1,169,902

PATENT SPECIFICATION

NO DRAWINGS

1,169,902

Inventor: EUGENE FARKAS

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Index at acceptance:—C2 U(2, 4A1, 4A2, 4B1, 4B2, 4C1, 4C2, 4C4, 4C5, 4C10, 4X)
International Classification:—C 07 c 169/66

COMPLETE SPECIFICATION

Novel Estranes and process for preparing the same

We, ELI LILLY AND COMPANY, a Corporation of the State of Indiana, United States of America, of 740 South Alabama Street, City of Indianapolis, State of Indiana, United States of America, 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 estranes having pharmaceutical utility and displaying a heretofore unknown configuration at the A—B ring junction.

Several years ago, it was determined that many of the structural features of the naturally occurring steroidal hormones were not necessary for hormonal activity. For example, it was found that 19-norprogesterone was somewhat more active as a progestational agent then the naturally occurring hormone, progesterone. Furthermore, Δ^1-cortisol (prednisolone) is a far more powerful anti-inflammatory agent than cortisol itself as is the 6α - fluoro - 16α - methyl derivative of prednisolone. Such discoveries have led to tremendous advances in the field of steroidal hormone therapy, particularly among the anti-inflammatory agents wherein substitution of fluorine for its isostere hydrogen as well as introduction of additional double bonds have been particularly profitable research areas.

In addition to the above cited modifications, another method of varying the structure of the steroidal hormones has been to change the spatial orientation of various groups or atoms, particularly those at ring junction carbons. This line of attack has not been as fruitful as the others, largely because the non-natural configuration thus produced is thermodynamically unstable compared with the naturally occurring configuration.

In general, most naturally occurring steroids have a trans-anti-trans configuration for the A—B and B—C ring junctures; that is to say, the A—B and B—C rings are both transfused, and the atoms or groups at the 9 and 10 positions are trans (anti) to one another. Furthermore, each of the A, B and C rings is able to be in the more stable chair configuration when the rings are fused trans to one another as in the normal steroid. Deviation from the natural configuration gives rise to various forces which tend to render a non-natural configuration relatively unstable. These forces are largely the result of steric and/or torsional strains and can result in forcing one of the rings into the relatively unstable boat conformation, or in deforming the steroid molecule from the essentially planar conformation of the naturally occurring trans-anti-trans steroids.

Despite the fact that non-natural ring juncture configurations result in a steroid which is relatively more strained compared to a steroid with a natural configuration, it has been possible to synthesize many of the non-natural steroid A—B—C ring systems. In general, however, these syntheses have been carried out on 19-nor compounds because of the great difficulty in synthesizing compounds with a methyl group at the ring junction. The fully hydrogenated 19-nor compounds, or estranes, have been prepared by reduction of the corresponding estratrienes, many of which are naturally occurring female hormones. For example, Birch reduction of estrone followed by hydrolysis of the reduction product to a 3 - keto - Δ^4 compound and subsequent elimination of the Δ^4 bond by reduction yields a 3-keto-estrane having a normal 5α,10β,9α,8β - configuration (trans-anti-trans). The 5α,10α,9α,8β-configuration (cis-syn-trans) has been prepared by Farkas and Rapala (see U.S. Patent 3,015,666) by reduction of an estratriene using a highly active rhodium or ruthenium catalyst. This type of reduction yields only compounds having hydrogen on the alpha side of the ring since the beta methyl group at C_{13} effectively blocks the estratriene from approaching the catalyst from the beta side. Another isomer,

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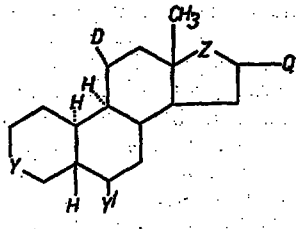
Price 25p

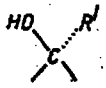
the one with the 5β,10β,9α,8β-configuration (cis-anti-trans), has been prepared by the reduction of estrone with platinum oxide in acetic acid, among other methods. Thus, there have been prepared only three of the four possible configurations at the A—B ring junction in steroids having natural stereochemistry at the B—C ring junctions — the 5α,10β,9α,8β, the 5α,10α,9α,8β, and the 5β,10β,9α,8β.

It is an object of this invention to provide 19-nor steroids having the heretofore unknown 5β,10α,9α,8β-configuration (trans-syn-trans). It is a further object of this invention to provide a process for the preparation of 5β,10α-estranes. Other objects of this invention will become apparent from the description which follows.

