

L141628



PATENT SPECIFICATION

NO DRAWINGS

L141.628

Date of Application and filing Complete Specification: 9 June, 1967.

No. 26765/67.

Application made in Switzerland (No. 8466) on 10 June, 1966.

Complete Specification Published: 29 Jan., 1969.

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Index at acceptance:—C2 U(2, 4A1, 4A2, 4C1, 4C5, 4D, 4X)

Int. Cl.:—C 07 c 169/26

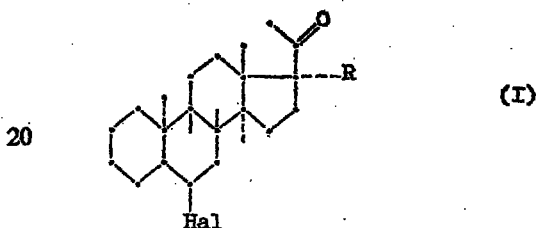
COMPLETE SPECIFICATION

Novel 6-Halo-9 β ,10 α -Steroids and a process for the manufacture thereof

We, F. HOFFMANN-LA ROCHE & Co., AKTIENGESELLSCHAFT, a Swiss Company of 124—184, Grenzacherstrasse, Basle, 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:—

The present invention is concerned with novel 6-halo-9 β ,10 α -steroids and a process for the manufacture thereof.

The novel 6-halo-9 β ,10 α -steroids provided by the present invention are 3-keto-4-dehydro, 3-keto-4,6-bisdehydro, 3-keto-1,4-bisdehydro, 3-keto-1,4,6-trisdehydro, 3-acyloxy-3,5-bisdehydro, 3-(alkoxy, cycloalkyloxy or aralkoxy)-3,5-bisdehydro and 3-acyloxy-2,4,6-trisdehydro derivatives of compounds of the general formula



wherein R represents a lower-alkyl group and Hal stands for a fluorine, chlorine or bromine atom which can have an α - or β -configuration in the case of the 3-keto-4-dehydro and 3-keto-1,4-bisdehydro derivatives. They possess hormonal activity. As compared with the corresponding steroids of the normal series they are differently decomposed *in vivo* and are not admitted into the hormone-pool of the body. They show more specific hormonal activity; for example, gestagenic or fertility-inhibiting activity. The influence on the gonadotrophin economy may also be mentioned as

[Price 4s. 6d.]

a further property of the 6-halo-9 β ,10 α -steroids of the invention. A particularly interesting 6-halo-9 β ,10 α -steroid is 6-chloro-17 α -methyl - 9 β ,10 α - pregna - 1,4,6 - triene-3,20-dione.

The novel 6-halo-9 β ,10 α -steroids of this invention may be used as medicaments in the form of pharmaceutical preparations (dosage unit 2—50 mg) which contain them in association with a compatible pharmaceutical carrier. This can be an organic or inorganic inert carrier material suitable for enteral or parenteral administration; for example, water, gelatin, lactose, starch, magnesium stearate, talc, vegetable oils, gums, polyalkyleneglycols or petroleum jelly. The pharmaceutical preparations may be made up in solid form (e.g. as tablets, dragées, suppositories or capsules) or in liquid form (e.g. as solutions, suspensions or emulsions). If desired, the preparations may be sterilized and/or may contain auxiliary substances such as preserving, stabilizing, wetting or emulsifying agents, salts for varying the osmotic pressure or buffers. They may also contain therapeutically valuable substances other than the novel 6-halo-9 β ,10 α -steroids provided by the invention.

It will be appreciated that, having regard to the foregoing formula, 9 β ,10 α -steroids are steroids in which the hydrogen atoms in positions 8 and 9 as well as the 13-methyl group have the β -configuration and the hydrogen atom in the 14-position as well as the 10-methyl group have the α -configuration such as is the case with dihydro-isolumisterone. A deviation from the normal series of steroids therefore exists with reference to the configuration of the hydrogen atom in the 9-position (9 β) and the 10-methyl group (10 α).

The characterising group of the 3-(alkoxy, cycloalkyloxy or aralkoxy)-3,5-bisdehydro derivatives aforesaid preferably contains not more than ten carbon atoms. Examples of such characterising groups are methyl, ethyl, propyl, *tert*butyl, cyclopentyl, cyclohexyl and

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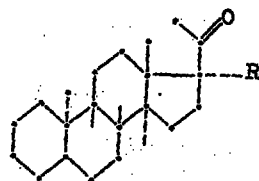
benzyl. The characterising acyl group of the 3-acyloxy-3,5-bisdehydro and 3-acyloxy-2,4,6-trisdehydro derivatives is preferably derived from a saturated or unsaturated aliphatic or cycloaliphatic, an araliphatic or an aromatic carboxylic acid containing not more than twenty carbon atoms. Examples of such acids are formic acid, acetic acid, pivalic acid, propionic acid, butyric acid, caproic acid, heptanoic acid, oleic acid, palmitic acid, stearic acid, succinic acid, malonic acid, citric acid and benzoic acid.

