1 575 983

PATENT SPECIFICATION

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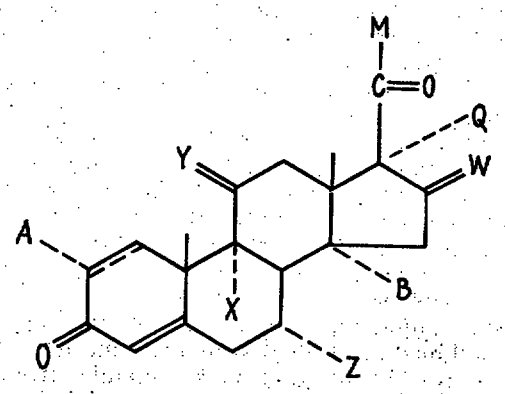
(19)

(54) NOVEL 7-HALO-3,20-DIOXO-1,4-PREGNADIENES AND -4-PREGNENES AND THEIR PREPARATION

(71) We, SCHERICO LTD., of Topferstrasse 5, 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 novel steroids of the pregnane series having valuable pharmacological properties, to processes for their preparation and to pharmaceutical compositions containing them.

According to the invention, we provide 3,20 - dioxo - 7α - halo - 4 - pregnenes and -1,4-pregnadienes of the formula



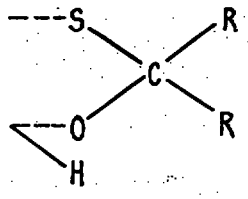
(I)

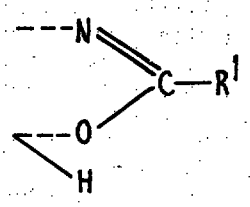
wherein the dotted line at the 1,2-positions indicates a 1,2-single bond or a 1,2-double bond;

W is a group (H,H), (H, lower alkyl), (H,α-OV¹) or =CHT, wherein V¹ is a hydrogen atom or an acyl radical of retinoic acid or of a carboxylic acid having up to 12 carbon atoms, and T is a hydrogen, fluorine or chlorine atom or a lower alkyl group;

Q is a chlorine or bromine atom or a group OV wherein V is a hydrogen atom or an acyl radical of a carboxylic acid having up to 12 carbon atoms, or, provided that W is a group (H,H) or (H, lower alkyl), Q can also be a hydrogen atom;

or Q and W taken together are a 16α,17α - lower - alkylidenedioxy, - cycloalkylidenedioxy or -aralkylidenedioxy group together with a 16β-hydrogen atom or a grouping





wherein R is a lower alkyl group and R^1 is a lower alkyl or phenyl group;

B is a hydrogen atom or, together with Q, is a 14α,17α-lower alkylidenedioxy group;

M is a group —CHO or such a group in the form of an acetal, hemiacetal or acylal, $—CH_3$, —COOR³, $—CH_2Hal$ or $—CH_2OV^2$, wherein R^3 is a hydrocarbyl group having up to 12 carbon atoms, Hal is a halogen atom having an atomic weight of less than 100, and V^2 is a hydrogen atom or an acyl radical of retinoic acid, of a carboxylic acid having up to 12 carbon atoms or of phosphoric acid, which may be in the form of a mono- or di-alkali or alkaline earth metal salt; or OV^2 together with Q is an alkylidenedioxy, cycloalkylidenedioxy, aralkylidenedioxy, alkylorthoalkanoate or alkylorthoarylcarboxylate group; or, provided that Q is an O-Acyl group,

M can also be a group $—OR^2$ wherein R^2 is a lower alkyl or halolower alkyl group;

X is a hydrogen atom or a halogen atom having an atomic weight of less than 100;

Y is an oxygen atom or a group (H,β—OH) or (H,β—OCOH), or, provided that X is chlorine or bromine, Y can also be a group (H,β-halogen), said halogen having an atomic weight of less than 100 and being at least as electro-negative as X, or, provided that X is hydrogen, Y can also be a group (H,H);

A, which is in the α-position in the 4-pregnenes, is a hydrogen atom or, provided that Y is (H,β—OH), A can also be a chlorine or fluorine atom or a methyl group; and

Z is a fluorine, chlorine, bromine or iodine atom; and

when W is (H,H), the D-homo analogs thereof.

Hydrocarbon groups in the substituent R^3 may for example be aliphatic groups having up to 12 carbon atoms including straight and branched chain alkyl groups, especially lower alkyl groups, and cycloaliphatic groups which can be saturated or unsaturated or substituted or unsubstituted, and aryl, aralkyl, and alkaryl groups. However, alkyl groups having up to four carbon atoms are preferred. Typical unsaturated aliphatic groups are vinyl, propenyl, propynyl, and butenyl; typical cycloalkyl groups are cyclopropyl, cyclopentyl, cyclohexyl, cyclopentenyl, and *p*-dicyclohexyl; typical aryl groups are phenyl, α-naphthyl, and *p*-diphenyl; typical alkaryl groups are tolyl, xylyl, and symdiethylphenyl; and typical aralkyl groups are benzyl and phenethyl.

The lower alkyl groups included within the definitions of W, T, R, R^1, R^2 and R^3 have up to six carbon atoms, and thus include pentyl and hexyl groups, but preferably have up to four carbon atoms, e.g. they are methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *sec*-butyl, or *t*-butyl. Similarly, lower alkylidenedioxy groups referred to herein have up to six and preferably 1 to 4 carbon atoms.

The acyl radicals of the carboxylic acids having up to 12 carbon atoms included in V, V^1 and V^2 may be saturated, unsaturated, straight-chained or branched-chained, aliphatic, cyclic, cyclic-aliphatic, aromatic, aromatic-heterocyclic, aryl-aliphatic, or alkyl-aromatic, and may be substituted by one or more hydroxy groups or by alkoxy groups containing from 1 to 5 carbon atoms or by halogen atoms. Typical ester groups of the 7 - halo - 3,20 - dioxo - 1,4 - pregnadienes of our invention are thus derived from hydrocarboncarboxylic acids such as alkanoic acids exemplified by formic, trimethyl-acetic, isobutyric, isovaleric, enanthic, capric, cyclopentylpropionic, undecylic, lauric and adamantanecarboxylic acids; substituted alkanoic acids such as phenoxyacetic, trifluoroacetic and β-chloropropionic acids; aromatic and substituted aromatic acids, especially benzoic acids substituted by a halogen atom or a methoxy group, such as benzoic, toluic, *p*-chlorobenzoic, *p*-fluorobenzoic, *p*-methoxybenzoic, and 3,5-dimethylbenzoic acids; aromatic-heterocyclic acids, in particular isonicotinic acid; aryl-alkanoic acids such as phenylacetic, phenylpropionic, and β-benzoylaminoisobutyric acids; unsaturated acids such as acrylic and sorbic acids; and dibasic acids such as succinic, tartaric and phthalic acids.

The preferred acyl groups are those derived from lower alkanoic acids having up to 8 carbon atoms, in particular from acetic, propionic, butyric, valeric, caprylic, caproic and *t*-butylacetic acids, and from benzoic acid or the substituted benzoic acids mentioned above, and in particular those derived from propionic, *n*-butyric and benzoic acid.

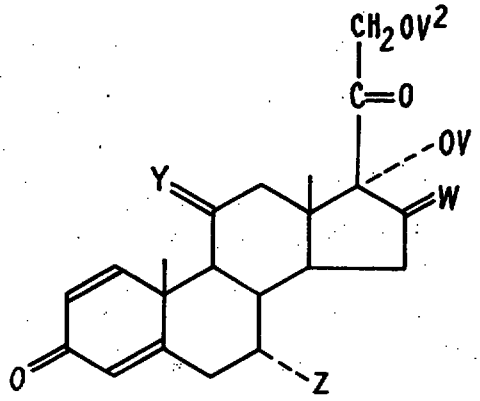
X is preferably a fluorine or especially a hydrogen atom, and Z is preferably a chlorine or bromine atom.

The alkylidene or alkylidenedioxy groups represented by =CHT, by W and Q

together, by B and Q together or by OV^2 and Q together preferably have up to 4 carbon atoms and thus include methylene, ethylidene, *n*-propylidene, isopropylidene, *n*-butylidene, and *sec*-butylidene and their corresponding dioxy derivatives. W is most preferably a methylene group or the group (H,CH_3), especially $(H,\alpha—CH_3)$.

Y is most preferably an oxygen atom or the group $(H,\beta—OH)$.

A particularly preferred group of 1,4-pregnadienes according to the invention has the formula



(II)

wherein

Z is a chlorine or bromine atom,

W is a methylene group or the group (H,CH_3),

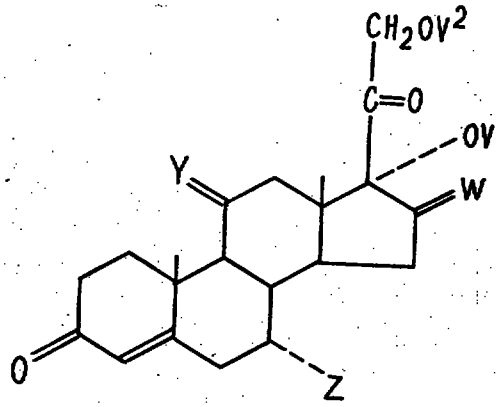
Y is an oxygen atom or the group $(H,\beta—OH)$, and

V and V^2, which may be the same or different,

are hydrogen atoms or acyl radicals of hydrocarbon carboxylic acids having up to 12, especially up to 8, carbon atoms.

The dotted line at the 1,2-positions preferably represents a 1,2-double bond since the 1,4-pregnadienes are in general much more stable and more convenient to prepare than the 4-pregnenes.

A preferred group of 3,20 - dioxo - 7α - halo - 4 - pregnenes according to the invention can be represented by the formula



(III)

wherein

Z is an iodine or (preferably) a chlorine or bromine atom,

Y is an oxygen atom or the group $(H,\beta—OH)$,

W is a methylene group or the group (H,CH_3) or (H,H) and

V and V^2, which may be the same or different, are hydrogen atoms or acyl radicals of hydrocarbon carboxylic acids having up to 12 (preferably up to 8) carbon atoms. In particular, V and V^2 in Formulae II and III can be any of the acyl groups hereinbefore defined.

A particular preferred compound of this group is 7α - chloro - 4 - pregnene - 11β,17α,21 - triol - 3,20 - dione - 17,21 - dipropionate.

The 7α - halo - 3,20 - dioxo - 4 - pregnenes and -1,4-pregnadienes of formula I are usually white to off-white crystalline solids, which are insoluble in water (with

the exception of alkali metal salts of their esters such as the hemisuccinate and phosphate esters) and soluble in most organic solvents, particularly in acetone, dioxan, dimethylformamide and dimethylsulfoxide, although of limited solubility in non-polar solvents such as dialkyl ethers and alkanes.

The 7α - halo - 1,4 - pregnadienes are preferably kept below room-temperature (e.g. at 0° to 5°C.) when stored for long periods of time to minimize decomposition to the corresponding 1,4,6-pregnatrienes (from which they are usually preparable). For short term storage, the 7α-chloro derivatives are relatively stable up to 100°C; however, the 7α-bromo derivatives should be stored below 55°C.

The 7α - halo - 3,20 - dioxo - 4 - pregnenes are preferably stored in an open vessel placed in a chamber under reduced pressures and at moderate temperatures (e.g. 0° to 40°C.) to minimise decomposition to the corresponding 4,6-pregnadienes (from which they are usually preparable) with release of hydrogen halide.

In general, the 3,20 - dioxo - 7α - halo - 1,4 - pregnadienes of formula I, particularly those wherein V is a hydrogen atom or an acyl group or wherein OV^2 and Q together are a 17α,21-alkylidenedioxy group, exhibit corticoid activity. Those that have halogens at both C-9 and C-11 or an oxygen function at C-11 and a halogen or hydrogen at C-9 possess glucocorticoid activity and are particularly valuable as anti-inflammatory agents. Preferred anti-inflammatory agents, particularly for topical administration, are 3,20 - dioxo - 7α - halo - 1,4 - pregnadiene - 17α,21 - diols and especially -11β,17α,21-triols of formula II above and their esters.

7α-Bromo and 7α-chloro compounds of formula I having a cortical side chain at C-17 (i.e. compounds of formula I wherein M is CH_2OV^2 and Q is OV) and ester derivatives thereof, particularly compounds unsubstituted at C-2, C-9 and C-14, are especially useful as topical anti-inflammatory agents; and in particular, compounds that are substituted at C-16 by a lower alkyl group (preferably a 16-methyl and especially a 16α-methyl group) or by a 16-methylene group exhibit excellent topical anti-inflammatory activity that is in general superior to the topical anti-inflammatory activity of the corresponding 7-unsubstituted analogs. Thus particularly valuable compounds of this invention include 7α - halo - 3,20 - dioxo - 1,4 - pregnadienes of formula II defined above, wherein Y is the group (H,β—OH).

The compounds of formula II wherein Y is the group (H,β—OH) and V is a hydrogen atom and in partciular wherein V^2 is also a hydrogen atom are valuable mainly as intermediates in preparing the preferred 17-mono- and 17,21-diester derivatives.

The 17,21-desoxy-, 17-hydroxy-21-desoxy- and 17-acyloxy-21-desoxy-derivatives of formula I exhibit anti-inflammatory activity but are more valuable as progestational agents.

Particularly useful topical anti-inflammatory agents of formula II are those wherein V and V^2 are acyl radicals of hydrocarboncarboxylic acids having up to 8 carbon atoms, particularly the 17-propionate, 17-*n*-butyrate and 17-benzoate derivatives which exhibit high topical anti-inflammatory activity with very low systemic corticoid effects. We have discovered that, when the compounds of formula II are administered topically or systemically, the topical anti-inflammatory effect of the compounds is dependent much more upon the nature of the ester group at C-17 than upon the ester group at C-21, and in particular that the topical anti-inflammatory activity of a 17-propionate 21-ester of formula II is to a large extent independent of the nature of the C-21 ester group. The 16α-methyl-17-mono- and 17,21-diacyl-derivatives of formula II are most valuable since their topical activity is greatly enhanced over that of the corresponding 7-unsubstituted compounds.

The superior topical activity of the preferred 3,20 - dioxo - 7α - halo - 1,4 - pregnadienes of formula II, particularly of the 16α-methyl derivatives, may be demonstrated by pharmacological tests in animals. Thus, for example, when tested topically in mice by a modification of the croton oil induced ear edema test (G. Tonelli *et al., Endocrinology 77:* 625—634 (1965)), 7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17 - benzoate 21-acetate exhibits about twice the topical activity but only a fraction of the systemic effect of betamethasone dipropionate (9α - fluoro - 16β - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate). Additionally, when tested in mice by a modification of the skin atrophy test (E. G. Weirich and J. Longauer,

Res. Exp. Med. 163, 229 (1974)), this 7α-bromo-compound of our invention shows markedly lower skin atrophy potency than betamethasone dipropionate. Moreover, 7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-benzoate 21-acetate shows great separation of local from systemic effects when injected locally in the rat and has very low glucocorticoid activity when administered orally to both mice and rats.

In similar manner, when tested by the above described tests in animals, other 7α - halo - 1,4 - pregnadienes of formula II, e.g. 7α-chloro- and 7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate, exhibit high topical anti-inflammatory activity coupled with low systemic effects following topical application, and low skin atrophy as well as low parenteral and oral glucocorticoid activity.

Preferred compounds of formula II include:

the 21-acetate, 21-propionate, 21-*n*-butyrate, 21-isobutyrate and 21-valerate of 7α-chloro- and 7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-propionate;

the 21-acetate, 21-propionate and 21-*n*-butyrate of 7α-chloro- and 7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17 - *n* - butyrate;

and the 21-acetate, 21-propionate, 21-*n*-butyrate and 21-benzoate of 7α-fluoro-7α-chloro- and 7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-benzoate.

In particular, 7α-chloro- and 7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate and 7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-benzoate 21-acetate are especially valuable since they have high topical anti-inflammatory activity coupled with low systemic effects following topical application, and low skin atrophy activity as well as low parenteral and oral glucocorticoid activity.

Other valuable compounds of formula II include:

7α-chloro and 7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-valerate 21-acetate;

7α-chloro- and 7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17 - isobutyrate 21-acetate;

7α-chloro- and 7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione and their 21-acetate, 21-benzoate, 21-pivalate, 17-propionate and 17-valerate;

the 16β-methyl epimers of these 16α-methyl derivatives such as the 21-acetate, the 17,21-dipropionate, the 17-propionate 21-*n*-butyrate, the 17-propionate 21-acetate and the 17-benzoate 21-acetate of 7α-chloro- and 7α - bromo - 16β - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione;

and 16-methylene derivatives such as 7α - chloro - 16 - methylene - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate.

The invention also includes 7α - halo - 3,20 - dioxo - 1,4 - pregnadienes of formula I such as:

9α-halo derivatives of the compounds of formula II, particularly their 9α-fluoro and 9α-chloro derivatives;

9α,11β - dihalo - pregnadienes of formula I such as 7α,9α,11β - trichloro - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione 21-acetate and in particular 7α,9α,11β - trichloro - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione 17,21-dipropionate;

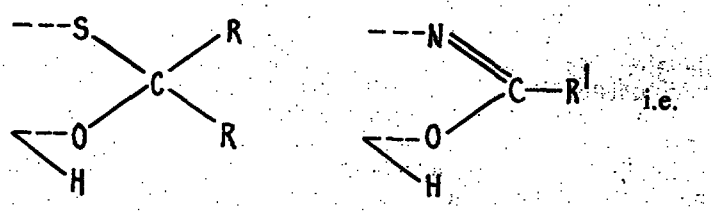
21 - halo - 21 - desoxy - pregnadienes such as 7α,21-dichloro-16α- and 16β - methyl - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate, and 7α,21 - dichloro - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate and its 7α-bromo analog;

21 - desoxy - pregnadienes such as 7α-chloro- and 7α - bromo - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate, and 7α-chloro-, 7α-bromo- and 7α - iodo - 1,4 - pregnadien - 17α - ol - 3,20 - dione and its 17-acetate and 17-propionate;

16α-hydroxy-pregnadienes and their ester derivatives such as 7α-chloro- and 7α - bromo - 1,4 - pregnadiene - 11β,16α,17α,21 - tetrol - 3,20 - dione and their 17-propionates, 16,21-diacetate 17-propionates, 17-benzoates and 17-benzoate 21-acetates;

16α,17α-lower alkylidenedioxy compounds, especially 7α - bromo - 16α,17α - isopropylidenedioxy - 1,4 - pregnadiene - 11β,21 - diol - 3,20 - dione 21-acetate;

compounds wherein Q and W together represent the grouping



i.e.

pregnadieno[17,16α-d] - 1',3' - oxathiolanes and 5'βH - pregnadieno[17,16-d]oxazoles respectively, R and R^1 preferably being methyl groups as in 7α-chloro- and 7α - bromo - 11β - hydroxy - 2',2' - dimethyl - 1,4 - pregnadieno[17,16α-d] - 1',3' - oxathiolane - 3,20 - dione and their 9α-chloro derivatives, and 7α-chloro- and 7α - bromo - 11β,21 - dihydroxy - 2' - methyl - 5'βH - 1,4 - pregnadieno[17,16α-d]oxazole - 3,20 - dione 21-acetate;

20 - carboxylate - pregnadienes such as *n* - butyl 7α - chloro - 11β - hydroxy - 3,20 - dioxo - 16α - methyl - 1,4 - pregnadien - 21 - oate, propyl 2,7α - dichloro - 11β - hydroxy - 3,20 - dioxo - 16α - methyl - 1,4 - pregnadien - 21 - oate, and their 7α-bromo analogs;

20-alkoxy- and 20 - haloalkoxy - 21 - nor - pregnadienes (which also may be termed alkyl androstadiene - 17β - carboxylates) such as 7α - chloro - 16β - methyl - 20 - chloromethoxy - 21 - nor - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate, 7α - chloro - 16 - methylene - 20 - fluoromethoxy - 21 - nor - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate, 7α - chloro - 16β - methyl - 20 - methoxy - 21 - nor - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate, and their corresponding 7α-bromo derivatives;

21-oxo pregnadienes and derivatives, e.g. acetals, hemiacetals and acylals thereof, such as 2,7α - dichloro - 9α - fluoro - 16α - methyl - 1,4 - pregnadiene - 11β,17α - diol - 3,20,21 - trione and its 21-methylhemiacetal, 7α - chloro - 9α - fluoro - 16α - methyl - 21,21 - diacetoxy - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate, 7α - chloro - 9α - fluoro - 16α - methyl - 1,4 - pregnadiene - 11β,17α - diol - 3,20,21 - trione and its 21-ethylene ketal and 21,21-dimethylacetal, and their corresponding 7α-bromo derivatives;

D-homo-pregnadienes such as 7α-chloro- and 7α - bromo - D - homo - 1,4 - pregnadiene - 11β,17aα,21 - triol - 3,20 - dione 17a,21-di-*n*-butyrate;

and 7α-fluoro and 7α-iodo derivatives such as 7α,9α - difluoro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-acetate and its 17-benzoate, 7α - fluoro - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-acetate and its 17-*n*-butyrate and 17-benzoate, and their 16α-methyl derivatives; 7α - iodo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione, its 21-acetate and its 17,21-dipropionate, their 16β-methyl epimers, and all their 9α-fluoro derivatives.

Another preferred group of compounds of this invention comprises the 11-oxo derivatives of formula I which possess anti-inflammatory activity but are more frequently used as intermediates in the preparation of the corresponding 11β-hydroxy derivatives according to procedures disclosed hereinbelow. Particularly valuable 11-oxo derivatives are the compounds of formula II defined above wherein Y is an oxygen atom.

Preferred compounds of formula III include the 21-acetate, 21-propionate, 21-*n*-butyrate, 21-isobutyrate and 21-valerate of 7α - chloro - 16α - methyl - 4 - pregnene - 11β,17α,21 - triol - 3,20 - dione 17-propionate, and the 21-acetate, 21-propionate, 21-*n*-butyrate and 21-isobutyrate of 7α - bromo - 16α - methyl - 4 - pregnene - 11β,17α,21 - triol - 3,20 - dione 17-propionate;

the 21-acetate, 21-propionate, and 21-*n*-butyrate of 7α-chloro- and 7α - bromo - 16α - methyl - 4 - pregnene - 11β,17α,21 - triol - 3,20 - dione 17-*n*-butyrate;

and the 21-acetate, 21-propionate, 21-*n*-butyrate and 21-benzoate of 7α-chloro- and 7α - bromo - 16α - methyl - 4 - pregnene - 11β,17α,21 - triol - 3,20 - dione 17-benzoate.

Other compounds of formula III include:

7α-chloro- and 7α - bromo - 16α - methyl - 4 - pregnene - 11β,17α,21 - triol - 3,20 - dione, their 17-valerate 21-acetate, 17-isobutyrate 21-acetate, 21-acetate, 21-benzoate, 21-pivalate, 17-propionate and 17-valerate;

their 16β-methyl epimers such as the 21-acetate, the 17,21-dipropionate, the

17-propionate 21-*n*-butyrate, the 17-propionate 21-acetate and the 17-benzoate 21-acetate of 7α-chloro- and 7α - bromo - 16β - methyl - 4 - pregnene - 11β,17α,21 - triol - 3,20 - dione;

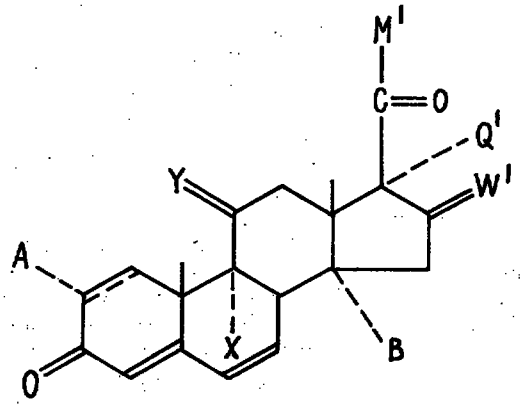
16-methylene derivatives such as 7α - chloro - 16 - methylene - 4 - pregnene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate;

and 16-unsubstituted analogs of the aforenamed 16-substituted derivatives, e.g. 7α - chloro - 4 - pregnene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate.

The 7α-halo-3,20-dioxo-4-pregnenes of formula III also exhibit topical anti-inflammatory activity and thus are useful in the treatment of corticosteroid-responsive dermatoses such as contact and allergic dermatitis and psoriasis. They may be applied topically or locally in any conventional pharmaceutical form provided that it is free of acids and bases. P. A. Diassi *et. al., J. Med. Chem.*, Vol. 10, 551 (1967), describe 7α-chloro-A-nor-progesterone and disclose that the introduction of the 7-chlorine atom greatly diminishes the progestational activity of the 7-unsubstituted precursor. Additionally, P. A. Diassi *et. al.* teach that no 7α-chloro-4-dehydro-3-one has ever been reported as obtained either by oxidation of a 4-dehydro-3-one with 2,3-dichloro-5,6-dicyanbenzoquinone in the presence of hydrogen chloride (the quinone being simultaneously reduced to the corresponding quinol) or by addition of hydrogen chloride to 4,6-*bis*-dehydro-3-ones; they postulate that steroids having a 7α-chloro-4-dehydro-3-one structure may exist in the reaction mixture but are unstable and revert to 4,6-*bis*-dehydro-3-ones when attempts are made to isolate said 7α-chloro-4-dehydro-3-ones and free them from the quinone and quinol.

However, we have now discovered that 7α-chloro-4-dehydro-3-ones can be isolated substantially pure and in particular free or substantially free of the corresponding 6,7-dehydrohalogenated compounds, quinone and quinol. We have also surprisingly discovered that 7α-halo-4-pregnene-3,20-diones and in particular 7α-halo-1,4-pregnadiene-3,20-diones are in general valuable steroids having valuable activity such as corticoid activity.

According to the invention, therefore, we provide a process for the preparation of a compound of the formula I defined above wherein Z is a chlorine, bromine or iodine atom, with the proviso that Z is not a chlorine atom when X is a halogen atom, which comprises, as main reaction step, the addition of a hydrogen halide selected from hydrogen chloride, hydrogen bromide and hydrogen iodide to the 6,7-double bond of a compound of the formula



(IV)

wherein the dotted line, A, B, X and Y are as defined above and W', Q' and M' are W, Q and M are as defined above,

or W' and Q' taken together are a 16α,17α-alkyl-orthoalkanoate or 16α,17α-alkylorthoarylcarboxylate group together with a 16β-hydrogen atom,

or M' is the group —CH_2OV^3, and OV^3 and Q' together with the oxygen atom of the C_{20} carbonyl group are a 17α,20; 20,21-*bis*-methylenedioxy group, in the presence of an inert solvent; with the provisos that

(i) when the hydrogen halide is hydrogen chloride, then X is a hydrogen atom;

(ii) when Y is the group (H,β—OH) and the hydrogen halide is hydrogen bromide, then X is a hydrogen atom; and

(iii) when Y is the group (H,β—OH) and the hydrogen halide is hydrogen iodide, then X is a hydrogen, chlorine or fluorine atom.

The hydrogen halide should be used in an amount at least equimolar to the steroid and preferably in at least a 5 molar excess, e.g. 10 to 50 molar excess.

In order to obtain a compound of the formula I, this main step may then be followed by at least one of the following steps:

when W' and Q' taken together are a 16α,17α-alkylorthoalkanoate or 16α,17α-alkylorthoarylcarboxylate group together with a 16β-hydrogen atom, the product is hydrolysed to yield a compound wherein Q is a hydroxy group and W is the group (H,α—OH);

or, when OV^3 and Q' together with the oxygen atom at the C_{20} carbonyl group are a 17α,20; 20,21-*bis*-methylenedioxy group, the product is hydrolysed to yield a compound wherein OV^3 and Q are hydroxy groups;

and/or when Y is an oxygen atom and either

(i) Z is a bromine atom and X is a halogen atom, or

(ii) Z is an iodine atom and X is a bromine atom, and a compound wherein Y is the group (H,β—OH) is required, this compound is prepared by reduction of a corresponding product wherein Y is an oxygen atom;

and/or, when X is a hydrogen atom, Y is the group (H,β—OH), and Z is a chlorine or bromine atom, a 9(11)-double bond is introduced by dehydration and the product is subjected to addition of halogen to the 9(11)-double bond or of a 9α-chlorine or bromine atom and of an 11β-hydroxy group to the 9(11)-double bond;

and finally a compound of the formula I is isolated.

