AMENDED SPECIFICATION

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PATENT SPECIFICATION

901,092

NO DRAWINGS

901,092

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International Classification:—C 07 c, A 61 k.

COMPLETE SPECIFICATION

Novel Steroids and Processes for the Manufacture Thereof

We, SCHERICO LIMITED, of Kapellplatz 10, Lucerne 2, Switzerland, a Swiss Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a group of novel alkylated steroid compounds and to methods of preparing the same.

Anti-inflammatory steroids of the pregnane series are now well known being used in medicine for the treatment of inflammatory conditions, rheumatic conditions and other diseases. Compounds of the pregnane series which possess anti-inflammatory action are characterised by the presence of a double bond in the 4-position or double bonds in the 1- and 4-positions, a ketonic oxygen atom in the 3- and 20-positions, a 17α-hydroxy group, a ketonic oxygen atom or β-hydroxyl group in the 11-position, and a hydroxyl or esterified hydroxyl group in the 21-position. The steroid molecule may, as is known, also contain other substituents but such other groups are not essential for the compound to have anti-inflammatory action although they may modify the exact nature thereof. It is the case however that all compounds of the pregnane series which possess the above-mentioned characteristic substituents have anti-inflammatory action.

We have now found that the introduction of a 16β-methyl group into anti-inflammatory steroids of the pregnane series confers further valuable properties on such compounds. Thus we have found that the presence of a 16β-methyl group confers upon the compound a pronounced and valuable naturetic and diuretic action. The presence of the 16β-methyl group also confers improved anti-inflamtory action upon the compound.

According to one feature of the invention therefore we provide novel compounds of the pregnane series having anti-inflammatory activity and characterised by possessing a double bond in the 4-position or double bonds in the 1- and 4-positions, ketonic oxygen atoms in the 3- and 20- positions, a 17α-hydroxy group, a β-hydroxy group or a ketonic oxygen atom in the 11-position, a hydroxyl or an esterified hydroxyl group in the 21-position, which compounds are also characterised by a β-methyl group in the 16-position.

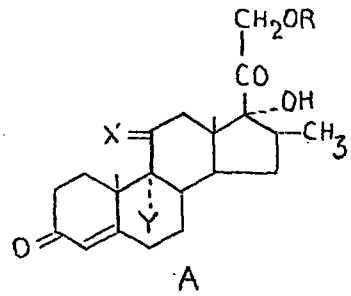
The anti-inflammatory compounds according to the invention may contain substituents in other parts of the molecule, for example, of the type hitherto used in anti-inflammatory steroids. As will appear hereinafter particularly valuable compounds are those which also possess a halogen atom (especially a fluorine atom) in the 9α-position. The invention also includes the 21-esters of the said 16β-methyl compounds.

As a result of the unique and unexpected property of naturesis and diuresis, steroid compounds which possess anti-inflammatory

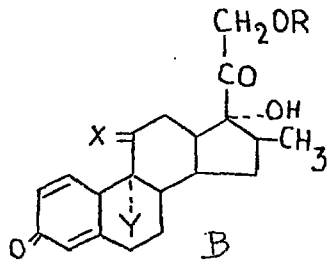
[Price 5s. 0d. (25p)]

properties but which are limited in their usefulness in the treatment of disease because of their inherent sodium-retaining effects have their usefulness extended by 16β-methylation. The invention also includes a therapeutic composition comprising a non-toxic carrier and a 16β-methyl compound as defined above.

The invention particularly relates to compounds represented by the following formulae:



A



B

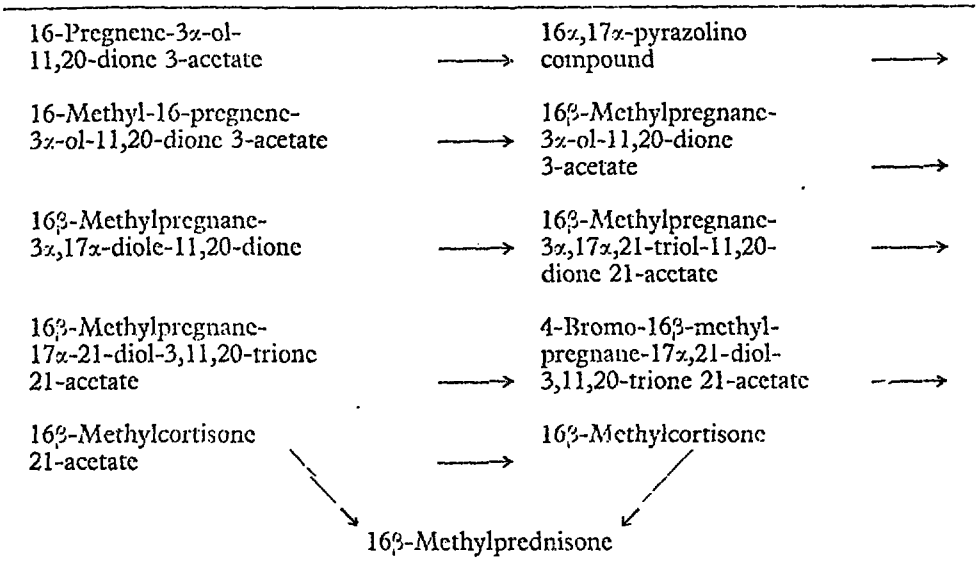
where R is hydrogen or a carboxylic acid acyl group having from 1 to 8 carbon atoms, e.g. a lower alkanoyl group, such as acetyl, propionyl, trimethylacetyl, cyclopentylacetyl or phenoxyacetyl, or phthaloyl or nicotinoyl; X is =O, or $<^{H}_{OH(\beta)}$; Y is hydrogen, bromine, chlorine or fluorine; By the expression "lower alkanoyl group" we mean a carboxylic acyl group having from 1 to 8 carbon atoms: "Lower" as applied to alkane or alkyl groups means having not more than 6 carbon atoms in the group.

Those compounds wherein X represents $<^{H}_{OH(\alpha)}$ and Y is hydrogen, although not therapeutically active *per se*, are convertible by known oxidative procedures into 11-keto compounds which possess physiological activity. Further, as noted above, the dienes as represented by formula B above, manifest a markedly greater therapeutic activity than the Δ^4-monoenes of formula A. The Δ^4-monoenes are, however, also valuable as intermediates in the preparation of the dienes of formula B. It is to be noted that the substitution of an α-halogen atom for hydrogen at position 9 is the 16β-methylated anti-inflammatory steroids of the invention will, as with those steroids previously known (e.g. prednisone, prednisolone and the like), enhance the anti-inflammatory properties thereof. Unfortunately, the introduction of these 9α-halogens has hitherto resulted in a marked increase in the salt-retaining properties of the known anti-inflammatory steroids, thus preventing their oral or injection administration in many instances, and making their use by topical application extremely hazardous. We have found unexpectedly, however, that the presence of a 16β-methyl radical, while inhibiting the increase in salt-retention effected by the introduction of the 9α-halogen, does not affect the enhanced therapeutic properties of these halo derivatives. Thus, these compounds can now be administered safely. Similarly, the salt-retaining properties of the non-halogenated steroids, such as, for example, cortisone and hydrocortisone, are markedly reduced. This is particularly surprising when it is noted that the substitution of a methyl group in the 2- or 6-position of such known steroids as 9α-fluoro-hydrocortisone or 9α-fluoro-prednisolone fails to alleviate their salt-retaining characteristic, which prevents their employment for therapeutic applications such as disclosed herein.

It should be noted that, while a lower alkyl substituent can be introduced into the 16-position by a number of procedures which result in the formation of 16β-alkyl corticoids and before or after the introduction of the 9α-halogen group, the following are preferred sequences for preparing the new anti-inflammatory compounds of our invention and useful homologues and anologues thereof. Alternative procedures for introducing the 16β-alkyl substituent comprise, for example reacting a 20-keto-16-dehydro steroid with a nitroalkane, following by reduction, quaternisation and pyrolysis, as hereinafter more particularly described.

Sequences A, B, and C illustrate desirable methods of preparation of the 16β-alkyl corticoids of our invention; sequence D a practicable procedure for obtaining the 16α-alkyl corticoid analogues, and sequence E a more convenient mode of effecting the production of the 9α-halogen derivatives of the 16α-alkyl and 16β-alkyl steroids described in the initial sequences A, B, C and D. For purposes of illustration, the methyl and acetyl groups are shown in these sequences, as well as in the subsequent description thereof, as the preferred 16-alkyl radical and 21-acyl substituent, respectively, and the 9α-bromo and 9α-fluoro substituents as the 9α-halogen radicals.

SEQUENCE A—



In that Sequence the 16β-methyl compounds of the invention are shown produced from the readily available 16-pregnene-3α-ol-11,20-dione 3-acetate. This is reacted with diazo-methane to give in excellent yield the pyrazolino derivative, which on pyrolysis is converted into 16β-methyl-16-pregnene-3-ol-11,20-dione 3-acetate. If the 16β-ethyl, 16β-propyl or 16β-butyl derivative is required the corresponding diazo-alkane is used. Although we prefer to pyrolyse the pyrazolino compound by heating it above its melting-point, pyrolysis may also be effected by heating the substance in a high boiling inert solvent, such as *p*-cymene or tetrahydronaphthalene. The unsaturation in the D-ring is conveniently removed by reductive hydrogenation preferably in the presence of a catalyst, such as palladium, whereupon there is obtained 16β-methyl-pregnane-3α-ol-11,20-dione 3-acetate.

For the introduction of a 17α-hydroxy group, we may convert the C—20 keto group of the 16β-methylpregnane-3α-ol-11,20-dione 3-acetate into an anol-acylate e.g. acetate by refluxing with acetic anhydride and a strong acid, e.g. *p*-toluene-sulphonic acid. We prefer not to isolate the enol-acylate but rather to react it *in situ* with a peroxy-acid, such as peracetic acid, whereby a second unisolated intermediate, the 17,20-oxido compound is obtained. Treatment of the reaction mixture with alkali hydrolyses the epoxide and forms 16β - methylpregnane - 3α,17α - diol - 11,20 - dione. In this procedure, whereby the hydroxyl group is introduced at C—17, other acylating agents, such as isopropenyl acetate, may also be used in place of acetic anhydride. Furthermore, the strong acid catalyst is not necessarily limited to *p*-toluenesulphonic acid, since other strong acids such as perchloric acid are equally effective in producing the intermediate enol-acetate. As indicated above, the enol-acetate is converted to the respective 17,20-epoxide by means of a peroxy-acid, as for example peracetic acid, perbenzoic acid, monoperphthalic acid or pertrifluoro-acetic acid.

The invention therefore provides a process for the production of a 16β-alkyl-17α-hydroxy steroid which comprises reacting a starting material having the pregnane carbon skeleton and containing a 16,17-double bond in conjugated relationship with a 20-keto group with a diazoalkane, pyrolysing the resultant 16,17-alkylidene diazo steroid to form a 16-alkyl-16-dehydro steroid and introducing a 17α-hydroxy group by epoxidising the 16,17-double bond, reacting the 16α,17α-epoxide with a hydrogen halide followed by catalytic hydrogenation whereby there is obtained the desired 16β-alkyl compounds, the 16-alkyl group of which contains up to 6-carbon atoms. Alternatively, the 17α-hydroxy group may be introduced by hydrogenating the 16,17-dehydro compound at the 16,17-positions by catalytic hydrogenation, enol-acylating the resulting compound, epoxidising the enol acetate at the 17,20 positions and hydrolysing the 17,20-epoxide to form the desired 16β-alkyl-17α-hydroxy steroid. In these processes the starting material may be a 3,11-diketo steroid.

Introduction of the 21-acetoxy group or other 21-ester is effected in the conventional manner, such as by bromination of the C—21 methyl group, followed by reaction of the bromo-compound with, for example, sodium or potassium acetate, whereby 16β-methyl-

pregnane-3α,17α,21-triol-11,20-dione 21-acetate is formed. Although acetoxylation has been shown by way of illustration, it will be apparent that other acyloxylations, such as the introduction of a propionoxy group, for example, can be analogously effected.

In order to obtain the 3-keto-Δ^4- or 3-keto-$\Delta^{1,4}$- system, the saturated pregnane 21-ester is oxidised, preferably with N-bromoacetamide, to 16β-methylprognane-17α-21-diol-3,11,20-trione 21-acetate. Other oxidising agents which may be used in this reaction are, for example, N-bromo-succinimide, chromium trioxide in pyridine, or chromium trioxide in acetone with sulphuric acid. The Δ^4-double bond is now conveniently introduced into the A-ring by brominating 16β-methylpregnane-17α,21-diol-3,11,20-trione 21-acetate in the conventional manner whereby the intermediate 4-bromo-compound is formed, which may or may not be isolated. Although we prefer to halogenate with bromine, other halogenating agents such as chlorine are equally effective. Dehydrohalogenation of this 4-bromo intermediate, also, in a conventional manner such as by reaction with semicarbazide followed by hydrolysis of the resultant 3-mono-semicarbazone, or by refluxing with dimethylformamide optionally in the presence of lithium chloride, or by refluxing with organic tertiary amines such as collidine, causes elimination of hydrogen halide and introduction of the Δ^4-double bond, yielding 16β-methylcortisone 21-acetate. The dehydrobromination may be effected in the presence of calcium carbonate. This compound can then be saponified to produce the dioltrione, 16β-methylcortisone, by reaction with hydrolytic agents such as aqueous methanolic potassium bicarbonate or with such reagents as sodium carbonate, sodium hydroxide, sodium alkoxides, (e.g. sodium ethoxide) or acids such as *p*-toluenesulphonic acid. 16β-Methylcortisone can now be re-esterified at C—21 by introducing any desired acid residue.

Introduction of the Δ^1-bond may be carried out by subjecting 16β-methylcortisone 21-acetate or 16β-methylcortisone to the microbiological action of a dehydrogenating microorganism. We prefer to use *Bacillus sphaericus* (American Type Culture Collection 7055) or *Carynebacterium simplex* (A.T.C.C.6946) according to analogous procedures described in Belgian Patent No. 540,478. It is essential, however, that the compound subjected to fermentative dehydrogenation contain a 3-keto-Δ^4-system and thus the first opportune time to insert the Δ^1-bond is after the formation of 16β-methylcortisone or its 21-ester. There is thus produced 16β-methyl-1,4-pregnadiene-17α,21-diol-3,11-20-trione.

The dehydrogenation of the A ring whereby the Δ^1-bond is inserted can also be accomplished by other known methods, such as by reacting the pregnane ester, 16β-methylcortisone 21-acetate, or the saturated pregnane, 16β-methyl - pregnane - 17α,21 - diol - 3,11,20-trione 21 - acetate with selenium dioxide for example, or with chloranil, at elevated temperatures or by the well-known methods of bromination and dehydrobromination.

This latter procedure is illustrated by reaction Sequence B:

Sequence B

16β - Methylpregnane - 17α,21 - diol - 3,11,20 - trione 21 - acetate
→2,4 - dibromo - 16β - methylpregnane - 17α,21 - diol - 3,11,20 - trione 21 - acetate
→16β - methylprednisone 21 - acetate.

In the second of these steps dehydrobromination may be effected as in Sequence A, preferably using dimethylformamide as the dehydrobrominating agent. The product may be hydrolysed and re-esterified with any desired lower alkanoic acid.

The foregoing reaction sequence and discussions have applied to the preparation of compounds containing a keto function at C—11. It is apparent that if any of the starting materials contains a hydroxyl group at C—11α, that group will be carried through the series of reactions. However, bearing in mind the ready availability of the original starting material, 16-pregnene-3α-ol-11,20-dione 3-acetate, we prefer initially to carry out the reactions so as to produce 11-keto compounds and, when required, to reduce the 11-keto group to an 11-hydroxyl group preferably having the β-configuration. Such a transformation is illustrated by reaction Sequence C.

Sequence C

16β-Methylcortisone 21-acetate
→16β-Methylcortisone 3,20-bis-semicarbazone 21-acetate
→16β - methylhydrocortisone - 3,20 - bis - semicarbazone
→16β-methylhydrocortisone
→16β-methylprednisolone
→16β-methylprednisolone 21-acetate

The 3,20-bis-semicarbazone of 16β-methylcortisone 21-acetate is first formed, and, the sensitive 3,20-keto groups having thus been protected, the 11-keto group is reduced with sodium borohydride in aqueous tetrahydrofuran to yield the bis-semicarbazone of 16β-

methylhydrocortisone. The semicarbazide groups are removed by means of pyruvic acid, or by hydrolysis with dilute hydrochloric or nitrous acid, giving 16β-methylhydrocortisone.

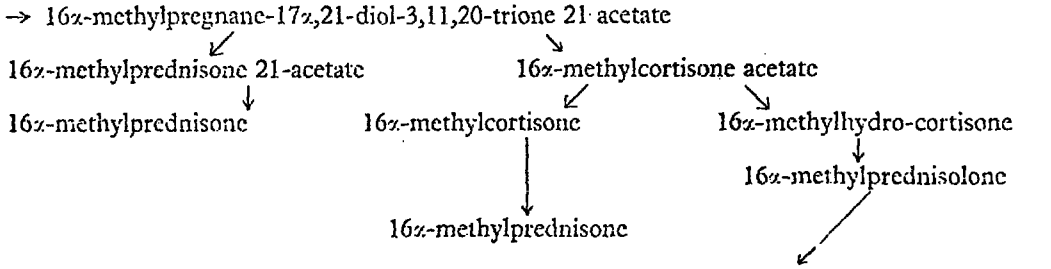
Other methods of protecting the 3,20-keto groups may be employed, such as forming a 3,20-bis-ethylene ketal and then reducing the 11-keto group by means of sodium borohydride, lithium borohydride, or lithium aluminium hydride. Acid hydrolysis of the 11-hydroxy-bis-ketal so formed yields 16β-methylhydrocortisone.

