

PATENT SPECIFICATION

NO DRAWINGS

Inventors: OTTO ENGELFRIED, HANS-GUNTER LEHMANN, FRIEDMUND NEUMANN and RUDOLF WIECHERT

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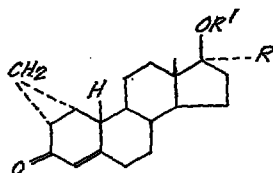
COMPLETE SPECIFICATION

Anabolically Active Steroids

We, SCHERING AKTIENGESELLSCHAFT, a Body Corporate organised according to the laws of Germany, of 1 Berlin 65, Postfach 59, Müllerstrasse 170—172, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

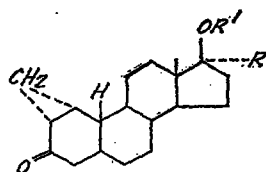
The present invention is concerned with new anabolically active steroids and with their manufacture and use.

The present invention provides 1,2 α - methylene - 19 - nor - testosterone derivatives of the general formula



in which R represents a hydrogen atom or a saturated or unsaturated hydrocarbon group and R¹ represents a hydrogen atom or an acyl group of an organic carboxylic acid.

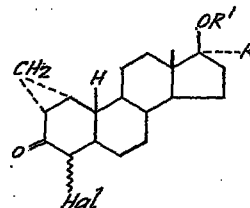
The present invention also provides a process for the manufacture of the aforesaid compounds, wherein either a compound of the formula



is dehydrogenated in a manner known *per se* in the 4,5-position,

[Price 4s. 6d.]

or a compound of the formula



is dehydrohalogenated, and, if desired, in the resulting compound obtained by either method any free 17-OH group is acylated or any 17-acyloxy group is saponified.

As examples of acyl groups there may be mentioned all those that are derived from acids normally used for esterifications in steroid chemistry. The acyl groups are preferably derived from aliphatic carboxylic acids containing especially 1—12 carbon atoms. Of course the acids may also be unsaturated, branched, polybasic or substituted in the usual manner, for example by hydroxyl or amino groups or by halogen atoms. Cycloaliphatic, aromatic, mixed aromatic-aliphatic or heterocyclic acids, which may also be substituted in the usual manner, are also suitable. As preferred acids from which the acyl group R¹ is derived there may be mentioned by way of example: acetic acid, propionic acid, oenanthic acid, caproic acid, undecylic acid, trimethylacetic acid, halogenacetic acid, cyclopentylpropionic acid, phenylacetic acid, phenoxyacetic acid, dialkylaminoacetic acid, piperidinoacetic acid, succinic acid, benzoic acid and similar acids.

The saturated or unsaturated hydrocarbon group R is especially a methyl, ethyl, vinyl or ethynyl group.

The dehydrogenation of the saturated carbon-carbon bond in the 4,5-position of the

methyleformamide, in an atmosphere of nitrogen. The product was cooled, diluted with ethyl acetate, inorganic salts were filtered off and the remainder was washed with ethyl acetate, and the filtrates were combined. After washing with water, dilute hydrochloric acid, water and bicarbonate solution the filtrate was dried and evaporated to dryness *in vacuo*. 0.62 g of crude 1,2 α - methylene - 17 α - ethynyl - 19 - nor - testosterone acetate of melting point 169—171°C was obtained. After filtration through acid alumina the methylene chloride filtrates yielded, after two recrystallisations from diisopropyl ether, 250 mg of analytically pure material of melting point 182—183°C.

EXAMPLE 3

1 g of 1,2 α - methylene - 19 - nor - 5 α - androstan - 17 β - ol - 3 - one [prepared as described in paragraph (d) above] was boiled for 30—52 hours with 1 g of 2,3-dichloro-5,6-dicyanobenzoquinone in 40 ml of absolute benzene. The mixture was then evaporated *in vacuo*, the residue was extracted with methylene chloride, and the methylene chloride solution was fractionally filtered through silica gel. After evaporation of the filtrates 1,2 α - methylene - 19 - nor - testosterone was obtained.

EXAMPLE 4

1.5 g of 1,2 α - methylene - 19 - nor - 5 α - androstan - 17 β - ol - 3 - one propionate [prepared as described in paragraph (b) above] were reacted with isopropenyl acetate in an analogous manner to that described in Example 1. After recrystallisation from ethyl acetate/hexane 1.2 g of 3-enol - acetate - 17 - propionate of melting point 122—124°C were obtained and this was brominated and dehydrobrominated in an analogous manner to that described in Example 1. After preparative thin layer chromatography 850 mg of 1,2 α - methylene - 19 - nor - testosterone propionate were obtained which melted at 113—114°C after recrystallisation from ethyl acetate/hexane. Ultraviolet light absorption: ϵ_{240} = 14,300.