The immediate product of this main step and/or the compound of the formula I may if desired be subjected to a number of finishing steps in any appropriate order, which may be more generally defined as follows:

a) Hydrolysis of an esterifying group or groups at the 16α-, 17α- and/or 21-position to hydroxy;

b) Hydrolysis of a 17α,20; 20,21-*bis*-methylenedioxy group to 20-oxo-17α,21-dihydroxy groups, or of a 21-ethylene ketal to 21-oxo, or of a 17α,21-alkylidenedioxy, -cycloalkylidenedioxy or aralkylidenedioxy group to 17α,21-dihydroxy groups;

c) Esterification of a hydroxy group at the 16α-,17α- and/or 21-position;

d) Reduction of an 11-oxo group to an 11β-hydroxy group;

e) 9(11)-Dehydration of a 9-unsubstituted-11β-ol to a 4,9(11)-pregnadiene or to a 1,4,9(11)-pregnatriene, except when Z is an iodine atom, followed by addition of halogen to the 9(11)-double bond,

or followed by addition of a chlorine or bromine atom and a hydroxy group to the 9(11)-double bond with the formation of a 9α-chloro- or 9α-bromo-11β-hydroxy steroid;

f) 17α-Chlorination or bromination;

whereafter a compound of the formula I is isolated.

The main step is preferably carried out under anhydrous conditions, especially when the starting material has a 1,2-double bond, to minimize side reactions such as hydrolysis of any ester groups present. Saturated solutions of hydrogen halide in an anhydrous solvent are preferably employed to minimize reaction time.

Non-reactive organic solvents suitable for use in this process are those in which the starting material of the formula IV and the hydrogen halide are soluble. By "non-reactive" is meant any organic solvent which will not react with the steroid substrate or the hydrogen halide so as to cause competing side reactions. Thus, in this process, solvents that are usually better avoided include water (which will cause hydrolysis of esters), alcohols (which might cause ester exchange under acid conditions), and nitriles, e.g. acetonitrile (which would form imino-ethers with steroidal alcohols).

Particularly useful solvents for use in this process are ethers such as dioxan, tetrahydrofuran and diethylether; chlorinated hydrocarbons such as chloroform, methylene chloride and ethylenedichloride; organic acids such as acetic and propionic acids; tertiary amides such as dimethylformamide, diethylformamide, and hexamethylphosphortriamide; and dimethylsulfoxide. Dioxan, acetic acid and tetrahydrofuran are particularly suitable solvents, tetrahydrofuran being preferred for reactions with hydrogen chloride, and acetic acid for reactions with hydrogen bromide or hydrogen iodide.

This reaction is preferably carried out at temperatures in the range of from about 0°C. to about 30°C. or preferably up to ambient temperature (e.g. 20°C). although lower temperatures (e.g. –20°C.) and temperatures as high as about 60°C. may be employed. (Temperatures above 30°C. are preferably not employed except when a 7α - chloro - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione or ester

thereof is being prepared). The reaction time depends upon the hydrogen halide, solvent, and concentration being employed. Thus, for example, in acetic acid, the addition of hydrogen iodide is usually complete within one or two minutes, whereas the addition of hydrogen bromide at room temperature may be completed in from 20 to 60 minutes. The addition of hydrogen chloride in tetrahydrofuran is preferably carried out at 0°C. rather than at room temperature, since the greater concentrations of hydrogen chloride thereby obtainable enable the reaction to be completed within an hour rather than in about 24 hours.

Substituents present in the 3,20-dioxo-1,4,6-pregnatriene and 3,20-dioxo-4,6-pregnadiene starting steroids usually remain unchanged under the conditions of this process, so that it is usually preferable for the starting steroids to have all the substituents desired in the 7α - halo - 3,20 - dioxo - 1,4 - pregnadiene and -4-pregnene products.

This process is preferably carried out by adding the starting 3,20-dioxo-1,4,6-pregnatriene or -4,6-pregnadiene, either in the solid state or in solution, to a saturated solution of dry hydrogen halide in an anhydrous solvent, usually at 0°C. to 20°C., the molar ratio of hydrogen halide to steroid being about 40 to 1. After the reaction is complete, as determined by thin layer chromatography, the reaction mixture is poured into ice water and the resultant precipitates of 7α - halo - 3,20 - dioxo - 1,4 - pregnadiene or -4-pregnene is separated by filtration or extraction and isolated in a pure state, usually by chromatography. In particular, the product especially when it is a 7α-halo-3,20-dioxo-4-pregnene, is preferably separated at temperatures no higher than about 25°C. in a state substantially free of acid and base by freeing it of excess acid and solvent without subjecting it to a substantially basic medium.

In the starting material of formula IV, X is preferably a hydrogen atom, since the 9-unsubstituted compounds of formula IV generally tend to undergo addition of hydrogen halide more readily than their 9α-halo-derivatives. It is indeed advantageous also for X in the final product of formula I to be a hydrogen atom, since the 9α-unsubstituted compounds of formula I generally have better topical anti-inflammatory activity than their 9α-halo derivatives.

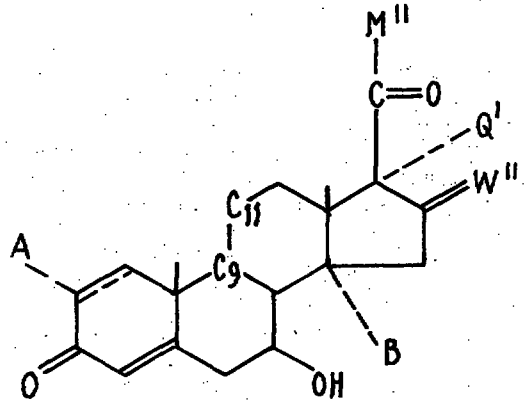
When the starting compound is a 1,2 - dihydro - 3,20 - dioxo - 4,6 - pregnadiene, its conversion into a 3,20-dioxo-7α-chloro-4-pregnene proceeds faster than the conversion of a 3,20 - dioxo - 1,4,6 - pregnatriene into a 3,20 - dioxo - 7α - chloro - 1,4 - pregnadiene, and can therefore if desired be carried out in the presence of water without causing significant hydrolysis of ester groups that may be present. Moreover, the 1,2-dihydro-4-pregnenes of the formula I, being much less stable than the 1,4-pregnadienes, must be isolated from the excess acid as quickly as possible without using a basic medium and should be stored *in vacuo* in an open vessel at temperatures no higher than about 25°C.

When a 7α - halo - 11β - hydroxy - 3,20 - dioxo - 1,4 - pregnadiene or -4-pregnene of formula I is prepared from a steroid of the formula IV, rather low yields of pure product are obtained if the steroid of formula IV contains an 11β-hydroxy group. Better overall yields of pure product are obtained if the steroid of the formula IV has an 11-oxo group, and the resulting 7α - halo - 3,11,20 - trioxo - 1,4 - pregnadiene or -4-pregnene is then reduced at the 11-position. Suitable reducing agents include sodium, potassium or lithium borohydride, tetra-*n*-butylammonium borohydride, or lithium tri-*t*-butoxy-aluminium hydride, in an inert organic solvent, preferably sodium borohydride in an inert organic solvent comprising methanol or dimethylformamide. When the starting material of the formula IV is a 3,11,20 - trioxo - 17α - hydroxy - 1,4,6 - pregnatriene 17-acylate wherein any 21-hydroxy group is esterified, reduction occurs very specifically at the 11-oxo group. However, when a 3 - oxo - 7α - halo - 11β - hydroxy - 1,2 - dihydro - 4 - pregnene is being prepared by reduction of the corresponding 11-oxo derivative (e.g. with sodium borohydride), concomitant reduction at the 3-keto group tends to occur so that better yields of the desired product are obtained when the resultant 7α-halo-11β-hydroxy product is oxidised with an oxidising agent capable of oxidizing an allylic hydroxy group to an oxo group under substantially non-basic conditions. The oxidising agent may for example be pyridinium chlorochromate in an inert organic solvent e.g. methylene chloride, preferably in the presence of a weak base e.g. sodium acetate, or a carbodiimide e.g. dicyclohexylcarbodiimide together with dimethylsulfoxide and a weak acid e.g. pyridinium trifluoroacetate, but is preferably neutral active manganese dioxide in an inert organic solvent at room temperature.

The 3,20-dioxo-1,4,6-pregnatriene and 3,20-dioxo-4,6-pregnadiene starting

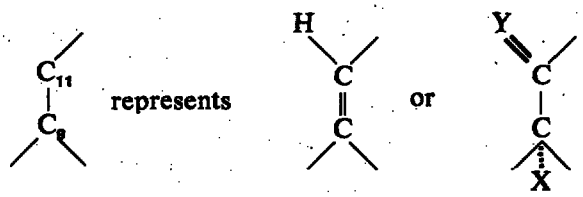
compounds of formula IV either are known compounds or are conveniently prepared from their 6,7-dihydro derivatives by standard techniques for effecting dehydrogenation between C-6 and C-7, e.g. by means of chloranil or 2,3 - dichloro - 5,6 - dicyanobenzoquinone (DDQ) or by bromination at C-6 followed by dehydrobromination. Since ester groups are usually present in the 6,7-dihydro derivatives, anhydrous conditions are preferably employed to minimize hydrolysis.

The invention further provides a process for the preparation of a compound of the formula I defined above wherein Z is a fluorine, chlorine or bromine atom, with the proviso that Z is a fluorine atom when a 1,2-single bond is present, which comprises, as main reaction step, reacting a compound of the formula



(V)

wherein the dotted line, Q', A and B are as defined above, M'' and W'' are respectively M' and W' defined above with the proviso that M'' is not a hydroxymethyl group and W'' is not the group (H,α—OH), and the grouping



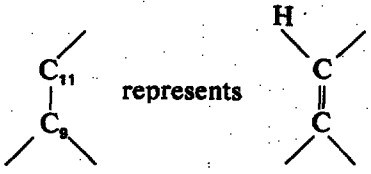
wherein Y and X are as defined above,

with a halogenating agent capable of replacing the 7β-hydroxy group with a 7α-halogen atom selected from fluorine, chlorine and bromine, in the presence of an inert organic solvent, with the proviso that a 7α-chlorine or 7α-bromine atom is introduced only when a 1,2-double bond is present.

In order to obtain a compound of the formula I, this main step may then be followed by at least one of the following steps:

when W'' and Q' taken together are a 16α,17α-alkylorthoalkanoate or 16α,17α - alkylorthoarylcarboxylate group together with a 16β-hydrogen atom, the product is hydrolysed to yield a compound wherein Q is a hydroxy group and W is the group (H,α—OH);

or, when OV^3 and Q' together with the oxygen atom of the C_{20} carbonyl group are a 17α,20; 20,21-*bis*-methylenedioxy group, the product is hydrolysed to yield a compound wherein OV^3 and Q are hydroxy groups; and/or, when the grouping



halogen is added to the 9,11-double bond or a chlorine or bromine atom and a hydroxy group are added to the 9,11-double bond with the formation of a 9α-chloro- or 9α-bromo-11β-hydroxy steroid.

The immediate product of this main step and/or the compound of the formula

I may if desired be subjected to a number of finishing steps in any appropriate order, which may be more generally defined as follows:

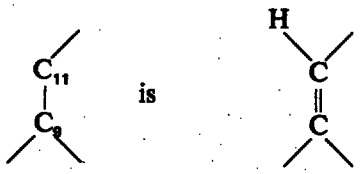
a) Hydrolysis of an esterifying group or groups at the 16α-, 17α- and/or 21-position to hydroxy;

b) Hydrolysis of a 17α,20; 20,21-*bis*-methylenedioxy group to 20-oxo-17α,21-dihydroxy groups, or of a 21-ethylene ketal to 21-oxo, or of a 17α,21-alkylidenedioxy, -cycloalkylidenedioxy, or aralkylidenedioxy group to 17α,21-dihydroxy groups;

c) Esterification of a hydroxy group at the 16α-, 17α- and/or 21-position;

d) Reduction of an 11-oxo group to an 11β-hydroxy group;

e) Addition to the 9,11-double bond of halogen or of a 9α-chlorine or bromine atom and of an 11β-hydroxy group, either when the grouping



or after such a 9(11)-double bond has been introduced by 9(11)-dehydration of a 9-unsubstituted-11β-ol;

f) 17α-Chlorination or bromination.

Preferably the halogenating agent is either a tertiary amine having an N-(2-chloro-1,1,2-trifluoroethyl) group, said amine being used alone for the preparation of a 7α-fluoro steroid but in the presence of a metal chloride or bromide that is soluble in the reaction mixture for the preparation of a 7α-chloro or 7α-bromo steroid respectively, or a tertiary amine having an N-trichlorovinyl group for the preparation of a 7α-chloro steroid. A particularly preferred halogenating agent is N-(2-chloro-1,1,2-trifluoroethyl)diethylamine, also known as fluoramine; the reaction between the steroid and fluoramine is preferably effected at moderately low temperatures (e.g. at about 0°C.), under an inert atmosphere (e.g. under argon, neon or nitrogen) and under anhydrous conditions. All primary and unhindered secondary alcohol groups (i.e. at the 21- and 16α-positions, but not at the 11β-position) should be protected, e.g. by esterification. The preferred molar ratio of fluoramine to steroid is about 6:1.

When fluoramine alone (i.e. without metal chloride and bromide) is used as fluorinating agent, the solvent is preferably a halohydrocarbon, especially methylene chloride, and the product is a 7α-fluoro steroid. The preferred metal chloride and bromide are lithium chloride and bromide. When fluoramine is used together with lithium bromide as brominating agent, the solvent is preferably a halohydrocarbon, especially methylene chloride, and the product is a 7α-bromo-steroid. When fluoramine is used together with lithium chloride as chlorinating agent, the solvent is preferably an ether, especially tetrahydrofuran, and the product is a 7α-chloro steroid. The molar ratio of lithium chloride or lithium bromide to steroid is preferably about 12 to 1.

The reaction of the steroid of the formula V with fluoramine (if desired in the presence of lithium chloride or bromide) is preferably allowed to proceed to completion, e.g. until thin layer chromatography shows that the starting steroid is no longer present. The product may then be isolated by evaporation of the reaction mixture and purified by chromatography to obtain the desired 7α-halo derivative, sometines in admixture with the corresponding 7-unsubstituted-6-dehydro derivative (especially when fluoramine alone is the halogenating agent). Such a mixture may be separated by converting this 6-dehydro derivative into a derivative that is easily separable from the 7α-halo product by chromatography, in particular into a 6,7-disubstituted derivative, e.g. into the corresponding 6β,7β-diol by reaction with osmium tetroxide in dioxan in the presence of pyridine.

7α-Chloro compounds of the formula I can also be prepared from a steroid of the formula V by reaction with N,N-diethyl - 1,2,2 - trichlorovinylamine in a halohydrocarbon, e.g. methylene chloride, as solvent and preferably at moderately low temperatures, e.g. at about 0°C., and under an inert atmosphere, e.g. nitrogen. The molar ratio of N,N - diethyl - 1,2,2 - trichlorovinylamine to steroid is preferably about 6 to 1.

The compound of the formula V, which in these processes reacts with the halogenating agent, preferably has a 1,2-double bond, since the resulting 1,4-

pregnadienes are in general more stable, more readily isolated and more active as topical anti-inflammatory agents than the corresponding 1,2-dihydro-4-pregnenes.

The steroids of the formula V, required as starting materials for this process, are novel compounds and can be prepared by conversion of the corresponding 6β,7β-dihydroxy derivatives into 6β,7β-alkylorthoalkanoate esters, hydrolysis at the 7-position with weak acid and then reduction of the resulting 6β - acyloxy - 7β - hydroxy - derivative, preferably with chromous acetate, sodium acetate and aqueous acetic acid in acetone.

The product of either of the two main reaction steps described above (starting from a steroid of the formula IV or V) may then be subjected to one or more of the finishing steps (a) to (f) mentioned above. Whether or not it is convenient or even essential to carry out such a finishing step will normally be clear to a skilled steroid chemist; it will often be more convenient to carry out the corresponding chemical changes during the preparation of the steroid of the formula IV or V.

7α - Halo - 3,20 - dioxo - 1,4 - pregnadienes and -4-pregnenes having ester functions at C-16, C-17 and/or C-21 can be converted into 7α - halo - 3,20 - dioxo - 1,4 - pregnadienes and -4-pregnenes having free hydroxyl groups at C-16, C-17 and/or C-21, for example by the action of acidic saponification agents, e.g. a strong mineral acid and preferably 70% perchloric acid in methanol. By regulating the reaction time and quantity of acid, a 17,21-dihydrocarboncarboxylate can be converted into the corresponding 17-monoester or 17,21-diol. The compounds of this invention have a halogen atom at C-7 so, basic hydrolyzing agents are usually not desirable since unwanted side reactions will often take place, such as elimination of the 7α-halogen atom; however, mild basic saponification agents such as aqueous sodium bicarbonate in methanol can often be employed successfully.

The hydrolysis of an esterifying group at C-21 or at C-16 is preferably effected by means of diastase enzyme of malt in aqueous ethanol. Malt diastase hydrolyses 7α-halo-3,20-dioxo-pregnadiene 17,21-dihydrocarboncarboxylates only at C-21 producing 17-monohydrocarboncarboxylates which, if desired, can be re-esterified at C-21 in known manner with an acylating agent introducing a different acyl function from that present at C-17 so as to produce mixed 17,21-diacyl derivatives.

16α,17α-Orthoesters and 17α,21-orthoesters can be hydrolysed at the 16α- and 21-positions to yield a 17-ester. This hydrolysis is preferably effected under mildly acidic conditions, e.g. in the presence of a lower alkanoic acid (e.g. acetic or propionic acid) or a strong mineral acid (e.g. hydrochloric or sulfuric acid). When no substituent is present at C-16 the hydrolysis is preferably carried out under buffered conditions at a pH in the range of 4 to 6.

The hydrolysis of a 17α,21-alkylidenedioxy, -cycloalkylidenedioxy or -aralkylidenedioxy group to 17α,21-dihydroxy groups is normally effected under mildly acidic conditions (e.g. 50% aqueous acetic acid), preferably under an inert atmosphere (e.g. nitrogen). 21-Ethylene ketals and 17α,20;20,21-*bis*-methylenedioxy groups can also be hydrolysed under mildly acidic conditions; 17α,20;20,21-*bis*-methylenedioxy groups can be hydrolysed under substantially neutral conditions by means of triphenylcarbenium tetrafluoroborate.

The preferred compounds of the present invention have ester groups at C-17 and include 17-mono- and 17,21-diesters, in particular 17-propionates, 17-*n*-butyrates and 17-benzoates. It is usually advantageous to have these ester groups already present in the starting materials of the formulae IV and V. However, it may sometimes be convenient to introduce these ester groups after one of the above-described main reaction steps according to the invention has been carried out.

Thus, the 17α,21-diesters can be prepared by acylation of the corresponding 17α,21-diols or 17α-hydroxy-21-acyloxy compounds, preferably by means of a carboxylic acid having up to 12 carbon atoms or retinoic acid together with an esterifying agent or by means of a reactive derivative of said acid. In particular, the steroid may be reacted with an appropriate acid anhydride in the presence of a strong acid catalyst, e.g. toluene-*p*-sulfonic acid, perchloric acid or a strongly acidic cation exchange resin, or with trifluoroacetic anhydride and the appropriate acid, e.g. a lower alkanoic acid, and a strong acid catalyst.

Before a 17α-hydroxyl group is esterified, any 11β-hydroxyl function should be protected, e.g. as the 11β-trifluoroacetate, which, after esterification at C-17, may be hydrolyzed with mild base (e.g. dilute aqueous sodium benzoate) without hydrolyzing other ester groups at C-17 and/or C-21. Alternatively, the 17α-esterification may be carried out on an 11-oxo compound, and the 11-oxo group may then be reduced (as described above after the discussion of the first main reaction step) to the required 11β,17α-diol 17-acylate.

17,21-Diesters may also be prepared by acylation of the corresponding 21-hydroxy-17α-monoesters 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*-methylpiperidine, *N*-methylmorpholine, *p*-dimethylaminopyridine or *N,N*-dimethylaniline.

The 17α-monoesters of our invention may be prepared by hydrolysis of a corresponding 17,21-orthoester or 17α,21-diester as described above; the 17,21-ortho-ester grouping may be introduced by reaction of a 17α,21-diol with an alkylorthoester either before or after a main process step according to the invention.

A 21-dihydrogenphosphate ester is preferably prepared in a finishing step by reaction of the corresponding 21-hydroxy compound with pyrophosphoryl chloride. The mono- and di-alkali metal salts and alkaline earth metal salts of the dihydrogen phosphate ester may be obtained by partial or complete neutralization with an alkali metal methoxide or alkaline earth metal methoxide.

The reduction of an 11-oxo group to an 11β-hydroxy group has already been described.

When 7α,9α,11β-trihalo compounds and 7α,9α-dihalo-11β-hydroxy compounds of formula I are being prepared, the 9α,11β-dihalogen or 9α-halogen atoms may be present in the molecule before introduction of the 7α-halogen atom. However, the 9α,11β-dihalogen or 9α-halogen atoms may be introduced into a 7α-halo-9(11)-dehydro compound (especially a 7α-halo-3,20-dioxo-1,4,9(11)-pregnatriene), which may have been derived from a 7α-halo-11β-hydroxy-3,20-dioxo compound by dehydration with methanesulfonyl chloride and a tertiary amine (e.g. collidine) in a dialkylamide (e.g. dimethylformamide) in the presence of sulfur dioxide. For example, reaction of a resulting 7α-halo-9(11)-dehydro compound with chlorine in a halogenated solvent (e.g. chloroform) in the presence of a tertiary amine (e.g. pyridine) yields the corresponding 7α-halo-9α,11β-dichloro derivative. Alternatively, reaction of the resulting 7α-halo-9(11)-dehydro compound with hydrogen fluoride and an *N*-chloro-amide or *N*-bromo-amide or with hydrogen chloride and an *N*-bromo-amide in an inert organic solvent yields 7α,9α,11β-trihalo derivatives wherein the more electronegative halogen substitutes the 11β-position. Furthermore, reaction of the resulting 7α-halo-9(11)-dehydro compound with an *N*-chloro-amide or *N*-bromo-amide (preferably *N*-chloro-succinimide or *N*-bromo-succinimide) and a strong mineral acid (preferably perchloric acid) in an inert organic solvent (e.g. moist dioxan or tetrahydrofuran) yields an 11β-ol having a 9α-chloro or 9α-bromo substituent.

17α-Chlorination or bromination may be effected by means of an *N*-chloro-amide or *N*-bromo-amide, especially *N*-chloro-succinimide or *N*-bromo-succinimide, in an inert organic solvent such as tetramethylene sulfone at reduced temperature and preferably in the presence of a mineral acid such as hydrofluoric acid.

The following Preparations show how the starting materials of the Formulae IV and V may be obtained:

Preparation 1
16α-Methyl-1,4,6-Pregnatriene-11β,17α,21-Triol-3,20-Dione and 21-Esters Thereof

A. 16α-Methyl-1,4,6-pregnatriene-11β,17α,21-triol-3,20-dione 21-acetate

To a solution of dry hydrogen chloride gas (22 gms.) in dioxan (660 ml.), add 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-acetate (10 gms.) followed by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (6.55 gms.) and stir at room temperature for 24 hours. Filter the reaction mixture and evaporate the filtrate at 40°C. *in vacuo*. Dissolve the resultant residue in chloroform: ethyl acetate (1:1) and filter the solution through a column of neutral alumina, washing the column with the same solvent system. Evaporate the eluates and recrystallize the resultant residue from methanol:hexane to give 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 21-acetate.

B. 16α-Methyl-1,4,6-pregnatriene-11β,17α,21-triol-3,20-dione

To a solution of 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 21-acetate (1.5 gms.) in methanol (360 ml.) add saturated aqueous sodium bicarbonate solution (40 ml.). Stir at room temperature for 2 hours; then filter and evaporate *in vacuo*. Dissolve the resultant residue in ethyl acetate, wash the ethyl acetate solution with water, dry it over magnesium sulfate and evaporate

it *in vacuo* to obtain 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione.

C. 16α-Methyl-1,4,6-pregnatriene-11β,17α,21-triol-3,20-dione 21-benzoate

(1) To 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione (0.68 gms.) in pyridine (6.12 ml.) add benzoyl chloride (1.36 ml.). Stir at room temperature for 30 minutes, then pour into 0.1 N hydrochloric acid solution (550 ml.). Extract the aqueous mixture with ethyl acetate, wash the organic extracts with aqueous saturated sodium bicarbonate solution, then with water, then dry them over magnesium sulfate and evaporate them *in vacuo* to a residue of 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 21-benzoate.

(2) In the above procedure, by substituting for benzoyl chloride equivalent quantities of a substituted benzoyl chloride, e.g. *p*-toluyl chloride, *p*-fluorobenzoyl chloride and 3',5'-dimethylbenzoyl chloride, there is obtained the corresponding 21-substituted benzoate ester, e.g. the 21-*p*-toluate, 21-*p*-fluorobenzoate and 21-(3',5'-dimethylbenzoate) of 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione.

D. 16α - Methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 21 - hydrocarboncarboxylates

(1) 16α - Methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 21-trimethylacetate

To 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione (0.4 gms.) in pyridine (3 ml.) at 0°C. add dropwise a solution of trimethylacetyl chloride (0.4 ml.) in pyridine (1 ml.). Allow the reaction mixture to warm to room temperature, then leave it at room temperature for 30 minutes. Pour the reaction mixture into water (250 ml.), extract the aqueous mixture with ethyl acetate, then wash the organic extracts successively with 1N hydrochloric acid, aqueous saturated sodium bicarbonate, and water. Dry the organic phase over magnesium sulfate and evaporate it *in vacuo* to a residue of 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 21-trimethylacetate.

(2) In the above procedure, by substituting for trimethyl-acetyl chloride equivalent quantities of other hydrocarbon-carboxylic acid chlorides, e.g. propionyl chloride, dodecanoyl chloride, valeryl chloride, n-butyryl chloride, cyclopentylpropionyl chloride, cyclohexylcarbonyl chloride, 1-adamantylacetyl chloride, and 1-adamantylcarboxylic acid chloride, there is obtained the corresponding 21-hydrocarboncarboxylate ester, e.g. the 21-propionate, 21-dodecanoate, 21-valerate, 21-*n*-butyrate, 21-cyclopentylpropionate, 21-cyclohexanecarboxylate, 21-(1'-adamantylacetate) and 21-(1 - adamantylcarboxylate) of 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione.

Preparaton 2

16α-Methyl-1,4,6-Pregnatriene-11β,17α,21-Triol-3,20-Dione 17-Lower Alkanoates and 17,21-Alkylorthoalkanoates

A. 16α - Methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17-propionate

(1) 16α - Methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17,21-ethylorthopropionate

To 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione (1.9 gms.) in dimethylsulfoxide (9.5 ml.) add triethylorthopropionate (3.8 ml.) and toluene-*p*-sulfonic acid monohydrate (0.142 gm.). Stir for 2 hours at room temperature, then pour into water (250 ml.), add saturated aqueous sodium bicarbonate (150 ml.) and extract with ethyl acetate. Combine the ethyl acetate extracts and wash them with water, dry them over magnesium sulfate and evaporate them *in vacuo* to a residue comprising 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17,21-ethylorthopropionate.

(2) Dissolve the product of Preparation 2A(1) in glacial acetic acid (15 ml.) and water (0.3 ml.). Allow to stand for one hour at room temperature, then pour into water (300 ml.) and add 8% aqueous sodium hydroxide solution (50 ml.). Separate the resultant precipitate by filtration, wash it with water and dry it at room temperature to give 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17-propionate. Further purify by recrystallization from acetone/hexane.

B. 16α - Methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17-lower alkanoates

(1) 16α - Methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17,21-alkylorthoalkanoates

In the procedure of Preparation 2A(1), substitute for triethylorthopropionate the following trialkylorthoalkanoates: triethylorthoacetate, triethylortho-*n*-butyrate, triethylorthoisobutyrate and tri-*n*-butylorthovalerate, to obtain the corresponding 17,21-alkylorthoalkanoate: the 17,21-ethylorthoacetate, the 17,21-ethylortho-*n*-butyrate, the 17,21-ethylorthoisobutyrate, and the 17,21-*n*-butylorthovalerate, respectively, of 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione.