16β-Methylhydrocortisone can be converted into 16β-methylprednisolone by means of the microbiological fermentation or chemical methods described above for the conversion of 16β-methylcortisone to 16β-methylprednisone. Similarly, 16β-methylprednisolone can be esterified according to any of the well-known techniques so as to produce the corresponding 21-acylate, e.g. 16β-methylprednisolone 21-acetate.

16β-Methylprednisone 21-acetate itself can be converted into 16β-methylprednisolone 21-acetate by first selectively protecting the 3,20-keto groups as described above for the monoenes and then selectively reducing the 11-keto function.

The 16α-lower alkyl compounds are desirably prepared by the procedure illustrated in Sequence D.

SEQUENCE D



3α-Hydroxy- (or acyloxy) 16-pregnene-11,20-dione is added to a standard Grignard reagent, for example methyl magnesium iodide, and refluxed to effect the production of the corresponding saturated 16α-methyl derivative, 3α-hydroxy-16α-methyl-pregnane-11,20-dione. The reaction is preferably carried out in the presence of a copper halide such as cuprous or cupric chloride. The methyl iodide derivative is again employed merely for purposes of illustration, and it will be apparent that where it is desired to prepare other 16α-lower alkyl compounds such as the 16α-ethyl, 16α-isopropyl or 16α-*tert.*-butyl homologues, for example, the corresponding alkyl magnesium iodide, or the bromine and chlorine analogues thereof is employed as the Grignard reagent.

The product of this Grignard reaction, 3α-hydroxy-16α-methyl-pregnane-11,20-dione, is then hydroxylated by standard procedures at the C—17 position, as for example, by reaction with acetic anhydride and *p*-toluene sulphonic acid, followed by peracetic acid and then by alkaline hydrolysis to form 16α-methylpregnane-3α,17α-diol-11,20-dione. Introduction of the 21-acetoxy group, or other 21-acyloxy group, is accomplished by known methods, such as for example, by bromination of the C—21 methyl group in an inert solvent such as chloroform with the sequential reaction of this product with sodium or potassium acetate in acetone or dimethylformamide. The product thus formed is 3α,17α,21-trihydroxy-16α-methylpregnane-11,20-dione 21-acetate. The hydroxyl group at position 3 in this latter compound is then transformed to a keto group, preferably by means of N-bromoacetamide to cause the production of 17α,21-dihydroxy - 16α - methylpregnane - 3,11,20 - trione 21 - acetate. Other known equivalent oxidizing agents such as those described hereinabove for preparing the 3-keto derivative of the 16β-methyl compounds can, of course, also be employed. The $\Delta^{1,4}$-double bonds are then introduced into the A-ring by dihalogenation, e.g. dibromination, of this 3-keto derivative by the rapid introduction of

bromine in a suitable non-reactive organic solvent such as dioxan followed by dehydrohalogenation in a conventional manner such as refluxing the brominated steroid with dimethylformamide preferably in the presence of calcium carbonate and lithium chloride or with a tertiary base e.g. collidine, or by the use of other standard procedures as described hereinabove with relation to the preparation of the 16β-methyldienes. The resultant product is 16α-methylprednisone 21-acetate.

A preferred method for introducing a 9α-halogeno (i.e. fluoro-, chloro- or bromo-) substituent is illustrated by reaction Sequence E.

SEQUENCE E

16-Methylprednisolone acetate
↓
16-methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 21-acetate
↓
9α-bromo-16-methylprednisolone acetate
↓
9β,11β-oxido-16-methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 21-acetate
↓
9α-fluoro-16-methylprednisolone 21-acetate
↙ ↘
9α-fluoro-16-methylprednisolone 9α-fluoro-16-methylprednisone 21-acetate
↘
9α-fluoro-16-methylprednisone

A 9α-halogen atom, preferably fluorine, is introduced into 16(α or β-methylprednisolone acetate by dehydration with an alkyl- or aryl sulphonyl chloride, e.g. methanesulphonyl chloride, in an alkaline organic medium, e.g. pyridine, with the production of 16(α or β)-methyl - 1,4,9(11) - pregnatriene - 17α,21-diol - 3,20 - dione 21 - acetate. For convenience in further describing this series of reactions, the α- or β- isomerism of the 16-methyl substituent will not normally be explicitly referred to since this characteristic does not affect the step-wise reactions, nor do these steps affect the specific 16α or 16β-isomerism of the reactant alkylated steroid.

Introduction of a halogen, preferably bromine at this point in the procedure, at the 9α-carbon position is accomplished by conventional means, such as, for example, by reacting the $\Delta^{9,(11)}$-steroid with hydrobromous acid which can be and indeed is preferably prepared *in situ* from the reaction of, for example, N-bromoacetamide and perchloric acid, yielding directly the corresponding 9α-bromo-16-methylprednisolone 21-acetate. Esters of this type are useful anti-inflammatory compounds and are at the same time readily converted by oxidation into the corresponding 11-ketones by known techniques such as, for example, with chromium trioxide in pyridine and readily hydrolyzed at the C—21 position by such standard hydrolytic agents as aqueous methanolic potassium bicarbonate, sodium carbonate or concentrated hydrochloric acid in methanol-chloroform as disclosed hereinabove, to prepare the corresponding 21-alcohols.

Again alternatively, the 9α-bromohydrins can be refluxed with mild alkali, such as sodium acetate in methanol, to form the corresponding 9β,11β - oxido derivative, 9β,11β - oxido - 16 - methyl - $\Delta^{1,4}$ - pregnadiene - 17α,21 - diol - 3,20 - dione 21 - acetate. This latter compound is then reacted with hydrogen fluoride in chloroform with or without ethanol and/or tetrahydrofuran to produce 9α - fluoro - 16 - methylprednisolone acetate. The substitution of anhydrous hydrogen chloride for hydrogen fluoride in this reaction results in the production of the corresponding 9α-chloro derivatives. Again these compounds can be oxidized to the corresponding 11-ketones by standard agents, e.g. chromium trioxide or N-halosuccinimides, or hydrolyzed to the corresponding 21-alcohols by standard saponification procedures (e.g. aqueous methanolic potassium bicarbonate or concentrated hydrochloric acid in methanol). 9α - Fluoro - 16 - lower alkyl prednisolones and 9α - fluoro - 16 - lower alkyl prednisones and particularly 9α - fluoro - 16α - methylprednisolone, 9α - fluoro - 16α - methylprednisone, 9α - fluoro - 16β - methylprednisolone and 9α - fluoro - 16β - methylprednisone may be prepared by these procedures.

The invention also provides processes for the preparation of a 16(α or β)-methyl - 1,4,9(11) - pregnatriene - 3,20 - dione - 17α,21 - diol or a 21 - carboxylates thereof which comprises dehydrating a 16(α or β) - methyl - 1,4 - pregnadiene - 11β,17α - 21 - triol - 3,20 - dione or a 21 - carboxylate thereof, whereafter, if desired, the triene is reacted with a hypohalous acid to produce a 9α-halo compound in which the 9-halogeno atom is bromine, chlorine or iodine, whereafter if desired the 9α-halo compound is reacted with a base to form a 9β,11β-oxido compound. The 9β,11β-oxido compound may then be

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In the
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(i) 16(α
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21-e
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(ii) 9β,1
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reacted with hydrogen fluoride to form a 9α - fluoro - 11β - hydroxy compound which is then, if desired, oxidised to form the 9α - fluoro - 11 - ketone.

In the above processes the following novel intermediates are hence important compound:—

(i) 16(α or β) - methyl - 1,4,9(11) - pregnatriene - 17α,21 - diol - 3,20 - dione and 21-esters thereof particularly the 21-acetate.

(ii) 9β,11β - oxido - 16(α or β) - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione and 21-esters thereof particularly the 21-acetate.

(iii) 9α - halogeno - 16(α or β) - methyl - 1,4 - pregnadiene - 11β,17α - 21 - triol - 3,20 - dione and 21-esters thereof, particularly the 21-acetate, in which the 9-halogeno atom is chlorine, bromine or iodine.

(iv) Δ^4 compound corresponding to (i).

In certain cases both the 16α- and the 16β-alkyl steroids are produced. For example from hydrocortisone, cortisone and their 9α-halogeno (i.e. bromo-, chloro- and fluoro) derivatives, there may be obtained the corresponding 16-dehydro compounds. This is illustrated by the following series of reactions (Sequence F) starting from 9α-fluoro-hydrocortisone:

SEQUENCE F

9α-Fluorohydrocortisone-bis-semicarbazone
↓
9α-fluoro-4,16-pregnadiene-11β,21-diol-3,20-dione
↓
9α-fluoro-16α-nitromethyl-4-pregnene-11β,21-diol-3,20-dione
↓
16α-aminomethyl derivative
↓
9α-fluoro-16-methylene-4-pregnene-11β,21-diol-3,20-dione
↓
9α-fluoro-16-methyl-4,16-pregnadiene-11β,21-diol-3,20-dione
↓
9α-fluoro-16α,17α-oxido-16-methyl-4-pregnene-11β,21-diol-3,20-dione
↓
9α-fluoro-16α-bromo-16-methyl-4-pregnene-11β,17α,21-triol-3,20-dione
↓
9α-fluoro-16-methyl-4-pregnene-11β,17α,21-triol-3,20-dione

9α-Fluorohydrocortisone, in the form of its bis-semicarbazone in order to protect the keto groups at C3 and C.20, is dehydrated by heating with acetic anhydride to give the 4,16-pregnadiene and the semicarbazide residues are removed with pyruvic acid and *p*-toluenesulphonic acid. The product is treated with nitromethane in pyridine to give the 16α-nitromethyl derivative, which is reduced, e.g. with tin and hydrochloric acid, to the 16α-aminomethyl compound. This is then converted by exhaustive methylation e.g. with methyl iodide and pyrolysis of the quaternary salt into the 16-methylene compounds, which isomerises to 9α - fluoro - 16 - methyl - 4,16 - pregnadiene - 11β,21 - diol - 3,20 - dione. This is reacted with hydrogen peroxide to yield the 16α,17α-oxido compound which is rearranged by hydrogen bromide to form the 17α-hydroxy compound which on reduction forms a mixture (separable by chromatography) of 9α - fluoro - 16α and 16β - methyl - 4 - pregnene - 11β,17α,21 - triol - 3,20 - diones. This product may be converted into the corresponding 1,4 - pregnadiene by means of cultures of *Bacillus sphaericus* (A.T.C.C. 7055) or *Corynebacterium simplex* (A.T.C.C. 6946).

If, instead of nitromethane, nitro derivatives of other lower alkanes are used in this series of reactions the corresponding 16-alkanes, e.g. 16-ethyl, 16-propyl and 16-butyl compounds.

The 16-alkyl-16-dehydro-20-keto steroids resulting from the pyrolysis of the quaternized steroids can be converted to corticoids in the manner already described, e.g. hydrogenation of the double bond with palladium on carbon or Raney nickel, introduction of the 17-hydroxy group by means of enol acylation and peroxidation (e.g., acetic anhydride and *p*-toluenesulphonic acid followed by treatment with peracetic acid), introduction of the 21-acetate by means of bromination and acetoxylation (sodium acetate in dimethylformamide) and elaboration of the A ring in the conventional manner to introduce the Δ^4 or $\Delta^{1,4}$-double bond(s) and 3-keto group. Alternatively, they may be epoxidised with alkaline hydrogen peroxide to yield 16α,17α-epoxy-16β-alkyl-20-keto-steroids. These are then treated with a hydrohalic acid such as hydrogen bromide and reduced e.g. with zinc dust or Raney nickel or palladium and hydrogen. This results in the formation of both 16α -

alkyl - 17α - hydroxy - 20 - keto steroids, and 16β - alkyl - 17α - hydroxy - 20 - keto steroids. After separation, e.g., by chromatography, these are then handled in the usual fashion, e.g. the 21-acetate is introduced via bromination and acetoxylation, and the A ring elaborated via oxidation of the 3-hydroxyl (if present), followed by bromination debromination.

Since the higher diazo-alkanese are not easily prepared it is preferred to follow reaction Sequence G when a 16β-alkyl steroid is desired.

SEQUENCE G

16α-Methyl-4-pregnene-3,11,20-trione
↓ Br
17-bromo-16α-methyl-4-pregnene-3,11,20-trione
↓ —HBr
16-methyl-4,16-pregnadiene-3,11,20-trione
↓ H_2
16β-methyl-4-pregnene-3,11-20-trione

Thus far, we have described as starting materials only compounds which are available from bile acids. There are, however, several other classes of starting material which are extremely useful, e.g. diosgenin and smilagenin.

For example, diosgenin is readily converted into 16-dehydropregnenolone and thence, by Grignard reaction with methyl magnesium halide, into 16α-methylpregnenolone or by the diazo-methane reaction, into 16β - methyl - 16 - pregnenolone. The former compound is hydrogenated, e.g. by means of palladium catalyst, to 16α - methylallopregnane - 3β - ol - 20 - one, and the cortical side chain elaborated in the usual way (enol acetylation at C—17 and epoxidation) to give the 17α - hydroxy - 20 ketone followed by bromination and acetoxylation at C—21. The C—3 hydroxyl is oxidized to the ketone, a 2,4-dibromo is prepared using bromine and dioxan or other inert solvent and dehydrobromination is effected by means of a tertiary base e.g. collidine, or dimethylformamide to yield 16α - methyl - $\Delta^{1,4}$ - pregnadiene - 17α,21 - diol - 3,20 - dione 21 - acetate. This can be hydroxylated at position C—11 to yield either 16α - methylprednisolone or 16α - methyl - 11 - epiprednisolone. This last compound may be acetylated selectively at C—21 to yield a monoacetate and then oxidized at C—11 to give 16α - methylprednisone 21 - acetate. Also, 16α - methyl - 11 - epiprednisolone 21 - acetate may be dehydrated at C—11 by tosylation of the C-11α-hydroxyl followed by treatment with sodium acetate to yield 16α - methyl$^{[1,4,9(11)]}$-pregnatriene - 17α,21 - diol - 3,20 - dione 21 - acetate, a compound previously described as an intermediate for the preparation of 9α - halo - 16α - methyl corticoids.

Alternatively, 16α- or 16β - alkyl - allopregnane - 17α - 21 - diol - 3,20 - dione or its 21 - acetate can be microbiologically hydroxylated in the 11-position, e.g. with *Rhizopus nigricans* (A.T.C.C. 6227B) or *Curvularia lunata* (N.R.R.L. 2380), the C—21 hydroxyl acetylated and the 3 - keto - Δ^4 - or 3 - keto - $\Delta^{1,4}$ - system introduced in the usual manner.

The 16 - methyl - 16 - dehydropregnenolone described above is hydrogenated to 16β - methylallopregnane - 3β - ol - 20 - one. This may be treated in an exactly analogous fashion to yield 16β - methyl - $\Delta^{1,4}$ - pregnadiene - 17α,21 - diol - 3,20 - dione 21 - acetate, 16β - methylprednisolone 21 - acetate, 16β - methyl - 11 - epi - prednisolone 21 - acetate, and 16β - methyl - $\Delta^{1,4,9,(11)}$ - pregnatriene - 17α,21 - diol - 3,20 - dione 21 - acetate (a compound previously described as an intermediate for the preparation of 9α - halo - 16β - methyl corticoids).

Other important starting materials are the 12-oxygenated sapogenins, such as hecogenin, rockogenin and gentrogeinin. For example, hecogenin has been converted to 11 - keto - 16 - dehydroallopregnane - 3β - ol - 20 - one. A 16α-methyl substituent can be introduced by means of the Grignard reaction and the side chain and A ring elaborated in the usual manner to contain the $^4\Delta$- or $\Delta^{1,4}$-double bonds(s) and 3-keto and 21-acyloxy or hydroxyl groups, or the 16β-methyl substituent can be introduced via the diazomethane reaction and the side chain and A ring elaborated again by these same procedures.

The invention also includes a process for

the preparation of 2,4 - dibromo - 16(α or β) - methyl pregnane (5α or 5β) - 17α,21 - diol - 3,11,20 - trione 21 - ester which comprises dibrominating 16(α or β) - methyl pregnane (5α or β) - 17α,21 - diol - 3,11,20 - trione 21 - ester with a brominating agent e.g. molecular bromine. The resulting 2,4 - dibromo compound may then be converted to the corresponding $\Delta^{1,4}$-compound by dehydrobromination with a dehydrobromination agent e.g. dimethylformamide (if desired in the presence of calcium carbonate) or a tertiary amine e.g. collidine.

The invention also includes a process for the preparation of 4-bromo-16β - methylpregnane - 17α,21 - diol - 3,11,20 - trione 21 - ester and a process for the dehydrobromination of this compound to the corresponding Δ^4-compound, the bromination and dehydrobromination being effected in an analogous manner to the preparation of the 2,4-dibromo and $\Delta^{1,4}$-compounds as described above.

