

PATENT SPECIFICATION

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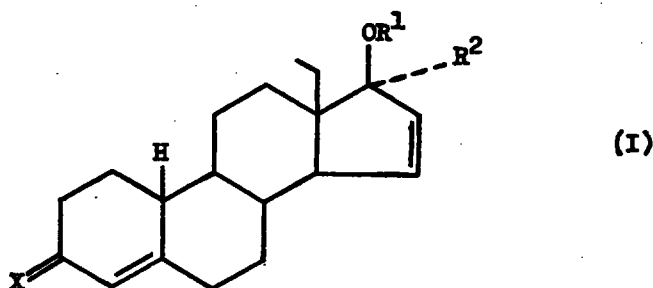


(54) Δ^{15} -STEROIDS

(71) We, SCHERING AKTIENGESellschaft, a Body Corporate organised according to the laws of Berlin and Bergkamen, 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:—

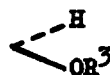
The present invention is concerned with new Δ^{15} -steroids and with their manufacture and use.

The present invention provides Δ^{15} -steroids of the general formula I



in which

- R^1 represents a hydrogen atom or a trialkylsilyl or acyl group,
 R^2 represents an ethynyl, chlorethynyl or propynyl group, and
 X represents an oxygen atom or a grouping of the formula



or NOR^4 , in which R^3 represents a hydrogen atom or an acyl group and R^4 represents a hydrogen atom or an acyl, alkyl, cycloalkyl or tetrahydropyranyl group.

As acyl groups represented by R^1 and R^3 there come into consideration those of acids capable of forming physiologically tolerable esters. Preferred acids are organic carboxylic and sulphonic acids containing 1 to 16, and especially 1 to 11, carbon atoms, which belong to the aliphatic, cycloaliphatic, aromatic, aromatic-aliphatic or heterocyclic series. These acids may also be saturated or unsaturated, mono-, di- or polybasic and/or substituted in the usual manner. As examples of substituents there may be mentioned alkyl, hydroxyl, alkoxy, oxo or amino groups or halogen atoms.

By way of example the following carboxylic acids are mentioned: formic acid,

acetic acid, propionic acid, butyric acid, isobutyric acid, valeric acid, isovaleric acid, caproic acid, oenanthic acid, caprylic acid, pelargonic acid, capric acid, undecanoic acid, lauric acid, tridecanoic acid, myristic acid, pentadecanoic acid, trimethylacetic acid, diethylacetic acid, tert.-butylacetic acid, β -cyclopentylpropionic acid, cyclohexylacetic acid, cyclohexane carboxylic acid, phenylacetic acid, phenoxyacetic acid, mono-, di- and tri-chloroacetic acids, aminoacetic acid, diethylaminoacetic acid, piperidinoacetic acid, morpholinoacetic acid, lactic acid, succinic acid, adipic acid, benzoic acid, nicotinic acid, isonicotinic acid and furan-2-carboxylic acid.

As sulphonic acids, which come into consideration especially for the acyl groups represented by R^3 , there may be mentioned, for example, methane-, ethane-, β -chloroethane-, propane-, isopropane-, butane-, cyclopentane-, cyclohexane-, benzene-, para-toluene- and para-chlorobenzene-sulphonic acids, and also N,N-dimethyl-, -diethyl- and -bis-(β -chloroethyl)-aminosulphonic acids and pyrrolidino-, piperidino-, piperazino-, N-methyl-piperazino- and morpholino-sulphonic acids.

As the trialkylsilyl group represented by R^1 there is advantageously to be understood one containing 1 to 4 carbon atoms in each alkyl group, and preferably the trimethylsilyl group.

As acyl groups represented by R^4 there come into consideration those containing 2 to 8 carbon atoms, for example acetyl, propionyl, butyryl, isobutyryl, valeryl, caproyl, heptanoyl and octanoyl groups.

As alkyl and cycloalkyl groups represented by R^4 there are advantageously to be understood lower alkyl groups containing 1 to 4 carbon atoms, especially methyl and ethyl groups, and cycloalkyl groups containing 3 to 8 carbon atoms, especially a cyclopentyl group.

The compounds of the present invention possess valuable steroid hormone properties and can be used as pharmaceuticals. The invention is thus also concerned with the use of the compounds of the present invention as medicaments or in pharmaceutical preparations. Thus, the compounds of the general formula I are distinguished by a strong gestagenic, ovulation- and nidation-inhibiting activity. For example, 17α -ethynyl- 17β -hydroxy- 18 -methyl- $\Delta^{4,15}$ -oestradien-3-one (A) is found to be superior in the usual Clauberg test to the known 17α -ethynyl- 17β -hydroxy- 18 -methyl- Δ^4 -oestren-3-one (B).

In the following Table are given the McPhail values after oral administration to infantile female rabbits.

TABLE
Clauberg test p.o.

Compound	Dose (mg)	McPhail
A 17α -Ethynyl- 17β -hydroxy- 18 -methyl- $\Delta^{4,15}$ -oestradien-3-one	0.1	3.0
	0.03	2.5
	0.01	1.5
B 17α -Ethynyl- 17β -hydroxy- 18 -methyl- Δ^4 -oestren-3-one	0.1	1.8
	0.03	1.4
	0.01	1.0

From the McPhail values it can be seen that the threshold dose (McPhail=1.5) for the compound A of the present invention is 0.01 mg and for the compound B of similar structure it is 0.03 to 0.1 mg.

The higher esters included within the scope of the compounds of the present invention are distinguished by a protracted activity.

The compounds may be used, for example, in contraceptive preparations, being used as a gestagenic component in combination with an oestrogenically active hormone component, for example 17α -ethynyl-oestradiol, or as the sole active component. The compounds can, however, also be used in preparations for the treatment of gynaecological disorders.

The present invention accordingly also provides a pharmaceutical preparation which comprises a compound of the general formula I, in admixture or conjunction with a pharmaceutically suitable carrier. The preparation may be in a form suitable for oral or parenteral administration.

The new compounds may be worked up with the additives, carrier substances and taste correctives normally used in galenical pharmacy by methods known *per se* to produce the usual forms of pharmaceutical preparations. For oral administration there come into consideration, more especially, tablets, dragées, capsules, pills, suspensions or solutions. For parenteral administration there come into

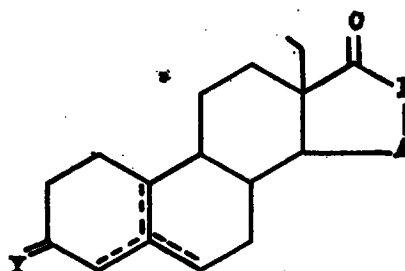
consideration, more especially, oily solutions, for example solutions in sesame oil or castor oil, which may, if desired, also contain a diluent, for example benzyl benzoate or benzyl alcohol. The concentration of the active substance depends on the form of application. Thus, for example, tablets for oral administration preferably each contain 0.01 to 0.5 mg of active substance and solutions for parenteral administration preferably contain 1—100 mg of active substance per 1 ml of solution. By the active substance there is meant the total amount present of the active component or components in the preparations.

The dose of the active compounds of the present invention may be varied by the form and the purpose of the administration. For example, the daily contraceptive dose when administered orally may be within the range of from 0.05 to 0.5 mg.

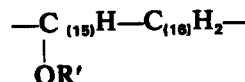
The present invention further provides a method of contraception, wherein there is administered in a contraceptive dose to a female mammal a compound of the general formula I. The female mammal is advantageously a female of the human species, and for a human female the preferred contraceptive dose of a compound of the general formula I is a daily dose administered orally within the range of from 0.01 to 0.1 mg.

The present invention further provides a contraceptive pack which comprises a compound of the general formula I together with instructions, which instructions require the administration of the compound in a contraceptive dose to a female mammal, advantageously a female of the human species. When the pack contains instructions for the administration to a human female, it preferably specifies that the contraceptive dose for a human female of a compound of the general formula I is a daily dose to be administered orally within the range of from 0.01 to 0.1 mg.

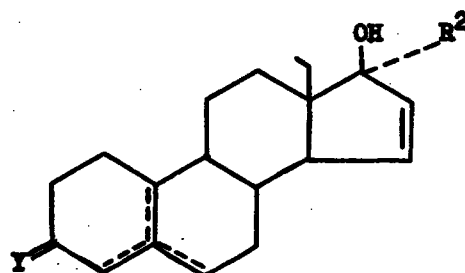
The present invention further provides a process for the manufacture of the Δ^{15} -steroids of the general formula I, wherein an ethynyl, chlorethynyl or propynyl group is introduced into the 17 α -position of a 17-oxo-steroid of the general formula II



in which Y represents a free or ketalised keto group, one of the == bonds in the 4,5-, 5,6- and 5,10-positions represents a carbon-to-carbon double bond and each of the others represents a carbon-to-carbon single bond, and —A—B— represents a —CH=CH— or



grouping, in which R' represents a hydrogen atom or a trialkylsilyl, dialkylsilyl, acyl, alkanesulphonyl, arylsulphonyl or nitro group, by means of an agent capable of yielding such a group with the formation of a hydroxyl group in the 17 β -position, and in the resulting compound of the general formula III



in which Y and R₂ have the meanings given above and one of the — bonds in the 4,5-, 5,6- and 5,10-positions represents a carbon-to-carbon double bond and each of the others represents a carbon-to-carbon single bond, any ketalised keto group in the 3-position is split off and, if desired (depending on the finally desired meanings of R' and X), the 17 β -hydroxyl group, before or after any splitting off of a ketalised keto group in the 3-position, is esterified or is converted into a 17 β -trialkylsilyloxy group, and/or, if desired, the 3-keto group is reduced to form a hydroxyl group in the 3 β -position together with a hydrogen atom in the 3 α -position or is reacted in the presence of a base with a hydroxylamine salt to form a 3-oxime and, if desired, any resulting 3 β -hydroxyl group is esterified or any resulting 3-oxime is esterified or is etherified to form an etherified group of the formula NOR⁴, in which R⁴ represents an alkyl, cycloalkyl or tetrahydropyranyl group.

In the trialkylsilyl and dialkylsilyl groups represented by R' each alkyl group preferably contains 1 to 4 carbon atoms and is especially a methyl group; thus, a silyl group represented by R' is especially a trimethylsilyl or dimethylsilyl group.

As acyl groups represented by R' there are suitable groups derived from organic carboxylic acids. Especially suitable are acyl groups containing about 1 to 10 carbon atoms, for example acetyl, trifluoroacetyl, propionyl, butyryl, valeryl, heptanoyl and benzoyl groups.

Among the alkanesulphonyl and arylsulphonyl groups represented by R' there are suitable, for example, mesyl, ethanesulphonyl, propanesulphonyl and paratolyl groups.