It will be appreciated that the term 'lower-alkyl' is used in this description and in the accompanying claims to mean alkyl groups which contain from 1 to 6 (preferably from 1 to 4) carbon atoms such as methyl, ethyl, propyl, isopropyl and butyl.

Examples of novel 6-halo- $9\beta,10\alpha$ -steroids of formula I are: 6β -chloro- 17α -methyl- $9\beta,10\alpha$ -pregn-4-ene-3,20-dione, 6α -chloro- 17α -methyl- $9\beta,10\alpha$ -pregn-4-ene-3,20-dione, 6 -chloro- 17α -methyl- $9\beta,10\alpha$ -pregna-4,6-diene-3,20-dione, 6β -chloro- 17α -methyl- $9\beta,10\alpha$ -pregna-1,4-diene-3,20-dione, 6 -chloro- 17α -methyl- $9\beta,10\alpha$ -pregna-1,4,6-triene-3,20-dione, 6α -fluoro- 17α -methyl- $9\beta,10\alpha$ -pregn-4-ene-3,20-dione, 6β -fluoro- 17α -methyl- $9\beta,10\alpha$ -pregn-4-ene-3,20-dione, 6 -fluoro- 17α -methyl- $9\beta,10\alpha$ -pregna-4,6-diene-3,20-dione, 6 -fluoro- 17α -methyl- $9\beta,10\alpha$ -pregna-1,4,6-triene-3,20-dione, 6β -bromo- 17α -methyl- $9\beta,10\alpha$ -pregn-4-ene-3,20-dione, 6 -bromo- 17α -methyl- $9\beta,10\alpha$ -pregna-4,6-diene-3,20-dione, 6 -bromo- 17α -methyl- $9\beta,10\alpha$ -pregna-1,4,6-triene-3,20-dione, 6β -chloro- 17α -ethyl- $9\beta,10\alpha$ -pregn-4-ene-3,20-dione, 6α -chloro- 17α -ethyl- $9\beta,10\alpha$ -pregn-4-ene-3,20-dione, 6β -chloro- 17α -ethyl- $9\beta,10\alpha$ -pregna-1,4-diene-3,20-dione, 6 -chloro- 17α -ethyl- $9\beta,10\alpha$ -pregna-4,6-diene-3,20-dione, 6 -chloro- 17α -ethyl- $9\beta,10\alpha$ -pregna-1,4,6-triene-3,20-dione, 6α -fluoro- 17α -ethyl- $9\beta,10\alpha$ -pregn-4-ene-3,20-dione, 6β -fluoro- 17α -ethyl- $9\beta,10\alpha$ -pregn-4-ene-3,20-dione, 6 -fluoro- 17α -ethyl- $9\beta,10\alpha$ -pregna-4,6-diene-3,20-dione, 6 -fluoro- 17α -ethyl- $9\beta,10\alpha$ -pregna-1,4,6-triene-3,20-dione, 6β -bromo- 17α -ethyl- $9\beta,10\alpha$ -pregn-4-ene-3,20-dione, 6 -bromo- 17α -ethyl- $9\beta,10\alpha$ -pregna-4,6-diene-3,20-dione, 6 -bromo- 17α -ethyl- $9\beta,10\alpha$ -pregna-1,4,6-triene-3,20-dione, 3 -ethoxy- 6 -chloro- 17α -methyl- $9\beta,10\alpha$ -pregna-3,5-dien-20-one, 3 -acetoxy- 6 -chloro- 17α -methyl- $9\beta,10\alpha$ -pregna-2,4,6-trien-20-one, 3 -acetoxy- 6 -fluoro- 17α -methyl- $9\beta,10\alpha$ -pregna-2,4,6-trien-20-one and 3 -ethoxy- 6 -

fluoro- 17α -methyl- $9\beta,10\alpha$ -pregna-3,5-dien-20-one.

According to the process provided by the invention, the novel 6-halo- $9\beta,10\alpha$ -steroids aforesaid are manufactured by halogenating a 3-keto-4-dehydro, 3-keto-4,6-bisdehydro or 3-(esterified or etherified hydroxy)-3,5-bisdehydro derivatives of a compound of the general formula



(II)

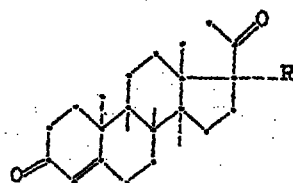
wherein R has the significance given earlier, in the 6-position in accordance with methods known *per se* (as hereinafter defined) to yield a 3-keto-4-dehydro, 3-keto-4,6-bisdehydro or 3-keto-4-dehydro derivative respectively of a compound of formula I hereinbefore and, where required, subjecting the product to dehydrogenation at the 1,2-and/or 6,7-positions or converting same into a 3-(enol ether) or 3-(enol ester) of a compound of formula I hereinbefore.

