carboxylic acids, say acetic, butyric, valeric or cyclopropylcarboxylic acids, in the presence of trifluoroacetic anhydride or with the respective acid anhydrides in pyridine similarly yields the corresponding di-esters, such as the acetate, butyrate, valerate or cyclopropylcarboxylate.

The mixed 17 α ,21-di-ester derivatives are also readily made by conventional esterification procedures which conveniently involve, as a first step, the preparation of the 21-mono-ester derivative of the starting compound. The 21-mono-ester itself is readily made by treating the corresponding diol, for instance, 9 α ,11 β - dichloro - 16 α - methyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione, with an aliphatic carboxylic acid chloride or anhydride in pyridine. Thus, the 21-mono-propionate ester, for example, may be prepared by treating the diol with propionic acid chloride or propionic anhydride in pyridine at a temperature of about 0° to about 30°C for about 1 to about 24 hours. Precipitation, recovery and purification of the 21-mono-ester may be accomplished by the techniques described previously for the di-ester. Any desired ester grouping may be introduced at the 21-position by substituting the appropriate acid chloride or anhydride for the propionic acid chloride or anhydride.

Introduction of the second and dissimilar ester group at the 17 α -position in the 21-mono-ester compound may be accomplished

by employing the same techniques as described herein for the di-esterification reaction. Thus, 9 α ,11 β -dichloro-16 α -methyl-1,4-pregnadiene - 17 α ,21 - diol - 3,20 - dione 17 α -butyrate-21-propionate, for example, may be prepared by treating the corresponding 21-propionate with a mixture of trifluoroacetic anhydride and butyric acid at a temperature of about 90° to about 100°C for about 30 to about 90 minutes. The 17 α -butyrate-21-propionate is worked up in the same manner as the 17 α ,21-di-propionate to yield the purified unsymmetrical di-ester compound.

Both the symmetrical and unsymmetrical 17 α ,21-di-ester compounds of this invention may be made by another known esterification procedure involving treating a 9 α ,11 β -dihalogeno - 16 α - lower alkyl - 1,4 - pregnadiene-17 α ,21-diol-3,20-dione compound with an alkyl ester of an orthocarboxylic acid in the presence of an acid catalyst, typically a mineral acid, and in solution in an appropriate organic solvent, to form the corresponding 17 α ,21-ortho-ester which upon acid hydrolysis is converted into the corresponding 17 α -mono-ester. Introduction of the ester group at the 21-position, which may be the same as, or different from the ester grouping at the 17 α -position, is readily accomplished by the methods previously described herein.

In those instances in which the starting compound for the process is a 9 α ,11 β -dihalogeno - 16 α - lower - alkyl - 1,4 - pregnadiene - 17 α ,21-diol-3,20-dione 21-carboxylic acid ester compound, or where the 21-monoester is initially formed from the 17 α ,21-free hydroxy compound, then the esterification of the 17 α -free hydroxy group may be accomplished by treating the 21-mono-ester, conveniently at ambient temperature over a period of from one to three hours, with an acylating medium comprising a trifluoroacetic anhydride, a strong acid catalyst and a lower aliphatic or cycloaliphatic carboxylic acid.

In those instances, in which the starting compound is a 1,4,9(11)-pregnatriene, for instance, 16 α - methyl - 1,4,9(11) - pregnatriene-17 α ,21-diol-3,20-dione, the initial step in the process involves esterification using conventional procedures, say one of those described hereinbefore, to introduce the desired acyl groups at the 17 α - and 21-positions, following which the di-ester is halogenated using known procedures which are selective in that only the 9(11)-double bond is attacked to provide the 9 α ,11 β -dihalogeno analogues.

Among suitable halogenation procedures are those described and claimed in our British patent No. 928,301 which, in broad terms, involve the reaction in one or two stages of the pregnatriene compound with a halogenating agent, preferably in a non-reactive solvent, followed by the isolation of the 9 α ,11 β -dihalogeno compound. The halogenating

agents used in the foregoing procedures include (1) molecular isoatomic halogens such as chlorine or bromine, (2) molecular halogen donors such as the addition compounds pyridinium bromide perbromide, iodobenzene dichloride and p-iodotoluene dichloride, (3) halogen halides such as iodine monochloride, (4) mixtures of reagents comprising a positive halogen donor such as a molecular halogen or a compound such as N-chloro-succinimide, and N-bromo-acetamide, together with a halogen having an electronegativity equal to or greater than that of the positive halogen donor, and (5) fluorinating agents such as heavy metal polyfluorides, for example, lead tetrafluoride or mixtures of heavy metal oxides with hydrogen fluoride.

For instance, chlorination, with the introduction of a chlorine atom at the 9 α - and 11 β -positions, may be accomplished following these procedures by reacting the pregnatriene compound with a chlorinating agent, say chlorine or N-chloro-succinimide, preferably in a non-reactive solvent, for instance, in glacial acetic acid or in a chlorinated hydrocarbon such as methylene chloride, chloroform or carbon tetrachloride to which has been added a tertiary organic base such as pyridine. Conveniently, the 9,11-di-halogenation procedure is performed at temperatures ranging from 5° to 50°C, with reaction periods ranging from 30 minutes to 24 hours, both depending on the reactivity of the reagents.

