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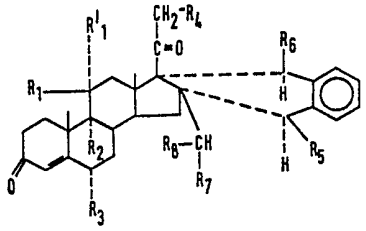
(54) STEROIDAL 16β-ALKYL-[16α,17-b)] NAPHTHALENES

(71) We, E.R. SQUIBB & SONS, INC., a corporation organised under the laws of the State of Delaware, United States of America, of Lawrenceville-Princeton Road, Princeton, New Jersey 08540, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to me, 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 steroidal 16β-alkyl-[16α,17-b]naphthalenes which are useful topical and systemic antiinflammatory agents. These new steroids have the structure



I

or the 1,2-dehydro derivates thereof, wherein R_1 is chlorine, fluorine or hydroxy and R'_1 is hydrogen, or R_1 and R'_1 together are $=O$; R_2 is hydrogen or halogen; R_3 is hydrogen, methyl or fluorine; R_4 is hydrogen, hydroxy, alkyl-C(=O)-O-, aryl-C(=O)-O- or halogen; R_5 and R_6 are the same or different and are hydrogen, alkyl, alkoxy, alkoxycarbonyl, formyl, alkyl-C(=O)-, alkyl-C(=O)-O-, hydroxy, halogen, phenyl or cyano, with the proviso that when R_5 and R_6 are different, R_5 is hydrogen; and R_7 and R_8 are the same or different and are hydrogen or alkyl.

Throughout the specification, the symbols are as defined above in connection with formula I.

The term "alkyl", as used throughout the specification, refers to straight or branched chain saturated aryclic hydrocarbon groups having 1 to 6 carbon atoms.

The term "alkoxy", as used throughout the specification, refers to groups having the formula Y-O- wherein Y is alkyl as defined above.

The term "aryl", as used throughout the specification, refers to phenyl or phenyl substituted with alkyl, alkoxy or halogen; phenyl is preferred.

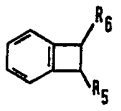
The term "halogen", as used throughout the specification, refers to fluorine, chlorine, bromine and iodine; fluorine, chlorine and bromine are preferred.

The steroids of formula I (and the 1,2-dehydro derivatives thereof) are physiologically active substances which possess glucocorticoid and antiinflammatory activity and hence can be used in lieu of known glucocorticoids in the treatment of rheumatoid arthritis, for which purpose they can be administered in the same manner as hydrocortisone, for example, the dosage being adjusted for the relative potency of the particular steroid. In addition, the steroids of this invention can be used topically in lieu of known glucocor-

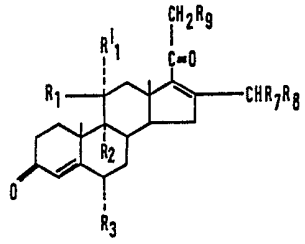
ticoids in the treatment of skin conditions such as dermatitis, psoriasis, sunburn, neurodermatitis, eczema and anogenital pruritus.

When given orally, the compounds of this invention may be used in a dosage range of 0.1 to 200 milligrams, preferably 0.1 to 100 milligrams. If administered topically, the compounds of this invention may be used in the range of 0.01 to 5.0% by weight, preferably 0.05 to 2.0% by weight, in a conventional cream or lotion.

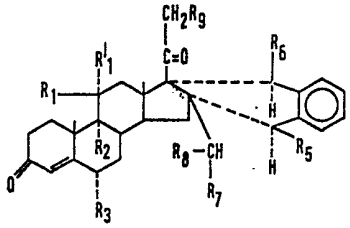
The steroids of formula I (and the 1,2-dehydro derivatives thereof) wherein R_4 is other than hydroxy can be prepared by reacting a benzocyclobutene having the structure

II 

with a steroid having the structure

III 

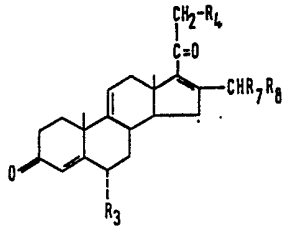
(or a 1,2-dehydro derivative thereof) to yield a steroid having the structure