(2) 16α - Methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17-lower alkanoates

Treat each of the 17,21-alkylorthoalkanoates prepared in Preparation 2B(1) with aqueous acetic acid in the manner of Preparation 2A(2) to obtain, respectively, the 17-acetate, 17-*n*-butyrate, 17-isobutyrate, and 17-valerate of 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione.

C. 16α - Methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17-benzoate

(1) 16α - Methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17,21-methylorthobenzoate

To a solution of 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione (1 gm.) in dioxan (56 ml.) and benzene (84 ml.) add pyridinium toluene-*p*-sulfonate (0.25 gm.) and trimethylorthobenzoate (1.5 ml.). Heat the reaction mixture at reflux temperature for 2 days, then add additional pyridinium toluene-*p*-sulfonate (0.1 gm.) and trimethylorthobenzoate (1 ml.). Heat at reflux temperature an additional 3 days, then again add additional pyridinium toluene-*p*-sulfonate (0.1 gm.) and trimethylorthobenzoate (1 ml.). Heat at reflux temperature another 3 days, cool, add pyridine (0.45 ml.) and evaporate *in vacuo*. Dissolve the resultant residue in ethyl acetate, wash the ethyl acetate solution with water, dry it over magnesium sulfate and evaporate it to a residue comprising 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17,21-methylorthobenzoate.

In the above procedure by substituting for trimethylorthobenzoate an equivalent quantity of trimethylortho-(*p*-fluorobenzoate) there is obtained 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17,21 - methylortho - (*p* - fluorobenzoate).

(2) 16α - Methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17-benzoate and 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17 - *p* - fluorobenzoate are obtained by hydrolysis of 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17α,21 - methylorthobenzoate and 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17α,21 - methylortho - (*p* - fluorobenzoate) respectively with aqueous acetic acid by the method of Preparation 2A(2).

Preparation 3

16α-Methyl-1,4,6-Pregnatriene-11β,17α,21-triol-3,20-dione 17,21-Dihydrocarboncarboxylic Acid Esters

A. 16α - Methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17-propionate 21-alkanoates

(1) 16α - Methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate

To 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17-propionate (2.8 gms.) in pyridine (23 ml.), add propionic anhydride (4.6 ml.) and allow to stand at room temperature for 3.5 hours. Pour into water (250 ml.) containing 1N hydrochloric acid (50 ml.). Extract with ethyl acetate (100 ml.), wash the combined organic extracts with water, dry over magnesium sulfate and evaporate *in vacuo*. Chromatograph the resultant residue on a silica gel column, eluting with chloroform: ethyl acetate (4:1). Evaporate the combined eluates to a residue comprising 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate.

(2) In the procedure of Preparation 3A(1) by substituting for propionic anhydride equivalent quantities of other alkanoic anhydrides, e.g. acetic anhydride, *n*-butyric anhydride, isobutyric anhydride, caprylic acid anhydride and valeric anhydride, there is obtained the corresponding 17-propionate 21-alkanoate

ester, e.g. the 17-propionate 21-acetate, 17-propionate 21-*n*-butyrate, 17-propionate 21-isobutyrate, 17-propionate 21-caprylate, and 17-propionate 21-valerate of 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione.

(3) 16α - Methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17-propionate 21-benzoate is prepared from 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17-propionate and benzoyl chloride by the method of Preparation 1C(1). 17-Propionate 21-substituted-benzoate esters, e.g. the 17-propionate 21-*p*-toluate, 17-propionate 21-*p*-fluorobenzoate, and the 17-propionate 21-(3',5'-dimethylbenzoate) of 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione, may be prepared similarly by using the corresponding substituted benzoyl chloride.

B. 16α - Methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17,21 - dihydrocarboncarboxylates

(1) In a manner similar to that described in Preparation 3A(1), treat each of the 17-acetate, the 17-*n*-butyrate, the 17-isobutyrate, the 17-valerate, and the 17-benzoate esters of 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione in pyridine with each of the following alkanoic acid anhydrides: acetic anhydride, propionic anhydride, *n*-butyric anhydride, isobutyric anhydride and valeric anhydride. Isolate and purify each of the resultant products in a manner similar to that described to obtain the corresponding 17-hydrocarboncarboxylate 21-alkanoates, respectively, of 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione; i.e. its 17,21-diacetate, 17-acetate 21-propionate, 17-acetate 21-*n*-butyrate, 17-acetate 21-isobutyrate, 17-acetate 21-valerate; 17-*n*-butyrate 21-acetate, 17-*n*-butyrate 21-propionate, 17,21-di-*n*-butyrate, 17-*n*-butyrate 21-isobutyrate, 17-*n*-butyrate 21-valerate; 17-isobutyrate 21-acetate, 17-isobutyrate 21-propionate, 17-isobutyrate 21-*n*-butyrate, 17,21-di-isobutyrate, 17-isobutyrate 21-valerate; 17-benzoate 21-acetate, 17-benzoate 21-propionate, 17-benzoate 21-*n*-butyrate, 17-benzoate 21-isobutyrate, 17-benzoate 21-valerate; 17-valerate 21-acetate, 17-valerate 21-propionate, 17-valerate 21-*n*-butyrate, 17-valerate 21-isobutyrate, and 17,21-divalerate.

(2) In a manner similar to that described in Preparation 1C treat each of the 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17-monoester starting compounds of Preparation 3B(1) in pyridine with each of benzoyl chloride, *p*-toluyl chloride, *p*-fluorobenzoyl chloride and 3',5'-dimethylbenzoyl chloride to obtain the corresponding 21-benzoate or substituted benzoate ester, i.e. the 21-benzoate, 21-*p*-toluate, 21-*p*-fluorobenzoate, and 21-(3',5'-dimethylbenzoate) of each of the 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17-monoester starting compounds.

Preparation 4

The 17-Esters, 21-Esters, and 17,21-Di-esters of 16β-Methyl-1,4,6-Pregnatriene-11β,17α,21-Triol-3,20-Dione and of 16α-Methyl-1,4,6-Pregnatriene-17α,21-Diol-3,11,20-Trione and the 16β-Methyl Epimers Thereof

16β - Methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 21-acetate is prepared from 16β - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-acetate by the procedure of Preparation 1A and is put through the sequence of reactions of Preparations 1—3 to produce the 16β - methyl epimers of the 16α-methyl products described therein.

(2) Similarly, 16α - methyl - 1,4,6 - pregnatriene - 17α,21 - diol - 3,11,20 - trione 21-acetate is prepared from 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 21-acetate by the procedure of Preparation 1A and is put through the sequence of reactions described in Preparations 1—3 to produce 11-oxo-16α-methyl pregnatriene derivatives corresponding to the 11β-hydroxy-16α-methyl pregnatriene products named therein.

(3) 16β - Methyl - 1,4,6 - pregnatriene - 17α,21 - diol - 3,11,20 - trione 21-acetate is prepared from 16β - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 21-acetate by the procedure of Preparation 1A and is put through the sequence of reactions of Preparations 1—3 to produce the 11-oxo-16β-methyl pregnatriene derivatives corresponding to the 11β-hydroxy-16α-methyl-pregnatriene products named therein.

Preparation 5
Alternative Procedure for Preparing 1,4,6-Pregnatriene-17α,21-Diol-3,11,20-Triones and 17,21-diesters Thereof

A. 6β - Bromo - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 21-acetate

To a solution of 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 21-acetate (11 gms.) in carbon tetrachloride (110 ml.) and chlorobenzene (110 ml.) at reflux temperature, add *N*-bromosuccinimide (7 gms.) followed by azo*bis*isobutyronitrile (530 mg.). Heat at reflux temperature for 30 minutes, cool, and add with stirring 300 ml. of a 10% aqueous sodium bisulfite solution. Add chloroform (150 ml.), separate the organic layer, wash it with water and dry it over anhydrous magnesium sulfate. Evaporate *in vacuo* to a residue comprising 6β - bromo - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 21-acetate.

B. 16α - Methyl - 1,4,6 - pregnatriene - 17α,21 - diol - 3,11,20 - trione 21-acetate

To a solution of 6β - bromo - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 21-acetate (from Preparation 5A) in dimethylacetamide (125 ml.) add lithium bromide (4.4 gms.) and calcium carbonate (7.75 gms.). Heat the reaction mixture at 120°C. under an atmosphere of nitrogen for 1 hour. Cool, filter and dilute the filtrate with chloroform (500 ml.). Wash the chloroform solution with water, dry it over magnesium sulfate and evaporate it to a residue comprising 16α - methyl - 1,4,6 - pregnatriene - 17α,21 - diol - 3,11,20 - trione 21-acetate.

C. 16α - Methyl - 1,4,6 - pregnatriene - 17α,21 - diol - 3,11,20 - trione is prepared from 16α - methyl - 1,4,6 - pregnatriene - 17α,21 - diol - 3,11,20 - trione 21-acetate by hydrolysis with aqueous sodium bicarbonate in methanol by the method of Preparation 1B.

D. 16α - Methyl - 1,4,6 - pregnatriene - 17α,21 - diol - 3,11,20 - trione 17,21-dialkanoates

(1) Stir at room temperature for 1 hour a solution of trifluoroacetic anhydride (8 ml.), propionic acid (200 ml.) and toluene-*p*-sulfonic acid monohydrate (200 mg.), then add 16α - methyl - 1,4,6 - pregnatriene - 17α,21 - diol - 3,11,20 - trione (2 gms.). Stir the reaction mixture for 17 hours, then add an additional 6 ml. of trifluoroacetic anhydride. Continue stirring for 5 hours, then pour into 400 ml. 0.5N sodium hydroxide. Extract the aqueous mixture with chloroform, wash the combined chloroform extracts with water, dry over magnesium sulfate and evaporate *in vacuo*. Dissolve the resultant residue in methanol and steam distil to remove volatile impurities. Decant the water from the residue of the distillation and dry the residue to obtain 16α - methyl - 1,4,6 - pregnatriene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate.

(2) In the above procedure, by substituting for propionic acid equivalent quantities of other alkanoic acids, e.g. acetic acid, valeric acid and *n*-butyric acid there is obtained the corresponding 17,21-dialkanoate, e.g. the 17,21-diacetate, 17,21-divalerate, and 17,21-dibutyrate of 16α - methyl - 1,4,6 - pregnatriene - 17α,21 - diol - 3,11,20 - trione.

Preparation 6
16α,17α-Isopropylidenedioxy-1,4,6-Pregnatriene-11β,21-Diol-3,20-Dione 21-Acetate

(1) 16α,17α - Isopropylidenedioxy - 1,4 - pregnadiene - 11β,21 - diol - 3,20 - dione 21-acetate is prepared from 16α,17α - isopropylidenedioxy - 1,4 - pregnadiene - 11β,21 - diol - 3,20 - dione and acetic anhydride in pyridine by the method of Preparation 3A.

(2) 16α,17α - Isopropylidenedioxy - 1,4,6 - pregnatriene - 11β,21 - diol - 3,20 - dione 21-acetate is prepared from 16α,17α - isopropylidenedioxy - 1,4 - pregnadiene - 11β,21 - diol - 3,20 - dione 21-acetate, DDQ and dry hydrogen chloride in dioxan by the method of Preparation 1A.

Preparation 7
21-Halo-1,4,6-Pregnatriene-11β,17α-Diol-3,20-Dione 17-Hydrocarboncarboxylates

A. 21 - Halo - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17 - hydrocarboncarboxylates

(1) 16α - Methyl - 21 - chloro - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate

To a solution of 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-*n*-butylorthopropionate (0.87 gm.) in chloroform (87 ml.) add trimethylsilyl chloride (1.15 ml.) and reflux for 24 hours. Evaporate the reaction mixture *in vacuo* and place the resultant residue on a silica gel column (80 gms.), eluting with chloroform: ethyl acetate (2:1). Evaporate the combined eluates to a residue comprising 16α - methyl - 21 - chloro - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate.

(2) 16α - Methyl - 21 - bromo - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate

In the above procedure, by using trimethylsilyl bromide as reagent, the corresponding 21-bromo derivative, 16α - methyl - 21 - bromo - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate, is obtained.

(3) Treat each of the following with trimethylsilyl chloride in the manner described in Preparaton 7A(1): 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-ethylorthoacetate, 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21 - ethylortho - *n* - butyrate, 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21 - *n* - butylorthovalerate, and 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21 - methylorthobenzoate. Isolate and purify each of the resultant products in a manner similar to that described to obtain, respectively, 16α - methyl - 21 - chloro - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-acetate, 16α - methyl - 21 - chloro - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-*n*-butyrate, 16α - methyl - 21 - chloro - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-valerate, and 16α - methyl - 21 - chloro - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-benzoate.

In the above procedure, by using trimethylsilyl bromide as reagent, the 21-bromo derivatives corresponding to each of the 21-chloro derivatives are obtained.

(4) In the procedures of Preparations 7A(1)—7A(3), by using as starting steroids the 16β-methyl epimers of the 16α-methyl compounds named therein, the corresponding 16β-methyl epimers of the 21-halo-pregnadiene products named therein are obtained. Similarly, by starting with derivatives having an 11-oxo function instead of an 11β-hydroxyl function, there are obtained the corresponding 21-halo derivatives containing an 11-oxo function.

B. 16α - Methyl - 21 - halo - 1,4,6 - pregnatriene - 11β,17α - diol - 3,20 - dione 17-alkanoate

(1) 16α - Methyl - 21 - halo - 1,4,6 - pregnatriene - 11β,17α - diol - 3,20 - dione 17-propionate

16α - Methyl - 21 - chloro - 1,4,6 - pregnatriene - 11β,17α - diol - 3,20 - dione 17-propionate and 16α - methyl - 21 - bromo - 1,4,6 - pregnatriene - 11β,17α - diol - 3,20 - dione 17-propionate are prepared from 16α - methyl - 21 - chloro - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate and 16α - methyl - 21 - bromo - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate respectively, DDQ and dry hydrogen chloride in dioxan by the method of Preparation 1A.

(2) Similarly treat the 21-halo-1,4-pregnadienes of Preparation 7A(3) and 7A(4) with DDQ and dry hydrogen chloride in dioxan to obtain the corresponding 21-halo-1,4,6-pregnatrienes.

(3) 16α - Methyl - 21 - fluoro - 1,4,6 - pregnatriene - 11β,17α - diol - 3,20 - dione 17-propionate

16α - Methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17-propionate 21-methanesulfonate is prepared from 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17-propionate and methanesulfonyl chloride in pyridine by the method of Preparation 1C, and is then allowed to react with silver fluoride in acetonitrile according to known procedures to yield 16α - methyl - 21 - fluoro - 1,4,6 - pregnatriene - 11β,17α - diol - 3,20 - dione 17-propionate.

Preparation 8

1,4,6-Pregnatriene-11β,17α-Diol-3,20-Dione 17-Hydrocarboncarboxylates

A. 1,4 - Pregnadiene - 11β,17α - diol - 3,20 - dione 17-hydrocarboncarboxylates

(1) To 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-ethylorthopropionate (4 gms.) in methylene chloride (100 ml.), under an atmosphere of nitrogen at 0°C. add trimethylsilyl iodide (3.68 ml.) and, after 1

minute, pour the reaction mixture into 1N sodium thiosulfate solution (300 ml.) with efficient stirring. Extract the reaction mixture with methylene chloride, wash it with water, dry it over magnesium sulfate and evaporate it to a residue, which is then purified on a column of silica gel (300 gms.) by elution with chloroform:ethyl acetate (4:1) to yield 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate.

(2) In similar manner, treat each of 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21 - ethylortho - *n* - butyrate, 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21 - *n* - butylorthovalerate, 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-ethylorthoacetate, and 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-methylorthobenzoate with trimethylsilyl iodide followed by the immediate isolation of the resultant product to obtain, respectively, the 17-*n*-butyrate, the 17-valerate, the 17-acetate, and the 17-benzoate of 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione.

B. 1,4,6 - Pregnatriene - 11β,17α - diol - 3,20 - dione 17-hydrocarboncarboxylates

In a manner similar to that described in Preparation 1A, treat each of the 1,4-pregnadiene 17-ester products of Preparation 8A with DDQ and hydrogen chloride in dioxan to obtain, respectively, 1,4,6 - pregnatriene - 11β,17α - diol - 3,20 - dione 17-propionate, 1,4,6 - pregnatriene - 11β,17α - diol - 3,20 - dione 17 - *n* - butyrate, 1,4,6 - pregnatriene - 11β,17α - diol - 3,20 - dione 17-valerate, 1,4,6 - pregnatriene - 11β,17α - diol - 3,20 - dione 17-acetate and 1,4,6 - pregnatriene - 11β,17α - diol - 3,20 - dione 17-benzoate.

Preparation 9

16-Methylene-1,4,6-Pregnatriene-11β,17α,21-Triol-3,20-Dione 21-Hydrocarboncarboxylates and 17,21-Dihydrocarboncarboxylates

A. 16 - Methylene - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-hydrocarboncarboxylates

(1) 16 - Methylene - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-propionate is prepared from 16 - methylene - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione (5 gms.) and propionic anhydride (10 ml.) in pyridine (100 ml.) by the method of Preparation 3A(1).

(2) In the above procedure, by using other alkanoic anhydrides in place of propionic anhydride, e.g. acetic anhydride, *n*-butyric anhydride, and valeric anhydride, there is obtained the corresponding 21-lower alkanoate ester, e.g. the 21-acetate, 21-*n*-butyrate, and 21-valerate of 16 - methylene - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione.

(3) 16 - Methylene - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-benzoate is prepared from 16 - methylene - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione and benzoyl chloride in pyridine by the method of Preparation 1C.

B. 16 - Methylene - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 11-trifluoroacetate 21-propionate

(1) To a solution of 16 - methylene - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-propionate (1 gm.) in pyridine (10 ml.) at –23°C., add trifluoroacetic anhydride (1 ml.) precooled to –23°C. Allow the reaction mixture to stand at –23°C. for 40 minutes, then pour it into ice water (200 ml.) containing concentrated hydrochloric acid (8.8 ml.). Separate the resultant precipitate by filtration, wash it with water and dry it to give 16 - methylene - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 11-trifluoroacetate 21-propionate.

(2) The 21-hydrocarboncarboxylates prepared in Preparation 9A(2) and (3) may be similarly converted into their 11-trifluoroacetates.

C. 16 - Methylene - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 11-trifluoroacetate 17,21-dihydrocarboncarboxylates

To a solution of 16 - methylene - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 11-trifluoroacetate 21-propionate (1.07 gm.) in propionic acid (10 ml.) containing toluene-*p*-sulfonic acid monohydrate (0.1 gm.) at 0°C. add trifluoroacetic anhydride (4 ml.) dropwise. Allow the reaction mixture to stand at 0°C. for 5 minutes, then to warm to room temperature and to remain at room temperature for 3 hours. Pour the reaction mixture into water, extract the aqueous mixture with ethyl acetate, wash the combined organic extracts with 5% sodium

hydroxide and then with water, dry them over magnesium sulfate and evaporate them to a residue comprising 16 - methylene - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 11-trifluoroacetate 17,21-dipropionate.

(2) In similar manner, treat each of the 11-trifluoro-acetate esters prepared in Preparation 9B(2) in the manner described above to obtain the corresponding 17-propionate ester, i.e. the 17-propionate 21-acetate, the 17-propionate 21-*n*-butyrate, the 17-propionate 21-valerate and the 17-propionate 21-benzoate of 16 - methylene - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 11-trifluoroacetate.

(3) In the procedure of Preparation 9C(1), by substituting for propionic acid other hydrocarboncarboxylic acids, e.g. *n*-butyric acid and acetic acid, 16 - methylene - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 11-trifluoroacetate 17-*n*-butyrate 21-propionate and 16 - methylene - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 11-trifluoroacetate 17-acetate 21-propionate respectively are obtained.

(4) The products of Preparation 9B(2) may be converted into their 17-*n*-butyrates and 17-acetates by the method of Preparation 9C(3).

D. 16 - Methylene - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 11-trifluoroacetate 17,21 - dihydrocarboncarboxylates

(1) 16 - Methylene - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 11-trifluoroacetate 17,21-dipropionate is prepared from 16 - methylene - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 11-trifluoroacetate 17,21-dipropionate, dry hydrogen chloride and DDQ in dioxan by the method of Preparation 1A.

(2) In similar manner, treat the products of Preparations 9C(2)—(4) with DDQ and dry hydrogen chloride in dioxan to obtain their corresponding 6-dehydro derivatives.

E. 16 - Methylene - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate

(1) To a solution of 16 - methylene - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 11-trifluoroacetate 17,21-dipropionate (0.52 gm.) in methanol (26 ml.) add sodium benzoate (1.5 gm.) and stir at room temperature for 2 1/2 hours. Evaporate the solution *in vacuo* at room temperature and wash the resultant residue thoroughly with water. Separate the solids by filtration and dry to obtain 16 - methylene - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate. Additional product is obtained by extracting the combined water washes and filtrate with ethyl acetate, washing the organic extract with water, drying it over magnesium sulfate and evaporating it to obtain a residue of 16 - methylene - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate.

(2) Similarly treat the 11-trifluoroacetate products of Preparation 9D(2) in methanol with sodium benzoate to obtain the corresponding 11β-hydroxy derivatives.

Preparation 10

16-Methylene-1,4,6-Pregnatriene-17α,21-Diol-3,11,20-Trione 17,21-Dihydrocarboncarboxylates

A. 16 - Methylene - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17,21-alkylorthohydrocarboncarboxylates

(1) 16 - Methylene - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17,21-methylorthobenzoate is prepared from 16 - methylene - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione and trimethylorthobenzoate with pyridinium toluene-*p*-sulfonate in dioxan and benzene by the method of Preparation 2C(1).

(2) In a manner similar to that described in Preparation 2A(2), treat 16 - methylene - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione in dimethylsulfoxide in the presence of toluene-*p*-sulfonic acid with each of triethylorthopropionate, triethylortho-*n*-butyrate, and tri-*n*-butylorthovalerate, to obtain the corresponding 17,21-alkylorthoalkanoate, i.e. the 17,21-ethylorthopropionate, 17,21-ethylortho-*n*-butyrate and 17,21-*n*-butylorthovalerate, respectively, of 16 - methylene - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione.

B. 16 - Methylene - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17-hydrocarboncarboxylates

(1) Dissolve 16 - methylene - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 -

trione 17,21-methylorthobenzoate (2 gms.) in glacial acetic acid (15 ml.) and water (0.3 ml.). Allow to stand at room temperature for 20 minutes, then pour into water (300 ml.) and add an 8% sodium hydroxide solution (50 ml.). Separate the resultant precipitate by filtration, wash it with water and dry it at room temperature. Isolate the desired compound by preparative thin layer chromatography on silica gel using ethyl acetate:chloroform (1:1) as developing solvent. Remove the most polar band as visualized by ultraviolet light and elute with ethyl acetate. Evaporate to a residue comprising 16 - methylene - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17-benzoate.

(2) Treat each of the 17,21-alkylorthoalkanoates of Preparation 10A(2) with aqueous acetic acid in the manner described above to obtain, respectively, the 17-propionate, 17-*n*-butyrate, and the 17-valerate of 16 - methylene - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione.

C. 16 - Methylene - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17,21-dihydrocarboncarboxylates

(1) Treat each of the 16 - methylene - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17-hydrocarboncarboxylates of Preparation 10B with benzoyl chloride in pyridine by the procedure of Preparation 1C to obtain, respectively, the 17α,21-dibenzoate, the 17-propionate 21-benzoate, the 17-*n*-butyrate 21-benzoate and the 17-valerate 21-benzoate of 16 - methylene - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione.

(2) In a manner similar to that described in Preparation 3A(1), treat each of the 17-hydrocarboncarboxylates of 16 - methylene - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione of Preparation 10B in pyridine with propionic anhydride to obtain, respectively, the 17-benzoate 21-propionate, the 17,21-dipropionate, the 17-*n*-butyrate 21-propionate, and the 17-valerate 21-propionate of 16 - methylene - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione.

D. 16 - Methylene - 1,4,6 - pregnatriene - 17α,21 - diol - 3,11,20 - trione 17,21-dihydrocarboncarboxylates

In a manner similar to that described in Preparation 1A, treat each of the 16 - methylene - 1,4 - pregnadienes prepared in Example 10C with dry hydrogen chloride and DDQ in dioxan, and isolate and purify each of the respective products to obtain the corresponding 1,4,6-pregnatrienes, i.e. the 17-benzoate 21-propionate, 17-benzoate 21-*n*-butyrate, 17-benzoate 21-valerate, 17-propionate 21-butyrate, 17,21-dipropionate, 17-*n*-butyrate 21-propionate, and 17-valerate 21-propionate.

Preparation 11
7β-Hydroxy-1,4-Pregnadiene-3,20-Diones

A. 9α - Fluoro - 16α - methyl - 1,4 - pregnadiene - 7β,11β,17α,21 - tetrol - 3,20 - dione 21-acetate

(1) 9α - Fluoro - 16α - methyl - 1,4 - pregnadiene - 6β,7β,11β,17α,21 - pentol - 3,20 - dione 21-acetate

To 9α - fluoro - 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 21-acetate (8.3 gms.) in dioxan (350 ml.) and pyridine (5 ml.) add osmium tetroxide (4.9 gms.). Stir the reaction mixture at room temperature for 5 days, then saturate the solution with hydrogen sulfide and filter the reaction solution through Celite (Registered Trade Mark). Evaporate the filtrate *in vacuo* at room temperature, triturate the resultant residue with chloroform:methanol and separate the resultant precipitate by filtration to obtain 9α - fluoro - 16α - methyl - 1,4 - pregnadiene - 6β,7β,11β,17α,21 - pentol - 3,20 - dione 21-acetate.

(2) 9α - Fluoro - 16α - methyl - 1,4 - pregnadiene - 6β,7β,11β,17α,21 - pentol - 3,20 - dione 6,7n-butylorthopropionate 21-acetate

To 9α - fluoro - 16α - methyl - 1,4 - pregnadiene - 6β,7β,11β,17α,21 - pentol - 3,20 - dione 21-acetate (3 gms.) in dimethylsulfoxide (15 ml.) add tri-*n*-butylorthopropionate (5.4 ml.) and toluene-*p*-sulfonic acid monohydrate (0.225 gm.) and stir at room temperature for 3.5 hours. Pour the reaction mixture into water (500 ml.) and saturated aqueous sodium bicarbonate (100 ml.). Extract the aqueous mixture with ethyl acetate, wash the combined extracts with water, dry over magnesium sulfate and evaporate to a residue comprising 9α - fluoro - 16α - methyl - 1,4 - pregnadiene - 6β,7β,11β,17α,21 - pentol - 3,20 - dione 6,7-*n*-butylorthopropionate 21-acetate.

(3) 9α - Fluoro - 16α - methyl - 1,4 - pregnadiene - 6β,7β,11β,17α,21 - pentol - 3,20 - dione 6-propionate 21-acetate

Dissolve the product of Preparation 11A(2) in glacial acetic acid (50 ml.) and water (1 ml.). Allow the reaction mixture to stand at room temperature for 1 hour, then pour it into ice water (500 ml.) and separate the resultant precipitate by filtration. Wash the precipitate with water and dry at room temperature to give 9α - fluoro - 16α - methyl - 1,4 - pregnadiene - 6β,7β,11β,17α,21 - pentol - 3,20 - dione 6-propionate 21-acetate.

(4) 9α - Fluoro - 16α - methyl - 1,4 - pregnadiene - 7β,11β,17α,21 - tetrol - 3,20 - dione 21-acetate

To 9α - fluoro - 16α - methyl - 1,4 - pregnadiene - 6β,7β,11β,17α,21 - pentol - 3,20 - dione 6-propionate 21-acetate (3 gms.) in acetone (750 ml.) add a solution of sodium acetate (21 gms.), water (60 ml.) and acetic acid (15 ml.) followed by chromous acetate sludge (freshly prepared from 70 gms. of chromic chloride reduced by zinc amalgam followed by treatment with sodium acetate according to known procedures). Stir the reaction mixture at room temperature for 2 1/2 hours, filter and evaporate. Add water to the resultant residue, extract with ethyl acetate, wash the combined organic extracts with water, dry and evaporate *in vacuo* to a residue comprising 9α - fluoro - 16α - methyl - 1,4 - pregnadiene - 7β,11β,17α,21 - tetrol - 3,20 - dione 21-acetate. Purify by recrystallization from acetone:hexane, m.p. 181—185°C.; $[\alpha]_D^{26}$+48.7° (dimethylformamide).

