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PATENT SPECIFICATION

NO DRAWINGS

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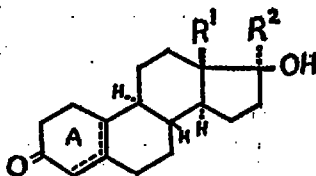
COMPLETE SPECIFICATION

13-Alkyl Steroid Ketones

I, HERCHEL SMITH, of 500 Chestnut Lane, Wayne, Delaware County, Pennsylvania, United States of America, of British nationality, do hereby declare the invention, for which I pray that a patent may be granted to me, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention concerns steroid ketones related to 19-nortestosterone and having an alkyl group of more than 1 carbon atom at the 13-position, processes for preparing them and pharmaceutical preparations containing them.

The steroid ketones of the invention are those of the structure (I)



(I)

wherein R¹ is an alkyl group of at least 2 carbon atoms, R² is an unsubstituted alkyl, alkenyl or alkynyl group, or a substituted alkyl, alkenyl or alkynyl group having the essential character of an unsubstituted alkyl, alkenyl or alkynyl group, and ring A contains an ethylenic bond terminating at the 5-position. These compounds are thus 3-ketones having an ethylenic bond either in the 4,5-position ($\alpha\beta$ -unsaturated ketones) or in the 5,10-position ($\beta\gamma$ -unsaturated ketones).

By "substituted alkyl, alkenyl or alkynyl group having the essential character of an unsubstituted alkyl, alkenyl or alkynyl group" is meant such a group substituted by a relatively inert atom or group of the kind known and used in medicinal chemistry. By 'relatively inert' is meant that the atom or group is not acidic or basic and is free from active hydro-

gen atoms and multiple (double, triple or co-ordinate) bonds. Examples of suitable substituents, for instance a methoxy group, are mentioned in the textbooks of medicinal chemistry. Such substituted groups behave as alkyl, alkenyl or alkynyl groups because of the substantial lack of functionality of the substituents. R¹ and R² preferably also each contain not more than 6 carbon atoms. The (unsubstituted) alkyl group R¹ can, for example, be an ethyl, *n*-propyl, isopropyl, *n*-butyl or isobutyl group. Examples of R² are methyl, ethyl, vinyl, ethynyl, *n*-propyl, isopropyl, allyl, 1-propynyl, *n*-butyl and 1- and 2-methallyl groups: groups of from 1 to 4 carbon atoms are thus particularly suitable.

Compounds in which R¹ is an ethyl group (that is, 18-homo compounds) are particularly important, especially those in which R² is also an ethyl, vinyl, ethynyl or *n*-propyl group. Specific compounds of this invention are the following:

17 α - Ethyl - 18 - homo - oestr - 5(10)-en - 17 β - ol - 3 - one

17 α - Ethynyl - 18 - homo - oestr - 5(10)-en - 17 β - ol - 3 - one

17 α - Allyl - 18 - homo - oestr - 5(10)-en - 17 β - ol - 3 - one

18 - Homo - 17 α - (1 - propynyl) - oestr - 5(10) - en - 17 β - ol - 3 - one

18 - Homo - 17 α - (2 - methallyl) - oestr - 5(10) - en - 17 β - ol - 3 - one

17 α - Methyl - 18 - nor - 13 β - *n* - propyl - oestr - 5(10) - en - 17 β - ol - 3 - one

17 α - Ethynyl - 18 - nor - 13 β - *n* - propyl - oestr - 5(10) - en - 17 β - ol - 3 - one

18 - Nor - 13 β - *n* - propyl - 17 α - (1 - propynyl) oestr - 5(10) - en - 17 β - ol - 3 - one

13 β - *n* - Butyl - 17 α - ethynyl - 18 - noroestr - 5(10) - en - 17 β - ol - 3 - one

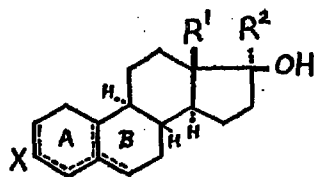
18 - Homo - 17 α - methyl - 19 - nortestosterone

17 α - Ethyl - 18 - homo - 19 - nortestosterone

[Price 4s. 6d.]

