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GB 1095665
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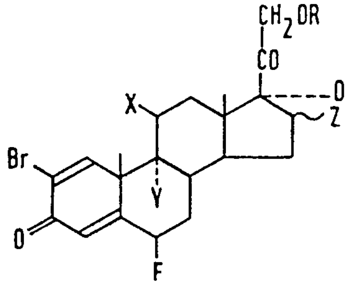
(54) Anti inflammatory 2-bromo-6β-fluoro-9α-halo steroids of the pregna-1,4-dien-3-one series

(57) A process for the preparation of the title compounds, which are of general formula:



(I)

in which:
X is an oxo group, a β-hydroxyl group or a chlorine atom;
Y is a fluorine or a chlorine atom but is not fluorine when X is a β-chlorine atom;
Z is a hydrogen atom or an α-hydroxyl or α- or β-methyl group;
R′ is a hydrogen atom or an alkanoyl group having from 2 to 8 carbon atoms; and when Z is α-hydroxyl and R′ is hydrogen, the corresponding 16α, 17α-acetonides and 16α-alkanoyl derivatives, the alkanoyl radical having from 2 to 8 carbon atoms; and
R is hydrogen or the acyl radical of a mono- or di-carboxylic organic acid having from 2 to 8 carbon atoms, of metasulfobenzoic acid or of phosphoric acid, comprises the bromination of the corresponding 2-unsubstituted-$\Delta^{1,4}$-dienes (wherein R is C_{2-8} acyl) dissolved or suspended in a suitable solvent by reaction with excess of bromine in the cold, to give the corresponding 1,2-dibromo-derivative, which is then reacted with a basic agent to give the desired product (I) which is isolated and purified in known manner, and subjected to ester hydrolysis and re-esterification when required.

Claimed *per se* are the anti inflammatory 17,21-dipropionate, 17-propionate-21-acetate, and 17-propionate-21-valerate of 2-bromo-6β, 9α-difluoroprednisolone.

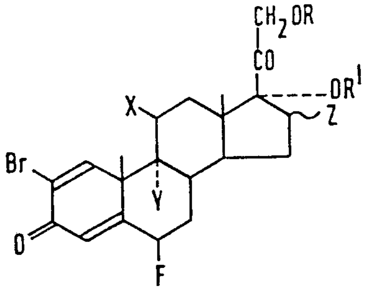
The chemical formulae appearing in the printed specification were submitted in formal form after the date of filing.

SPECIFICATION

Process for the preparation of 2-bromo-6β-fluoro-3-keto-$\Delta^{1,4}$-steroids of the pregnane series and products obtained thereby.

The present invention relates to a process for the preparation of steroid derivatives of the pregnane series and to products obtained thereby.

More particularly, the present invention relates to a process for the preparation of 2-bromo-6β-fluoro-3-keto-$\Delta^{1,4}$-steroids of the pregnane series of the general structural formula:



(1)

in which:

X is a keto- or a β-hydroxyl-group or a chlorine atom;

Y is a fluorine or a chlorine atom, but is not fluorine when X is a β-chlorine atom;

Z is a hydrogen atom, or an α-hydroxyl- or α- or β-methyl-group;

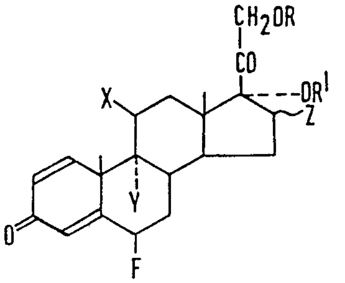
R′ is a hydrogen atom or an alkanyl group having from 2 to 8 carbon atoms; and when Z is α-hydroxyl and R′ is hydrogen, the corresponding 16α, 17α-acetonides and 16α-alkanoyl-derivatives, the alkanoyl group having from 2 to 8 carbon atoms; and

R is hydrogen or the alkanoyl radical of a mono- or di-carboxyl organic acid having from 2 to 8 carbon atoms, of metasulfobenzoic acid or of phosphoric acid.