As mentioned earlier, the halogenation is carried out in accordance with methods known *per se* and it will be appreciated that this term means methods in actual use for or described in the literature on the manufacture of 6-(fluoro or chloro or bromo)-steroids of the normal series from the corresponding 6-des halo steroids of the normal series.

The starting materials for the present process, insofar as they are not already known, can be prepared in accordance with known methods.

Thus, for example, the halogenation can be carried out according to any one of the following methods:

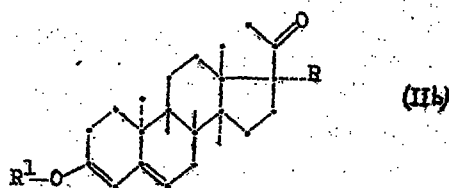
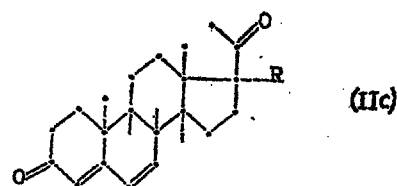
a) A 3-keto-4-dehydro- $9\beta,10\alpha$ -steroid of the general formula



(IIa)

wherein R has the significance given earlier, can be halogenated in the 6-position by reaction with a halogenating agent such as an N-halo-imide (e.g. N-bromo-succinimide) or with a halogen (e.g. with elementary bromine) [see J. Am. Chem. Soc., 1950, 72, 4534].

b) A 3-(esterified or etherified hydroxy)-3,5-bisdehydro- $9\beta,10\alpha$ -steroid of the general formula



wherein R has the significance given earlier and R¹-O— represents an esterified or etherified hydroxy group (preferably an acyloxy, alkoxy, cycloalkyloxy or aralkoxy group of the type previously defined), can be halogenated in the 6-position by reaction with chlorine or bromine [J. Am. Chem. Soc., 1959, 81, 5259; Chem. and Ind., 1959, 1317].

This procedure is particularly adapted to the manufacture of 6-(fluoro or chloro or bromo)-3-keto-4-dehydro-9 β ,10 α -steroids.

The 6-fluoro-steroids are preferably manufactured by reacting a 3-(esterified or etherified hydroxy)-9 β ,10 α -steroid of formula IIb with perchloryl fluoride, preferably in dioxane/water or acetone/ethanol in the presence of an alkali acetate. The fluorination leads to a mixture of the 6 β -fluoro and the 6 α -fluoro isomers in which the latter isomer preponderates. The isomers may be separated from one another by, for example, chromatography and/or fractional crystallization. By isomerisation with a hydrohalic acid (e.g. hydrogen chloride or hydrogen bromide in acetic acid, ethanol, dioxan or chloroform) the α -isomers can be converted into the more stable β -isomers if desired.

The 6-chloro-steroids are preferably manufactured by treating a 3-(esterified or etherified hydroxy)-9 β ,10 α -steroid of formula IIb with a chlorinating agent such as chlorine or an N-chloro-imide or N-chloro-amide (e.g. N-chloro-acetamide or N-chloro-succinimide). The resulting mixture of 6 α -chloro and 6 β -chloro isomers can be separated by chromatography and/or fractional crystallization. The 6 α -isomers can be isomerised to the 6 β -isomers in accordance with the methods mentioned earlier in respect of the 6-fluoro-steroids.

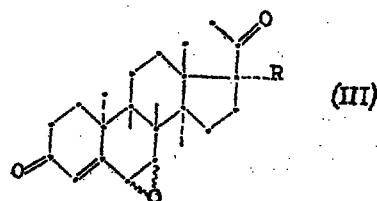
The 6-bromo-steroids are preferably manufactured in an analogous manner to the 6-chloro-steroids by treatment with a brominating agent. The separation of the mixture of isomers which is obtained as well as the isomerisation of the 6 α -bromo isomers to the 6 β -bromo isomers can be carried out in an analogous manner to that described earlier.

c) A 4,6-bisdehydro-9 β ,10 α -steroid of the general formula

wherein R has the significance given earlier, can be converted into the desired 6-chloro-steroid by reaction with chromyl chloride [e.g. in accordance with United States Patent Specification No: 3,076,823] and subsequent dehydration of the 6-chloro-7-hydroxy-steroid which is formed.

The reaction of a 4,6-bisdehydro-9 β ,10 α -steroid of formula IIc with chromyl chloride is conveniently carried out in anhydrous solvents such as chloroform or carbon tetrachloride. The dehydration of the 6-chloro-7-hydroxy-steroid which is obtained by the reaction can be carried out, for example, in acid media (e.g. hydrogen chloride or hydrogen bromide in acetic acid, acetone, methanol, dioxan or tetrahydro-furan).