- 18 - Homo - 17 α - vinyl - 19 - nortestosterone
 17 α - Ethynyl - 18 - homo - 19 - nortestosterone
 5 17 α - Allyl - 18 - homo - 19 - nortestosterone
 18 - Homo - 17 α - (1 - propynyl) - 19 - nortestosterone
 18 - Homo - 17 α - (2 - methallyl) - 19 - nortestosterone
 10 18 - Homo - 19 - nor - 17 α - *n* - propyltestosterone
 18,19 - Bisnor - 17 α - methyl - 13 β - *n* - propyltestosterone
 15 18,19 - Bisnor - 17 α - ethyl - 13 β - *n* - propyltestosterone
 18,19 - Bisnor - 13 β - *n* - propyl - 17 α - vinyltestosterone
 18,19 - Bisnor - 13 β , 17 α - bis - *n* - propyltestosterone
 20 17 α - Allyl - 18,19 - bisnor - 13 β - *n* - propyltestosterone
 18,19 - Bisnor - 13 β - *n* - propyl - 17 α - (1 - propynyl)testosterone
 25 18,19 - Bisnor - 17 α - (1 - methallyl) - 13 β - *n* - propyltestosterone
 18,19 - Bisnor - 17 α - (2 - methallyl) - 13 β - *n* - propyltestosterone
 18,19 - Bisnor - 13 β - *n* - butyl - 17 α - ethyltestosterone
 30 18,19 - Bisnor - 13 β - *n* - butyl - 17 α - ethynyltestosterone

- In one process for preparing a steroid ketone of the invention, there is hydrolysed a corresponding compound of the structure (II)



(II)

- where X is an acid-hydrolysable protected 3-oxo group which is accompanied by an ethylenic bond terminating at the 5-position, with or without a second ethylenic bond terminating at the 3-position.

- Preferably either (a) X represents a divalent organic radical linked to ring A by two oxygen or sulphur atoms, or one oxygen and one sulphur atom, and rings A and B have a single ethylenic bond terminating at the 5-position, or (b) X represents a monovalent organic radical linked to ring A by an oxygen or sulphur atom, or one divalent or two monovalent organic radicals linked to ring A by a nitrogen atom, and rings A and B have two ethylenic bonds, one of which terminates at the 3-position, and the other at the 5-position.

Where the unsaturation present in ring A

and ring B consists of a single ethylenic bond terminating at the 5-position (so that it is in the 4,5-, the 5,6- or the 5,10-position), the compounds are ones in which two hetero atoms are attached to the carbon at the 3-position, and are exemplified by 3-ketals, 3-mercaptols, and 3-hemithioketals, all representing derivatives of a 3-ketone. Where the unsaturation present in ring A and ring B consists of two ethylenic bonds, one of which terminates at the 3-position (so that it is in the 2,3- or the 3,4-position) and the other at the 5-position, the ethylenic bonds can be conjugated or unconjugated, and the compounds are those having only one hetero atom attached to the carbon at the 3-position, and these are exemplified by enol ethers, enol thioethers and tertiary-amino compounds, representing derivatives of the enol form of a 3-ketone.

X can for instance be an alkoxy group (for example, a methoxy, ethoxy, methoxymethoxy or dihydroxypropyloxy group), an alkylthio group (for example, an ethylthio or benzylthio group), an acyloxy group (for example, an acetoxo group), a dialkylamino group, an N-pyrrolidyl group, an alkylenedioxy group (for example, an ethylenedioxy group), an alkylenedithio or alkylenthiooxy group. Preferably the organic radical or radicals of X are wholly hydrocarbon radicals. By "alkoxy group" is meant the alcoholate radical derived from an alcohol by exclusion of the hydrogen atom of its hydroxy group.

Typical arrangements of the unsaturation and group X are to be found in mixtures of 3-alkoxy-3,5- and -3,5,10)-dienes (enol ethers from 4,5-ethylenic 3-ketones), 3-alkoxy-2,5(10)-dienes (enol ethers of 5,10-ethylenic 3-ketones), 3-acyloxy-3,5-dienes (enol esters from 4,5-ethylenic 3-ketones), mixtures of 3,3-alkylenedioxy-5- and -5(10)-enes (alkylene ketals from 4,5-ethylenic 3-ketones), 3,3-alkylenedioxy-5(10)-enes (alkylene ketals of 5,10-ethylenic 3-ketones) and 3-tertiary-alkyl-amino-3,5(6)-dienes (the tertiary enamines from 4,5-ethylenic 3-ketones). Particularly useful are hydrolysis processes using as starting materials 3-alkoxy-2,5(10)-dienes (for instance the 3-methoxy compounds), 3,3-alkylenedioxy-5- and -5(10)-enes (for instance the 3,3-ethylenedioxy compounds) and 3-alkoxy-3,5(6)- or 3,5(10)-dienes (for instance the 3-ethoxy compounds).