In fulfillment of the above and other objects, this invention provides a group of novel steroids having the heretofore unknown 5β,10α,9α,8β configuration (trans-syn-trans) which are represented by the following formula:



wherein Y is —CHOH— or ; Z is



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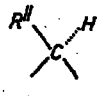


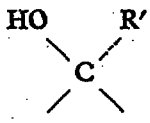
R is hydrogen, acetyl or hydroxyacetyl; R' is hydrogen, C_1—C_4 alkyl, vinyl, ethynyl or halo-ethynyl; and R'' is acetyl or hydroxyacetyl; Y' is hydrogen, methyl, fluoro or chloro; D is hydrogen, hydroxy or keto, and Q is hydrogen, methyl or fluoro.

Also included within the scope of this invention are compounds having protecting esterifying or etherifying groups replacing the hydrogen of the hydroxyl at the 3 or 17 positions. Among such protecting groups are the tetrahydropyranyl, acetyl, benzoyl, succinoyl, methyl, ethyl, propionyl and other like groups.

Illustrative compounds included within the scope of this invention include the following:

5β,10α-estrane-17α-ol-3-one
5β,10α-estrane-3β,17α-diol
5β,10α-estrane-3β,17β-diol
6α-fluoro-17α-chloroethynyl-5β,10α-estrane-11β,17β-diol-3-one-17β-acetate
17α-n-propyl-5β,10α-estrane-3β,17β-diol
17α-methyl-5β,10α-estrane-17β-ol-3-one-17β-benzoate
19-nor-5β,10α-pregnane-3,20-dione
19-nor-5β,10α-pregnane-3β,11β,17α,21-tetrol-20-one
19-nor-5β,10α-pregnane-3β,21-diol-3,20-dione

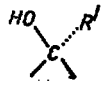
Compounds represented by the above formulas are high-melting white crystalline solids soluble in most polar organic solvents. The compounds wherein R' is hydrogen or C_1—C_4 alkyl are readily prepared by reducing a corresponding 3 - keto - Δ^4 - 19 - nor - 10 - isosteroid by means of lithium in liquid ammonia—a standard Birch reduction. The compounds wherein Z is



and R' is vinyl, ethynyl or halo-ethynyl are prepared as set out hereinbelow. The compounds are isolated from the reaction mixture by conventional processes and can either be crystallized directly or after purification by chromatography.

It is quite surprising that Birch reduction of a Δ^4 - 10α,9α,8β-steroid would yield the 5β-derivative inasmuch as it is generally believed that the 5α-steroid would be more stable thermodynamically. Specifically, the trans-syn-trans conformation of the steroids of this invention is theoretically less stable thermodynamically than the cis-syn-trans conformation (the 5α,10α,9α,8β-configuration) which would be a possible product of a Birch reduction of a 3 - keto - Δ^4 - 19 - nor - 10 isosteroid. Furthermore, it has generally been held that the Birch reduction, inasmuch as it is a "one-electron" reduction, would yield the thermodynamically more stable derivative, although there has been a recent exception found to this rule. Nevertheless, in the synthetic process of this invention, quite surprisingly, the thermodynamically-less stable 5β-compounds are formed.

Compounds represented by the above formula are in general anti-hormones. When Z in the above formula is either



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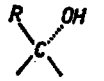
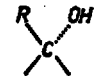
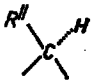


R is hydrogen and R′ is defined as above, the resulting compounds are anti-androgens or, in some cases, anti-progesterones. The compounds in which Z is



or



and R and R″ are either acetyl or hydroxyacetyl have the same carbon skeleton as progesterone and cortisone and thus these tend to have an anti-progestational or anti-cortisone action, depending on the structure of the C_{17} side chain. Among the compounds of this invention, 5β,10α - estran - 17β - ol - 3 - one, in particular, is an extremely potent anti-androgen.

Accordingly, the present invention also provides a pharmaceutical composition comprising a steroid of the invention and a pharmaceutical carrier.

The starting materials for the above-mentioned Birch reduction process which leads to the compounds of this invention can be named either 19 - nor - 10α - steroids or 19 - nor - 10 - isosteroids. The synthesis of many of these steroids is fully described in U.K. Patent Specification No. 1,120,814. In this application, we used the preferred nomenclature, calling the compounds 19 - nor - 10 - isotestosterones, 19 - nor - 10 - iso - 4 - androsten - 3 - ones, 19 - nor - 10 - iso-progesterones, etc. The synthetic procedure used to prepare these compounds involves a catalytic hydrogenation of the corresponding $\Delta^{4,9}$-diene with palladium-on-carbon at atmospheric pressure.

