

## [54] ANDROSTANE CARBOTHIOATES

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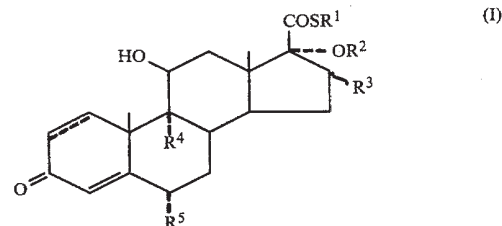
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## [57] ABSTRACT

Compounds of the formula



wherein R<sup>1</sup> represents a fluoro-, chloro- or bromo-methyl group or a 2'-fluoroethyl group, R<sup>2</sup> represents a group COR<sup>6</sup> where R<sup>6</sup> is a C<sub>1-3</sub> alkyl group or OR<sup>2</sup> and R<sup>3</sup> together form a 16 $\alpha$ ,17 $\alpha$ -isopropylidenedioxy group; R<sup>3</sup> represents a hydrogen atom, a methyl group (which may be in either the  $\alpha$ - or  $\beta$ -configuration) or a methylene group; R<sup>4</sup> represents a hydrogen, chlorine or fluorine atom; R<sup>5</sup> represents a hydrogen or fluorine atom and symbol  $\cdots\cdots\cdots$  represents a single or double bond have good anti-inflammatory activity, particularly on topical applications.

The compounds of formula I are prepared by esterification, halogenation, reduction, deprotection and reaction at a 9,11-double bond to form a 9 $\alpha$ -halo-11 $\beta$ -hydroxy grouping.

Pharmaceutical compositions containing the compounds of formula I and methods for the use of the compounds are described and claimed.

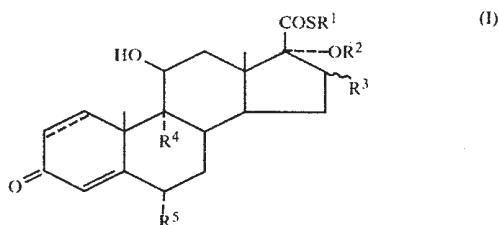
25 Claims, No Drawings

## ANDROSTANE CARBOTHIOATES

The present invention relates to anti-inflammatory steroids of the androstane series.

Anti-inflammatory steroids are most typically of the corticoid type, i.e. are pregnane derivatives. Our United Kingdom Pat. Nos. 1,384,372, 1,438,940 and 1,514,476 describe esters of certain androstane 17 $\alpha$ -carboxylic acids having anti-inflammatory activity. European Patent Application No. 79300500.0 (Publication No. 0004741) describes esters of androstane 17 $\beta$ -carbothioic acids also possessing anti-inflammatory activity. We have now discovered that certain androstane compounds containing a haloalkyl carbothioate grouping in the 17 $\beta$ -position have particularly advantageous anti-inflammatory properties as discussed in greater detail below.

The new androstane compounds may be represented by the formula



wherein R<sup>1</sup> represents a fluoro-, chloro- or bromomethyl group or a 2'-fluoroethyl group; R<sup>2</sup> represents a group COR<sup>6</sup> where R<sup>6</sup> is a C<sub>1-3</sub> alkyl group or OR<sup>2</sup> and R<sup>3</sup> together form a 16 $\alpha$ ,17 $\alpha$ -isopropylidenedioxy group; R<sup>3</sup> represents a hydrogen atom, a methyl group (which may be in either the  $\alpha$ - or  $\beta$ - configuration) or a methylene group; R<sup>4</sup> represents a hydrogen, chlorine or fluorine atom; R<sup>5</sup> represents a hydrogen or fluorine atom and symbol  $\text{---}$  represents a single or double bond.

The new compounds of formula (I) have good anti-inflammatory activity, particularly on topical application, as judged by the McKenzie patch test in man and as measured by the reduction of croton oil induced oedema when the compounds are applied topically to the skin of mice and rats.