The hydrolysis can be carried out by bringing the starting material into contact with an acid and water at a suitable temperature. Where the starting material contains an ethylenic bond in the 5,10-position, β -unsaturated ketones of the invention can be obtained under conditions of mild acid hydrolysis, as with aqueous alcoholic oxalic acid at 30°C, and below: under more vigorous acid conditions, as with 6N aqueous hydrochloric acid at 80°C, isomerisation to the $\alpha\beta$ -unsaturated ketones is facilitated and the pro-

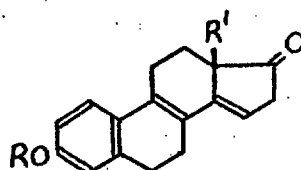
duct recovered is the conjugated one. Where the starting material does not contain an ethylenic bond in the 5,10-position, hydrolysis proceeds with formation of the ketone with conjugated unsaturation. In some instances, for example where X is an acyloxy group, the hydrolysis reaction can be carried out by the use of a base, for instance sodium hydroxide in aqueous methanol. In many instances hydrolysis with water is unnecessary, and all that is required is a hydroxylic medium for example an alcohol or a carboxylic acid.

The starting materials for such a process

are preferably those obtained starting with a suitable tetracyclic aromatic dicene ketone described in Patent Specification 991,592 or 17736/63 (Serial No. 1,041,275), and applying to it a suitable sequence of steps described in Patent Specifications 991,594; 991,933; 1,024,911; 1,024,912; 1,010,051; 1,010,052; 1,010,053; 37616/61 (Serial No. 1,041,277) and 37617/61 (Serial No. 1,041,278).

In such a sequence of steps of particular value, a process for the preparation of a steroid ketone of the invention is one in which a corresponding compound of the structure (III)

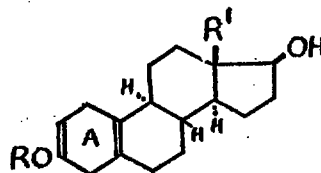
(III)



where R is an alkyl group, is selectively reduced (a) by hydrogenation in solution in a non-protonic solvent using a palladium or Raney nickel catalyst until sufficient hydrogen has been absorbed for saturation of the 14,15-ethylenic bond, (b) by a carbonyl-reducing reagent before or after the catalytic hydrogenation step, to convert the carbonyl group to a hydroxymethylene group, (c) by the action of alkali metal in liquid ammonia after the

catalytic hydrogenation and simultaneously with or after the carbonyl-reducing step, to saturate the 8,9-ethylenic bond, and (d) by the action of alkali metal in liquid ammonia in the presence of a proton donor that is an alcohol having less than 6 carbon atoms, simultaneously with or after the saturation of the 8,9-ethylenic bond, to give a compound of the structure (IV)

(IV)

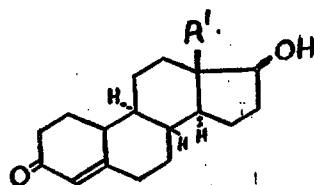


which is then selectively oxidised to convert the hydroxymethylene group to a carbonyl group without rearomatisation of ring A; the resulting ketone and an organometallic reagent containing the group R² are reacted together to introduce the group R² at the 71 α -position with formation of a 17 β -hydroxy group, and the product is finally hydrolysed. The earlier stages of this sequence are fully illustrated in Patent Specification 37617/61 (Serial No. 1,041,278). The carbonyl-reducing reagent can be sodium borohydride or lithium aluminium hydride, or it can be alkali metal in liquid ammonia where carbonyl reduction is effected

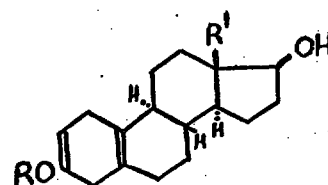
simultaneously with saturation of the 8,9-ethylenic bond: the selective oxidation can be carried out under Oppenauer conditions. Preferably R is a methyl group. R¹ and R² can be as indicated earlier in this specification but preferably in such a process R¹ is a 13- β -group, especially an ethyl group and R² is preferably an ethyl or ethynyl group.

In another process sequence, a 4,5-ethylenic steroid ketone of the structure (I) above where R¹ is an alkyl group of at least 2 carbon atoms and R² is an ethynyl group is prepared by ketalising a corresponding compound of either of the structures (V) and (VI)

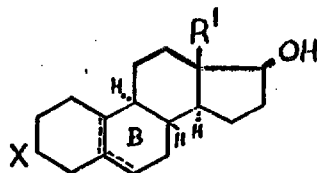
(V)



(VI)



where R is an alkyl group, with an alkylene glycol to give a compound of the structure (VII)



(VII)