EXAMPLE 5

288 mg of 1,2 α - methylene - 19 - nor - 5 α - androstan - 17 β - ol - 3 - one [prepared as described in paragraph (d) above] were dissolved in 12 ml of absolute dioxane and treated with 0.053 ml of bromine. When discoloured, the mixture was precipitated in ice water; 340 mg of a monobromo-compound were thus obtained. For the purpose of dehydrobromination this was heated in 10 ml of dimethylformamide, in the presence of 170 mg of lithium bromide and 170 mg of lithium carbonate, for 45 hours under argon at 125°C, and the reaction mixture was then precipitated in water and the re-

sulting precipitate separated off. The crude product so obtained was purified by preparative thin layer chromatography. 1,2 α - methylene - 19 - nor - Δ^4 - androsten - 17 β - ol - 3 - one was obtained and after recrystallisation from ethyl acetate it melted at 216—220°C.

EXAMPLE 6

500 mg of 1,2 α - methylene - 19 - nor - Δ^4 - androsten - 17 β - ol - 3 - one acetate (prepared as described in Example 1) were dissolved in 32 ml of tetrahydrofuran, and the solution was cooled to -10 to -20°C, treated with 3 ml of approximately 1 molar sodium methylate solution and stirred for 30 minutes. The reaction solution was then warmed to 0°C, decomposed with saturated ammonium chloride solution and extracted with ether. 1,2 α - methylene - 19 - nor - Δ^4 - androsten - 17 β - ol - 3 - one was obtained in an almost quantitative yield; after recrystallisation from ethyl acetate it melted at 219—222°C. The compound was identical with that described in Example 5.

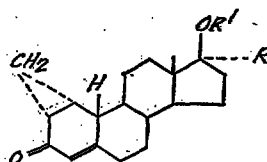
The same compound was also obtained by an analogous treatment of 1,2 α - methylene - 19 - nor - Δ^4 - androsten - 17 β - ol - 3 - one propionate (prepared as described in Example 4).

EXAMPLE 7

200 mg of 1,2 α - methylene - 19 - nor - testosterone (prepared as described in Example 5) were treated with 2 ml of pyridine and 2 ml of oenanthic anhydride for 2 hours, while heating. The reaction solution was then decomposed with water and extracted with ether. The ether solution was successively washed with dilute sulphuric acid, dilute sodium carbonate solution, N/10 caustic soda and water and after drying was evaporated to dryness. 1,2 α - methylene - 19 - nor - testosterone oenanthate was obtained as an oil. Ultraviolet light absorption: ϵ_{295} = 13,900.

WHAT WE CLAIM IS:—

1. A compound of the general formula



in which R represents a hydrogen atom or a saturated or unsaturated hydrocarbon group and R¹ represents a hydrogen atom or an acyl group of an organic carboxylic acid.

2. 1,2 α - Methylene - 19 - nor - testosterone acetate.

3. 1,2 α - Methylene - 17 α - ethynyl - 19 - nor - testosterone acetate.

methylethylformamide, in an atmosphere of nitrogen. The product was cooled, diluted with ethyl acetate, inorganic salts were filtered off and the remainder was washed with ethyl acetate, and the filtrates were combined. After washing with water, dilute hydrochloric acid, water and bicarbonate solution the filtrate was dried and evaporated to dryness *in vacuo*. 0.62 g of crude 1,2 α - methylene - 17 α - ethynyl - 19 - nor - testosterone acetate of melting point 169—171°C was obtained. After filtration through acid alumina the methylene chloride filtrates yielded, after two recrystallisations from diisopropyl ether, 250 mg of analytically pure material of melting point 182—183°C.

EXAMPLE 3

1 g of 1,2 α - methylene - 19 - nor - 5 α - androstan - 17 β - ol - 3 - one [prepared as described in paragraph (d) above] was boiled for 30—52 hours with 1 g of 2,3-dichloro-5,6-dicyanobenzoquinone in 40 ml of absolute benzene. The mixture was then evaporated *in vacuo*, the residue was extracted with methylene chloride, and the methylene chloride solution was fractionally filtered through silica gel. After evaporation of the filtrates 1,2 α - methylene - 19 - nor - testosterone was obtained.

