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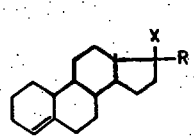
COMPLETE SPECIFICATION

New biologically-active Steroid Compounds and Process for the Preparation thereof

We, ORGANON LABORATORIES LIMITED, a British Company, of Brettenham House, Lancaster Place, London, W.C.2, 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 invention relates to new biologically active 19-nor steroid compounds which have a non-oxygenated C-atom 3 and to the preparation thereof.

More particularly, this invention relates to new 19-nor-androstane compounds with a saturated or unsaturated bond between the C-atoms 4 and 5, which are not oxygenated in 3-position, having in 17-position either a hydrogen atom and a free or functionally converted hydroxyl group or a lower aliphatic hydrocarbon radical and a free or functionally converted hydroxyl group, or a free or functionally converted oxo group and which may in addition have a lower alkyl group in 1-position and/or a free or functionally converted hydroxyl or oxo group in 16-position. The present invention is particularly concerned with the production of the new compounds of the structural formula:

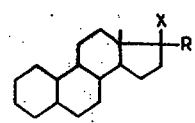


in which

X represents hydrogen or a lower aliphatic hydrocarbon radical;

R a hydroxyl group or an acyloxy group having 1 to 10 carbon atoms, or X and R together represent a free or functionally converted oxo group,

and with the production of the new compounds of the structural formula:



in which X and R have the meanings as defined above.

It is known that aromatic hydrocarbons can be reduced to the corresponding cyclohexenes by treatment with an alkali metal dissolved in an amine with a low molecular weight (see J. Am. Chem. Soc. *74*, 5669 (1952)).

In addition it is known that an aromatic compound, which has an etherified hydroxyl group as a substituent, for example anisol, is converted, by treatment with an alkali metal dissolved in ethylamine, into a mixture of compounds in which no splitting off of the oxygen containing substituent has taken place (see J. Am. Chem. Soc. *77*, 6043 (1955)).

Now a process for the preparation of new biologically active 19-nor-steroids has been discovered, characterised in that a steroid compound with an aromatic ring A, which in 3-position has an etherified hydroxyl group, in 17-position either a free or functionally converted hydroxyl group and a hydrogen atom or a free or functionally converted hydroxyl group and a lower aliphatic hydrocarbon radical, and which may contain in addition one or more double bonds, free or functionally converted hydroxyl and oxo groups, lower alkyl groups and halogen atoms, is allowed to react with an alkali metal in a lower aliphatic primary amine, as a result of which a Δ^4-19-nor-androstene compound is formed which is not oxygenated in 3-position, after which, if desired, the double bond or bonds present is/are reduced and/or one or more of the free and functionally converted secondary hydroxyl groups present are oxidized or hydrolyzed and oxidized to an oxo group.

The etherified hydroxyl group present in the

[*Price 3s. 6d.*]

starting substances in 3-position may be an alkoxy, aryloxy, or aralkoxy group, for example a methoxy, ethoxy, isopropoxy, pentoxy, phenyloxy, benzoxy, or triphenyl methoxy group. A lower aliphatic hydrocarbon residue, which may be present in 17-position, may have 1—6 C-atoms which may be substituted by one or more free or functionally converted hydroxyl and oxo groups.

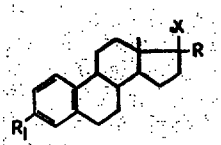
In addition to the said substituents in the positions 3 and 17 the starting substances may moreover contain one or more lower alkyl groups and free or functionally converted hydroxyl or oxo groups in other positions, for example in the positions, 1, 2, 4, 6, 7, 8, 9, 11, 12, 14, 15, and 16.

By a functionally converted hydroxyl group is understood an etherified or esterified hydroxyl group. The esterified hydroxyl group may be derived from an aliphatic, aromatic or araliphatic carboxylic acid. By a functionally converted oxo group there is understood, for example, an enolester, enolether, acetal, enamine, semicarbazone, mercaptal or hydrazone group.

The starting substances may in addition be substituted by one or more halogen atoms, for example in the positions 2, 4, 6, 7, 8, 9, 11, 12, 14, 15, and 16 and may moreover contain one or more double bonds, for example in the positions 11 and 14.