Certain of the compounds show good topical anti-inflammatory activity in the croton oil ear test coupled with minimal hypothalamus-pituitary-adrenal-suppressive activity after topical application in the same animal species. These results indicate that such compounds may be of value in the local treatment of inflammation in man and animals with minimal liability to cause undesired systemic side effects.

Compounds of formula (I) which are preferred for their good anti-inflammatory activity include the following categories namely (a) those in which R<sup>1</sup> is chloro- or fluoromethyl (b) those in which R<sup>2</sup> is acetyl or propionyl, preferably propionyl, (c) those in which R<sup>4</sup> is fluorine (d) those in which R<sup>5</sup> is fluorine (e) the 1,4-dienes, and (f) those 1,4-dienes in which R<sup>4</sup> is fluorine and R<sup>3</sup> is hydrogen,  $\alpha$ - and  $\beta$ -methyl or methylene.

Compounds of formula (I) which have good anti-inflammatory activity coupled with minimal hypothalamuspituitary-adrenal-suppressive activity when applied topically include 1,4-dienes in which R<sup>1</sup> is chloro-

or fluoro-methyl, R<sup>4</sup> and R<sup>5</sup> are fluorine and in particular those in which R<sup>3</sup> is  $\alpha$ -methyl.

Especially preferred compounds according to the invention in view of their good topical anti-inflammatory activity and favourable ratio of topical anti-inflammatory activity to undesired systemic activity include:

S-chloromethyl 9 $\alpha$ -fluoro-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-17 $\alpha$ -propionyloxyandrosta-1,4-diene-17 $\beta$ -carbothioate;

S-chloromethyl 9 $\alpha$ -fluoro-11 $\beta$ -hydroxy-16-methylene-3-oxo-17 $\alpha$ -propionyloxyandrosta-1,4-diene-17 $\beta$ -carbothioate;

S-fluoromethyl 6 $\alpha$ ,9 $\alpha$ -difluoro-11 $\beta$ -hydroxy-16 $\alpha$ ,17 $\alpha$ -isopropylidenedioxy-3-oxoandrosta-1,4-diene-17 $\beta$ -carbothioate;

S-fluoromethyl 6 $\alpha$ ,9 $\alpha$ -difluoro-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-17 $\alpha$ -propionyloxyandrosta-1,4-diene-17 $\beta$ -carbothioate;

S-chloromethyl 6 $\alpha$ ,9 $\alpha$ -difluoro-11 $\beta$ -hydroxy-16 $\alpha$ -methyl-3-oxo-17 $\alpha$ -propionyloxyandrosta-1,4-diene-17 $\beta$ -carbothioate. The last compound is especially preferred in view of its particularly favourable ratio and in addition minimal skin atrophy.

The compounds of formula (I) may be prepared by a variety of different processes.

One such process comprises esterifying an androstane compound corresponding to formula (I) but containing either a free 17 $\beta$ -carbothioic acid group (or functionally equivalent group) or a free 17 $\alpha$ -hydroxy group (R<sup>3</sup> being a hydrogen atom or a methyl or methylene group), any other reactive groups present in the molecule being suitably protected as desired.

For example, a salt of the parent 17 $\beta$ -carbothioic acid such as an alkali metal, e.g. lithium, sodium or potassium, salt or an alkylammonium, e.g. triethylammonium or tetrabutylammonium, salt may be reacted with an appropriate alkylating agent, preferably in a polar solvent such as a ketone, e.g. acetone or an amide such as dimethylformamide, dimethylacetamide or hexamethylphosphoramide, conveniently at a temperature of 15° to 100° C. The alkylating agent may comprise an appropriate dihalo compound i.e. one containing a further halogen atom (preferably a bromine or iodine atom) in addition to the halogen atom of the desired R<sup>1</sup> group. This process is particularly applicable to the preparation of compounds in which R<sup>1</sup> is a chloromethyl group, the alkylating agent advantageously being bromochloromethane.