The invention is further described in the following examples, which are given for the purpose of illustration only, and are not to be construed as limiting the scope of the invention in any way.

EXAMPLE 1

9 α ,11 β - Dichloro - 16 α - methyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione 17 α ,21-Di-propionate

Five grams of 9 α ,11 β -dichloro-16 α -methyl-1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione is added to a freshly prepared solution containing 50 ml. of propionic acid and 20 ml. of trifluoroacetic anhydride. The reaction mixture is heated on a steam bath at approximately 90°C for about 45 minutes, then cooled and diluted with 20 ml. of water. The reaction mixture is then poured into 700 ml. of water whereupon a solid precipitates. The crude di-ester as the precipitated substance is collected by filtration and then purified by chromatography on a column containing 500 g. of Florisil (Florisil is a Registered Trade Mark). Like fractions eluted with increasing percentages of ether in hexane are combined and evaporated to dryness, and the purified di-ester so obtained is recrystallized from acetone-hexane melting point 207°C.

EXAMPLE 2

9 α ,11 β - Dichloro - 16 α - methyl - 1,4 -
pregnadiene - 17 α ,21 - diol - 3,20 - dione
17 α -Butyrate-21-acetate

- 5 A. 9 α ,11 β - Dichloro-16 α - methyl - 1,4 -
pregnadiene - 17 α ,21 - diol - 3,20 - dione
21-Acetate

10 One gram of 9 α ,11 β -dichloro-16 α -methyl-
1,4 - pregnadiene - 17 α ,21 - diol - 3,20 -
dione is added to a solution containing 5 ml.
of pyridine and 1 ml. of acetic anhydride. The
reaction mixture is allowed to remain at room
15 temperature for 18 hours, and then diluted
with water and the precipitate which forms
collected by filtration. The crude mono-
ester is purified by recrystallization from aque-
ous methanol.

- 20 B. 9 α ,11 β - Dichloro - 16 α - methyl - 1,4 -
pregnadiene - 17 α ,21 - diol - 3,20 - dione
17 α -Butyrate-21-acetate

To a freshly prepared solution of 2.5 ml. of
butyric acid and 1 ml. of trifluoroacetic an-
hydride is added 250 mg. of the purified 9 α ,
11 β - dichloro - 16 α - methyl - 1,4 - preg-
25 nadiene - 17 α ,21 - diol - 3,20 - dione 21 -
acetate. The reaction mixture is heated at
approximately 95°C for 1 hour, then poured
into water, whereupon a solid precipitates.
The crude di-ester as the precipitated sub-
30 stance is purified by chromatography over
silica gel, using increasing percentages of
ether in hexane as the elutant. Like portions
of the eluted di-ester (evaluated by thin-layer
chromatography, infra red and ultra-violet
35 absorption spectroscopy), are combined, and
the combined eluate evaporated to dryness.
The di-ester is recrystallized from aqueous
methanol melting point 196°—199°C.

EXAMPLE 3

- 40 9 α ,11 β - Dichloro - 16 α - methyl - 1,4 -
pregnadiene - 17 α ,21 - diol - 3,20 - dione
17 α -Butyrate-21-propionate

- A. 9 α ,11 β - Dichloro - 16 α - methyl - 1,4 -
pregnadiene - 17 α ,21 - diol - 3,20 - dione
45 17 α ,21-Methyl-orthobutyrate

To a mixture of 5 g. of 9 α ,11 β -dichloro-
16 α - methyl - 1,4 - pregnadiene - 17 α ,21 -
diol-3,20-dione in 1150 ml. of dry benzene,
is added 2.85 ml. of trimethyl-orthobutyrate
50 and 136.5 mg. of *para*-toluenesulfonic acid
monohydrate as an acid catalyst. The re-
action mixture is stirred for 30 minutes, then
5 g. of sodium bicarbonate and 5 ml. of
pyridine are added. It is then evaporated
55 to a low volume and hexane added until a
precipitate forms. This precipitate is sepa-
rated by filtration, and then purified by
chromatography over silica gel, using initially
chloroform and then 10 per cent ethyl acetate
60 in chloroform as the elutants. Like fractions
(evaluated by thin-layer chromatography, and
infra-red and ultra-violet spectroscopy) are
combined, the combined eluate evaporated to

dryness and the orthobutyrate recrystallized
from acetone-hexane.