As starting substances for the present process there may be used for example the 3-ethers of oestrone, oestriol, oestradiol, 1-alkyl-oestrone, 1-alkyl-oestradiol, and the 3-ethers of the oestradiols or esters thereof substituted by an alkyl group in 17-position, which compounds may in addition be substituted in the way as described above.

As starting products may particularly be applied compounds of the structural formula:



in which

R_1 represents an alkoxy, aryloxy or aralkoxy group;

X hydrogen or a lower aliphatic hydrocarbon radical;

R a hydroxyl group or an acyloxy group having 1 to 10 carbon atoms.

As examples of starting substances are mentioned the 3-ethers of: 17α-methyl oestradiol; 17α-ethyl oestradiol; 17α-methyl oestradiol-17-propionate; 17β-butyl oestradiol-17-phenylpropionate, 17β-ethyl oestradiol-17-phenylpropionate; 17α-capryloestradiol-17-capronate; 17α-ethyl oestradiol-17-isocapronate 17α-methyl oestradiol-17-cyclohexylbutyrate; 1-methyl oestradiol; 1-methyl oestradiol-17-acetate; 1-methyl oestradiol-17-phenylpropionate; oestriol; oestriol-16:17-diacetate; oestriol-16-propionate-17-acetate; $\Delta^{1:3:5(10)}$-3-hydroxy-20-oxo-pregnatriene and $\Delta^{1:3:5(10)}$-3:20-dihydroxy-pregnatriene.

Before being subjected to the action of the reagent the starting substances are dissolved in a suitable organic solvent, such as a lower aliphatic ether, for example dimethyl ether, methylethyl ether, diethyl ether, dioxane, or tetrahydrofurane. To this solution is added a solution of an alkali metal in a primary amine, as a result of which the desired reaction may occur. The reaction according to the present process is preferably carried out at the boiling point of the amine used, but occurs also already at lower temperature.

In principle any alkali metal such as lithium, sodium or potassium may be applied in this reaction, but it has appeared of advantage to use lithium. As examples of a lower aliphatic primary amine are mentioned methylamine, ethylamine, n-propylamine, and isopropylamine. Preferably ethylamine is used.

From the resulting reaction mixture the Δ^4-19-nor-androstene compounds which are not oxygenated in 3-position, can be obtained for example by means of crystallisation or chromatography, for example over aluminium oxide.

Preferably the Δ^4-19-nor-androstene compounds are separated by distributing the resulting crude reaction mixture between a mixture of aqueous methanol and petroleum ether, followed by separation of the petroleum ether layer and isolation of the Δ^4-19-nor-androstene compounds from the solvent. The mixture of methanol, petroleum ether and water used in this distribution is preferably applied in a volume ratio of 7:10:3.

It is possible to subject the crude reaction mixture—before isolating the desired compound—to an acid hydrolysis, as a result of which the 3-enolethers, formed in this reaction as by-products, of the starting substances partly reduced in ring A, are converted into saturated or unsaturated ketones, which can be removed by means of a ketone reagent, such as Girard reagent T or P, a semicarbazide, hydrazine or a derivative thereof. Also fractional crystallisation or chromatography may be applied for this purpose.

The new Δ^4-19-nor-androstene compounds are white crystalline solids. Their molecular structure follows from the data obtained in the elementary analyses, oxidation and reduction reactions, and from infrared spectra. For example, the Δ^4-17β-hydroxy-19-nor-androstene which is obtained from 17β-oestradiol-3-methylether affords, on oxidation with a large excess of chromic acid or t.butyl chromate, the known Δ^4-3:17-dioxo-19-nor-androstene, identified by mixed melting-point determination and comparison of the IR-spectra of this compound and the Δ^4-3:17-

dioxo-19-nor-androstene prepared according to a known method.