B. Treat each of 9α - chloro - 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 21-acetate, 9α - bromo - 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 21-acetate and 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 21-acetate in a manner similar to that of Preparation 11A to obtain, respectively, 9α - chloro - 16α - methyl - 1,4 - pregnadiene - 7β,11β,17α,21 - tetrol - 3,20 - dione 21-acetate, 9α - bromo - 16α - methyl - 1,4 - pregnadiene - 7β,11β,17α,21 - tetrol - 3,20 - dione 21-acetate and 16α - methyl - 1,4 - pregnadiene - 7β,11β,17α,21 - tetrol - 3,20 - dione 21-acetate.

C. (1) Similarly, by treating according to the procedures of Preparation 11A the pregnatrienes prepared in Preparations 1—8, the corresponding 7β-hydroxy-1,4-pregnadienes are obtained.

(2) Similarly, by treating according to the procedure of Preparation 11A the corresponding 9α-fluoro-, 9α-chloro, and 9α-bromo-derivatives of the 9-unsubstituted-1,4,6-pregnatrienes prepared in Preparations 1—8, the corresponding 7β - hydroxy - 9α - fluoro - 1,4 - pregnadienes are obtained.

D. 7β-Hydroxy-16-methylene-1,4-pregnadienes

(1) 16β - Methyl - 16α,17α - epoxy - 1,4 - pregnadiene - 6β,7β,11β,21 - tetrol - 3,20 - dione 21-acetate is prepared from 16β - methyl - 16α,17α - epoxy - 1,4,6 - pregnatriene - 11β,21 - diol - 3,20 - dione 21-acetate and osmium tetroxide in dioxan and pyridine by the method of Preparation 11A.

(2) 16 - Methylene - 1,4 - pregnadiene - 6β,7β,11β,17α,21 - pentol - 3,20 - dione 21-acetate

To a solution of 16β - methyl - 16α,17α - epoxy - 1,4 - pregnadiene - 6β,7β,11β,21 - tetrol 21-acetate (100 mg.) and toluene-*p*-sulfonic acid (10 mg.) in acetic acid (1 ml.) at 5°C. add trifluoroacetic anhydride (0.1 ml.). Allow the reaction mixture to stand at room temperature for 25 minutes, then pour into water and collect by filtration 16 - methylene - 1,4 - pregnadiene - 6β,7β,11β,17α,21 - pentol - 3,20 - dione 21-acetate.

(3) 16 - Methylene - 1,4 - pregnadiene - 7β,11β,17α,21 - tetrol - 3,20 - dione 21-acetate is prepared from 16 - methylene - 1,4 - pregnadiene - 6β,7β,11β,17α,21 - pentol - 3,20 - dione 21-acetate by procedures similar to those of Preparations 11A(2), (3) and (4).

(4) In similar manner, treat each of 16β - methyl - 16α,17α - epoxy - 1,4,6 - pregnatrien - 21 - ol - 3,11,20 - trione 21-acetate, its 9α-fluoro and 9α-chloro derivatives, 9α - fluoro - 16β - methyl - 16α,17α - epoxy - 1,4,6 - pregnatriene - 11β,21 - diol - 3,20 - dione 21-acetate and 16β - methyl - 16α,17α - epoxy - 9α - chloro - 1,4,6 - pregnatriene - 11β,21 - diol - 3,20 - dione 21-acetate in a manner similar to that of Preparations 11D(1)—(3) to obtain, respectively, 16 - methylene - 1,4 - pregnadiene - 7β,17α,21 - triol - 3,11,20 - trione 21-acetate, its

9α-fluoro- and 9α-chloro-derivatives, 9α - fluoro - 16 - methylene - 1,4 - pregnadiene - 7β,11β,17α,21 - tetrol - 3,20 - dione 21-acetate and 9α - chloro - 16 - methylene - 1,4 - pregnadiene - 7β,11β,17α,21 - tetrol - 3,20 - dione 21-acetate.

Preparation 12
11-Oxygenated-4,6-pregnadiene-17α,21-diol-3,20-diones and Esters thereof

In the procedures of Preparations 1 and 4, by using as starting compounds the 1,2-dihydro derivatives of the 1,4-pregnadienes named therein, there are obtained 1,2-dihydro-4,6-pregnadienes corresponding to the 1,4,6-pregnatrienes of Preparations 1 and 4 which, when put through the procedures of Preparations 2, 3 and 9, will produce 4,6-pregnadienes corresponding to the 1,4,6-pregnatrienes named therein.

The following Examples illustrate the invention but do not limit it.

EXAMPLE 1
7α-Chloro-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17,21-dipropionate

A. Add 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate (2.0 gms.) to dioxan (24 ml.) which has been saturated with dry hydrogen chloride gas. Stir at room temperature for 16 hours, pour into ice water (600 ml.), separate the resultant precipitate by filtration, wash the precipitate with water and dry it in air. Separate the components in this precipitate on silica gel by thin layer chromatography using as developing solvent ether:hexane (2:1), and elute with ethyl acetate the band containing 7α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate as shown by ultraviolet light. Evaporate the combined ethyl acetate eluates and triturate the resultant residue with acetone:ether, then filter off and dry the triturated precipitate to obtain 7α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate.

Alternatively, the compound of this Example is prepared according to following procedures 1B and 1C.

B. 7α - Chloro - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate

Saturate dry tetrahydrofuran (137 ml.) at 0°C. with dry hydrogen chloride gas. Add 16α - methyl - 1,4,6 - pregnatriene - 17α,21 - diol - 3,11,20 - trione 17,21 - dipropionate (6.85 gms.) and stir the reaction mixture at 0°C. for 1 hour. Pour into ice water (1 liter) and stir for 1/2 hour. Separate the resultant precipitate by filtration, wash it with water, and dry it in air to give 7α - chloro - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate. Purify by recrystallisation from methanol:acetone containing a trace of propylene oxide; $[\alpha]_D^{26}$+76.2° (dimethylformamide); $[M]^+$ 520, 518; m.p. 180—183°C.; λ_{max}^{MeOH} 238 nm (ε=15,800).

C. To a solution of 7α - chloro - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate (3.2 gms.) in tetrahydrofuran (24 ml.) and methanol (8 ml.) at 0°C. under an atmosphere of nitrogen add sodium borohydride (0.697 gm.) and stir the reaction mixture for 15 minutes at 0°C. Pour into ice water (1.8 liters) and 250 ml. of 1N hydrochloric acid. Filter off the resultant precipitate and dry it in air to give 7α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate. Purify it by recrystallization twice from acetone:methanol:isopropyl ether; m.p. 212—216°C.; $[\alpha]_D^{26}$+42.6° (dimethylformamide); $[M]^+$ 522, 520; $\lambda_{max}^{methanol}$ 242 nm (ε 15,600); ν_{max}^{Nujol} 1743, 1730, 1720, 1652, 1610, 1595 cm^{-1}; nmr (dmso—d_6) δ 0.84 (C_{16}—CH_3, d J7Hz), 1.02 (C_{13}—CH_3, s), 1.42 (C_{10}—CH_3, s), 4.38 (11α—H, mult.), 4.67 (7β—H, mult), 4.80 (C_{21}—H, s), 5.95 (C_4—H, s), 6.20 (C_2—H, dd J10, 2Hz), 7.35 (C_1—H, d J10Hz). ("Nujol" is a Registered Trade Mark).

EXAMPLE 2
7α-Bromo-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17,21-dipropionate

A. Add 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate (0.29 gm.) to a solution of 30% (w/v) dry hydrogen bromide in acetic acid (4 ml.) precooled to 0°C. Stir the reaction mixture at 0°C. for 1 hour,

pour into ice water, separate the resultant solids by filtration, and wash the precipitate with water and dry it. Purify it by trituration with acetone:ether; dry the triturated precipitate to obtain 7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate (0.19 gm.).

Alternatively, the compound of this example is prepared according to following procedures 2B and 2C.

B. 7α - Bromo - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate

To a solution of 16α - methyl - 1,4,6 - pregnatriene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate (0.5 gm.) in glacial acetic acid (2 ml.), at 0°C. add a freshly prepared solution of dry hydrogen bromide gas (3 gms.) in glacial acetic acid (8 ml.) at 0°C. Stir the reaction mixture for 1 hour at 0°C., pour it into ice water (400 ml.), stir for 30 minutes, filter off the resultant precipitate and wash it with water until the water washings are neutral. Dry it in air to obtain 7α - bromo - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate (0.51 gms.); $[\alpha]_D^{26}$+105.1° (dimethylformamide), λ_{max}^{MeOH} 238 nm (ε=15,400).

C. To a mixture of 7α - bromo - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate (2.84 gms.) and sodium borohydride (0.573 gm.) under an atmosphere of nitrogen at 0°C. add methanol (8 ml.) precooled to 0°C. and stir the reaction mixture for 5 minutes at 0°C. Pour the reaction mixture into ice water (2 liters) and 1N hydrochloric acid (300 ml.), filter off the resultant precipitate and wash it with water. Dry it in air to obtain 7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate (2.6 gms.). Purify by recrystallization from acetone:ether:hexane; 1.44 gm.; m.p. >295°C.; $[\alpha]_D^{26}$+37.3° (dimethylformamide); $\lambda_{max}^{methanol}$ 242 nm (ε 15,350); ν_{max}^{Nujol} 1743, 1735, 1660, 1612, 1600 $cm.^{-1}$; nmr (dmso—d_6) δ 0.85 (C_{16}—CH_3, d J7Hz), 1.03 (C_{13}—CH_3, s), 1.43 (C_{10}—CH_3, s), 4.38 (11α—H, mult.), 4.75 (7β—H, mult.), 4.81 (C_{21}—H, s), 5.86 (C_4—H, s), 6.19 (C_9—H, dd J10, 2Hz), 7.31 (C_1—H, d J10 Hz).

EXAMPLE 3

7α-Bromo-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17-benzoate 21-acetate

A. To 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17-benzoate 21-acetate (0.31 gm.) add a solution of 30% dry hydrogen bromide in glacial acetic acid (6.2 ml.) at 0°C. After 1 hour at 0°C., pour the mixture into ice water, filter off the resultant precipitate, wash it with water and dry it in air. Purify it by thin layer chromatography on silica gel using as developing solvent ether:hexane (2:1) and eluting with ethyl acetate the band containing the desired product as shown by ultraviolet light. Evaporate the combined ethyl acetate eluates to a residue comprising 7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-benzoate 21-acetate. Further purify the residue by trituration with isopropyl ether (yield 0.125 gm.).

Alternatively, the compound of this example is prepared according to following procedures 3B and 3C.

B. 7α - Bromo - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17-benzoate 21-acetate

To a freshly prepared solution of dry hydrogen bromide gas (9.3 gms.) in glacial acetic acid (16 ml.) at 0°C. add dropwise a solution of 16α - methyl - 1,4,6 - pregnatriene - 17α,21 - diol - 3,11,20 - trione 17-benzoate 21-acetate (1.56 gm.) in glacial acetic acid (5 ml.). Stir the mixture for 1 hour at 0°C., pour into ice water, stir the aqueous mixture for 30 minutes, filter off the resultant precipitate, wash it with water and dry it in air to give 7α - bromo - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17-benzoate 21-acetate (1.6 gm.). Further purify by recrystallization from acetone:hexane; m.p. 190—192.5°C.; $[\alpha]_D^{26}$+77.3° (dimethylformamide); $\lambda_{max}^{methanol}$ 232 nm (ε 27,600).

C. 7α - Bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-benzoate 21-acetate

(1) To a mixture of 7α - bromo - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17-benzoate 21-acetate (1.05 gm.) and sodium borohydride (0.1 gm.) under an atmosphere of nitrogen at 0°C. add a precooled solution of

tetrahydrofuran (7.5 ml.) and methanol (2.5 ml.) and stir the reaction mixture for 25 minutes at 0°C. Pour into ice water (500 ml.) and 1N hydrochloric acid (100 ml.). Filter off the resultant precipitate, wash it with water and dry it in air to obtain 7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-benzoate 21-acetate (0.53 gm.). Further purify by recrystallization from acetone:hexane:ether; m.p. 156—159°C.; $[\alpha]_D^{26}$+21.1° (dimethylformamide); $\lambda_{max}^{methanol}$ 233 nm (ε 26,800); nmr (dmso—d_6) δ 0.89 (C_{18}—CH_3, d J7Hz), 1.12 (C_{13}—CH_3, s), 1.48 (C_{10}—CH_3, s) 2.13 (OAc, s), 4.46 (11α—H, mult.), 4.96 (C_{21}—H, quart.), 4.90 (7β—H, mult.), 6.00 (C_4—H, s), 6.28 (C_2—H, d,d J10,2Hz), 7.39 (C_1—H, d, J10Hz), 7.50—8.00 (phenyl, mult.).

(2) Alternatively, the compound of this example is prepared as follows. To a mixture of 7α - bromo - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17-benzoate 21-acetate (0.65 gm.) and sodium borohydride (61.7 mg.) under an atmosphere of nitrogen at room temperature add dimethylformamide (6.2 ml.) and water (0.3 ml.). Stir at room temperature under an atmosphere of nitrogen for 1 hour and pour into a mixture of water (200 ml.) and 1N hydrochloric acid (50 ml.). Filter off the resultant precipitate, wash it with water and dry it in air to give 7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-benzoate 21-acetate. Further purify by recrystallization from ether:acetone.

EXAMPLE 4

7α-Chloro- and 7α-bromo-11-oxo-1,4-pregnadiene-17α,21-diol-3,20-diones and Esters thereof

A. 7α-Chloro-derivatives

In a manner similar to that described in Example 1B treat each of the following 11-oxo-1,4,6-pregnatrienes with dry hydrogen chloride in tetrahydrofuran:

the 21-acetate, 21-*n*-butyrate, 21-isobutyrate, 21-valerate, 21-caprylate, 21-(1'-adamantyl)-carboxylate, 21-(1'-adamantyl)-acetate, 21-benzoate, and 21-*p*-methoxy-benzoate esters of 16α-methyl-1,4,6-pregnatriene-17α,21-diol-3,11,20-trione 17-propionate;

the 21-acetate, 21-*n*-butyrate, 21-isobutyrate, 21-valerate, 21-caprylate, 21-(1'-adamantyl)-carboxylate, 21-(1'-adamantyl)-acetate, 21-benzoate and 21-*p*-methoxybenzoate esters of 16α - methyl - 1,4,6 - pregnatriene - 17α,21 - diol - 3,11,20 - trione 17-*n*-butyrate;

the 21-acetate, 21-*n*-butyrate, 21-isobutyrate, 21-valerate, 21-caprylate, 21-(1'-adamantyl)-carboxylate, 21-(1'-adamantyl)-acetate, 21-benzoate and 21-*p*-methoxybenzoate esters of 16α - methyl - 1,4,6 - pregnatriene - 17α,21 - diol - 3,11,20 - trione 17-benzoate;

16α - methyl - 1,4,6 - pregnatriene - 17α,21 - diol - 3,11,20 - trione 17,21-diacetate;

the 21-acetate, 21-propionate and 21-valerate esters of 16α - methyl - 1,4,6 - pregnatriene - 17α,21 - diol - 3,11,20 - trione 17-valerate;

16α - methyl - 1,4,6 - pregnatriene - 17α,21 - diol - 3,11,20 - trione 17-isobutyrate 21-acetate; and

16α - methyl - 1,4,6 - pregnatriene - 17α,21 - diol - 3,11,20 - trione 17-dodecanoate 21-propionate;

and the 16β-epimers and 16-unsubstituted analogs of the foregoing and the 16-methylene derivatives corresponding to the foregoing.

Isolate and purify each of the resulting products in a manner similar to that described in Example 1B to obtain, respectively,

the 21-acetate, 21-*n*-butyrate, 21-isobutyrate, 21-valerate, 21-caprylate, 21-(1'-adamantyl)-carboxylate, 21-(1'-adamantyl)-acetate, 21-benzoate and 21-*p*-methoxybenzoate esters of 7α - chloro - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17-propionate;

the 21-acetate, 21-*n*-butyrate, 21-isobutyrate, 21-valerate, 21-caprylate, 21-(1'-adamantyl)-carboxylate, 21-(1'-adamantyl)-acetate, 21-benzoate and 21-*p*-methoxy-benzoate esters of 7α - chloro - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17-*n*-butyrate;

the 21-acetate, 21-*n*-butyrate, 21-isobutyrate, 21-valerate, 21-caprylate, 21-(1'-adamantyl)-carboxylate, 21-(1'-adamantyl)-acetate, 21-benzoate and 21-*p*-methoxybenzoate esters of 7α - chloro - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17-benzoate;

7α - chloro - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17,21-diacetate;

the 21-acetate, 21-propionate, and 21-valerate esters of 7α - chloro - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17-valerate;

7α - chloro - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17-isobutyrate 21-acetate;

and 7α - chloro - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17-dodecanoate 21-propionate;

and the 16β-epimers and 16-unsubstituted analogs of the foregoing and the 16-methylene derivatives corresponding to the foregoing.

B. 7α-Bromo Derivatives

In a manner similar to that described in Examples 2B and 3B, treat each of the starting compounds listed in Example 4A with dry hydrogen bromide in glacial acetic acid. Isolate and purify each of the resultant products in a manner similar to that described in Examples 2B and 3B to obtain, respectively, the 7α-bromo derivatives corresponding to the 7α-chloro products of Example 4A.

Thus the following compounds in particular can be obtained by the method of Example 4(A) or 4(B):

7α - chloro - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 21-acetate m.p. 220—221°C.; $[\alpha]_D^{26}$+113.3° (dimethylformamide); λ_{max}^{MeOH} 238 nm (ε=15,000).

7α - chloro - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 21-acetate $[\alpha]_D^{26}$+101.6° (dimethylformamide); λ_{max}^{MeOH} 240 nm (ε=15,350).

7α - chloro - 16β - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 21-acetate m.p. 175—178°C.; $[\alpha]_D^{26}$+134.3° (dimethylformamide) λ_{max}^{MeOH} 237 nm (ε=17,450).

7α - chloro - 16β - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17-benzoate 21-acetate m.p. 209°C. (dec.); $[\alpha]_D^{26}$+124.7° (dimethylformamide); λ_{max}^{MeOH} 233 nm (ε=30,000).

7α - bromo - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17-acetate; m.p. 168°C. (dec.); $[\alpha]_D^{26}$+100.7° (dimethylformamide).

7α - bromo - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17,21-dibenzoate m.p. >285°C.; λ_{max}^{MeOH} 231 nm (ε=31,500); $[\alpha]_D^{26}$+65.8° (dimethylformamide).

7α - bromo - 16β - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17-benzoate 21-acetate m.p. 160°C. (dec.); $[\alpha]_D^{26}$+131.9° (dimethylformamide); λ_{max}^{MeOH} 235 nm (ε=28,400).

EXAMPLE 5

7α-Chloro- and 7α-bromo-11β-hydroxy-1,4-pregnadiene-17α,21-diol-3,20-diones and Esters thereof

A. By Reduction of 11-keto Analogs

In a manner similar to that described in Examples 1C, 2C and 3C, treat each of the 7α-chloro- and 7α - bromo - 11 - oxo - 1,4 - pregnadienes prepared in Example 4 with sodium borohydride in tetrahydrofuran and methanol at 0°C. under an atmosphere of nitrogen, then isolate and purify each of the resultant products in a manner similar to that described to obtain:

the 7α-chloro- and the 7α-bromo-derivatives of each of the 21-acetate, 21-*n*-butyrate, 21-isobutyrate, 21-valerate, 21-caprylate, 21-(1'-adamantyl)-carboxylate, 21-(1'-adamantyl)-acetate, 21-benzoate and 21-*p*-methoxybenzoate esters of 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-propionate, of 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-*n*-butyrate, and of 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-benzoate;

the 7α-chloro- and the 7α-bromo- derivatives of 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-diacetate;

the 7α-chloro- and the 7α-bromo derivatives of each of the 21-acetate, 21-propionate, and 21-valerate esters of 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-valerate;

the 7α-chloro- and the 7α-bromo- derivatives of 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-isobutyrate 21-acetate;

and the 7α-chloro- and the 7α-bromo-derivatives of 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-dodecanoate 21-propionate;

and the 16β-epimers and 16-unsubstituted analogs of the foregoing and the 16-methylene derivatives corresponding to the foregoing.

B. Alternatively, the compounds of this example are prepared by treating the corresponding 11β - hydroxy - 7 - unsubstituted 1,4,6-pregnatriene, e.g. the 21-

acetate, 21-pivalate and 21-benzoate of 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione, with hydrogen chloride or hydrogen bromide in the manner described in Examples 1A, 1B and 1C and isolating and purifying each of the resultant products in the described manner to obtain the corresponding 7α - chloro- and 7α-bromo-1,4-pregnadiene.

Thus the following compounds in particular can be obtained by the method of Example 5(A) or 5(B):

7α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-acetate, m.p. 197—203°C; $[\alpha]_D^{26}$+49.9° (dimethylformamide); λ_{max}^{MeOH} 242 (ε=14,300).

7α - chloro - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-acetate, m.p. 230—233°C; $[\alpha]_D^{26}$+60.8° (dimethylformamide); λ_{max}^{MeOH} 243 nm (ε=11,600).

7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dibenzoate, m.p. 230—234°C.; λ_{max}^{MeOH} 232 nm (ε=39,800); $[\alpha]_D^{26}$+30.5° (dimethylformamide).

7α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21 - benzoate, $[M]^+$ 514, 512.

7α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17 - *n* - butyrate 21 - propionate; m.p. 155—160°C.; $[M]^+$ 536, 534.

7α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-di-*n*-butyrate $[M]^+$ 550, 548; m.p. 145—147°C.; λ_{max}^{MeOH} 240 nm (ε=16,500); $[\alpha]_D^{26}$+40.2° (dimethylformamide).

7α - chloro - 16β - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-benzoate 21-acetate m.p. 195—198°C.; $[\alpha]_D^{26}$+69.3° (dimethylformamide); λ_{max}^{MeOH} 235 nm (ε=27,000).

7α - chloro - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate m.p. 125—130°C.; $[\alpha]_D^{26}$+31.3° (dimethylformamide); λ_{max}^{MeOH} 240 nm (ε=16,000).

7α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-propionate 21-isobutyrate; $[M]^+$ 536, 534; nmr (dmso—d_6) δ 0.84, 1.04, 1.44, 4.69, 5.99, 6.24, 7.37.

7α - chloro - 16β - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-propionate 21-*n*-butyrate nmr (dmso—d_6) δ 0.92, 1.25, 1.44, 4.62, 4.72, 4.44, 6.00, 6.25, 7.39.

7α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-propionate 21-valerate; m.p. 134—137°C; $[\alpha]_D^{26}$+37.5° (dimethylformamide); λ_{max}^{MeOH} 240 nm (ε=13,700).

7α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-isobutyrate 21-acetate; $[M]^+$ 522, 520.

7α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-benzoate 21-acetate; $[M]^+$ 556, 554; nmr (dmso—d_6) δ 0.88, 1.12, 1.46, 4.73, 6.02, 6.26, 7.40, 7.50—8.00.

7α - chloro - 16 - methylene - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate; nmr (dmso—d_6) δ 0.98; 1.44, 4.45, 4.73, 4.88, 5.50, 6.00, 6.26, 7.38.

7α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-propionate 21-acetate; $[M]^+$ 508, 506; nmr (dmso—d_6) δ 0.84, 1.01, 1.42, 4.84, 4.67, 4.40, 5.99, 6.24, 7.37.

7α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-propionate 21-*n*-butyrate; $[M]^+$ 536, 534; nmr (dmso—d_6) δ 0.85, 1.02, 1.44, 4.69, 5.99, 6.25, 7.37.

7α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-valerate 21-acetate; $[M]^+$ 536, 534.

7α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-*n*-butyrate 21-acetate; $[M]^+$ 522, 520.

7α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-pivalate; m.p. 227—230°C; λ_{max}^{MeOH} 243 nm (ε=13,900); $[M]^+$ 494, 492.

7α - chloro - 16β - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-acetate m.p. 228°C. (dec.); $[\alpha]_D^{26}$+78.3° (dimethylformamide); λ_{max}^{MeOH} 241 nm (ε=15,500).

7α - chloro - 16β - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate; m.p. 125°C. (dec.); $[\alpha]_D^{26}$+74.4° (dimethylformamide); λ_{max}^{MeOH} 241 nm (ε=15,200).

7α - bromo - 16β - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 -

dione 17-benzoate 21-acetate; $[M]^+$ 600, 598; m.p. 170°C. (dec.); $[\alpha]_D^{26}$+72.8°; λ_{max}^{MeOH} 235 nm (ϵ=26,500).

7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-*n*-butyrate 21-propionate m.p. 147°C. (dec.); $[\alpha]_D^{26}$+30.8° (dimethylformamide); λ_{max}^{MeOH} 243 nm (ϵ=15,600).

7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-di-*n*-butyrate m.p. 143—146°C.; $[\alpha]_D^{26}$+31.8° (dimethylformamide); λ_{max}^{MeOH} 243 nm (ϵ=15,600).

7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-benzoate 21-propionate m.p. 163—170°C.; $[\alpha]_D^{26}$+27.1° (dimethylformamide); λ_{max}^{MeOH} 233 nm (ϵ=27,900).

7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-benzoate 21-*n*-butyrate m.p. 138—144°C.; $[\alpha]_D^{26}$+24.2° (dimethylformamide); λ_{max}^{MeOH} 234 nm (ϵ=27,100).

7α - bromo - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate $[\alpha]_D^{26}$+29.8° (dimethylformamide); λ_{max}^{MeOH} 242 nm (ϵ=15,700).

7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-acetate λ_{max}^{MeOH} 244 nm (ϵ=13,700); $[M]^+$ 496, 494.

7α - bromo - 16β - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-acetate m.p. 165°C. (dec.); $[\alpha]_D^{26}$+64.6°; λ_{max}^{MeOH} 242 nm (ϵ=15,600).

7α - bromo - 16β - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate, m.p. 135—137°C.; $[\alpha]_D^{26}$+66.4° (dimethylformamide); λ_{max}^{MeOH} 242 nm (ϵ=15,500).

7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-propionate 21-acetate $[M]^+$ 552, 550.

7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-propionate 21-*n*-butyrate; $[M]^+$ 580, 578; m.p. 153—155°C.; $[\alpha]_D^{26}$+34.7° (dimethylformamide); λ_{max}^{MeOH} 241 nm (ϵ=15,800).

7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-*n*-butyrate 21-acetate.

7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-valerate 21-acetate; $[M]^+$ 580, 578.

7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-valerate.

7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-propionate 21-isobutyrate m.p. 168—172°C.; $[M]^+$ 580, 578; $[\alpha]_D^{26}$+36.3° (dimethylformamide); λ_{max}^{MeOH} 240 nm (ϵ=15,500).

7α - bromo - 16β - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-propionate 21-acetate; $[M]^+$ 552, 550; nmr (dmso—d_6) δ 0.90, 1.44, 4.89, 5.96, 6.25, 7.38.

7α - bromo - 16β - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-propionate 21-butyrate m.p. 145°C.; $[M]^+$ 580, 578; nmr (dmso—d_6) δ 0.94, 1.28, 1.44, 4.90, 4.61, 4.45, 5.98, 6.28, 7.39.