- B. 9 α ,11 β - Dichloro - 16 α - methyl - 1,4 -
pregnadiene - 17 α ,21 - diol - 3,20 - dione
17 α -Butyrate

To a solution of 34.8 ml. of acetic acid
and 0.69 ml. of water is added 2.32 g. of
9 α ,11 β - dichloro - 16 α - methyl - 1,4 - preg-
nadiene - 17 α ,21 - diol - 3,20 - dione 17 α ,21 -
methyl-orthobutyrate. The reaction mixture
is kept at room temperature with constant stir-
ring for 17 hours. Water is then added
70 until a precipitate forms, and the precipitate
separated by filtration. The crude product
is purified by recrystallization from acetone-
hexane.

- C. 9 α ,11 β - Dichloro - 16 α - methyl - 1,4 -
pregnadiene - 17 α ,21 - diol - 3,20 - dione
17 α -Butyrate-21-propionate

To a solution of 1 ml. of pyridine and 0.5
ml. of propionic anhydride, is added 0.1 g.
of the purified 9 α ,11 β -dichloro-16 α -methyl-
1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione
17 α -butyrate. The reaction mixture is
warmed at 70°C for 1 hour, then cooled and
poured into water. The precipitate which is
separated by filtration, is purified by recryst-
90 tallization from aqueous methanol.

EXAMPLE 4

- 9 α ,11 β - Dichloro - 16 α - methyl - 1,4 -
pregnadiene - 17 α ,21 - diol - 3,20 - dione
17 α -Propionate-21-butyrate

- A. 9 α ,11 β - Dichloro - 16 α - methyl - 1,4 -
pregnadiene - 17 α ,21 - diol - 3,20 - dione
21-Butyrate

Employing the procedure set forth in Part
A of Example 2, 1 g. of 9 α ,11 β -dichloro-
16 α - methyl - 1,4 - pregnadiene - 17 α ,21 -
diol-3,20-dione is added to a solution of 5 ml.
of pyridine and 1 ml. of butyric anhydride.
The crude product recovered by filtration and
purified by recrystallization from aqueous
105 methanol.

- B. 9 α ,11 β - Dichloro - 16 α - methyl - 1,4 -
pregnadiene - 17 α ,21 - diol - 3,20 - dione
17 α -Propionate-21-butyrate

Two hundred and fifty milligrams of 9 α ,
11 β - dichloro - 16 α - methyl - 1,4 - preg-
nadiene - 17 α ,21 - diol - 3,20 - dione 21 -
butyrate is added to a freshly prepared solu-
tion of 2.5 ml. of propionic acid and 1 ml.
of trifluoroacetic anhydride. The reaction
mixture is then heated at 95°C for 1 hour,
and the crude product is recovered and puri-
fied following the procedure described in
Part B of Example 2.

EXAMPLE 5

- 9 α ,11 β - Dichloro - 16 α - methyl - 1,4 -
pregnadiene - 17 α ,21 - diol - 3,20 - dione
17 α -Valerate-21-acetate

To a mixture of 5 g. of 9 α ,11 β -dichloro-

65

70

75

80

85

90

95

100

105

110

115

120

16 α - methyl - 1,4 - pregnadiene - 17 α ,21 - diol-3,20-dione in 1150 ml. of dry benzene is added 2.85 ml. of trimethylortho-
 5 valerate and 136.5 mg. of *para*-toluenesulfonic acid monohydrate and the procedure set forth in Part A of Example 3 is followed to give 9 α ,11 β - dichloro - 16 α - methyl - 1,4 -
 10 pregnadiene - 17 α ,21 - diol - 3,20 - dione 17 α ,21-methyl-ortho-
 15 valerate. The methyl-ortho-
 20 valerate is hydrolyzed according to the procedure described in Part B of Example 3 to give 9 α ,11 β - dichloro - 16 α - methyl - 1,4 -
 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione 17 α -valerate. The 17 α -valerate (0.1 mg.) is then treated with 0.5 mg. of acetic anhydride in 1 ml. of pyridine according to the procedure of Part C of Example 3 to yield 9 α ,11 β - dichloro - 16 α - methyl - 1,4 -
 17 α -valerate-21-acetate melting point 180°—182°C.

EXAMPLE 6

9 α ,11 β - Dichloro - 16 α - methyl - 1,4 -
 25 pregnadiene - 17 α ,21 - diol - 3,20 - dione 17 α ,21-Di-butyrate

To a freshly prepared solution of 50 ml. of butyric acid and 20 ml. of trifluoroacetic anhydride is added 5 g. of 9 α ,11 β -dichloro-16 α -methyl - 1,4 - pregnadiene - 17 α ,21 - diol -
 30 3,20-dione. The reaction mixture is heated at approximately 90°C on a steam bath for 45 minutes, then allowed to cool and 20 ml. of water added. The resulting mixture is poured into 700 ml. of water and the precipitate which forms separated by filtration. The crude di-ester is purified by chromatography on a column containing 500 g. of Florisil (Florisil is a Registered Trade Mark). Like fractions eluted with increasing percentages of ether in hexane are combined, and evaporated to dryness. The purified di-ester so obtained is recrystallized from acetone-hexane melting point 176°—180°C.

