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Phillipps et al.

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[54] **CHEMICAL COMPOUNDS**

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[58] **Field of Search** ...../Machine Searched Steroids

[56] **References Cited**

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[57] **ABSTRACT**

Steroid anaesthetics of the pregnane and 19-norpregnane series are described, the compounds having a 5α-hydrogen atom or a 4,5-double bond, a 3α-hydroxy group, a 17α-hydrogen atom, a 20-oxo group and a 21-fluorine atom.

4 Claims, No Drawings

CHEMICAL COMPOUNDS

This invention is concerned with compounds of the pregnane series having anaesthetic activity.

It has long been known that a number of steroids give rise to profound depression of the central nervous system and act pharmacodynamically as anaesthetics or hypnotics. Such compounds having been the subject of considerable study in an attempt to find anaesthetics to replace such substances as thiopentone sodium normally used but well known to be accompanied by some degree of hazard or disadvantage. The literature shows that very many steroid compounds have been studied in this regard. Reviews and discussions of some of the work carried out are to be found, for example, in "Methods in Hormone Research" (Edited by Ralph I. Dorfman, Vol. III Part A, Academic Press, London and New York, 1964, pages 415–475); H. Witzel, Z. Vitamin Hormon-Fermentforsch 1959, 10, 46–74; H. Selye, Endocrinology, 1942, 30, 437–453; S. K. Figdor et al., J. Pharmacol. Exptl. Therap., 1957, 119, 299–309 and Atkinson et al., J. Med. Chem. 1965, 8, 426–432.

A thorough review of the literature indicates that many anaesthetic steroids possess poor activity and/or long induction periods. A variety of undersired side effects such as paraesthesia and vein damage have also been noted.

We have now found useful anaesthetic activty in a new group of pregnane steroids.

Thus the invention provides steroids of the pregnane or 19-nor-pregnane series possessing a 5α-hydrogen atom or a 4,5-double bond, a 3α-hydroxy group, a 17α-hydrogen atom, a 20-oxo group, and a 21-fluorine atom, and, where the steroids carry basic groups, the acid addition salts thereof.

As will be discussed in detail below, the invention also provides pharmaceutical compositions comprising an anaesthetic steroid in accordance with the invention and processes for the preparation of the compounds of the invention.

The compounds of the invention may possess substituents at other positions of the steroid nucleus, for example at the 2, 3β, 11 or 16 positions. They may also be unsaturated, for example at the $\Delta^{8(9)}$ and/or Δ^{1} or Δ^{4} position.

Compounds having an 11-oxo group are particularly preferred, and compounds in the pregnane series are generally preferred.

In general, the compounds of the invention are good anaesthetics with generally short induction periods, the anaesthetic action at suitable doses being in general instantaneous; these compounds are thus excellent anaesthetics for inducing anaesthesia which is to be maintained e.g. by an inhalation anaesthetic such as ether, halothane, nitrous oxide, or trichloroethylene. The compounds are however capable of maintaining anaesthesia to a sufficient degree to enable various surgical operations to be conducted without the aid of an inhalation anaesthetic, the required degree of anaesthesia being maintained if necessary by repeated administration (or even continuous administration). Moreover, the said anaesthetics in accordance with the invention in general give rise to minimal side-effects as compared to many previously described steroidal anaesthetics.

Examples of substituents which may be present at the 2β-position include an acyloxy group having for example 1 to 9 carbon atoms, an ether or thioether group

(i.e. the residue of an alcohol, a phenol or a thiol) containing for example 1–9 carbon atoms (e.g. methoxy), an alkyl or cycloalkyl group for example containing up to 9 carbon atoms, an aryl group (e.g. a phenyl group), an aralkyl group (e.g. a benzyl group), a hydroxy group, a thiocyanato group, a nitro-oxy group, or a halogen atom.

Acyloxy substitutents (which may be saturated or unsaturated) include lower (C_1–C_6) alkanoyloxy groups, (substituted if desired, for example, with one or more halogen, e.g. chlorine atoms, lower alkoxy, amino or substituted amino groups), aroyloxy groups (e.g. a benzoyloxy group), or aralkanoyloxy groups (e.g. a phenylacetoxy group).