The introduction of the group represented by R² may be carried out by a known method with an organo-metal ethynyl, chlorethynyl or propynyl compound. Such an organo-metal compound is, for example, an alkali metal acetylide, for example potassium or lithium acetylide, potassium or lithium chloroacetylide or potassium or lithium methylacetylide. The organo-metal compound may also be formed *in situ* and brought into reaction with the 17-ketone of the general formula II. Thus, for example, the 17-ketone can be reacted in a suitable solvent with acetylene and an alkali metal, especially potassium, sodium or lithium, in the presence of a C₄- or C₅-alcohol or of ammonia or in the form of, for example, lithium butyl. Lithium chloroacetylide can be formed from 1,2-dichloroethylene and an ethereal solution of lithium methyl.

As organo-metal ethynyl compounds there are also suitable ethynyl magnesium halides or ethynyl zinc halides, and especially ethynyl magnesium bromide or iodide.

As solvents there are suitable, for example, dialkyl ethers, tetrahydrofuran, dioxan, benzene and toluene.

When R' representing a hydrogen atom or a silyl, acyl, sulphonyl or nitro group is present in the starting compound of the general formula II, a compound of the general formula HOR' is split off simultaneously with the introduction of the ethynyl, chlorethynyl or propynyl group.

For the optional subsequent esterification there come into consideration the processes customarily used in steroid chemistry for esterification.

For the esterification of the 17-hydroxyl group there may be mentioned, for example, reaction with acids or acid anhydrides in the presence of strong acids, for example trifluoroacetic acid or para-toluene sulphonic acid, at room temperature or a somewhat raised temperature, or reaction with an acid anhydride in the presence of a tertiary amine in the warm at about 20—200°C.

If pyridine and 4-(dimethylamino)-pyridine are used together as tertiary amines the esterification can be carried out at room temperature.

For the optional conversion of the 17 β -hydroxyl group into a 17 β -trialkylsilyloxy group there may be mentioned, for example, reaction with a trialkylchlorosilane in the presence of a tertiary amine, for example pyridine.

The splitting off of the 3-ketalised keto group, which may be effected before or also after a possible esterification, is carried out by a method known to the expert. For the ketal splitting there come into consideration, for example, mineral acids, for example perchloric acid, sulphuric acid or hydrochloric acid, or organic acids, for example oxalic acid. The ketal splitting is preferably carried out in an alcoholic solution or in another polar solvent, for example acetone, at a temperature from about 20 to 100°C.

The reduction of the 3-keto group may be carried out by a method known *per se* by hydrogenation with a metal hydride. As hydrogen donors there are preferred, more especially, complex hydrides, for example sodium borohydride and lithium tri - (tert. - butoxy) - aluminium hydride. The reduction with sodium borohydride

is preferably carried out in an aqueous-alcoholic solution and that with lithium tri - (tert. - butoxy) - aluminium hydride in an ethereal solution. In order to avoid simultaneous reduction of the carbon-to-carbon bonds mild reaction conditions are used, that is to say, the reduction is carried out at a temperature between about 0 and 50°C.

For the esterification of the hydroxyl group in the 3-position there may be mentioned, for example, reaction with an acid anhydride or halide in the presence of a tertiary amine, for example pyridine, collidine or triethylamine, at room temperature. The 3 hydroxyl group may also be esterified with the acid anhydride with the use of a strong acid, for example para-toluene sulphonic acid, or with the corresponding acid and trifluoroacetic anhydride at room temperature.

By esterifying in the presence of an acid catalyst at room temperature or in the presence of a basic catalyst at a raised temperature of 20—200°C hydroxyl groups in the 3- and 17-positions can be esterified simultaneously.

The reaction of the 3-ketone with a hydroxylamine salt to form the 3-oxime is carried out in the presence of a base. As the base there is suitable, for example, pyridine, collidine, sodium bicarbonate, sodium carbonate, sodium acetate or sodium hydroxide in an aqueous-alcoholic solution. As the salt of hydroxylamine the hydrochloride or the hydrogen sulphate is preferred. The reaction is carried out at a temperature between about 20 and 150°C.

The 3-oxime can be esterified or etherified by the usual methods. The esterification is carried out, for example, with the desired acid, or the halide or anhydride of this acid in the presence of a tertiary amine, for example pyridine or collidine, at room temperature. As the tertiary amine there is also suitable 4-dimethylaminopyridine in pyridine. When the two free hydroxyl groups of a 3-oxime-17-carbinol are to be esterified simultaneously, the operation is carried out at a temperature between 20 and 150°C, or esterification is effected with the desired acid in the presence of trifluoroacetic anhydride or the anhydride of the desired acid in the presence of a strong acid, for example trifluoroacetic acid, perchloric acid or para-toluene sulphonic acid.

The etherification of the 3-oxime with an alkyl or cycloalkyl group is preferably carried out with the corresponding alkyl or cycloalkyl halide in the presence of a strong base, for example a sodium hydroxide solution, with the use of a polar solvent, for example hexamethyl-phosphoric acid triamide, at 0 to 30°C, or in the presence of a strong base, for example sodium hydride, with the use of an ether, for example tetrahydrofuran, or of a polar solvent, for example dimethyl sulphoxide, at 30 to 100°C. Etherification of the 3-oxime is also possible with a diazoalkane, especially with diazomethane.

The etherification of the 3-oxime with a tetrahydropyranyl group is preferably carried out with dihydropyran in the presence of a strong acid, for example para-toluene sulphonic acid.

The preparation of the 17-oxo-steroids of the general formula II used as starting materials is described with reference to the following Examples A to F:

A. 18 - Methyl - 3,3 - (2',2' - dimethyl - 1',3' - propylenedioxy) - 15 α - trimethylsiloxy - Δ^5 - and - $\Delta^{5(10)}$ - oestren - 17 - one.

10.0 Grams of a mixture of 15 α - hydroxy - 18 - methyl - 3,3 - (2',2' - dimethyl - 1',3' - propylenedioxy) - Δ^5 - and - $\Delta^{5(10)}$ - oestren - 17 - one in 40 ml of pyridine were stirred with 10 ml of trimethyl-chlorosilane for 4 hours at room temperature. The solution was stirred into ice-water, and the reaction product was extracted with methylene chloride. The solution was washed with water, dried over sodium sulphate and evaporated to dryness *in vacuo*. The crude product was chromatographed over silica gel with 2.5—3.5% acetone/hexane. There were obtained 3.2 grams of a mixture of 18 - methyl - 3,3 - (2',2' - dimethyl - 1',3' - propylenedioxy) - 15 α - trimethylsiloxy - Δ^5 - and - $\Delta^{5(10)}$ - oestren - 17 - one in the form of an oily product.

B. 15 α - Benzoyloxy - 18 - methyl - 3,3 - (2',2' - dimethyl - 1',3' - propylenedioxy) - Δ^5 - and - $\Delta^{5(10)}$ - oestren - 17 - one.

To 10.0 grams of a mixture of 15 α - hydroxy - 18 - methyl - 3,3 - (2',2' - dimethyl - 1',3' - propylenedioxy) - Δ^5 - and - $\Delta^{5(10)}$ - oestren - 17 - one in 25 ml of pyridine in an ice-bath were added 10 ml of benzoyl chloride. The mixture was stirred at room temperature and added, after 4.5 hours, to ice-water. The reaction product was extracted with methylene chloride, washed with water and dried over

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sodium sulphate. After chromatography of the crude product over silica gel with 2—3.5% acetone/hexane 7.3 grams of a mixture of 15 α - benzyloxy - 18 - methyl - 3,3 - (2',2' - dimethyl - 1',3' - propylenedioxy) - Δ^5 - and - $\Delta^{5(10)}$ - oestren - 17 - one were obtained in the form of a foamy product.

5 C. 18 - Methyl - 15 α - nitrooxy - Δ^4 - oestrene - 3,17 - dione. 5

To 8.0 grams of 15 α - hydroxy - 18 - methyl - Δ^4 - oestrene - 3,17 - dione in 60 ml of acetic anhydride were added dropwise at -20°C 6 ml of concentrated nitric acid. After 1 hour the reaction solution was introduced into ice/water. The precipitated product was filtered off with suction, washed several times with water, taken up in methylene chloride and dried over sodium sulphate. After chromatography of the crude product over silica gel with acetone/hexane 6.4 grams of 18 - methyl - 15 α - nitrooxy - Δ^4 - oestrene - 3,17 - dione were obtained. 10

15 D. 18 - Methyl - 15 α - nitrooxy - 3,3 - (2',2' - dimethyl - 1',3' - propylenedioxy) - Δ^5 - and - $\Delta^{5(10)}$ - oestren - 17 - one.

5.9 Grams of 18 - methyl - 15 α - nitrooxy - Δ^4 - oestrene - 3,17 - dione in 40 ml of methylene chloride and 10 ml of ortho-formic acid triethyl ester were stirred with 18 grams of 2,2 - dimethyl - 1,3 - propanediol and 50 mg of para-toluene sulphonic acid for 3 hours at room temperature. The solution was diluted with ethyl acetate, neutralized with a sodium bicarbonate solution, washed with water, dried over sodium sulphate and concentrated *in vacuo*. After chromatography of the crude product over silica gel with acetone/hexane 4.7 grams of a mixture of 18 - methyl - 15 α - nitrooxy - 3,3 - (2',2' - dimethyl - 1',3' - propylenedioxy) - Δ^5 - and - $\Delta^{5(10)}$ - oestren - 17 - one were obtained in the form of an oily product. 20

25 E. 15 α - Acetoxy - 18 - methyl - 3,3 - (2',2' - dimethyl - 1',3' - propylenedioxy) - Δ^5 - and - $\Delta^{5(10)}$ - oestren - 17 - one. 25

To 12.0 grams of a mixture of 15 α - hydroxy - 18 - methyl - 3,3 - (2',2' - dimethyl - 1',3' - propylenedioxy) - Δ^5 - and - $\Delta^{5(10)}$ - oestren - 17 - one in 30 ml of pyridine in an ice-bath were added 10 ml of acetic anhydride. The mixture was stirred at room temperature and, after 3 hours, introduced into ice/water. The precipitated product was filtered off with suction, washed several times with water, dried over sodium sulphate and concentrated to dryness *in vacuo*. 9.7 Grams of a mixture of crude 15 α - acetoxy - 18 - methyl - 3,3 - (2',2' - dimethyl - 1',3' - propylenedioxy) - Δ^5 - and - $\Delta^{5(10)}$ - oestren - 17 - one were obtained in the form of an oil. 30

35 F. 18 - Methyl - 3,3 - (2',2' - dimethyl - 1',3' - propylenedioxy) - $\Delta^{5,15}$ - and - $\Delta^{5(10),15}$ - oestradien - 17 - one. 35