IV 

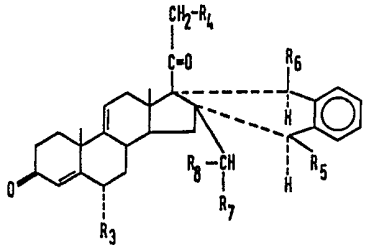
(or a 1,2-dehydro derivative thereof). In formulas III and IV, and throughout the specification, R_9 represents hydrogen, alkyl-$\overset{O}{\overset{\|}{C}}$-O-, aryl-$\overset{O}{\overset{\|}{C}}$-O- or halogen. The above reaction can be run with or without an inert solvent. Preferably, the reaction will be run neat, in an inert atmosphere, at temperatures up to the boiling point of the solution.

Those steroids of formula I (and the 1,2-dehydro derivatives thereof) wherein R_4 is hydroxy or halogen can be prepared from the corresponding 21-acyloxy steroid of formula IV (or a 1,2-dehydro derivatives thereof). Hydrolysis of the 21-acyloxy steroid yields the corresponding 21-hydroxy steroid which can in turn be converted to a 21-halo steroid using procedures well known in the art. Also, an 11β,21-bis-(acyloxy) derivative (or a 1,2-dehydro derivative thereof) may be used.

Alternatively, the compounds of formula I (and the 1,2-dehydro derivatives thereof) can be prepared from benzocyclobutenes of formula II and steroids having the structure

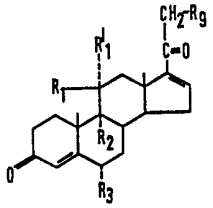
V 

(and the 1,2-dehydro derivatives thereof). Reaction of a benzocyclobutene of formula II and a steroid of formula V (or a 1,2-dehydro derivative thereof) yields a novel steroidal intermediate having the structure

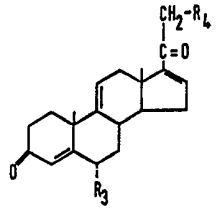
VI 

(or a 1,2-dehydro derivative thereof). A steroid of formula VI (or a 1,2-dehydro derivative thereof) can be converted to the corresponding 9,11β-dihalo steroid or 9-halo-11β-hydroxy steroid using procedures well known in the art. The 21-acyloxy steroids can be readily converted to the corresponding 21-hydroxy and 21-halo steroids.

The steroids of formulas III and V (and the 1,2-dehydro derivatives thereof) can be prepared from a corresponding steroid starting material having the structure

VII 

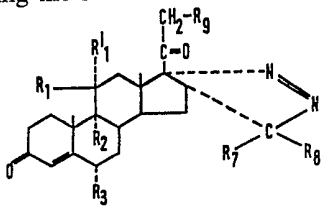
(or a 1,2-dehydro derivative thereof (or an 11β acyloxy derivative thereof) or

VIII 

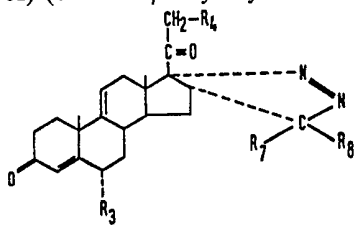
(or a 1,2-dehydro derivative thereof). Reaction of a steroid of formula VII (or a 1,2-dehydro derivative thereof) (or an 11β-acyloxy derivative thereof) or a steroid of formula VIII (or a 1,2-dehydro derivative thereof) with a diazoalkane having the formula

IX N_2-CR_7R_8

yields a pyrazoline steroid having the structure

X 

(or a 1,2-dehydro derivative thereof) (or an 11β acyloxy derivative thereof) or

XI 

(or a 1,2-dehydro derivative thereof) which can be heated to yield a 16β-alkylpregnene of formula III or V (or a 1,2-dehydro derivative thereof).

Many variations of the above-described procedures for preparing the steroids of this invention will be apparent to a person of ordinary skill in the steroid art.