Ether substituents, which may be saturated or unsaturated, include lower (C_1–C_6) alkoxy groups, lower alkenyloxy groups (e.g. an allyloxy group), cycloalkoxy groups (e.g. a cyclohexyloxy group), aryloxy groups (e.g. a phenoxy group) an aralkoxy groups (e.g. a benzyloxy group). Thioether groups corresponding to the above-mentioned ether groups are representative of 2β-thioether substituents.

The 2β-substituent may alternatively be an azido, sulphonyloxy (e.g. tosyloxy) group or an acylthio group.

Examples of 2β-alkyl groups include especially lower alkyl groups containing 1–5 carbon atoms such as methyl, ethyl, propyl, butyl, isobutyl and t-butyl groups. An example of a cycloalkyl group is a cyclohexyl group

Examples of lower alkanoyloxy 2β-substituents include acetoxy, propionyloxy, butyryloxy, piperidinoacetoxy, morpholinoacetoxy, diethylaminoacetoxy and chloroacetoxy groups.

Examples of lower alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, n-butoxy and t-butoxy groups, and the corresponding thio compounds exemplify lower alkyl thio substituents.

Lower alkoxy and lower alkylthio substituents at the 2β-position may themselves be substituted for example by one or more halogen (e.g. chlorine) atoms, lower alkoxy, esterified carboxyl (e.g. ethoxycarbonyl), hydroxy, amino or substituted amino (e.g. morpholino) groups, or substituted or unsubstituted acyloxy (e.g. morpholinoacetoxy, chloroacetoxy or diethylaminoacetoxy), or heterocylcic groups, e.g. a tetrahydrofuranyl group. Alkyl, cycloalkyl and aryl groups may also be substituted.

The 2β-position may also carry amino substituents, e.g. amino or substituted amino groups, for example mono- or di-alkylamino or saturated, unsaturated or aromatic heterocyclic amino groups, e.g. a morpholino group.

A particularly important 2β-substituent is an ethoxy group.

Examples of substituents which may be present at the 2α-position are alkyl groups, e.g. having 1 to 6 carbon atoms such as methyl or ethyl, or halogen atoms, e.g. chlorine or bromine.

Examples of substituents which may be present at the 3β-position are alkyl groups, e.g. having 1 to 6 carbon atoms such as methyl, ethyl or pentyl.

An oxo group may be present at the 11-position and compounds having this substituent are particularly important. Alternatively, a hydroxy group may be present at the 11-position, in either the α configuration or, in the presence of absence of an 60 -alkyl or alkenyl (C_{1-6}) group e.g. methyl or allyl, in the 62 configura-

tion. Another possible grouping is an epoxy group linked also to the 9-position.

The 16-position may be substituted by one or more alkyl or alkoxy groups having 1 to 6 carbon atoms (e.g. methyl, ethyl, methoxy, or gem-diemthyl) or by a halogen atom (e.g. fluorine or chlorine). A single 16-substituent may be in the α or β configuration.

Certain of the compounds of the invention, e.g. those containing a basic nitrogen atom, are capable of forming acid addition salts and this has the advantage of tending to improve the water solubility of the compounds. Such salts include, in the case of amino-substituted compounds, hydrochlorides, hydrobromides, phosphates, sulphates, p-toluenesulphonates, methanesulphonates, citrates, tartrates, acetates, ascorbates, lactates, maleates and succinates.

When these salts are used as anaesthetics they should be non-toxic, i.e. physiologically acceptable in the dosage at which they are administered. Other salts may, however, be of use in for example, isolation of the product from a synthetic reaction.

Particularly preferred compounds in accordance with the invention by virtue of their excellent anaesthetic properties are 21-fluoro-3α-hydroxy-5α-pregnane-11,20-dione and 2β-ethoxy-21-fluoro-3α-hydroxy-5α-pregnane-11,20 -dione.

PHARMACEUTICAL FORMULATIONS

The anaesthetic compounds of the invention may be formulated as convenient, following generally known pharmaceutical practices, (including both human and veterinary medical practices), with the aid of one or more pharmaceutical carriers or excipients. For anaesthetic purposes, the steroids will be given by injection and thus one aspect of this invention comprises an anaesthetic composition for parenteral administration comprising an anaesthetic compound in accordance with the invention in a parenterally acceptable vehicle.