The invention also includes analogous processes for the preparation of corresponding 11 - desoxy - 2,4 - dibromo,11 - desoxy $\Delta^{1,4}$, 11 - desoxy 4 - bromo and 11 - desoxy Δ^4 compounds.

The various bromine compounds produced in these processes are also included in the invention i.e.

a) 2,4 - dibromo - 16(α or β)methyl pregnane (5α or 5β) - 17α,21 - diol - 3,11,20 - trione 21-ester e.g. the 21-acetate

b) 4 - bromo - 16β methyl pregnane 17α,21 - diol - 3,11,20 - trione 21-ester e.g. the 21-acetate.

c) 2,4 - dibromo - 16β methyl pregnane (5α or 5β) - 17α,21 - diol - 3,20 - dione 21-ester e.g. the 21-acetate.

d) 4 - bromo - 16β - methyl pregnane - 17α,21 - diol - 3,20 - dione - 21 - ester e.g. the 21-acetate.

The invention also provides a process for the preparation of 11 - desoxy - 16(α or β) - alkyl - 17α - hydroxy - 20 - keto compounds of the pregnane (5α or 5β) series in which an 11 - desoxy - 16 - alkyl - 20 - keto compound of the pregnane series, said alkyl group containing 1—6 carbon atoms, is enol acylated with a lower alkanoic acid anhydride in the presence of a strong acid catalyst; the $\Delta^{17(20)}$ - dehydro - 20 - acyloxy compound thereby formed is reacted with a peroxy acid and the resultant 17,20-epoxide is hydrolyzed. The resulting compound may then be subjected to the further steps of introducing a C—21 alkanoyloxy group by bromination at C—21 followed by treatment with an alkali metal lower alkanoate to form a 21-alkanoate of a 3,17α,21 - trihydroxy - 20 - keto - 16 - alkylpregnane (α or 5β), oxidizing the 3-hydroxy group to keto, and introducing Δ^4 or $\Delta^{1,4}$ unsaturation in the A-ring. Hydroxylation may be effected at C—16 by a microbiological oxidation procedure.

It should be noted that the invention specifically includes within its scope the following useful intermediates.

1) A 16 - (α or β) - alkyl - 17α - hydroxy - 20 - keto - pregnane (5α or 5β) having a 3—X—21—R substituent wherein R represents hydrogen, bromine, hydroxyl or alkanoyloxy; and X represents hydroxy, alkanoyloxy or oxo, the 16-alkyl group containing 1—6 carbon atoms.

2) A 16(α or β) - alkyl - 21 - alkanoyloxy - 17(20) - pregnene (5α or 5β) - 3 - ol and 3-alkanoyl esters thereof, the 16-alkyl group containing 1—6 carbon atoms.

3) A 16(α or β) - alkyl - 17,20 - oxido - 20 - alkanoyloxy - pregnane (5α or 5β) - 3 - ol and 3-alkanoyl esters thereof, the 16-alkyl group containing 1—6 carbon atoms.

4) A 16(α or β) - alkyl - 20 - keto - 21 - R - pregnane (5α or 5β) - 3,17α - diol and 3-alkanoyl esters thereof wherein R is a hydrogen or a bromine atom or an alkanoyloxy group, the 16-alkyl group containing 1—6 carbon atoms.

5) A 16(α or β) - alkyl - 3,20 - diketo-pregnane (5α or 5β) - 17α,21 - diol and 21-alkanoyl esters thereof, the 16-alkyl group containing 1—6 carbon atoms.

6) A 16(α or β) - alkyl - 3,20 - diketo - 4 - pregnane - 17α,21 - diol and 21-alkanoyl esters thereof, the 16-alkyl group containing 1—6 carbon atoms.

7) A 16(α or β) - alkyl - 3,20 - diketo - 1,4 - pregnadiene - 17α,21 - diol and 21-alkanoyl esters thereof, the 16-alkyl group containing 1—6 carbon atoms.

8) 16α - Methylallopregnane - 3β,17α - diol - 20 - one.

9) 16α - Methylpregnane - 3α,17α - diol - 20 - one.

10) 16α - Methylallopregnane - 3β,17α,21 - triol - 20 - one 21 - alkanoate.

11) 16α - Methylpregnane - 3α,17α,21 - triol - 20 - one 21 - alkanoate.

12) 16α - Methylpregnane - 17α,21 - diol - 3,20 - dione 21 - alkanoate.

13) 16α - methylallopregnane - 17α,21 - diol - 3,20 - dione 21 - alkanoate.

14) 16α - Methyl - 4 - pregnene - 17α,21 - diol - 3,20 - dione 21 - alkanoate.

15) 16α - Methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione 21 - alkanoate.

16) 16α - Methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione.

We have found that, as is generally known in the art, esterification e.g. with mono- or poly-carboxylic acids can further enhance the duration of activity of the active steroid alcohol and provides a compound which is more effectively administered patenterally. We have found that acid residues, e.g. derived from unsubstituted or cycloalkyl substituted alkanoic acids having not more than 8 carbon

atoms such as obtained from acetic acid, propionic acid, trimethylacetic acid, tert-butylacetic acid, cyclopenylpropionic acid, furoic acid or phenoxyacetic acid provide useful esters. Similarly, partial-esters of poly-basic acids, such as obtained from phthalic, succinic, tartaric, citric and the like, provide esters which can be solubilized by formation of a salt of the free carboxyl group with an alkali metal, such as sodium. In place of the dibasic organic acids, there can be used mono- or poly-basic inorganic acids which may form partial esters suitable for salt formation, such as phosphate, thus producing a dihydrogen phosphate ester which itself can be further solubilised by salt formation. Such esters can be formed by conventional methods.

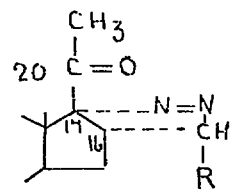
Certain of the novel compounds of our invention are valuable as intermediates in the formation of the corresponding 11-keto steroids, e.g. 16β-alkyl cortisone, 16β-alkyl prednisone. The alkylated (notably the 16β-methyl-substituted) dienes with or without the 9α-halogen substituent are particularly valuable therapeutic agents possessing similar therapeutic effects in the treatment of inflammatory diseases, such as for example, arthritis, dermatitis, asthma, and the like, and are normally administered in a daily maintenance dosage range of 0.50 to 10 mg.; the preferred daily dose of the non-halogenated dienes being from about 2 mg. to about 10 mg. and that of the halogenated, and preferably the 9α-fluoro-alkylated dienes being in the range of 0.5 mg. to 5.0 mg.

The non-halogenated 16β-methyl anti-inflammatory monoenes of our invention are, in addition to being valuable intermediates in the formation of the corresponding dienes, also active as anti-inflammatory agents and in inhibiting renal tubular reabsorption of sodium. A daily dosage of 25 mg. to 100 mg. is recommended for oral administration of these monoenes to induce sodium and water diuresis, e.g. in the treatment of ascites, congestive heart failure and cyclical edema.

Similarly, the 9-halo-16β-methylated anti-inflammatory monoenes of our invention are also useful as anti-inflammatory agents, since they manifest an enhanced activity in the treatment of such inflammatory disease as arthritis, dermatitis, asthma, and the like. When administered orally, the recommended daily dosage is in the range of 4 mg. to 15 mg.

When treatment so indicates, these 16β-methylated dienes and monoenes can be administered parenterally in the form of therapeutically acceptable solutions and suspensions, e.g., in aqueous media, or where oral administration is indicated, can be incorporated into tablets (Normally from about 0.50 mg. to 5 mg. per tablets), elixirs and other known pharmaceutical dosage forms by standard procedures. They can also be administered topically in the form of ointments or creams, or as solutions, e.g. in dimethyl acetamide or diethyl acetamide, or in the form of suppositories dissolved or suspended in a fatty or waxy vehicle which melts at approximately body temperature, or as aerosols when mixed with suitable materials, such as isopropyl myristate and dichlorodifluoromethane.

In the specification of the copending application No. 7840/62 (Serial No. 901093). there is described and claimed a steroid of the pregnane [5α, 5β or $\Delta^{(5(6))}$] series having a 3-hydroxy or alkanoyloxy substituent, a 20-keto substituent, an 11-hydroxy or 11-keto substituent and at C—16 and C—17 an alkylenediazo grouping, said compounds having a D-ring with substituents as shown in the formula



wherein R represents hydrogen or an alkyl group containing 1—5 carbon atoms, and the preparation thereof by reacting the corresponding 16(17)-ene with diazomethane or with a diazoalkane containing 2 to 6 carbon atoms.

The following Examples are further illustrative of the invention:—

EXAMPLE 1

16β-Methylcortisone 21-Acetate

A. Product from the reaction of 16-pregnen-3α-ol-11,20-dione 3-acetate and diazomethane

A solution of 3.72 grams of 16-pregnen-3α-ol-11,20-dione 3-acetate in 5 ml. of methylene chloride is added to a solution of about 1 gram of diazomethane in 70 ml. of ether which had been cooled to −10°C. The mixture is kept at 0° C for four hours, then allowed to warm up to room temperature. The resulting pyrazoline crystallizes directly from the reaction mixture to yield 3.32 g., m.p. 199—200° C. dec., $[\alpha]_D$+149.6° (dioxan).

Anal. Calcd. for $C_{24}H_{34}O_4N_2$: C, 69.23; H, 8.27; N, 6.76.
Found: C, 69.51; H, 7.98; N, 6.69.

B. 16 - Methyl - 16 - pregnen - 3α - ol - 11,20 - dione 3 - acetate

The pyrazoline of Example 1A (3.00 g.) is heated under reduced pressure to about 210° C until the evolution of nitrogen ceases. The resulting oil is cooled to room temperature, then crystallized by the addition of ether. The precipitate is filtered and dried, yielding 2.12 g. of 16-methyl-16-pregnen-3α-ol-11,20-dione 3-acetate, m.p. 163—166°C., $[\alpha]_D$ +69.9° (dioxan) λ max 248 mμ (ε 10,800).

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87.
Found: C, 74.85; H, 8.55.

C. 16β - Methylpregnan - 3α - ol - 11,20 - dione 3 - acetate

A solution of 12.0 g. of the 16-pregnene compound of Example 1B in 250 ml. of glacial acetic acid is hydrogenated at room temperature and atmospheric pressure in the presence of 3.0 g. of 10% palladium on charcoal catalyst. After the reduction is completed (about 1.5 hours), the catalyst is removed by filtration, and the filtrate concentrated under reduced pressure to about 100 ml. The residue is poured into water, and the precipitated solid filtered, washed and dried, yielding 11.4 g. of impure 16β-methylpregnan-3α-ol-11,20-dione 3-acetate, m.p. 148—155° C. After recrystallization from acetone-hexane there is obtained 8.40 g. of the product of this example i.e. m.p. 160—163° C, no U.V. absorption at 220—300 mμ, $[\alpha]_D$ +93.6° (dioxan).

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 74.19; H, 9.34
Found: C, 74.37; H, 9.06

D. 16β - Methylpregnane - 3α,17α - diol - 11,20 - dione

A solution of 6.77 g. of 16β-methylpregnane-3α-ol-11,20-dione 3-acetate, in 156 ml. of acetic anhydride containing 3.89 g. of *p*-toluene-sulphonic acid is kept at 100° C for six hours; during which time about 16 ml. of distillate is removed every half hour by the application of vacuum. The resulting oily residue is dissolved in 80 ml. of benzene and washed three times with water, then with a solution of 1.55 g. of sodium acetate in 20 ml. of water. The benzene layer is dried over magnesium sulphate, and then stirred for 18 hours at 25° C with a mixture of 0.52 g. of sodium acetate in 12 ml. of commercial 40% peracetic acid. Excess peracetic acid is then destroyed by the dropwise addition of a solution of 15.5 g. of sodium sulphite in 52 ml. of water, while maintaining the temperature between 10—20° C. An additional 1.57 g. of sodium sulphite is then added, and the mixture stirred overnight until a starch-iodide test is negative. The benzene layer is separated, washed three times with water, and evaporated. To the resulting residue which is dissolved in 345 ml. of methanol, there is added a solution of 3.62 g. of sodium hydroxide in 39.5 ml. of water, and the mixture refluxed for 15 minutes. After neutralization with 4 ml. of glacial acetic acid, the solution is concentrated under reduced pressure to a volume of about 50 ml. This concentrate is poured into a mixture of ice and water and the solid which precipitates is filtered and dried, yielding 6.69 g. of impure 16β - methylpregnane - 3α,17α - diol - 11,20 - dione, m.p. 105—154° C. This is chromatographed on "Florisil," (Registered Trade Mark) and the material eluted with 33—50% ether hexane is combined and crystallized from acetone-hexane, yielding 2.09 g. of 16β - methylpregnane - 3α,17α-diol-11,20-dione, m.p. 181.5—185°C. $[\alpha]_D$ 83.6 (dioxan).

Anal. Calcd. for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45
Found: C, 72.82; H, 9.25.

16β - Methylpregnane - 3α,17α - diol - 11,20 - dione 3 - acetate is prepared by adding to 1 gram of the corresponding 16β - methylpregnane - diol a solution of 0.5 ml. of acetic anhydride in 2.3 ml. of pyridine. After standing one hour at room temperature, the reaction mixture is poured into ice and hydrochloric acid. The resulting solid is filtered, dried, and recrystallized from acetone-hexane to yield 16β - methylpregnane - 3α,-17α - diol - 11,20 - dione 3 - acetate, m.p. 169—172° C. Its infrared spectrum indicates the presence of an acetate, hydroxyl and two ketonic groups.

Anal. Calcd. for $C_{24}H_{36}O_5$: C, 71.25; H, 7.97
Found: C, 71.29; H, 7.92.

E. 16β - Methylpregnane - 3α,17α,21 - triol - 11,20 - dione 21 - acetate

A solution of 362 mg. of 16β - methylpregnane - 3α,17α - diol - 11,20 - dione in 18 ml. of chemically pure Chloroform (containing a few drops of chloroform previously saturated with hydrogen bromide) is brominated at −25° C by the addition (over a three

hour period) of 165 mg. of bromine in 10 ml. of chloroform. After removal of the solvent under reduced pressure, 10 ml. of dimethylformamide and one gram of sodium acetate are added to the resulting corresponding 2,4-dibromo compound. The mixture is stirred at 60° C for two hours, allowed to stand overnight at room temperature, then heated another two hours at 60°C. The mixture is then poured into water, and the precipitated solid filtered and dried, yielding 370 mg. of impure 16β - methylpregnane - 3α,17α,21 - triol - 11,20 - dione 21 - acetate, m.p. 192—203° C. Recrystallization from acetone hexane gives 280 mg. of the product of this example, m.p. 199—205° C. The analytical sample, after another recrystallization, melts at 200—205.5° C.

Anal. Calcd. for $C_{24}H_{36}O_5$: C, 68.54; H, 8.63
Found: C, 68.79; H, 8.39.

F. 16β - Methylpregnane - 17α,21 - diol - 3,11,20 - trione 21 - acetate

A solution of 180 mg of 16β - methylpregnane - 3α,17α,21 - triol - 11,20 - dione 21 - acetate, in 30 ml. of 80% acetone-water is cooled to 10° C. One drop of concentrated hydrochloric acid is added, along with 150 mg. of N-bromo-succinimide, and the mixture allowed to react 22 hours at 10° C in the dark. Excess sodium sulphite solution is then added, and the mixture concentrated under reduced pressure to a small volume from which precipitates 120 mg. of impure 16β - methylpregnane - 17α,21 - diol - 3,11,20 - trione 21-acetate, m.p. 190—195° C. dec. Purification is effected by means of zinc dust in aqueous acetone containing 2 drops of acetic acid. The zinc is removed by filtration, the filtrate concentrated, and hot water added to crystallize 100 mg. of the product of this example, m.p. 198—202° C.

G. 4β - Bromo - 16β - methylpregnane - 17α,21 - diol - 3,11,20 - trione 21 - acetate

A solution of 84 mg. of 16β - methylpregnane - 17α,21 - diol - 3,11,20 - trione 21 - acetate in 3 ml. of *tert.*-butyl alcohol and 3 ml. of methylene chloride is brominated at 30—35° C by the rapid addition of a solution of 32 mg. of bromine in 3 ml. of *tert.*-butyl alcohol. After bromination is complete (1-3/4 hours), the solution is evaporated to dryness under reduced pressure. The residue is slurried with water, filtered and dried to yield 90 mg. of 4β - bromo - 16β - methylpregnane - 17α,21 - diol - 3,11,20 - trione 21 - acetate m.p. 115—130° C. dec., which is of sufficient purity for the conversion described in the following procedure.

H. 16β - Methylcortisone 21 - acetate

The 4β - bromo - 16β - methylpregnane - 17α,21 - diol - 3,11,20 - trione 21 - acetate of above Example 1G is dissolved in a mixture of 30 mg. of semicarbazide, 4 ml. of *tert.*-butyl alcohol and 2 ml. of methylene chloride, and stirred in a nitrogen atmosphere for two hours at 25—30° C. After removing the solvent under reduced pressure, the residue is dissolved in 5 ml. of 80% acetic acid-water along with excess 70% pyruvic acid, and the reaction mixture allowed to stand at room temperature for 20 hours. The solution is brought to about pH 7 with dilute (5%) sodium hydroxide, and then is extracted with methylene chloride. The organic extracts are evaporated to a residue, and the residue chromatographed on "Florisil". Crystalline material (25 mg.) obtained from the 50% ether-hexane and 100% ether eluates, on crystallization from acetone-hexane yields 20 mg. of 16β-methylcortisone 21-acetate, m.p. 198—208° C. λ_{max}^{MeOH} 238 mμ (ε 12,800).