The compounds of formula I which possess valuable pharmacological properties particularly anti-inflammatory and anti-rheumatoid arthritic activity are described and claimed in my U.K. Patent No. 1504132, No. 1504133 and No. 1504134.

I have now surprisingly found that the compounds of formula I can be prepared in a more simple and advantageous manner in comparison with the process described and claimed in my above mentioned U.K. patents.

This new process, the object of the present invention, which will be illustrated in detail hereinafter, comprises the bromination of a compound of the formula:

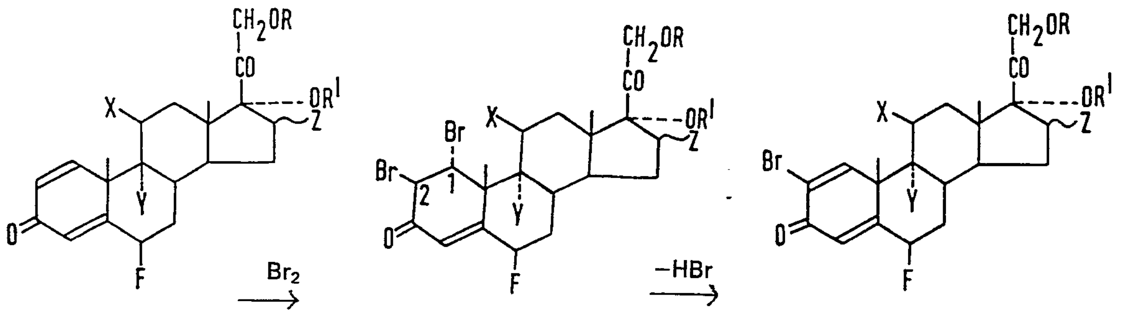


(A)

in which X, Y, Z, have the same significance as in formula I above, R is an alkanoyl group having from 2 to 8 carbon atoms, and R′ is hydrogen or an alkanoyl group having from 2 to 8 carbon atoms, and when Z is α-hydroxyl and R′ is hydrogen, the corresponding 16α-17α-acetonides and 16α-alkanoyl-derivatives, the alkanoyl group having from 2 to 8 carbon atoms.

The compounds of formula A, starting materials for the new process of the present invention, are described in detail and claimed in my U.K. Patent Nos. 1504294 and 1504295.

The process of the present invention may be represented by the following reaction scheme:



(A) (1′) (1)

A compound of formula A, dissolved or suspended in a suitable solvent, such as dioxantetrahydrofuran or dimethylsulfoxide, is reacted with an excess of bromine in the cold, preferably at room temperature, to give the corresponding 1,2-dibromo-derivative (1′). This intermediate may be isolated as such, but it is preferred to convert it directly into the desired end product (1).

This conversion can be achieved by splitting off hydrogen bromide by means of a suitable basic agent such as an organic tertiary base, for instance pyridine, lutidine or collidine, or an inorganic base such as sodium or potassium acetate, and by operating generally at room temperature. After the reaction is completed, the mixture is poured into ice-cooled water and the desired crude product can be recovered by filtration, washing with water and drying at 40°C "in vacuo" to a constant weight.

Alternatively, the crude product can be extracted from the aqueous mixture with a water-immiscible solvent such as chloroform. The combined chloroform extracts are washed with water, dried over anhydrous sodium sulfate and evaporated "in vacuo" to dryness to a constant weight.

On crystallization of the crude product from a suitable solvent, or from a mixture of solvents, the desired pure compound (I) is obtained.

If desired, the alkanoyl, group R of the compound (I), thus obtained can be converted via the corresponding 21-free-hydroxy-derivative into another alkanoyl group deriving from a mono or di-carboxylic acid having from 2 to 8 carbon atoms of metasulfobenzoic or of phosphoric acid, by a method well known to those skilled in the art.