EXAMPLE 6

7α,9α,11β-Trihalo-1,4-pregnadiene-17α,21-diol-3,20-dione 17,21-dihydrocarboncarboxylates

A. 7α - Chloro - 16α - methyl - 1,4,9(11) - pregnatriene - 17α,21 - diol - 3,20 - dione 17,21-dipropionate

(1) To 7α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate (0.37 gm.) in dimethylformamide (11.1 ml.) and collidine (0.67 ml.) add a 3.5% by weight solution of sulfur dioxide in methanesulfonyl chloride (0.22 ml.). Stir the reaction mixture at 0°C. for ½ hour, then at room temperature for ½ hour. Add aqueous 1N hydrochloric acid, extract the reaction mixture with ethyl acetate, wash the combined organic extracts with water, dry them over magnesium sulfate and evaporate them *in vacuo* to a residue comprising 7α - chloro - 16α - methyl - 1,4,9(11) - pregnatriene - 17α,21 - diol - 3,20 - dione 17,21-dipropionate. Purify the residue by trituration with ether and filtration of the resultant precipitate; m.p. 198—201°C.; $[\alpha]_D^{26}$+26.3° (dimethylformamide); λ_{max}^{MeOH} 238 nm (ϵ=16,500).

(2) In similar manner, treat each of 7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate and 7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17 - benzoate 21-acetate in dimethylformamide and collidine with a 5.5% by weight solution of sulfur dioxide in methanesulfonyl chloride to obtain, respectively, 7α -

bromo - 16α - methyl - 1,4,9(11) - pregnatriene - 17α,21 - diol - 3,20 - dione 17,21-dipropionate and 7α - bromo - 16α - methyl - 1,4,9(11) - pregnatriene - 17α,21 - diol - 3,20 - dione 17-benzoate 21-acetate.

B. 7α,9α,11β - Trichloro - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione 17,21-dipropionate

(1) To a solution of 7α - chloro - 16α - methyl - 1,4,9(11) - pregnatriene - 17α,21 - diol - 3,20 - dione 17,21-dipropionate (0.18 gm.) in chloroform (5 ml.) and pyridine (0.9 ml.), add a solution of dry chlorine gas (28 mg., 1.1 equivalents) in chloroform (4 ml.) and let the mixture stand at room temperature for 3 hours. Add methylene chloride (300 ml.), wash the reaction mixture sequentially with 10% aqueous sodium thiosulfate solution, 1N hydrochloric acid, and water, dry it over magnesium sulfate and evaporate it. Purify the resultant residue on silica gel by thick layer chromatography using as developing solvent chloroform:ethyl acetate (9:1). Remove the least polar band as shown by ultraviolet light and elute with ethyl acetate. Evaporate the combined ethyl acetate eluates to a residue comprising 7α,9α,11β - trichloro - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione 17,21-dipropionate. Further purify by trituration with acetone, and filtering off the triturated precipitate; m.p. 225—228°C.; λ_{max}^{MeOH} 236 nm (ε=15,600).

(2) In similar manner treat the 7α - bromo - 1,4,9(11) - pregnatrienes prepared in Example 6A(2) with chlorine to obtain, respectively, 7α - bromo - 9α,11β - dichloro - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione 17,21-dipropionate and 7α - bromo - 9α,11β - dichloro - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione 17-benzoate 21-acetate.

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

(1) To a solution of 7α - chloro - 16α - methyl - 1,4,9(11) - pregnatriene - 17α,21 - diol - 3,20 - dione 17,21-dipropionate (0.5 gms.) in chloroform (10 ml.) and pyridine (1 ml.), add a solution of hydrogen fluoride (5 gms.) in tetrahydrofuran (5 ml.) followed by *N*-chlorosuccinimide (128 mg.). Dilute the reaction mixture with sufficient methylene chloride to form a solution, and stir the reaction mixture for 48 hours at room temperature. Pour the reaction mixture into aqueous sodium carbonate, extract the aqueous mixture with methylene chloride, wash the combined organic extracts successively with water, dilute hydrochloric acid and finally with water. Dry over magnesium sulfate, filter and evaporate to a residue comprising 7α,9α - dichloro - 11β - fluoro - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione 17,21-dipropionate. Purify the residue by trituration with ether, filtration and recrystallization from acetone:hexane.

(2) In similar manner, treat the 7α - bromo - 1,4,9(11) - pregnatrienes prepared in Example 6A(2) in chloroform with hydrogen fluoride and *N*-chlorosuccinimide in the presence of pyridine and isolate the resultant products to obtain, respectively, 7α - bromo - 9α - chloro - 11β - fluoro - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione 17,21-dipropionate and 7α - bromo - 9α - chloro - 11β - fluoro - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione 17-benzoate 21-acetate.

D. 7α - Chloro - 9α - bromo - 11β - fluoro - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione 17,21-dipropionate

(1) To a solution of 7α - chloro - 16α - methyl - 1,4,9(11) - pregnatriene - 17α,21 - diol - 3,20 - dione 17,21-dipropionate (0.5 gm.) in chloroform (10 ml.) and pyridine (1 ml.) add a solution of hydrogen fluoride (5 gms.) in tetrahydrofuran (5 ml.) followed by *N*-bromoacetamide (130 mg.). Dilute the reaction mixture with sufficient methylene chloride to form a solution and stir for 48 hours at room temperature. Pour the reaction mixture into aqueous sodium carbonate, extract the aqueous mixture with methylene chloride, and wash the combined organic extracts successively with water, dilute hydrochloric acid and water. Dry the solution over magnesium sulfate, filter and evaporate. Dissolve the resultant residue in acetone:ether and filter through a column of Florisil (Registered Trade Mark) and elute with ether. Combine the eluates and evaporate *in vacuo* to a residue comprising 7α - chloro - 9α - bromo - 11β - fluoro - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione 17,21-dipropionate.

(2) In the foregoing procedure by using as starting compounds the 7α - bromo - 1,4,9(11) - pregnatrienes prepared in Example 6A(2), 7α,9α - dibromo - 11β - fluoro - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione

17,21-dipropionate and 7α,9α - dibromo - 11β - fluoro - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione 17-benzoate 21-acetate respectively are obtained.

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

(1) To a stirred solution of 7α - chloro - 16α - methyl - 1,4,9(11) - pregnatriene - 17α,21 - diol - 3,20 - dione 17,21-dipropionate (0.5 gm.) in chloroform (10 ml.) and pyridine (1 ml.) at −20°C. add *N*-bromoacetamide (130 mg.) and a solution of hydrogen chloride (100 mg.) in tetrahydrofuran (5 ml.). Continue stirring at −20°C. for 15 minutes, then allow the reaction mixture to attain room temperature and stand at room temperature an additional 15 minutes. Add methylene chloride to the reaction mixture and wash the reaction mixture with thiosulfate solution, water, 10% aqueous sodium bicarbonate and finally with water. Dry over magnesium sulfate, filter and evaporate *in vacuo*. Recrystallize the resultant residue from acetone:hexane to give 7α,11β - dichloro - 9α - bromo - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione 17,21-dipropionate.

(2) In the foregoing procedure, by using as starting compound the 7α - bromo - 1,4,9(11) - pregnatrienes prepared in Example 6A(2), 7α,9α - dibromo - 11β - chloro - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione 17,21-dipropionate and 7α,9α - dibromo - 11β - chloro - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione 17-benzoate 21-acetate respectively are obtained.

F. Treat each of the 7α-chloro- and 7α - bromo - 11β - hydroxy - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - diones prepared in Example 5 in a manner similar to that described in Example 6A followed by reaction of the resulting 7α-chloro- and 7α - bromo - 1,4,9(11) - pregnatriene - 17α,21 - diol - 3,20 - diones with chlorine in the manner described in Example 6B or with a mixture of halogenating reagents in a manner similar to that described in Example 6C—6E to obtain the corresponding 7α-chloro- and 7α - bromo - 9α,11β - dihalo - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - diones, e.g. 7α,9α,11β - trichloro - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione 21-acetate, m.p. 299—301°C.; $[\alpha]_D^{26}$+71.1° (dimethylformamide); λ_{max}^{MeOH} 239 nm (ε=14,500).

EXAMPLE 7

7α-Chloro-9α-halo-1,4-pregnadiene-17α,21-diol-3,20-diones

A. 7α - Chloro - 9α - fluoro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-acetate

To 9α - fluoro - 16α - methyl - 1,4 - pregnadiene - 7β,11β,17α,21 - tetrol - 3,20 - dione 21-acetate (0.5 gm.) in methylene chloride (100 ml.) at 0°C. under an atmosphere of nitrogen add *N,N*-diethyl-1,2,2-trichlorovinylamine (1.67 ml.). Stir at 0°C. for 7 hours, evaporate *in vacuo*, place the resultant residue on a silica gel column (50 gms.) and elute with chloroform:ethyl acetate (3:1). Combine like fractions containing the desired compound as determined by thin layer chromatography and evaporate. Further purify the resultant residue on thin layer silica gel plates, developing with chloroform:ethyl acetate (3:1). Remove the band containing the desired product as visualized under ultraviolet light and elute with ethyl acetate. Evaporate the eluate to a residue comprising 7α - chloro - 9α - fluoro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-acetate. Further purify by recrystallization from acetone:hexane; $[M]^+$ 470, 468; NMR (dmso—d_6) δ 0.82, 0.90, 1.50, 4.17, 4.55, 4.95, 6.09, 6.27, 7.32.

B. In the procedure of Example 7A, by starting with each of the 9α-chloro- and 9α-bromo-analogs of the 9α - fluoro-7β - hydroxy - 1,4 - pregnadiene starting compound, the corresponding 7α-chloro derivatives are obtained, i.e. 7α,9α - dichloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-acetate and 7α - chloro - 9α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-acetate, respectively.

C. Similarly, using as starting materials the 7β-hydroxy derivatives prepared in Preparation 11 in the procedure of Example 7A, 7α - chloro - 9α - fluoro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate, 7α - chloro - 9α - fluoro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-benzoate 21-propionate, 7α - chloro - 9α - fluoro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-*n*-butyrate 21-

propionate, their 9α-bromo- and 9α-chloro-analogs, their 16β-methyl epimers and 16-unsubstituted analogs and 16-methylene derivatives corresponding thereto are obtained.

EXAMPLE 8

7α-Fluoro-1,4-pregnadiene-3,20-diones

A. 7α - Fluoro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-acetate

To 16α - methyl - 1,4 - pregnadiene - 7β,11β,17α,21 - tetrol - 3,20 - dione 21-acetate (0.13 gm.) in methylene chloride (15 ml.) at 0°C. under an atmosphere of nitrogen, add *N* - (2 - chloro - 1,1,2 - trifluoroethyl) - diethylamine (fluoramine) (0.286 ml.). Stir at 0°C. for 18 hours, then evaporate *in vacuo* and purify the resultant residue by thin layer chromatography, developing with chloroform:ethyl acetate (5:2) to obtain a mixture comprising 7α - fluoro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-acetate and 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 21-acetate. Treat the foregoing mixture (55 mg.) in dioxan (0.58 ml.) and pyridine (3 drops) with osmium tetroxide (10 mg.) at room temperature for 5 days. Saturate the reaction mixture with hydrogen sulfide, filter the reaction mixture, evaporate the filtrate *in vacuo* at room temperature, and purify the resultant residue by thin layer chromatography on silica gel, developing with chloroform:ethyl acetate (2:1). Evaporate the combined eluates containing the desired product and triturate the resultant residue with ether:hexane to obtain 7α - fluoro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-acetate; $[M]^+$ 434; nmr (dmso—d_6) δ 0.80, 0.91 1.42, 4.36, 4.89, 4.92, 5.99, 6.21, 7.37.

B. 7α,9α-Difluoro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-acetate

To 9α - fluoro - 16α - methyl - 1,4 - pregnadiene - 7β,11β,17α,21 - tetrol - 3,20 - dione 21-acetate (0.35 gm.) in methylene chloride (350 ml.) at 0°C. under an atmosphere of nitrogen add fluoramine (0.76 ml.). Stir at 0°C. for 24 hours, and evaporate the reaction mixture *in vacuo*. Chromatograph the resultant residue on silica gel by thin layer chromatography, developing with chloroform:ethyl acetate (2:1) and eluting with ethyl acetate the band containing the desired product as visualized under ultraviolet light. Evaporate the combined eluates to a residue of 7α,9α - difluoro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-acetate. Further purify by recrystallization from acetone:methanol:hexane; m.p. 234—237°C.; $[\alpha]_D^{26}$+45.4° (dimethylformamide).

C. Similarly, by treating the 7β - hydroxy - 1,4 - pregnadienes prepared as described in Preparation 11 with fluoramine according to the procedures of Examples 8A and 8B, there is obtained the corresponding 7α - fluoro - 1,4 - pregnadiene, e.g. 7α - fluoro - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-acetate; m.p. 243—246°C.; $[\alpha]_D^{26}$+62.7°.

EXAMPLE 9

7α-Iodo-9α-unsubstituted-1,4-pregnadiene-3,20-diones

A. 7α - Iodo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-acetate

Add 16α - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 21-acetate (0.1 gm.) to a solution of dry hydrogen iodide (0.512 gm.) in glacial acetic acid (2 ml.) and stir the reaction mixture at room temperature for 50 minutes. Pour into ice water, filter off the precipitate and dry it; triturate it with ether, filter off the solid, dissolve it in methylene chloride, wash the methylene chloride solution with aqueous 0.1N sodium thiosulfate solution and with water, dry it over magnesium sulfate and evaporate it *in vacuo*. Triturate the resultant residue with hexane and filter to obtain 7α - iodo - 16α - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-acetate (8 mg.); $[M]^+$ 542.

B. In similar manner, treat each of the 9-unsubstituted 1,4,6-pregnatriene-3,20-diones prepared in Preparations 1—10 with hydrogen iodide in acetic acid according to the procedure of Example 9A to obtain the corresponding 7α - iodo - 9 - unsubstituted - 1,4 - pregnadiene - 3,20 - dione, e.g. 7α - iodo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate, m.p. 150°C. (dec.), $[\alpha]_D^{26}$+22.0° (dimethylformamide), λ_{max}^{MeOH} 241 nm (ε=14,500); its 16β-analog, $[\alpha]_D^{26}$+52.0° (dimethylformamide), λ_{max}^{MeOH} 241 nm (ε=14,500); and 7α - iodo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-benzoate 21-acetate, $[\alpha]_D^{26}$+34.3° (dimethylformamide); λ_{max}^{MeOH} 233 nm (ε=24,400).

EXAMPLE 10

7α-Bromo-9α-halo-1,4-pregnadiene-3,20-diones

A. 7α - Bromo - 9α - fluoro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-acetate

To a solution of 7β - hydroxy - 9α - fluoro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-acetate (0.1 gm.) and lithium bromide (0.1 gm.) in methylene chloride (100 ml.) cooled to 0°C. add fluoramine (0.23 ml.). Stir at 0°C. for 24 hours and then evaporate *in vacuo*. Dissolve the resultant residue in chloroform, wash the chloroform solution with water, dry it over magnesium sulfate and evaporate. Purify by thin layer chromatography using as developing solvent chloroform:ethyl acetate (2:1). Remove the band containing the desired product as visualized under ultraviolet light and elute with ethyl acetate. Evaporate the combined ethyl acetate eluates *in vacuo* to a residue comprising 7α - bromo - 9α - fluoro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-acetate.

B. In the procedure of Example 10A, by starting with each of the 9α-chloro and 9α-bromo analogs of the 9α - fluoro - 7β - hydroxy - 1,4 - pregnadiene starting compound, the corresponding 7α-bromo derivative is obtained i.e. 7α - bromo - 9α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-acetate and 7α,9α - dibromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-acetate, respectively.

C. Similarly, by treating any of the 7β-hydroxy-1,4-pregnadienes prepared in Preparation 11 with fluoramine and lithium bromide according to the procedure of Example 10A, the corresponding 7α-bromo-1,4-pregnadiene derivative is obtained.

D. In the procedure of Example 10A, by substituting for lithium bromide an equivalent quantity of lithium chloride and by using tetrahydrofuran as solvent instead of methylene chloride, the corresponding 7α-chloro compound, i.e. 7α - chloro - 9α - fluoro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-acetate, is obtained.

EXAMPLE 11

7α-Halo-21-desoxy-1,4-pregnadiene-3,20-diones and certain 21-ester Derivatives

A. 7α - Chloro - 21 - desoxy - 1,4 - pregnadiene - 3,20 - diones

(1) 7α - Chloro - 1,4 - pregnadien - 17α - ol - 3,20 - dione and its 17-acetate

To 17α - hydroxy - 1,4,6 - pregnatriene - 3,20 - dione (0.5 gm.) add glacial acetic acid (20 ml.) saturated with dry hydrogen chloride gas, and lithium chloride (2 gms.). Stir at room temperature for 45 minutes, then pour into an aqueous sodium carbonate solution and extract the aqueous mixture with ether. Wash the combined organic extracts with water, dry over magnesium sulfate and evaporate to a residue comprising 7α - chloro - 1,4 - pregnadiene - 17α - ol - 3,20 - dione. Purify by recrystallization from methanol; m.p. 229—231°C.; $[\alpha]_D^{26}$+50.7° (dioxan).

7α - Chloro - 17α - acetoxy - 1,4 - pregnadiene - 3,20 - dione

(m.p. 200—206°C.; $[\alpha]_D^{26}$+4.8° (dimethylformamide); λ_{max}^{MeOH} 242 nm (ε=16,100)) can be prepared similarly from 17α - acetoxy - 1,4,6 - pregnatriene - 3,20 - dione.

(2) In the above procedure, by using as starting compounds the 17-propionate, 17-*n*-butyrate, 17-valerate and 17-benzoate of 1,4,6 - pregnatriene - 11β,17α - diol - 3,20 - dione, the corresponding 7α-chloro derivatives, i.e. the 17-propionate, 17-*n*-butyrate, 17-valerate and 17-benzoate of 7α - chloro-1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione, respectively, are obtained.

B. 7α - Bromo - 21 - desoxy - 1,4 - pregnadiene - 3,20 - diones

(1) In the procedure of Example 11A(1), by using as reagents an equivalent quantity of dry hydrogen bromide instead of dry hydrogen chloride and an equivalent quantity of lithium bromide instead of lithium chloride, the corresponding 7α-bromo derivative, i.e. 7α - bromo - 1,4 - pregnadien - 17α - ol - 3,20 - dione, is obtained.

7α - Bromo - 17α - acetoxy - 1,4 - pregnadiene - 3,20 - dione

($[\alpha]_D^{26}$+5.7° (dimethylformamide); λ_{max}^{MeOH} 242 nm (ε=14,000)) may be prepared similarly from 17α - acetoxy - 1,4,6 - pregnatriene - 3,20 - dione.

(2) Treat each of the starting compounds of Example 11A(2) with dry hydrogen bromide and lithium bromide in glacial acetic acid in the manner of Example

11B(1) to obtain, respectively, the 17-propionate, 17-*n*-butyrate, 17-valerate and 17-benzoate of 7α - bromo - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione.

C. 7α - Fluoro - 21 - desoxy - 1,4 - pregnadiene - 3,20 - diones and certain 21-ester derivatives

In a manner similar to that described in Example 8A, treat each of 1,4 - pregnadiene - 7β,17α - diol - 3,20 - dione and the 17-propionate, 17-*n*-butyrate, 17-valerate and 17-benzoate of 1,4 - pregnadiene - 7β,11β,17α - triol - 3,20 - dione with fluoramine in methylene chloride under an atmosphere of nitrogen. Isolate and purify each of the resultant products in a manner similar to that described to obtain, respectively, 7α - fluoro - 1,4 - pregnadiene - 17α - ol - 3,20 - dione and the 17-propionate, 17-*n*-butyrate, 17-valerate and 17-benzoate of 7α - fluoro - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione.

7α - Fluoro - 17α - acetoxy - 1,4 - pregnadiene - 3,20 - dione (m.p. 262—265°C.) and 7α - fluoro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate (m.p. 157—161°C.; $[\alpha]_D^{26}$+32.9° (dimethylformamide); λ_{max}^{MeOH} 240 nm (ε=15,900)) can be prepared similarly from 1,4 - pregnadiene - 7β,17α - diol - 3,20 - dione 17-acetate and 16α - methyl - 1,4 - pregnadiene - 7β,11β,17α,21 - tetrol - 3,20 - dione 17,21-dipropionate.

D. 7α - Iodo - 21 - desoxy - 1,4 - pregnadiene - 3,20 - diones

In a manner similar to that described in Example 9A, treat each of the pregnatriene starting compounds of Example 11A(1) and 11A(2) with hydrogen iodide in glacial acetic acid and isolate each of the resultant products in the described manner to obtain, respectively, 7α - iodo - 1,4 - pregnadien - 17α - ol - 3,20 - dione, and the 17-propionate, 17-*n*-butyrate, 17-valerate and 17-benzoate of 7α - iodo - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione.

7α - Iodo - 17α - acetoxy - 1,4 - pregnadiene - 3,20 - dione (m.p. 144°C. (dec.); $[\alpha]_D^{26}$—3.5° (dimethylformamide); λ_{max}^{MeOH} 242 nm (ε=15,100)) may be prepared similarly from 17α - acetoxy - 1,4,6 - pregnatriene - 3,20 - dione.

EXAMPLE 12

7α,21-Dihalo-1,4-pregnadiene-3,20-diones

A. 7α-Chloro-21-halo derivatives

(1) 7α,21 - Dichloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate

is prepared by reaction of 16α-methyl-21-chloro-1,4,6-pregnatriene-11β,17α, - diol - 3,20 - dione 17-propionate with dry hydrogen chloride gas in dioxan by the method of Example 1A; $[M]^+$ 458, 456, 454.

(2) By using as starting compound the 21-fluoro and 21-bromo analogs of the 21-chloro starting compound of Example 12A(1), the corresponding 21-fluoro and 21-bromo derivatives are obtained, i.e. 7α - chloro - 21 - fluoro - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate and 7α - chloro - 21 - bromo - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate.

(3) In the procedure of Example 12A, by using starting compounds having different esters at C-17, e.g. the 17-*n*-butyrate and the 17-benzoate corresponding to the 17-propionate ester named therein, the corresponding 7α - chloro - 21 - halo derivative is obtained, i.e. the 17-*n*-butyrate and 17-benzoate of 7α,21 - dichloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione, of 7α - chloro - 21 - fluoro - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione and of 7α - chloro - 21 - bromo - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione.

(4) By using as starting compounds the 16β-methyl epimers or the 16-unsubstituted or 16-methylene derivatives of 16α-methyl starting compounds of Examples 12A(1)—(3), the corresponding 16β-methyl, 16-unsubstituted or 16-methylene derivatives of the 7α,21-dihalo products named therein can be obtained, e.g. 7α,21 - dichloro - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate; $[M]^+$ 472, 470, 468; nmr (dmso—d_6) δ 0.87, 0.97, 1.41, 2.32, 4.41, 4.75, 5.95, 6.36, 7.35.

B. 7α-Bromo- and 7α-iodo-21-halo derivatives

Treat each of the 1,4,6-pregnatriene starting compounds of Example 12A(1)—(4) with dry hydrogen bromide in acetic acid in a manner similar to that described in Example 2A and B or with dry hydrogen iodide in acetic acid according to the procedure of Example 9A to obtain each of the 7α-bromo- and 7α-iodo-analogs corresponding to the 7α-chloro derivatives of Example 12A, e.g. 7α - bromo - 21 -

chloro - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate; nmr (dmso—d_6) δ 0.90, 1.00, 1.45, 2.33, 4.43, 4.85, 5.93, 6.21, 7.36.

C. 7α-Fluoro-21-halo derivatives

(1) 7α - Fluoro - 21 - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate is prepared by reaction of 16α - methyl - 21 - chloro - 1,4 - pregnadiene - 7β,11β,17α - triol - 3,20 - dione 17-propionate with fluoramine in methylene chloride under an atmosphere of nitrogen by the method of Example 8A.

(2) By using as starting compounds the 21-fluoro- and 21-bromo- analogs of the 21-chloro starting compound of Example 12C(1), the corresponding 21-fluoro- and 21-bromo- derivatives are obtained i.e. 7α - fluoro - 21 - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate and 7α,21 - difluoro - 16α - methyl - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate.

(3) By using the 9α-fluoro- and 9α-chloro-derivatives of the starting compounds of Example 12C(1) and 12C(2), the corresponding 9α-fluoro- and 9α-chloro- derivatives of the 7α - fluoro - 1,4 - pregnadienes obtained therein are produced.

EXAMPLE 13

Other 7α-Halo-9-unsubstituted-1,4-pregnadiene-3,20-diones

A. 9α - Unsubstituted - 1,4,6 - pregnatriene - 3,20 - diones

(1) In a manner similar to that described in Preparation 1A treat each of the following 1,4-pregnadiene-3,20-diones with dry hydrogen chloride gas in dioxan and DDQ:

1) 16α,17α - isopropylidenedioxy - 1,4 - pregnadiene - 11β,21 - diol - 3,20 - dione 21-acetate,

2) 14α,17α - butylidenedioxy - 1,4 - pregnadiene - 11β,21 - diol - 3,20 - dione 21-acetate,

3) 2',2' - dimethyl - 1,4 - pregnadieno[17,16α—d] - 1',3' - oxathiolane - 3,11,20 - trione,

4) 11β - hydroxy - 2',2' - dimethyl - 1,4 - pregnadieno[17,16α—d] - 1',3' - oxathiolane - 3,20 - dione,

5) D - homo - 1,4 - pregnadiene - 17aα,21 - diol - 3,11,20 - trione 17a,21-dipropionate,

6) D - homo - 1,4 - pregnadiene - 11β,17aα,21 - triol - 3,20 - dione 17a,21-di-*n*-butyrate,

7) *n*-butyl 11β - hydroxy - 3,20 - dioxo - 16α - methyl - 1,4 - pregnadien - 21 - oate,

8) propyl 2 - chloro - 11β - hydroxy - 3,20 - dioxo - 16α - methyl - 1,4 - pregnadien - 21 - oate,

9) 16β - methyl - 20 - chloromethoxy - 21 - nor - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate,

10) 16β - methyl - 20 - fluoromethoxy - 21 - nor - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate,

11) 16 - methylene - 20 - chloromethoxy - 21 - nor - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate,

12) 16 - methylene - 20 - fluoromethoxy - 21 - nor - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate,

13) 16 - fluoromethylene - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate,

14) 16 - chloromethylene - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17-benzoate 21-propionate,

15) 16 - butylidene - 1,4 - pregnadien - 17α - ol - 3,20 - dione 17-propionate,

16) 16 - ethylidene - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate,

17) 16α,17α - cyclopentylidenedioxy - 1,4 - pregnadiene - 11β,21 - diol - 3,20 - dione 21-acetate,

18) 16β - methyl - 20 - methoxy - 21 - nor - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate, and

19) 16α - methyl - 1,4 - pregnadiene - 11β,21 - diol - 3,20 - dione 21-pivalate.

Isolate and purify each of the resultant products in a manner similar to that described in Preparation 1A to obtain the 6-dehydro derivative of each of the starting compounds.

(2) Treat each of the following compounds with dry hydrogen chloride in dioxan followed by DDQ in the manner described in Preparation 1A:

1) 14α,17α - (2' - butylidenedioxy) - 1,4 - pregnadiene - 11β,21 - diol - 3,20 - dione 21-isonicotinate, and

2) 11β,21 - dihydroxy - 2' - methyl - 5'βH - 1,4 - pregnadieno[17,16α—d]oxazole - 3,20 - dione 21-acetate.

After stirring the reaction mixture at room temperature for 24 hours, filter and evaporate the filtrate at 40°C. *in vacuo*. Dissolve the resultant residue in water, neutralize with sodium hydroxide and extract with chloroform. Wash the organic solution with water, dry over magnesium sulfate and filter through a column of neutral alumina, washing the column with chloroform:ethyl acetate. Evaporate each of the eluates to a residue comprising the 6-dehydro derivative of each of the starting compounds.

B. 7α - Chloro - 9 - unsubstituted - 1,4 - pregnadienes

(1) In a manner similar to that described in Example 1A, treat each of the 1,4,6 - pregnatriene - 3,20 - diones prepared in Example 13A(1) with dry hydrogen chloride in dioxan, and isolate and purify each of the resultant products in a manner similar to that described to obtain the 7α-chloro derivative of each of the starting compounds of Example 13A(1), e.g. 7α - chloro - 16α,17α - isopropylidenedioxy - 1,4 - pregnadiene - 11β,21 - diol - 3,20 - dione; m.p. 255—257°C.; $[\alpha]_D^{26}$+104.9° (dimethylformamide); λ_{max}^{MeOH} 242 (ε=15,600).