Example 2

16β-Methylcortisone

One gram of 16β-methylcortisone 21-acetate (prepared as in Example 1) is dissolved in 25 ml. of methanol and 5 ml. of water containing 0.2 g. of potassium bicarbonate. This solution is refluxed for 1/2 hour, then concentrated under reduced pressure. Water is added to the residue, and the resulting precipitate is filtered and dried. Crystallization from acetone-hexane gives 16β-methylcortisone.

Example 3

16β-Methylhydrocortisone

A. 16β - Methylcortisone 3,20 - bis - semicarbazone

A mixture of 5.0 g. of 16β-methylcortisone, 8.3 g. of semicarbazide hydrochloride, 6 g. of pyridine, 50 ml. of water and 200 ml. of methanol is refluxed for 16 hours. The solution is concentrated to about 60 ml., then poured into water to precipitate 16β-methylcortisone-3,20-bis-semicarbazone.

B. 16β - Methylhydrocortisone 3,20 - bis - semicarbazone

A solution of 6.0 g. of the bis-semicarbazone of above Example 3A and 4 g. of potassium borohydride in 200 ml. of tetrahydrofuran and 100 ml. of water is refluxed for 6 hours. The solution is cooled, and acetic acid added to pH 5.5. The organic solvent is distilled and the solids in the residue are filtered to give 16β-methylhydrocortisone 3,20-bis-semicarbazone.

C. 16β-Methylhydrocortisone

Under a nitrogen atmosphere, 5.0 g. of the bis-semicarbazone of above Example 3B is dissolved in 250 ml. of 2.4 N hydrochloric acid. The solution is cooled to 5° C, then 2.5 g. of sodium nitrite in 25 ml. of water is added over a 15 minute period at 5° C. The reaction mixture is stirred an additional 30 minutes, then cooled to below 15° C, neutralized with 20% sodium hydroxide, and extracted several times with chloroform. The

solvent is evaporated under reduced pressure to give a solid residue which, after crystallization from acetone-hexane, yields 16β-methylhydrocortisone.

EXAMPLE 4

16β-Methylhydrocortisone 21-Acetate

To one gram of 16β-methylhydrocortisone, prepared as in Example 3, is added 0.5 ml. of acetic anhydride in 2.3 ml. of pyridine. After standing for one hour at room temperature, the mixture is poured into ice and hydrochloric acid. The resulting precipitate is filtered and recrystallized from aqueous methanol to yield 16β-methylhydrocortisone 21-acetate.

EXAMPLE 5

9α-Bromo-16β-methylhydrocortisone 21-Acetate

A. 16β - Methyl - 4,9 - pregnadiene - 17α,21 - diol - 3,20 - dione 21 - Acetate

To a solution of 16β-methylhydrocortisone 21-acetate (0.3 g.), prepared as in Example 4, in 5 ml. of pyridine there is added 0.2 ml. of benzenesulphonyl chloride in 3 ml. of pyridine. The solution is allowed to stand for 4 hours, then is poured into ice-hydrochloric acid. A solid precipitate which is filtered and crystallized from acetone-hexane to give 16β-methyl - 4,9 - pregnadiene - 17α,21 - diol - 3,20 - dione 21 - acetate, λ_{max}^{MeOH} 239 mμ (ε16,020).

B. 9α - Bromo - 16β - methylhydrocortisone 21 - Acetate

A suspension of 0.2 g. of the 16β-methyl-4,9-pregnadiene of above Example 5A in 20 ml. of purified dioxan, 2 ml. of water and containing 0.1 g. of N-bromoacetamide and 1 ml. of 1.5 N perchloric acid is gently agitated for two hours. During this time the mixture becomes homogeneous. A solution of 0.2 g. of sodium sulphite in 2 ml. of water is then added, and the solution extracted with methylene chloride. The organic extracts are washed with water, dried and evaporated to a solid residue which is crystallized from acetone to give 9α-bromo-16β-methylhydrocortisone 21-acetate, λ_{max}^{MeOH} 243 mμ (ε 16,100).

EXAMPLE 6

9α-Bromo-16β-methylhydrocortisone

A mixture of 0.5 g. of 9α-bromo-16β-methylhydrocortisone 21-acetate, prepared as in Example 5 in 100 ml. of methanol, 20 ml. of chloroform, 5 ml. of water and 5 ml. of concentrated hydrochloric acid is allowed to stand 48 hours at room temperature. Water is then added, and the mixture extracted with methylene chloride. The organic extracts are washed with water, dried and concentrated to a residue. Crystallization of this residue from acetone yields 9α-bromo-16β-methylhydrocortisone.

EXAMPLE 7

9α-Fluoro-16β-methylcortisone 21-Acetate

A. 9β,11β - Oxido - 16β - methyl - 4 - pregnene - 17α,21 - diol - 3,20 - dione 21 - Acetate

To 9α-bromo-16β-methylhydrocortisone 21-acetate (0.3 g.), prepared as in Example 5, in 20 ml. of methanol there is added 0.3 g. of potassium acetate. The mixture is refluxed for 2 hours, then concentrated *in vacuo* to a residue. Water is added to the residue, and a solid separates which is filtered and crystallized from methanol-water to give 0.1 g. of 9α,11β - oxido - 16β - methyl - 4 - pregnene - 17α,21 - diol 3,20 - dione 21 - acetate.

B. 9α - Fluoro - 16β - methylhydrocortisone 21 - Acetate

A solution 0.2 g. of the 9β,11β-oxido-4-pregnene of above Example 7A in 10 ml. of alcohol-free chloroform is saturated with anhydrous hydrogen fluoride at 0°C. The mixture is allowed to stand 4 hours at 0°C, then concentrated in a residue *in vacuo*. Crystallization of the residue from acetone-hexane gives 0.1 g. 9α-fluoro-16β-methylhydrocortisone 21-acetate.

C. 9α - Fluoro - 16β - Methyl - 4 - Pregnene - 17α,21 - Diol - 3,11,20-Trione

To a solution of 100 mg. of 9α-fluoro-16β-methyl hydrocortisone 21-acetate in 5 ml. of acetone, add a solution of 50 mg. of chromium trioxide in 5 ml. of acetone containing 1 ml. of 5 N sulphuric acid. Allow the mixture to stand for five minutes at room temperature. Dilute with water and filter the precipitated 11-ketone. Upon crystallization from acetone-hexane, there is obtained 9α-fluoro-16β-methyl cortisone 21-acetate. Hydrolysis of the 21-ester is effected by following the procedure described in Example 6 and there is obtained the compound of this example.

EXAMPLE 8

9α-Chloro-16β-methylhydrocortisone 21 Acetate

A solution of 0.2 g. of the 9β,11β-oxido-4-pregnene of Example 7A in 30 ml. of alcohol-free chloroform is saturated at 0°C with anhydrous hydrogen chloride, and the mixture allowed to stand at 0°C for six hours. The solvent is distilled *in vacuo* from the reaction mixture leaving a residue which, when crystallized from acetone-water gives 0.2 g. of 9α-chloro-16β-methylhydrocortisone, λ_{max}^{MeOH} 241 mμ (ε 16,600).

EXAMPLE 9

9α-Fluoro-16β-methylhydrocortisone

In the manner described in Example 6, 9α-fluoro-16β-methylhydrocortisone 21-acetate, prepared as in Example 7, is converted to 9α-fluoro-16β-methylhydrocortisone by means of hydrochloric acid in methyl-chloroform-water.

EXAMPLE 10

9α-Bromo-16α-methylhydrocortisone 21-Acetate

A. 16α-Methylpregnane-3α-ol-11,20-dione

A mixture of 3.72 g. of 16-pregnene-3α-ol-11,20-dione in 20 ml. of dry toluene is added to a Grignard reagent prepared from 7 g. of methyl iodide and 1.2 g. of magnesium in 40 ml. of ether, and containing 200 mg. of cupric chloride. The reaction mixture is distilled until a vapour temperature of 100°C is reached. The distillation is then stopped, and the reaction temperature maintained at 100°C for five hours. The mixture is then cooled, poured onto ice and an aqueous solution of ammonium chloride, and the solvent layers separated. The organic layer is distilled *in vacuo* to an oily residue (3.98 g.) which is chromatographed on "Forisil". The 20% ether-hexane eluates are combined and evaporated to give 2.08 g. of a residue which is crystallized from acetone-hexane to yield 16α-methylpregnane-3α-ol-11,20-dione, m.p. 149—154° C, $[\alpha]_D$ + 100.5° (dioxan).

B. 16α - Methylpregnane - 3α,17α - diol - 11,20 - dione

16α - Methylpregnane - 3α - ol - 11,20 - dione (7.44 g.), prepared as in above Example 10A is dissolved in 156 ml. of acetic anhydride containing 3.89 g. of *p*-toluenesulphonic acid. The reaction mixture is heated to 100° C, and ca. 10 ml. of distillate removed *in vacuo* every 30 minutes. After 6 hours, the remaining oily residue is dissolved in 80 ml. of benzene, and the solution washed three times with water, and once with a solution of 1.55 g. of sodium acetate in 20 ml. of water. A mixture of 12 ml. of 40% peracetic acid containing 0.52 g. of sodium acetate is added to the benzene solution and the mixture stirred at room temperature for 19 hours. A solution of 15.5 g. of sodium sulphite in 80 ml. of water is added at a temperature below 25° C, then an additional 1.6 g. of sodium sulphite is added and the mixture stirred overnight. The solvent layers are separated. The organic layer is washed three times with water, dried over calcium chloride, filtered, and evaporated to an oily residue under reduced pressure. The residual oil is dissolved in 345 ml. of methanol and 39.5 ml. of water containing 3.62 g of sodium hydroxide, and the mixture refluxed 15 minutes. After neutralizing the excess alkali with 5 ml. of acetic acid, the methanol is distilled *in vacuo*. Water is added to the resultant residue, and a solid (5.25 g., m.p. 173—179° C) separates which, when filtered and crystallized from acetone, yields 2.36 g. of 16α-methyl - pregnane - 3α,17α - diol - 11,20 - dione, m.p. 181.5—184° C, $[\alpha]_D$ + 74.4° (dioxan).

C. 16α - Methylpregnane - 3α,17α,21 - triol - 11,20 - dione 21 - Acetate

A solution of 362 mgm. of the 16α-methylpregnane-diol of Example 10B in 18 ml. of chloroform is brominated at −20 to −30° C by the dropwise addition of 160 mg. of bromine in 10 ml. of chloroform over a 45 minute period. Stirring is continued an additional 20 minutes, then the solvent removed under reduced pressure at 10° C. The residue is dissolved in 10 ml. of dimethylformamide, one gram of sodium acetate added, and the reaction mixture stirred at 60° C for 12 hours. The reaction mixture is then poured into 10 ml. of concentrated hydrochloric acid and ice, and the precipitated solid filtered, washed with water and dried: 250 mg., m.p. 150—158°. The filtrate is extracted with methylene chloride and the extracts evaporated to give an oily residue of 180 mg. The solid (250 mg.) and the oil (180 mg.) are combined and chromagraphed on "Florisil." Eluates of 40% ether-hexane are combined and distilled to a residue (110 mg., m.p. 140—155° C) substantially of 16α-methylpregnane-3α,17α,21-triol-11,20-dione 21-acetate. This product is used without further purification as the starting compound in the procedure immediately following.

D. 16α - Methylpregnane - 17α,21 - diol - 3,11,20 - trione 21 - acetate

To a solution of 110 mg. of the product of above Example 10C in 2.5 ml. of 80% *tert.*-butyl alcohol, 1.0 ml. of glacial acetic acid and one drop of concentrated hydrochloric acid is added 100 mg. of N - bromoacetamide at 5° C, and the reaction mixture kept at −5° C for 20 hours. Aqueous sodium bisulphite solution is added, and the mixture extracted with methylene chloride. The organic solvent extracts are evaporated to give a residue which is debrominated by treatment with zinc dust in acetone-acetic acid. After filtering the zinc from the reaction mixture, water is added to the filtrate. The resultant precipitate is filtered and dried to yield 40 mg. of 16α - methylpregnane - 17α,21 - diol - 3,11,20 - trione 21 - acetate, m.p. 205—211°C.

E. 4 - Bromo - 16α - methylpregnane - 17α,21 - diol - 3,11,20 - trione 21 - acetate

16α - Methylpregnane - 17α,21 - diol - 3,11,20 - trione (80 mg.), prepared as described in Example 10D is dissolved in 3 ml. of *tert.*-butyl alcohol and 3 ml. of methylene chloride and is brominated at 30—35° C by the rapid addition of a solution of 32 mg. of bromine in 4 ml. of *tert.*-butyl alcohol. Bromination is complete in 2 hours, and the solution evaporated to dryness under reduced pressure. The resultant residue is slurried with water, filtered and dried to give 92 mg. of a solid of substantially 4 - bromo - 16α - methylpregnane - 17α,21 - diol - 3,11,20 - trione 21 - acetate, which is used without further purification in the procedure immediately following.

F. 16α-Methylcortisone 21-acetate

4 - Bromo - 16α - methylpregnane - 17α,21 - diol - 3,11,20 - trione 21 - acetate (92

...) of above Example 10E is dissolved in a mixture of 30 mg. of semicarbazide, 4 ml. of *tert.*-butyl alcohol and 2 ml. of methylene chloride, and stirred in a nitrogen atmosphere for two hours at 25—30° C. The solvent is removed *in vacuo* and the resultant residue dissolved in 5 ml. of 80% acetic acid-water, along with an 8 molar excess of 70% pyruvic acid with respect to the molar quantity of the 4-bromo-16α-methylpregnane starting compound. The reaction mixture is allowed to stand at room temperature for 20 hours. Dilute (5%) aqueous sodium hydroxide is added until the reaction mixture is at about pH 7, then the solution is extracted with methylene chloride. The organic extracts are evaporated to a residue which is chromatographed on "Florisil". The 50% ether-hexane eluates and the 100% ether eluates are combined and evaporated to a crystalline residue (25 mg.) which is crystallized from acetone-hexane to give 20 mg. of 16α-methylcortisone 21-acetate, λ_{max}^{MeOH} 238 mμ (ε14,800).

G. 16α - Methylcortisone 21 - acetate 3,20 - bis - semicarbazone

A mixture of 16α-methylcortisone 21-acetate (2.5 g.), prepared as in Example 10F, 4.2 g. of semicarbazide hydrochloride, 3 g. of pyridine, 25 ml. of water and 100 ml. of methanol is refluxed for 16 hours. The solution is concentrated to ca. 30 ml., then poured into water to precipitate an almost quantitative yield of 16α-methylcortisone 21-acetate 3,20-bis-semicarbazone which is filtered and dried, and used without further purification in the procedure immediately following.

H. 16α - Methylhydrocortisone 3,20 - bis - semicarbazone

A solution of 3.0 g. of the bis-semicarbazone of Example 10G and 2 g. of potassium borohydride in 100 ml. of tetrahydrofuran and 50 ml. of water is refluxed for 3 hours. The solution is cooled, and acetic acid added to pH 5.5. The organic solvent is removed by distillation, and the solids collected by filtration to give 16α-methylhydrocortisone 3,20-bis-semicarbazone which is used without further purification in the procedure immediately following.

I. 16α-Methylhydrocortisone

Under a nitrogen atmosphere, 5.0 g. of the bis-semicarbazone of Example 10H is dissolved in 250 ml. of 2.4 N hydrochloric acid. The solution is cooled to 5° C, and a solution of 2.5 g. of sodium nitrite in 25 ml. of water is added at 5° C over a 15 minute period. The reaction mixture is stirred an additional 30 minutes, and then is brought to neutrality with 20% sodium hydroxide, at a temperature below 15° C. The reaction mixture is extracted several times with chloroform. The chloroform extracts are combined and distilled *in vacuo* to a solid residue which, when crystallized from acetone yields 16α-methylhydrocortisone, λ_{max}^{MeOH} 240 mμ (ε 14,700).

J. 16α-Methylhydrocortisone 21-Acetate

16α-Methylhydrocortisone (100 mg.), prepared as in Example 10I, is dissolved in 2 ml. of pyridine containing 100 mg. of acetic anhydride and is allowed to stand at room temperature for one hour. The reaction mixture is poured into ice and hydrochloric acid, and a solid precipitates which is filtered and crystallized from aqueous methanol to yield 16α-methylhydrocortisone 21-acetate, λ_{max}^{MeOH} 240 mμ (ε 15,000).

K. 16α - Methyl - 4,9 (11) - pregnadiene - 17α,21 - diol - 3,20 - dione 21 - Acetate

16α - Methylhydrocortisone 21 - acetate (0.2 g.), prepared as in Example 10J, is dissolved in 3 ml. of pyridine and 0.1 ml. of benzenesulfonyl chloride in 2 ml. of pyridine is added. The solution is allowed to stand for 4 hours, then is poured into ice-hydrochloric acid. A solid precipitates which is filtered and crystallized from acetone to give 16α - methyl - 4,9 - pregnadiene - 17α,21 - diol - 3,20 - dione 21 - acetate, λ_{max}^{MeOH} 238 mμ (ε 16,300).