EXAMPLE 7

45 9 α ,11 β - Dichloro - 16 α - methyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione 17 α ,21-Di-cyclopropyl-carboxylate

Five grams of 9 α ,11 β - dichloro - 16 α - methyl - 1,4 - pregnadiene - 17 α ,21 - diol -
 50 3,20-dione is treated with a freshly prepared solution containing 50 ml. of cyclopropyl-carboxylic acid and 20 ml. of trifluoroacetic anhydride and the procedure of Part A of Example 1 is followed to give the purified and recrystallized di-ester melting point 227°—231°C.

EXAMPLE 8

9 α ,11 β - Dichloro - 16 α - methyl - 1,4 -
 60 pregnadiene - 17 α ,21 - diol - 3,20 - dione 17 α ,21 - Di - acetate

To a mixture of 5 g. of 9 α ,11 β -dichloro-16 α - methyl - 1,4 - pregnadiene - 17 α ,21 - diol-3,20-dione in 1150 ml. of dry benzene there is added 2.85 ml. of triethyl-orthoacetate

and 136.5 mg of *para*-toluenesulfonic acid monohydrate and the procedure of Part A of Example 3 is followed to yield 9 α ,11 β -dichloro - 16 α - methyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione 17 α ,21 - methyl-orthoacetate. The 17 α ,21-methylorthoacetate is hydrolyzed according to the procedure of Part B of Example 3 to give 9 α ,11 β -dichloro - 16 α - methyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione 17 α -acetate. The 17 α -acetate (0.1 mg.) is treated with 0.5 ml. of acetic anhydride in 1 ml. of pyridine according to the procedure of Part C of Example 3 to give 9 α ,11 β - dichloro - 16 α - methyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione 17 α ,21-di-acetate melting point 246°—248°C.

The di-esters of this invention can be used as medicaments, conveniently in the form of therapeutic preparations, which contain the active substance in admixture or conjunction with a pharmaceutical carrier, and these preparations are considered to constitute another aspect of this invention.

For topical application, say for the alleviation of inflammatory conditions, the therapeutic preparations are typically in form of ointments, both hydrophilic and hydrophobic, in the form of lotions, which may be aqueous, non-aqueous, or of the emulsion type, or in the form of creams. Suitable pharmaceutical carriers are substances which do not deleteriously affect the di-esters and include, for example, one or a mixture of the following substances: water, oils, greases, polyesters, fatty acids, polyalkylene glycols, waxes and gels. Generally, the di-esters of this invention will be present in a minor proportion, and the carrier will comprise a major proportion of such therapeutic preparations. More particularly, typical preparations suitable for topical application are so proportioned as to contain from about .01 to about .25 per cent by weight of the di-ester. Other substances, such as bacteriostatic agents, pigments, perfumes and anesthetics may also be incorporated in the preparations if desired.

Examples 9 to 13 which follow describe, by way of illustration, some of the therapeutic preparations suitable for topical application provided by this invention and methods for their formulation.

EXAMPLE 9

The preparation of this Example is in the form of a hydrophilic anhydrous ointment.

Components:		Grams per Kilogram	
Polyethylene glycol (Molecular weight: 4000), USP	- -	315.0	120
Polyethylene glycol (Molecular weight: 400), USP	- -	634.9	
9 α ,11 β -Dichloro-16 α -methyl-1,4-pregnadiene-17 α ,21-diol-3,20-dione 17 α ,21-Di-propionate	- - - -	0.1	125
Perfume	- - - -	QS	

The ointment is made by melting the polyethylene glycol 4000 together with the polyethylene glycol 400 at 60°C. The glycol mixture is cooled to 55°C and the 9 α ,11 β -dichloro - 16 α - methyl - 1,4 - pregnadiene - 17 α ,21-diol-3,20-dione 17 α ,21-di-propionate added, while the mixture is stirred. The perfume is then added and the mixture cooled with continued stirring to 30°C.

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EXAMPLE 10

The preparation of this Example is in the form of an aqueous lotion.

	Components:	Grams per Kilogram
15	9 α ,11 β -Dichloro-16 α -methyl-1,4-pregnadiene-17 α ,21-diol-3,20-dione 17 α -Propionate-21-butyrate - - - -	1.0
	*ACRYSOL A3 - - - -	850.0
20	(available from Rohm and Haas)	
	Purified water - - - -	149.0
	Perfume - - - -	QS
	*(ACRYSOL is a Registered Trade Mark)	

The lotion is made by dispersing the 9 α ,11 β - dichloro - 16 α - methyl - 1,4 - pregna - diene - 17 α ,21 - diol - 3,20 - dione 17 α - propionate-21-butyrate in the water and adding the dispersion to the ACRYSOL A3 at room temperature with continuous stirring. The perfume is added and the mixture stirred until homogeneous.

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EXAMPLE 11

The preparation of this Example is in the form of an oil/water lotion.