The infra-red spectrum of the said Δ^4-17β-hydroxy-19-nor-androstene shows characteristic bands at about 2.81 μ, 2.90 μ, 6.02 μ, 12.4 μ and 14.8 μ. The two bands at short wave length are characteristic for a hydroxy group. The other bands are highly characteristic for a double bond between the carbon atoms 4 and 5 and occur in the IR-spectra of all unsaturated compounds obtained according to the invention, provided bands due to other functional groups do not interfere therewith. On catalytic hydrogenation one mol. of hydrogen is consumed giving a saturated dihydro derivative. In the IR-spectrum of this derivative the bands at 6.02 μ, 12.4 μ, and 14.8 μ have disappeared.

The double bond between the C-atoms 4 and 5 and other double bonds, if any, present in the compounds, obtained by conversion of the starting product with an alkali metal in a lower aliphatic primary amine, may be reduced for example by means of hydrogen in the presence of a catalyst.

Of the resulting unsaturated or saturated 19-nor-steroids one or more of the secondary free or functionally converted hydroxyl groups present may be converted, if desired, by oxidation or hydrolysis followed by oxidation into an oxo-group. In this manner, starting from an unsaturated or saturated 17-hydroxy steroid, the corresponding 17-oxo compound can be prepared by oxidation, for example according to the Oppenauer method or with chromium trioxide.

If desired, the resulting saturated and unsaturated 19-nor steroids can be esterified with an aliphatic, aromatic or araliphatic carboxylic acid, for example acetic acid, propionic acid, butyric acid, valeric acid, caproic acid, isocaproic acid, succinic acid, tartaric acid, cyclopentyl acetic acid, β-cyclopentylpropionic acid, cyclohexyl acetic acid, γ-cyclohexylbutyric acid, phthalic acid, phenyl acetic acid, β-phenyl propionic acid, benzoic acid.

The final products of the present process are biologically active or are useful as intermediates in the preparation of biologically active compounds.

Some of these compounds have a progestative and/or anabolic activity. In some cases also an inhibitory effect was observed of the production of the gonadotropic hormone.

The new compounds according to the invention can be produced in any form suitable for administration, for example in emulsion form or, by dissolving in a solvent suitable for injection, as an injection preparation. The oral mode of administration being the most simple, it is advisable to bring the present compound into a form suitable for this way of administration, for example tablets, pills or coated tablets. For this purpose use is made of filling substances, such as lactose, a disintegrating agent, such as starch, a lubricant such, for example, as talc and magnesium stearate, and, if necessary, also taste correcting agents and dyes. A mass formed in this way can be readily pressed to tablets.

The following examples illustrate the invention.

Example I

To 145 ml. of dry ethylamine, which is cooled in ice, 1.5 gm. of lithium cut to small pieces are added. After 10 to 20 minutes blue coloration occurs. Then a solution of 3.0 gm. of 17α-methyl-oestradiol-3-methyl-ether in absolute ether is added at such a rate that the solution is not discoloured. Subsequently the reaction mixture is stirred at a temperature of 0—5° C. for 20 hours, after which 50 ml. of absolute ethanol are added. Then the ethylamine is distilled off at low pressure. To the remaining solution 50 ml. of ether and 50 ml. of water are added. The water layer is separated and extracted a few times with ether. The collected ether extracts are added to the ethereal layer, after which this ethereal solution is washed with a 2 N hydrochloric acid solution, subsequently with a saturated sodium bicarbonate solution, and then with water. The ethereal solution is then dried on sodium sulphate and finally evaporated to dryness.

The resulting crude reaction product is dissolved in a mixture of benzene and petroleum ether (1:5) and chromatographed over a column prepared with 70 gm. of aluminium oxide. From the benzene-petroleum ether eluates 1.85 gm. of the Δ^4-17α-methyl-17β-hydroxy-19-nor-androstene melting at 142°—148° C. are obtained. After recrystallisation from acetone it has a melting point of 147°—151° C.

The infra red spectrum of this compound in CS_2 solutions shows characteristic bands at 2.82 μ, 2.90 μ (hydroxyl group) and 6.02 μ, 12.3 μ and 14.8 μ (double bond). The empirical formula is $C_{19}H_{30}O$ calculated C 83.15%; H 11.02%; found C 82.96%; H 10.87%.