Certain of the starting materials, particularly those containing a vinyl or ethynyl group at C_{17}, cannot be prepared directly by the above catalytic hydrogenation procedure, and it is necessary to prepare these starting materials in a somewhat round-about fashion. A particularly useful synthetic procedure which can be applied to the synthesis of many of the compounds having unsaturation at C_{17} is the following: 5β,10α - Estran - 17β - ol - 3 - one is reacted with ethylene glycol in the presence of acid to form a protective ketal grouping for the C_3 ketone. With the C_3 ketone protected, the hydroxyl at 17 can then readily be oxidized, using chromium trioxide in pyridine as the oxidizing agent. The resulting ketone at C_{17} can now be reacted with sodium acetylide or a sodium haloacetylide to form the 17α-ethynyl or a 17α-haloethynyl-17β-hydroxy steroid. Additionally, the ethynyl group can be semi-hydrogenated at this point to a vinyl group to produce the 17α-vinyl derivative. Hydrolysis of the protecting ketal group with acid then yields the desired 17-ethynyl or 17-vinyl steroid reaction product.

This invention is further illustrated by the following specific examples.

Example I

5β,10α-Estran-17β-ol-3-one

One hundred milliliters of redistilled liquid ammonia were placed in a three-neck flask and 0.4 g. of lithium were added in small pieces. Next, a solution of 0.2 g. of 19-nor10-isotestosterone in 30 ml. of anhydrous tetrahydrofuran was added. The resulting reaction mixture was stirred for about 20 minutes, after which time excess ammonium chloride was added. The reaction mixture was allowed to warm up to room temperature while the ammonia evaporated. A mixture of 100 ml. of water and 100 ml. of methylene dichloride was added. The organic layer was separated, and the aqueous layer was extracted twice more with 100-ml. portions of methylene dichloride. The organic extracts were combined, were washed with 100 ml. of saturated sodium chloride solution and were dried. Evaporation of the resulting solution to dryness yielded an orange-yellow residue which was dissolved in 20 ml. of a 3:1 benzene-hexane solvent mixture, and the resulting solution was chromatographed over 20 g. of Grade III neutral alumina. Fifty milliliters of eluate fractions were obtained and numbered serially. The organic solvent was removed by evaporation *in vacuo* from each fraction. The residue from fractions 7—11 were combined and recrystallized from a mixture of ether and hexane, thus yielding 5β,10α - estran - 17β - ol - 3 - one, which melted in the range 122—123°C. The material gave a single spot on this layer chromatography. An optically rotatory dispersion curve of the compound was a typically negative CE curve with minimum value of M = −1022, a value consistent with the 5β,10α-steroid structure.

Recrystallization of the material thus obtained from the same solvent system as above yielded purified material, 5β,10α - estran - 17β - ol - 3 - one, melting in the range 135—137°C.

The above reaction was repeated employing 19 - nor - 10 - isotestosterone acetate as a starting material. The acetate group was hydrolyzed during the reaction and the same

product was obtained as above.

5β,10α - Estrane - 3β,17β - diol as well as the α-isomer are prepared from 5β,10α - estran - 17β - ol - 3 - one by reduction with lithium aluminum hydride or other appropriate hydride reducing agent.

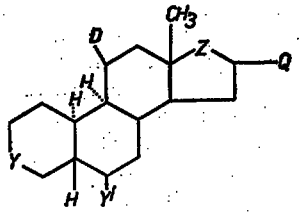
EXAMPLE II

17α-Methyl-5β,10α-estran-17β-ol-3-one

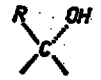
Following the procedure of Example I, 17α - methyl - 19 - nor - 10 - isotestosterone was reduced by the action of lithium in liquid ammonia solvent to yield 17α - methyl - 5β,10α - estran - 17β - ol - 3 - one, which was isolated and purified by the procedure of the same example. 17α - methyl - 5β,10α - estran - 17β - ol - 3 - one thus prepared melted at about 139—141°C. after recrystallization from an ether-hexane solvent mixture. Similar compounds in which the 17α-methyl is replaced by either n-propyl, n-butyl, ethyl or the like, or in which the grouping at C_{17} is β-acetyl or β-(hydroxyacetyl), with or without an α-hydroxyl at the 17 position, are also readily prepared by a Birch reduction of the corresponding 3 - keto - Δ^4 - 19 - nor - 10 - isosteroid.