(2) Treat 14α,17α - (2' - butylidenedioxy) - 1,4,6 - pregnatriene - 11β,21 - diol - 3,20 - dione 21-isonicotinate with hydrogen chloride gas in dioxan for 16 hours at room temperature in a manner similar to that described in Example 1A. Pour the reaction mixture into ice water, neutralize the aqueous solution with sodium hydroxide, then filter off the resultant precipitate, wash it with water and dry it in air. Separate the components of the foregoing precipitate in a manner similar to that described in Example 1 to obtain 7α - chloro - 14α,17α - (2' - butylidenedioxy) - 1,4 - pregnadiene - 11β,21 - diol - 3,20 - dione 21-isonicotinate. 11β,21 - Dihydroxy - 2' - methyl - 5'βH - 1,4,6 - pregnadieno[17,16α—d]oxazole - 3,20 - dione 21-acetate is similarly transformed into 7α - chloro - 11β,21 - dihydroxy - 2' - methyl - 5'βH - 1,4 - pregnadieno[17,16α—d]oxazole - 3,20 - dione 21-acetate.

C. 7α-Bromo-9-unsubstituted-1,4-pregnadienes

(1) In a manner similar to that described in Example 2 treat each of the 1,4,6-pregnatriene-3,20-diones prepared in Example 13A(1) with dry hydrogen bromide in acetic acid. Isolate and purify each of the resultant products to obtain the corresponding 7α-bromo derivative of each of the starting compounds of Example 13A(1), e.g. 7α - bromo - 16α,17α - isopropylidenedioxy - 1,4 - pregnadiene - 11β,21 - diol - 3,20 - dione 21-acetate; m.p. 197—200°C.; $[\alpha]_D^{26}$+91.9° (dimethylformamide); λ_{max}^{MeOH} 242 (ε=15,000).

(2) Treat each of the 1,4,6-pregnatriene-3,20-dione derivatives prepared in Example 13A(2) with dry hydrogen bromide in acetic acid in a manner similar to that described in Example 2A. After stirring the reaction mixture at 0°C. for 1 hour, pour it into water, neutralize with sodium hydroxide, filter off the resultant precipitate, wash it with water and dry it; purify it in a manner similar to that described in Example 2A. The 7α-bromo derivatives of each of the starting compounds of Example 13A(2) are thereby obtained.

D. 7α-Iodo-9-unsubstituted-1,4-pregnadienes

(1) In a manner similar to that described in Example 9A, treat each of the 1,4,6-pregnatriene-3,20-dione derivatives prepared in Example 13A(1) with dry hydrogen iodide in glacial acetic acid. Isolate and purify each of the resultant products in a manner similar to that described to obtain the 7α-iodo derivative of each of the 1,4-pregnadiene-3,20-dione starting compounds of Example 13A(1).

(2) Treat each of the 1,4,6-pregnatriene-3,20-dione compounds of Example 13A(2) with dry hydrogen iodide in acetic acid in the manner described in Example 9A. After stirring the reaction mixture at room temperature for 15 minutes, pour it into ice water, neutralize with sodium hydroxide, filter off the resultant precipitate, and purify it in a manner similar to that described in Example 9A. The 7α-iodo derivatives of the 1,4-pregnadiene-3,20-dione starting compounds of Example 13A(2) are thereby obtained.

E. 7α-Fluoro-9-unsubstituted-1,4-pregnadienes

(1) 7β-Hydroxy-1,4-pregnadiene-3,20-diones

Subject the following 1,4,6-pregnatriene-3,20-diones to a sequence of reactions similar to those described in Preparation 11A(1)—(4).

1) 16α,17α - isopropylidenedioxy - 1,4,6 - pregnatriene - 11β,21 - diol - 3,20 - dione 21-acetate,

2) 14α,17α - *n* - butylidenedioxy - 1,4,6 - pregnatriene - 11β,21 - diol - 3,20 - dione 21-acetate,

3) D - homo - 1,4,6 - pregnatriene - 17aα,21 - diol - 3,11,20 - trione 17a,21 - dipropionate,

4) D - homo - 1,4,6 - pregnatriene - 11β,17aα,21 - triol - 3,20 - dione - 17a,21 - di - *n* - butyrate,

5) 16β - methyl - 20 - chloromethoxy - 21 - nor - 1,4,6 - pregnatriene - 11β,17α - diol - 3,20 - dione 17-propionate,

6) 16β - methyl - 20 - fluoromethoxy - 21 - nor - 1,4,6 - pregnatriene - 11β,17α - diol - 3,20 - dione 17-propionate, and

7) 16α,17α - cyclopentylidenedioxy - 1,4,6 - pregnatriene - 11β,21 - diol - 3,20 - dione 21-acetate.

Isolate and purify each of the respective products in a manner similar to that described in Preparation 11A(4) to obtain, respectively,

1) 16α,17α - isopropylidenedioxy - 1,4 - pregnadiene - 7β,11β,21 - triol - 3,20 - dione 21-acetate,

2) 14α,17α - *n* - butylidenedioxy - 1,4 - pregnadiene - 7β,11β,21 - triol - 3,20 - dione 21-acetate,

3) D - homo - 1,4 - pregnadiene - 7β,17aα,21 - triol - 3,11,20 - trione 17a,21-dipropionate,

4) D - homo - 1,4 - pregnadiene - 7β,11β,17aα,21 - tetrol - 3,20 - dione - 17a,21 - di - *n* - butyrate,

5) 16β - methyl - 20 - chloromethoxy - 21 - nor - 1,4 - pregnadiene - 7β,11β,17α - triol - 3,20 - dione 17-propionate,

6) 16β - methyl - 20 - fluoromethoxy - 21 - nor - 1,4 - pregnadiene - 7β,11β,17α - triol - 3,20 - dione 17-propionate, and

7) 16α,17α - cyclopentylidenedioxy - 1,4 - pregnadiene - 7β,11β,21 - triol - 3,20 - dione 21-acetate.

(2) In a manner similar to that described in Example 8A, treat each of the 7β-hydroxy derivatives of Example 13E(1) with fluoramine in methylene chloride at 0°C. under an atmosphere of nitrogen. Isolate and purify each of the resultant products in a manner similar to that described to obtain, respectively,

1) 7α - fluoro - 16α,17α - isopropylidenedioxy - 1,4 - pregnadiene - 11β,21 - diol - 3,20 - dione 21-acetate,

2) 7α - fluoro - 14α,17α - *n* - butylidenedioxy - 1,4 - pregnadiene - 11β,21 - diol - 3,20 - dione 21-acetate,

3) 7α - fluoro - D - homo - 1,4 - pregnadiene - 17aα,21 - diol - 3,11,20 - trione 17a,21-dipropionate,

4) 7α - fluoro - D - homo - 1,4 - pregnadiene - 11β,17aα,21 - triol - 3,20 - dione 17a,21-di-*n*-butyrate,

5) 7α - fluoro - 16β - methyl - 20 - chloromethoxy - 21 - nor - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate,

6) 7α - fluoro - 16β - methyl - 20 - fluoromethoxy - 21 - nor - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate, and

7) 7α - fluoro - 16α,17α - cyclopentylidenedioxy - 1,4 - pregnadiene - 11β,21 - diol - 3,20 - dione 21-acetate.

EXAMPLE 14

Other 7α,9α-dihalo-11β-hydroxy-1,4-pregnadiene-3,20-diones

A. 7β - Hydroxy - 9α - halo - 1,4 - pregnadiene - 3,20 - diones

(1) Treat each of the following 6,7 - unsubstituted - 9α - halo - 1,4 - pregnadiene - 3,20 - diones with dry hydrogen chloride gas and DDQ in dioxan in a manner similar to that described in Preparation 1A, and then subject each of the resulting 9α - halo - 1,4,6 - pregnatriene - 3,20 - diones to a sequence of reactions similar to those described in Preparation 11A(1)—(4):

1) 9α - fluoro - 11β,21 - dihydroxy - 2' - methyl - 5'βH - 1,4 - pregnadieno[17,16α—d]oxazole - 3,20 - dione 21-acetate,

2) 9α - fluoro - 16α,17α - cyclopentylidenedioxy - 1,4 - pregnadiene - 11β,21 - diol - 3,20 - dione 21-acetate,

3) 9α - fluoro - 11β - hydroxy - 2',2' - dimethyl - 1,4 - pregnadieno[17,16α—d]1',3' - oxathiolane - 3,20 - dione,

4) 9α - chloro - 11β - hydroxy - 21,21 - dimethoxy - 1,4 - pregnadieno - [17,16α—d] - 1',3' - oxathiolane - 3,20 - dione,

5) 9α - fluoro - 16α - methyl - 21,21 - diacetoxy - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate,

6) 9α - fluoro - 16α - methyl - 1,4 - pregnadien - 11β - ol - 3,20,21 - trione 21,21-dimethylacetal,

7) 9α - fluoro - 16α - methyl - 1,4 - pregnadien - 11β - ol - 3,20,21 - trione 21-ethyleneketal,

8) 2 - chloro - 9α - fluoro - 16α - methyl - 1,4 - pregnadiene - 11β,17α - diol - 3,20,21 - trione,

9) 2 - chloro - 9α - fluoro - 16α - methyl - 1,4 - pregnadiene - 11β,17α - diol - 3,20,21 - trione 21-methylhemiacetal,

10) 9α - fluoro - 16β - methyl - 20 - fluoromethoxy - 21 - nor - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate,

11) 9α - fluoro - 16β - methyl - 20 - chloromethoxy - 21 - nor - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate, and

12) 9α - fluoro - 16α - methyl - 1,4 - pregnadiene - 11β,21 - diol - 3,20 - dione 21-acetate.

Isolate and purify each of the resultant products in a manner similar to that described in Preparation 11A(4) to obtain the corresponding 7β-hydroxy derivatives of the foregoing starting compounds.

(2) In a manner similar to that described in Example 1A treat each of the following 6,7 - unsubstituted - 9α - fluoro - 1,4 - pregnadiene - 3,20 - diones with dry hydrogen chloride and DDQ in dioxan followed by treatment of the resulting 9α - fluoro - 1,4,6 - pregnatriene - 3,20 - dione in a manner similar to that described in Preparation 11D:

1) 9α - fluoro - 16 - methylene - 20 - fluoromethoxy - 21 - nor - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate,

2) 9α - fluoro - 16 - methylene - 20 - chloromethoxy - 21 - nor - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17-propionate, and

3) 9α - fluoro - 16 - fluoromethylene - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-acetate.

Isolate and purify each of the resultant products in a manner similar to that described in Preparation 11D(3) to obtain the corresponding 7β-hydroxy derivative, i.e.

1) 9α - fluoro - 16 - methylene - 20 - fluoromethoxy - 21 - nor - 1,4 - pregnadiene - 7β,11β,17α - triol - 3,20 - dione 17-propionate,

2) 9α - fluoro - 16 - methylene - 20 - chloromethoxy - 21 - nor - 1,4 - pregnadiene - 7β,11β,17α - triol - 3,20 - dione 17-propionate, and

3) 9α - fluoro - 16 - fluoromethylene - 1,4 - pregnadiene - 7β,11β,17α,21 - tetrol - 3,20 - dione 21-acetate.

(3)(a) Treat *n*-butyl 9α - fluoro - 11β - hydroxy - 16α,17α - isopropylidenedioxy - 3,20 - dioxo - 1,4 - pregnadien - 21 - oate with dry hydrogen chloride and DDQ in dioxan according to the procedure of Example 1A followed by treatment of the resulting 1,4,6-pregnatriene in a manner similar to that described in Preparation 11A(1), (2) and (3) to obtain *n*-butyl 6β - propionyloxy - 7β,11β - dihydroxy - 9α - fluoro - 16α,17α - isopropylidenedioxy - 3,20 - dioxo - 1,4 - pregnadien - 21 - oate.

(3)(b) Treat *n*-butyl 6β - propionyloxy - 7β,11β - dihydroxy - 9α - fluoro - 16α,17α - isopropylidenedioxy - 3,20 - dioxo - 1,4 - pregnadien - 21 - oate (1 gm.) with zinc (1 gm.) and acetic acid (10 ml.) at room temperature for 1 hour. Filter the reaction mixture, pour the filtrate into water, filter off the resultant precipitate and dry it in air to obtain *n*-butyl 7β,11β - dihydroxy - 9α - fluoro - 16α,17α - isopropylidenedioxy - 3,20 - dioxo - 1,4 - pregnadien - 21 - oate.

B. 7α-Fluoro-9α-halo-1,4-pregnadiene-3,20-diones

In a manner similar to that described in Example 8A, treat each of the 7β-hydroxy-1,4-pregnadienes prepared in Example 14A with fluoramine in methylene chloride at 0°C. under an atmosphere of nitrogen. Isolate and purify each of the resultant products in a manner similar to that described to obtain the 7α-fluoro derivative of each of the starting compounds of Example 14A(1), 14A(2) and 14A(3).

C. 7α - Bromo - 9α - halo - 1,4 - pregnadiene - 3,20 - diones

In a manner similar to that described in Example 10A, treat each of the 7β - hydroxy - 1,4 - pregnadiene - 3,20 - diones prepared in Example 14A with fluoramine and lithium bromide in methylene chloride and isolate and purify each of the resultant products in the described manner to obtain the 7α-bromo derivative of each of the starting compounds listed in Examples 14A(1), 14A(2) and 14A(3).

D. 7α - Chloro - 9α - halo - 1,4 - pregnadiene - 3,20 - diones

In a manner similar to that described in Example 10D, treat each of the 7β - hydroxy - 1,4 - pregnadiene - 3,20 - diones prepared in Example 14A with fluoramine and lithium chloride in methylene chloride and isolate and purify each of the resultant products in a manner similar to that described to obtain, respectively, the 7α-chloro derivative of each of the starting compounds listed in Examples 14A(1), 14A(2) and 14A(3).

E. 7α,9α,17α - Trihalo - 1,4 - pregnadiene - 3,20 - diones

(1) 7α,9α - Difluoro - 17α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,21 - diol - 3,20 - dione 21-acetate and the corresponding 17α-bromo derivative

At −78°C. add anhydrous hydrogen fluoride (15 ml.) to a mixture of 7α,9α - difluoro - 16α - methyl - 1,4 - pregnadiene - 11β,21 - diol - 3,20 - dione 21-acetate (5 gms.) and *N*-chloro-succinimide (2 gms.) in tetramethylene sulfone (5 ml.). Allow the reaction mixture to stand at 3°C. for 7 days, then pour with stirring into a mixture of equal parts of water, ice and 25% aqueous ammonium hydroxide (300 ml.). Filter off the resultant precipitate, wash it with water and dissolve it in methylene chloride. Wash the organic solution with 10% aqueous sodium sulfite and water, dry it over sodium sulfate and evaporate it *in vacuo*. Chromatograph the resultant residue on silica gel eluting with chloroform:ethyl acetate (2:1). Combine like eluates containing the desired compound as determined by thin layer chromatography and evaporate them *in vacuo* to a residue comprising 7α,9α - difluoro - 17α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,21 - diol - 3,20 - dione 21-acetate.

In the above procedure, by substituting for *N*-chloro-succinimide an equivalent quantity of *N*-bromosuccinimide, there is obtained the corresponding 17α-bromo compound, i.e. 7α,9α - difluoro - 17α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,21 - diol - 3,20 - dione 21-acetate.

(2) In similar manner, treat 7α,9α - difluoro - 16α - methyl - 1,4 - pregnadien - 11β - ol - 3,20,21 - trione 21-ethylene ketal with either *N*-chlorosuccinimide or *N*-bromosuccinimide and hydrogen fluoride in tetramethylene sulfone in a manner similar to that described in Example 14E(1) to obtain either 7α,9α - difluoro - 17α - chloro - 16α - methyl - 1,4 - pregnadien - 11β - ol - 3,20,21 - trione or 7α,9α - difluoro - 17α - bromo - 16α - methyl - 1,4 - pregnadien - 11β - ol - 3,20,21 - trione, respectively.

(3) In the procedures of Examples 14E(1) and 14E(2), by starting with the 7α-chloro or 7α-bromo analog corresponding to the 7α-fluoro-1,4-pregnadiene starting compound named therein, there is obtained either the 7α-chloro-17α-halo or 7α-bromo-17α-halo derivative corresponding to the 7α-fluoro-17α-halo products named therein, i.e. 7α,17α-dichloro - 9α - fluoro - 16α - methyl - 1,4 - pregnadiene - 11β,21 - diol - 3,20 - dione 21-acetate, 7α - bromo - 9α - fluoro - 17α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,21 - diol - 3,20 - dione 21-acetate, 7α - chloro - 9α - fluoro - 17α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,21 - diol - 3,20 - dione 21-acetate, 7α,17α - dibromo - 9α - fluoro - 16α - methyl - 1,4 - pregnadiene - 11β,21 - diol - 3,20 - dione 21-acetate, 7α,17α - dichloro - 9α - fluoro - 16α - methyl - 1,4 - pregnadien - 11β - ol - 3,20,21 - trione, 7α - chloro - 9α - fluoro - 17α - bromo - 16α - methyl - 1,4 - pregnadien - 11β - ol - 3,20,21 - trione, 7α - bromo - 9α - fluoro - 17α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β - ol - 3,20,21 - trione, and 7α,17α - dibromo - 9α - fluoro - 16α - methyl - 1,4 - pregnadien - 11β - ol - 3,20,21 - trione.

EXAMPLE 15

Other 7α,9α,11β-trihalo-1,4-pregnadiene-3,20-diones

A. 7α,9α,11β - Trichloro - 21 - fluoro - 16 - methylene - 1,4 - pregnadien - 17α - ol - 3,20 - dione 17-propionate

(1) 7α - Chloro - 21 - fluoro - 16 - methylene - 1,4,9(11) - pregnatrien - 17α - ol - 3,20 - dione 17-propionate

is prepared by reaction of 7α - chloro - 21 - fluoro - 16 - methylene - 1,4 - pregnadiene - 11β,17α - diol - 3,20 - dione 17 - propionate with methanesulfonyl chloride and sulfur dioxide in dimethylformamide and collidine by the method of Example 6A(1).

(2) 7α,9α,11β - Trichloro - 21 - fluoro - 16 - methylene - 1,4 - pregnadien - 17α - ol - 3,20 - dione 17-propionate is prepared by reaction of the 7α - chloro - 21 - fluoro - 1,4,9(11)-pregnatriene of Example 15A(1) with chlorine in chloroform and pyridine by the method of Example 6B(1).

B. 7α,9α,17α - Trichloro - 11β - fluoro - 16α - methyl - 1,4 - pregnadien - 21 - ol - 3,20 - dione 21-pivalate

(1) 7α - Chloro - 16α - methyl - 1,4,9(11) - pregnatrien - 21 - ol - 3,20 - dione 21-pivalate

is prepared by reaction of 7α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,21 - diol - 3,20 - dione 21-pivalate with methanesulfonyl chloride and sulfur dioxide in dimethylformamide and collidine by the method of Example 6A(1).

(2) 7α,9α,17α - Trichloro - 11β - fluoro - 16α - methyl - 1,4 - pregnadien - 21 - ol - 3,20 - dione 21-pivalate

is prepared by reaction of 7α - chloro - 16α - methyl - 1,4,9(11) - pregnatrien - 21 - ol - 3,20 - dione 21-pivalate with anhydrous hydrogen fluoride and *N*-chlorosuccinimide in tetramethylene sulfone by the method of Example 14E(1).

C. Treat each of the following 7 - unsubstituted - 1,4 - pregnadiene - 3,20 - diones with DDQ and hydrogen chloride in a manner similar to that described in Preparation 1A, then react the resulting 1,4,6-pregnatriene-3,20-dione according to the procedures described in Preparation 11A followed by treatment of the resulting 7β - hydroxy derivative thereby obtained with fluoramine according to the procedure of Example 8A or fluoramine together with lithium chloride according to the procedure of Example 10D or with fluoramine together with lithium bromide according to the procedure of Example 10A to obtain the corresponding 7α-fluoro- or 7α-chloro- or 7α-bromo derivative of the following starting compounds: *n*-butyl 9α - chloro - 11β - fluoro - 14α,17α - ethylidenedioxy - 3,20 - dioxo - 1,4 - pregnadien - 21 - oate, methyl 9α,11β - dichloro - 16α - methyl - 17α - acetoxy - 3,20 - dioxo - 1,4 - pregnadien - 21 - oate, *n*-butyl 11β - fluoro - 9α - chloro - 14α,17α - ethylidene - dioxy - 3,20 - dioxo - 1,4 - pregnadien - 21 - oate, *n*-butyl 9α - chloro - 11β - fluoro - 14α,17α - ethylidenedioxy - 3,20 - dioxo - 1,4 - pregnadien - 21 - oate, *n*-butyl - 9α - chloro - 11β - fluoro - 14α,17α - ethylidenedioxy - 3,20 - dioxo - 1,4 - pregnadien - 21 - oate, methyl 9α,11β - dichloro - 16α - methyl - 17α - acetoxy - 3,20 - dioxo - 1,4 - pregnadien - 21 - oate, methyl 9α,11β - dichloro - 16α - methyl - 17α - acetoxy - 3,20 - dioxo - 1,4 - pregnadien - 21 - oate and methyl 9α,11β - dichloro - 16α - methyl - 17α - acetoxy - 3,20 - dioxo - 1,4 - pregnadien - 21 - oate.

EXAMPLE 16
Preparation of 17α-monoesters

A. Using malt diastase

(1) 7α - Bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-valerate

To a suspension of diastase enzyme of malt (1.67 gm.) in ethanol (33.5 ml.) and water (167.5 ml.) add 7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-valerate 21-acetate (33.5 mg.). Stir the reaction mixture at room temperature for 3 days, then evaporate *in vacuo* at room temperature. Dissolve the resultant residue in ethyl acetate and water and filter the solution through a Celite pad, washing with ethyl acetate. Separate the organic and aqueous layers, then extract the aqueous layer with ethyl acetate. Wash the combined organic extracts with water, dry them over magnesium sulfate and evaporate them *in vacuo*. Purify the resultant residue by thin layer chromatography using as developing solvent chloroform:ethyl acetate (3:1). Remove the band containing the desired product as visualized under ultraviolet light. Elute with ethyl acetate and evaporate to a residue comprising 7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-valerate. Purify by triturating with ether:hexane.

(2) In similar manner, treat each of 7α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-valerate 21-acetate and 7α -

chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate with diastase enzyme of malt in aqueous ethanol according to the procedure of Example 16A(1) to obtain, respectively, 7α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-valerate and 7α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-propionate.

(3) In similar manner, by treating any of the 7α - halo - 21 - acyloxy - 1,4 - pregnadienes of Examples 1—15 with diastase enzyme of malt in aqueous ethanol in a manner similar to that described in Example 16A(1), the corresponding 21-hydroxy derivative is obtained.

B. By acid hydrolysis

7α - Bromo - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-benzoate and its 16α-methyl derivative

To 7α - bromo - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-benzoate 21-acetate (0.44 gm.) in methanol (69 ml.) add 70% aqueous perchloric acid (1.76 ml.) and stir the reaction mixture for 4 hours. Bring the reaction mixture to neutrality with saturated aqueous sodium bicarbonate and remove the methanol by evaporation *in vacuo*. Cool the aqueous reaction mixture and filter off the resultant precipitate comprising a mixture of 7α - bromo - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione and the 17-monobenzoate and 21-monobenzoate esters thereof. Separate by thin layer chromatography on silica gel developing with ethyl acetate:chloroform(1:1), remove the band containing the desired 17-benzoate ester as visualized under ultraviolet light, elute with ethyl acetate and evaporate to a residue of 7α - bromo - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-benzoate. 7α - Bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-benzoate, m.p. 144—144.5°C., λ_{max}^{MeOH} 233 nm (ε=24,700), may be similarly prepared by hydrolysis of 7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dibenzoate.

C. 7α - Halo - 9α - fluoro - 1,4 - pregnadiene - 11β,16α,17α,21 - tetrol - 3,20 - dione 17-hydrocarboncarboxylates

(1) 7α - Chloro- and 7α - bromo - 9α - fluoro - 1,4 - pregnadiene - 11β,16α,17α,21 - tetrol - 3,20 - dione 17-propionate and 17-n-butyrate

(a) 9α - Fluoro - 1,4,6 - pregnatriene - 16α,17α,21 - triol - 3,11,20 - trione 16,21-diacetate 17-propionate and 17-n-butyrate are prepared by reaction of 9α - fluoro - 1,4,6 - pregnatriene - 16α,17α,21 - triol - 3,11,20 - trione 16,21-diacetate with trifluoroacetic anhydride, toluene-*p*-sulfonic acid monohydrate and either propionic acid or *n*-butyric acid by the method of Preparation 5D.

(b) 9α - Fluoro - 1,4 - pregnadiene - 7β,16α,17α,21 - tetrol - 3,11,20 - trione 16,21-diacetate 17-propionate and 17-n-butyrate are prepared by subjecting 9α - fluoro - 1,4,6 - pregnatriene - 16α,17α,21 - triol - 3,11,20 - trione 16,21-diacetate 17-propionate and 17-*n*-butyrate to a sequence of reactions similar to that described in Preparation 11A(1—4).

(c) 7α,9α - Difluoro - 1,4 - pregnadiene - 16α,17α,21 - triol - 3,11,20 - trione 16,21-diacetate 17-propionate and 17-n-butyrate are prepared by reaction of 7α,9α - difluoro - 1,4 - pregnadiene - 16α,17α,21 - triol - 3,11,20 - trione 16,21-diacetate 17-propionate and 17-*n*-butyrate with fluoramine in methylene chloride by the method of Example 8A.

The 17-propionate and 17-*n*-butyrate of 7α - bromo - 9α - fluoro - 1,4 - pregnadiene - 16α,17α,21 - triol - 3,11,20 - trione 16,21-diacetate and of 7α - chloro - 9α - fluoro - 1,4 - pregnadiene - 16α,17α,21 - triol - 3,11,20 - trione 16,21-diacetate can be obtained by the methods of Examples 10A and 10C by reaction of the 7β-hydroxy-pregnadienes of Example 16C(1)(b) with lithium bromide and fluoramine or with lithium chloride and fluoramine in methylene chloride.

(d) 7α - Halo - 9α - fluoro - 1,4 - pregnadiene - 11β,16α,17α,21 - tetrol - 3,20 - dione 16,21-diacetate 17-propionates and 17-n-butyrates

In a manner similar to that described in Example 1C and 2C, treat all six products of Example 16C(1)(c) with sodium borohydride in tetrahydrofuran and methanol under an atmosphere of nitrogen, and isolate each of the resultant products in a manner similar to that described to obtain, respectively, the 17-propionate and 17-*n*-butyrate of 7α,9α - difluoro - 1,4 - pregnadiene - 11β,16α,17α,21 - tetrol - 3,20 - dione 16,21-diacetate, the 17-propionate and the

17-*n*-butyrate of 7α - chloro - 9α - fluoro - 1,4 - pregnadiene - 11β,16α,17α,21 - tetrol - 3,20 - dione 16,21-diacetate, and the 17-propionate and 17-*n*-butyrate of 7α - bromo - 9α - fluoro - 1,4 - pregnadiene - 11β,16α,17α,21 - tetrol - 3,20 - dione 16,21-diacetate.

(e) 7α - Halo - 9α - fluoro - 1,4 - pregnadiene - 11β,16α,17α,21 - tetrol - 3,20 - dione 17-propionates and 17-n-butyrates

In a manner similar to that described in Example 16A, treat all six products of Example 16C(1)(d) with diastase enzyme of malt in aqueous ethanol and isolate and purify each of the resultant products in a manner similar to that described to obtain, respectively, the 17-propionate and the 17-*n*-butyrate of 7α,9α - difluoro - 1,4 - pregnadiene - 11β,16α,17α,21 - tetrol - 3,20 - dione, the 17-propionate and 17-*n*-butyrate of 7α - chloro - 9α - fluoro - 1,4 - pregnadiene - 11β,16α,17α,21 - tetrol - 3,20 - dione, and the 17-propionate and 17-*n*-butyrate of 7α - bromo - 9α - fluoro - 1,4 - pregnadiene - 11β,16α,17α,21 - tetrol - 3,20 - dione.