When the anaesthetic compounds are sufficiently soluble in water (e.g. the salts, particularly the citrates referred to above) they may be formulated in aqueous solutions (e.g. isotonic sterile solutions). Many of the anaesthetic steroids of the invention are poorly soluble in water. We have found however that they may be formulated for parenteral administration in an aqueous solution of a parenterally acceptable non-ionic surface active agent. These surface active agents may also be used even where the steroid is sufficiently water soluble as they may reduce the risk of thrombophlebitis.

The non-ionic surface active agents used for the purpose of this invention are generally those of the water-soluble type, conveniently having an HLB value of at least 9, preferably at least about 12, advantageously at least about 13. Preferably the HLB value of the surface active agent is not greater than about 18. A mixture of surface agents may be used, in which case it is the HLB value of the mixture which is conveniently between the values just mentioned.

The surface active agent must naturally be one which is physiologically compatible, i.e. of itself give rise to no physiologically unacceptable side effects in the dosages employed in the intended species to be treated (man or animal).

Surface active agents for use in accordance with the invention are for example to be found among the following non-ionic surfactants and classes of surfactants:

Polyoxyethylated derivatives of fatty (C12–C20) glyceride oils, e.g. castor oil, containing from 35 to 60 oxyethylene groups per mole of fatty oil. Polyoxyethylene ethers (containing from 10 to 30 oxyethylene groups) of long chain alcohols (containing for example from 12–28 carbon atoms).

Polyoxyethylene-polyoxypropylene ethers containing from 5 to 150 and from 15 to 50 oxyethylene and oxypropylene groups respectively. Polyoxyethylene ethers (containing from 6 to 12 oxyethylene groups) of alkyl phenols the alkyl groups of which preferably contain 6–10 carbon atoms.

Polyoxyethylated (containing from 15 to 30 oxyethylene groups) fatty acid (e.g. C12–18) esters of sugar alcohol anhydrides e.g. sorbitan or mannitan.

Long-chain (e.g. C10–16) alkanoyl mono- and di-alkanolamides (the alkanol portions of which for example contain 1–5 carbon atoms) for example lauroyl mono- and di-ethanolamides. Polyethylene glycol esters (containing from 6 to 40 ethylene oxide units) of long chain fatty acids (containing for exammple 12–18 carbon atoms) e.g. polyethyleneglycol monooleate (containing for example 8 ethylene oxide units).

Other useful surfactants include phospholipids such as lecithins, e.g. egg or soyabean lecithins.

Examles of non-ionic surface active agents, of the foregoing types, useful in accordance with the invention include:

Cremophor EL, a polyoxyethlated castor oil containing about 40 ethylene oxide units per triglyceride unit;

Tween 80, polyoxyethylene sorbitan monooleate containing about 20 ethylene oxide units;

Tween 60, polyoxyethylene sorbitan monostearate containing about 20 ethylene oxide units; and

Tween 40, polyoxyethylene sorbitan monopalmitate containing about 20 ethylene oxide units.

The expression "solutions" is used herein to denote liquids which have the appearance of true solutions and are thus optically clear and capable of passage, for example, through a micro-porous filter, irrespective of whether such solutions are true solutions in the classical chemical sense and irrespective of whether they are stable or metastable. Thus it may be that the steroid is associated with micelles. The solutions of this invention, irrespective of their precise physical nature, behave as true solutions for the practical purpose of intravenous injection.

The proportion of surface active agent to be used in the compositions of this invention depends upon its nature and upon the concentration of steroid desired in the final composition.

In preferred compositions according to the invention the proportion of surfactant is preferably at least 5 percent by weight and advantageously above 10 percent by weight. A very convenient proportion of surfactant has been found to be 20 percent by weight but 30 percent and up to 50 percent may be used. The proportions of surfactant are expressed by weight in relation to the total volume of the composition.