Alkali and alkaline earth metal salts of these compounds when the alkanoyl group is derived from a polybasic organic acid, such as succinic acid, tartaric acid, citric acid, metasulfobenzoic acid, or an inorganic acid, such as phosphoric acid, are also included within the scope of the present invention.

Preferred carboxylic acids which esterify the hydroxyl group in the 21-position are: acetic, propionic, butyric, isobutyric, valeric, trimethyl-acetic, succinic, tartaric, citric, maleic, glutaric, pimelic, aminoacetic, cyclopentylpropionic, benzoic, phenylacetic, nicotinic and isonicotinic acid.

Preferred carboxylic acids which esterify the hydroxyl group in the 17-position are: acetic, propionic, butyric, isobutyric, valeric, cyclopentylpropionic, benzoic and phenylacetic.

The preparation of the 17-monoesters of 17α, 21-dihydroxy-2-bromo-6β-fluoro-3,20-diketo-1, 4-pregnadienes of formula (I) in which R=R′=hydrogen with one of the above mentioned acids may be carried out according to methods already known from the literature, for instance through the corresponding cyclic 17, 21-ortho-esters which, on acidic hydrolysis, give the desired 17-mono-esters (British Patent Nos. 996,079 and 996,080). The 17-monoesters thus obtained, having a free hydroxyl group in the 21-position, can be converted according to methods known per se, into the corresponding 17,21-diesters, having the alkanoyl radical in the 21-position equal to or different from that in the 17-position.

Also following within the scope of the present invention are a few 17, 21-di-esters of formula (I) wherein the radicals R and R′ are equal or different. Such compounds comprise:

1. 2-Bromo-6β,9α-difluoro-1,4-pregnadiene-11β,17α,21-triol-3,20-dione-17,21-dipropionate.
2. 2-Bromo-6β,9α-difluoro-1,4-pregnadiene-11β,17α,21-triol-3,20-dione-17-propionate-21-acetate.
3. 2-Bromo-6β,9α-difluoro-1,4-pregnadiene-11β,17α,21-triol-3,20-dione-17-propionate-21-valerate.

The present invention also comprises a pharmaceutical composition comprising one or more of the above three specific compounds in admixture with a suitable carrier for local or parenteral administration.

The following examples illustrate methods of carrying out the present invention, but it is to be understood that these Examples are given for the purpose of illustration and not of limitation.

EXAMPLE 1

2-Bromo-6β,9α-difluoro-1,4-pregnadiene-11β,17α,21-triol 3, 20-dione-17,21-diacetate (Compound 1, R = R′ = -acetyl; X = -OH; Y = F).

15 g of 6β,9α-difluoro-prednisolone-17α,21-diacetate, prepared according to Example 9 of my British

Patent No. 1,504,294 is suspended in 900 ml of peroxides-free dioxan. 31.9 g (10 ml) of bromine was added dropwise to this suspension at 20°C over a period of 30 minutes with stirring. The reaction mixture was kept at 20°C with stirring for a further 48 hours. Then 100 ml of pyridine was added to the reaction mixture which was kept overnight with stirring at 20°C.

The dark-coloured resultant mass was slowly poured into 5 litres of ice-cooled water with stirring. After 3 hours the precipitate was collected by filtration, washed with water and dried at 40°C "in vacuo" to a constant weight.

Yield = ~16.2 g of crude title product.

Upon crystallization from acetone-hexane, 14.3 g of pure 2-bromo-6β, 9α-difluoro-1,4-pregnadiene-11β, 17α, 21-triol-3,20-dione-17,21-diacetate was obtained showing the following characteristics:

UV - Spectrum λ_{max}^{MeOH} = 246 mμ; $E_{1cm}^{1\%}$ = 240
IR - Spectrum (Nujol): 3500-1760-1730-1700-1650-1615-1240 cm^{-1}
$[\alpha]_D$ = -46° (c = 0.5, dioxan)
M.P. 312-315°C Molecular weight 559.5

	$C_{25}H_{29}BrF_2O_7$		
Analysis Calculated for	C	53.68%	H 5.22%
	Br	14.29%	F 6.8 %
Found	C	53.65%	H 5.13%
	Br	14.0 %	F 6.65%

The N.M.R. analysis confirmes the presence of 2-bromo-3-keto-$\Delta^{1,4}$, and the epimeric β-configuration of the 6-fluoro-substituent.