(2) 7α - Chloro and 7α - bromo - 9α - fluoro - 1,4 - pregnadiene - 11β,16α,17α,21 - tetrol - 3,20 - dione 17-benzoate

(a) 9α - Fluoro - 1,4,6 - pregnatriene - 11β,16α,17α,21 - tetrol - 3,20 - dione 16,17-methylorthobenzoate 21-acetate

is prepared by reaction of 9α - fluoro - 1,4,6 - pregnatriene - 11β,16α,17α,21 - tetrol - 3,20 - dione 21-acetate with trimethylorthobenzoate and pyridinium toluene-*p*-sulfonate in dioxan and benzene by the method of Preparation 2C(1).

(b) 7α - Chloro and 7α - bromo - 9α - fluoro - 1,4 - pregnadiene - 11β,16α,17α,21 - tetrol - 3,20 - dione 16,17 - methyl - orthobenzoate 21-acetate

are prepared from 9α - fluoro - 1,4,6 - pregnatriene - 11β,16α,17α,21 - tetrol - 3,20 - dione 16,17-methylorthobenzoate 21-acetate by reaction with hydrogen chloride in tetrahydrofuran and with hydrogen bromide in glacial acetic acid respectively by the methods of Examples 1B and 2B.

(c) 7α-Chloro- and 7α - bromo - 9α - fluoro - 1,4 - pregnadiene - 11β,16α,17α,21 - tetrol - 3,20 - dione 17-benzoate 21-acetate

are prepared from 7α-chloro- and 7α - bromo - 9α - fluoro - 1,4 - pregnadiene - 11β,16α,17α,21 - tetrol - 3,20 - dione 16,17 - methylorthobenzoate 21-acetate respectively by hydrolysis with aqueous acetic acid by the method of Preparation 2A(2).

(d) 7α-Chloro- and 7α - bromo - 9α - fluoro - 1,4 - pregnadiene - 11β,16α,17α,21 - tetrol - 3,20 - dione 17-benzoate

are prepared from 7α - chloro- and 7α - bromo - 9α - fluoro - 1,4 - pregnadiene - 11β,16α,17α,21 - tetrol - 3,20 - dione 17 - benzoate 21-acetate respectively by hydrolysis with diastase enzyme of malt in aqueous ethanol by the method of Example 16A.

EXAMPLE 17

7α-Halo-1,4-pregnadiene-17α,21-diol-3,20-dione 17-hydrocarboncarboxylate 21-retinoates

A. 7α - Chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-propionate 21-retinoate

To a suspension of 7α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-propionate (464 mg., 1 mmol), in methylene chloride (50 ml.) under nitrogen and in the dark, add retinoic acid (300 mg., 1 mmol) and 1 - cyclohexyl - 3 - (2 - morpholinoethyl)carbodiimide metho-*p*-toluene-sulfonate (424 mg., 1 mmol). Stir at room temperature for 17 hours then add an additional mmol of retinoic acid and an additional mmol of the diimide, and continue stirring the reaction mixture for an additional 24 hours. Extract the reaction mixture sequentially with 2% hydrochloric acid, water, 5% aqueous sodium bicarbonate and again with water. Dry over sodium sulfate and evaporate *in vacuo*. Chromatograph the resultant residue on silica gel GF thick layer plates, eluting with ethyl acetate: chloroform (1:2). Remove the steroidal retinoate band from the thick layer plate, extract with ethyl acetate and evaporate *in vacuo* to a residue comprising 7α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-propionate 21-retinoate. Further purify by recrystallization from ether:petroleum ether.

B. Similarly, by treating any 21 - hydroxy - 7α - halo - 1,4 - pregnadiene - 3,20 - dione of this invention by the method of Example 17A, its 21-retinoate is obtained.

EXAMPLE 18

7α-Chloro-16α-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione

To a solution of 7α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate (3.5 gms.) in methanol (300 ml.) add saturated aqueous sodium bicarbonate solution (30 ml.) and allow to stand at room temperature for 18 hours. Pour into water, filter off the resultant precipitate, wash it with water until neutral, then dry it in air. Recrystallize the dried precipitate from acetone/hexane to give 7α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione, yield 1.3 gm., m.p. 176—179°C., $[\alpha]_D^{26}$+47.5° (dimethylformamide); λ_{max}^{MeOH} 242 nm (ε=15,500).

EXAMPLE 19

7α-Bromo-1,4-pregnadiene-11β,17α,21-triol-3,20-dione and its 21-acetate

To a solution of 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 21-acetate (5 gms.) in glacial acetic acid (62 ml.) add dry hydrogen bromide (37.5 gms.) and allow the reaction mixture to stand at 0—5°C. for 45 minutes. Pour the reaction mixture into water, filter off the resultant precipitate, wash it with water and dry it in air to obtain 7α - bromo - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21-acetate.

Dissolve the foregoing product in methanol (525 ml.), add 70% aqueous perchloric acid (13.2 ml.) and stir the reaction mixture at room temperature for 18 hours. Add water, then saturated aqueous sodium bicarbonate until the solution is neutral, and evaporate the reaction mixture until the methanol is removed. Extract the aqueous reaction mixture with ethyl acetate, wash the combined ethyl acetate extracts with water, dry them over sodium sulfate and evaporate them. Recrystallize the resultant residue from acetone to obtain 7α - bromo - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione, yield 0.3 gm., m.p. >320°C., $[\alpha]_D^{26}$+48.2° (dimethylformamide), λ_{max}^{MeOH} 241 nm (ε=15,100).

7α - Chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione, m.p. 176—179°C., $[\alpha]_D^{26}$+47.5° (dimethylformamide), λ_{max}^{MeOH} 242 nm (ε=15,500), may be prepared similarly.

EXAMPLE 20

7α-Chloro-4-pregnene-17α,21-diol-3,11,20-trione 17,21-diproprionate and its 16α-methyl and 16β-methyl derivatives

A. At 10°C. dissolve 4,6 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate (911 mg.) in a freshly prepared solution of hydrogen chloride in tetrahydrofuran and water (10 ml.) comprising 38.2% by weight of hydrogen chloride and 3.7% by weight of water. Stir the reaction mixture for 15 minutes at 0—2°C., then pour into ice water (100 ml.). Filter off the resultant precipitate, wash it with water, and dry it, partially under a blanket of nitrogen and then at room temperature *in vacuo* for 17 hours to obtain a mixture of 7α - chloro - 4 - pregnene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate and 4,6 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate. Separate the components of this mixture by thick layer chromatography on silica gel, developing with hexane:dimethoxyethane (2:1), and elute with ethyl acetate the band containing 7α - chloro - 4 - pregnene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate as shown by ultraviolet spectrum. Evaporate the ethyl acetate eluate at room temperature and recrystallize the resultant residue from acetone:hexane at room temperature to obtain 7α - chloro - 4 - pregnene - 17α,21 - diol - 3,11,20 - trione 17,21 - dipropionate. Store in an open vessel at room temperature *in vacuo*.

B. 7α - Chloro - 16α - methyl - 4 - pregnene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate and 7α - chloro - 16β - methyl - 4 - pregnene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate are prepared by reaction of 16α - methyl - 4,6 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate and 16β - methyl - 4,6 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate with hydrogen chloride in aqueous tetrahydrofuran by the method of Example 20A.

EXAMPLE 21

7α-Bromo-4-pregnene-17α,21-diol-3,11,20-trione-17,21-dipropionate and its 16α-methyl and 16β-methyl derivatives

A. Dissolve at room temperature 4,6 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate (235 mg.) in a freshly prepared solution of hydrogen bromide in acetic acid (44%, 2.5 ml.). Stir at room temperature for 30 minutes, then add the reaction mixture to water (100 ml.), filter off the resultant precipitate, wash with water and dry it under a blanket of nitrogen to obtain a mixture of 7α - bromo - 4 - pregnene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate and 4,6 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate. Isolate 7α - bromo - 4 - pregnene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate from this mixture by the method of Example 20A, and store it in an open vessel at room temperature *in vacuo*.

B. 7α - Bromo - 16α - methyl - 4 - pregnene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate and 7α - bromo - 16β - methyl - 4 - pregnene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate are prepared by reaction of 16α - methyl - 4,6 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate and 16β - methyl - 4,6 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate with hydrogen bromide in acetic acid by the method of Example 21A.

EXAMPLE 22

7α-Halo-4-pregnene-11β,17α,21-triol-3,20-dione 17,21-dipropionate and its 16α-methyl and 16β-methyl derivatives

A. 7α - Chloro - 4 - pregnene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate and its 16α-methyl and 16β-methyl derivatives

(1) At room temperature dissolve 7α - chloro - 4 - pregnene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate (3.1 g.) in methanol (375 ml.) and add water (30 ml.). To this solution at 0°—2°C. under an atmosphere of nitrogen add sodium borohydride (2.38 gms.). After 30 minutes, cautiously add the reaction solution to 4.2 liters of water containing 80 ml. of N hydrochloric acid. Filter off the resulting precipitate and chromatograph it on silica gel, eluting with chloroform:ethyl acetate (3:1). Evaporate the combined eluates *in vacuo*. To 152 mg. of the resultant residue, add a suspension of manganese dioxide (600 mg.) in benzene (7 ml.), stir for 5 hours, filter, and chromatograph the filtrate on silica gel by thin layer chromatography, developing with chloroform:ethyl acetate (3:1) and eluting with ethyl acetate the band containing the desired product as determined by ultraviolet spectrum. Evaporate the ethyl acetate solution *in vacuo* to a residue comprising 7α - chloro - 4 - pregnene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate. Further purify by recrystallization from ether:hexane at room temperature; $\lambda_{max}^{methanol}$ 237 nm (ε=15,500).

(2) 7α - Chloro - 16α - methyl - 4 - pregnene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate and 7α - chloro - 16β - methyl - 4 - pregnene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate are prepared by reaction of 7α - chloro - 16α - methyl - 4 - pregnene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate and 7α - chloro - 16β - methyl - 4 - pregnene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate with sodium borohydride in aqueous methanol and reaction of the product therefrom with manganese dioxide in benzene by the method of Example 22A(1).

B. 7α - Bromo - 4 - pregnene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate and its 16α-methyl and 16β-methyl derivatives are prepared by the method of Example 22A from the 7α-bromo analogs of the 7α-chloro starting compounds named therein.

EXAMPLE 23

Other 7α-Halo-11-oxygenated-4-pregnene-17α,21-diol-3,20-diones and Ester Derivatives thereof

Esters of 4,6 - pregnadiene - 3,11,20 - trione - 17α,21 - diols (prepared as described in Preparation 12) may similarly be used as starting materials in Examples 20 and 21, and the resulting esters of 7α-chloro- and 7α - bromo - 4 - pregnene - 3,11,20 - dione - 17α,21 - diols may be treated according to the procedure of Example 22 to yield esters of 7α-chloro- and 7α - bromo - 4 - pregnene - 3,20 - dione - 11β,17α,21 - triols.

EXAMPLE 24

7α-Iodo-9α-fluoro-16β-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17,21-dipropionate

(A) To a solution of dry hydrogen iodide (0.4 gm.) in glacial acetic acid (1.5 ml.) at room temperature, protected from light, add a solution of 9α - fluoro - 16β - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate (0.05 gm.) in glacial acetic acid (0.5 ml.). Stir the reaction mixture (protected from light) at room temperature for 30 minutes and then add 5% sodium thiosulfate solution (20 ml.). Extract the mixture with methylene chloride (two 50 ml. portions), wash the combined organic extracts twice with water, dry them over anhydrous sodium sulfate and evaporate them at room temperature *in vacuo*. Purify the resultant residue on silica gel by thick layer chromatography, developing with ethyl acetate/chloroform (1:9). Scrape off the more polar band as shown under ultraviolet light, wash the silica gel with ethyl acetate, evaporate the combined ethyl acetate washings *in vacuo* and recrystallize the resultant residue from ether to obtain 7α - iodo - 9α - fluoro - 16β - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate, yield 16 mg. (39%); m.p. 145°C. (decomp.); nmr (dmso—d_6) δ 0.95, 1.28, 1.55, 4.20, 4.59, 4.70, 5.99, 6.20, 7.25.

Alternatively, the compound of this example is prepared according to Examples 24(B) and 24(C) below.

(B) 7α - Iodo - 9α - fluoro - 16β - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate is prepared in a manner similar to that described in Example 24(A) from 9α - fluoro - 16β - methyl - 1,4,6 - pregnatriene - 17α,21 - diol - 3,11,20 - trione, 17,21-dipropionate (100 mg.) and dry hydrogen iodide (0.8 gm.) in glacial acetic acid (4 ml.); yield =80 mg., (64% theory). It is further purified by recrystallization from ether, m.p. 106°C. (decomp.).

(C) 7α - Iodo - 9α - fluoro - 16β - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate is prepared in a manner similar to that described in Example 3C(1) from 7α - iodo - 9α - fluoro - 16β - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate by reduction with sodium borohydride at 0°C. in tetrahydrofuran and methanol under nitrogen.

EXAMPLE 25

7α-Iodo-9α-chloro-16β-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17,21-dipropionate

(A) 7α - Iodo - 9α - chloro - 16β - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate is prepared in a manner similar to that described in Example 24(A) from 9α - chloro - 16β - methyl - 1,4,6 - pregnatriene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate and hydrogen iodide in glacial acetic acid; yield=15%.

(B) Alternatively, the compound of this example is made by treating 9α - chloro - 16β - methyl - 1,4,6 - pregnatriene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate with hydrogen iodide in acetic acid according to Example 24(A) followed by reduction of the resulting 7α - iodo - 9α - chloro - 16β - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate with sodium borohydride in methanol/tetrahydrofuran according to Example 3C(1).

EXAMPLE 26

7α-Iodo-9α-bromo-16β-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17,21-dipropionate

Treat 9α - bromo - 16β - methyl - 1,4,6 - pregnatriene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate with hydrogen iodide in glacial acetic acid according to Example 24(B), followed by reduction of the resulting 7α - iodo - 9α - bromo - 16β - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate with sodium borohydride in methanol/tetrahydrofuran according to the procedure of Example 24(C) to obtain 7α - iodo - 9α - bromo - 16β - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate.

EXAMPLE 27

7α-Bromo-9α-fluoro-16β-methyl-1,4-pregnadiene-11β,17α,21-triol-3,20-dione 17,21-dipropionate

(A) 7α - Bromo - 9α - fluoro - 16β - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate

To a solution of 9α - fluoro - 16β - methyl - 1,4,6 - pregnatriene - 17α,21 -

diol - 3,11,20 - trione 17,21-dipropionate (0.5 gm.) in glacial acetic acid (1 ml.) add a solution of dry hydrogen bromide in glacial acetic acid (48% w/w; 5 ml.). Stir at 5°C. for one hour, then pour into ice water (300 ml.). Filter off the resultant precipitate, wash it thoroughly with water and dry it in air at room temperature. Purify the precipitate on thick layer silica gel plates, developing with ethyl acetate/chloroform (1:5). Scrape off the band containing the desired compound as shown under ultraviolet light and extract the compound from the silica gel with ethyl acetate. Evaporate the ethyl acetate solution to a residue comprising 7α - bromo - 9α - fluoro - 16β - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate, yield=60% theory, m.p. 115°C. (decomp.).

(B) In a manner similar to that described in Example 3C(1) reduce the product of Example 27(A) with sodium borohydride in methanol/tetrahydrofuran to obtain 7α - bromo - 9α - fluoro - 16β - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate.

EXAMPLE 28

7α-Bromo-9α-chloro-16β-methyl-1,4-pregnadiene-11β, 17α,21-triol-3,20-dione 17,21-dipropionate

Treat 9α - chloro - 16β - methyl - 1,4,6 - pregnatriene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate with hydrogen bromide in acetic acid in a manner similar to that described in Example 27(A) followed by reduction of the resulting 7α - bromo - 9α - chloro - 16β - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate with sodium borohydride in methanol and tetrahydrofuran according to Example 3C(1) to obtain 7α - bromo - 9α - chloro - 16β - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate.

EXAMPLE 29

(A) 7α - Iodo - 9α - fluoro - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate is prepared by reaction of 9α - fluoro - 16α - methyl - 1,4,6 - pregnatriene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate with hydrogen iodide in glacial acetic acid in the dark by the method of Example 24(A).

(B) 7α - Iodo - 9α - fluoro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate is prepared by reduction of the compound of part (A) with sodium borohydride by the method of Example 3C(1).

EXAMPLE 30

(A) 7α - Bromo - 9α - fluoro - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate is prepared by reaction of 9α - fluoro - 16α - methyl - 1,4,6 - pregnatriene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate with hydrogen bromide in glacial acetic acid in the dark by the method of Example 24(A).

(B) 7α - Bromo - 9α - fluoro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate is prepared by reduction of the compound of part (A) with sodium borohydride by the method of Example 3C(1).

EXAMPLE 31

(A) 7α - Iodo - 9α - chloro - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate is prepared by reaction of 9α - chloro - 16α - methyl - 1,4,6 - pregnatriene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate with hydrogen iodide in glacial acetic acid in the dark by the method of Example 24(A).

(B) 7α - Iodo - 9α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate is prepared by reduction of the compound of part (A) with sodium borohydride by the method of Example 3C(1).

EXAMPLE 32

(A) 7α - Bromo - 9α - chloro - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate is prepared by reaction of 9α - chloro - 16α - methyl - 1,4,6 - pregnatriene - 17α,21 - diol - 3,11,20 - trione 17,21-dipropionate with hydrogen bromide in glacial acetic acid in the dark by the method of Example 24(A).

(B) 7α - Bromo - 9α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate is prepared by reduction of the compound of part (A) with sodium borohydride by the method of Example 3C(1).

EXAMPLE 33

(A) 7α - Iodo - 9α - fluoro - 16α,17α - isopropylidenedioxy - 1,4 - pregnadien - 21 - ol - 3,11,20 - trione 21-acetate is prepared by reaction of 9α - fluoro - 16α,17α - isopropylidenedioxy - 1,4,6 - pregnatrien - 21 - ol - 3,11,20 - trione 21-acetate with hydrogen iodide in glacial acetic acid in the dark by the method of Example 24(A).

(B) 7α - Iodo - 9α - fluoro - 16α,17α - isopropylidenedioxy - 1,4 - pregnadiene - 11β,21 - diol - 3,20 - dione 21-acetate is prepared by reduction of the compound of part (A) with sodium borohydride by the method of Example 3C(1).

EXAMPLE 34

(A) 7α - Bromo - 9α - fluoro - 16α,17α - isopropylidenedioxy - 1,4 - pregnadien - 21 - ol - 3,11,20 - trione 21-acetate is prepared by reaction of 9α - fluoro - 16α,17α - isopropylidenedioxy - 1,4,6 - pregnatrien - 21 - ol - 3,11,20 - trione 21-acetate with hydrogen bromide in glacial acetic acid in the dark by the method of Example 24(A).

(B) 7α - Bromo - 9α - fluoro - 16α,17α - isopropylidenedioxy - 1,4 - pregnadiene - 11β,21 - diol - 3,20 - dione 21-acetate is prepared by reduction of the compound of part (A) with sodium borohydride by the method of Example 3C(1).

The invention further provides pharmaceutical compositions suitable especially for the treatment of inflammatory conditions in animals and humans and comprising at least one compound of the formula I defined above, together with a compatible pharmaceutical carrier or excipient.

The compositions may take the form of dosage units, for example tablets, pellets, capsules, dragees, suppositories or injectable preparations in ampoules. Dosage units preferably contain from 0.05 to 10 mg. of active ingredient. The compositions may also be formulated as sprays, powders, drops, aerosols, retention enemas, suspensions, syrups, elixirs, emulsions, ointments, lotions or creams; such compositions preferably contain from 0.0001% to 5% by weight, preferably from 0.001 to 0.5%, especially from 0.01 to 0.25% of active ingredient of the formula I hereinabove defined.

The compositions may be administered orally for inflammatory disorders, particularly arthritis and rheumatism; intravenously in aqueous solution as the 21-hemisuccinate or 21-phosphate ester for the treatment of shock; intramuscularly for long-term systemic activity or intra-articularly for long-term local activity with low systemic effects in the treatment of rheumatoid arthritis, tennis elbow, bursitis, gout and similar conditions by administration in aqueous suspension as the 17,21-dihydrocarboncarboxylates, e.g. 17,21-dipropionate, 17,21-dibutyrate and 17-benzoate 21-acetate; topically in creams, lotions or ointments as the 17-mono lower alkanoate or benzoate in the treatment of contact and allergic dermatitis and psoriasis and of corticosteroid-responsive conditions such as alopecia areata and alopecia totalis; in the form of ophthalmic suspensions or nasal sprays; or as inhalation aerosols in the treatment of asthma and allergic rhinitis. Such pharmaceutical forms are prepared according to procedures well known in the art and may contain other active ingredients, such as antibacterials, e.g. neomycin sulfate in creams for topical use.

The following examples illustrate topical formulations according to this invention. In each, a preferred active ingredient is 7α - chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate; however, this compound may be replaced by equivalent quantities of other active compounds of this invention, e.g. by the 17,21-dipropionate or the 17-benzoate 21-propionate of 7α - bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione. The formulations are prepared by standard methods.

FORMULATION EXAMPLES

1. Ointment	mg/g
Active ingredient	0.1—5.0
Mineral oil	20.0
White petrolatum to make	1.00 g
2. Glycol Ointment	mg/g
Active ingredient	0.1—0.5
Hexylene glycol	100.0
Propylene glycol monostearate	20.0

White wax	60.0
White petrolatum to make	1.00 g
3. Lotion	mg/g
Active ingredient	0.1—5.0
Ethyl alcohol	400.0
Polyethylene glycol 400	300.0
Hydroxypropyl cellulose	5.0
Propylene glycol to make	1.0 g
4. Gel	mg/g
Active ingredient	0.1—5.0
Ethyl alcohol	400.0
Polyethylene glycol 400	300.0
Carbopol 940 (Registered Trade Mark Goodrich Chemical Co.)	15.0
Potassium hydroxide	5.0
Propylene glycol to make	1.00 g
5. Cream	mg/g
Active ingredient	0.1—5.0
Isopropyl palmitate	100.0
Glyceryl stearate	80.0
Promulgen-type D (Robinson, Wagner Co.)	50.0
White wax	50.0
Propylene glycol	100.0
Purified water to make	1.00 g
6. Topical Aerosol	mg/can
Active ingredient	6.4
Mineral oil	1,250.0
Neobee M-5 (Caprylic/capric glyceride) (PVO International, Inc.)	3,743.6
Dichlorodifluoromethane	17,200.0
Trichloromonofluoromethane	68,800.0
	91,000.0
7. Inhalation Aerosol	mg/can
Active ingredient	12.60
Oleic acid	1.26
Trichloromonofluoromethane	5,686.14
Dichlorodifluoromethane	14,700.00
	20,400.00
8. Intra-Articular Injection	mg/ml
Active ingredient	0.1—5.0
Sodium phosphate, dibasic, anhydrous R	2.00
Sodium chloride, USP	5.00
Disodium edetate, USP	0.10
Polysorbate 80, USP	0.50
Benzyl alcohol, R	9.00
Methyl *p*-hydroxybenzoate, USP	1.80
Propyl *p*-hydroxybenzoate, USP	0.20
Sodium carboxymethylcellulose	5.00
Polyethylene glycol 4000, USP	20.00
HCl 1N qs pH 7.1	
Water for injection qs ad	1.00 ml
9. Solution	mg/ml
Active ingredient	0.1—5.0
N-Methylpyrrolidone	200
Isopropyl myristate	50
Isopropyl alcohol qs to	1.0 ml

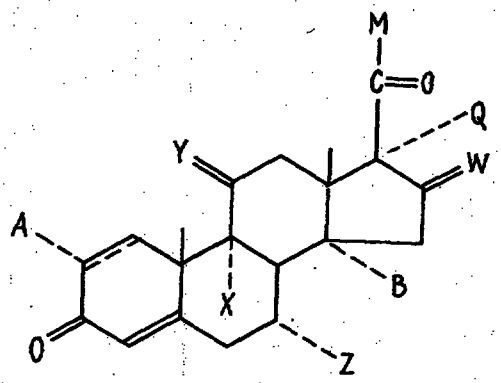
WHAT WE CLAIM IS:—

1. A 3,20 - dioxo - 7α - halo - 4 - pregnene or -1,4-pregnadiene of the formula

White wax	60.0
White petrolatum to make	1.00 g
3. Lotion	mg/g
Active ingredient	0.1—5.0
Ethyl alcohol	400.0
Polyethylene glycol 400	300.0
Hydroxypropyl cellulose	5.0
Propylene glycol to make	1.0 g
4. Gel	mg/g
Active ingredient	0.1—5.0
Ethyl alcohol	400.0
Polyethylene glycol 400	300.0
Carbopol 940 (Registered Trade Mark Goodrich Chemical Co.)	15.0
Potassium hydroxide	5.0
Propylene glycol to make	1.00 g
5. Cream	mg/g
Active ingredient	0.1—5.0
Isopropyl palmitate	100.0
Glyceryl stearate	80.0
Promulgen-type D (Robinson, Wagner Co.)	50.0
White wax	50.0
Propylene glycol	100.0
Purified water to make	1.00 g
6. Topical Aerosol	mg/can
Active ingredient	6.4
Mineral oil	1,250.0
Neobee M-5 (Caprylic/capric glyceride) (PVO International, Inc.)	3,743.6
Dichlorodifluoromethane	17,200.0
Trichloromonofluoromethane	68,800.0
	91,000.0
7. Inhalation Aerosol	mg/can
Active ingredient	12.60
Oleic acid	1.26
Trichloromonofluoromethane	5,686.14
Dichlorodifluoromethane	14,700.00
	20,400.00
8. Intra-Articular Injection	mg/ml
Active ingredient	0.1—5.0
Sodium phosphate, dibasic, anhydrous R	2.00
Sodium chloride, USP	5.00
Disodium edetate, USP	0.10
Polysorbate 80, USP	0.50
Benzyl alcohol, R	9.00
Methyl *p*-hydroxybenzoate, USP	1.80
Propyl *p*-hydroxybenzoate, USP	0.20
Sodium carboxymethylcellulose	5.00
Polyethylene glycol 4000, USP	20.00
HCl 1N qs pH 7.1	
Water for injection qs ad	1.00 ml
9. Solution	mg/ml
Active ingredient	0.1—5.0
N-Methylpyrrolidone	200
Isopropyl myristate	50
Isopropyl alcohol qs to	1.0 ml

WHAT WE CLAIM IS:—

1. A 3,20 - dioxo - 7α - halo - 4 - pregnene or -1,4-pregnadiene of the formula

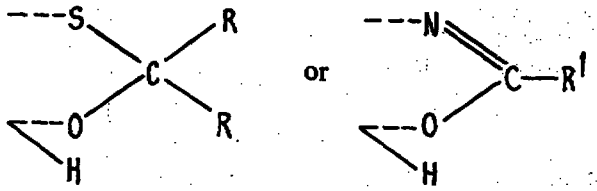


(I)

wherein the dotted line at the 1,2-positions indicates a 1,2-single bond or a 1,2-double bond;

W is a group (H,H), (H, lower alkyl), (H, α—OV^1) or =CHT, wherein V^1 is a hydrogen atom or an acyl radical of retinoic acid or of a carboxylic acid having up to 12 carbon atoms, and T is a hydrogen, fluorine or chlorine atom or a lower alkyl group;

Q is a chlorine or bromine atom or a group OV wherein V is a hydrogen atom or an acyl radical of a carboxylic acid having up to 12 carbon atoms, or, provided that W is a group (H,H) or (H, lower alkyl), Q can also be a hydrogen atom, or Q and W taken together are a 16α,17α - lower - alkylidenedioxy, -cycloalkylidenedioxy or -aralkylidenedioxy group together with a 16β-hydrogen atom or a grouping



wherein R is a lower alkyl group and R^1 is a lower alkyl or phenyl group;

B is a hydrogen atom or, together with Q, is a 14α,17α-lower alkylidenedioxy group;

M is a group —CHO or such a group in the form of an acetal, hemiacetal or acylal, —CH_3, —$COOR^3$, —CH_2Hal or —CH_2OV^2, wherein R^3 is a hydrocarbyl group having up to 12 carbon atoms, Hal is a halogen atom having an atomic weight of less than 100, and V^2 is a hydrogen atom or an acyl radical of retinoic acid, of a carboxylic acid having up to 12 carbon atoms or of phosphoric acid, which may be in the form of a mono- or di-alkali or alkaline earth metal salt; or OV^2 together with Q is an alkylidenedioxy, cycloalkylidenedioxy, aralkylidenedioxy, alkylorthoalkanoate or alkylorthoarylcarboxylate group; or, provided that Q is an O-Acyl group, M can also be a group —OR^2 wherein R^2 is a lower alkyl or halolower alkyl group;

X is a hydrogen atom or a halogen atom having an atomic weight of less than 100;

Y is an oxygen atom or a group (H,β—OH) or (H,β—OCOH), or, provided that X is chlorine or bromine, Y can also be a group (H,β-halogen), said halogen having an atomic weight of less than 100 and being at least as electronegative as X, or, provided that X is hydrogen, Y can also be a group (H,H);

A, which is in the α-position in the 4-pregnenes, is a hydrogen atom or, provided that Y is (H,β—OH), A can also be a chlorine or fluorine atom or a methyl group;

and Z is a fluorine, chlorine, bromine or iodine atom;

and, when W is (H,H), the D-homo analogs thereof.