	Components:	Grams per Kilogram
35	(Premix A)	
	Stearic acid - - - -	50.0
	(USP)	
40	Anhydrous lanolin - - - -	20.0
	(USP)	
	Oleic acid - - - -	15.0
	(USP)	
45	Propyl-para-hydroxybenzoate - -	0.2
	(USP)	
	Mineral Oil - - - -	225.0
	(USP)	
	(Premix B)	
50	Methyl-para-hydroxybenzoate - -	1.5
	(USP)	
	Glycerine - - - -	35.0
	(USP)	
	Triethanolamine (a mixture of alkanolamines) - - - -	18.0
55	(USP)	
	9 α ,11 β -Dichloro-16 α -methyl-1,4-pregnadiene-17 α ,21-diol-3,20-dione 17 α ,21-Di-butyrate - - - -	2.5
60	Purified water - - - -	632.8
	Perfume - - - -	QS

The lotion is made by adding Premix B which has previously been heated to 72°C to Premix A which has been heated to 75°C, with continuous stirring of the mixture. The mixture is cooled to 45°C and the perfume added, after which the mixture is again cooled, this time to 30°C, while the stirring is continued.

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EXAMPLE 12

The preparation of this Example is in the form of a hydrophobic anhydrous ointment.

Components:	Grams per Kilogram	
Stearyl alcohol - - - -	30.0	75
(USP)		
White wax - - - -	84.0	
(USP)		
White petrolatum - - - -	885.0	80
(USP)		
9 α ,11 β -Dichloro-16 α -methyl-1,4-pregnadiene-17 α ,21-diol-3,20-dione 17 α -Butyrate-21-propionate - - - -	1.0	
Perfume - - - -	QS	85

The ointment is made by melting together the petrolatum, stearyl alcohol and white wax at 65° to 70°C. The mixture is then cooled with stirring to 50°C, and the 9 α ,11 β -dichloro - 16 α - methyl - 1,4 - pregnadiene - 17 α ,21-diol-3,20-dione 17 α -butyrate-21-propionate added and dispersed in the mixture by stirring. The perfume is added and stirring continued while the mixture is cooled to 30°C.

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EXAMPLE 13

The preparation of this Example is in the form of a cream.

Components:	Grams per Kilogram	
(Premix A)		100
*ARLACEL - - - -	155.0	
(available from Atlas Chemical Inc.)		
Spermaceti - - - -	38.0	105
(USP)		
Cetyl alcohol - - - -	12.0	
Mineral oil - - - -	20.0	
(USP)		
Glycerine - - - -	45.0	110
(USP)		
*(ARLACEL is a Registered Trade Mark)		
(Premix B)		
Purified water - - - -	728.7	
Methyl-para-hydroxybenzoate - -	1.2	115
(USP)		
9 α ,11 β -Dichloro-16 α -methyl-1,4-pregnadiene-17 α ,21-diol-3,20-dione 17 α ,21-Di-propionate - - - -	0.1	120
Perfume - - - -	QS	
The cream is made by adding, with con-		

tinuous stirring, Premix B which has been heated to 75°C to Premix A which has been heated to 72°C. The mixture is cooled to 40°C and the perfume then added, after which the mixture is again cooled, this time to 30°C, while the stirring is continued.

Effective anti-inflammatory response is usually achieved by 2 to 3 daily applications of topical therapeutic preparations such as those described in Examples 9 to 13. In severe or aggravated conditions, additional medication may be applied.

In addition to the topical preparations described above, the di-esters of this invention may, for the alleviation of certain inflammatory conditions, be administered subcutaneously and/or intramuscularly, conveniently in the form of aqueous suspensions suitable for injection. The injection of therapeutic preparations containing the di-esters of this invention is associated with an unusually prolonged systemic anti-inflammatory response. This prolongation of activity has been confirmed by conventional survival-rate assays in adrenalectomized rats. Usually, injectable therapeutic preparations will be so proportioned as to afford from 1 to 3 grams per litre of the di-ester as the active substance.

An injectable therapeutic preparation, in this instance, in the form of an aqueous suspension, is described in the following Example:

EXAMPLE 14

Component	Grams per Liter
9 α ,11 β -Dichloro-16 α methyl-1,4-pregnadiene-17 α ,21-diol-3,20-dione 17 α ,21-Di-butyr-ate - - - - -	3.0
Anhydrous disodium phosphate (USP)	7.1
Monosodium phosphate monohydrate - - - - -	3.4
Alkyl-dimethyl-benzylammonium chloride - - - - - (USP)	0.2
Water-for-injection - - - - - (USP)	1.01

The aqueous suspension is made by dissolving the phosphate-buffers and the benzylammonium chloride in approximately 80 per cent of the water-for-injection and agitating the solution until it is homogeneous. It is then filtered through a bacteria retentive filter and the filtrate collected in a closed sterile vessel. The 9 α ,11 β -dichloro-16 α -methyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20-dione 17 α ,21-di-butyrate (previously sterilized) is aseptically slurried in a portion of the solution and then passed through a colloid mill until all the steroid particles are uniformly dispersed. The colloid mill is

rinsed with the remainder of the solution and the volume of the batch adjusted with sufficient sterile water-for-injection to make 1 litre.