The following Examples are specific embodiments of this invention.

Example 1

9-Fluoro-1',2',3',4'-tetrahydro-11β,21-dihydroxy-16β-methyl- pregna-1,4-dieno[16α, 17-b]naphthalene-3, 20-dione

A. *11β,21-bis (Acetyloxy)-9-fluoro-4',5'-dihydropregna-1, 4-dieno-[17,16α-c] [3H]pyrazole-2, 20-dione*

A solution of 250 ml of ethereal diazomethane [from 25 g of N-methyl-N- nitroso-N'-nitroguanidine] is diluted with 550 ml of dichloromethane and 7.0 g of 11β,21-bis(acetyloxy)- 9-fluoropregna-1,4,16- triene-3,20-dione is added. The solution is stirred at room temperature for 1 hour. Acetic acid is added until the yellow color of the solution disappears. The solvent is removed *in vacuo* and the residue redissolved in dichloromethane. The dichloromethane solution is washed with a saturated sodium bicarbonate solution, dried over anhydrous sodium sulfate and evaporated *in vacuo* to give 8.0 g of the title compound.

B. *11β,21-bis(Acetyloxy)-9-fluoro-16-methylpregna- 1,4,16-triene-3,20-dione*

11β,21-bis(Acetyloxy)-9-fluoro-4',5'-dihydropregna-1,4-dieno- [17,16α-c] [3*H*]pyrazole (7.5 g) is stirred at 175°C (oil bath temperature) for 3 hours in 100 ml of ethylene glycol. The solution is cooled and diluted with 100 ml of chloroform and water. The chloroform layer is separated and the aqueous layer is washed with chloroform. The chloroform solutions are combined, washed with water, dried over anhydrous sodium sulfate and evaporated *in vacuo* to give 7.2 g of a foam which is dissolved in 9:1 chloroform-hexane and chromatographed on a 110 g-silica gel column. Elution with 1:1 chloroform-hexane and 3:2 chloroform-hexane gives 4.3 g of the title compound, melting point 240-241°C.

C. *9-Fluoro-1',2',3',4'-tetrahydro-11β,21-dihydroxy-16β-methylpregna- 1,4-dieno[16α, 17-b]naphthalene-3,20-dione*

A mixture of 1 g of 11β,21-bis(acetyloxy-9-fluoro-16-methylpregna-1,4,16-triene-3, 20-dione and 6.5 ml of 1,2-dihydro-benzocyclobutene is stirred at 185°C (oil bath temperature) under nitrogen for 7 days. The solution is cooled, diluted with 3:1 chloroform-hexane and chromatographed on an 80 g silica gel column. Elution with 1:1 chloroform-hexane gives 640 mg of material as a foam. This is dissolved in a mixture of methanol (20 ml) and tetrahydrofuran (20 ml), a 10% potassium carbonate solution (0.6 ml) is added and the mixture is stirred at room temperature under nitrogen for 6 hours. The resulting solution is neutralized with 3% acetic acid. The solvent is partially removed *in vacuo* to give 490 mg of the title compound. Crystallization from chloroform-methanol gives the analytical sample of the title compound, melting point 306-307×C.

Example 2

21-(Acetyloxy)-9-fluoro-1',2',3',4'-tetrahydro-11β-hydroxy-16β-methylpregna-1, 4-dieno[16α,17-b]naphthalene-3,20-dione

A solution of 280 mg of 9-fluoro-1',2',3',4-tetrahydro-11β, 21-dihydroxy-16β-methylpregna-1,4-dieno [16α,17-b]naphthalene-3, 20-dione and 0.3 ml of acetic anhydride in 25 ml of pyridine is stirred at room temperature under nitrogen for three hours. The resulting solution is poured into cold 5% hydrochloric acid and extracted with chloroform. The chloroform solution is washed with water, dried over anhydrous sodium sulfate and evaporated *in vacuo* to give a foam. This is dissolved in 1:3 hexane-chloroform and chromatographed on a 40 g silica gel column. Elution with hexane-chloroform (1:3 and 1:4) gives 243 mg of material. Crystallization from ethyl acetate-hexane gives 212 mg of the title compound, melting point 169-178°C.