2. A compound as claimed in claim 1 wherein the dotted line indicates a 1,2-double bond.

3. A compound as claimed in claim 2 wherein X, Y and Z are as defined in claim 1;

W is a group (H,H), (H, lower alkyl), (H,α—OV^1) or =CHT, wherein V^1 is a

hydrogen atom or an acyl radical of isonicotinic acid, of benzoic acid substituted by a halogen atom or by a methoxy group, of retinoic acid or of a hydrocarboncarboxylic acid having up to 12 carbon atoms, and T is a hydrogen, fluorine or chlorine atom or a lower alkyl group;

Q is a chlorine or bromine atom or a group OV wherein V is a hydrogen atom or an acyl radical of a hydrocarboncarboxylic acid having up to 12 carbon atoms or of benzoic acid substituted by a halogen atom or by a methoxy group, or, provided that W is a group (H,H) or (H, lower alkyl), Q can also be a hydrogen atom; or Q and W taken together are a 16α,17α-lower-alkylidenedioxy or 16α,17α-cycloalkylidenedioxy group;

A and B are hydrogen atoms; and,

M is a group —CHO or such a group in the form of an acetal, hemiacetal or acylal, —CH_3, —$COOR^3$, —CH_2Hal or —CH_2OV^2, wherein R^3 is a hydrocarbyl group having up to 12 carbon atoms, Hal is a halogen atom having an atomic weight of less than 100, and V^2 is a hydrogen atom or an acyl radical of retinoic acid, of isonicotinic acid, of benzoic acid substituted by a halogen atom or by a methoxy group, of a hydrocarboncarboxylic acid having up to 12 carbon atoms or of phosphoric acid, which may be in the form of a mono- or di-alkali or alkaline earth metal salt; or OV^2 together with Q is an alkylidenedioxy, alkylorthoalkanoate or alkylorthoarylcarboxylate group; or, provided that Q is an O-Acyl group, M can also be a group —OR^2 wherein R^2 is a lower alkyl or halolower alkyl group.

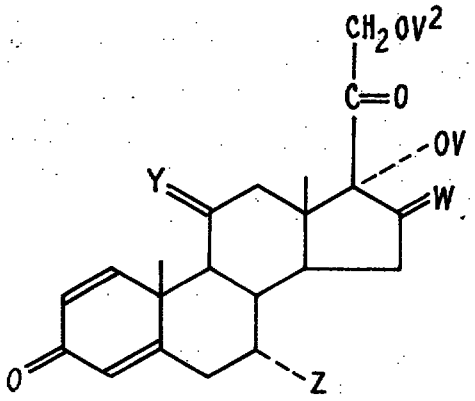
4. A compound as claimed in claim 3 wherein Z is a chlorine or bromine atom.

5. A compound as claimed in claim 3 or claim 4 wherein X is a hydrogen atom.

6. A compound as claimed in any of claims 3 to 5 wherein W is a methylene group or the group (H,CH_3).

7. A compound as claimed in any of claims 3 to 6 wherein Y is an oxygen atom or the group (H,β—OH).

8. A compound as claimed in any of claims 3 to 7 having the formula



(II)

wherein

Z is a chlorine or bromine atom,

W is a methylene group or the group (H,CH_3),

Y is an oxygen atom or the group (H,β—OH), and

V and V^2, which may be the same or different, are hydrogen atoms or acyl radicals of hydrocarbon carboxylic acids having up to 12 carbon atoms.

9. A compound as claimed in claim 8 wherein V and V^2, which may be the same or different, are acyl radicals of hydrocarboncarboxylic acids having up to 8 carbon atoms.

10. A compound as claimed in claim 8 or claim 9 wherein W is (H,α—CH_3).

11. A compound as claimed in any of claims 8 to 10 wherein V is a propionyl, *n*-butyryl or benzoyl group.

12. A compound as claimed in claim 10 wherein Y is the group (H,β—OH), V is a benzoyl or propionyl group, and V^2 is a lower alkanoyl group having up to 8 carbon atoms.

13. 7α - Chloro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate.

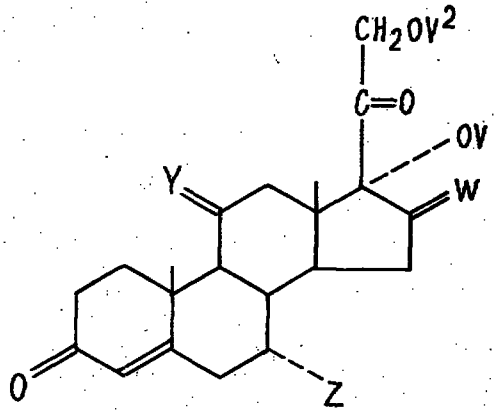
14. 7α - Bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate.

15. 7α - Bromo - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-benzoate 21-acetate.

16. 7α - Chloro - 16 - methylene - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate.

17. 7α,9α,11β - Trichloro - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione 17,21-dipropionate.

18. A 3,20 - dioxo - 7α - halo - 4 - pregnene having the formula



(III)

wherein

Z is a chlorine, bromine or iodine atom,

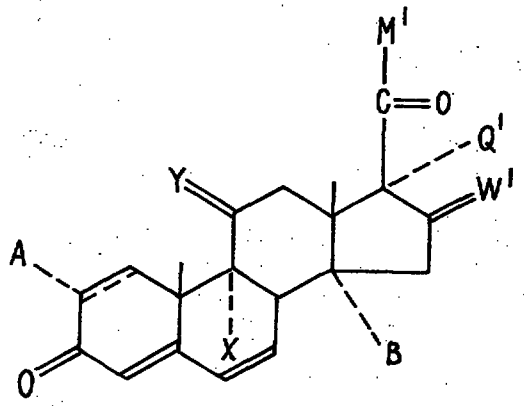
Y is an oxygen atom or the group (H,β—OH),

W is a methylene group or the group (H,CH_3) or (H,H), and

V and V^2, which may be the same or different, are hydrogen atoms or acyl radicals of hydrocarboncarboxylic acids having up to 12 carbon atoms.

19. 7α - Chloro - 4 - pregnene - 11β,17α,21 - triol - 3,20 - dione 17,21-dipropionate, 7α - bromo - 16α,17α - isopropylidenedioxy - 1,4 - pregnadiene - 11β,21 - diol - 3,20 - dione 21-acetate or 7α - fluoro - 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 17-benzoate 21-acetate.

20. A process for the preparation of a compound as claimed in claim 1 wherein Z is a chlorine, bromine or iodine atom, with the proviso that Z is not a chlorine atom when X is a halogen atom, which comprises the addition, of a hydrogen halide selected from hydrogen chloride, hydrogen bromide and hydrogen iodide to the 6,7-double bond of a compound of the formula



(IV)

wherein the dotted line, A, B, X and Y are as defined in claim 1 and W', Q' and M' are W, Q and M as defined in claim 1,

or W' and Q' taken together are a 16α,17α-alkylorthoalkanoate or 16α,17α-alkylorthoarylcarboxylate group together with a 16β-hydrogen atom,

or M' is the group $—CH_2OV^3$, and OV^3 and Q' together with the oxygen atom of the C_{20} carbonyl group are a 17α,20;20,21-*bis*-methylenedioxy group,

in the presence of an inert solvent, with the provisos that

(i) when the hydrogen halide is hydrogen chloride, then X is a hydrogen atom;

(ii) when Y is the group (H,β—OH) and the hydrogen halide is hydrogen bromide, then X is a hydrogen atom; and

(iii) when Y is the group (H,β—OH) and the hydrogen halide is hydrogen iodide, then X is a hydrogen, chlorine or fluorine atom;

whereafter, when W' and Q' taken together are a 16α,17α-alkylorthoalkanoate or 16α,17α-alkylorthoarylcarboxylate group together with a 16β-hydrogen atom, the product is hydrolysed to yield a compound wherein Q is a hydroxy group and W is the group (H,α—OH),

or, when OV^3 and Q' together with the oxygen atom of the C_{20} carbonyl group are a 17α,20;20,21-*bis*-methylenedioxy group, the product is hydrolysed to yield a compound wherein OV^3 and Q are hydroxy groups;

and/or, when Y is an oxygen atom and either

(i) Z is a bromine atom and X is a halogen atom, or

(ii) Z is an iodine atom and X is a bromine atom, and a compound wherein Y is the group (H,β—OH) is required, this compound is prepared by reduction of a corresponding product wherein Y is an oxygen atom;

and/or, when X is a hydrogen atom, Y is the group (H,β—OH), and Z is a chlorine or bromine atom, a 9(11)-double bond, is introduced by dehydration and the product is subjected to addition of halogen to the 9(11)-double bond or to addition of a 9α-chlorine or bromine atom and of an 11β-hydroxy group to the 9(11)-double bond;

and a compound claimed in claim 1 is then isolated.

21. A process for the preparation of a compound as claimed in claim 1 wherein Z is a chlorine, bromine or iodine atom, with the proviso that Z is not a chlorine atom when X is a halogen atom, which comprises the addition of a hydrogen halide selected from hydrogen chloride, hydrogen bromide and hydrogen iodide to the 6,7-double bond of a compound of the formula IV defined in claim 20 in the presence of an inert organic solvent;

with the provisos that

(i) when the hydrogen halide is hydrogen chloride, then X is a hydrogen atom;

(ii) when Y is the group (H,β—OH) and the hydrogen halide is hydrogen bromide, then X is a hydrogen atom; and

(iii) when Y is the group (H,β—OH) and the hydrogen halide is hydrogen iodide, then X is a hydrogen, chlorine or fluorine atom;

subjecting the resulting product, if desired or necessary, to one or more of the following finishing steps in any appropriate order, and then isolating a compound claimed in claim 1:

a) Hydrolysis of an esterifying group or groups at the 16α-, 17α- and/or 21-position to hydroxy;

b) Hydrolysis of a 17α,20;20,21-*bis*-methylenedioxy group to 20-oxo-17α,21-dihydroxy groups, or of a 21-ethylene ketal to 21-oxo, or of a 17α,21-alkylidenedioxy, -cycloalkylidenedioxy or -aralkylidenedioxy group to 17α,21-dihydroxy groups;

c) Esterification of a hydroxy group at the 16α-, 17α- and/or 21-position;

d) Reduction of an 11-oxo group to an 11β-hydroxy group;

e) 9(11)-Dehydration of a 9-unsubstituted-11β-ol to a 4,9(11)-pregnadiene or to a 1,4,9(11)pregnatriene, except when Z is an iodine atom, followed by addition of halogen to the 9(11)-double bond;

or followed by addition of a chlorine or bromine atom and a hydroxy group to the 9(11)-double bond with the formation of a 9α-chloro- or 9α-bromo-11β-hydroxy steroid;

f) 17α-Chlorination or bromination.

22. A process as claimed in claim 20 or claim 21 wherein the compound of the formula IV has a 1,2-double bond and the inert organic solvent is anhydrous.

23. A process as claimed in claim 22 wherein the solvent is an ether, a chlorinated hydrocarbon, an organic acid, a tertiary amide or dimethyl sulfoxide.

24. A process as claimed in claim 22 wherein the solvent is dioxan, acetic acid or tetrahydrofuran.

25. A process as claimed in any of claims 22 to 24 wherein the compound of the formula IV is reacted with hydrogen chloride in tetrahydrofuran.

26. A process as claimed in any of claims 22 to 24 wherein the compound of the formula IV is reacted with hydrogen bromide or hydrogen iodide in glacial acetic acid.

27. A process as claimed in any of claims 22 to 26 wherein the reaction is effected at a temperature from 0°C. up to ambient temperature.

28. A process as claimed in any of claims 22 to 27 wherein the hydrogen halide is present in at least a 5 molar excess.

29. A process as claimed in claim 28 wherein the hydrogen halide is present in a 10 to 50 molar excess.

30. A process as claimed in any of claims 22 to 29 wherein the resulting 7α-halo-steroid is separate at temperatures no higher than about 25°C. in a state substantially free of acid and base by freeing it of excess acid and solvent without subjecting it to a substantially basic medium.

31. A process as claimed in any of claims 20 to 30 wherein a steroid claimed in claim 1 wherein Y is the group (H,β—OH) is prepared from a steroid of the formula IV defined in claim 20 wherein Y is an oxygen atom by reaction with hydrogen chloride, hydrogen bromide or hydrogen iodide in an inert organic solvent, followed by reduction at the 11-position.

32. A process as claimed in claim 31 wherein the reduction is effected with sodium, potassium or lithium borohydride, tetra-*n*-butyl-ammonium borohydride or lithium tri-*t*-butoxy-aluminium hydride, in an inert organic solvent.

33. A process as claimed in claim 31 wherein the reduction is effected with sodium borohydride in an inert organic solvent comprising methanol or dimethylformamide.

34. A process as claimed in claim 20 or claim 21 wherein the compound of formula IV has a 1,2-single bond, the reaction with hydrogen chloride, hydrogen bromide or hydrogen iodide is effected at a temperature no higher than 30°C., and the resulting 7α-halo-steroid is isolated at temperatures no higher than 25°C. in a state substantially free of acid and base by freeing it of excess acid and solvent without subjecting it to a substantially basic medium.

35. A process as claimed in claim 34 having the features of any of claims 23 to 29.

36. A process as claimed in claim 34 or claim 35 wherein the inert organic solvent is not anhydrous and the hydrogen halide is hydrogen chloride.

37. A process as claimed in any of claims 34 to 36 having the features of claim 32 and/or claim 33.

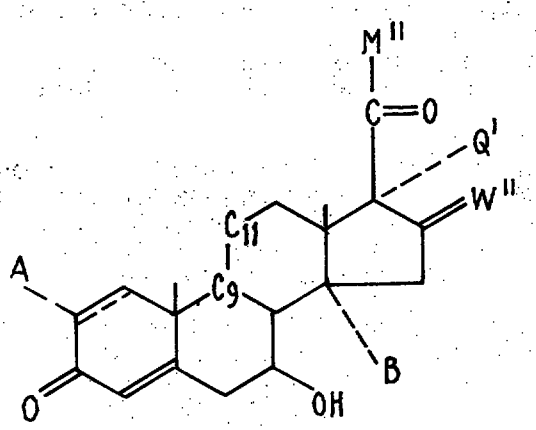
38. A process as claimed in claim 37 wherein the product of the reduction is oxidised with an oxidising agent capable of oxidising an allylic hydroxy group to an oxo group under substantially non-basic conditions.

39. A process as claimed in claim 38 wherein the oxidising agent is neutral active manganese dioxide in an inert organic solvent at room temperature.

40. A process as claimed in claim 38 wherein the oxidising agent is pyridinium chlorochromate in an inert organic solvent, or a carbodiimide with dimethylsulfoxide and a weak acid.

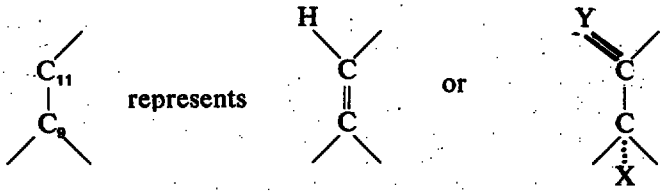
41. A process as claimed in any of claims 20 to 40 wherein X in the compound of formula IV is a hydrogen atom.

42. A process for the preparation of a compound claimed in claim 1 wherein Z is a fluorine, chlorine or bromine atom, with the proviso that Z is a fluorine atom when a 1,2-single bond is present, which comprises reacting a compound of the formula



(V)

wherein the dotted line, A and B are as defined in claim 1, Q' is as defined in claim 20, M'' and W'' are respectively M' and W' defined in claim 20 with the proviso that M'' is not a hydroxymethyl group and W'' is not the group (H,α—OH), and the grouping



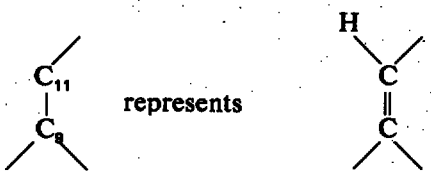
wherein Y and X are as defined in claim 1,

with a halogenating agent capable of replacing the 7β-hydroxy group with a 7α-halogen atom selected from fluorine, chlorine and bromine, in the presence of an inert organic solvent, with the proviso that a 7α-chlorine or 7α-bromine atom is introduced only when a 1,2-double bond is present;

whereafter, when W″ and Q′ taken together are a 16α,17α-alkylorthoalkanoate or 16α,17α-alkylorthoarylcarboxylate group together with a 16β-hydrogen atom, the product is hydrolysed to yield a compound wherein Q is a hydroxy group and W is the group (H,α—OH),

or, when OV^3 and Q′ together with the oxygen atom of the C_{20} carbonyl group are a 17α,20;20,21-*bis*-methylenedioxy group, the product is hydrolysed to yield a compound wherein OV^3 and Q are hydroxy groups,

and/or, when the grouping



halogen is added to the 9,11-double bond or a chlorine or bromine atom and a hydroxy group are added to the 9,11-double bond with the formation of a 9α-chloro- or 9α-bromo-11β-hydroxy steroid.

43. A process for the preparation of a compound as claimed in claim 1 wherein Z is a fluorine, chlorine or bromine atom, with the proviso that Z is a fluorine atom when a 1,2-single bond is present, which comprises reacting a compound of the formula V defined in claim 42 with a halogenating agent capable of replacing the 7β-hydroxy group with a 7α-halogen atom selected from fluorine, chlorine and bromine, in the presence of an inert organic solvent, with the proviso that a 7α-chlorine or 7α-bromine atom is introduced only when a 1,2-double bond is present;

and then the resulting product is subjected, if desired or necessary, to one or more of the following finishing steps in any appropriate order:

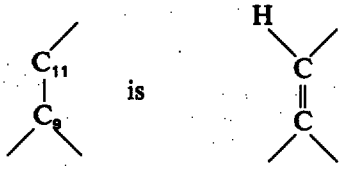
a) Hydrolysis of an esterifying group or groups at the 16α-, 17α- and/or 21-position to hydroxy;

b) Hydrolysis of a 17α,20;20,21-*bis*-methylenedioxy group to 20-oxo-17α,21-dihydroxy groups, or of a 21-ethylene ketal to 21-oxo, or of a 17α,21-alkylidenedioxy, -cycloalkylidenedioxy or -aralkylidenedioxy group to 17α,21-dihydroxy groups;

c) Esterification of a hydroxy group at the 16α-, 17α- and/or 21-position;

d) Reduction of an 11-oxo group to an 11β-hydroxy group;

e) Addition to the 9,11-double bond of halogen or of a 9α-chlorine or bromine atom and of an 11β-hydroxy group, either when the grouping



or after such a 9(11)-double bond has been introduced by 9(11)-dehydration of a 9-unsubstituted-11β-ol;

f) 17α-Chlorination or bromination.

44. A process as claimed in claim 42 or claim 43 wherein the halogenating agent is either a tertiary amine having an N-(2-chloro-1,1,2-trifluoroethyl) group, said amine being used alone for the preparation of a 7α-fluoro steroid but in the

presence of a metal chloride or bromide that is soluble in the reaction mixture for the preparation of a 7α-chloro or 7α-bromo steroid respectively, or a tertiary amine having an N-trichlorovinyl group for the preparation of a 7α-chloro steroid.

45. A process as claimed in claim 44 wherein the halogenating agent is N-(2-chloro-1,1,2-trifluoroethyl)diethylamine and the reaction is effected at moderately low temperatures under an inert atmosphere.

46. A process as claimed in claim 45 wherein the reaction is effected at about 0°C. under anhydrous conditions.

47. A process as claimed in claim 45 or claim 46 wherein the molar ratio of N-(2-chloro-1,1,2-trifluoroethyl)diethylamine to steroid is about 6 to 1.

48. A process as claimed in any of claims 44 to 47 wherein the reaction mixture is free of metal chloride and bromide, the solvent is a halohydrocarbon, and the product is a 7α-fluoro steroid.

49. A process as claimed in any of claims 44 to 47 wherein the reaction mixture contains lithium bromide as metal bromide, the solvent is a halohydrocarbon, and the product is a 7α-bromosteroid.

50. A process as claimed in any of claims 44 to 47 wherein the reaction mixture contains lithium chloride as metal chloride, the solvent is an ether, and the product is a 7α-chloro steroid.

51. A process as claimed in claim 49 or 50 wherein the molar ratio of lithium chloride or lithium bromide to steroid is about 12 to 1.

52. A process as claimed in any of claims 48 to 51 wherein the halohydrocarbon is methylene chloride and the ether is tetrahydrofuran.

53. A process as claimed in claim 44 wherein the halogenating agent is N,N-diethyl-1,2,2-trichlorovinylamine in a halohydrocarbon as solvent.

54. A process as claimed in claim 53 wherein the halohydrocarbon is methylene chloride and the reaction is effected at moderately low temperatures.

55. A process as claimed in claim 54 wherein the reaction is effected at about 0°C. under an inert atmosphere.

56. A process as claimed in any of claims 53 to 55 wherein the molar ratio of N,N-diethyl-1,2,2-trichlorovinylamine to steroid is about 6 to 1.

57. A process as claimed in any of claims 42 to 56 wherein the compound of the formula V has a 1,2-double bond.

58. A process as claimed in any of claims 21 to 41 and 43 to 57 wherein the hydrolysis of an esterifying group at the 16α-, 17α- or 21-position is effected by means of mild base.

59. A process as claimed in any of claims 21 to 41 and 43 to 57 wherein the hydrolysis of an esterifying group at the 16-, 17- and 21-position is effected by means of a strong mineral acid.

60. A process as claimed in any of claims 21 to 41 and 43 to 57 wherein the hydrolysis of a 17α,21-orthoester at the 21-position to yield a 17-ester is effected under mildly acidic conditions.

61. A process as claimed in any of claims 20 to 57 wherein the hydrolysis of a 16α,17α-orthoester at the 16α-position to yield a 17-ester is effected under mildly acidic conditions.

62. A process as claimed in any of claims 21 to 41 and 43 to 57 wherein the hydrolysis of a 16- or 21-hydrocarboncarboxylate is effected by means of malt diastase.

63. A process as claimed in any of claims 21 to 41 and 43 to 57 wherein the hydrolysis of a 21-ethylene ketal or of a 17α,21-alkylidenedioxy, -cycloalkylidenedioxy or -aralkylidenedioxy group is effected by means of mild acid.

64. A process as claimed in any of claims 20 to 57 wherein the hydrolysis of a 17α,20;20,21-*bis*-methylenedioxy group is effected by means of mild acid or under substantially neutral conditions by means of triphenylcarbenium tetrafluoroborate.

65. A process as claimed in any of claims 21 to 41 and 43 to 57 wherein the esterification of a hydroxy group at the 16α- and/or 21-position and/or, in the absence of an 11β-hydroxy group, at the 17α-position, is effected by means of a carboxylic acid having up to 12 carbon atoms or retinoic acid together with an esterifying agent or by means of a reactive derivative of said acid.

66. A process as claimed in any of claims 21 to 41 and 43 to 57 wherein the esterification of a resulting steroid having 11β- and 17α-hydroxy groups is effected at the 17-position by conversion of the 11β-hydroxy group into 11β-trifluoroacetate with trifluoroacetic anhydride, esterification at the 17-position with the required

acid, trifluoroacetic anhydride and a strong acid catalyst, and hydrolysis of the 11β-trifluoroacetate group with mild base.

67. A process as claimed in any of claims 21 to 41 and 43 to 57 wherein the esterification of a 21-ol is effected by means of pyrophosphoryl chloride to yield a 21-phosphate; which, if desired is converted into a mono- or di-alkali metal or alkaline earth metal salt.

68. A process as claimed in claim 67 wherein the metal salt is prepared by partial or complete neutralisation of the 21-phosphate with an alkali metal methoxide or an alkaline earth metal methoxide.

69. A process as claimed in any of claims 21 to 41 and 43 to 57 wherein the esterification of a 17α-hydroxy group in a 17α,21-diol or 11β,17α,21-triol is effected by formation of a 17α,21-orthoester followed by hydrolysis at the 21-position.

70. A process as claimed in any of claims 20 to 30, 34 to 36 and 42 to 57 wherein the reduction of an 11-keto group is effected by means of sodium, potassium or lithium borohydride, tetra-*n*-butylammonium borohydride or lithium tri-*t*-butoxy-aluminium hydride, in an inert organic solvent.

71. A process as claimed in any of claims 20 to 41 and 43 to 57 wherein the 9(11)-dehydration is effected by means of mesyl chloride, a tertiary amine, a dialkylamide and sulfur dioxide.

72. A process as claimed in any of claims 20 to 57 and 71 wherein there is introduced a 9α-chlorine or 9α-bromine atom together with an 11β-hydroxy group by means of an *N*-chloro-amide or *N*-bromo-amide and a strong mineral acid in an inert organic solvent.

73. A process as claimed in any of claims 20 to 57 and 71 wherein the introduction of 9α- and 11β-halogen atoms is effected by means of molecular chlorine in chloroform and pyridine, by means of hydrogen fluoride and an *N*-chloro-amide or *N*-bromo-amide in an inert organic solvent, or by means of hydrogen chloride and an *N*-bromo-amide in an inert organic solvent.

74. A process as claimed in any of claims 21 to 41 and 43 to 57 wherein the introduction of a 17α-chlorine or 17α-bromine atom is effected by means of an *N*-chloro-amide or *N*-bromo-amide in an inert solvent at reduced temperature.

75. A process as claimed in claim 73 or claim 74 wherein the *N*-chloro-amide or *N*-bromo-amide is *N*-chloro-succinimide or *N*-bromosuccinimide.

76. A process for the preparation of a compound as claimed in any of claims 1 to 19 substantially as herein described.

77. A process for the preparation of a compound as claimed in any of claims 1 to 19 substantially as herein described in any of Examples 1 to 34.

78. Compounds as claimed in claim 1 whenever prepared by a process as claimed in any of claims 20 to 77.

79. Pharmaceutical compositions comprising as active ingredient at least one compound as claimed in any of claims 1 to 19 and 78, together with a pharmaceutical carrier or excipient.

80. Compositions as claimed in claim 79 in the form of dosage units.

81. Compositions as claimed in claim 80 in the form of tablets, pellets, capsules, dragees, suppositories or injectable preparations in ampoules.

82. Compositions as claimed in claim 80 or claim 81 containing from 0.05 to 10 mg. of active ingredient per dosage unit.

83. Compositions as claimed in claim 79 in the form of sprays, powders, drops, aerosols, suspensions, syrups, elixirs, emulsions, ointments, lotions, creams, or retention enemas.

84. Compositions as claimed in claim 83 containing from 0.001 to 0.5% by weight of active ingredient.

85. Compositions as claimed in any of claims 79 to 84 wherein the active ingredient is a compound claimed in any of claims 13 to 17.

86. Pharmaceutical compositions as claimed in claim 79 substantially as herein described.

87. Pharmaceutical compositions as claimed in claim 79 substantially as herein described in any of the Formulation Examples.

88. A process for the preparation of a composition as claimed in claim 80 which comprises bringing a compound as claimed in any of claims 1 to 19 and 78

into a form suitable for therapeutic administration, by admixing it with a pharmaceutical carrier or excipient.

89. A method for eliciting a corticoid effect in non-human animal which comprises administering to said animal an effective amount of a compound as claimed in any of claims 1 to 19 and 78.

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