Alternatively, the parent 16-hydrogen, methyl or methylene-17 $\alpha$ -hydroxy-17 $\beta$ -carbothioates corresponding to compounds of formula I may be subjected to esterification of the 17 $\alpha$ -hydroxyl group. This may be effected by conventional techniques, e.g. by reacting the parent 17 $\alpha$ -hydroxy compound with a mixed anhydride of the required carboxylic acid, which may, for example, be generated in situ by reacting the carboxylic acid with an appropriate anhydride such as trifluoroacetic anhydride, preferably in the presence of an acid catalyst, e.g. p-toluenesulphonic acid or sulphosalicylic acid. Alternatively, the mixed anhydride may be generated in situ by reaction of a symmetrical anhydride of the required acid with an appropriate further acid, e.g. trifluoroacetic acid.

The reaction is advantageously effected in an organic solvent medium such as benzene, methylene chloride or an excess of the carboxylic acid employed, the reaction

being conveniently effected at a temperature of 20°–100° C.

Alternatively, the 17 $\alpha$ -hydroxy group may be esterified by reaction of the parent 17 $\alpha$ -hydroxy compound with the appropriate acid anhydride or acid chloride, if desired, in the presence of non-hydroxylic solvents, e.g. chloroform, methylene chloride or benzene, and preferably in the presence of a strong acid catalyst, e.g. perchloric acid, p-toluene sulphonic acid or a strongly acidic cation exchange resin, e.g. Amberlite IR 120, the reaction being conveniently effected at a temperature of 25° to 100° C.

The compounds of formula (I) may also be prepared by reacting a corresponding androstane compound containing a 17 $\beta$ -substituent of formula —COS(CH<sub>2</sub>)<sub>n</sub>Y (wherein Y represents a displaceable substituent and n is 1 or 2) with a compound serving to replace the group Y by a halogen atom.

Thus the compounds of formula (I) may be subjected to a halogen exchange reaction serving to replace the group Y where this is halogen by a different halogen substituent. Thus the bromomethyl, fluoromethyl and fluoroethyl 17 $\beta$ -carbothioate compounds may be prepared from the corresponding iodomethyl or bromoethyl 17 $\beta$ -carbothioate compounds using a bromide salt such as lithium bromide in the case of the bromomethyl 17 $\beta$ -carbothioate compounds or an appropriate fluoride e.g. silver monofluoride or silver difluoride in the case of the fluoromethyl or fluoroethyl 17 $\beta$ -carbothioate compounds. The starting iodomethyl 17 $\beta$ -carbothioate compounds may be prepared from the corresponding chloromethyl 17 $\beta$ -carbothioate compounds using for example, an alkali metal, alkaline earth metal or quaternary ammonium iodide e.g. sodium iodide.

The reaction is advantageously effected in a solvent medium comprising for example acetone, acetonitrile, methyl ethyl ketone, dimethylformamide, dimethylacetamide or ethanol.

The foregoing reactions may also be carried out on starting materials having a variety of substituents or groupings which are subsequently converted into those substituents or groupings which are present in the compounds of the invention as defined above.

The 11 $\beta$ -hydroxy compounds of formula (I) may thus be prepared by reduction of a corresponding 11-oxo compound, e.g. using an alkali metal or alkaline earth metal borohydride, e.g. sodium or calcium borohydride, conveniently in an alcoholic or aqueous alcoholic solvent such as methanol or ethanol.

Such an 11-keto compound may be prepared by oxidation of a corresponding 11 $\alpha$ -hydroxysteroid, for example using a chromic acid reagent such as Jones' reagent.