Example II

0.6 mg. of the compound prepared in Example I is dissolved in 50 ml. of glacial acetic acid and after the addition of 50 mg. of a Pt-catalyst shaken in a hydrogen atmosphere. After 45 minutes the reaction mixture does not take up any more hydrogen. The catalyst is then filtered off and the filtrate is evaporated to dryness. 17α-methyl-17β-hydroxy-19-nor-androstane, melting at 157—160° C. is obtained from the residue by crystallisation from acetone-ether. According to the results of the elementary analysis the compound has the empirical formula $C_{19}H_{32}O$ (calculated C 82.54%; H 11.66%; found C 82.29%; H 11.76%). The infra red spectrum shows bands at 2.82 and 2.92 μ (OH-group) and no characteristic absorption above 11 μ.

EXAMPLE III

To 140 ml. of dry methylamine, which is cooled in a mixture of ice and salt, 4.7 gm. of sodium cut to small pieces are added. After some time blue coloration occurs. Then a solution of 3.0 gm. of 17α-methyl-oestradiol-3-methylether in absolute ether is added at such a rate that the solution is not discoloured. Subsequently the reaction mixture is stirred at −10° C. for 35 hours, after which, in an analogous manner as described in Example I, the crude reaction product is obtained. This is dissolved in 100 ml. of methanol. After having added 4.5 ml. of concentrated hydrochloric acid, the mixture is heated to 60° C. and stirred at this temperature for 15 minutes. The solution is then cooled to room temperature and subsequently diluted with 1 l. of water and extracted with chloroform.

The chloroform solution is washed with water and evaporated to dryness. The residue is dissolved in a mixture of 30 ml. of absolute ethanol and 3 ml. of dry glacial acetic acid. To this solution 2 gm. of Girard-reagent P are added, after which the mixture is boiled under reflux for 30 minutes. After the reaction mixture has been cooled to room temperature it is poured into 375 ml. of icy water and adjusted to a pH of 6.0—6.5 with sodium carbonate. The solution is extracted with chloroform, the chloroform extracts are washed with water and evaporated to dryness. On crystallisation of the residue from acetone-ether 1.75 gm. of the compound described in Example I are obtained.

EXAMPLE IV

4.5 gm. of lithium cut to small pieces are added to 435 ml. of dry ethylamine which is cooled in ice. After the solution turns blue 9 gm. of 17α-ethyloestradiol-3-ethyl ether dissolved in 900 ml. of dry ether are added. The reaction mixture is then treated as described in Example I. The crude product is distributed between equal parts of petroleum ether and 70% methanol. From the petroleum ether layer 5.6 gm. of Δ^4-17α-ethyl-17β-hydroxy-19-nor-androstene with a melting point of about 50° C. are obtained. The IR-spectrum shows bands at 2.81 μ, 2.90 μ (OH-group) and 6.02 μ, 12.35 μ and 14.88 μ (Δ^4 double bond).

EXAMPLE V

2.2 gm. of Δ^4-17α-ethyl-17β-hydroxy-19-nor-androstene, dissolved in 75 ml. of glacial acetic acid, are reduced as described in Example III. The 17α-ethyl-17β-hydroxy-19-nor-androstane shows no characteristic absorption in IR-light above 11 μ.

EXAMPLE VI

To 145 ml. of dry methylamine which is cooled to −20° C. 1.5 gm. of lithium cut to small pieces are added. To the solution which is blue in colour after 10—20 minutes is added drop by drop a solution of 3.0 gm. of oestradiol-3-methyl-ether in 145 ml. of absolute ether. Subsequently the reaction mixture is stirred at −10° C. for 40 hours, after which 50 ml. of absolute ethanol are added. Then the methylamine is distilled off at low pressure and the remaining solution is further treated in the corresponding manner as described in Example I. The Δ^4-17β-hydroxy-19-nor-androstene ($C_{18}H_{28}O$) obtained after chromatographic purification has a melting point of 80—90° C. and of 95—100° C. after repeated crystallisation from petroleum ether. Yield 62%. The IR-spectrum shows bands at 2.89 μ and 2.92 μ (OH-group) and 6.02 μ, 12.4 μ and 14.85 μ (Δ^4-double bond).