To 123 grams of a mixture of 15 α - hydroxy - 18 - methyl - 3,3 - (2',2' - dimethyl - 1',3' - propylenedioxy) - Δ^5 - and - $\Delta^{5(10)}$ - oestren - 17 - one, prepared as described in our United Kingdom Patent Specification No. 1,536,875 in 1 litre of pyridine were slowly added dropwise, while cooling with ice and stirring, 100 ml of methane sulphonic acid chloride. After 3.5 hours, 500 ml of dimethylformamide and 317 grams of sodium acetate were added, and the mixture was stirred for 24 hours at room temperature. The reaction mixture was introduced into ice-water. The precipitated product was filtered off with suction, taken up in ethyl acetate, washed with water and dried over sodium sulphate. The crude product (103 grams) was chromatographed over silica gel with 10—14% acetone/hexane. 48.5 Grams of a mixture of 18 - methyl - 3,3 - (2',2' - dimethyl - 1',3' - propylenedioxy) - $\Delta^{5,15}$ - and - $\Delta^{5(10),15}$ - oestradien - 17 - one were obtained. 45

The following 17-oxo-steroids of the general formula II may be prepared as described in our United Kingdom Patent Specification No. 1,536,875:— 50

15 α - hydroxy - 18 - methyl - Δ^4 - oestrene - 3,17 - dione,
15 α - hydroxy - 18 - methyl - 3,3 - (2',2' - dimethyl - 1',3' - propylenedioxy) - Δ^5 - and - $\Delta^{5(10)}$ - oestren - 17 - one,

15 α - mesyloxy - 18 - methyl - 3,3 - (2',2' - dimethyl - 1',3' - propylenedioxy) - Δ^5 - and - $\Delta^{5(10)}$ - oestren - 17 - one and 55

18 - methyl - 3,3 - (2',2' - dimethyl - 1',3' - propylenedioxy) - $\Delta^{5,15}$ - and - $\Delta^{5(10),15}$ - oestradien - 17 - one.

The following Examples illustrate the invention:—

Example 1

17 α - Ethynyl - 17 β - hydroxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one.

7.5 Grams of magnesium shavings in 140 ml of tetrahydrofuran were reacted with 24 ml of ethyl bromide to form ethyl magnesium bromide. To this Grignard solution were added 300 ml of tetrahydrofuran and acetylene was introduced while cooling with ice for about 40 minutes. A solution of 5 grams of a mixture of 18 - methyl - 3,3 - (2',2' - dimethyl - 1',3' - propylenedioxy) - $\Delta^{5,15}$ - and - $\Delta^{5(10),15}$ - oestradien - 17 - one in 200 ml of tetrahydrofuran was then added dropwise, and the solution was stirred at room temperature. After 2 hours there was cautiously added to the solution an ammonium chloride solution, and the mixture was diluted with ether. The organic phase was washed several times with water, dried over sodium sulphate and evaporated to dryness *in vacuo*. After chromatography of the crude product over silica gel with 2.5—2.9% acetone/hexane there were obtained 3.1 grams of a mixture of 17 α - ethynyl - 18 - methyl - 3,3 - (2',2' - dimethyl - 1',3' - propylenedioxy) - $\Delta^{5,15}$ - and - $\Delta^{5(10),15}$ - oestradien - 17 β - ol, which were stirred in 70 ml of methanol and 14 ml of water with 2.3 grams of oxalic acid for 40 minutes under reflux. The solution was diluted with ether, washed until neutral with water, dried and treated with active charcoal. After recrystallization from acetone/hexane 1.4 grams of 17 α - ethynyl - 17 β - hydroxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one were obtained. Melting point: 197.9°C.

Example 2

17 α - Ethynyl - 17 β - hydroxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one.

3.0 Grams of magnesium shavings were reacted in 36 ml of tetrahydrofuran with 9.6 ml of ethyl bromide to form ethyl magnesium bromide. The Grignard solution was diluted with 100 ml of tetrahydrofuran and cooled to 0°C. Acetylene was introduced for 30 minutes, a solution of 2.0 grams of a mixture of 18 - methyl - 3,3 - (2',2' - dimethyl - 1',3' - propylenedioxy) - 15 α - trimethyl - siloxy - Δ^5 - and - $\Delta^{5(10)}$ - oestren - 17 - one in 80 ml of tetrahydrofuran was then added dropwise, and the mixture was stirred for 1 hour at room temperature. The solution was worked up as described in Example 1. The crude product was chromatographed over silica gel. With 3.5—4.5% acetone/hexane 700 mg of 17 α - ethynyl - 18 - methyl - 3,3 - (2',2' - dimethyl - 1',3' - propylenedioxy) - $\Delta^{5(10),15}$ - oestradien - 17 β - ol [melting point: 223—225°C (with decomposition)] were eluted, which, as described in Example 1, were stirred with 500 mg of oxalic acid in 12 ml of methanol and 1.5 ml of water for 15 minutes under reflux. The crude product was recrystallized from acetone/hexane. Yield: 510 mg of 17 α - ethynyl - 17 β - hydroxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one melting at 190—192°C.

Example 3

17 α - Ethynyl - 17 β - hydroxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one.

5.0 Grams of magnesium shavings were reacted in 100 ml of tetrahydrofuran with 18 ml of ethyl bromide to form ethyl magnesium bromide. The solution was diluted with 100 ml of tetrahydrofuran and cooled to 0°C. Acetylene was introduced for 30 minutes, a solution of 4.5 grams of a mixture of 15 α - acetoxy - 18 - methyl - 3,3 - (2',2' - dimethyl - 1',3' - propylenedioxy) - Δ^5 - and - $\Delta^{5(10)}$ - oestren - 17 - one in 80 ml of tetrahydrofuran was then added, stirred for 1 hour at room temperature and worked up, as described in Example 1. The resulting crude 17 α - ethynyl - 18 - methyl - 3,3 - (2',2' - dimethyl - 1',3' - propylenedioxy) - $\Delta^{5,15}$ - and - $\Delta^{5(10),15}$ - oestradien - 17 β - ol (3.7 grams) was stirred in 70 ml of methanol and 14 ml of water with 2.5 grams of oxalic acid for 45 minutes under reflux. The solution was diluted with ether, washed with water and dried over sodium sulphate. The crude product was chromatographed over silica gel with acetone/hexane. 2.1 Grams of 17 α - ethynyl - 17 β - hydroxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one were obtained. Melting point: 189—192°C.

Example 4

17 β - Acetoxy - 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one.

A solution of 2.0 grams of 17 α - ethynyl - 17 β - hydroxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one in 40 ml of collidine and 13 ml of acetic anhydride was heated at the boil for 5 hours under nitrogen. After cooling, the solution was poured into ice/water. The reaction product was extracted with methylene chloride, washed in succession with 2N-hydrochloric acid, a sodium bicarbonate

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solution and water, and dried over sodium sulphate. The crude product was chromatographed over silica gel. With 25—30% ethyl acetate/hexane 950 mg of 17 β - acetoxy - 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one were eluted, which melted at 163—164°C after recrystallization from acetone/methanol.

Example 5

17 α - Ethynyl - 17 β - butyryloxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one.

500 mg of 17 α - ethynyl - 17 β - hydroxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one in 2 ml of butyric anhydride and 2 ml of collidine were heated under reflux for 10 hours under nitrogen. Working up was carried out as described in Example 4. After chromatography of the crude product over silica gel with acetone/hexane 310 mg of 17 α - ethynyl - 17 β - butyryloxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one were obtained, which melted at 160—162°C after recrystallization from acetone/methanol.

Example 6

17 α - Ethynyl - 17 β - heptanoyloxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one

300 mg of 17 α - ethynyl - 17 β - hydroxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one in 2 ml of oenanthic anhydride and 2 ml of collidine were stirred for 17 hours under nitrogen at 170°C. The reaction product was worked up as described in Example 4. The excess of oenanthic acid was removed by steam distillation. The product obtained by extraction with ether was chromatographed over silica gel with acetone/hexane. 175 mg of 17 α - ethynyl - 17 β - heptanoyloxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one were obtained in the form of an oil.

Example 7

17 α - Ethynyl - 18 - methyl - 17 β - octanoyloxy - $\Delta^{4,15}$ - oestradien - 3 - one

From a solution of 3.5 ml of caprylic anhydride in 250 ml of benzene 50 ml were distilled off. After cooling to room temperature, 3.5 ml of trifluoroacetic anhydride were added. After 30 minutes 4.0 grams of 17 α - ethynyl - 17 β - hydroxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one were added, and the mixture was stirred for a further 2 hours. To the reaction solution were added, while cooling with ice, 50 ml of acetone/water (1:1), and the mixture was stirred for 30 minute and then concentrated *in vacuo*. The residue was taken up in methylene chloride, washed with a sodium bicarbonate solution and water, and dried over sodium sulphate. The crude product was chromatographed over silica gel. With 14—18% ethyl acetate/hexane 2.3 grams of 17 α - ethynyl - 18 - methyl - 17 β - octanoyloxy - $\Delta^{4,15}$ - oestradien - 3 - one were eluted in the form of an oil.

Example 8

17 α - Ethynyl - 18 - methyl - 17 β - undecanoyloxy - $\Delta^{4,15}$ - oestradien - 3 - one

From a solution of 4.0 grams of undecanoic acid in 300 ml of benzene 50 ml were distilled off. After cooling to room temperature, 4.5 ml of trifluoroacetic anhydride were added. After 30 minutes 4.0 grams of 17 α - ethynyl - 17 β - hydroxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one were added. The whole was stirred for 2.5 hours, and the solution was worked up as described in Example 7. The crude product was chromatographed over silica gel with 18—25% ethyl acetate/hexane. 2.6 Grams of 17 α - ethynyl - 18 - methyl - 17 β - undecanoyloxy - $\Delta^{4,15}$ - oestradien - 3 - one were obtained in the form of an oil.

Example 9

17 α - Ethynyl - 17 β - hexadecanoyloxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one

From a solution of 4.1 grams of palmitic acid in 200 ml of benzene 40 ml were distilled off. After cooling to room temperature, 2.3 ml of trifluoroacetic anhydride were added. After 30 minutes 4.2 grams of 17 α - ethynyl - 17 β - hydroxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one were added, and the whole was stirred for a further 2 hours. To the reaction product were added, while cooling with ice, 30 ml of acetone-water (1:1), and the mixture was stirred for 30 minutes and then evaporated to dryness *in vacuo*. The residue was taken up in methylene chloride, and washed with 10 ml of a solution of 10% strength of sodium hydroxide. The precipitate of sodium palmitate that separated was filtered off with suction, and the solution was washed until neutral, dried and concentrated *in vacuo*. The crude

product was chromatographed over silica gel. With 12—16% ethyl acetate/hexane 2.8 grams of 17 α - ethynyl - 17 β - hexadecanoyloxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one were eluted in the form of an oil.