An 11 $\beta$ -hydroxy compound of formula (I) may also be obtained by deprotection of a corresponding compound having a protected hydroxyl group at the 11 $\beta$ -position, for example a tri C<sub>1-6</sub>alkylsilyloxy group such as the trimethylsilyloxy group or a perfluoro- or chloro-alkanoyloxy group such as the trifluoroacetoxy group. Removal of the protecting group may be effected by hydrolysis, the trialkylsilyl group, being readily removed by mild acid or basic hydrolysis or particularly conveniently using fluoride e.g. hydrogen fluoride or an ammonium fluoride. The perfluoro- or chloro-alkanoyl protecting group may also be removed by mild acid or basic hydrolysis or alcoholysis, but preferably under acidic conditions when R<sup>4</sup> is a chlorine atom. Such a protected hydroxyl group may be introduced, for exam-

ple, by reacting an 11 $\beta$ -hydroxy steroid with an appropriate reagent such as a trialkylsilyl halide or a perfluoro- or chloro-alkanoic anhydride.

Compounds of formula (I) may also be produced by reaction of a corresponding compound having a 9,11-double bond (and no substituent in the 11-position) with reagents serving to introduce the required 9 $\alpha$ -halo-11 $\beta$ -hydroxy grouping. This may involve initial formation of a bromohydrin by reaction with an N-bromo-amide or -imide such as N-bromosuccinimide, followed by formation of the corresponding 9 $\beta$ ,11 $\beta$ -epoxide by treatment with a base and reaction of the epoxide with hydrogen fluoride or hydrogen chloride to introduce the required fluorohydrin or chlorohydrin grouping respectively. Alternatively, the 9,11-olefin compound may be reacted with an N-chloro-amide or -imide to introduce the required 9 $\alpha$ -chloro-11 $\beta$ -hydroxy grouping directly.

The  $\Delta^4$ -compounds according to the invention can conveniently be prepared by partial reduction of the corresponding  $\Delta^{1,4}$ -compound, for example, by hydrogenating using a palladium catalyst, conveniently in a solvent e.g. ethyl acetate or by homogeneous hydrogenation using for example tris(triphenylphosphine)rhodium chloride, conveniently in a solvent such as benzene, or by exchange hydrogenation using for example cyclohexene in the presence of a palladium catalyst in a solvent e.g. ethanol, preferably under reflux. This reduction may be carried out on a haloalkyl ester where this is sufficiently stable in such a reaction or may be effected at an earlier stage.

The above mentioned compounds containing a free —COSH group in the 17 $\beta$ -position may be prepared for example by aminolysis with rearrangement of a suitable 17 $\beta$ -thiocarbamoyloxycarbonyl androstane. The 17 $\beta$ -thiocarbamoyloxycarbonyl androstane is a mixed anhydride of the corresponding 17 $\beta$ -carboxylic acid and a thiocarbamic acid and is conveniently prepared by reaction of a salt of the 17 $\beta$ -carboxylic acid 17 $\alpha$ -ester or 16 $\alpha$ , 17 $\alpha$ -acetonide with a thiocarbamoyl halide. The thiocarbamoyl group is N,N-disubstituted, and may thus have the formula —COOSNR<sup>A</sup>R<sup>B</sup>, where R<sup>A</sup> and R<sup>B</sup>, which may be the same or different, are alkyl groups, e.g. C<sub>1-4</sub> alkyl groups or R<sup>A</sup> and R<sup>B</sup> together with the nitrogen atom to which they are attached form a 5–8 membered ring which may optionally contain an additional hetero atom selected from oxygen, nitrogen and sulphur and/or which may optionally be substituted by one or two C<sub>1-3</sub> alkyl e.g. methyl groups. Preferably R<sup>A</sup> and R<sup>B</sup> are C<sub>1-4</sub> alkyl substituents, the N,N-dimethylthiocarbamoyl group being preferred. The thiocarbamoyl halide is preferably the chloride. The reaction may be accelerated by the addition of an iodide salt e.g. sodium iodide.

The initial androstane 17 $\beta$ -carboxylate salt may be for example, an alkali metal, e.g. sodium or potassium, alkaline earth metal, e.g. calcium, salt or a salt of a tertiary amine, e.g. triethylamine.