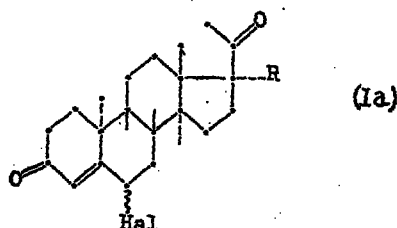
d) A 4,6-bisdehydro-9 β ,10 α -steroid of formula IIc can also be halogenated in the 6-position by first converting it with a peracid (such as perphthalic acid) into a 4-dehydro-6,7-epoxy-9 β ,10 α -steroid of the general formula



wherein R has the significance given earlier, treating this epoxy-steroid (which can also be obtained by treatment of the above-mentioned 6-chloro-7-hydroxy-steroid with alkali) with hydrogen fluoride, hydrogen chloride or hydrogen bromide [see Chem. Ber. 1961, 94, 1225] and splitting off water from the resulting product.

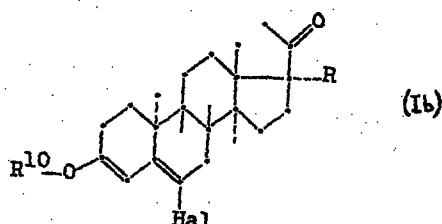
The dehydrogenation at the 6-position (i.e. the introduction of a double bond into the 6,7-position of a 6,7-saturated 6-halo-9 β ,10 α -steroid halogenation product) can be carried out as follows:

a) A 6-halo-3-keto-4-dehydro-9 β ,10 α -steroid of the general formula



wherein R and Hal have the significance given earlier, can be dehydrogenated in the 6,7-position; for example, with a substituted benzoquinone such as chloranil [see J. Am. Chem. Soc., 1960, 82, 4293; *ibid.*, 1959, 81, 5951] or with 2,3-dichloro-5,6-dicyano-benzoquinone or with manganese dioxide [see J. Am. Chem. Soc., 1953, 75, 5932].

- b) A 6-halo-3-(alkoxy, cycloalkyloxy or aralkoxy)-3,5-bisdehydro-9 β ,10 α -steroid of the general formula

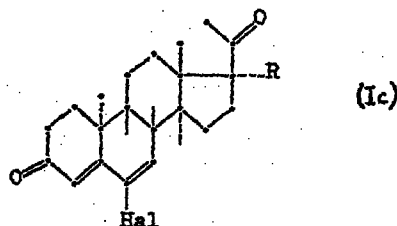


wherein R and Hal have the significance given earlier and R¹⁰-O- represents an alkoxy, cycloalkyloxy or aralkoxy group, can be converted into the corresponding 6-halo-3-keto-4,6-bisdehydro-9 β ,10 α -steroid by reaction with 2,3-dichloro-5,6-dicyano-benzoquinone or manganese dioxide.

- c) A 6-halo-3-(alkoxy, cycloalkyloxy or aralkoxy)-3,5-bisdehydro-9 β ,10 α -steroid of formula Ib can be converted into the corresponding 6-halo-3-keto-4,6-bisdehydro-9 β ,10 α -steroid by means of a two-stage sequence of halogenation and dehydrohalogenation.

The dehydrogenation at the 1-position (i.e. introduction of a double bond in the 1,2-position) can be carried out as follows:

- A 6-halo-3-keto-4-dehydro-9 β ,10 α -steroid of formula Ia or a 6-halo-3-keto-4,6-bisdehydro-9 β ,10 α -steroid of the general formula



- wherein R and Hal have the significance given earlier, can be dehydrogenated at the 1-position by means of microorganisms or using dehydrogenation agents such as iodine

pentoxide, periodic acid or selenium dioxide [see J. Am. Chem. Soc., 1959, 81, 1235; 5951], 2,3-dichloro-5,6-dicyano-benzoquinone [see Proc. Chem. Soc., 1960, 14], lead tetraacetate [see J. Am. Chem. Soc., 1955, 77, 661] or chloranil [see J. Am. Chem. Soc., 1960, 82, 4293]. 1,4,6-trisdehydro derivatives of compounds of formula I can be obtained directly from the 3-keto-4-dehydro derivatives of compounds of formula I using chloranil or 2,3-dichloro-5,6-dicyano-benzoquinone.

Methods which are known from the chemistry of steroids of the normal series can be used for the enol-esterification or enol-etherification of 3-keto-4-dehydro or 3-keto-4,6-bisdehydro derivatives of compounds of formula I. Thus the enol-etherification of 6-halo-3-keto-4-dehydro-9 β ,10 α -steroids to yield 6-halo-3-(alkoxy, cycloalkyloxy or aralkoxy)-3,5-bisdehydro-9 β ,10 α -steroids be carried out, for example, as follows:

The 6-halo-3-keto-4-dehydro-9 β ,10 α -steroid is reacted with an alcohol (e.g. methanol, ethanol or benzyl alcohol) in the presence of a catalyst (e.g. *paratoluene*-sulphonic acid), with an orthoformic acid ester in the presence of a catalyst (e.g. orthoformic acid ethyl ester and hydrochloric acid) or with a dialkoxypropane (e.g. dimethoxy-propane in a mixture of methanol and N,N-dimethyl-formamide in the presence of a catalyst such as *paratoluene*-sulphonic acid).