δ (Me_2SO)	0.87	(3H, s, 18 CH_3)
	1.55	(3H, d, 18 CH_3)
	1.97	(3H, s, CH_3COO-)
	2.06	(3H, s, CH_3COO-)
	4.77	(2H, s, -CO-CH_2-O-CO)
	6.47	(1H, d, =C (4) - H)
	7.84	(1H, s, =C (1) - H) p.p.m.

Analogous results can be achieved when, instead of pyridine, the intermediate product formed after bromination is shaken with an aqueous solution of sodium acetate.

EXAMPLE 2

2-Bromo-6β, 9α-difluoro-1,4-pregnadiene-11β, 16α, 17α, 21-tetrol-3,20-dione-21-acetate 16,17-acetonide

To a suspension of 10 g of 6 β, 9α-difluoro-16α-hydroxy-prednisolone-16,17-acetonide-21-acetate (prepared according to Example 17 of my British Patent No. 1,504,294 in 500 ml of tetrahydrofuran, 21.25 g of bromine is added dropwise at 20°C over a period of 15 minutes with stirring. The reaction mixture was kept at 20°C with stirring for a further 36 hours. Then 70 ml of lutidine was added to the reaction mixture which was kept at room temperature overnight with stirring, and then it was slowly poured into 4 liters of ice-cooled water with stirring.

After 4 hours the precipitate was filtered, washed with water and dried at 40°C "in vacuo" to a constant weight.

Yield = 9.6 g of crude title compound.

Upon crystallization from acetone-ethyl ether, 8.3 g of pure 2-bromo-6β, 9α-difluoro-1,4-pregnadiene-11β,16α,17α, 21-tetrol-3,20-dione-21-acetate-16, 17-acetonide was obtained, and having the following characteristics:

UV Spectrum λ_{max}^{MeOH} = 245 mμ: $E_{1cm}^{1\%}$ = 221
IR Spectrum (Nujol): 3500-1760-1730-1670-1640-1610-1235 cm^{-1}.
$[\alpha]_D$ = +0.2 (c=1, dioxan)
M.P. = 148 - 151°C

Analogous results can be achieved when, instead of pyridine, the intermediate formed after bromination is shaken with an aqueous solution of potassium acetate.

EXAMPLE 3

2-Bromo-6β-fluoro-9α, 11β-dichloro-1,4-pregnadiene-17α,21-diol-3,20-dione-17, 21-diacetate.

20 grams of 6β-fluoro-9α, 11β-dichloro-1,4-pregnadiene-17α, 21-diol-3,20-dione-17,21-diacetate, prepared according to Example 18 of my British Patent No. 1,504,294 was suspended in 1000 ml of peroxides-free dioxan. 42.5 g (13.3 ml) of bromine was added dropwise to this suspension at 20°C over a period of 30 minutes with stirring.

The reaction mixture was kept at 20° with stirring for a further 48 hours. Then 133 ml of pyridine was added to the reaction mixture which was kept overnight with stirring at 20°C and then it was slowly poured into 6.7 litres of ice-cooled water with stirring.

After 4 hours the precipitate was collected by filtration, washed with water and dried at 40°C "in vacuo" to a constant weight.

Yield = ~21.6 g of crude title compound.

Upon crystallization of the crude product from aqueous acetone, 15.8 g of pure 2-bromo-6β-fluoro-9α, 11β-dichloro-1,4-pregnadiene-17α, 21-diol-3,20-dione-17, 21-diacetate was obtained, and having the following characteristics:

UV - Spectrum λ_{max}^{MeOH} = 244 mμ: $E_{1cm}^{1\%}$ = 215
IR - Spectrum (Nujol): 1760-1745-1675-1650-1610-1230 cm^{-1}
$[\alpha]_D$ = +0.2° (c=1, dioxan)
M.P. = 268 - 272°C.