Aminolysis with rearrangement may be carried out for example by heating the mixed anhydride to an elevated temperature e.g. in the presence of ammonia, a primary amine or more preferably a secondary amine such as diethylamine or pyrrolidine. In the starting 17 $\beta$ -carboxylic acids, the 16- and 17 $\alpha$ -positions will conveniently be substituted by the —R<sup>3</sup> and —OR<sup>2</sup> groupings desired for the final product of formula (I).

17 $\alpha$ -Hydroxy androstane compounds in the 16-methylene series which contain the desired 17 $\beta$ -carbo-

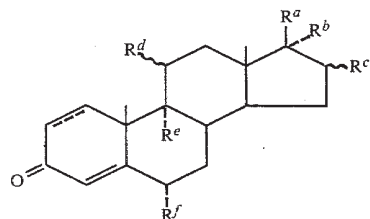
thioic acid grouping, as described above, may be prepared from the corresponding 16 $\beta$ -methyl-16 $\alpha$ ,17 $\alpha$ -epoxy 17 $\beta$ -thiocarboxylic acid, by effecting a rearrangement using a strong acid e.g. a strong carboxylic acid such as trifluoroacetic acid. These 16 $\alpha$ ,17 $\alpha$ -epoxides may be prepared from the corresponding 17 $\beta$ -carboxylic acids by treatment with an onium salt of a 2-halo-azaaromatic compound, followed by treatment of the resulting product with hydrogen sulphide or a salt thereof to give the free 17 $\beta$ -carbothioic acid which may be alkylated as described above, preferably in situ to give the desired 17 $\beta$ -carbothioate group.

16 $\alpha$ ,17 $\alpha$ -Isopropylidenedioxy compounds of formula (I) may similarly be prepared by treating a corresponding 17 $\beta$ -carboxylic acid with an onium salt of a 2-halo-azaaromatic compound followed by treatment of the resulting product with hydrogen sulphide to give the free 17 $\beta$ -carbothioic acid which may then be esterified as described above.

Onium salts of 2-halo-aza-aromatic compounds are capable of effecting carboxyl activation. Such reagents include 2-halo-N-alkyl- or 2-halo-N-phenyl-pyridinium or pyrimidinium salts carrying 1 to 2 further substituents selected from phenyl and lower (e.g. C<sub>1-4</sub>) alkyl groups, such as methyl. The 2-halogen atoms can be fluorine, chlorine, bromine or iodine atoms. The salts are preferably sulphonates, e.g. tosylates; halides e.g. iodides; fluoroborates or perfluoroalkylsulphonates, a convenient salt being 2-fluoro-N-methylpyridinium tosylate or 2-chloro-N-methylbenzothiazolium trifluoromethanesulphonate.

The 16 $\alpha$ ,17 $\alpha$ -epoxy-16 $\beta$ -methyl-17 $\beta$ -carboxylic acid compounds used as starting materials in the above process may be prepared in conventional manner, e.g. as described in British Patent Specification No. 1,517,278.

The starting materials employed in the process described herein for the preparation of compounds of formula (I) are new and constitute a further feature of the invention; they include compounds of the general formula (II)



(wherein R<sup>a</sup> represents a thiocarbamoyloxycarbonyl group —COOCSNR<sup>A</sup>R<sup>B</sup> where R<sup>A</sup> and R<sup>B</sup> are as defined above, or a group of the formula —COSR<sup>1A</sup>, where R<sup>1A</sup> represents a hydrogen atom or is a group as defined above for R<sup>1</sup> or is a group convertible thereto and R<sup>b</sup> represents an esterified hydroxyl group or R<sup>b</sup> and R<sup>c</sup> together represent in isopropylidenedioxy group; or where R<sup>a</sup> represents a group COSR<sup>1A</sup>, R<sup>b</sup> is optionally a hydroxyl group;