One of the 3-(esterified hydroxy)-3,5-bisdehydro-9 β ,10 α -steroids of formula IIb hereinbefore, namely 3-acetoxy-17 α -methyl-9 β ,10 α -pregna-3,5-dien-20-one, is claimed *per se* in the specification of our copending Application for Letters Patent No. 43204/68 (now Serial No. 1,141,629) and may be prepared as described therein.

The following Examples illustrate the process provided by the invention:

EXAMPLE 1.

(i) A solution of 20.0 g of 3-acetoxy-17 α -methyl-9 β ,10 α -pregna-3,5-dien-20-one [prepared as described in the specification of our copending Application No. 43204/68 (now Serial No. 1,141,629)] in 300 ml of absolute ether is added with stirring to a solution of 40.0 g of potassium acetate in 700 ml of acetic acid and 120 ml of water. The mixture is cooled to 0°C to 5°C and a solution of 3.5 g of chlorine in 120 ml of acetic acid is added dropwise with stirring and cooling. The mixture is subsequently stirred at 0°C for a further 10 minutes, then poured into water and extracted with ether. The ether extracts are washed well with glacial acetic acid and then with water and dried over sodium sulphate. After evaporating off the solvent, the 6 β -chloro-17 α -methyl-9 β ,10 α -pregna-4-ene-3,20-dione is recrystallized from acetone/(isopropyl ether). Ultraviolet absorp-

tion: $\epsilon_{235}=15\ 500$; melting point 147° — 148°C , $[\alpha]_{\text{D}}^{25}=-86^{\circ}$ (dioxan).

(ii) A mixture of 4.2 g of 6 β -chloro-17 α -methyl - 9 β ,10 α - pregn - 4 - ene - 3,20-dione, 230 mg of *paratoluene*-sulphonic acid, 3.6 g of orthoformic acid ethyl ester and 60 ml of dioxan is allowed to stand at room temperature in the dark for 16 hours. This solution is added dropwise within 5 minutes to a well stirred mixture of 240 ml of glacial acetic acid, 17 ml of water and 21.0 g. of manganese dioxide. The mixture is stirred at 25°C for 1 hour, manganese dioxide is filtered off and washed well with glacial acetic acid and methylene chloride. The filtrate is poured into ice/water and extracted with (methylene chloride)/(petroleum ether) (1:1). The organic extract is washed with sodium carbonate solution and water, dried with sodium sulphate and evaporated. The residue (4.0 g) is dissolved in benzene and filtered through 50 g. of aluminium oxide. The 6-chloro-17 α -methyl - 9 β ,10 α - pregn - 4,6 - diene - 3,20-dione obtained from the eluate is recrystallized from acetone/(isopropyl ether). Ultraviolet absorption: $\epsilon_{235}=21\ 900$, melting point 177° — 178°C , $[\alpha]_{\text{D}}^{25}=-381^{\circ}$ (dioxan).

(iii) A solution of 1.7 g of 6-chloro-17 α -methyl - 9 β ,10 α - pregn - 4,6 - diene - 3,20-dione and 1.6 g of 2,3 - dichloro - 5,6 - dicyano - benzoquinone in 180 ml of dioxan is heated to reflux under nitrogen for 5 hours.

For purpose of working up, the mixture is diluted with 200 ml of benzene and filtered through 30 g of aluminium oxide (activity II). The substance is completely eluted with ether. The eluate is evaporated and there are obtained 1.4 g of crude product which is chromatographed on aluminium oxide. The (petroleum ether)/benzene fractions yield pure 6-chloro-17 α - methyl - 9 β ,10 α - pregn - 1,4,6-triene - 3,20 - dione. Ultraviolet absorption $\epsilon_{228}=11\ 800$, $\epsilon_{251}=10\ 800$ and $\epsilon_{300}=10\ 400$, melting point 221° — 222°C , $[\alpha]_{\text{D}}^{25}=-220^{\circ}$ (dioxan).

EXAMPLE 2.