Example 10

- 5 17 α - Ethynyl - 17 β - hydroxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one 5
- 10 Acetylene was passed for about 45 minutes through a solution, cooled with ice-water, of 100 ml of lithium *n*-butyl (about 15% strength in hexane) in 350 ml of tetrahydrofuran. There were then added dropwise, while stirring, 10.0 grams of a mixture of 18 - methyl - 3,3 - (2',2' - dimethyl - 1',3' - propylenedioxy) - $\Delta^{5,15}$ - and - $\Delta^{5(10),15}$ - oestradien - 17 - one in 100 ml of tetrahydrofuran. After 30 minutes a saturated solution of ammonium chloride was added to the solution, and the whole was diluted with ethyl acetate, washed until neutral with water and dried over sodium sulphate. The solution was evaporated to dryness *in vacuo*, and 11.4 grams of a mixture of crude 17 α - ethynyl - 18 - methyl - 3,3 - (2',2' - dimethyl - 1',3' - propylenedioxy) - $\Delta^{5,15}$ - and - $\Delta^{5(10),15}$ - oestradien - 17 β - ol were obtained, which was suspended in 70 ml of acetone. 0.1 ml of concentrated hydrochloric acid was added, the mixture was stirred for 2 hours at room temperature and the solution was introduced into ice-water. The precipitated product was filtered off with suction and dried over sodium sulphate. After chromatography of the crude product over silica gel with 20% acetone/hexane 4.8 grams of 17 α - ethynyl - 17 β - hydroxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one melting at 199—200°C were obtained. 20

Example 11

- 25 17 β - Acetoxy - 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one 25
- 30 To 2.0 grams of 17 α - ethynyl - 17 β - hydroxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one in 20 ml of methylene chloride were added 40 ml of acetic anhydride and 10 mg of para-toluene sulphonic acid. The solution was stirred under nitrogen for 6 hours at room temperature, and it was then diluted with ethyl acetate, washed until neutral with a sodium bicarbonate solution and dried over sodium sulphate. After chromatography over silica gel with 7—9% acetone/hexane 560 mg of 17 β - acetoxy - 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one were obtained. Melting point after recrystallization from acetone/hexane: 163—164°C. 30
- 35 In an analogous manner there were obtained: 17 β - Butyryloxy-, heptanoyloxy-, octanoyloxy-, undecanoyloxy- and hexadecanoyloxy - 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one. 35

Example 12

- 40 17 α - Ethynyl - 17 β - trimethylsiloxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one 40
- 45 To 1.5 grams of 17 α - ethynyl - 17 β - hydroxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one in 30 ml of pyridine were added, while cooling with ice, 8 ml of trimethylchlorosilane. After 3 hours, the reaction mixture was introduced into ice-water. The precipitated product was filtered off with suction, dissolved in methylene chloride, washed with water and dried over sodium sulphate. After treating the crude product in acetone with active charcoal and recrystallization from acetone/hexane, 1.18 grams of 17 α - ethynyl - 17 β - trimethylsiloxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one were obtained. Melting point: 158—159°C. 45

Example 13

- 50 17 α - Ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradiene - 3 β ,17 β - diol 50
- 55 To 2.0 grams of 17 α - ethynyl - 17 β - hydroxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one in 60 ml of tetrahydrofuran was slowly added a solution of 5.0 grams of lithium tri - (tert. - butoxy) - aluminium hydride in 30 ml of tetrahydrofuran, and the whole was stirred for 1 hour at room temperature under nitrogen. The solution was stirred into ice-water containing sulphuric acid. The precipitated product was filtered off, dissolved in ethyl acetate, washed with water and dried over sodium sulphate. After chromatography of the crude product over silica gel with 10—13% acetone/hexane and recrystallization from acetone/hexane 400 mg of 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradiene - 3 β ,17 β - diol were obtained. Melting point: 143—144°C. 55

Example 14

17 β - Acetoxy - 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 β - ol

1.5 Grams of 17 β - acetoxy - 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one in 40 ml of tetrahydrofuran were reacted in a manner analogous to that described in Example 13 with 4.5 grams of lithium tri - (tert. - butoxy) - aluminium hydride in 30 ml of tetrahydrofuran. After one hour the solution was introduced into ice-water containing sulphuric acid and worked up in a manner analogous to that described in Example 13. After chromatography of the crude product over silica gel with 5—8% acetone/hexane 530 mg of 17 β - acetoxy - 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 β - ol were obtained.

Example 15

17 α - Ethynyl - 18 - methyl - 17 β - trimethylsiloxy - $\Delta^{4,15}$ - oestradien - 3 β - ol

2.0 Grams of 17 α - ethynyl - 18 - methyl - 17 β - trimethylsiloxy - $\Delta^{4,15}$ - oestradien - 3 - one in 60 ml of tetrahydrofuran were reacted, as described in Example 13, with 5 grams of lithium tri - (tert. - butoxy) - aluminium hydride in 30 ml of tetrahydrofuran. After 45 minutes the solution was introduced into ice-water and worked up in a manner analogous to that described in Example 13. After chromatography of the crude product over silica gel with 4—7% acetone/hexane 960 mg of 17 α - ethynyl - 18 - methyl - 17 β - trimethyl - siloxy - $\Delta^{4,15}$ - oestradien - 3 β - ol were obtained.

Example 16

3 β - Acetoxy - 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 17 β - ol

230 mg of 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradiene - 3 β , 17 β - diol in 3 ml of pyridine were stirred with 1.5 ml of acetic anhydride for 2 hours at room temperature. The solution was introduced into ice-water, extracted with methylene chloride, washed in succession with dilute sulphuric acid and water, and dried over sodium sulphate. After purifying the crude product by preparative layer chromatography [system: ether/chloroform 8+2] 115 mg of 3 β - acetoxy - 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 17 β - ol were obtained.

Example 17

17 α - Ethynyl - 3 β - heptanoyloxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 17 β - ol

800 mg of 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradiene - 3 β , 17 β - diol in 5 ml of pyridine were stirred with 3 ml of oenanthic anhydride for 4 hours at room temperature. The solution was diluted with benzene and subjected to steam distillation. The reaction product was extracted from the aqueous distillation residue with methylene chloride. After chromatography of the crude product over silica gel with acetone/hexane 210 mg of 17 α - ethynyl - 3 β - heptanoyloxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 17 β - ol were obtained in the form of an oily product.

Example 18

17 α - Ethynyl - 3 β - isopropylsulphonyloxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 17 β - ol

To a solution of 450 mg of 17 α - ethynyl - 18 - methyl - 17 β - trimethylsiloxy - $\Delta^{4,15}$ - oestradien - 3 β - ol in 40 ml of absolute benzene were added at room temperature 5 ml of triethylamine and then, while stirring strongly, 2.5 ml of isopropyl-sulphonic acid chloride. The whole was stirred for 48 hours at room temperature, then poured into ice-water and extracted with ether. The ether phase was washed with water, dried over sodium sulphate and evaporated. The crude 17 α - ethynyl - 3 β - isopropylsulphonyloxy - 18 - methyl - 17 β - trimethylsiloxy - $\Delta^{4,15}$ - oestradiene (430 mg) so obtained was mixed at room temperature with 50 ml of methanol acidified with hydrochloric acid, and the whole was stirred for 10 minutes at room temperature. The solution was neutralized with a sodium bicarbonate solution and then concentrated *in vacuo*. The residue was taken up in methylene chloride, washed with water and dried over sodium sulphate. After chromatography of the crude product over silica gel with acetone/hexane 170 mg of 17 α - ethynyl - 3 β - isopropylsulphonyloxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 17 β - ol were obtained.

Example 19

17 α - Ethynyl - 18 - methyl - 3 β ,17 β - diundecanoyloxy - $\Delta^{4,15}$ - oestradiene

From a solution of 4.0 grams of undecanoic acid in 300 ml of benzene 50 ml were distilled off. After cooling to room temperature 4.5 ml of trifluoroacetic anhydride were added. After 30 minutes 3.2 grams of 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradiene - 3 β ,17 β - diol were added. The mixture was stirred for 2.5 hours, and to the reaction solution were added 50 ml of acetone/water (1:1). The mixture was stirred for 30 minutes and then concentrated *in vacuo*. The residue was taken up in methylene chloride, washed with a sodium bicarbonate solution and water and dried over sodium sulphate. After chromatography of the crude product over silica gel with 15—20% ethyl acetate/hexane 1.3 grams of 17 α - ethynyl - 18 - methyl - 3 β ,17 β - diundecanoyloxy - $\Delta^{4,15}$ - oestradiene were obtained in the form of an oil.

Example 20

17 β - Acetoxy - 17 α - ethynyl - 3 β - heptanoyloxy - 18 - methyl - $\Delta^{4,15}$ - oestradiene

450 mg of 17 β - acetoxy - 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 β - ol in 3 ml of pyridine were stirred with 2.5 ml of oenanthic anhydride for 3 hours at room temperature. The solution was diluted with benzene and worked up in a manner analogous to that described in Example 17. After chromatography of the crude product over silica gel with acetone/hexane 85 mg of 17 β - acetoxy - 17 α - ethynyl - 3 β - heptanoyloxy - 18 - methyl - $\Delta^{4,15}$ - oestradiene were obtained in the form of an oil.

Example 21

17 α - Ethynyl - 3 β ,17 β - dihexadecanoyloxy - 18 - methyl - $\Delta^{4,15}$ - oestradiene

From a solution of 5 grams of palmitic acid in 250 ml of benzene 65 ml were distilled off. After cooling to room temperature 2.8 ml of trifluoroacetic anhydride were added dropwise, and after 30 minutes 2.7 grams of 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradiene - 3 β ,17 β - diol were added. After 5 hours there were added to the reaction mixture, while cooling with ice, 35 ml of acetone/water (1:1), and the mixture was stirred for 30 minutes and then evaporated to dryness *in vacuo*. The residue was taken up in methylene chloride and washed with 10 ml of a solution of 10% strength of sodium hydroxide. The precipitate of palmitate that separated was filtered off with suction, and the solution was washed until neutral, dried and concentrated *in vacuo*. The crude product was chromatographed over silica gel. With ethyl acetate/hexane 820 mg of 17 α - ethynyl - 3 β ,17 β - dihexadecanoyloxy - 18 - methyl - $\Delta^{4,15}$ - oestradiene were obtained.