EXAMPLE 4

2-Bromo-6β-fluoro-9α,11β-dichloro-16α-methyl-1, 4-pregnadiene-17α, 21-diol-3,20-dione-17, 21-diacetate

By starting from 6β -fluoro-9α, 11β-dichloro-16α-methyl-1,4-pregnadiene-17α, 21-diol-3,20-dione-17, 21-diacetate prepared according to Example 19 of my British Patent No. 1,504,294 and by operating as indicated in Example 3, the title compound was prepared having the following characteristics:

UV - Spectrum λ_{max}^{MeOH} = 244 mμ: $E_{1cm}^{1\%}$ = 196
IR - Spectrum (Nujol): 1735-1605-1570-1235 cm^{-1}.
M.P. = 242 - 246°C.

EXAMPLE 5

2-bromo-6β,9α-difluoro-16α-methyl-predisolone-21-pivalate

By starting from 6β, 9α-difluoro-16α-methyl-prednisolone prepared according to Example 11 of my British Patent No. 1,504,294 and by operating as indicated in the previous Examples, the title compound was prepared.

EXAMPLE 6

2-Bromo-6β,9α-difluoro-1,4-pregnadiene-11β, 17α, 21-triol-3,20-dione

A 10% aqueous solution of potassium carbonate was added dropwise with stirring to a solution of 2 g of 2-bromo-6β, 9α-difluoro-1,4-pregnadiene-11β, 17α, 21-triol-3, 20-dione-17, 21-diacetate in 20 ml of methanol at 0°C under nitrogen. After 1 hour, the reaction mixture was neutralized with acetic acid, concentrated "in vacuo" to a small volume. The crude title product was collected by filtration, washed with water and dried "in vacuo" at 40°C to a constant weight. On crystallization from aqueous acetone, the pure product was obtained having the following characteristics:

UV - Spectrum λ_{max}^{MeOH} = 246 mμ; $E_{1cm}^{1\%}$ = 251
IR - Spectrum (Nujol): 3420-1720-1665-1640-1600-1245 cm^{-1}.
M.P. = 225 - 228°C
$[\alpha]_D$ = -5.0° (c = 1, dioxan).

EXAMPLE 7

2-Bromo-6β-fluoro-9α,11β-dichloro-1,4-pregnadiene-17α,21-diol-3, 20-dione

By operating as described in Example 6, and by employing 2-bromo-6β-fluoro-9α, 11β-dichloro-1,4-pregnadiene-17α, 21-diol-3,20-dione-17, 21-diacetate as starting material, obtained according to Example 3, the title compound was obtained having the following characteristics:

UV - Spectrum λ_{max}^{MeOH} = 245 mμ; $E_{1cm}^{1\%}$ = 235
IR - Spectrum (Nujol): 3500-1715-1675-1645-1605 cm^{-1}
$[\alpha]_D$ = +35° (c=0.5, dioxan).

EXAMPLE 8

2-Bromo-6β-fluoro-9α, 11β-dichloro-16α-methyl-1,4-pregnadiene-17α, 21-diol-3, 20-dione

By operating as described in the previous Examples 6 and 7, and by employing 2-bromo-6β-fluoro-9α,11β-dichloro-16α-methyl-1,4-pregnadiene-17α, 21-diol-3, 20-dione-17, 21-diacetate as starting material obtained according to Example 4, the title compound was prepared, showing the following characteristics:

UV - Spectrum λ_{max}^{MeOH} = 244 mμ; $E_{1cm}^{1\%}$ = 182
IV - Spectrum (Nujol): 3640-3500-3400-1705-1665-1642-1605 cm^{-1}
$[\alpha]_D$ = +21° (c=0.5, dioxan).

EXAMPLE 9

By operating as described in the previous Examples, the 16β-methyl-derivatives may also be obtained.