L. 9α - Bromo - 16α - methylhydrocortisone 21 - Acetate

A suspension of 0.2 g. of the 16α-methylpregnadiene of Example 10K in 20 ml. of purified dioxane, 2 ml. of water and containing 0.08 g. of N-bromoacetamide and 0.8 ml. of 1.5 N perchloric acid is gently agitated for two hours. During this time the mixture becomes homogeneous. A solution of 0.2 g. of sodium sulphite in 4 ml. of water is added, then the solution is extracted with methylene chloride. The organic extracts are washed with water, dried, filtered and evaporated to a residue which is crystallized from methanol to yield 0.1 g. of 9α-bromo-16α-methylhydrocortisone 21-acetate λ_{max}^{MeOH} 242 mμ (ε 16,400).

Example 11

9α-Fluoro-16α-methylhydrocortisone

A. 9β,11β - Oxido - 16α - methyl - 4 - pregnene - 17α,21 - diol - 3,20 - dione 21 - Acetate

A mixture of 0.3 g. of 9α-bromo-16α-methylhydrocortisone 21-acetate, prepared as in Example 10, in 20 ml. of methanol and 0.3 g. of potassium acetate is refluxed for 2 hours, then concentrated to a residue. Water is added to the residue, and a solid separates which is filtered and crystallized from methanol to give 0.1 g. of 9β,11β - oxido - 16α - methyl - 4 - pregnene - 17α,21 - diol 3,20 - dione 21 - acetate.

B. 9α - Fluoro - 16α - methylhydrocortisone 21 - acetate

A solution of 0.2 g. of the 9β,11β - oxido - 16α - methyl - 4 - pregnene of above Example IIA in 10 ml. of alcohol-free chloroform is saturated with anhydrous hydrogen fluoride at 0° C. The mixture is allowed to stand 5 hours at 0° C, then concentrated to a residue under reduced pressure. Crystallization of the residue from acetone-hexane yields 0.1 g. of 9α - fluoro - 16α - methylhydrocortisone 21 - acetate, λ_{max}^{MeOH} 238 mμ, (ε 16,200).

Example 12

16β-n-Butylcortisone 21-Acetate

A. 16α - n - Butylpregnane - 3α - ol - 11,20 - dione

16-Pregnene-3α-ol-11,20-dione is reacted with n-butyl-iodide and magnesium in the manner of Example 10A to yield 16α-n-butylpregnane-3α-ol-11,20-dione, which is crystallized from acetone-hexane.

B. 17 - Bromo - 16α - n - butylpregnane - 3α - ol - 11,20 - dione

One gram of 16α-n-butylpregnane 3α-ol-11,20-dione, prepared as in Example 12A, is dissolved in 10 ml. of acetic acid and is then brominated with 1.1 equivalents of bromine in acetic acid. When the bromine colour is discharged, the solution is poured into water and there is precipitated a solid of substantially 17 - bromo - 16α - n - butylpregnane - 3α - ol - 11,20 - dione. This 17-bromo-product is filtered and used in the next procedure without further purification.

C. 16 - n - Butyl - 16 - pregnen - 3α - ol - 11,20 - dione

To the 17 - bromo - 16α - n - butylpregnane prepared in above Example 12B there is added 10 ml. of dimethylformamide, and the reaction mixture is refluxed two hours. The solution is poured into dilute hydrochloric acid and then extracted with methylene chloride. The organic extracts are washed with water, dried over magnesium sulphate, filtered, and evaporated *in vacuo* to a residue of substantially 16 - n - butyl - 16 - pregnene - 3α - ol - 11,20 - dione which is used without further purification in the reaction procedure immediately following.

D. 16β - n - Butylpregnane - 3α - ol - 11,20 - dione

The 16 - n - butyl - 16 - pregnene - 3α - ol - 11,20 - dione, prepared in above Example 12C, is dissolved in 10 ml. of acetic acid and hydrogenated using palladium on charcoal as catalyst. When one mole of hydrogen is adsorbed, the reaction is stopped, the catalyst removed by filtration, and the filtrate poured into water. A solid precipitates which is filtered and crystallized from acetone-hexane to give 16β - n - butylpregnane - 3α - ol - 11,20 - dione.

E. 16β - n - Butylpregnane - 3α,17α - diol - 11,20 - dione

In the manner described in Example ID, 16β - n - butylpregnane - 3α - ol - 11,20 - dione, prepared as in Example 12D, is reacted first with *p*-toluene-sulphonic acid in acetic anhydride, then with sodium acetate in 40% peracetic acid, and finally with aqueous sodium hydroxide. The resulting product is isolated and purified in the manner of Example ID to yield 16β - n - butylpregnane - 3α,17α - diol - 11,20 - dione.

F. 16β - n - Butylpregnane - 3α,17α,21 - triol - 11,20 - dione 21 - Acetate

The 16β-n-butylpregnane of Example 12E is reacted first with bromine in chloroform, then with sodium acetate and dimethylformamide and the product isolated and purified in the manner described in Example IE, to give 16β - n - butylpregnane - 3α,17α,21 - triol - 11,20 - dione 21 - acetate.

G. 16β - n - Butylpregnane - 17α,21 - diol - 3,11,20 - trione 21 - Acetate

In the manner described in Example 1F, 16β - n - butylpregnane - 3α,17α,21 - triol - 11,20 - dione 21 - acetate is brominated and the resulting product isolated and purified to give 16β - n - butylpregnane - 17α,21 - diol - 3,11,20 - trione 21 - acetate.

H. 4 - Bromo - 16β - n - butylpregnane - 17α,21 - diol - 3,11,20 - trione 21 - Acetate

16β - n - Butylpregnane - 17α,21 - diol - 3,11,20 - trione 21 - acetate is brominated in the manner of Example 1G, to obtain 4 - bromo - 16β - n - butylpregnane - 17α,21 - diol - 3,11,20 - trione 21 - acetate.

I. 16β - n - Butylcortisone 21 - Acetate

The 4-bromo-derivative of above Example 12H is dehydrobrominated by means of semicarbazide and aqueous 80% acetic acid and 70% pyruvic acid in the manner of Example 1H to obtain 16B-n-butylcortisone 21-acetate, λ_{max}^{MeOH} 238 mμ (ε 14,500).

Example 13

16β-n-Butylcortisone

16β-n-Butylcortisone 21-acetate is hydrolyzed by means of aqueous alcoholic potassium bicarbonate in the manner described in Example 2 to yield 16β-n-butylcortisone, λ_{max}^{MeOH} 238 mμ (ε 15,000).

Example 14

16β-Methylprednisone 21-Acetate

A. 2,4 - Dibromo - 16β - methylpregnane - 17α,21 - diol - 3,11,20 - trione 21 - Acetate

A solution of 167 mg. 16β - methylpregnane - 17α,21 - diol - 3,11,20 - trione 21 - acetate, the compound of Example 1F, in 3 ml. of dioxan is dibrominated in positions 2

and 4 by the rapid addition of 130 mg. of bromine in 1 ml. of dioxan at room temperature. The solution is poured into water and the precipitated solid is filtered, yielding 180 mg. of 2,4 - dibromo - 16β - methylpregnane - 17α,21 - diol - 3,11,20 - trione 21 - acetate of sufficient purity to be used in the conversion described in the following procedure.

B. 16β-Methylprednisone 21-acetate

The 2,4-dibromide (180 mg.) as prepared in above Example 14A is dehydrobrominated by refluxing for 2 hours with 4 ml. of dimethylformamide containing 30 mg. of calcium carbonate. The mixture is poured into dilute hydrochloric acid and extracted with methylene chloride. The organic extract is evaporated to a residue (150 mg.), which is chromatographed on "Florisil". The fractions obtained by elution with 20% ether-hexane are crystallized from acetone-hexane to give 40 mg. of 16β-methylprednisone 21-acetate, m.p. 210—216°. One further crystallization gave m.p. 215—218°, λ_{max}^{MeOH} 237 mμ (ε 13,500).

Example 15

16β-Methylprednisone

16β-methylprednisone 21-acetate (0.5 g.), the compound of Example 14, when hydrolyzed by means of aqueous alcoholic potassium bicarbonate in the manner described in Example 2 yields 16β-methylprednisone.

An alternative method of the preparation of the compound of this example is as follows:

Bacillus sphaericus var. fusiformis (A.T.C.C. 7055) is incubated on a nutrient agar (composed of Bacto-beef extract, 3 g; Bacto-peptone, 5 g; sodium chloride, 8 g; agar, 15 g; tap water, 1 litre) for 24 hours at 28° C.

To 100 ml. of a sterile nutrient broth (composed of Bacto-Beef extract, 3 g; Bacto-peptone, 5 g; per litre of tap water) in a 300 ml. flask is added one loopful of the incubated culture and the broth mixture is further incubated for 24 hours at 28° C on a shaking machine. The broth culture so obtained is employed as an inoculum (1%).

Into each of ten flasks containing 100 ml. of sterile nutrient broth is added 1 ml. of the inoculum. The flasks are agitated on a rotary shaker for 8 hours at 28° C at 240 strokes per minute. After this growth period, a solution of 25 mg. of 16β-methylcortisone, the compound of Example 2, in 0.5 ml. of methanol is aseptically added to each flask which in turn is reshaken and incubated for an additional 24 hours. The final pH is 7.8.

The contents of the flasks are then combined and extracted three times with 2 litres of chloroform per extraction. The combined chloroform extracts are evaporated to dryness yielding 310 mg. of crude product. The crude steroid is purified by chromatography on a chromatographic system described by G. M. Shull, Abstracts of Papers of the 126th Meeting of the American Chemical Society, December 12—17, 1954, page 9a, paper No. 24. Chromatographic evaluation shows a quantitative conversion of the starting material to the diene when an authentic sample of the 16β-methylprednisone is used as a control.

Alternatively, the crude product is recrystallized from acetone affording 225 mg. of 16β-methylprednisone.

Example 16

16β-Methylprednisolone 21-acetate

A. 16β-Methylprednisolone

16β-Methylhydrocortisone, the compound of Example 3, is fermented by means of *Bacillus sphaericus var. fusiformis* (A.T.C.C. 7055) in the manner described in the alternate procedure of Example 15 to produce 16β-methylprednisolone.

B. 16β-Methylprednisolone 21-Acetate

16β-Methylprednisolone of Example 16A is treated with acetic acid and pyridine in the manner described in Example 4 to yield 16β-methylprednisolone 21-acetate.

Example 17

9α-Bromo-16β-methylprednisolone 21-Acetate

A. 16β - Methyl - 1,4,9(11) - pregnatriene - 17α,21 - diol - 3,20 - dione 21 - Acetate

A solution of 0.5 g. of 16β-methylprednisolone 21-acetate, the compound of Example 16, in 3 ml. of pyridine is reacted with 0.3 ml. of methane-sulphonyl chloride in 4 ml. of pyridine. The solution is allowed to stand for 6 hours, then poured into ice-hydrochloric acid. A solid precipitate which is removed by filtration and crystallized from acetone-hexane to give 16β - methyl - 1,4,9(11) - pregnatriene - 17α,21 - diol - 3,20 - dione 21 - acetate, λ_{max}^{MeOH} 238 mμ (ε 14,750).

B. 9α - Bromo - 16β - methylprednisolone 21 - Acetate

A suspension of 0.5 g. of the 16β-methylpregnatriene of above Example 17A in 50 ml. of purified dioxan in a 5 ml. of water containing 0.2 g. of N-bromoacetamide and 2 ml. of 1.5 N perchloric acid is gently agitated for a period of two hours, during which time the mixture becomes homogeneous. A solution of 0.5 g. of sodium sulphite in 5 ml. of water is added, and the reaction mixture is extracted with methylene chloride. The organic extracts are washed with water, dried over magnesium sulphate, filtered and evaporated. The resulting solid is crystallized from acetone to yield 0.3 g. of 9α - bromo - 16β - methylprednisolone 21 - acetate, λ_{max}^{MeOH} 242 mμ, (ε 14,950).

EXAMPLE 18

9α-Fluoro-16β-methylprednisolone 21-Acetate

A. 9β,11β - Oxido - 16β - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione 21 - acetate

One gram of 9α-bromo-16β-methylprednisolone 21-acetate, the compound of Example 17, is added to 65 ml. of methanol and 1.0 g. of potassium acetate and the mixture is refluxed for 2 hours, then concentrated to a residue. Water is added to the residue and the resulting solid is removed by filtration and crystallized from methanol-water to 0.6 g. of 9β,11β - oxido - 16β - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione 21 - acetate, λ_{max}^{MeOH} 242 mμ, (ε 13,850).

B. 9α - Fluoro - 16β - methylprednisolone 21 - Acetate

A solution of 0.4 g. of the 9β,11β - oxido - 1,4 - pregnadiene of Example 18A in 20 ml. of alcohol-free chloroform is saturated with anhydrous hydrogen fluoride at 0° C. The mixture is allowed to stand 4 hours at 0° C, then concentrated to a residue under reduced pressure. Crystallization of the residue from acetone-hexane gives 0.2 g. 9α - fluoro - 16β - methylprednisolone 21 - acetate, λ_{max}^{MeOH} 238 mμ (ε 15,100).

EXAMPLE 19

9α-Fluoro-16β-methylprednisolone

9α - Fluoro - 16β - methylprednisolone 21 - acetate, the compound of Example 18, is converted to 9α-fluoro-16β-methylprednisolone by means of hydrochloric acid in methanol-chloroform-water in the manner described in Example 6.

EXAMPLE 20

9α-Bromo-16β-methylprednisolone

9α - Bromo - 16β - methylprednisolone 21 - acetate, the compound of Example 19, is converted to 9α - bromo - 16β - methylprednisolone in the manner of Example 6 using hydrochloric acid in methanol-chloroform-water.

EXAMPLE 21

9α-Chloro-16β-methylprednisolone 21-acetate

A solution of 0.3 g. of 9β,11β - oxido - 16β - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione 21 - acetate, the compound of Example 18A, in 40 ml. of alcohol-free chloroform is saturated at 0° C with anhydrous hydrogen chloride and the mixture allowed to stand at 0°C for 6 hours. The mixture is concentrated under reduced pressure to a residue which is crystallized from acetone-water to give 0.2 g. of 9α - chloro - 16β - methylprednisolone 21 - acetate, λ_{max}^{MeOH} 240 mμ (ε 15,000).

EXAMPLE 22

9α-Chloro-16β-methylprednisolone

In the manner of Example 6, 9α - chloro - 16β - methylprednisolone 21 - acetate is converted to 9α - chloro - 16β - methylprednisolone.

EXAMPLE 23

9α-Fluoro-16β-methylprednisone 21-Acetate

To a solution of 0.3 g. of 9α - fluoro - 16β - methylprednisolone 21 - acetate, the compound of Example 18, in 15 ml. of acetic acid is added dropwise a solution of 60 mg. of chromium trioxide in 1 ml. of water and 3 ml. of acetic acid. The resulting mixture is allowed to stand 5 hours, then diluted with water and extracted with methylene chloride. The organic extracts are washed with water, dried over magnesium sulphate, filtered and evaporated in a residue which is crystallized from methanol to give 0.1 g. of 9α - fluoro - 16β - methylprednisone 21 - acetate.

EXAMPLE 24

9α-Fluoro-16β-methylprednisone

In the manner described in Example 6, 9α - fluoro - 16β - methylprednisone 21 - acetate is hydrolyzed to 9α - fluoro - 16β - methylprednisone by means of HCl in methanol-chloroform-water.

EXAMPLE 25

9α-Chloro-16β-methylprednisone

A. 9α - Chloro - 16β - methylprednisone - 21 - acetate

9α - Chloro - 16β - methylprednisolone 21 - acetate, the compound of Example 21, is reacted with chromium trioxide in aqueous acetic acid in the manner of Example 23 to give 9α - chloro - 16β - methylprednisone 21 - acetate.

B. 9α - Chloro - 16β - methylprednisone

In the manner described in Example 6, the 21-acetate ester of Example 25A is reacted with hydrochloric acid in methanol-chloroform-water to give 9α - chloro - 16β - methylprednisone.

EXAMPLE 26

9α-Bromo-16β-methylprednisone

A. 9α - Bromo - 16β - methylprednisone 21 - Acetate

9α - Bromo - 16β - methylprednisolone 21 - acetate, the compound of Example 17, is reacted with chromium trioxide in aqueous acetic acid in the manner of Example 23 to give 9α - bromo - 16β - methylprednisone 21 - acetate.

B. 9α - Bromo - 16β - methylprednisone

In the manner of Example 6, the 21-acetate ester of Example 39A is reacted with hydrochloric acid in methanol-chloroform-water to give 9α - bromo - 16β - methylprednisone.

Example 27

9α-Bromo-16α-methylprednisolone

A. 16α-Methylprednisolone

Bacillus sphaericus var. fusiformis (A.T.C.C. 7055) is incubated on a nutrient agar (composed of Bacto-beef extract, 3 g., Bacto-peptone, 5 g., sodium chloride, 8 g., agar, 15 g., tap water, 1 litre) for 24 hours at 28° C.

To 100 ml. of sterile nutrient broth (compound of Bacto-beef extract, 3 g., Bacto-peptone, 5 g., per litre of tap water) in a 300 ml. flask is added one loopful of the incubated culture and the broth mixture is further incubated for 24 hours at 28°C on a shaking machine. The broth culture so obtained is employed as an inoculum (1%).