The quantity and frequency of injection of the therapeutic preparation of the Example will depend upon the nature of the inflammatory condition under treatment. Usually, an effective anti-inflammatory response can be achieved by the injection of 1 cc. of the preparation, either as a single injection or in divided doses. Additional medication may be required in severe or aggravated conditions.

WHAT WE CLAIM IS:—

1. 9 α ,11 β - Dihalogeno - 16 α - lower alkyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione compounds having a carboxylic acid ester group attached at each of the 17 α - and 21-positions.

2. 9 α ,11 β - Dihalogeno - 16 α - methyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione compounds having a carboxylic acid ester group attached at each of the 17 α - and 21-positions.

3. Compounds as claimed in claim 1 or 2, wherein the halogen at the 9 α - and 11 β -positions is chlorine.

4. Compounds as claimed in any one of the preceding claims, wherein the carboxylic acid ester group at the 17 α - and 21-positions is an acyl radical containing from 1 to 5 carbon atoms.

5. Compounds as claimed in claim 4, wherein the acyl radical at the 17 α -position is different from the acyl radical at the 21-position.

6. 9 α ,11 β - Dichloro - 16 α - methyl - 1,4-pregnadiene-17 α ,21-diol-3,20-dione 17 α ,21-di-acetate.

7. 9 α ,11 β - Dichloro - 16 α - methyl - 1,4-pregnadiene-17 α ,21-diol-3,20-dione 17 α ,21-di-propionate.

8. 9 α ,11 β - Dichloro - 16 α - methyl - 1,4-pregnadiene-17 α ,21-diol-3,20-dione 17 α ,21-di-butyrate.

9. 9 α ,11 β - Dichloro - 16 α - methyl - 1,4-pregnadiene-17 α ,21-diol-3,20-dione 17 α ,21-di-cyclopropylcarboxylate.

10. 9 α ,11 β - Dichloro - 16 α - methyl - 1,4-pregnadiene-17 α ,21-diol-3,20-dione 17 α ,21-di-propionate-21-butyrate.

11. 9 α ,11 β - Dichloro - 16 α - methyl - 1,4-pregnadiene-17 α ,21-diol-3,20-dione 17 α ,21-di-butyrate-21-acetate.

12. 9 α ,11 β - Dichloro - 16 α - methyl - 1,4-pregnadiene-17 α ,21-diol-3,20-dione 17 α ,21-di-butyrate-21-propionate.

13. 9 α ,11 β - Dichloro - 16 α - methyl - 1,4-pregnadiene-17 α ,21-diol-3,20-dione 17 α ,21-di-valerate-21-acetate.

14. 17 α ,21-Di-carboxylic acid ester derivatives of 9 α ,11 β - dihalogeno - 16 α - lower alkyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20-dione compounds substantially as described.

15. Process for the preparation of a 9 α ,11 β -

tinuous stirring, Premix B which has been heated to 75°C to Premix A which has been heated to 72°C. The mixture is cooled to 40°C and the perfume then added, after which the mixture is again cooled, this time to 30°C, while the stirring is continued.

Effective anti-inflammatory response is usually achieved by 2 to 3 daily applications of topical therapeutic preparations such as those described in Examples 9 to 13. In severe or aggravated conditions, additional medication may be applied.

In addition to the topical preparations described above, the di-esters of this invention may, for the alleviation of certain inflammatory conditions, be administered subcutaneously and/or intramuscularly, conveniently in the form of aqueous suspensions suitable for injection. The injection of therapeutic preparations containing the di-esters of this invention is associated with an unusually prolonged systemic anti-inflammatory response. This prolongation of activity has been confirmed by conventional survival-rate assays in adrenalectomized rats. Usually, injectable therapeutic preparations will be so proportioned as to afford from 1 to 3 grams per litre of the di-ester as the active substance.

An injectable therapeutic preparation, in this instance, in the form of an aqueous suspension, is described in the following Example:

EXAMPLE 14

Component	Grams per Liter
9 α ,11 β -Dichloro-16 α -methyl-1,4-pregnadiene-17 α ,21-diol-3,20-dione 17 α ,21-Di-butyr-ate - - - - -	3.0
Anhydrous disodium phosphate (USP)	7.1
Monosodium phosphate monohydrate - - - - -	3.4
(USP)	
Alkyl-dimethyl-benzylammonium chloride - - - - -	0.2
(USP)	
Water-for-injection - - - - -	1.01
(USP)	

The aqueous suspension is made by dissolving the phosphate-buffers and the benzylammonium chloride in approximately 80 per cent of the water-for-injection and agitating the solution until it is homogeneous. It is then filtered through a bacteria retentive filter and the filtrate collected in a closed sterile vessel. The 9 α ,11 β -dichloro-16 α -methyl-1,4-pregnadiene-17 α ,21-diol-3,20-dione 17 α ,21-di-butyrate (previously sterilized) is aseptically slurried in a portion of the solution and then passed through a colloid mill until all the steroid particles are uniformly dispersed. The colloid mill is

rinsed with the remainder of the solution and the volume of the batch adjusted with sufficient sterile water-for-injection to make 1 litre.