Example 3

4',21-bis-(Acetyloxy)-6α-fluoro-11β-hydroxy-16β-propyl-1',2',3',4'- tetrahydropregna-1,4-dieno]16α,17-b] naphthalene-3,20-dione

A. *21-(Acetyloxy)-5'-ethyl-6α-fluoro-4',5'-dihydro-11β-hydroxypregna-1, 4-dieno[17,16α-c] [3H]pyrazole-3,20-dione*

A solution of 21-(acetyloxy)-6α-fluoro-11β-hydroxypregna-1,4,16-triene-3,20-dione (748 mg, 2.0 mmol) in dichloromethane is stirred at room temperature and a solution of 1-diazopropane (6 mmol) in ether is added. Stirring is continued for about 3 hours, and excess diazopropane is then decomposed by the addition of the requisite amount of acetic acid. The solvent is evaporated yielding the title compound.

B. *21-(Acetyloxy)-6α-fluoro-11β-hydroxy-16-propylpregna-1,4,16-triene-3,20-dione*

21-(Acetyloxy-5'-ethyl-6α-fluoro-4',5'-dihydro-11β-hydroxy-pregna-1, 4-dieno[17,16α-c] [3*H*]pyrazole-3,20-dione (850 mg) is suspended in ethylene glycol (20 ml) and stirred in a bath at 175°C for 3 hours. The resulting solution is cooled, diluted with water, and extracted with chloroform. The chloroform extract is absorbed on a column of silica gel (30 g) and the column is eluted successively with chloroform-hexane and chloroform to yield the title compound.

C. *4',21-bis-(Acetyloxy)-6α-fluoro-11β-hydroxy-16β-propyl-1',2',3',4'- tetrahydropregna-1, 4-dieno[16α,17-b] naphthalene-3,20-dione*

A solution of 21-(acetyloxy)-6α-fluoro-11β-hydroxy-16-propylpregna-1,4,16-triene-3, 20-dione (2.0 mmol) in *o*-dichlorobenzene (30 ml) is heated with 1-acetyloxy-1, 2-dihydro-benzocyclobutene (6.0 mmol) in a bath at 170°C for 3 days. The resulting solution is cooled, diluted with chloroform-hexane and absorbed on a column of silica gel (50 g). The column is eluted successively with chloroform-hexane, chloroform, and chloroform-ethyl acetate to yield the title compound.

Example 4

21-(Acetyloxy)-11β-chloro-9-fluoro-16β-isopropyl-1',2',3',4'-tetrahydropregna-1, 4-dieno[16α, 17-b]naphthalene-3,20-dione

A. *21(Acetyloxy)-4',5'-dihydro-5',5'-dimethylpregna-1,4,9(11)-trieno [17,16α-c] [3H]pyrazole-3,20-dione*

A solution of 21-(acetyloxy)pregna-1,4,9(11),16-tetraene-3,20-dione (2.0 mmol) in dichloromethane is stirred at room temperature and a solution of 2-diazopropane (6 mmol) in ether is added. Stirring is continued for about 3 hours, and excess diazopropane is then decomposed by the addition of the requisite amount of acetic acid. The solvent is evaporated yielding the title compound.

B. *21-(Acetyloxy)-16-isopropylpregna-1,4,9(11),16-tetraene-3,20-dione*

21-(Acetyloxy)-4',5'-dihydro-5',5'-dimethylpregna-1,4,9(11)-trieno[17,16α-c] [3*H*]pyrazole-3,20-dione (2.0 mmol) is suspended in ethylene glycol (25 ml) and stirred in a bath at 175°C for about 3 hours. The resulting solution is cooled, diluted with water, and extracted with chloroform. The chloroform extract is absorbed on a column of silica gel (30 g) and the column is eluted successively with chloroform-hexane and chloroform to yield the title compound.