Into each of ten flasks containing 100 ml. of sterile nutrient broth is added 1 ml. of the inoculum. The flasks are agitated on a rotary shaker for 8 hours at 28°C at 240 strokes per minute. After this growth period, a solution of 25 mg. of 16α-methylhydrocortisone, the compound of Example 10I, in 0.5 ml. of methanol is aseptically added to each flask which, in turn, is reshaken and incubated for an additional 24 hours. The final pH is 7.8.

The contents of the flasks are combined and extracted three times with 2 litres of chloroform per extraction. The combined chloroform extracts are evaporated to dryness yielding 310 mg. of a residue which is crystallized from acetone-hexane to give 16α-methylprednisolone.

B. 16α-Methylprednisolone 21-Acetate

A solution of 100 mg. of 16α-methylprednisolone in 2 ml. of pyridine containing 100 mg. of acetic anhydride is allowed to stand for 1 hour. The mixture is then poured into ice-HCl and a precipitate results which is removed by filtration. Crystallization of the precipitate from aqueous methanol gives 16α-methylprednisolone 21-acetate.

C. 16α - Methyl - 1,4,9(11) - pregnatriene - 17α,21 - diol - 3,20 - dione 21 - Acetate

A solution of 0.2 g. of 16α - methylprednisolone 21 - acetate, the compound of Example 27B, in 2 ml. of pyridine is reacted with 0.1 ml. of methane-sulphonyl chloride in 2 ml. of pyridine. The solution is allowed to stand for five hours, then poured into ice-hydrochloric acid. A solid precipitates which is filtered and crystallized from acetone to give 16α - methyl - 1,4,9(11) - pregnatriene - 17α,21 - diol - 3,20 - dione 21 - acetate, λ_{max}^{MeOH} 238 mμ, (ε 15,200).

D. 9α - Bromo - 16α - methylprednisolone 21 - Acetate

A suspension of 0.3 g. of the 16α - methyl - 1,4,9(11) - pregnatriene of Example 27C in 30 ml. of purified dioxan, 3 ml. of water containing 0.1 g. of N-bromoacetamide and 1 ml. of 1.5 N perchloric acid is gently agitated for a period of two hours, during which time the mixture becomes homogeneous. A solution of 0.3 g. of sodium sulphite in 5 ml. of water is added, then the solution extracted with methylene chloride. The organic extracts are washed with water, dried over magnesium sulphate, filtered and evaporated. The resulting solid residue is crystallized from methanol to yield 0.2 g. of 9α - bromo - 16α - methylprednisolone 21 - acetate, λ_{max}^{MeOH} 243 mμ, (ε 14,800).

E. 9α-Bromo-16α-methylprednisolone

In the manner of Example 6, 9α - bromo - 16α - methylprednisolone 21 - acetate is reacted with hydrochloric acid in chloroform-methanol-water to give 9α - bromo - 16α - methylprednisolone.

Example 28

9α-Fluoro-16α-methylprednisolone

A. 9β,11β - Oxido - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione 21 - Acetate

A mixture of 0.5 g. of 9α - bromo - 16α - methylprednisolone 21 - acetate, the compound of Example 27D, 30 ml. of methanol and 0.5 g. of potassium acetate is refluxed for 2 hours, then concentrated to a residue. Water is added to the residue and the resulting solid is filtered and crystallized from methanol to give 0.3 g. of 9β,11β - oxido - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione 21 - acetate, λ_{max}^{MeOH} 243 mμ (ε 14,050).

B. 9α - Fluoro - 16α - methylprednisolone 21 - Acetate

A solution of 0.2 g. of the 9β,11β - oxido - 16α - methylpregnadiene of above Example 28A in 10 ml. of alcohol-free chloroform is saturated with anhydrous hydrogen fluoride at 0° C. The mixture is allowed to stand 5 hours at 0° C, then concentrated to a residue under reduced pressure. Crystallization of the residue from acetone-hexane gives 0.15 g. of 9α - fluoro - 16α - methylprednisolone 21 - acetate, λ_{max}^{MeOH} 238 mμ (ε 15,200).

C. 9α-Fluoro-16α-methylprednisolone

According to the procedure of Example 6 using hydrochloric acid in chloroform-methanol-water, 9α - fluoro - 16α - methylprednisolone 21 - acetate is converted to 9α - fluoro - 16α - methylprednisolone.

Example 29

9α-Chloro-16α-methylprednisolone

A. 9α - Chloro - 16α - methylprednisolone 21 - Acetate

A solution of 0.2 g. of the 9β,11β - oxido - pregnadiene of Example 28A in 30 ml. of

alcohol-free chloroform is saturated at 0° C with anhydrous hydrogen chloride, and the mixture allowed to stand at this temperature for 6 hours. The mixture is concentrated under reduced pressure to a residue which is crystallized from acetone-hexane to give 0.15 g. of 9α - chloro - 16α - methylprednisolone 21 - acetate, λ_{max}^{MeOH} 241 mμ, (ε 15,250).

B. 9α-Chloro-16α-methylprednisolone

According to the procedure of Example 6 using hydrochloric acid in chloroform-methanol water, the 21-acetate compound of Example 29A is converted to 9α - chloro - 16α - methylprednisolone.

EXAMPLE 30

9α-Fluoro-16α-methylprednisone

A. 9α - Fluoro - 16α - methylprednisone 21 - Acetate

To a solution of 0.2 g. of 9α - fluoro - 16α - methylprednisolone 21 - acetate, the compound of Example 28B, 10 ml. of acetic acid there is added dropwise a solution of 40 mg. of chromium trioxide in 1 ml. of water and 2 ml. of acetic acid. The resulting mixture is allowed to stand 6 hours, then diluted with water and extracted with methylene chloride. The organic extracts are washed with water, dried over magnesium sulphate, filtered and evaporated to a residue which is crystallized from methanol to give 0.1 g. of 9α - fluoro - 16α - methylprednisone 21 - acetate, λ_{max}^{MeOH} 237 mμ (ε 14,000).

B. 9α-Fluoro-16α-methylprednisone

In the manner of Example 6, the 21-acetate ester of Example 30A is hydrolyzed to 9α-fluoro-16α-methylprednisone.

EXAMPLE 31

9α-Chloro-16α-methylprednisone

In the manner described in Example 30, 9α - chloro - 16α - methylprednisolone 21 - acetate, the compound of Example 29A, is reacted with chromium trioxide to yield 9α-chloro-16α-methylprednisone 21-acetate.

In the manner described in Example 6, the 21-acetate ester of the compound of this example is reacted with hydrochloric acid in chloroform-methanol-water to yield 9α-chloro-16α-methylprednisone.

EXAMPLE 32

9α-Bromo-16α-methylprednisone

In the manner described in Example 30, 9α - bromo - 16α - methylprednisolone 21 - acetate, the compound of Example 27D, is reacted with chromium trioxide to yield 9α - bromo - 16α - methylprednisone 21 - acetate.

In turn, the 21-acetate of the compound of this example is converted to the free alcohol, 9α - bromo - 16α - methylprednisone, by means of hydrochloric acid in chloroform-methanol-water according to the procedure of Example 6.

EXAMPLE 33

9α-Chloro-16α-methylhydrocortisone

In the manner described in Example 29, 9β,11β - oxido - 16α - methyl - 4 - pregnene - 17α,21 - diol 21 - acetate, the compound of Example 11A is reacted with hydrogen chloride in chloroform to give 9α - chloro - 16α - methylhydrocortisone 21 - acetate, λ_{max}^{MeOH} 242 mμ, (ε 16,400).

The 21-acetate of the compound of this example is hydrolyzed by means of hydrochloric acid in chloroform-methanol-water according to the procedure of Example 6, to obtain 9α-chloro-16α-methylhydrocortisone.

EXAMPLE 34

9α-Chloro-16α-methylcortisone

In the manner described in Example 23, 9α - chloro - 16α - methylhydrocortisone 21 - acetate is reacted with chromium trioxide in water and acetic acid to yield 9α - chloro - 16α - methylcortisone 21 - acetate, λ_{max}^{MeOH} 239 mμ (ε 15,100).

The 21-acetate of the compound of this example is hydrolyzed by means of hydrochloric acid in chloroform-methanol-water according to the procedure of Example 6 to give 9α-chloro-16α-methylcortisone.

EXAMPLE 35

9α-Bromo-16α-methylcortisone

In the manner described in Example 23, 9α - bromo - 16α - methylhydrocortisone 21 - acetate, the compound of Example 10L, is reacted with chromium trioxide in aqueous acetic acid to give 9α - bromo - 16α - methylcortisone 21 - acetate, λ_{max}^{MeOH} 241 mμ (ε 14,700).

The 21-acetate of the compound of this example is hydrolyzed by means of hydrochloric acid in methanol-water-chloroform in the manner described in Example 6 to give 9α-bromo-16α-methylcortisone.

EXAMPLE 36

16α-Methylallopregnane-3β-ol-20-one

A solution of 0.5 g 16α-methylpregnenolone [Marker & Crookes J.A.C.S. 64, 1280 (1942)] in 15 ml. of acetic acid is reduced at atmospheric pressure with hydrogen and 0.3 g. of 5% palladium of charcoal catalyst. The reaction is ceased after one mole of hydrogen is consumed, the catalyst is removed by filtration, and the filtrate poured into water. The precipitated solid is removed by filtration and crystallized from acetone-hexane to yield 0.3 g. of 16α - methylallopregnane - 3β - ol - 20 - one.

In a similar manner, 16β-methylpregnenol-

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one is reduced to 16β - methylallopregnane - 3β - ol - 20 - one by means of hydrogen and a palladium catalyst.

EXAMPLE 37

16α-Methylallopregnane-3β,17α-diol-20-one

A solution of 3.5 g. of 16α - methylallopregnane - 3β - ol - 20 - one in 100 ml. of acetic anhydride containing 0.7 g. of *p*-toluenesulfonic acid is kept at 100°C. for 6 hours: during this time about 8 ml. of distillate is removed each half hour by the application of vacuum. The resulting oily residue is dissolved in 50 ml. of benzene and washed three times with water; then with a solution of 1.0 g. of sodium acetate in 15 ml. of water. The benzene layer is dried with anhydrous magnesium sulphate, filtered, then evaporated to a small volume, followed by chromatography on 70 grams of hexane washed magnesium silicate ("Florisil"). Elution with 50% ether-hexane mixture affords, after evaporation of the solvent, 3β,20 - diacetoxy - 16α - methyl - 17,20 - allopregnene. The enol acetate so obtained is dissolved in 50 ml. of benzene (or prior to isolation of the enol acetate): the benzene solution is then stirred for 18 hours at room temperature with a mixture of 0.25 g. of sodium acetate in 6 ml. of commercial 40% peracetic acid. The excess peracetic acid is destroyed by the dropwise addition of a solution of 8 g. of sodium sulphite in 25 ml. of water, at a temperature of ca. 10—20°C. An additional 1 g. of sodium sulphite is then added and the mixture stirred overnight until a starch-iodide test is negative. The benzene layer is separated, washed three times with water and evaporated. The residue is triturated with ether-hexane mixture in the cold. The resulting 3β,20 - diacetoxy - 16α - methyl - 17,20 - epoxy - allopregnane is isolated by filtration and dried. The 17α-epoxy compound so obtained, or the residue from the evaporation of the benzene layer mentioned above, is dissolved in 200 ml. of methanol and 30 ml. of water containing 2.7 g. of sodium hydroxide, and the mixture refluxed for 15 minutes. After neutralization with 3 ml. of acetic acid, the solution is concentrated under reduced pressure to a volume of ca. 30 ml., and this is poured into an ice-water mixture. The precipitated solid is removed by filtration and crystallized from methanol-water to give 2.5 g. of 16α - methylallopregnane - 3β,17α - diol - 20 - one.

In a similar fashion by subjecting 16β - methylallopregnane - 3β - ol - 20 - one to the reaction procedure herein described, there is prepared 16β - methylallopregnane - 3β,17α - diol - 20 - one.

EXAMPLE 38

16β-Methylpregnane-3α,17α-diol-20-one

A. 16 - Methyl - 16 - pregnene - 3α - ol - 20 - one 3 - acetate

A solution of 3.71 grams of 16 - pregnene - 3α - ol - 20 - one 3 - acetate in 5 ml. of methylene chloride is added to a solution of about 1 gram of diazomethane in 70 ml. of ether which has been cooled to −10°C. The mixture is kept at 0°C. for four hours, then allowed to warm up to room temperature. The resulting pyrazoline crystallizes directly from the reaction mixture and is heated under reduced pressure to about 210°C. until the evolution of nitrogen ceases. The resulting oil is cooled to room temperature, then crystallized by the addition of ether. The precipitate is filtered and dried, yielding 2.12 g. of 16 - methyl - 16 - pregnene - 3α - ol - 20 - one 3 - acetate.

B. 16β - Methylpregnane - 3α - ol - 20 - one 3 - acetate

A solution of 12.0 g. of the 16-pregnene compound of Example 38A in 250 ml. of glacial acetic acid is hydrogenated at room temperature and at atmospheric pressure in the presence of 3.0 g. of 10% palladium on charcoal catalyst. After the reduction is completed (about 1.5 hours), the catalyst is removed by filtration, and the filtrate concentrated under reduced pressure to about 100 ml. The residue is poured into water, and the precipitated solid filtered, washed and dried, yielding 11.4 g. of impure 16β - methylpregnane - 3α - ol - 20 - one 3 - acetate. After recrystallization from acetone-hexane there is obtained 8.40 g. of the product of this example.

C. 16β - Methylpregnane - 3α,17α - diol - 20 - one

A solution of 3.5 g. of 16β - methylpregnane - 3α - ol - 20 - one 3 - acetate, in 100 ml. of acetic anhydride containing 2.0 g. of *p*-toluenesulfonic acid is treated according to the procedure of Example 37. There is thus prepared the compound of this example, 16β-methylpregnane-3α,17α-diol-20-one.

EXAMPLE 39

16α-Methylpregnane-3α-ol-20-one

A mixture of 3.72 g. of 16 - pregnen - 3α - ol - 20 - one in 20 ml. of dry toluene is added to a Grignard reagent prepared from 7 g. of methyl iodide and 1.2 g. of magnesium in 40 ml. of ether, and containing 200 mg. of cupric chloride. The reaction mixture is distilled until a vapour temperature of 100°C. is reached. The distillation is then stopped, and the reaction temperature maintained at 100°C for five hours. The mixture is then cooled, poured onto ice and an aqueous solution of ammonium chloride, and the solvent

layers separated. The organic layer is distilled *in vacuo* to an oily residue which is chromatographed on "Florisil". The 20% ether-hexane eluates are combined and evaporated to give a residue which is crystallized from acetone-hexane to yield 16α - methyl - pregnane - 3α - ol - 20 - one.

EXAMPLE 40

16α-Methylpregnane-3α,17α,21-triol-20-one 21-acetate

A solution of 300 mg. of 16α - methylpregnane - 3α,17α - diol - 20 - one in 15 ml. of chloroform is brominated at −20 to −30°C. by the dropwise addition of 165 mg. of bromine in 10 ml. of chloroform over a 45 minute period. Stirring is continued an additional 20 minutes, then the solvent removed under reduced pressure at 10°C. The residue is dissolved in 10 ml. of dimethylformamide, one gram of sodium acetate added, and the reaction mixture stirred at 60°C. for 12 hours. The reaction mixture is then poured into 10 ml. of concentrated hydrochloric acid and ice, and the precipitated solid filtered, washed with water and dried. The filtrate is extracted with methylene chloride and the extracts evaporated to give an oily residue. The solid and the oil are combined and chromatographed on "Florisil". Eluates of 40% ether-hexane are combined and distilled to a residue substantially of 16α - methylpregnane - 3α,17α,21 - triol - 20 - one 21 - acetate. This product is used without further purification as the starting compound in the procedure of Example 41.

In a similar fashion, 16α - methylallopregnane - 3α,17α - diol - 20 - one; 16β - methylpregnane - 3α,17α - diol - 20 - one; and 16β - methylallopregnane - 3α,17α - diol - 20 - one are subjected to the procedure described immediately above and there are formed respectively the following compounds: 16α - methylallopregnane - 3α,17α,21 - triol - 20 - one 21 - acetate; 16β - methylpregnane - 3α,17α,21 - triol - 20 - one 21 - acetate; and 16β - methylallopregnane - 3α,17α,21 - triol - 20 - one 21 - acetate.

EXAMPLE 41

16α-Methylpregnane-17α,21-diol-3,20-dione 21-acetate

To a solution of 100 mg. of 16α - methylpregnane - 3α,17α,21 - triol - 20 - one 21 - acetate in 2.5 ml. of 80% tert. - butyl alcohol, 1.0 ml of glacial acetic acid and one drop of concentrated hydrochloric acid is added 100 mg. of N-bromoacetamide at 5°C., and the reaction mixture kept at −5°C. for 20 hours. Aqueous sodium bisulphite solution is added, and the mixture extracted with methylene chloride. The organic solvent extracts are evaporated to give a residue which is debrominated by treatment with zinc dust in acetone-acetic acid. After filtering the zinc from the reaction mixture, water is added to the filtrate. The resultant precipitate is filtered and dried to yield 40 mg. of 16α - methylpregnane - 17α,21 - diol - 3,20 - dione 21 - acetate.