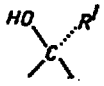
WHAT WE CLAIM IS:—

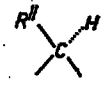
1. A steroid of the formula



wherein Y is —CHOH— or $-\overset{\overset{O}{\|}}{C}-$; and H of the hydroxyl may be replaced by esterifying or etherifying groups, Z is





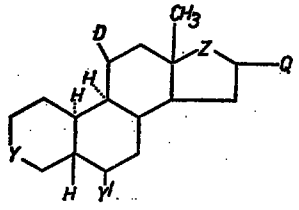


and H of the hydroxyl may be replaced by esterifying or etherifying groups, R is hydrogen, acetyl or hydroxyacetyl; R′ is hydrogen, C_1—C_4 alkyl, vinyl, ethynyl or halo-ethynyl; and R″ is acetyl or hydroxyacetyl; Y′ is hydrogen, methyl, fluoro or chloro; D is hydrogen, hydroxy or keto, and Q is hydrogen, methyl or fluoro.

2. 5β, 10α-Estran-17β-ol-3-one.

3. 17α-Methyl-5β, 10α-estran-17β-ol-3-one.

4. A process for preparing a steroid of the fomula



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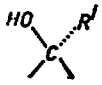

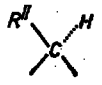

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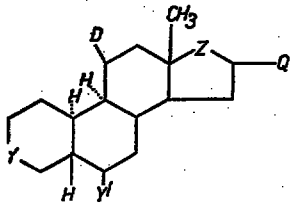
5. A process for preparing a steroid of the formula



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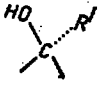

product was obtained as above.

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EXAMPLE II

17α-Methyl-5β,10α-estran-17β-ol-3-one

Following the procedure of Example I, 17α - methyl - 19 - nor - 10 - isotestosterone was reduced by the action of lithium in liquid ammonia solvent to yield 17α - methyl - 5β,10α - estran - 17β - ol - 3 - one, which was isolated and purified by the procedure of the same example. 17α - methyl - 5β,10α - estran - 17β - ol - 3 - one thus prepared melted at about 139—141°C. after recrystallization from an ether-hexane solvent mixture. Similar compounds in which the 17α-methyl is replaced by either n-propyl, n-butyl, ethyl or the like, or in which the grouping at C_{17} is β-acetyl or β-(hydroxyacetyl), with or without an α-hydroxyl at the 17 position, are also readily prepared by a Birch reduction of the corresponding 3 - keto - Δ^4 - 19 - nor - 10 - isosteroid.

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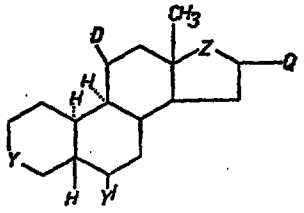

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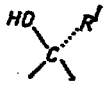

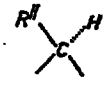

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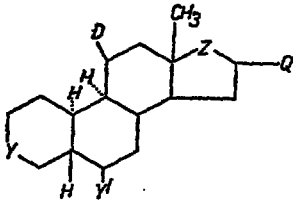
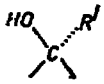
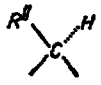


wherein Y is ; Z is





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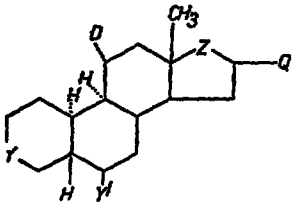
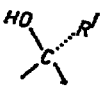


wherein Y is or ; Z is



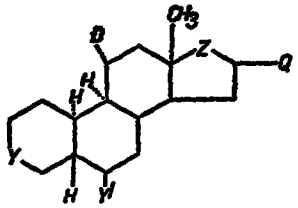
wherein R′ is vinyl, ethynyl or halo-ethynyl; Y′ is hydrogen, methyl, fluoro or chloro; D is hydrogen, hydroxy or keto; and Q is hydrogen, methyl or fluoro; which comprises reacting a 5β, 10α-estran-17β-ol-3-one with ethylene glycol in the presence of acid to form a protective ketal grouping for the C_3 ketone, oxidizing the 17-hydroxyl group using chromium trioxide in pyridine as the oxidizing agent, and reacting the resulting ketone at C_{17} with sodium acetylide or a sodium halo-acetylide; and if desired, semi-hydrogenating the resulting 17α-ethynyl or 17α-halo-ethynyl product to the corresponding vinyl derivative; and hydrolyzing the ketal group of the ethynyl, haloethynyl or vinyl derivative to the corresponding steroid.