In one method of preparing the solutions comprising a surfactant, the steroid is first dissolved in the selected surfactant, for example with heating, and the resulting solution dissolved in water. Alternatively the steroid may be dissolved in a volatile organic solvent advantageously having a boiling point of less than about 80°C which is miscible with the surface active agent such as a volatile lower aliphatic ketone e.g. acetone or methyl

ethyl ketone or a volatile halogenated hydrocarbon e.g. chloroform or methylene choride. The surface active agent is then added to this solution, the organic solvent removed by evaporation, for example by passing a stream of an inert gas through the solution e.g. nitrogen and the resulting solution of steroid in surfactant is mixed with water.

The solutions may also be prepared by shaking the steroid with an aqueous solution of the surface active agent.

In all cases simple tests enable one to determine the relative proportions of surface active agent required.

As will be clear, the proportion of steroid which is dissolved in the aqueous medium according to the invention depends upon the water-solubility of the steroid and, where present, the nature and amount of surface active agent used. The composition will generally contain at least 1 mg/ml of steroid but solutions can be made containing for example up to 6 mg/ml of steroid or even 10 mg/ml.

The anaesthetic solutions according to the invention are generally administered by intravenous injection although as is known in the anaesthetic art in certain cases, e.g. with young children, intramuscular injection might be preferred.

As is usual in the case of anaesthetics, the quantity of steroid used to induce anaesthesia depends upon the weight of the individual to be anaesthetised. For intravenous administration in the average man a dose of from 0.2 to 5 mg/kg will in general be found to be satisfactory to induce anaesthesia, the preferred dose being within the range of from 0.5 to 3.5 mg/kg. The dose will naturally vary to some extent dependent upon the physical condition of the patient, and the degree and period of anaesthesia required, all as is well known in the art. It is thus possible by adjustment of the dose to achieve durations of anaesthesia varying from about 10 minutes to up to an hour or more. If it is desired to maintain prolonged anesthesia, repeated doses of the solutions of this invention may be used, such repeated doses being generally either of the same order or lower than the original dose. Alternatively continuous administration may be undertaken at for example a rate of 0.025–2.0 (e.g. 0.09–1.4) mg/kg/min.

Where the anaesthetic solutions are administered intramusuclarly, higher doses are generally necessary.

COMPOUND PREPARATION

The compounds of the invention may in general be prepared by the nucleophilic displacement of a readily eliminatable substituent at the 21-position of a corresponding steroid whereby the desired 21-fluoro substituent is introduced.

The starting 21-substituted steroid is preferably the corresponding 21-iodo steroid, but other compounds may be used, for example a corresponding 21-chloro, 21-bromo or 21-sulphonyloxy (e.g. methanesulphonyloxy) compound.

Thus, in the preparation of the 21-fluoro compounds, the starting compound may be reacted with a source of fluoride ions e.g. silver fluoride or an alkali metal fluoride such as sodium fluoride or potassium hydrogen fluoride. The reaction may be carried out in any suitable inert and preferably polar solvent (e.g. an alkanol such as ethanol or methanol, a ketone such as acetone or methyl ethyl ketone, a nitrile solvent such as acetonitrile, an amide solvent such as dimethylformamide or diemthylacetamide, a cyclic ether such as dioxan or tetrahydrofuran, or diemthylsulphoxide), in the presence or absence of water. The reaction may be effected at any suitable temperature up to reflux, and may be catalysed by the addition of iodide ions when the starting compound is other than a 21-iodo compound.

The 21-substituted compounds used as starting materials in the preparation of the compounds of the invention may readily be prepared from known compounds by conventional methods.

Thus, a 21-iodo compound for use as a starting material may be prepared by reacting the corresponding 21-bromo or 21-chloro (preferably the bromo compound) with a source of iodide ions e.g. an alkali metal iodide such as sodium iodide. The reaction may be carried out in solvents such as those referred to above regarding the preparation of the 21-fluoro compounds, at any suitable temperature up to reflux.

The 21-bromo compounds required in the latter preparation may be prepared by bromination of the corresponding 21-unsubstituted compound, for example with molecular bromine in a solvent such as methanol or ethanol. The reaction is preferably effected at a temperature of $-10°$ to $+30°C$. If desired the reaction may be accelerated by a catalyst such as hydrogen bromide (in acetic acid) or acetyl chloride.