Example 22

17 α - Ethynyl - 18 - methyl - 3 - oximino - $\Delta^{4,15}$ - oestradien - 17 β - ol

To 2.0 grams of 17 α - ethynyl - 17 β - hydroxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one in 60 ml of methanol and 2 ml of water were added 1.0 gram of hydroxylamine hydrochloride and 1.0 gram of sodium bicarbonate. The reaction mixture was stirred for 2.5 hours at 65°C, and was then concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water and dried over sodium sulphate. After chromatography of the crude product over silica gel with acetone/hexane 350 mg of 17 α - ethynyl - 18 - methyl - 3 - oximino - $\Delta^{4,15}$ - oestradien - 17 β - ol were obtained. Melting point: 110—112°C.

Example 23

17 β - Acetoxy - 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - onoxime

2.4 Grams of 17 β - acetoxy - 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one in 60 ml of methanol and 2 ml of water were reacted, as described in Example 22, with 1.0 gram of hydroxylamine hydrochloride and 1.0 gram of sodium bicarbonate. After 1.5 hours the reaction mixture was worked up in a manner analogous to that described in Example 22. After chromatography of the crude product over silica gel with acetone/hexane 760 mg of 17 β - acetoxy - 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - onoxime were obtained.

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Example 24

17 α - Ethynyl - 18 - methyl - 17 β - undecanoyloxy - $\Delta^{4,15}$ - oestradien - 3 - onoxime

5 1.9 Grams of 17 α - ethynyl - 18 - methyl - 17 β - undecanoyloxy - $\Delta^{4,15}$ - oestradien - 3 - one in 50 ml of methanol and 1.5 ml of water were reacted, as described in Example 22, with 1.0 gram of hydroxylamine hydrochloride and 1.0 gram of sodium bicarbonate. After 2 hours the reaction mixture was worked up in a manner analogous to that described in Example 22. The crude product was chromatographed over silica gel with acetone/hexane. 600 mg of 17 α - ethynyl - 18 - methyl - 17 β - undecanoyloxy - $\Delta^{4,15}$ - oestradien - 3 - onoxime were obtained in the form of an oil. 10

Example 25

17 α - Ethynyl - 3 - methoximino - 18 - methyl - $\Delta^{4,15}$ - oestradien - 17 β - ol

15 To 4.8 grams of 17 α - ethynyl - 18 - methyl - 3 - oximino - $\Delta^{4,15}$ - oestradien - 17 β - ol in 100 ml of hexamethyl-phosphoric acid triamide were added, while cooling with ice and introducing nitrogen, 10 ml of a solution of 25% strength of sodium hydroxide and 10 ml of methyl iodide. After 1 hour the solution was introduced into ice/water containing hydrochloric acid. The mixture was extracted with ether, and the solution was washed until neutral with water and dried over sodium sulphate. The crude product was chromatographed over silica gel with acetone/hexane. 700 mg of 17 α - ethynyl - 3 - methoximino - 18 - methyl - $\Delta^{4,15}$ - oestradien - 17 β - ol were obtained. Melting point: 149—150°C. 20

Example 26

17 α - Ethynyl - 3 - cyclopentyloximino - 18 - methyl - $\Delta^{4,15}$ - oestradien - 17 β - ol

25 2.7 Grams of 17 α - ethynyl - 18 - methyl - 3 - oximino - $\Delta^{4,15}$ - oestradien - 17 β - ol in 65 ml of hexamethyl-phosphoric acid triamide were reacted at room temperature under nitrogen with 7 ml of a solution of 25% strength of sodium hydroxide and 7 ml of cyclopentyl bromide, and after 4 hours working up was carried out in a manner analogous to that described in Example 25. The crude product was chromatographed over silica gel with acetone/hexane, and 145 mg of 17 α - ethynyl - 3 - cyclopentyloximino - 18 - methyl - $\Delta^{4,15}$ - oestradien - 17 β - ol were obtained. 30

Example 27

3 - Acetoximino - 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 17 β - ol

35 250 mg of 17 α - ethynyl - 18 - methyl - 3 - oximino - $\Delta^{4,15}$ - oestradien - 17 β - ol in 3 ml of pyridine were stirred with 1.5 ml of acetic anhydride for 1 hour at room temperature. The solution was introduced into ice/water, extracted with methylene chloride, washed in succession with dilute sulphuric acid and water, and dried over sodium sulphate. The crude product was purified by preparative layer chromatography (system: ether/chloroform 8+2). 135 mg of 3 - acetoximino - 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 17 β - ol were obtained. 40

Example 28

17 α - Ethynyl - 3 - isobutyryloximino - 18 - methyl - $\Delta^{4,15}$ - oestradien - 17 β - ol

45 380 mg of 17 α - ethynyl - 18 - methyl - 3 - oximino - $\Delta^{4,15}$ - oestradien - 17 β - ol in 4 ml of pyridine were stirred with 2 ml of isobutyric anhydride for 30 minutes at room temperature. After working up in a manner analogous to that described in Example 27 and chromatography of the crude product over silica gel with acetone/hexane 170 mg of 17 α - ethynyl - 3 - isobutyryloximino - 18 - methyl - $\Delta^{4,15}$ - oestradien - 17 β - ol were obtained. 50

Example 29

17 α - Ethynyl - 3 - heptanoyloximino - 18 - methyl - $\Delta^{4,15}$ - oestradien - 17 β - ol

55 700 mg of 17 α - ethynyl - 18 - methyl - 3 - oximino - $\Delta^{4,15}$ - oestradien - 17 β - ol in 5 ml of pyridine were stirred with 3 ml of oenanthic anhydride for 3 hours at room temperature. The solution was diluted with benzene and subjected to steam distillation. The reaction product was extracted from the aqueous distillation residue with methylene chloride. After chromatographing the crude product over

silica gel with acetone/hexane 190 mg of 17 α - ethynyl - 3 - heptanoyloximino - 18 - methyl - $\Delta^{4,15}$ - oestradien - 17 β - ol were obtained in the form of an oily product.

Example 30

5 17 β - Acetoxy - 3 - acetoximino - 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradiene 5

460 mg of 17 β - acetoxy - 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - onoxime in 5 ml of pyridine were stirred with 2 ml of acetic anhydride for 1 hour at room temperature. The solution was introduced into ice/water and worked up as described in Example 27. The crude product was chromatographed over silica gel with acetone/hexane. 290 mg of 17 β - acetoxy - 3 - acetoximino - 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradiene were obtained. 10 10

Example 31

15 17 β - Acetoxy - 17 α - ethynyl - 3 - isobutyryloximino - 18 - methyl - $\Delta^{4,15}$ - oestradiene 15

400 mg of 17 β - acetoxy - 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - onoxime in 4 ml of pyridine were stirred with 2 ml of isobutyric anhydride for 30 minutes at room temperature. After working up in a manner analogous to that described in Example 27 and chromatographing the crude product over silica gel 180 mg of 17 β - acetoxy - 17 α - ethynyl - 3 - isobutyryloximino - 18 - methyl - $\Delta^{4,15}$ - oestradiene were obtained. 20 20

Example 32

25 17 β - Acetoxy - 17 α - ethynyl - 3 - heptanoyloximino - 18 - methyl - $\Delta^{4,15}$ - oestradiene 25

800 mg of 17 β - acetoxy - 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - onoxime in 6 ml of pyridine were stirred with 3.5 ml of oenanthalic anhydride for 2.5 hours at room temperature. The solution was diluted with benzene and worked up in a manner analogous to that described in Example 29. After chromatographing the crude product over silica gel with acetone/hexane 380 mg of 17 β - acetoxy - 17 α - ethynyl - 3 - heptanoyloximino - 18 - methyl - $\Delta^{4,15}$ - oestradiene were obtained. 30 30

Example 33

35 17 β - Acetoxy - 17 α - ethynyl - 3 - methoximino - 18 - methyl - $\Delta^{4,15}$ - oestradiene 35

1.3 Grams of 17 β - acetoxy - 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - onoxime in 30 ml of hexamethyl-phosphoric acid triamide were reacted in a manner analogous to that in Example 25 with 3.5 ml of a solution of 25% strength of sodium hydroxide and 3.5 ml of methyl iodide. After 1.5 hours the solution was introduced into ice/water containing hydrochloric acid, and working up was carried out in a manner analogous to that described in Example 25. The crude product was chromatographed over silica gel with acetone/hexane. 580 mg of 17 β - acetoxy - 17 α - ethynyl - 3 - methoximino - 18 - methyl - $\Delta^{4,15}$ - oestradiene were obtained. 40 40

Example 34

45 3 - Acetoximino - 17 α - ethynyl - 17 β - butyryloxy - 18 - methyl - $\Delta^{4,15}$ - oestradiene 45

500 mg of 17 α - ethynyl - 17 β - butyryloxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - onoxime in 5 ml of pyridine were stirred with 25 ml of acetic anhydride for 1 hour at room temperature. The solution was introduced into ice/water and worked up as described in Example 27. After chromatography of the crude product over silica gel with acetone/hexane 370 mg of 3 - acetoximino - 17 α - ethynyl - 17 β - butyryloxy - 18 - methyl - $\Delta^{4,15}$ - oestradiene were obtained. 50 50

Example 35

55 17 α - Chlorethynyl - 17 β - hydroxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one 55
To 2.3 ml of 1,2-dichlorethylene in 40 ml of absolute ether were added under argon at room temperature 32 ml of a 2 mol. ethereal solution of lithium methyl.

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After 30 minutes 2.0 grams of a mixture of 18 - methyl - 3,3 - (2',2' - dimethyl - 1',3' - propylenedioxy) - $\Delta^{5,15}$ - and - $\Delta^{5(10),15}$ - oestradien - 17 - one in 70 ml of tetrahydrofuran were added dropwise, and the whole was stirred for 1.5 hours at 60°C. After cooling, a saturated solution of ammonium chloride was cautiously added to the solution, and it was diluted with ether, washed until neutral with water and dried over sodium sulphate. The crude product was chromatographed over silica gel with acetone/hexane. 1.2 Grams of a mixture of 17 α - chlorethynyl - 3,3 - (2',2' - dimethyl - 1',3' - propylenedioxy) - 18 - methyl - $\Delta^{5,15}$ - and - $\Delta^{5(10),15}$ - oestradien - 17 β - ol were obtained, which in 10 ml of methanol and 1 ml of water were stirred with 400 mg of oxalic acid for 4 hours at 65°C. The solution was neutralized with a sodium bicarbonate solution and concentrated *in vacuo*. The residue was dissolved in ethyl acetate, washed with water and dried over sodium sulphate. After purification by preparative layer chromatography (system: ether/chloroform 8+2) and recrystallization from acetone/hexane 170 mg of 17 α - chlorethynyl - 17 β - hydroxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one were obtained. Melting point: 153—154°C.