Similarly the corresponding 16β - methylpregnane, 16α - methylallopregnane, and 16β - methylpregnane analogs upon subjection to this procedure are converted to respectively, 16β - methyl - pregnane - 17α,21 - diol - 3,20 - dione 21 - acetate, 16α - methylallopregnane - 17α,21 - diol - 3,20 - dione 21 - acetate, and 16β - methylallopregnane - 17α,21 - diol - 3,20 - dione 21 - acetate.

EXAMPLE 42

16α-Methyl-4-pregnene-17α,21-diol-3,20-dione 21-acetate

A. 4β - Bromo - 16α - methylpregnane - 17α,21 - diol - 3,20 - dione 21 - acetate

A solution of 84 mg. of 16α - methylpregnane - 17α,21 - diol - 3,20 - dione 21 - acetate in 3 ml. of tert-butyl alcohol and 3 ml. of methylene chloride is brominated at 30—35°C. by the rapid addition of a solution of 32 mg. of bromine in 3 ml. of tert-butyl alcohol. After bromination is complete (1 3/4 hours), the solution is evaporated to dryness under reduced pressure. The residue is slurried with water, filtered and dried to yield 4β - bromo - 16α - methylpregnane - 17α,21 - diol - 3,20 - dione 21 - acetate which is of sufficient purity for the conversion described in the following procedure.

B. 16α - Methyl - 4 - pregnene - 17α,21 - diol - 3,20 - dione 21 - acetate

The 4β - bromo - 16β - methylpregnane - 17α,21 - diol - 3,11,20 - trione 21 - acetate of above Example 42 is dissolved in a mixture of 30 mg. of semicarbazide, 4 ml. of tert-butyl alcohol and 2 ml. of methylene chloride, and stirred in a nitrogen atmosphere for two hours at 25—30°C. After removing the solvent under reduced pressure, the residue is dissolved in 5 ml. of 80% acetic acid-water along with excess 70% pyruvic acid, and the reaction mixture allowed to stand at room temperature for 20 hours. The solution is brought to about pH 7 with dilute (5%) sodium hydroxide, and then is extracted with methylene chloride. The organic extracts are evaporated to a residue, and the residue chromatographed on "Flosisil". Crystalline material (25 mg.) obtained from the 50% ether-hexane and 100% ether eluates, on crystallization from acetone-hexane yields 16α - α - methyl - 4 - pregnene - 17α,21 - diol - 3,20 - dione 21 - acetate.

The identical compound is obtained by subjecting 16α - allopregnane - 17α,21 - diol - 3,20 - dione 21 - acetate to this procedure.

Similarly, by employing either 16β - methylpregnane - 17α,21 - diol - 3,20 - dione

21 - acetate or 16β - methylallopregnane - 17α,21 - diol - 3,20 - dione 21 - acetate there is prepared in both instances, 16β - methyl - 4 - pregnene - 17α,21 - diol - 3,20 - dione 21 - acetate.

16α-Methyl-1,4-pregnadiene-17α,21-diol-3,20-dione 21-acetate

C. 2,4 - Dibromo - 16α - methylpregnane - 17α,21 - diol - 3,20 - dione 21 - acetate

A solution of 167 mg. 16α - methylpregnane - 17α,21 - diol - 3,20 - dione 21 - acetate, the compound of Example 41, in 3 ml. of dioxan is dibrominated in positions 2 and 4 by the rapid addition of 130 mg. of bromine in 1 ml. of dioxan at room temperature. The solution is poured into water and the precipitated solid is filtered, yielding 2,4 - dibromo - 16α - methyl - pregnane - 17α,21 - diol - 3,20 - dione 21 - acetate of sufficient purity to be used in the conversion described in the following procedure.

D. 16α - Methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione 21 - acetate

The 2,4-dibromide (180 mg.) as prepared in above Example 41 is dehydrobrominated by refluxing for 2 hours with 4 ml. of dimethylformamide containing 30 mg. of calcium carbonate. The mixture is poured into dilute hydrochloric acid and extracted with methylene chloride. The organic extract is evaporated to a residue, which is chromatographed on "Florisil". The fractions obtained by elution with 20% ether-hexane are crystallized from acetone-hexane to give 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione 21 - acetate. The 21 - acetate is then hydrolysed by the process of Example 2 to yield the 21-alcohol.

In a similar fashion the corresponding 16β - methyl - pregnane, 16α - methylallopregnane and 16β - methylallopregnane analogs may be subjected to the procedures of Parts C and D above to yield the identical product as obtained in Part D.

Alternatively the 1,4-diene system may be introduced into 16α - methyl - 4 - pregnene - 17α,21 - diol - 3,20 - dione or the 16β - methyl analog as follows:

16α - Methyl - 4 - pregnene - 17α,21 - diol - 3,20 - dione 21 - acetate (0.5 g.) is dissolved in 20 ml. of methanol and 2 ml. of water containing 0.1 g. of potassium bicarbonate. The solution is refluxed for 1/2 hour, then concentrated in vacuo to 1/2 the volume and water added. The precipitated solid is dried and recrystallized from methanol to yield 16α - methyl - 4 - pregnene - 17α,21 - diol - 3,20 - dione. This compound is then subjected to microbiological dehydrogenation as follows:

Bacillus sphaericus var. fusiformis (A.T.C.C. 7055) is incubated on a nutrient agar (composed of Bacto-beef extract, 3 g.; Bacto-peptone, 5 g.; sodium chloride, 8 g.; agar, 15 g.; tap water, 1 litre) for 24 hours at 28°C.

To 100 ml. of a sterile nutrient broth (composed of Bacto-beef extract, 3 g.; Bacto-peptone, 5 g.; per litre of tap water) in a 300 ml. flask is added one loopful of the incubated culture and the broth mixture is further incubated for 24 hours at 28°C on a shaking machine. The broth culture so obtained is employed as an inoculum (1%).

Into each of ten flasks containing 100 ml. of sterile nutrient broth is added 1 ml. of the inoculum. The flasks are agitated on a rotary shaker for 8 hours at 28°C at 240 strokes per minute. After this growth period, a solution of 25 mg. of 16α - methyl - 4 - pregnene - 17α,21 - diol - 3,20 - dione, in 0.5 ml. of methanol is aseptically added to each flask which in turn is reshaken and incubated for an additional 24 hours. The final pH is 7.8.

The contents of the flasks are then combined and extracted three times with 2 litres of chloroform per extraction. The combined chloroform extracts are evaporated to dryness yielding 310 mg. of crude product. The crude steroid is purified by chromatography on a chromatographic system described by G. M. Shull, Abstracts of Papers of the 126th Meeting of the America Chemical Society, December 12—17, 1954, page 9a, paper No. 24. Chromatographic evaluation shows a quantitative conversion of the starting material to the diene when an authentic sample of the 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione is used as a control.

Similarly the 16β-methyl analogue is subjected to this procedure to obtain 16β - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione.

E. 16α - Methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione

A culture of *Curvularia lunata* (NRRL—2380) is grown in shaker flasks for 48 hours at 28°C on a malt extract-sucrose-salt medium. An inoculum of 100 ml. of this preparation is introduced into 2000 ml. of a nutrient agar (composed of 6 g. of Bacto-beef extract; 10 g. of Bacto-peptone; 16 g. of sodium chloride; 30 g. of agar; 200 ml. of tap water). The medium is agitated rapidly with aeration for 22 hours at 28°C. The resultant broth is filtered and 50 g. of the wet mycelium thus obtained is added to 200 ml. of water and 0.5 g. of 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione. The suspension is agitated as described above for 22 hours at 28°C. At the end of this time the mixture is extracted with chloroform. The chloroform extracts are then concentrated and the residue chromatographed according to the alternative procedures referred to in stage D of this Example. There is thus prepared 16α - methyl - 1,4 -

pregnadiene - 11β,17α,21 - triol - 3,20 - dione.

In a similar fashion the 16β-methyl analog may be subjected to the above procedure to yield 16β - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione.

Alternatively 16 (α or β) - methyl - 4 - pregnene - 17α,21 - diol - 3,20 - dione is treated according to the above-procedure and there is obtained 16 (α or β) - methyl - 4 - pregnene - 11β,17α,21 - triol - 3,20 - dione. These compounds may then be subjected to the microbiological procedure described in the alternative process of stage D of this Example to yield 16 (α or β) - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione.

Again alternatively 16(α or β) - methylpregnane - 17α,21 - diol - 3,20 - dione or 16(α or β) - methylallopregnane - 17α,21 - diol - 3,20 - dione may be subjected to the action of the fungus *Curvularia lunata* and the 11β-hydroxylated products obtained then treated according to procedures in stages A and B and/or C and D of this Example for the introduction of the Δ^1-monoene- or $\Delta^{1,4}$-diene systems. There can thus be prepared by this alternative method the compounds recited above, 16(α or β) - methyl - 4 - pregnene - 11β,17α,21 - triol - 3,20 - dione and 16(α or β) - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione.

EXAMPLE 43

In a completely analogous manner as described in stage E of Example 42 but employing the fungus *Rhizopus nigricans* (ATCC 6227b) and the appropriate conditions analogous to those of Petersen et al. as described in the J.A.C.S., *75*, 412(1953), the corresponding 11α-hydroxy compounds may be prepared. Thus there is obtained 16(α or β) - methyl - 1,4 - pregnadiene - 11α,17α,21 - triol - 3,20 - dione; 16(α or β) - methyl - 4 - pregnene - 11α,17α,21 - triol - 3,20 - dione; 16(α or β) - methylpregnane - 11α,17α,21 - triol - 3,20 - dione; and 16(α or β) - methyl - allopregnane - 11α,17α,21 - triol - 3,20 - dione, interconversions as previously indicated.

EXAMPLE 44

16α-Methyl-1,4-pregnadiene-17α,21-diol-3,11,20-trione

To a solution of 0.3 g of 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21 - acetate, the compound of Example 27B in 15 ml. of acetic acid is added dropwise a solution of 60 mg. of chromium trioxide in 1 ml. of water and 3 ml. of acetic acid. The resulting mixture is allowed to stand 5 hours, then diluted with water and extracted with methylene chloride. The organic extracts are washed with water, dried over magnesium sulphate, filtered and evaporated in a residue which is crystallized from methanol to give 0.1 g. of 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 21 - acetate.

This compound is then dissolved in 20 ml. of methanol and 2 ml. of water containing 0.1 g. of potassium bicarbonate. The solution is refluxed for 1/2 hour, then concentrated *in vacuo* to 1/2 the volume and water added. The precipitated solid is dried and recrystallized from methanol to yield 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione.

Alternatively 16α - methyl - 1,4 - pregnadiene - 11α,17α,21 - triol - 3,20 - dione 21 - acetate may be oxidized and hydrolyzed to yield the same product.

In a similar manner, the 16β-methyl analog may be treated according to these procedures to yield 16β - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione.

WHAT WE CLAIM IS:—

1. Compounds of the pregnane series having anti-inflammatory activity and characterised by possessing a double bond in the 4-position or double bonds in the 1- and 4-positions, ketonic oxygen atoms in the 3- and 20-positions, a 17α-hydroxyl group, a β-hydroxyl group or a ketonic oxygen atom in the 11-position, a hydroxyl or an esterified hydroxyl group in the 21-position, which compounds are also characterised by a β-methyl group in the 16-position.

2. Compounds as claimed in claim 1 substituted by halogen at the 9α-position.

3. Compounds as claimed in claim 2 wherein the halogen at the 9α-position is fluorine.

4. 16β - Methyl - 4 - pregnene - 17α,21 - diol - 21 - triol - 3,20 - dione.

5. 16β - Methyl - 4 - pregnene - 11β,17α,21 - triol - 3,20 - dione.

6. 16β - Methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione.

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

8. 9α - Fluoro - 16β - methyl - 4 - pregnene - 17α,21 - diol - 3,11 20 - trione.

9. 9α - Fluoro - 16β - methyl - 4 - pregnene - 11β,17α,21 - triol - 3,20 - dione.

10. 9α - Fluoro - 16β - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione.

11. 9α - Fluoro - 16β - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione.

12. A 21-ester of a compound as claimed in any of claims 4—11.

13. A 21-ester as claimed in claim 1 or claim 12 wherein the ester radical is derived from an organic carboxylic acid.

14. A 21-ester as claimed in claim 13 in which the ester radical is derived from an unsubstituted or cycloalkyl substituted alkanoic acid having not more than 8 carbon atoms.

15. A 21-ester as claimed in claim 13 in

pregnadiene - 11β,17α,21 - triol - 3,20 - dione.

In a similar fashion the 16β-methyl analog may be subjected to the above procedure to yield 16β - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione.

Alternatively 16 (α or β) - methyl - 4 - pregnene - 17α,21 - diol - 3,20 - dione is treated according to the above-procedure and there is obtained 16 (α or β) - methyl - 4 - pregnene - 11β,17α,21 - triol - 3,20 - dione. These compounds may then be subjected to the microbiological procedure described in the alternative process of stage D of this Example to yield 16 (α or β) - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione.

Again alternatively 16(α or β) - methylpregnane - 17α,21 - diol - 3,20 - dione or 16(α or β) - methylallopregnane - 17α,21 - diol - 3,20 - dione may be subjected to the action of the fungus *Curvularia lunata* and the 11β-hydroxylated products obtained then treated according to procedures in stages A and B and/or C and D of this Example for the introduction of the Δ^1-monoene- or $\Delta^{1,4}$-diene systems. There can thus be prepared by this alternative method the compounds recited above, 16(α or β) - methyl - 4 - pregnene - 11β,17α,21 - triol - 3,20 - dione and 16(α or β) - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione.

EXAMPLE 43

In a completely analogous manner as described in stage E of Example 42 but employing the fungus *Rhizopus nigricans* (ATCC 6227b) and the appropriate conditions analogous to those of Peterson et al. as described in the J.A.C.S., *75*, 412(1953), the corresponding 11α-hydroxy compounds may be prepared. Thus there is obtained 16(α or β) - methyl - 1,4 - pregnadiene - 11α,17α,21 - triol - 3,20 - dione; 16(α or β) - methyl - 4 - pregnene - 11α,17α,21 - triol - 3,20 - dione; 16(α or β) - methylpregnane - 11α,17α,21 - triol - 3,20 - dione; and 16(α or β) - methyl - allopregnane - 11α,17α,21 - triol - 3,20 - dione, interconversions as previously indicated.

EXAMPLE 44

16α-Methyl-1,4-pregnadiene-17α,21-diol-3,11,20-trione

To a solution of 0.3 g of 16α - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione 21 - acetate, the compound of Example 27B in 15 ml. of acetic acid is added dropwise a solution of 60 mg. of chromium trioxide in 1 ml. of water and 3 ml. of acetic acid. The resulting mixture is allowed to stand 5 hours, then diluted with water and extracted with methylene chloride. The organic extracts are washed with water, dried over magnesium sulphate, filtered and evaporated in a residue which is crystallized from methanol to give 0.1 g. of 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 21 - acetate.

This compound is then dissolved in 20 ml. of methanol and 2 ml. of water containing 0.1 g. of potassium bicarbonate. The solution is refluxed for 1/2 hour, then concentrated *in vacuo* to 1/2 the volume and water added. The precipitated solid is dried and recrystallized from methanol to yield 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione.

Alternatively 16α - methyl - 1,4 - pregnadiene - 11α,17α,21 - triol - 3,20 - dione 21 - acetate may be oxidized and hydrolyzed to yield the same product.

In a similar manner, the 16β-methyl analog may be treated according to these procedures to yield 16β - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione.

WHAT WE CLAIM IS:—

1. Compounds of the pregnane series having anti-inflammatory activity and characterised by possessing a double bond in the 4-position or double bonds in the 1- and 4-positions, ketonic oxygen atoms in the 3- and 20-positions, a 17α-hydroxyl group, a β-hydroxyl group or a ketonic oxygen atom in the 11-position, a hydroxyl or an esterified hydroxyl group in the 21-position, which compounds are also characterised by a β-methyl group in the 16-position.

2. Compounds as claimed in claim 1 substituted by halogen at the 9α-position.

3. Compounds as claimed in claim 2 wherein the halogen at the 9α-position is fluorine.

4. 16β - Methyl - 4 - pregnene - 17α,21 - diol - 21 - triol - 3,20 - dione.

5. 16β - Methyl - 4 - pregnene - 11β,17α,21 - triol - 3,20 - dione.

6. 16β - Methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione.

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

8. 9α - Fluoro - 16β - methyl - 4 - pregnene - 17α,21 - diol - 3,11,20 - trione.

9. 9α - Fluoro - 16β - methyl - 4 - pregnene - 11β,17α,21 - triol - 3,20 - dione.

10. 9α - Fluoro - 16β - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione.

11. 9α - Fluoro - 16β - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione.

12. A 21-ester of a compound as claimed in any of claims 4—11.

13. A 21-ester as claimed in claim 1 or claim 12 wherein the ester radical is derived from an organic carboxylic acid.

14. A 21-ester as claimed in claim 13 in which the ester radical is derived from an unsubstituted or cycloalkyl substituted alkanoic acid having not more than 8 carbon atoms.

15. A 21-ester as claimed in claim 13 in

which the ester radical is derived from acetic, propionic, or trimethyl-acetic acid.