EXAMPLE 10

2-Bromo-6β, 9α-difluoro-1,4-pregnadiene-11β, 17α, 21-triol-3, 20-dione-17-propionate

A) *2-Bromo-6β, 9α-difluoro-1,4-pregnadiene-11β, 17α, 21-triol-3, 20-dione-17, 21-cyclic orthopropionate:*

To a suspension of 5 g- of 2-bromo-6β, 9α-difluoro-1,4-pregnadiane-11β, 17α, 21-triol-3, 20-dione (prepared according to Example 6) in 100 ml of ethyl acetate, gently warmed to 40°C there was added 6 g of methyl orthopropionate and 0.3 g of p-toluensulfonic- acid monohydrate, with stirring. After a few minutes a complete solution was obtained. The reaction mixture was stirred and kept under nitrogen for about one hour. Completion of the desired conversion into cyclic 17α, 21-orthopropionate was checked at T.L.C.

After cooling, the reaction mixture was neutralized with about 1 ml of pyridine and evaporated "in vacuo" to dryness.

B) *2-Bromo-6β, 9α-difluoro-1,4-pregnadiene-11β, 17α, 21-triol-3,20-dione-17-propionate*

The oily residue obtained in A) was dissolved in 30 ml of methanol and to this solution 0,5 ml of diluted aqueous sulfuric acid (3% by weight) was added. The reaction mixture was refluxed for 30 minutes, filtered in the warm and left overnight in a refrigerator to crystallize.

The crystalline product was collected by filtration, washed with little ice-cooled methanol and dried "in vacuo". Yield about 3,75 g of product undertitle B) having the following characteristics:

UV - Spectrum $\lambda_{max}^{MeOH} = 246$ mμ; $E_{1cm}^{1\%} = 231$
IR - Spectrum (Nujol): 3410-3320-1680-1660-1630-1620-1565-1220 cm^{-1}.
$[\alpha]_D = -74.8$ (c=1, dioxan).

EXAMPLE 11

2-Bromo-6β, 9α-difluoro-1,4-pregnadiene-11β, 17α, 21-triol-3, 20-dione-17-valerate

A) *2-Bromo-6β, 9α-difluoro-1,4-pregnadiene-11β, 17α, 21-triol-3, 20-dione-17, 21-cyclic orthovalerate*

To a solution of 5 g of 2-bromo-6β, 9α-difluoro-1,4-pregnadiene-11β, 17α, 21-triol-3, 20-dione in 20 ml of anhydrous dimethylformamide, there was added 6 ml of methylorthovalerate, 0.2 g of p-toluensulfonic acid. The reaction mixutre was stirred and kept under nitrogen at 120°C for about 3 hours. After cooling, the reaction mixture was neutralized with about 1 ml of pyridine and was poured in 100 ml of ice-cooled water. The precipitate was collected by filtration, washed with water and dried in vacuo to constant weight.

B) *2-Bromo-6β, 9α-difluoro-1,4-pregnadiene-11β, 17α, 21-triol-3, 20-dione-17-valerate*

The crude product obtained in A) was dissolved in 30 ml of methanol and to this solution 0.6 ml of diluted aqueous- sulfuric acid (3% by weight) was added. The reaction mixture was refluxed for 40 minutes and then poured in 100 ml of ice-cooled water and it was kept overnight at room temperature. The precipitate was collected by filtration, washed with water and dried "in vacuo" to a constant weight. The crude product was recrystallized from acetone-hexane. Yield = ~3g of pure product, having the following characteristics;

UV - Spectrum $\lambda_{max}^{MeOH} = 246$ mμ; $E_{1cm}^{1\%} = 225$
IR - Spectrum (Nujol) 3500-1725-1718-1668-1645-1580 cm^{-1}
$[\alpha]_D = -73.8°$ (c=1, dioxan).