Example 36

17 β - Acetoxy - 17 α - chlorethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one
1.0 Gram of 17 α - chlorethynyl - 17 β - hydroxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one in 10 ml of pyridine was stirred with 5 ml of acetic anhydride and 50 mg of 4-(dimethylamino)-pyridine for 4 hours under nitrogen at room temperature. The solution was introduced into ice/water containing sulphuric acid. The precipitated product was filtered off with suction, dissolved in methylene chloride, washed with water and dried over sodium sulphate. After chromatography of the crude product over silica gel with acetone/hexane 760 mg of 17 β - acetoxy - 17 α - chlorethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one were obtained.

Example 37

17 β - Butyryloxy - 17 α - chlorethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one
400 mg of 17 α - chlorethynyl - 17 β - hydroxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one in 4 ml of pyridine were stirred with 2 ml of butyric anhydride and 20 mg of 4-(dimethylamino)-pyridine for 8 hours at room temperature. The reaction product was introduced into ice/water containing sulphuric acid, and worked up as described in Example 36. After chromatography of the crude product over silica gel with acetone/hexane 220 mg of 17 β - butyryloxy - 17 α - chlorethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one were obtained.

Example 38

17 α - Chlorethynyl - 18 - methyl - 17 β - undecanoyloxy - $\Delta^{4,15}$ - oestradien - 3 - one

From a solution of 3.5 grams of undecanoic acid in 300 ml of benzene 70 ml were distilled off. After cooling to room temperature 4 ml of trifluoroacetic anhydride were added. After 30 minutes 3.2 grams of 17 α - chlorethynyl - 17 β - hydroxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one were added. The whole was stirred for 2.5 hours. While cooling with ice 50 ml of acetone/water (1:1) were added, and the mixture was stirred for 30 minutes and then concentrated *in vacuo*. The residue was taken up in methylene chloride, washed with a sodium bicarbonate solution and water, and dried over sodium sulphate. The crude product was chromatographed over silica gel. With ethyl acetate/hexane 1.1 grams of 17 α - chlorethynyl - 18 - methyl - 17 β - undecanoyloxy - $\Delta^{4,15}$ - oestradien - 3 - one were obtained in the form of an oil.

Example 39

17 α - Chlorethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradiene - 3 β ,17 β - diol

To 1.2 grams of 17 α - chlorethynyl - 17 β - hydroxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one in 30 ml of tetrahydrofuran was slowly added a solution of 3.0 grams of lithium tri-(tert.-butoxy)-aluminium hydride in 25 ml of tetrahydrofuran, and the whole was stirred for 1 hour at room temperature under nitrogen. The solution was stirred into ice/water containing sulphuric acid. The precipitated product was filtered off, dissolved in ethyl acetate, washed with water and dried over sodium sulphate. After chromatography of the crude product over silica gel

21

15		1,569,135	15
		with acetone/hexane 380 mg of 17 α - chlorethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradiene - 3 β ,17 β - diol were obtained.	
		Example 40	
5	17 β - Acetoxy - 17 α - chlorethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 β - ol		5
10	900 mg of 17 β - acetoxy - 17 α - chlorethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one in 25 ml of tetrahydrofuran were reacted, as described in Example 39, with 2.3 grams of lithium tri-(tert.-butoxy)-aluminium hydride in 20 ml of tetrahydrofuran. After one hour the solution was introduced into ice/water containing sulphuric acid and worked up in a manner analogous to that described in Example 39. After purification of the crude product by preparative layer chromatography (system: ether/chloroform 8+2) there were obtained 410 mg of 17 β - acetoxy - 17 α - chlorethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 β - ol		10
		Example 41	
15	17 β - Acetoxy - 17 α - chlorethynyl - 3 β - heptanoyloxy - 18 - methyl - $\Delta^{4,15}$ - oestradiene		15
20	400 mg of 17 β - acetoxy - 17 α - chlorethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 β - ol in 3 ml of pyridine were stirred with 2.5 ml of oenanthic anhydride for 3 hours at room temperature. The solution was diluted with benzene and subjected to steam distillation. The reaction product was extracted from the aqueous distillation residue with methylene chloride. After chromatography of the crude product over silica with acetone/hexane 170 mg of 17 β - acetoxy - 17 α - chlorethynyl - 3 β - heptanoyloxy - 18 - methyl - $\Delta^{4,15}$ - oestradiene were obtained.		20
25		Example 42	25
	17 α - Chlorethynyl - 18 - methyl - 3 - oximino - $\Delta^{4,15}$ - oestradien - 17 β - ol		
30	To 2.3 grams of 17 α - chlorethynyl - 17 β - hydroxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one in 60 ml of methanol and 2 ml of water were added 1.0 gram of hydroxylamine hydrochloride and 1.0 gram of sodium bicarbonate. The reaction mixture was stirred for 3 hours at 65°C and then concentrated <i>in vacuo</i> . The residue was taken up in ethyl acetate, washed with water and dried over sodium sulphate. After chromatography of the crude product over silica gel with acetone/hexane 1.4 grams of 17 α - chlorethynyl - 18 - methyl - 3 - oximino - $\Delta^{4,15}$ - oestradien - 17 β - ol were obtained.		30
35		Example 43	35
	17 β - Acetoxy - 17 α - chlorethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - onoxime		
40	1.2 Grams of 17 β - acetoxy - 17 α - chlorethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one in 35 ml of methanol and 1.2 ml of water were reacted, as described in Example 42, with 600 mg of hydroxylamine hydrochloride and 700 mg of sodium bicarbonate. After one hour the reaction mixture was worked up in a manner analogous to that described in Example 42. After chromatography of the crude product over silica gel with acetone/hexane 750 mg of 17 β - acetoxy - 17 α - chlorethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - onoxime were obtained.		40
45		Example 44	45
	17 α - Chlorethynyl - 3 - heptanoyloximino - 18 - methyl - $\Delta^{4,15}$ - oestradien - 17 β - ol		
50	850 mg of 17 α - chlorethynyl - 18 - methyl - 3 - oximino - $\Delta^{4,15}$ - oestradien - 17 β - ol in 6 ml of pyridine were stirred with 3.5 ml oenanthic anhydride for 3 hours at room temperature. The solution was diluted with benzene and subjected to steam distillation. The reaction product was extracted from the aqueous distillation residue with methylene chloride. After chromatography of the crude product over silica gel with acetone/hexane 210 mg of 17 α - chlorethynyl - 3 - heptanoyloximino - 18 - methyl - $\Delta^{4,15}$ - oestradien - 17 β - ol were obtained.		50
55		Example 45	55
	17 α - Chlorethynyl - 3 - methoximino - 18 - methyl - $\Delta^{4,15}$ - oestradien - 17 β - ol		
	2.6 Grams of 17 α - chlorethynyl - 18 - methyl - 3 - oximino - $\Delta^{4,15}$ - oestradien - 17 β - ol in 50 ml of hexamethyl-phosphoric acid triamide were mixed,		

while cooling with ice and introducing nitrogen, with 2 ml of a solution of 25% strength of sodium hydroxide and 5 ml of methyl iodide. After one hour the solution was introduced into ice/water containing hydrochloric acid. Extraction with ether was carried out, and the solution was washed until neutral with water and dried over sodium sulphate. The crude product was chromatographed over silica gel with acetone/hexane. 510 mg of 17 α - chlorethynyl - 3 - methoximino - 18 - methyl - $\Delta^{4,15}$ - oestradien - 17 β - ol were obtained.

Example 46

17 β - Hydroxy - 18 - methyl - 17 α - propyn - 1 - yl - $\Delta^{4,15}$ - oestradien - 3 - one
Methyl-acetylene was passed for about 30 minutes through a solution, cooled with ice/water, of 60 ml of lithium *n*-butyl (15% strength in hexane) in 250 ml of tetrahydrofuran. Then 5.8 grams of a mixture of 18 - methyl - 3,3 - (2',2' - dimethyl - 1',3' - propylenedioxy) - $\Delta^{5,15}$ - and - $\Delta^{5(10),15}$ - oestradien - 17 - one in 60 ml of tetrahydrofuran were added dropwise while stirring. After 2 hours there was cautiously added to the solution a saturated solution of ammonium chloride, and the mixture was diluted with ethyl acetate, washed until neutral with water and dried over sodium sulphate. The solution was concentrated to dryness *in vacuo* and 4.6 grams of a mixture of crude 18 - methyl - 3,3 - (2',2' - dimethyl - 1',3' - propylenedioxy) - 17 α - propyn - 1 - yl - $\Delta^{5,15}$ - and - $\Delta^{5(10),15}$ - oestradien - 17 β - ol were obtained, which were suspended in 50 ml of acetone and 0.1 ml of concentrated hydrochloric acid was added at room temperature. After one hour the solution was introduced into ice/water. The precipitated product was filtered off with suction, dissolved in ethyl acetate and dried over sodium sulphate. The crude product was chromatographed over silica gel with acetone/hexane. 1.8 Grams of 17 β - hydroxy - 18 - methyl - 17 α - propyn - 1 - yl - $\Delta^{4,15}$ - oestradien - 3 - one were obtained.

Example 47

17 β - Acetoxy - 18 - methyl - 17 α - propyn - 1 - yl - $\Delta^{4,15}$ - oestradien - 3 - one
250 mg of 17 β - hydroxy - 18 - methyl - 17 α - propyn - 1 - yl - $\Delta^{4,15}$ - oestradien - 3 - one in 2.5 ml of pyridine were stirred with 1 ml of acetic anhydride and 10 mg of 4-(dimethylamino)-pyridine for 2 hours under nitrogen at room temperature. After working up, as described in Example 36, and chromatography of the crude product over silica gel with acetone/hexane 110 mg of 17 β - acetoxy - 18 - methyl - 17 α - propyn - 1 - yl - $\Delta^{4,15}$ - oestradien - 3 - one were obtained.

Example 48

18 - Methyl - 17 α - propyn - 1 - yl - $\Delta^{4,15}$ - oestradiene - 3 β ,17 β - diol
800 mg of 17 β - hydroxy - 18 - methyl - 17 α - propyn - 1 - yl - $\Delta^{4,15}$ - oestradien - 3 - one in 25 ml of tetrahydrofuran were reacted, as described in Example 39, with 1.4 grams of lithium tri-(tert.-butoxy)-aluminium hydride in 15 ml of tetrahydrofuran. After one hour the solution was introduced into ice/water containing sulphuric acid, and worked up in a manner analogous to that described in Example 39. After chromatography of the crude product over silica gel with acetone/hexane 250 mg of 18 - methyl - 17 α - propyn - 1 - yl - $\Delta^{4,15}$ - oestradiene - 3 β ,17 - diol were obtained.