C. *21-(Acetyloxy)-16β-isopropyl-1',2',3',4'-tetrahydropregna-1,4,9(11)- trieno [16α,17-b]naphthalene-3,20-dione*

A solution of 21-(acetyloxy)-16-isopropylpregna-1,4,9(11),16-tetraene-3,20-dione (1.0 mmol) in 1,2-dihydro-benzocyclobutene (15 ml) is refluxed under a nitrogen atmosphere for 6 days. After cooling, the mixture is subjected to column chromatography on silica gel to isolate the title compound.

D. *21-(Acetyloxy)-11β-chloro-9-fluoro-16β-isopropyl-1',2',3',4'- tetrahydropregna-1, 4-dieno[16α,17-b]naphthalene-3,20-dione*

A suspension of 21-(acetyloxy)-16β-isopropyl-1,',2',3',4'- tetrahydropregna-1,4,9 (11)-trieno[16α,17-b]naphthalene-3,20-dione (2.0 mmol) and N-chloroacetamide (2.2 mmol) in dry dichloromethane (30 ml) is added over a 2-3 minute period with stirring to a mixture of anhydrous hydrogen fluoride (12 g) in dry tetrahydrofuran (20 ml) in a polyethylene bottle at -78°. After 1.0 hour of stirring, the mixture is maintained at 0°C for 1.0 hour and poured into an ice cold sodium bicarbonate solution. Extraction with dichloromethane followed by column chromatography on silica gel yields the title compound.

Examples 5-16

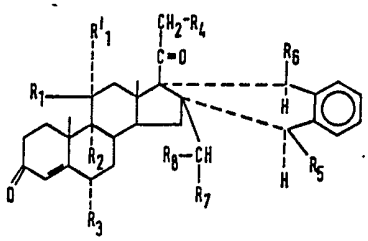
Following the procedure of Example 3, but substituting the steroid listed in column I for 21-(acetyloxy)- 6α-fluoro-11β-hydroxypregna-1,4,16-triene-3,20-dione, the compound listed in column II for 1-diazopropane, and the compound listed in column III for 1-acetyloxy-1, 2-dihydro-benzocyclobutene, yields the steroid listed in column IV.

Example	*Column I*	*Column II*	*Column III*	*Column V*
5	*21-(acetyloxy)-6α*,9-difluoro-11β-hydroxypregna-1,4,16-triene-3,20-dione	diazomethane	1-cyano-1,2-dihydro-benzocyclobutene	21-(acetyloxy)-6α,9-difluoro-11β-hydroxy-16β-methyl-3,20-dioxo-1′,2′,3′,4′-tetrahydro-pregna-1,4-dieno [16α,17-b]-naphthalene-4′β-carbonitrile
6	9-fluoro-11β-hydroxy-6α-methylpregna-1,4,16-triene-3,20-dione	diazomethane	1-carbomethoxy-1,2-dihydro-benzocyclo-butene	9-fluoro-1′,2′,3′,4′-tetrahydro-11β-hydroxy-6α,16β-dimethyl-3,20-dioxopregna-1,4-dieno [16α,17-b]naphthalen-4′β-carboxylic acid, methyl ester
7	21-(acetyloxy)-9-fluoro-11β-hydroxypregna-1,4,16-triene-3,20-dione	diazomethane	*trans*-1,2-diethoxy-1,2-dihydro-benzocyclo-butene	21-(acetyloxy)-1′β,4′β-di-ethoxy-9-fluoro-1′,2′,3′,4′-tetrahydro-11β-hydroxy-16β-methylpregna-1,4-dieno[16α,17-b]naphthalene-3,20-dione
8	21-(acetyloxy)-9-fluoro-11β-hydroxy-pregna-1,4,16-triene-3,20-dione	1-diazobutane	1-carbomethoxy-1,2-dihydro-benzocyclobutene	21-(acetyloxy)-16β-butyl-9-fluoro-1′,2′,3′,4′-tetrahydro-11β-hydroxy-3,20-dioxopregna-1,4-dieno[16α,17-b]naphthalene-4′β-carboxylic acid, methyl ester
9	21-(acetyloxy)-9-fluoro-11β-hydroxy-pregna-1,4,16-triene-3,20-dione	1-diazohexane	*trans*-1,2-dicarbometh-oxy-1,2-dihydro-benzocyclo-butene	21-(acetyloxy)-9-fluoro-16β-hexyl-1′,2′,3′,4′-tetrahydro-11β-hydroxy-3,20-dioxopregna-1,4-dieno[16α,17-b]naphtha-lene-1′β,4′β-dicarboxylic acid, dimethyl ester