In the preparation of compounds in accordance with the invention possessing an optional substituent or a carbon-carbon double bond such as described above, it is convenient for this substituent or unsaturation to be present in the 21-substituted starting material. Alternatively, these substituents may be introduced subsequently, for example by generally known techniques using known compounds as starting materials. For convenience a number of methods of introducing the desired substituents or unsaturation into a 3-oxygenated-20-oxo-pregnane are set out below; certain of these methods are new.

Substitution at the 2β-position can be effected for example by way of the corresponding 2α, 3α, -epoxy compound. The epoxy compound itself may be prepared by first dehydrating a 3-hydroxy compound to give the corresponding Δ^2 compound (e.g. by first tosylating the hydroxy group and then detosylating the product), and then treating the Δ^2 compound with a peracid to form the 2α, 3α epoxide ring.

A 2β-substituent may then be introduced by the method described in pending U.S. patent application Ser. No. 197,915 of Phillipps et al., filed Nov. 11, 1971. This general method may be used to introduce all the 2β-substituents described above.

Methods for introducing substituents at the 2β, 3β, 11 and 16 positions are described in U.S. patent applications Ser. No. **208,959** of Cook et al., filed Dec. 16, 1971 and now abandoned in favor of pending continuation thereof Ser. No. 443,451, field Feb. 19, 1974, Ser. No. 194,918 of Gregory et al., filed Nov. 2, 1971 and to issue as U.S. Pat. No. 3,825,565 on July 23, 1974. These or analogous methods may be used to introduce all the substituents referred to above at these positions. For example, an 11-alkenyl or 16-alkyl group may be introduced by methods analogous to those described in U.S. patent application Ser. No. 208,959 for the introduction of an 11-allyl or 16-methyl substituent.

Compounds possessing Δ^1 unsaturation may also be prepared by known methods, but we prefer to use a method which comprises converting a 2β-bromo-3α-

hydroxy pregnane into its corresponding 2β, 21-dibromo compound, if desired protecting the 3α-hydroxy group (e.g. as its tetrahydropyranyl ether), dehydrobrominating to give the Δ^1 compound, and then deprotecting the product where necessary to give the desired 1,2-dehydro-3α-hydroxy-20-oxo-21-bromo compound.

The dehydrobromination may be effected, for example, using a nitrogen containing Lewis base such as a di-lower alkyl lower acylamide e.g. dimethylformamide or dimethylacetamide advantageously in the presence of an alkali metal or alkaline earth metal carbonate, for example calcium carbonate.

In general it has been found convenient to effect the dehydrobromination at an elevated temperature for example from 80° to 170°C. Lower temperatures may be employed when a lithium or calcium halide is present.

Compounds possessing Δ^4 unsaturation may be prepared from Δ^3-steroids by methods analogous to those described for obtaining Δ^1 compounds from Δ^2-steroids. Alternatively, Δ^4-steroids may be obtained by the methods described in U.S. patent application Ser. No. 194,918.

Compounds having a double bond between the 8 and 9 positions and an 11-oxo group may be prepared for example by the method described in U.S. patent application Ser. No. 208,959. These compounds may also be prepared by dehydration of the corresponding 9α-hydroxy compound, for example by using thionyl chloride in pyridine.

5α-Steroids of the invention may also be prepared from the corresponding 3-oxo compound by stereospecific reduction, e.g. by the method of Browne and Kirk (J. Chem. Soc. C., 1969, 1653) or by the method of U.S. patent application Ser. No. 305,246 of Clayton et al., filed Nov. 10, 1972 and to issue as U.S. Pat. No. 3,822,298 on July 2, 1974. The latter method preferably uses a pre-formed iridium catalyst reduction system. For example, a reduction system may be prepared from an iridium acid or salt (e.g. chloroiridic acid), a trivalent phosphorus compound such as a phosphorous acid ester (e.g. trimethyl phosphite), water and an organic reaction medium (e.g. an alcohol such as isopropanol). The reduction system is then neutralised (e.g. to a pH of 6 to 8.5) with an organic base such as a secondary or tertiary amine (e.g. triethylamine) and reacted with the steroid. When the catalyst system is preformed by heating at reflux for 16 to 72 hours, the reduction can be accomplished in 2–3 hours; longer times may be necessary at room temperature.