The benzoate of the Δ^4-17β-hydroxy-19-nor-androstene was prepared by the action of benzoylchloride in pyridine solution. The melting point is 133—134° C. The IR-spectrum shows bands at 5.8 μ, 14.1 μ, 14.6 μ (benzoyloxy group) and 12.4 μ and 14.82 μ (Δ^4-double bond). In this spectrum the 6.02 μ band could not be detected due to the strong absorption of the benzoyloxy group at 5.8 μ.

The acetate of the Δ^4-17β-hydroxy-19-nor-androstene was prepared with acetic anhydride in pyridine. The melting point is 67—71° C. The IR-~~spectrum~~ spectrum shows bands at 5.78 μ and 8.05 μ (acetoxy group) and 6.00 μ, 12.38 μ and 14.83 μ (Δ^4-double bond).

By catalytic hydrogenation of these compounds the corresponding dihydro derivatives are obtained. The 17β-hydroxy-19-nor-androstane has a melting point of 110—113° C. The benzoate has a melting point of 120—121° C. The IR-spectrum shows bands at 5.83 μ, 14.1 μ, 14.58 μ (benzoxy group). No absorption, due to isolated double bonds, is observed.

Starting from the 3-glycolether of oestradiol the same compounds are obtained.

EXAMPLE VII

1 gm. Δ^4-17β-hydroxy-19-nor-androstene obtained according to Example VI ($C_{18}H_{28}O$) is dissolved in 20 ml. of glacial acetic acid. At room temperature a solution of 760 mg. of chromium trioxide in 1.9 ml. of water and 7.5 ml. of glacial acetic acid is added. The reaction mixture is left to stand at room temperature. Then it is diluted with 360 ml. of water and extracted with chloroform. The chloroform extracts are washed successively with a dilute sulphuric acid solution, a sodium carbonate solution and water, and then dried on sodium sulphate. The solution is subsequently evaporated to dryness. From the residue Δ^4-17-oxo-19-nor-androstene of melting point 113—115° C. is obtained by crystallisation from acetone-petroleum ether. The IR-spectrum shows bands at 5.75μ (CO-group) and 6.00 μ, 12.38 μ and 14.8 μ (Δ^4-double bond).

Catalytic hydrogenation of this compound,

in which the reaction is interrupted after consumption of 1 mol of hydrogen, yields the 17-oxo-19-nor-androstane, with a melting point of 120—122° C.

The IR-spectrum shows a band at 5.76 μ (CO-group) and no characteristic absorption above 11 μ.

EXAMPLE VIII

In an analogous manner to that described in Example I oestriol-3-methyl ether is converted into the Δ^4-16α:17β-dihydroxy-19-nor-androstene. Yield 64%. Catalytic hydrogenation of this compound yields 16α:17β-dihydroxy-19-nor-androstane.

EXAMPLE IX

According to the process of Example I and starting from 1 gm. of $\Delta^{1:3:5(10)}$-1-methyl-3-ethoxy-17-hydroxy-oestratriene, Δ^4-1-methyl-17-hydroxy-19-nor-androstene is obtained, which shows in the IR-spectrum the characteristic band of the Δ^4-double bond.

Oxidation of this compound in the manner as described in Example VII yields 1-methyl-17-oxo-19-nor-androstene.

EXAMPLE X

In an analogous manner to that described in Example II 1 gm. of the 1-methyl-17-hydroxy-19-nor-androstene prepared in Example IX is reduced to 1-methyl-17-hydroxy-19-nor-androstane. Oxidation of this compound in the manner as described in Example VII yields 1-methyl-17-oxo-19-nor-androstane.

WHAT WE CLAIM IS:—

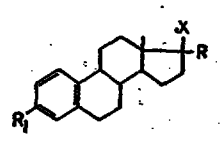
1. Process for the preparation of new biologically active 19-nor-steroid compounds, characterised in that a steroid compound with an aromatic ring *A* which in 3-position has an etherified hydroxyl group, in 17-position either a free or functionally converted hydroxyl group and a hydrogen atom or a free or functionally converted hydroxyl group and a lower aliphatic hydrocarbon radical, and which may in addition contain in the steroid nucleus one or more double bonds, free or functionally converted hydroxyl groups and oxo groups, lower alkyl groups and halogen atoms, is allowed to react with an alkali metal in a lower aliphatic primary amine, as a result of which a Δ^4-19-nor-androstene compound is formed which is not oxygenated in 3-position after which, if desired, the double bond or bonds present is/are reduced and/or one or more of the free or functionally converted secondary hydroxyl groups present are oxidized, or hydrolyzed and oxidized to an oxo group.