Example	*Column I*	*Column II*	*Column III*	*Column IV*
10	21-(acetyloxy)-9-fluoro-11β-hydroxy-pregna-1,4,16-triene-3,20-dione	diazomethane	*trans*-1,2-dibromo-1,2-dihydro-benzocyclobutene	21-(acetylocy)-1′β,4′β-dibromo-9-fluoro-1′,2′,3′,4′-tetrahydro-11β-hydroxy-16β-methylpregna-1,4-dieno[16α,17-b]naphthalene-3,20-dione
11	21-(acetyloxy)-9-fluoro-11β-hydroxy-pregna-1,4-16-triene-3,20-dione	diazoethane	1-acetyl-1,2-dihydro-benzocyclobutene	21-(acetyloxy)-4′β-acetyl-16β-ethyl-9-fluoro-1′,2′ 3′,4′-tetrahydro-11β-hydroxy-pregna-1,4-dieno[16α,17-b]-naphthalene-3,20-dione
12	21-(acetyloxy)-9-fluoro-11β-hydroxy-pregna-1,4,16-triene-3,20-dione	diazomethane	1-bromo-1,2-dihydro-benzocyclobutene	21-(acetyloxy)-4′β-bromo-9-fluoro-1′,2′,3′,4′-tetra-hydro-11β-hydroxy-16β-methyl-pregna-1,4-dieno[16α,17-b]-naphthalene-3,20-dione
13	21-(acetyloxy)-6α-methylpregna-1,4,16-triene-3,11,20-trione	diazomethane	1-formyl-1,2-dihydro-benzocyclobutene	21-(acetyloxy)-4′β-formyl-1′,2′,3′,4′-tetrahydro-6α,16β-dimethylpregna-1,4-dieno[16α,17-b]naphthalene-3,11,20-trione
14	21-chloro-11β-hydroxypregna-4,16-diene-3,20-dione	diazomethane	1-phenyl-1,2-dihydro-benzocyclobutene	21-chloro-1′,2′,3′,4′-tetra-hydro-11β-hydroxy-16β-methyl-4′β-phenylpregn-4-eno[16α,17-b]-naphthalene-3,20-dione
15	21-(benzoyloxy)-11β-hydroxypregna-1,4,16-triene-3,20-dione	diazomethane	1-ethyl-1,2-dihydro-benzocyclobutene	21-(benzoyloxy)-4′β-ethyl-1′,2′,3′,4′-tetrahydro-11β-hydroxy-16β-methylpregna-1,4-dieno[16α,17-b]naphthalene-3,20-dione
16	*21-chloro-11*β-hydroxypregna-4,16-diene-3,20-dione	diazomethane	1,2-dihydro-benzo-cyclobuten-1-ol	21-chloro-1′,2′,3′,4′-tetra-hydro-4′β,11β-dihydroxy-16β-methylpregn-4-eno[16α,17-b]-naphthalene-3,20-dione

WHAT WE CLAIM IS:-

1. A steroid having the formula



or a 1,2-dehydro derivative thereof, wherein R_1 is chlorine, fluorine or hydroxy and R'_1 is hydrogen, or R_1 and R'_1 together are $=O$; R_2 is hydrogen or halogen; R_3 is hydrogen, methyl or fluorine; R_4 is hydrogen, hydroxy, alkyl-$\overset{O}{\overset{\|}{C}}$-O-, aryl-$\overset{O}{\overset{\|}{C}}$-O- or halogen; R_5 and R_6 are the same or different and are hydrogen, alkyl, alkoxy, alkoxycarbonyl, formyl, alkyl-$\overset{O}{\overset{\|}{C}}$-, alkyl-$\overset{O}{\overset{\|}{C}}$-O-, hydroxy, halogen, phenyl or cyano, with the proviso that when R_5 and R_6 are different, R_5 is hydrogen; and R_7 and R_8 are the same or different and are hydrogen or alkyl.