In the preparative methods described above, it may be desirable to protect a 30α-hydroxy or 20-oxo group during the reaction, the protecting group being subsequently removed to regenerate the hydroxy or oxo group. A 3α-hydroxy group may be for example be protected in the form of a nitrate ester or tetrahydropyranyl ether. A 20-oxo group may be protected as a ketal and regenerated for example by hydrolysis in the presence of an aicd (e.g. hydrochloric or acetic) at a temperature of 0°–100°C.

The following Examples are given by way of illustration only.

All temperatures are in degree Celsius. Optical rotations were measured in chloroform at approximately 1%w/v concentration unless stated otherwise. 'Petrol' refers to petroleum ether (b.p. 60°–80°). Preparative thin layer chromatography (preparative t.l.c.) was carried out on silica gel.

PREPARATION 1

3α-Hydroxy-21-iodo-5α-pregnane-11,20 -dione

A solution of 21 bromo-3α-hydroxy-5α-pregnane-11,20-dione (0.4 g) in acetone (4ml) was treated with sodium iodide (0.4 g). The resulting mixture was refluxed for 30 min., cooled and partitioned between water and ether. The organic layer was washed with water, dried (Na_2SO_4) and evaporated. The residue (387 mg) was recrystallised from acetone/petrol to afford title compound as white needles, m.p. 127°; $[\alpha]_D$ + 102°.

PREPARATION 2

21-Bromo-2β-ethoxy-3α-hydroxy-5α-pregnane-11,20 -dione

2α, 3α-Epoxy-5α-pregnane-11,20 -dione (500 mg) was dissolved in dry ethanol (30 ml), and concentrated sulphuric acid (0.15 ml) was added. The solution was stirred at 25°–30° for 15 minutes, then water (100 ml) was added to give a fine crystalline precipitate which was filtered off, washed with water and dried in vacuo over phosphorus pentoxide to give 2β-ethoxy-3α-hydroxy-5α-pregnane-11,20-dione (340 mg) as white crystals, m.p. 74°–78°, $[\alpha]_D$ + 100°.

Bromine (0.53 g) in methanol (1.45 ml) was added dropwise to a stirred solution of 3α-hydroxy-2β-ethoxy-5α-pregnane-11,20-dione (2.0 g) in methanol (15ml) containing a trace of acetyl chloride at 0°. The addition took 2 hr. and the clear solution was then poured into water and collected by filtration, washed with water and dired in vacuo to give title compound. $[\alpha]_D$ + 80.9 (cl·l)

PREPARATION 3

21-Fluoro-5α-pregnane-3,11,20-trione

A solution of 21-bromo-5α-pregnane-3,11,20-trione (2 g) in acetone (70 ml) was treated with sodium iodide (2 g) and the mixture was refluxed for one-half hour, cooled, poured into water and the emulsion formed was extracted into ethyl acetate. The organic layer was washed with water, dried (Na_2SO_4), and evaporated to a foam (2.0 g).

The foam was dissolved in acetonitrile (40 ml) and the solution was treated with 25 percent aqueous silver fluoride (4 ml). After 3 hours at 50°C., the mixture was poured into water and the emulsion extracted into ether. The extracts were washed with water, dried (Na_2SO_4) and evaporated to a foam (890 mg) which was purified by preparative t.l.c. and crystallisation from ether to give the title compound (350 mg) m.p. 174°–178°C $[\alpha]_D$ + 142° (c =0.93%)

PREPARATION 4

21-Bromo-5α-pregnane-3,11,20-trione

21 -Bromo-3α-hydroxy-5α-pregnane-11,20-dione (412 mg.) in acetone (20 ml) was stirred during dropwise addition of Jones reagent (0.4 ml) at room temperature. After 10 minutes, the reaction mixture was poured onto water extracted with chloroform and the combined choroform extract was washed with water, dried ($MgSO_4$) and evaporated. The residue was crystallised from ether/petrol to give title compound (350

mg) as white microcrystals m.p. 170°, $[\alpha]_D$ + 132° (c 1.1).

Jones reagent is a solution of chromium trioxide (267 g) in a mixture of concentrated sulphuric acid (230 ml) and water (400 ml) made up to 1 litre with water (8N w.r.t. oxygen).