A solution of 42.0 g of chromyl chloride in 200 ml of methylene chloride is added with stirring under nitrogen gassification within 0.5 hour to a solution (cooled to -15°C) of 25.0 g of 17 α -methyl-9 β ,10 α -pregna-4,6-diene-3,20-dione in 12000 ml of methylene chloride. The mixture is subsequently stirred at -15°C for a further 2 hours. The brown-red precipitate is then filtered off, washed with a little methylene chloride and subsequently introduced portionwise, with stirring, into a solution of 150 g of sodium acetate and 185 g of sodium pyrosulphite in 3000 ml of ice-water. After the addition of 3000 ml of ethyl acetate, the mixture is further stirred for 20 minutes. The organic phase is separated off, washed with sodium acetate solution and sodium chloride solution, dried over sodium sulphate and evaporated in a vacuum. The

residue is dissolved in 400 ml of dioxan and 100 ml of methylene chloride and, after the addition of 50 ml of (hydrochloric acid)/dioxan (13% mg), stirred for 4 hours at room temperature. The reaction solution is poured on ice-water and extracted with ethyl acetate. The organic extract yields 19 g of crude product which is chromatographed on silicagel. Pure 6-chloro-17 α -methyl-9 β ,10 α -pregna-4,6-diene-3,20-dione in 1200 ml of methylene acetone (9:1).

EXAMPLE 3.

(i) 15.0 g of 3-acetoxy-17 α -methyl-9 β ,10 α -pregna-3,5-dien-20-one in a solution of 8.0 g of anhydrous potassium acetate in 350 ml of acetone and 250 ml of ethanol are treated with perchloryl fluoride for 6 hours. There are obtained 15.5 g of crude product which is chromatographed on silicagel. The (methylene chloride)/acetone (97:3) fractions yield 6 α - fluoro - 17 α - methyl - 9 β ,10 α - pregn - 4-ene-3,20-dione. Ultraviolet absorption $\epsilon_{238}=13\ 300$. The later fractions yield pure 6 β - fluoro - 17 α - methyl - 9 β ,10 α - pregn - 4-ene-3,20-dione. Ultraviolet absorption $\epsilon_{234}=16\ 400$.

(ii) 4.0 ml of orthoformic acid ethyl ester and 150 mg of *paratoluene*-sulphonic acid are added to a solution of 4.5 g of 6 β -fluoro-17 α -methyl-9 β ,10 α -pregn-4-ene-3,20-dione in 100 ml of absolute dioxan and the solution is held at room temperature for 15 hours. The solution is then diluted with 150 ml of acetone and cooled to 0°C . A solution of 1.5 g of sodium acetate in 20 ml of water, 4.0 g of N-bromo-succinimide and 2 ml of acetic acid are then successively added with stirring. The mixture is further stirred for 0.5 hours and then worked up in the usual manner. The crude product is heated with 8 ml of pyridine at 90°C for 0.75 hour. The usual working up yields 4.0 g of crude product which is chromatographed on silicagel. The fractions which are uniform according to thin-layer chromatogram are recrystallized from acetone/(isopropyl ether) and yield 6-fluoro-17 α -methyl - 9 β ,10 α - pregn - 4,6 - diene - 3,20-dione. Ultraviolet absorption $\epsilon_{235}=24000$.

(iii) 6 - Fluoro - 17 α - methyl - 9 β ,10 α -pregna-4,6-diene-3,20-dione is dehydrogenated with 2,3 - dichloro - 5,6 - dicyano - benzoquinone in an analogous manner to that described in Example 1 (iii). The 6-fluoro-17 α -methyl - 9 β ,10 α - pregn - 1,4,6 - triene - 3,20 - dione obtained after chromatography of the crude product exhibits 3 maxima in the ultraviolet spectrum, namely $\epsilon_{228}=11\ 600$, $\epsilon_{255}=10\ 500$ and $\epsilon_{301}=10\ 200$.

EXAMPLE 4.

A mixture of 1.0 g of 6-chloro-17 α -methyl-9 β ,10 α - pregn - 4,6 - diene - 3,20 - dione [obtained in accordance with Example 1 (ii) or Example 2], 100 mg of *paratoluene*-sulphonic

acid, 60 ml of benzene and 30 ml of isopropenyl acetate is heated to reflux for 6 hours. The reaction mixture is diluted with 50 ml of petroleum ether and chromatographed through 10 g of aluminium oxide. 3-Acetoxy-6-chloro-17 α -methyl-9 β ,10 α -pregna-2,4,6-trien-20-one is obtained in the form of yellowish crystals which are recrystallized from methanol containing 0.5% pyridine. Ultraviolet absorption $\epsilon_{265} = 13,000$.

The following Examples illustrate pharmaceutical preparations containing the novel 6-halo-9 β ,10 α -steroids provided by the invention:

EXAMPLE A.

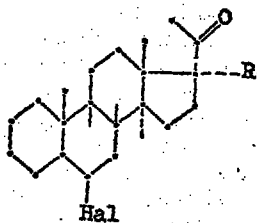
A typical tablet weighs 150.0 mg and contains 5 mg of 6-chloro-17 α -methyl-9 β ,10 α -pregna-1,4,6-triene-3,20-dione, 71 mg of lactose, 71 mg of corn starch, 2.7 mg of talc and 0.3 mg of magnesium stearate.

EXAMPLE B.