Example 49

18 - Methyl - 3 - oximino - 17 α - propyn - 1 - yl - $\Delta^{4,15}$ - oestradien - 17 β - ol
1.2 Grams of 17 β - hydroxy - 18 - methyl - 17 α - propyn - 1 - yl - $\Delta^{4,15}$ - oestradien - 3 - one in 30 ml of methanol and 1 ml of water were stirred with 800 mg of hydroxylamine hydrochloride and 800 mg of sodium bicarbonate for 3 hours at 65°C. The reaction mixture was then concentrated *in vacuo*. The residue was dissolved in ethyl acetate, washed with water and dried over sodium sulphate. After chromatography of the crude product over silica gel with acetone/hexane 430 mg of 18 - methyl - 3 - oximino - 17 α - propyn - 1 - yl - $\Delta^{4,15}$ - oestradien - 17 β - ol were obtained.

Example 50

17 β - Acetoxy - 18 - methyl - 17 α - propyn - 1 - yl - $\Delta^{4,15}$ - oestradien - 3 - onoxime
700 mg of 17 β - acetoxy - 18 - methyl - 17 α - propyn - 1 - yl - $\Delta^{4,15}$ -

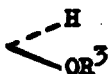
17	1,569,135	17
5	oestradien - 3 - one in 30 ml of methanol and 1 ml of water were reacted, as described in Example 49, with 600 mg of hydroxylamine hydrochloride and 700 mg of sodium bicarbonate. After one hour the reaction mixture was worked up in a manner analogous to that described in Example 49. The crude product was chromatographed over silica gel with acetone/hexane. 240 mg of 17β - acetoxy - 18 - methyl - 17α - propyn - 1 - yl - $\Delta^{4,15}$ - oestradien - 3 - onoxime were obtained.	5
10	Example 51 3 - Cyclopentyloximino - 18 - methyl - 17α - propyn - 1 - yl - $\Delta^{4,15}$ - oestradien - 17β - ol	10
15	1.1 Grams of 18 - methyl - 3 - oximino - 17α - propyn - 1 - yl - $\Delta^{4,15}$ - oestradien - 17β - ol in 30 ml of hexamethyl-phosphoric acid triamide were reacted at room temperature under nitrogen with 3 ml of a solution of 25% strength of sodium hydroxide and 3 ml of cyclopentyl bromide. After 4 hours working up was carried out in a manner analogous to that described in Example 45. The crude product was chromatographed over silica gel with acetone/hexane. 115 mg of 3 - cyclopentyloximino - 18 - methyl - 17α - propyn - 1 - yl - $\Delta^{4,15}$ - oestradien - 17β - ol were obtained.	15
20	Example 52 (composition of a tablet). 0.050 mg of 17α-ethynyl-17β-hydroxy-18-methyl-$\Delta^{4,15}$-oestradien-3-one	20
25	0.050 mg of 17α-ethynyl-oestradiol 109.900 mg of lactose (DAB 6) 8.000 mg of maize starch (USP XVI) 1.000 mg of magnesium stearate (USP XVI) 1.000 mg of talcum 120.000 mg Total weight of the tablet.	25
30	"DAB 6" is an abbreviation for Deutsches Arzneibuch, 6th edition, and "USP XVI" is an abbreviation for United States Pharmacopeia, 16th edition. Example 53 (composition of a dragée). 0.030 mg of 17α-ethynyl-17β-hydroxy-18-methyl-$\Delta^{4,15}$-oestradien-3-one	30
35	0.050 mg of 17α-ethynyl-oestradiol 31.920 mg of lactose 18.425 mg of maize starch 2.060 mg of polyvinylpyrrolidone 25 0.010 mg of para-hydroxybenzoic acid methyl ester 0.005 mg of para-hydroxybenzoic acid propyl ester 2.500 mg of talcum	35
40	55.000 mg Total weight of the tablet, which was made into a dragée with the usual sugar mixture up to approximately 90 mg. Example 54 (composition of a dragée). 0.030 mg of 17α-ethynyl-17β-hydroxy-18-methyl-$\Delta^{4,15}$-oestradien-3-one	40
45	0.030 mg of 17α-ethynyl-oestradiol 31.938 mg of lactose 18.425 mg of maize starch 2.060 mg of polyvinylpyrrolidone 25	45
50	0.011 mg of para-hydroxybenzoic acid methyl ester 0.006 mg of para-hydroxybenzoic acid propyl ester 2.500 mg of talcum	50
55	55.000 mg Total weight of the tablet, which was made into a dragée with the usual sugar mixture up to approximately 90 mg.	55

80.000 mg Total weight of the tablet.

1. A Δ^{15} -steroid of the general formula I



R¹ represents a hydrogen atom or a trialkylsilyl or acyl group, **R²** represents an ethynyl, chlorethynyl or propynyl group, and **X** represents an oxygen atom or a grouping of the formula



or NOR⁴, in which R³ represents a hydrogen atom or an acyl group and R⁴ represents a hydrogen atom or an acyl, alkyl, cycloalkyl or tetrahydropyranyl group.

2. A compound as claimed in claim 1, wherein each of the acyl groups represented by R¹ and R³ is derived from an organic carboxylic or sulphonic acid containing 1 to 16 carbon atoms.

3. A compound as claimed in claim 1, wherein each of the acyl groups represented by R¹ and R³ is derived from an organic carboxylic or sulphonic acid containing 1 to 11 carbon atoms.

4. A compound as claimed in any one of claims 1 to 3, wherein the trialkylsilyl group represented by R¹ is a trimethylsilyl group.

5. A compound as claimed in any one of claims 1 to 4, wherein the acyl group represented by R⁴ contains 2 to 8 carbon atoms.

6. A compound as claimed in any one of claims 1 to 4, wherein the alkyl group represented by R⁴ is a methyl or ethyl group.

7. A compound as claimed in any one of claims 1 to 4, wherein the cycloalkyl group represented by R⁴ is a cyclopentyl group.

8. 17α - Ethynyl - 17β - hydroxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one.

9. 17β - Acetoxy - 17α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one.

10. 17 α - Ethynyl - 17 β - butyryloxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one.

11. 17 α - Ethynyl - 17 β - heptanoyloxy - 18 - methyl - $\Delta^{4,18}$ - oestradien - 3 - one.

12. 17α - Ethynyl - 18 - methyl - 17β - octanoyloxy - $\Delta^{4,15}$ - oestradien - 3 - one.

13. 17 α - Ethynyl - 18 - methyl - 17 β - undecanoyloxy - $\Delta^{4,15}$ - oestradien - 3 - one.

14. 17α - Ethynyl - 17β - hexadecanoyloxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one.

15. 17α - Ethynyl - 17β - trimethylsiloxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one.

16. 17α - Ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradiene - $3\beta,17\beta$ - diol.

Example 55 (composition of a tablet).

0.030 mg of 17 α -ethynyl-17 β -hydroxy-18-methyl- $\Delta^{4,15}$ -
oestradien-3-one

63.670 mg of lactose

15.000 mg of microcrystalline cellulose

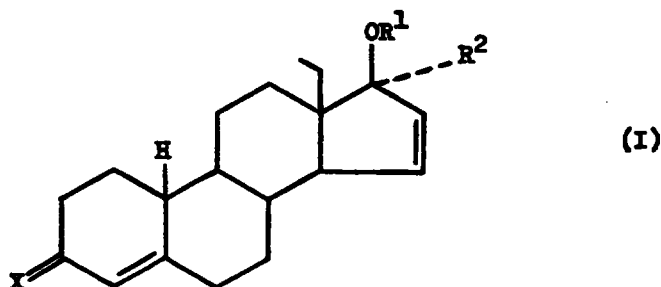
1.000 mg of talcum

0.300 mg of magnesium stearate

80.000 mg Total weight of the tablet.

WHAT WE CLAIM IS:—

1. A Δ^{15} -steroid of the general formula I



in which

R¹ represents a hydrogen atom or a trialkylsilyl or acyl group,

R² represents an ethynyl, chlorethynyl or propynyl group, and

X represents an oxygen atom or a grouping of the formula



or NOR⁴, in which R³ represents a hydrogen atom or an acyl group and R⁴ represents a hydrogen atom or an acyl, alkyl, cycloalkyl or tetrahydropyranyl group.

2. A compound as claimed in claim 1, wherein each of the acyl groups represented by R¹ and R³ is derived from an organic carboxylic or sulphonic acid containing 1 to 16 carbon atoms.

3. A compound as claimed in claim 1, wherein each of the acyl groups represented by R¹ and R³ is derived from an organic carboxylic or sulphonic acid containing 1 to 11 carbon atoms.

4. A compound as claimed in any one of claims 1 to 3, wherein the trialkylsilyl group represented by R¹ is a trimethylsilyl group.

5. A compound as claimed in any one of claims 1 to 4, wherein the acyl group represented by R⁴ contains 2 to 8 carbon atoms.

6. A compound as claimed in any one of claims 1 to 4, wherein the alkyl group represented by R⁴ is a methyl or ethyl group.

7. A compound as claimed in any one of claims 1 to 4, wherein the cycloalkyl group represented by R⁴ is a cyclopentyl group.

8. 17 α - Ethynyl - 17 β - hydroxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one.

9. 17 β - Acetoxy - 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one.

10. 17 α - Ethynyl - 17 β - butyryloxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one.

11. 17 α - Ethynyl - 17 β - heptanoyloxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one.

12. 17 α - Ethynyl - 18 - methyl - 17 β - octanoyloxy - $\Delta^{4,15}$ - oestradien - 3 - one.

13. 17 α - Ethynyl - 18 - methyl - 17 β - undecanoyloxy - $\Delta^{4,15}$ - oestradien - 3 - one.

14. 17 α - Ethynyl - 17 β - hexadecanoyloxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one.

15. 17 α - Ethynyl - 17 β - trimethylsiloxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one.

16. 17 α - Ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradiene - 3 β ,17 β - diol.