EXAMPLE 12

By operation as described in Examples 10 and 11 and by suitably varying the methyl orthoester and the "steroid-17α, 21-diol" the following compounds were prepared:

2-bromo-6β, 9α-difluoro-1,4-pregnadiene-11β, 17α, 21-triol-3, 20-dione-17-butyrate;
2-bromo-6β, 9α-difluoro-1,4-pregnadiene-11β, 17α, 21-triol-3,20-dione-17-benzoate;

EXAMPLE 13

2-Bromo-6β,9α-difluoro-1,4-pregnadiene-11β, 17α, 21-triol-3, 20-dione-21-propionate

1 g of 2-Bromo-6β, 9α-difluoro-1,4-pregnadiene-11β, 17α, 21-triol-3,20-dione (prepared according to Example 6) was dissolved in 10 ml of anhydrous pyridine. To this solution 6 ml of propionic anhydride was added and the reaction mixture was kept overnight at room temperature, and then poured in about 400 ml of -ice-cooled water. The crude product was collected by filtration, washed with water and dried at 40°C "in vacuo" to a constant weight.

By recrystallization of the crude product from acetone-hexane, 0.80 g of pure product was obtained, showing the following characteristics:

UV - Spectrum $\lambda_{max}^{MeOH} = 246$ mμ; $D_{1cm}^{1\%} = 218$
IV - Spectrum (Nujol): 3640-3470-1720-1680-1665-1640-1600-1205 cm^{-1}
$[\alpha]_D = + 20.9$ (c=1, dioxan).

EXAMPLE 14

2-Bromo-6β,9α-difluoro-1, 4-pregnadiene-11β, 17α, 21-triol-3, 20-dione-17, 21-dipropionate

By operating as described in Example 13, 2-bromo-6β, 9α-difluoro-1,4-pregnadiene-11β, 17α, 21-triol-3, 20-dione-17-propionate when reacted with propionic anhydride was converted to 2-bromo-6β, 9α-difluoro-1,4-pregnadiene-11β, 17α, 21-triol-3, 20-dione-17, 21-dipropionate having the following characteristics:

UV - Spectrum λ_{max}^{MeOH} = 246 mμ; $E_{1cm}^{1\%}$ = 207
IR - Spectrum (Nujol): 3500-1735-1675-1650-1610-1200 cm^{-1}
$[\alpha]_D$ = 37.3° (c=1, dioxan).

EXAMPLE 15

2-Bromo-6β, 9α-difluoro-1,4-pregnadiene-11β, 17α, 21-triol-3, 20-dione-17-propionate-21-acetate

By operating as described in Example 13, 2-bromo-6β, 9α-difluoro-1,4-pregnadiene-11β, 17α, 21-triol-3, 20-dione-17-propionate when reacted with acetic anhydride was converted to 2-bromo-6β, 9α-difluoro-1,4-pregnadiene-11β, 17α, 21-triol-3, 20-dione-17-propionate-21-acetate having the following characteristics:

UV - Spectrum λ_{max}^{MeOH} = 246 mμ; $E_{1cm}^{1\%}$ = 215
IR - Spectrum (Nujol): 3500-1750-1740-1715-1675-1600-1245 cm^{-1}.
$[\alpha]_D$ = -43.6° (c=1, dioxan).

EXAMPLE 16

2-Bromo-6β, 9α-difluoro-1, 4-pregnadiene-11β, 17α, 21-triol-3, 20-dione-17-propionate-21-valerate

By operating as described in Example 13, 2-bromo-6β, 9α-difluoro-1, 4-pregnadiene-11β, 17α, 21-triol-3, 20-dione-17-propionate when reacted with valeric anhydride was converted to 2-bromo-6β, 9α-difluoro-1,4-pregnadiene-11β, 17α, 21-triol-3, 20-dione-17-propionate-21-valerate, having the following characteristics:

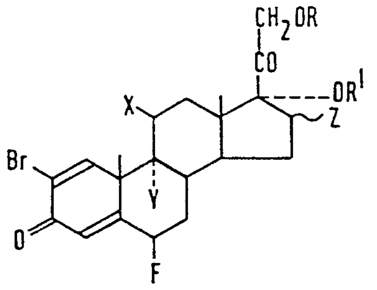
UV - Spectrum λ_{max}^{MeOH} = 246 mμ; $E_{1cm}^{1\%}$ = 199
IR - Spectrum (Nujol): 3470-1755-1730-1720-1670-1645-1610-1215 cm^{-1}.
$[\alpha]_D$ = -35° (c=1, dioxan).