The quantity and frequency of injection of the therapeutic preparation of the Example will depend upon the nature of the inflammatory condition under treatment. Usually, an effective anti-inflammatory response can be achieved by the injection of 1 cc. of the preparation, either as a single injection or in divided doses. Additional medication may be required in severe or aggravated conditions.

WHAT WE CLAIM IS:—

1. 9 α ,11 β - Dihalogeno - 16 α - lower alkyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione compounds having a carboxylic acid ester group attached at each of the 17 α - and 21-positions. 80
2. 9 α ,11 β - Dihalogeno - 16 α - methyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20 - dione compounds having a carboxylic acid ester group attached at each of the 17 α - and 21-positions. 85
3. Compounds as claimed in claim 1 or 2, wherein the halogen at the 9 α - and 11 β -positions is chlorine. 90
4. Compounds as claimed in any one of the preceding claims, wherein the carboxylic acid ester group at the 17 α - and 21-positions is an acyl radical containing from 1 to 5 carbon atoms. 95
5. Compounds as claimed in claim 4, wherein the acyl radical at the 17 α -position is different from the acyl radical at the 21-position.
6. 9 α ,11 β - Dichloro - 16 α - methyl - 1,4-pregnadiene-17 α ,21-diol-3,20-dione 17 α ,21-di-acetate. 100
7. 9 α ,11 β - Dichloro - 16 α - methyl - 1,4-pregnadiene-17 α ,21-diol-3,20-dione 17 α ,21-di-propionate. 105
8. 9 α ,11 β - Dichloro - 16 α - methyl - 1,4-pregnadiene-17 α ,21-diol-3,20-dione 17 α ,21-di-butyrate. 110
9. 9 α ,11 β - Dichloro - 16 α - methyl - 1,4-pregnadiene-17 α ,21-diol-3,20-dione 17 α ,21-di-cyclopropylcarboxylate. 115
10. 9 α ,11 β - Dichloro - 16 α - methyl - 1,4-pregnadiene-17 α ,21-diol-3,20-dione 17 α ,21-propionate-21-butyrate. 120
11. 9 α ,11 β - Dichloro - 16 α - methyl - 1,4-pregnadiene-17 α ,21-diol-3,20-dione 17 α ,21-butyrate-21-acetate. 125
12. 9 α ,11 β - Dichloro - 16 α - methyl - 1,4-pregnadiene-17 α ,21-diol-3,20-dione 17 α ,21-butyrate-21-propionate. 130
13. 9 α ,11 β - Dichloro - 16 α - methyl - 1,4-pregnadiene-17 α ,21-diol-3,20-dione 17 α ,21-valerate-21-acetate. 135
14. 17 α ,21-Di-carboxylic acid ester derivatives of 9 α ,11 β - dihalogeno - 16 α - lower alkyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20-dione compounds substantially as described. 140
15. Process for the preparation of a 9 α ,11 β -