R<sup>c</sup> represents a hydrogen atom, a methyl group (which may be in either the  $\alpha$ - or  $\beta$ -configuration) or a methylene group;

R<sup>d</sup> represents a hydroxy or protected hydroxy group (in either the  $\alpha$ - or  $\beta$ -configuration) or an oxo group;

R<sup>e</sup> represents a hydrogen, bromine, chlorine or fluorine atom; or R<sup>d</sup> and R<sup>e</sup> together represent a carbon-carbon bond or an epoxy group in the  $\beta$ -configuration;

R<sup>f</sup> represents a hydrogen or a fluorine atom; and the symbol  $\equiv$  represents a single or double bond and salts of these compounds which have a free carbothioic acid group; with the exclusion of compounds of formula (I) as hereinbefore defined.

Where R<sup>d</sup> represents a protected hydroxyl group, this may, for example be a trialkylsilyloxy group or a perfluoro- or perchloro-alkanoyloxy group as defined previously.

The 17 $\alpha$ -hydroxy 17 $\beta$ -carbothioic acids of formula (II) and salts thereof may be converted into the 17 $\alpha$ -hydroxy 17 $\beta$ -carbothioates of formula (II) where R<sup>a</sup> represents the group COSR<sup>1</sup> as defined in formula (I) or into the 17 $\beta$ -carbothioic acid 17 $\alpha$ -esters of formula (II) by the processes described above for preparing the compounds of formula (I). The esterification of the 17 $\alpha$ -hydroxy group is preferably effected with the appropriate carboxylic acid chloride in a solvent such as a halogenated hydrocarbon e.g. dichloromethane, and advantageously in the presence of a base such as triethylamine, preferably at a low temperature e.g. 0° C.

The 17 $\alpha$ -hydroxy 17 $\beta$ -carbothioic acids of formula (II) and salts thereof are thus particularly useful intermediates for preparing the androstane 17 $\beta$ -carbothioates of formula (I); those in which R<sup>c</sup> represents a hydrogen atom, an  $\alpha$ - or  $\beta$ -methyl group or a methylene group, R<sup>e</sup> represents a hydrogen, chlorine or fluorine atom, R<sup>d</sup> represents a hydroxy group in the  $\beta$ -configuration or an oxo group being preferred. More preferred compounds and salts thereof include those compounds in which R<sup>c</sup> represents a methyl group in the  $\alpha$ - or  $\beta$ -configuration or a methylene group; R<sup>e</sup> represents a fluorine atom, R<sup>d</sup> represents a hydroxy group in the  $\beta$ -configuration or an oxo group and the symbol  $\equiv$  in the 1,2 position represents a carbon-carbon double bond.

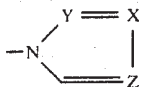
Especially preferred compounds of formula II thus include, for example, the following:

9 $\alpha$ -fluoro-11 $\beta$ ,17 $\alpha$ -dihydroxy-16 $\beta$ -methyl-3-oxoandrosta-1,4-diene-17 $\beta$ -carbothioic acid; 9 $\alpha$ -fluoro-11 $\beta$ ,17 $\alpha$ -dihydroxy-16 $\alpha$ -methyl-3-oxoandrosta-1,4-diene-17 $\beta$ -carbothioic acid; 9 $\alpha$ -fluoro-11 $\beta$ ,17 $\alpha$ -dihydroxy-16-methylene-3-oxoandrosta-1,4-diene-17 $\beta$ -carbothioic acid; 6 $\alpha$ ,9 $\alpha$ -difluoro-11 $\beta$ ,17 $\alpha$ -dihydroxy-16 $\alpha$ -methyl-3-oxoandrosta-1,4-diene-17 $\beta$ -carbothioic acid and the corresponding 11-ketones and salts thereof.