16. A 21-ester as claimed in claim 11 in which the ester radical is derived from a polycarboxylic acid.

17. A 21-ester as claimed in claim 16 in which said polycarboxylic acid is phthalic, succinic, tartaric or citric acid.

18. An alkali metal salt of a partial 21-ester of a polycarboxylic acid as claimed in claim 16 or claim 17.

19. A 21-ester as claimed in claim 12 in which the ester radical is derived from furoic acid.

20. A 21-ester as claimed in claim 12 in which the ester radical is derived from a polybasic inorganic acid.

21. A 21-ester as claimed in claim 20 in which said polybasic inorganic acid is phosphoric acid.

22. A salt of a partial 21-ester of a polybasic inorganic acid as claimed in claim 20 or 21.

23. A therapeutic composition comprising a non-toxic carrier and a compound as claimed in any of the preceding claims.

24. A process for the production of a 16β-alkyl-17α-hydroxy steroid which comprises reacting a starting material having the pregnane carbon skeleton and containing a 16,17-double bond in conjugated relationship with a 20-keto group with a diazoalkane, pyrolysing the resultant 16,17-alkylidene diazo steroid to form a 16-alkyl-16-dehydro-steroid and introducing a 17α-hydroxy group by epoxidizing the 16,17-double bond, reacting the 16α,17α-epoxide with a hydrogen halide followed by catalytic hydrogenation whereby there is obtained the desired 16β-alkyl compounds, the 16-alkyl group of which contains up to 6-carbon atoms.

25. A process for the production of a 16β-alkyl-17α-hydroxy steroid which comprises reacting a starting material having the pregnane carbon skeleton and containing a 16,17-double bond in conjugated relationship with a 20-keto group with a diazoalkane, pyrolysing the resultant 16,17-alkylidene diazo steroid to form a 16-alkyl-16-dehydro steroid and introducing a 17α-hydroxy group by hydrogenating the 16,17-dehydro compound at the 16,17-positions by catalytic hydrogenation, enolacylating the resultant compound, epoxidising the enolacylate at the 17,20 positions and hydrolysing the 17,20 epoxide to form the desired 16β-alkyl-17α-hydroxy steroid.

26. A process as claimed in claim 24 or claim 25 in which the starting material is a 3,11-diketo steroid.

27. A process as claimed in any of claims 24—26 in which the 16β-alkyl group is a 16β-methyl group and the diazoalkane is diazomethane.

28. A process as claimed in any of claims 24—27 in which the pyrolysis is effected by heating the 16,17-alkylidene-diazo compound above its melting point.

29. A process as claimed in any of claims 24—27 in which the pyrolysis is effected by heating the 16,17-alkylidene-diazo compound in a high boiling inert solvent.

30. A process for the preparation of a 16-alkyl steroid which comprises reacting a 3,11-dioxygenated-16-dehydro-20-keto compound of the pregnane (5α- or 5β-) series with a diazoalkane containing not more than six carbon atoms to form a 16,17-alkylidene-diazo pregnane and pyrolysing this to yield a 3,11 - dioxygenated - 16 - alkyl - 16 - dehydro - 20 - keto compound of said pregnane series.

31. A process as claimed in claim 30 in which said diazoalkane is diazomethane.

32. 16 - Methyl - 16 - pregnene - 3α - ol - 11,20 - dione 3 - esters.

33. 16β - Methylpregnane - 3α - ol - 11,20 - dione 3 - esters.

34. 16β - Methylpregnane - 3α,17α - diol - 11,20 - dione 3 - esters.

35. 16β - Methylpregnane - 3α,17α,21 - triol - 11,20 - dione 21 - esters.

36. 16β - Methylpregnane - 17α, 21 - diol - 3,11,20 - trione 21 - esters.

37. 16β - Methylpregnane - 3α - ol - 11,20 - dione 3 - acetate.

38. 16β - Methylpregnane - 3α,17α - diol - 11,20 - dione.

39. 16β - Methylpregnane - 3α,17α - diol - 11,20 - dione 3 - ester of an alkanoic acid containing 1—8 carbon atoms.

40. 16β - Methylpregnane - 3α,17α,21 - triol - 11,20 - dione 21 - ester of an alkanoic acid containing 1—8 carbon atoms.

41. 16β - Methylpregnane - 17α,21 - diol - 3,11,20 - trione 21 - ester of an alkanoic acid containing 1—8 carbon atoms.

42. A compound as claimed in any of claims 39—41 in which the 21-ester is the 21-acetate.

43. 16β - Methylcortisone - 3,20 - bis - semicarbazone 21 - acetate.

44. 16β - Methylhydrocortisone - 3,20 - bis - semicarbazone.

45. 16β - Methyl - 4 - pregnene - 11α,17α,21 - triol - 3,20 - dione.

46. 16(α or β) - Methyl - 1,4 - pregnadiene - 11α,17α,21 - triol - 3,20 - dione.

47. 16β - Methyl - 1,4,9(11) - pregnatriene - 3,20 - 17α,21 - diol and 21 - esters thereof.

48. 16β - Methyl - 1,4,9(11) - pregnatriene - 3,20 - dione - 17α,21 - diol 21 - acetate.

49. 9β,11β - Oxido - 16β - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione and 21 - esters thereof.

50. 9β,11β - Oxido - 16β - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione 21 - acetate.

51. 16α - Methyl - 1,4,9(11) - pregna-

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triene - 3,20 - dione - 17α,21 - diol and 21 - esters thereof.

52. 16α - Methyl - 1,4,9(11) - pregnatriene - 3,20 - dione - 17α,21 - diol 21 - acetate.

53. 9β,11β - Oxido - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione and 21 - esters thereof.

54. 9β,11β - Oxido - 16α - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione 21 - acetate.

55. A process for the preparation of a 16(α or β) - methyl - 1,4,9(11) - pregnatriene - 3,20 - dione - 17α,21 - diol or a 21 - carboxylates thereof which comprises dehydrating a 16(α or β) - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione or a 21 - carboxylate thereof.

56. A process for the preparation of a 9α - halo - 16(α or β) - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione or a 21-carboxylate thereof (in which the halogen atom at the 9-position is chlorine, bromine or iodine) which comprises reacting a 16 (α or β) - methyl - 1,4,9(11) - pregnatriene - 3,20 - dione - 17α,21 - diol or a 21-carboxylate thereof with a hypohalous acid corresponding to the desired 9α-halo substituent.

57. A process for the preparation of a 9β,11β - oxido - 16(α or β) - methyl - 1,4 - pregnadiene - 3,20 - dione - 17α,21 - diol or a 21-carboxylate thereof which comprises reacting a 9α - halo - 16(α or β) - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione or a 21-carboxylate thereof (in which the halogen atom at the 9-position is chlorine, bromine or iodine) with a base.

58. A process for the preparation of a 9α - fluoro - 16(α or β) - methyl - 1,4 - pregnadiene 11β,17α,21 - triol - 3,20 - dione or a 21-ester thereof which comprises reacting a 9β,11β-oxido - 16(α or β) - methyl - 1,4 - pregnadiene - 17α,20 - diol - 3,20 - dione or 21-carboxylate thereof with hydrogen fluoride.

59. A process for the preparation of a 9α - fluoro - 16(α or β) - methyl - 1,4 - pregnadiene 11β,17α,21 - triol - 3,20 - dione or a 21-ester thereof which comprises dehydrating a 16(α or β) - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione or a 21 - carboxyate thereof to form a 16(α or β) - methyl - 1,4,9(11) - pregnatriene - 3,20 - dione - 17α,21 - diol or a 21 - carboxylate thereof, reacting a 16(α or β) - methyl - 1,4,9(11) - pregnatriene - 3,20 - dione - 17α,20 - diol or a 21 - carboxylate thereof with a hypohalous acid corresponding to the desired 9α-halo substituent to form a 9α-halo-16(α or β) - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione or a 21-carboxylate thereof (in which the halogen atom at the 9-position is chlorine, bromine or iodine), reacting a 9α - halo - 16(α or β) - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione or a 21 - carboxylate thereof with a base to form a 9β,11β - oxido - 16(α or β) - methyl - 1,4 - pregnadiene - 3,20 - dione - 17α,21 - diol or a 21 - carboxylate thereof and reacting a 9β,11β - oxido - 16(α or β) - methyl - 1,4 - pregnadiene - 17α,20 - diol - 3,20 - dione or an ester thereof with hydrogen fluoride to form the desired compound.

60. A process as claimed in claim 58 or claim 59 in which the resulting compound is oxidised to form the corresponding 11-ketone.

61. A process as claimed in any of claims 55—59 in which the 21-carboxylate is the 21-acetate.

62. 9α - Halogeno - 16β - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione and 21-esters thereof, in which the 9-halogeno atom is chlorine bromine or iodine.

63. 9α - Halogeno - 16β - methyl - 4 - pregnene - 11β,17α,21 - triol - 3,20 - dione and 21-esters thereof, in which the 9-halogeno atom is chlorine bromine or iodine.

64. 9α - Halogeno - 16α - methyl - 1,4 - pregnadiene - 11β,17α21 - triol - 3,20 - dione and 21-esters thereof, in which the 9-halogeno atom is chlorine bromine or iodine.

65. 9α - Halogeno - 16α - methyl - 4 - pregnene - 11β,17α,21 - triol - 3,20 - dione and 21-esters thereof, in which the 9-halogeno atom is chlorine bromine or iodine.

66. A process for the preparation of 2,4 - dibromo - 16(α or β) - methyl - pregnane (5α or 5β) - 17α,21 - diol - 3,11,20 - trione 21-ester which comprises dibrominating 16(α or β) - methyl pregnane (5α or 5β) - 17α, 21 - diol - 3,11,20 - trione 21 - ester with a brominating agent.

67. A process as claimed in claim 66 in which the brominating agent is molecular bromine.

68. A process for the preparation of 16(α or β) - methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,11,20 - trione 21 - ester which comprises dehydrobrominating 2,4 - dibromo - 16(α or β) - methyl - pregnane (5α or 5β) - 17α,21 - diol - 3,11,20 - trione 21 - ester with a dehydrobrominating agent.

69. A process as claimed in claim 68 in which dimethylformamide is employed as dehydrobrominating agent.

70. A process as claimed in claim 69 in which the dehydrobromination is effected in the presence of calcium carbonate.

71. A process as claimed in claim 68 in which the dehydrobrominating agent is a tertiary amine.

72. A process as claimed in claim 71 in which the tertiary amine is collidine.

73. A process for the preparation of 4 - bromo - 16β - methylpregnane - 17α,21 - diol - 3,11,20 - trione 21 - ester which com-

prise... 17α,2... agent 74. ... which ... bromi... 75. ... methy... 3,11,2... dehyd... pregn... 21 - ... 76. ... which ... hydrol... 77. ... which ... the pr... 78. ... which ... tertiary ... 79. ... which ... 80. ... 66—79 ... 81. ... 17α,21 ... 82. ... 17α,21 ... 83. ... pregnar... trione ... 84. ... pregnar... triene ... 85. ... pregnan... dione 2... 86. ... pregnan... dione 2... 87. A... desoxy... 20 - ket... 5β) seri... alkyl - ... series, ... carbon ... alkanoic ... strong a... 20 - acy... reacted ... 17,20-ep... 88. A... in the 16... 89. A... claim 88... 11 - de... hydroxy... nane seri... 90. A... 87—89 ... ing a C... tion at C...

prises brominating 16β - methylpregnane - 17α,21 - diol 21 - ester with a brominating agent.

74. A process as claimed in claim 73 in which the brominating agent is molecular bromine.

75. A process for the preparation of 16β - methyl - 4 - pregnene - 17α,21 - diol - 3,11,20 - trione 21 - ester which comprises dehydrobrominating 4 - bromo - 16β - methylpregnane - 17α,21 - diol - 3,11,20 - trione 21 - ester with a dehydrobrominating agent.

76. A process as claimed in claim 75 in which dimethylformamide is employed as dehydrobrominating agent.

77. A process as claimed in claim 76 in which the dehydrobromination is effected in the presence of calcium carbonate.

78. A process as claimed in claim 76 in which the dehydrobrominating agent is a tertiary amine.

79. A process as claimed in claim 78 in which the tertiary amine is collidine.

80. A process as claimed in any of claims 66—79 in which the 21-ester is the 21-acetate.

81. 4 - Bromo - 16β - methylpregnane - 17α,21 diol - 3,11,20 - trione 21 - ester.

82. 4 - Bromo - 16β - methylpregnane - 17α,21 - diol - 3,11,20 - trione 21 - acetate.

83. 2,4 - Dibromo - 16(α or β)methylpregnane (5α or 5β) - 17α,21 - diol - 3,11,20 - trione 21 - ester.

84. 2,4 - Dibromo - 16(α or β)methylpregnane(5α or 5β) - 17α,21 - diol - 3,11,20 - trione 21 - acetate

85. 2,4 - Dibromo - 16(α or β)methylpregnane(5α or 5β) - 17α,21 - diol - 3,20 - dione 21 - ester.

86. 2,4 - Dibromo - 16(α or β) methylpregnane(5α or 5β) - 17α,21 - diol - 3,20 - dione 21 - acetate.

87. A process for the preparation of 11 - desoxy - 16(α or β) - alkyl - 17α - hydroxy - 20 - keto compounds of the pregnane (5α or 5β) series in which an 11 - desoxy - 16 - alkyl - 20 - keto compound of the pregnane series, said alkyl group containing 1—6 carbon atoms, is enol acylated with a lower alkanoic acid anhydride in the presence of a strong acid catalyst; the $\Delta^{17(20)}$ - dehydro - 20 - acyloxy - compound thereby formed is reacted with a peroxy acid and the resultant 17,20-epoxide is hydrolyzed.

88. A process as claimed in claim 87 wherein the 16-alkyl group is 16 (α or β)-methyl.

89. A process as claimed in claim 87 or claim 88 wherein the starting material is an 11 - desoxy - 16(α or β) - methyl - 3 - hydroxy - 20 - keto compound of the pregnane series or an ester thereof.

90. A process as claimed in any of claims 87—89 including the further steps of introducing a C—21 alkanoyloxy group by bromination at C—21 followed by treatment with an alkali metal lower alkanoate to form a 21-alkanoate of a 3,17α,21 - trihydroxy - 20 - keto - 16 - alkylpregnane (5α or 5β), oxidizing the 3-hydroxy group to keto, and introducing Δ^1 or $\Delta^{1,4}$ unsaturation in the A-ring.

91. A process as claimed in any of claims 87—90 including the further step of hydroxylating at C—11 by a microbiological oxidative procedure.

92. A 16 - (α or β) - alkyl - 17α - hydroxy - 20 - keto - pregnane (5α or 5β) having a 3—X—21—R substituent wherein R represents hydrogen, bromine, hydroxyl or alkanoyloxy; and X represents hydroxy, alkanoxy or oxo, the 16-alkyl group containing 1—6 carbon atoms.

93. A 16(α or β) - alkyl - 21 - alkanoyloxy - 17(20) - pregnene (5α or 5β) - 3 - ol and 3-alkanoyl esters thereof, the 16-alkyl group containing 1—6 carbon atoms.

94. A 16(α or β) - alkyl - 17,20 - oxido - 20 - alkanoyloxy pregnane (5α or 5β) - 3 - ol and 3-alkanoyl esters thereof, the 16-alkyl group containing 1—6 carbon atoms.

95. A 16(α or β) - alkyl - 20 - keto - 21 - R - pregnane (5α or 5β) - 3,17α - diol and 3-alkanoyl esters thereof wherein R is a hydrogen or a bromine atom or an alkanoyloxy group, the 16-alkyl group containing 1—6 carbon atoms.

96. A 16(α or β) - alkyl - 3,20 - diketo-pregnane (5α or 5β) - 17α,21 - diol and 21-alkanoyl esters thereof, the 16-alkyl group containing 1—6 carbon atoms.

97. A 16(α or β) - alkyl - 3,20 - diketo - 4 - pregnene - 17α,21 - diol and 21 - alkanoyl esters thereof, the 16-alkyl group containing 1—6 carbon atoms.

98. A 16(α or β) - alkyl - 3,20 - diketo - 1,4 - pregnadiene - 17α,21 - diol and 21-alkanoyl esters thereof, the 16-alkyl group containing 1—6 carbon atoms.

99. 16(α or β) - Methylallopregnane - 3β,-17α - diol - 20 - one.

100. 16(α or β) - Methylpregnane - 3α,-17α - diol - 20 - one.

101. 16(α or β) - Methylallopregnane - 3β,17α,21 - triol - 20 - one 21 - alkanoate.

102. 16(α or β) - Methylpregnane - 3α,-17α,21 - triol - 20 - one 21 - alkanoate.

103. 16(α or β) - Methylpregnane - 17α,21 - diol - 3,20 - dione 21 - alkanoate.

104. 16(α or β) - Methylallopregnane - 17α,21 - diol - 3,20 - dione 21 - alkanoate.

105. 16(α or β) - Methyl - 4 - pregnene - 17α,21 - diol - 3,20 - dione 21 - alkanoate.

106. 16(α or β) - Methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione 21 - alkanoate.

107. 16(α or β) - Methyl - 1,4 - pregnadiene - 17α,21 - diol - 3,20 - dione.

108. 4 - Bromo - 16(α or β) - methyl - pregnane - 17α,21 - diol - 3,20 - dione 21 - ester.

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109. 4 - Bromo - 16(α or β) - methyl - pregnane - 17α,21 - diol - 3,20 - dione 21 - acetate.

110. 16(α or β) - methylpregnane(5α or 5β) - 11α,17α,21 - triol - 3,20 - dione.

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