EXAMPLE 17

By esterification of the products obtained according to Examples 10, 11 and 12 with a suitable anhydride there were obtained the corresponding diesters or "hetero-diesters", i.e. the 17, 21-diesters having the alkanoyl radicals in the 17- and 21-positions either the same or different.

CLAIMS

1. A process for the preparation of a 2-bromp-6β-fluoro-3-keto-$\Delta^{1,4}$-steroid of the pregnane series of the general structural formula:



(I)

in which:

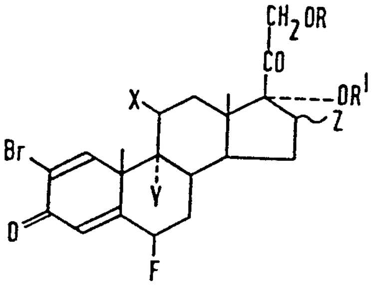
X is a keto-or a β-hydroxyl group or a chlorine atom;

Y is a fluorine or a chlorine atom but is not fluorine when X is a β-chlorine atom;

Z is a hydrogen atom or an α-hydroxyl or α- aor β- methyl group;

R' is a hydrogen atom or an alkanoyl group having from 2 to 8 carbon atoms; and when Z is α-hydroxyl and R' is hydrogen, the corresponding 16α, 17α-acetonides and 16α-alkanoyl derivatives, the alkanoyl radical having from 2 to 8 carbon atoms; and

R is hydrogen or the alkanoyl radical of a mono- or di-carboxyl organic acid having from 2 to 8 carbon atoms, of metasulfobenzoic acid or of phosphoric acid, comprising the bromination of a compound of the general structural formula:



in which X, Y, Z and R′ have the same significance as above and R is an alkanoyl group having from 2 to 8 carbon atoms wherein such compound dissolved or suspended in a suitable solvent is reacted with an excess or bromine in the cold, to give the corresponding 1, 2-dibromo-derivative, which is then reacted with a suitable basic agent to give the desired product (I) which is isolated and purified in manner known "per se".

2. A process as claimed in claim 1, in which the solvent is dioxan, tetrahydrofuran or dimethylsulfoxide.

3. A process as claimed in claim 1 or 2, in which the reaction with excess bromine is carried out at room temperature.

4. A process as claimed in any preceding claim, in which the basic agent is an organic tertiary base or an inorganic base.

5. A process as claimed in claim 4, in which the organic tertiary base is pyridine, lutidine or collidine.

6. A process as claimed in claim 4, in which the inorganic base is sodium or potassium acetate.

7. A process as claimed in any preceding claim, substantially as hereinbefore described and exemplified.

8. A 2-bromo-6β-fluoro-3-keto-$\Delta^{1,4}$-steroid of the pregnane series of the general formula (I), whenever prepared by a method as claimed in any one of claims 1 to 7.

9. 2-bromo-6β, 9α-difluoro-1,4-pregnadiene-11β, 17α, 21-triol-3, 20-dione-17, 21-dipropionate.

10. 2-bromo-6β, 9α-difluoro-1,4-pregnadiene-11β, 17α, 21-triol-3, 20-dione-17-propionate-21-acetate.

11. 2-bromo-6β, 9α-difluoro-1,4-pregnadiene-11β, 17α, 21-triol-3, 20-dione-17-propionate-21-valerate.

12. A pharmaceutical composition having anti-inflammatory activity comprising one or more compounds of claims 9, 10 or 11 in admixture with a suitable carrier for local or parenteral administration.

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