EXAMPLE 4

1.5 g of 1,2 α - methylene - 19 - nor - 5 α - androstan - 17 β - ol - 3 - one propionate [prepared as described in paragraph (b) above] were reacted with isopropenyl acetate in an analogous manner to that described in Example 1. After recrystallisation from ethyl acetate/hexane 1.2 g of 3-enol - acetate - 17 - propionate of melting point 122—124°C were obtained and this was brominated and dehydrobrominated in an analogous manner to that described in Example 1. After preparative thin layer chromatography 850 mg of 1,2 α - methylene - 19 - nor - testosterone propionate were obtained which melted at 113—114°C after recrystallisation from ethyl acetate/hexane. Ultraviolet light absorption: ϵ_{240} = 14,300.

EXAMPLE 5

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EXAMPLE 6

500 mg of 1,2 α - methylene - 19 - nor - Δ^4 - androsten - 17 β - ol - 3 - one acetate (prepared as described in Example 1) were dissolved in 32 ml of tetrahydrofuran, and the solution was cooled to -10 to -20°C, treated with 3 ml of approximately 1 molar sodium methylate solution and stirred for 30 minutes. The reaction solution was then warmed to 0°C, decomposed with saturated ammonium chloride solution and extracted with ether. 1,2 α - methylene - 19 - nor - Δ^4 - androsten - 17 β - ol - 3 - one was obtained in an almost quantitative yield; after recrystallisation from ethyl acetate it melted at 219—222°C. The compound was identical with that described in Example 5.

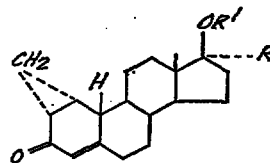
The same compound was also obtained by an analogous treatment of 1,2 α - methylene - 19 - nor - Δ^4 - androsten - 17 β - ol - 3 - one propionate (prepared as described in Example 4).

EXAMPLE 7

200 mg of 1,2 α - methylene - 19 - nor - testosterone (prepared as described in Example 5) were treated with 2 ml of pyridine and 2 ml of oenanthic anhydride for 2 hours, while heating. The reaction solution was then decomposed with water and extracted with ether. The ether solution was successively washed with dilute sulphuric acid, dilute sodium carbonate solution, N/10 caustic soda and water and after drying was evaporated to dryness. 1,2 α - methylene - 19 - nor - testosterone oenanthate was obtained as an oil. Ultraviolet light absorption: ϵ_{235} = 13,900.

WHAT WE CLAIM IS:—

1. A compound of the general formula



in which R represents a hydrogen atom or a saturated or unsaturated hydrocarbon group and R' represents a hydrogen atom or an acyl group of an organic carboxylic acid.

2. 1,2 α - Methylene - 19 - nor - testosterone acetate.

3. 1,2 α - Methylene - 17 α - ethynyl - 19 - nor - testosterone acetate.



4. 1,2 α - Methylene - 19 - nor - testosterone.

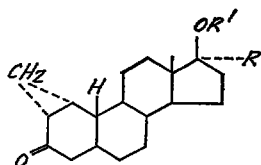
5. 1,2 α - Methylene - 19 - nor - testosterone propionate.

5 6. 1,2 α - Methylene - 19 - nor - testosterone oenanthate.

7. A pharmaceutical preparation which comprises a compound as claimed in claim 1, in admixture or conjunction with a pharmaceutically suitable carrier.

10 8. A pharmaceutical preparation which comprises the compound claimed in any one of claims 2 to 6, in admixture or conjunction with a pharmaceutically suitable carrier.

15 9. A process for the manufacture of a compound as claimed in claim 1, wherein a compound of the formula



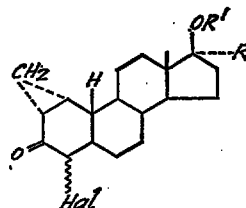
20 in which R and R¹ have the meanings given in claim 1, is dehydrogenated in the 4,5-position and, if desired, in the resulting compound any free 17-OH group is acylated or any 17-acyloxy group is saponified.

25 10. A process as claimed in claim 9, wherein the dehydrogenation is carried out by means of selenium dioxide.

11. A process as claimed in claim 9, wherein the dehydrogenation is carried out by means of a quinone.

12. A process as claimed in claim 11, 30 wherein the quinone is 2,3 - dichloro - 5,6 - dicyanobenzoquinone.

13. A process for the manufacture of a compound as claimed in claim 1, wherein a 35 compound of the formula



in which R and R¹ have the meanings given in claim 1 and Hal represents a halogen atom, is dehydrohalogenated and, if desired, in the resulting compound any free 17-OH group 40 is acylated or any 17-acyloxy group is saponified.

14. A process for the manufacture of a compound as claimed in claim 1, conducted 45 substantially as described in any one of Examples 1 to 7 herein.

ABEL & IMRAY,
Chartered Patent Agents,
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London, W.C.2.

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