25

19	1,569,135	19
	17. 17 β - Acetoxy - 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 β - ol.	
	18. 17 α - Ethynyl - 18 - methyl - 17 β - trimethylsiloxy - $\Delta^{4,15}$ - oestradien - 3 β - ol.	
5	19. 3 β - Acetoxy - 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 17 β - ol.	5
	20. 17 α - Ethynyl - 3 β - heptanoyloxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 17 β - ol.	
	21. 17 α - Ethynyl - 3 β - isopropylsulphonyloxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 17 β - ol.	
10	22. 17 α - Ethynyl - 18 - methyl - 3 β ,17 β - diundecanoyloxy - $\Delta^{4,15}$ - oestradiene.	10
	23. 17 β - Acetoxy - 17 α - ethynyl - 3 β - heptanoyloxy - 18 - methyl - $\Delta^{4,15}$ - oestradiene.	
	24. 17 α - Ethynyl - 3 β ,17 β - dihexadecanoyloxy - 18 - methyl - $\Delta^{4,15}$ - oestradiene.	
15	25. 17 α - Ethynyl - 18 - methyl - 3 - oximino - $\Delta^{4,15}$ - oestradien - 17 β - ol.	15
	26. 17 β - Acetoxy - 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - onoxime.	
	27. 17 α - Ethynyl - 18 - methyl - 17 β - undecanoyloxy - $\Delta^{4,15}$ - oestradien - 3 - onoxime.	
20	28. 17 α - Ethynyl - 3 - methoximino - 18 - methyl - $\Delta^{4,15}$ - oestradien - 17 β - ol.	20
	29. 17 α - Ethynyl - 3 - cyclopentyloximino - 18 - methyl - $\Delta^{4,15}$ - oestradien - 17 β - ol.	
25	30. 3 - Acetoximino - 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 17 β - ol.	25
	31. 17 α - Ethynyl - 3 - isobutyryloximino - 18 - methyl - $\Delta^{4,15}$ - oestradien - 17 β - ol.	
	32. 17 α - Ethynyl - 3 - heptanoyloximino - 18 - methyl - $\Delta^{4,15}$ - oestradien - 17 β - ol.	
30	33. 17 β - Acetoxy - 3 - acetoximino - 17 α - ethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradiene.	30
	34. 17 β - Acetoxy - 17 α - ethynyl - 3 - isobutyryloximino - 18 - methyl - $\Delta^{4,15}$ - oestradiene.	
35	35. 17 β - Acetoxy - 17 α - ethynyl - 3 - heptanoyloximino - 18 - methyl - $\Delta^{4,15}$ - oestradiene.	35
	36. 17 β - Acetoxy - 17 α - ethynyl - 3 - methoximino - 18 - methyl - $\Delta^{4,15}$ - oestradiene.	
	37. 3 - Acetoximino - 17 α - ethynyl - 17 β - butyryloxy - 18 - methyl - $\Delta^{4,15}$ - oestradiene.	
40	38. 17 α - Chlorethynyl - 17 β - hydroxy - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one.	40
	39. 17 β - Acetoxy - 17 α - chlorethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one.	
45	40. 17 β - Butyryloxy - 17 α - chlorethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - one.	45
	41. 17 α - Chlorethynyl - 18 - methyl - 17 β - undecanoyloxy - $\Delta^{4,15}$ - oestradien - 3 - one.	
	42. 17 α - Chlorethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradiene - 3 β ,17 β - diol.	
50	43. 17 β - Acetoxy - 17 α - chlorethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 β - ol.	50
	44. 17 β - Acetoxy - 17 α - chlorethynyl - 3 β - heptanoyloxy - 18 - methyl - $\Delta^{4,15}$ - oestradiene.	
	45. 17 α - Chlorethynyl - 18 - methyl - 3 - oximino - $\Delta^{4,15}$ - oestradien - 17 β - ol.	
55	46. 17 β - Acetoxy - 17 α - chlorethynyl - 18 - methyl - $\Delta^{4,15}$ - oestradien - 3 - onoxime.	55
	47. 17 α - Chlorethynyl - 3 - heptanoyloximino - 18 - methyl - $\Delta^{4,15}$ - oestradien - 17 β - ol.	
60	48. 17 α - Chlorethynyl - 3 - methoximino - 18 - methyl - $\Delta^{4,15}$ - oestradien - 17 β - ol.	60
	49. 17 β - Hydroxy - 18 - methyl - 17 α - propyn - 1 - yl - $\Delta^{4,15}$ - oestradien - 3 - one.	
	50. 17 β - Acetoxy - 18 - methyl - 17 α - propyn - 1 - yl - $\Delta^{4,15}$ - oestradien - 3 - one.	
65	51. 18 - Methyl - 17 α - propyn - 1 - yl - $\Delta^{4,15}$ - oestradiene - 3 β ,17 β - diol.	65



52. 18 - Methyl - 3 - oximino - 17 α - propyn - 1 - yl - $\Delta^{4,15}$ - oestradien - 17 β - ol.

53. 17 β - Acetoxy - 18 - methyl - 17 α - propyn - 1 - yl - $\Delta^{4,15}$ - oestradien - 3 - onoxime.

54. 3 - Cyclopentyloximino - 18 - methyl - 17 α - propyn - 1 - yl - $\Delta^{4,15}$ - oestradien - 17 β - ol.

55. 17 α - Ethynyl - 3 β - isopropylsulphonyloxy - 18 - methyl - 17 β - trimethylsilyloxy - $\Delta^{4,15}$ - oestradiene.

56. A pharmaceutical preparation which comprises a compound as claimed in any one of claims 1 to 7, in admixture or conjunction with a pharmaceutically suitable carrier.

57. A pharmaceutical preparation which comprises the compound claimed in any one of claims 8 to 55, in admixture or conjunction with a pharmaceutically suitable carrier.

58. A preparation as claimed in claim 56 or 57, which also contains an oestrogenically active hormone.

59. A preparation as claimed in claim 58, wherein the oestrogenically active hormone is 17 α -ethynyl-oestradiol.

60. A preparation as claimed in any one of claims 56 to 59, which is in a form suitable for oral administration.

61. A preparation as claimed in claim 60, which is in the form of a tablet, dragée, capsule, pill, suspension or solution.

62. A preparation as claimed in claim 60, which is in the form of a tablet containing 0.01 to 0.5 mg of active substance.

63. A preparation as claimed in any one of claims 56 to 59, which is in a form suitable for parenteral administration.

64. A preparation as claimed in claim 63, which is in the form of an oily solution.

65. A preparation as claimed in claim 64, containing 1 to 100 mg of active substance per 1 ml of solution.

66. A pharmaceutical preparation having a composition substantially as described in any one of Examples 52 to 55 herein.

67. A method of contraception, wherein there is administered in a contraceptive dose to a female mammal a compound as claimed in any one of claims 1 to 7.

68. A method of contraception, wherein there is administered in a contraceptive dose to a female mammal the compound claimed in any one of claims 8 to 55.

69. A method as claimed in claim 67 or 68, wherein the female mammal is a female of the human species.

70. A method as claimed in claim 69, wherein the contraceptive dose is a daily dose administered orally within the range of from 0.01 to 0.1 mg.

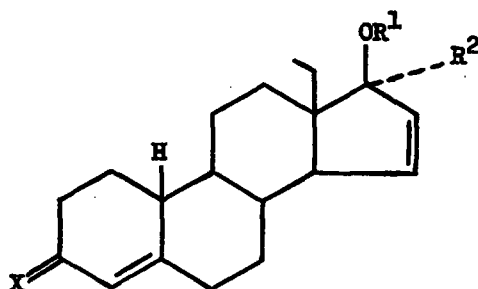
71. A contraceptive pack which comprises a compound as claimed in any one of claims 1 to 7 together with instructions, which instructions require the administration of the compound in a contraceptive dose to a female mammal.

72. A contraceptive pack which comprises the compound claimed in any one of claims 8 to 55 together with instructions, which instructions require the administration of the compound in a contraceptive dose to a female mammal.

73. A pack as claimed in claim 71 or 72, wherein the female mammal is a female of the human species.

74. A pack as claimed in claim 73, wherein the contraceptive dose is a daily dose to be administered orally within the range of from 0.01 to 0.1 mg.

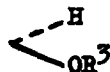
75. A process for the manufacture of a Δ^{15} -steroid of the general formula I



in which



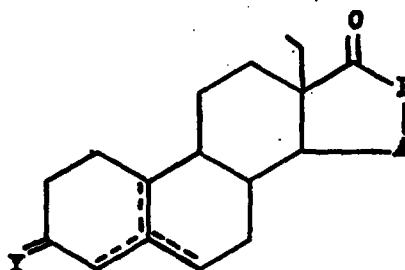
R¹ represents a hydrogen atom or a trialkylsilyl or acyl group,
R² represents an ethynyl, chlorethynyl or propynyl group, and
X represents an oxygen atom or a grouping of the formula



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or NOR⁴, in which R³ represents a hydrogen atom or an acyl group and R⁴ represents a hydrogen atom or an acyl, alkyl, cycloalkyl or tetrahydropyranyl group, wherein an ethynyl, chlorethynyl or propynyl group is introduced into the 17 α -position of a 17-oxo-steroid of the general formula II

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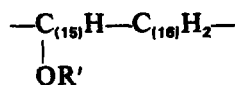


(II) ,

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in which Y represents a free or ketalised keto group, one of the == bonds in the 4,5-, 5,6- and 5,10-positions represents a carbon-to-carbon double bond and each of the others represents a carbon-to-carbon single bond, and —A—B— represents a —CH=CH— or

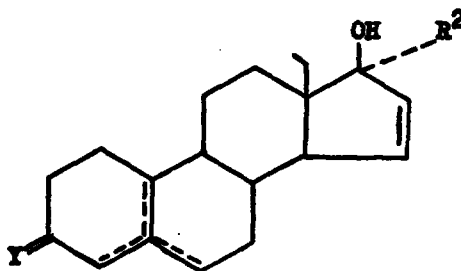
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grouping, in which R' represents a hydrogen atom or a trialkylsilyl, dialkylsilyl, acyl, alkanesulphonyl, arylsulphonyl or nitro group, by means of an agent capable of yielding such a group with the formation of a hydroxyl group in the 17 β -position, and in the resulting compound of the general formula III

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(III) ,

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in which Y and R₂ have the meanings given above and one of the == bonds in the 4,5-, 5,6- and 5,10-positions represents a carbon-to-carbon double bond and each of the others represents a carbon-to-carbon single bond, any ketalised keto group in the 3-position is split off and, if desired, the 17 β -hydroxyl group, before or after any splitting off of a ketalised keto group in the 3-position, is esterified or is converted into a 17 β -trialkylsilyloxy group, and/or, if desired, the 3-keto group is reduced to form a hydroxyl group in the 3 β -position together with a hydrogen atom in the 3 α -position or is reacted in the presence of a base with a hydroxylamine salt to form a 3-oxime and, if desired, any resulting 3 β -hydroxyl group is esterified or any resulting 3-oxime is esterified or is etherified to form an etherified group of the formula NOR⁴, in which R⁴ represents an alkyl, cycloalkyl or tetrahydropyranyl group.

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76. A process as claimed in claim 75, conducted substantially as described herein.

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77. A process for the manufacture of a compound as claimed in claim 1, conducted substantially as described in any one of Examples 1 to 9 herein.

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78. A process for the manufacture of a compound as claimed in claim 1, conducted substantially as described in any one of Examples 10 to 12 herein.

79. A process for the manufacture of a compound as claimed in claim 1, conducted substantially as described in any one of Examples 13 to 21 herein.

80. A process for the manufacture of a compound as claimed in claim 1, conducted substantially as described in any one of Examples 22 to 34 herein.

81. A process for the manufacture of a compound as claimed in claim 1, conducted substantially as described in any one of Examples 35 to 51 herein.

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