One advantage of the above intermediates is that they permit direct haloalkylation to give haloalkyl 17 $\beta$ -carbothioates when the corresponding thiols R<sup>1</sup>SH are not available. The salts of these 17 $\alpha$ -hydroxy 17 $\beta$ -carbothioic acids may, for example be alkali metal, e.g. lithium, sodium or potassium salts; alkaline earth metal, e.g. calcium or magnesium salts; tertiary amine salts, e.g. pyridinium or triethylammonium salts; or quaternary ammonium salts, e.g. tetrabutylammonium salts.

The 17 $\alpha$ -hydroxy 17 $\beta$ -carbothioic acids may, for example, be prepared by reaction of a reactive derivative of a corresponding 17 $\alpha$ -hydroxy-17 $\beta$ -carboxylic acid with hydrogen sulphide or a sulphide or hydrosulphide salt thereof. In general, the cation of the sulphide or hydrosulphide salt may be for example an alkali metal salt such as sodium or potassium hydrogen sulphide. The above-mentioned reactive derivatives correspond to compounds of formula (II) where R<sup>b</sup> is a hydroxyl group and the group —COR<sup>7</sup> is present at the 17 $\beta$ -position wherein R<sup>7</sup> represents a group of the formula

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in which X, Y and Z, which may be the same or different, each represent CH or N, one or two of X, Y and Z being N, the heterocyclic ring optionally being substituted on at least one carbon atom by a lower alkyl group (e.g. with 1 to 4 carbon atoms, such as a methyl group) and/or where the heterocyclic ring contains two adjacent carbon atoms, the said ring optionally carrying a benzene ring fused to the said adjacent carbon atoms.

The reactive derivatives of formula (III) are preferably prepared by reacting corresponding 17 $\alpha$ -hydroxy 17 $\beta$ -carboxylic acids of formula (II) with a symmetric or asymmetric compound of the formula:



wherein W represents the group CO, CS, SO or SO<sub>2</sub> and the groups R<sup>7</sup>, which may be the same or different, have the above meanings.

The compounds of formula (III) are conveniently symmetric. In general, compounds of formula (III) in which W represents CO, CS or SO will be used. Thus, for example, especially useful compounds include N,N'-carbonyldi(1,2,4-triazole), N,N'-carbonyldibenzotriazole, N,N'-carbonyldibenzimidazole, N,N'-carbonyldi(3,5-dimethylpyrazole), N,N'-thionyl-diimidazole and especially N,N'-carbonyldiimidazole and N,N'-thiocarbonyldiimidazole.

The preparation of a 17 $\alpha$ -hydroxy 17 $\beta$ -carbothioic acid having the formula (II) as herein defined is conveniently effected by reaction of a 17 $\alpha$ -hydroxy 17 $\beta$ -carboxylic acid with a compound of formula (III) followed by reaction of the intermediate product having the 17 $\beta$ -COR<sup>7</sup> grouping with hydrogen sulphide or a salt thereof preferably in situ without isolation of the intermediate.

The 17 $\alpha$ -acyloxy 17 $\beta$ -carbothioic acid of formula II may be obtained in a similar manner directly from the corresponding 17 $\alpha$ -acyloxy 17 $\beta$ -carboxylic acid by reaction with a compound of formula (III). The 17 $\alpha$ -acyloxy 17 $\beta$ -carboxylic acids may be prepared by esterification of the corresponding 17 $\alpha$ -acyloxy 17 $\beta$ -carboxylic acids by the methods described in BP No. 1,384,372.

The reaction with the compound of formula (III) is conveniently effected in the presence of an inert anhydrous solvent e.g. a substituted amide solvent such as N,N-dimethylformamide or N,N-dimethylacetamide, desirably in the absence of water, advantageously at or below ambient temperature e.g. at a temperature of from -30° C. to +30° C. The reaction is conveniently effected under approximately neutral conditions, advantageously in an inert atmosphere, e.g. under nitrogen. The same solvents and conditions are also applicable to the subsequent reaction with H<sub>2</sub>S or a salt thereof. The heterocyclic compound e.g. imidazole or 1,2,4-triazole formed as a by-product may, for example, be readily removed by extraction with water.