6. The process of claim 4 which comprises reducing an estran-3-one product to the corresponding 3-ol by reduction with lithium aluminium hydride.

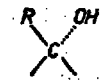
7. The process of claim 4 for preparing 5β, 10α-estran-17β-ol-3-one which comprises mixing a solution of 19-nor-10-isotestosterone in anhydrous tetrahydrofuran with lithium in liquid ammonia, stirring the reaction mixture, adding ammonium chloride, permitting the reaction mixture to warm to room temperature with evaporation of the ammonia, extracting the residue with aqueous methylene dichloride, and evaporating the extract to dryness.

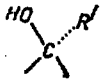
8. The process of claim 4 for preparing 17α-methyl-5β, 10α-estran-17β-ol-3-one which comprises mixing a solution of 17α-methyl-19-nor-10-isotestosterone in tetrahydrofuran with lithium in liquid ammonia, stirring the reaction mixture, adding ammonium chloride, permitting the reaction mixture to warm to room temperature with evaporation of the ammonia, extracting the residue with aqueous methylene dichloride, and evaporating the extract to dryness.

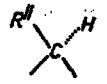
9. A steroid of the formula



wherein Y is —CHOH— or ; and H of the hydroxyl may be replaced by esterifying or etherifying groups, Z is

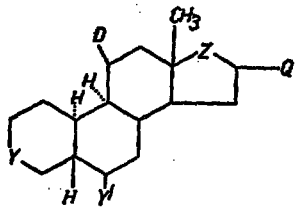




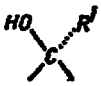


; and H of the hydroxyl may be replaced by esterifying or etherifying groups, R is hydrogen, acetyl or hydroxyacetyl; R′ is hydrogen, C_1—C_4 alkyl, vinyl ethynyl or halo-ethynyl; and R″ is acetyl or hydroxyacetyl; Y′ is hydrogen, methyl, fluoro or chloro; D is hydrogen, hydroxy or keto, and Q is hydrogen, methyl or fluoro; substantially as herein described.

10. A process for preparing a steroid of the formula



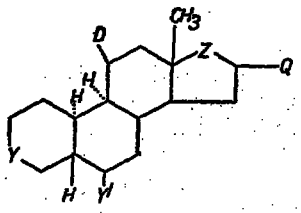
wherein Y is or ; Z is



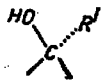
* C L M S *

; and H of the hydroxyl may be replaced by ester or ether groups, R is hydrogen, acetyl or hydroxyacetyl; R′ is hydrogen or C_1—C_4 alkyl; and R″ is acetyl or hydroxyacetyl; Y′ is hydrogen, methyl, fluoro or chloro; D is hydrogen, hydroxy or keto, and Q is hydrogen, methyl or fluoro; which comprises reducing the corresponding 3-keto-Δ^4-19-nor-10-iso-steroid in the presence of lithium in liquid ammonia; substantially as herein described with particular reference to Examples I and II.

11. A process for preparing a steroid of the formula



wherein Y is or and Z is



wherein R′ is vinyl, ethynyl or haloethynyl; Y′ is hydrogen, methyl, fluoro or chloro; D is hydrogen, hydroxy or keto; and Q is hydrogen, methyl, or fluoro; which comprises reacting a 5β-10α-estran-17β-ol-3-one with ethylene glycol in the presence of acid to form a protective ketal grouping for the C_3 ketone, oxidizing the 17-hydroxyl-group, using chromium trioxide in pyridine as the oxidizing agent and reacting the resulting ketone at C_{17} with sodium acetylide or a sodium haloacetylide; and if desired, semi-hydrogenating the resulting 17α ethynyl or 17α-haloethynyl product to the corresponding vinyl derivative; and hydrolyzing the ketal group of the ethynyl, haloethynyl or vinyl derivative to the corresponding steroid; substantially as herein described.

12. A steroid as claimed in claim 1 whenever prepared by the process claimed in any one of claims 4 to 8 or claim 10.

13. A pharmaceutical composition comprising a steroid as claimed in any one of claims 1 to 3, claim 9 or claim 12, and a pharmaceutical carrier.

12. A process as claimed in any one of claims 5, 10 and 11 wherein H of the 17 hydroxyl group is replaced with an esterifying or etherifying group.

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