A typical solution for injection contains 5 mg (or 50 mg) of 6-chloro-17 α -methyl-9 β ,10 α -pregna-1,4,6-triene-3,20-dione in 2 ml of olive oil.

WHAT WE CLAIM IS:—

1) A 3-keto-4-dehydro, 3-keto-4,6-bisdehydro, 3-keto-1,4-bisdehydro, 3-keto-1,4,6-trisdehydro, 3-acyloxy-3,5-bisdehydro, 3-(alkoxy, cycloalkoxy or aralkoxy)3,5-bisdehydro or a 3-acyloxy-2,4,6-trisdehydro derivative of a compound of the general formula



wherein R represents a lower-alkyl group and Hal stands for a fluorine, chlorine or bromine atom which can have an α - or β -configuration in the case of the 3-keto-4-dehydro or 3-keto-1,4-bisdehydro derivatives.

2) 6 β -Chloro-17 α -methyl-9 β ,10 α -pregn-4-ene-3,20-dione.

3) 6 α -Fluoro-17 α -methyl-9 β ,10 α -pregn-4-ene-3,20-dione.

4) 6 β -Fluoro-17 α -methyl-9 β ,10 α -pregn-4-ene-3,20-dione.

5) 6-Chloro-17 α -methyl-9 β ,10 α -pregna-4,6-diene-3,20-dione.

6) 6-Fluoro-17 α -methyl-9 β ,10 α -pregna-4,6-diene-3,20-dione.

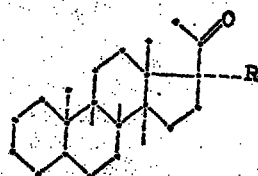
7) 6-Chloro-17 α -methyl-9 β ,10 α -pregna-1,4,6-triene-3,20-dione.

8) 6-Fluoro-17 α -methyl-9 β ,10 α -pregna-1,4,6-triene-3,20-dione.

9) 3-Acetoxy-6-chloro-17 α -methyl-9 β ,10 α -pregna-2,4,6-trien-20-one.

10) A pharmaceutical preparation comprising a 6-halo-9 β ,10 α -steroid as set forth in any one of the preceding claims in admixture with a compatible pharmaceutical carrier.

11) A process for the manufacture of the 6-halo-9 β ,10 α -steroids claimed in claim 1, which process comprises halogenating a 3-keto-4-dehydro, 3-keto-4,6-bisdehydro or 3-(esterified or etherified hydroxy)3,5-bisdehydro derivative of a compound of the general formula



wherein R has the significance given in claim 1, in the 6-position in accordance with methods known *per se* (as hereinbefore defined) to yield a 3-keto-4-dehydro, 3-keto-4,6-bisdehydro or 3-keto-4-dehydro derivative respectively of a compound formulated in claim 1 and, where required, subjecting this product to dehydrogenation at the 1,2- and/or 6,7-positions or converting same into a 3-(enol ether) or 3-(enol ester) derivative of the type formulated in claim 1.

12) A process as set forth in claim 11, wherein a 3-keto-4-dehydro derivative of a compound formulated in that claim is treated with a N-haloimide or a halogen.

13) A process as set forth in claim 11, wherein a 3-(esterified or etherified hydroxy)-3,5-bisdehydro derivative of a compound formulated in that claim is treated with chlorine, bromine, an N-(chloro or bromo)-imide, an N-(chloro or bromo)-amide or perchloryl fluoride.

14) A process as set forth in claim 11, wherein a 3-keto-4,6-bisdehydro derivative of a compound formulated in that claim is converted into a 3-keto-4,6-bisdehydro derivative of a compound formulated in claim 1 in which Hal stands for a chlorine atom by reaction with chromyl chloride and subsequent dehydration of the 6-chloro-7-hydroxy-steroid which is formed.

15) An obvious chemical equivalent of the process claimed in any one of claims 11 to 14 inclusive.

16) A process for the manufacture of the 6-halo-9 β ,10 α -steroids claimed in claim 1, substantially as described with reference to Examples 1 to 4.

17) 6-Halo-9 β ,10 α -steroids as formulated

- acid, 60 ml of benzene and 30 ml of isopropenyl acetate is heated to reflux for 6 hours. The reaction mixture is diluted with 50 ml of petroleum ether and chromatographed through 10 g of aluminium oxide. 3-Acetoxy-6-chloro-17 α -methyl-9 β ,10 α -pregna-2,4,6-trien-20-one is obtained in the form of yellowish crystals which are recrystallized from methanol containing 0.5% pyridine. Ultraviolet absorption ϵ_{308} = 13 000.