The foregoing reactions may also be carried out on compounds having a variety of substituents or groupings which are subsequently converted as described previously to compounds of formula (I).

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The androstane 17 $\beta$ -carboxylic acid starting materials employed in the above processes may be prepared in conventional manner, e.g. by oxidation of an appropriate 21-hydroxy-20-keto pregnane for example with periodic acid, in a solvent medium and preferably at room temperature. Alternatively, sodium bismuthate may be employed to effect the desired oxidative removal of the 21-carbon atom of a 17 $\alpha$ -acyloxy pregnane compound. As will be appreciated should the starting pregnane compound contain any substituent sensitive to the above desired oxidation, such a group should be suitably protected.

The following examples illustrate the invention.

Melting points were determined in °C. on a Kofler block and are uncorrected. Optical rotations were determined at room temperature on solutions in dioxan.

T.l.c. (Thin layer chromatography), p.l.c. (Preparative layer chromatography) and h.p.l.c. (High performance liquid chromatography) were carried out over silica.

Solutions were dried over magnesium sulphate unless stated otherwise.

#### PREPARATION I

9 $\alpha$ -Fluoro-11 $\beta$ -hydroxy-16 $\beta$ -methyl-3-oxo-17 $\alpha$ -propionyloxyandrosta-1,4-diene-17 $\beta$ -carbothioic acid (I)

A solution of 9 $\alpha$ -fluoro-11 $\beta$ -hydroxy-16 $\beta$ -methyl-3-oxo-17 $\alpha$ -propionyloxyandrosta-1,4-diene-17 $\beta$ -carboxylic acid (5.00 g) solvated with ethyl acetate ( $\frac{1}{2}$  mole) and triethylamine (5.3 ml) in dichloromethane (75 ml) was stirred under nitrogen and treated with dimethylthiocarbamoyl chloride (5.071 g). After 24 h more reagent (5.320 g) was added. After 47 h the mixture was diluted with ethyl acetate and washed with N-hydrochloric acid, 5% sodium bicarbonate solution and water, dried and evaporated to give a viscous yellow oil (9.043 g). This was dissolved in diethylamine (50 ml) then stirred and heated at reflux under nitrogen for 5.75 h. The resulting brown solution was added to a mixture of concentrated hydrochloric acid (50 ml), water (250 ml) and ethyl acetate (50 ml). The products were further extracted with ethyl acetate, then the acid products were back-extracted into 5% sodium carbonate solution. The aqueous phase was acidified with 6 N-hydrochloric acid (50 ml) and extracted with ethyl acetate. The extracts were washed with N-hydrochloric acid and water, dried and evaporated to a buff solid (3.440 g). This was recrystallised from acetone to give pale buff crystals (1.980 g) of the title 17 $\beta$ -carbothioic acid, m.p. 172°-173°.

The analytical sample was obtained after two recrystallizations from acetone as white crystals, m.p. 177°-179°, [ $\alpha$ ]<sub>D</sub>+110° (c 1.05).

#### PREPARATION II

##### S-Chloromethyl

9 $\alpha$ -fluoro-16 $\beta$ -methyl-3,11-dioxo-17 $\alpha$ -propionyloxyandrosta-1,4-diene-17 $\beta$ -carbothioate (II)

8 N-Jones reagent (1.5 ml) was added dropwise over 10 mins to a stirred solution of the compound of Example 1 (hereinafter disclosed) (998 mg) in acetone (2 ml) and dimethylformamide (2 ml). After 30 mins the reaction mixture was slowly diluted with water (100 ml) with stirring, and the resulting suspension was refrigerated for 1 h. The precipitate was collected by filtration, washed with water and dried to give a cream coloured solid (877 mg). P.l.c. in chloroform-acetone (10:1) gave

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