2. Process according to claim 1, characterised in that lithium is applied as alkali metal.

3. Process according to one of the claims 1 and 2, characterised in that ethylamine is applied as primary amine.

4. Process according to one or more of the claims 1—3, characterised in that the reaction is carried out at the boiling point of the amine.

5. Process according to one or more of the claims 1—4, characterised in that as starting product is applied a compound of the structural formula:



in which

R_1 represents an alkoxy, aryloxy or aralkoxy group;

X hydrogen or a lower aliphatic hydrocarbon radical;

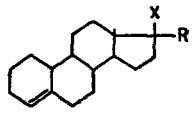
R a hydroxyl group or an acyloxy group having 1 to 10 carbon atoms.

6. Process according to any of the preceding claims, characterised in that the Δ^4-19-nor-androstene compounds are isolated by distributing the crude reaction mixture, obtained after the treatment of the starting product with an alkali metal in a primary amine, between aqueous methanol and petroleum ether, subsequently separating the petroleum ether layer and separating therefrom the Δ^4-19-nor-steroid.

7. Process according to claim 6, characterised in that the reaction mixture is distributed between methanol, water, and petroleum ether in a volume ratio of 7:3:10.

8. 19-nor-androstane compounds with a saturated or unsaturated bond between the C-atoms 4 and 5, which are not oxygenated in 3-position, having in 17-position either a hydrogen atom and a free or functionally converted hydroxyl group or a lower aliphatic hydrocarbon radical and a free or functionally converted hydroxyl group, or a free or functionally converted oxo group and which may in addition have a lower alkyl group in 1-position and/or a free or functionally converted hydroxyl or oxo group in 16-position.

9. The compounds of the structural formula:



in which

X represents hydrogen or a lower aliphatic hydrocarbon radical;

R a hydroxyl group or an acyloxy group having 1 to 10 carbon atoms or X and R together represent a free or functionally converted oxo group.

10. The compounds of the structural formula:

* C L M S *

in which the reaction is interrupted after consumption of 1 mol of hydrogen, yields the 17-oxo-19-nor-androstane, with a melting point of 120—122° C.

The IR-spectrum shows a band at 5.76 μ (CO-group) and no characteristic absorption above 11 μ.

EXAMPLE VIII

In an analogous manner to that described in Example I oestriol-3-methyl ether is converted into the Δ^4-16α:17β-dihydroxy-19-nor-androstene. Yield 64%. Catalytic hydrogenation of this compound yields 16α:17β-dihydroxy-19-nor-androstane.

EXAMPLE IX

According to the process of Example I and starting from 1 gm. of $\Delta^{1:3:5(10)}$-1-methyl-3-ethoxy-17-hydroxy-oestratriene, Δ^4-1-methyl-17-hydroxy-19-nor-androstene is obtained, which shows in the IR-spectrum the characteristic band of the Δ^4-double bond.

Oxidation of this compound in the manner as described in Example VIII yields 1-methyl-17-oxo-19-nor-androstene.

EXAMPLE X

In an analogous manner to that described in Example III 1 gm. of the 1-methyl-17-hydroxy-19-nor-androstene prepared in Example IX is reduced to 1-methyl-17-hydroxy-19-nor-androstane. Oxidation of this compound in the manner as described in Example VIII yields 1-methyl-17-oxo-19-nor-androstane.