2. A steroid in accordance with claim 1 wherein R_7 and R_8 are hydrogen.

3. A steroid in accordance with claim 1 or 2 wherein R_1 is hydroxy and R'_1 is hydrogen.

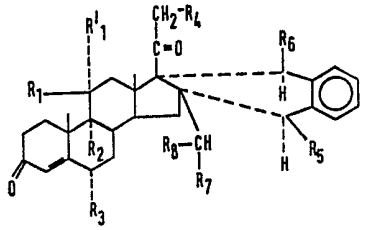
4. A steroid in accordance with claim 1, 2 or 3 wherein R_3 is hydrogen.

5. A steroid in accordance with claim 1, 2, 3 or 4 wherein R_2 is fluorine.

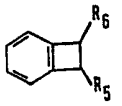
6. 9-Fluoro-1′,2′,3′,4′-tetrahydro-11β,21-dihydroxy-16β-methylpregna-1,4-dieno[16α,17-b]naphthalene-3,20-dione.

7. 21-(Acetyloxy)-9-fluoro-1′,2′,3′,4′-tetrahydro-11β-hydroxy-16β-methylpregna-1,4-dieno[16α,17-b]naphthalene-3,20-dione.

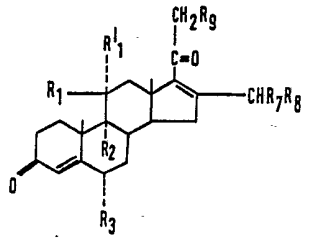
8. A process for the preparation of a steroid having the formula



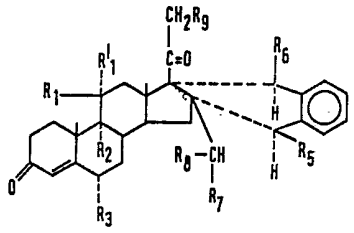
or a 1,2-dehydro derivative thereof, wherein R_1 is chlorine, fluorine or hydroxy and R'_1 is hydrogen, or R_1 and R'_1 together are $=O$; R_2 is hydrogen or halogen; R_3 is hydrogen, methyl or fluorine; R_4 is hydrogen, hydroxy, alkyl-$\overset{O}{\overset{\|}{C}}$-O-, aryl-$\overset{O}{\overset{\|}{C}}$-O- or halogen; R_5 and R_6 are the same or different and are hydrogen, alkyl, alkoxy, alkoxycarbonyl formyl, alkyl-$\overset{O}{\overset{\|}{C}}$-, alkyl-$\overset{O}{\overset{\|}{C}}$-O-, hydroxy, halogen, phenyl or cyano, with the proviso that when R_5 and R_6 are different, R_5 is hydrogen; and R_7 and R_8 are the same or different and are hydrogen or alkyl, which comprises reacting a compound of the formula



with a steroid having the formula



or a 1,2-dehydro derivative thereof, wherein R_9 is hydrogen, alkyl-C(=O)-O-, aryl-C(=O)-O- or halogen, to yield a steroid product having the formula



or a 1,2-dehydro derivtive thereof, and optionally, subjecting a 21-acyloxy steroid product prepared as above to hydrolysis to yield a corresponding 21-hydroxy steroid product (R_4 is hydroxy), and optionally, converting such 21-hydroxy steroid product to a 21-halo steroid product (R_4 is hlaogen), and optionally using an 11β,21 bis (acyloxy) derivative and conversion to a corresponding di-hydroxy derivative.

9. A steroid as claimed in claim 1, substantially as herein described or given in any one of the Examples 3 to 16.

10. A process as claimed in claim 8, substantially as herein described or given in the Examples.

11. A steroid as claimed in any of claims 1 to 7 and 9 when prepared using a process as claimed in claim 8 or claim 10.

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