EXAMPLE 1

21-Fluoro-3α-hydroxy-5α-pregnane-11,20-dione

A solution of 3α-hydroxy-21-iodo-5α-pregnane-11,20-dione (0.3 g) in acetonitrile (50 ml.) was treated with 20 percent aqueous silver fluoride (1 ml.) at 45° for 3 hr. The solution was then evaporated to small bulk and partitioned between water and ether. After filtering the mixture, the organic layer was washed with water, dried (Na_2SO_4) and evaporated. The residue was subjected to preparative t.l.c. (C_6H_6, EtOAc; 3:1) and recrystallised from acetone/petrol to afford title compound (0.09 g.) as white prisms, m.p. 150°; $[\alpha]_D$ + 120° (c 0.3)

EXAMPLE 2

2β-Ethoxy-21-fluoro-3α-hydroxy-5α-pregnane-11,20-dione.

A solution of 21-bromo-2β-ethoxy-3α-hydroxy-5α-pregnane-11,20 -dione (1 g.) in acetone (10 ml.) was refluxed with sodium iodide (1 g.) for 30 min. The mixture was allowed to cool and was then partitioned between water and ether. The organic layer was washed with dilute aqueous sodium thiosulphate and water, dried (Na_2SO_4) and evaporated.

A solution of the residue (1.025 g.) in acetonitrile (30 ml) was treated with a 50 percent solution of silver fluoride in water (1.2 ml) at 50° for 4 hr. The mixture was then partitioned between water and ether. The organic layer was washed with water, dried (Na_2SO_4) and evaporated. The residue was purified by preparative t.l.c. (EtOAc, $CHCl_3$ 1:1.) and recrystallised from methyl acetate/petrol to give the title compound, $[\alpha]_D$ + 105° (c 1.3).

EXAMPLE 3

0.058 g of 21-fluoro-3α-hydroxy-5α-pregnane-11,20-dione were dissolved in 2 ml of acetone at 20°C. The resulting solution was added to 2 g of Cremophor EL at 20°C and stirred until homogeneous. The acetone was removed by a vigorous stream of nitrogen. The solution was diluted with sterile distilled water containing 0.05 g of sodium chloride to give a final volume of 10 ml.

EXAMPLE 4

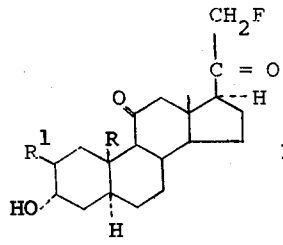
21-Fluoro-3α-hydroxy-5α-pregnane-11,20-dione

21-Fluoro-5α-pregnane-3,11,20-trione (200 mg) was treated with the chloroiridic acid reagent, neutralised with triethylamine, (10 ml) at reflux for 6 hours. The cooled mixture was poured into water and the emulsion was extracted into ethyl acetate. The extracts were washed with water, dried (Na_2SO_4) and evaporated to a foam which was purified by preparative t.l.c. to give the title compound (100 mg) shown to be identical with the product described in Example 1 by n.m.r. spectroscopy and analytical t.l.c.

The chloroirdic acid reagent was prepared by refluxing a mixture of chloroiridic acid (0.9 g). 90 percent isopropanol (200 ml) and trimethylphosphite (16 ml) for 16 hours. The solution was neutralised with triethylamiine immediately before use.

We claim:

1. A steroid selected from the group consisting of a compound of the formula



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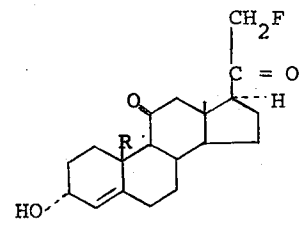

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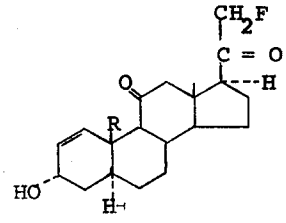

III

where R is —H or —CH_3 and R^1 is H or C_1–C_6 alkoxy.

2. A compound as claimed in formula I in claim 1 wherein R^1 is ethoxy.

3. 21-Fluoro-3α-hydroxy-5α-pregnane-11,20-dione.

4. 2β-ethoxy-21-fluoro-3α-hydroxy-5α-pregnane-11,20-dione.

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