The following Examples illustrate pharmaceutical preparations containing the novel 6-halo-9 β ,10 α -steroids provided by the invention:

15 EXAMPLE A.

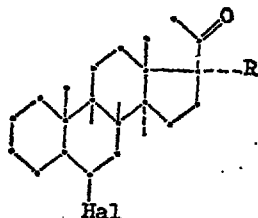
- A typical tablet weighs 150.0 mg and contains 5 mg of 6-chloro-17 α -methyl-9 β ,10 α -pregna-1,4,6-triene-3,20-dione, 71 mg of lactose, 71 mg of corn starch, 2.7 mg of talc and 0.3 mg of magnesium stearate.

EXAMPLE B.

- A typical solution for injection contains 5 mg (or 50 mg) of 6-chloro-17 α -methyl-9 β ,10 α -pregna-1,4,6-triene-3,20-dione in 2 ml of olive oil.

WHAT WE CLAIM IS:—

- 1) A 3-keto-4-dehydro, 3-keto-4,6-bisdehydro, 3-keto-1,4-bisdehydro, 3-keto-1,4,6-trisdehydro, 3-acyloxy-3,5-bisdehydro, 3-(alkoxy, cycloalkyloxy or aralkoxy)3,5-bisdehydro or a 3-acyloxy-2,4,6-trisdehydro derivative of a compound of the general formula



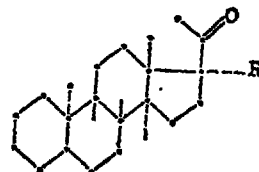
- wherein R represents a lower-alkyl group and Hal stands for a fluorine, chlorine or bromine atom which can have an α - or β -configuration in the case of the 3-keto-4-dehydro or 3-keto-1,4-bisdehydro derivatives.
- 2) 6 β -Chloro-17 α -methyl-9 β ,10 α -pregn-4-ene-3,20-dione.
- 3) 6 α -Fluoro-17 α -methyl-9 β ,10 α -pregn-4-ene-3,20-dione.
- 4) 6 β -Fluoro-17 α -methyl-9 β ,10 α -pregn-4-ene-3,20-dione.
- 5) 6-Chloro-17 α -methyl-9 β ,10 α -pregna-4,6-diene-3,20-dione.
- 6) 6-Fluoro-17 α -methyl-9 β ,10 α -pregna-4,6-diene-3,20-dione.
- 7) 6-Chloro-17 α -methyl-9 β ,10 α -pregna-1,4,6-triene-3,20-dione.

8) 6-Fluoro-17 α -methyl-9 β ,10 α -pregna-1,4,6-triene-3,20-dione.

9) 3-Acetoxy-6-chloro-17 α -methyl-9 β ,10 α -pregna-2,4,6-trien-20-one.

10) A pharmaceutical preparation comprising a 6-halo-9 β ,10 α -steroid as set forth in any one of the preceding claims in admixture with a compatible pharmaceutical carrier.

11) A process for the manufacture of the 6-halo-9 β ,10 α -steroids claimed in claim 1, which process comprises halogenating a 3-keto-4-dehydro, 3-keto-4,6-bisdehydro or 3-(esterified or etherified hydroxy)3,5-bisdehydro derivative of a compound of the general formula



wherein R has the significance given in claim 1, in the 6-position in accordance with methods known *per se* (as hereinbefore defined) to yield a 3-keto-4-dehydro, 3-keto-4,6-bisdehydro or 3-keto-4-dehydro derivative respectively of a compound formulated in claim 1 and, where required, subjecting this product to dehydrogenation at the 1,2- and/or 6,7-positions or converting same into a 3-(enol ether) or 3-(enol ester) derivative of the type formulated in claim 1.

12) A process as set forth in claim 11, wherein a 3-keto-4-dehydro derivative of a compound formulated in that claim is treated with a N-haloimide or a halogen.

13) A process as set forth in claim 11, wherein a 3-(esterified or etherified hydroxy)-3,5-bisdehydro derivative of a compound formulated in that claim is treated with chlorine, bromine, an N-(chloro or bromo)-imide, an N-(chloro or bromo)-amide or perchloryl fluoride.

14) A process as set forth in claim 11, wherein a 3-keto-4,6-bisdehydro derivative of a compound formulated in that claim is converted into a 3-keto-4,6-bisdehydro derivative of a compound formulated in claim 1 in which Hal stands for a chlorine atom by reaction with chromyl chloride and subsequent dehydration of the 6-chloro-7-hydroxy-steroid which is formed.

15) An obvious chemical equivalent of the process claimed in any one of claims 11 to 14 inclusive.

16) A process for the manufacture of the 6-halo-9 β ,10 α -steroids claimed in claim 1, substantially as described with reference to Examples 1 to 4.

17) 6-Halo-9 β ,10 α -steroids as formulated



in claim 1, when manufactured by the process
claimed in any one of claims 11 to 16 inclu-
sive.

W. D. WHITAKER,
Patent Agent,
for F. Hoffmann-la Roche & Co.,
Aktiengesellschaft.

Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1969.
Published by the Patent Office, 25 Southampton Buildings, London, W.C.2, from which
copies may be obtained.