WHAT WE CLAIM IS:—

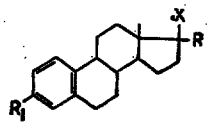
1. Process for the preparation of new biologically active 19-nor-steroid compounds, characterised in that a steroid compound with an aromatic ring *A* which in 3-position has an etherified hydroxyl group, in 17-position either a free or functionally converted hydroxyl group and a hydrogen atom or a free or functionally converted hydroxyl group and a lower aliphatic hydrocarbon radical, and which may in addition contain in the steroid nucleus one or more double bonds, free or functionally converted hydroxyl groups and oxo groups, lower alkyl groups and halogen atoms, is allowed to react with an alkali metal in a lower aliphatic primary amine, as a result of which a Δ^4-19-nor-androstene compound is formed which is not oxygenated in 3-position after which, if desired, the double bond or bonds present is/are reduced and/or one or more of the free or functionally converted secondary hydroxyl groups present are oxidized, or hydrolyzed and oxidized to an oxo group.

2. Process according to claim 1, characterised in that lithium is applied as alkali metal.

3. Process according to one of the claims 1 and 2, characterised in that ethylamine is applied as primary amine.

4. Process according to one or more of the claims 1—3, characterised in that the reaction is carried out at the boiling point of the amine.

5. Process according to one or more of the claims 1—4, characterised in that as starting product is applied a compound of the structural formula:



in which

R_1 represents an alkoxy, aryloxy or aralkoxy group;

X hydrogen or a lower aliphatic hydrocarbon radical;

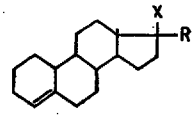
R a hydroxyl group or an acyloxy group having 1 to 10 carbon atoms.

6. Process according to any of the preceding claims, characterised in that the Δ^4-19-nor-androstene compounds are isolated by distributing the crude reaction mixture, obtained after the treatment of the starting product with an alkali metal in a primary amine, between aqueous methanol and petroleum ether, subsequently separating the petroleum ether layer and separating therefrom the Δ^4-19-nor-steroid.

7. Process according to claim 6, characterised in that the reaction mixture is distributed between methanol, water, and petroleum ether in a volume ratio of 7:3:10.

8. 19-nor-androstane compounds with a saturated or unsaturated bond between the C-atoms 4 and 5, which are not oxygenated in 3-position, having in 17-position either a hydrogen atom and a free or functionally converted hydroxyl group or a lower aliphatic hydrocarbon radical and a free or functionally converted hydroxyl group, or a free or functionally converted oxo group and which may in addition have a lower alkyl group in 1-position and/or a free or functionally converted hydroxyl or oxo group in 16-position.

9. The compounds of the structural formula:

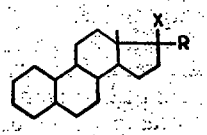


in which

X represents hydrogen or a lower aliphatic hydrocarbon radical;

R a hydroxyl group or an acyloxy group having 1 to 10 carbon atoms or X and R together represent a free or functionally converted oxo group.

10. The compounds of the structural formula:



in which

X represents hydrogen or a lower aliphatic hydrocarbon radical;

R a hydroxyl group or an acyloxy group having 1 to 10 carbon atoms or X and R together represent a free or functionally converted oxo group.

11. Δ^4-17-hydroxy-19-nor-androstene and esters thereof.

12. Δ^4-17-oxo-19-nor-androstene.

13. Δ^4-17β-hydroxy-17α-methyl-19-nor-androstene and esters thereof.

14. Δ^4-17β-hydroxy-17α-ethyl-19-nor-androstene and esters thereof.

15. Δ^4-16:17-dihydroxy-19-nor-androstene and esters thereof.

16. Δ^4-1-methyl-17-hydroxy-19-nor-androstene and esters thereof.

17. Δ^4-1-methyl-17-oxo-19-nor-androstene.

18. 17-hydroxy-19-nor-androstene and esters thereof.

19. 17-oxo-19-nor-androstane.

20. 17β-hydroxy-17α-methyl-19-nor-androstane.

21. 17β-hydroxy-17α-ethyl-19-nor-androstane and esters thereof.

22. 16:17-dihydroxy-19-nor-androstane and esters thereof.

23. 1-methyl-17-hydroxy-19-nor-androstane and esters thereof.

24. 1-methyl-17-oxo-19-nor-androstane and esters thereof.

25. Methods of producing 19-nor-steroid compounds substantially as herein described and illustrated and such compounds whenever so produced.

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