- dihalogeno - 16 α - lower - alkyl - 1,4 - pregnadiene-17 α ,21-diol-3,20-dione compound having a carboxylic acid ester group attached at each of the 17 α - and 21-positions, which comprises diesterification, using a known procedure, of a corresponding 9 α ,11 β -dihalogeno-16 α - lower - alkyl - 1,4 - pregnadiene - 17 α ,21-diol-3,20-dione compound, whereby the desired acyl groups are introduced at the 17 α - and 21-positions. 70
16. Process for the preparation of a 9 α ,11 β -dihalogeno - 16 α - lower - alkyl - 1,4 - pregnadiene-17 α ,21-diol-3,20-dione compound having a carboxylic acid ester group attached at each of the 17 α - and 21-positions, which comprises dihalogenation using a known procedure, of a corresponding 16 α -lower-alkyl-1,4,9(11) - pregnatriene - 17 α ,21 - diol - 3,20-dione 17 α ,21-di-carboxylic acid ester compound, whereby a halogen atom is introduced at the 9 α - and 11 β -positions. 75
17. Process for the preparation of a 9 α ,11 β -dihalogeno - 16 α - lower - alkyl - 1,4 - pregnadiene-17 α ,21-diol-3,20-dione compound having a carboxylic acid ester group attached at each of the 17 α - and 21-positions, which comprises esterification, using a known procedure, of a corresponding 9 α ,11 β -dihalogeno-16 α - lower - alkyl - 1,4 - pregnadiene - 17 α ,21-diol-3,20-dione 17 α -carboxylic acid ester compound, whereby the desired acyl group is introduced at the 21-position. 80
18. Process for the preparation of a 9 α ,11 β -dihalogeno - 16 α - lower - alkyl - 1,4 - pregnadiene-17 α ,21-diol-3,20-dione compound having a carboxylic acid ester group attached at each of the 17 α - and 21-positions, which comprises esterification, using a known procedure, of a corresponding 9 α ,11 β -dihalogeno-16 α - lower - alkyl - 1,4 - pregnadiene - 17 α ,21-diol-3,20-dione 21-carboxylic acid ester compound, whereby the desired acyl group is introduced at the 17 α -position. 85
19. Process as claimed in claim 15, wherein the 9 α ,11 β -dihalogeno-16 α -lower-alkyl-1,4-pregnadiene-17 α ,21-diol-3,20-dione compound is diesterified by treating it with a mixture of trifluoroacetic anhydride and a lower aliphatic carboxylic acid chloride or anhydride in an organic solvent. 90
20. Process as claimed in claim 18, wherein the 9 α ,11 β -dihalogeno-16 α -lower-alkyl-1,4-pregnadiene-17 α ,21-diol-3,20-dione 21-carboxylic acid ester compound is esterified by treating it with an acylating medium comprising trifluoroacetic anhydride, a strong acid catalyst and a lower aliphatic or cycloaliphatic carboxylic acid. 95
21. Process as claimed in claim 18, wherein the 9 α ,11 β -dihalogeno-16 α -lower-alkyl-1,4-pregnadiene-17 α ,21-diol-3,20-dione 21-carboxylic acid ester compound is esterified by treating it with an acylating medium comprising trifluoroacetic anhydride, a strong acid catalyst and a lower aliphatic or cycloaliphatic carboxylic acid. 100
22. Process as claimed in claim 15, wherein the 9 α ,11 β -dihalogeno-16 α -lower-alkyl-1,4-pregnadiene-17 α ,21-diol-3,20-dione compound is firstly esterified with a lower alkyl ester of an orthocarboxylic acid in the presence of an acid catalyst to form the corresponding 17,21-orthoester, this orthoester is then hydrolyzed with an acid to give the corresponding 17 α -monoester, which is then treated with a lower aliphatic carboxylic acid chloride or anhydride in an organic solvent such as pyridine to introduce the desired acyl group at the 21-position. 105
23. Process as claimed in any one of claims 19 to 22, wherein the starting compound which is esterified or diesterified is a 9 α ,11 β -dichloro-16 α -methyl compound. 110
24. Process as claimed in any one of claims 19, 21 and 23, wherein the esterification procedure involves as the carboxylic acid component of the mixture, acetic, propionic, butyric, isobutyric, valeric or cyclopropyl-carboxylic acid. 115
25. Process as claimed in any one of claims 20, 22 and 23, wherein the esterification procedure involves acetic, propionic, butyric, isobutyric or valeric anhydride or the chlorides of these acids. 120
26. Process as claimed in claim 16, wherein the 16 α -lower-alkyl-1,4,9(11)-pregnatriene-17 α ,21-diol-3,20-dione 17 α ,21-di-carboxylic acid ester compound is dihalogenated by one of the procedures described and claimed in British patent No. 928,301. 125
27. Process as claimed in claim 26, wherein the 16 α - lower - alkyl - 1,4,9(11) - pregnatriene - 17 α ,21 - diol - 3,20 - dione 17 α ,21 - di-carboxylic acid ester compound is dichlorinated. 130
28. Process for the preparation of a 9 α ,11 β -dichloro - 16 α - methyl - 1,4 - pregnadiene - 17 α ,21-diol-3,20-dione 17 α ,21-di-carboxylic acid ester compound substantially as described with particular reference to any one of Examples 1 to 8. 135
29. 9 α ,11 β - Dihalogeno - 16 α - lower - alkyl - 1,4 - pregnadiene - 17 α ,21 - diol - 3,20-dione 17 α ,21-di-carboxylic acid ester compounds whenever obtained by a process as claimed in any one of claims 15 to 28, or by an obvious chemically equivalent process. 140
30. A therapeutic preparation with anti-inflammatory activity, which comprises one or more of the di-ester compounds claimed in any one of claims 1 to 14 and 29, in admixture or conjunction with a pharmaceutical carrier. 145
31. A therapeutic preparation as claimed in claim 30, which is in a form suitable for topical administration. 150
32. A therapeutic preparation as claimed in the preceding claim, which is in the form of an ointment, lotion, or a cream. 155
33. A therapeutic preparation as claimed in any one of claims 30 to 32, which contains 0.01 to 0.25 percent by weight of the di-ester compound. 160
34. A therapeutic preparation as claimed in claim 31, substantially as described with particular reference to any one of Examples 9 to 13. 165
35. A therapeutic preparation as claimed in

claim 30, which is in a form suitable for subcutaneous and/or intramuscular administration.

5 36. A therapeutic preparation as claimed in the preceding claim, which is in the form of an aqueous suspension.

10 37. A therapeutic preparation as claimed in the preceding claim, which contains from 1 to 3 grams per litre of the dihalogeno-di-ester compound.

38. A therapeutic preparation as claimed in claim 35, substantially as described with particular reference to Example 14.

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* C L M S *

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