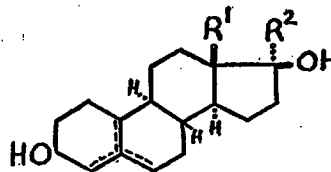
5 where X is an alkylendioxy group and ring B has an ethylenic bond terminating at the 5-position, then oxidising this to convert the hydroxymethylene group to a carbonyl group, reacting the resulting 17-ketone with an
10 organometallic ethynylating agent to introduce the group R² at the 17 α -position and form a 17 β -hydroxy group, and finally hydrolysing the product. The compound of structure (VI) is the 3-enol ether of the 5,10-ethylenic ketone
15 corresponding to the 4,5-ethylenic ketone of structure (V), and ketalisation proceeds with replacement of the alkoxy group and formation of a 3,3-alkylendioxy group without a 2,3-ethylenic bond, accompanied by some rearrangement of the 5,10-ethylenic bond to the
20 5,6-position. Where the starting material is a 3-enol ether, preferably R is a methyl group. Preferably R¹ is an ethyl group. The ketalisation is conveniently effected with ethylene glycol and toluene-*p*-sulphonic acid, and the resulting 17-alcohol is oxidised with chromic acid or under Oppenauer conditions. The
25 earlier stages of this sequence are illustrated in Example 11 of Patent Specification 37617/61 (Serial No. 1,041,278).

30 Steroid ketones of the invention having an ethylenic bond in the 4,5-position can also be obtained by the isomerisation of the corresponding compounds with an ethylenic bond at the 5,10-position. This isomerisation can be carried out under basic conditions, as with
35 aqueous alcoholic sodium or potassium hydroxide at room temperature, or with sodium alkoxide in an alcohol at 60°C. Vigorous acid conditions, such as heating in
40 methanol with concentrated hydrochloric acid, can also be used. The isomerisation process proceeds with the appearance of the hydrogen atom at the 10-position *anti* to that at the
45 9-position.

50 Steroid ketones of the invention, especially those having a 4,5-ethylenic bond, can also be obtained by the selective reduction of other such steroid ketones whose group R² has a greater degree of unsaturation. Thus, a compound with an ethynyl or an allyl group at the 17-position can be catalytically hydrogenated to the corresponding compound where
55 R² is a vinyl, ethyl or *n*-propyl group. Hydrogenation of such compounds can be carried

out by dissolving the compound in a suitable solvent and shaking the solution with hydrogen in the presence of a palladium or Raney nickel catalyst until the appropriate amount of hydrogen for selective conversion of the group
60 R² has been absorbed.

In a further process, a steroid ketone of the invention is obtained by the oxidation of a corresponding steroid diol of the structure
65 (VIII)



(VIII).

containing an ethylenic bond terminating at the 5-position, accompanied, where the starting material contains a 5,6-ethylenic bond, by conjugation of the ethylenic bond with the carbonyl group formed. Such an oxidation can be carried out using an Oppenauer reagent, for example aluminium isopropoxide, or using chromic acid. Where conjugation does not occur during oxidation, it can be achieved by treatment with alkali or acid.

Starting materials for such an oxidation process can be obtained by the reaction of the corresponding 17-ketones with suitable organometallic compounds. Thus, an 18-homologated 19 - norandrost - 5(6) - en - 3-ol - 17 - one can be reacted with an organomagnesium halide, or an organolithium compound (for example lithium acetylide or lithium ethyl), and the 17-alkyl compound obtained then oxidised with aluminium isopropoxide to give a 17 - alkyl - 18 - homologated 19 - nortestosterone. The homologated norandrostenolone itself can be obtained from the corresponding 19 - norandrost - 5(10)-ene - 3,17 - dione 17 - ethylene ketal by rearrangement with alkali to the 4,5-ethylenic compound, followed in turn by acylation in pyridine with acetic anhydride or acetyl chloride, borohydride reduction and acid hydrolysis. Alternatively, the homologated norandrostenolone can be obtained from the corresponding homologated 19-nortestosterone by (a) acylation with acetyl chloride and acetic anhydride in pyridine to give the enol diacetate, followed by (b) sodium borohydride reduction to the 5(6)-en-3-ol 17-acetate, (c) protection of the 3-hydroxy group by conversion to the tetrahydropyranyl ether by reaction with dihydropyran in the presence of hydrochloric acid catalyst, (d) basic hydrolysis of the 17-acetate group, (e) oxidation of the resulting 17-hydroxy group with chromic acid to the 17-ketone, and (f) regeneration of the 3-hydroxy group by acid hydrolysis. 18-Homologated 19 - norandrost - 5(10) - en-

3,17 - dione 17 - ethylene ketals and 18-homologated 19-nortestosterones are described in Patent Specifications 1,010,053 and 1,010,054.

5 In the product of a total synthesis which has not included a suitable resolution stage the compounds of the invention, which have the 13β configuration, will be present in equimolecular mixture or racemate form with the corresponding 13α enantiomers, as in the Examples below. The racemates are designated as $(\pm)$ -13 β -compounds using the Horeau-Reichstein Convention approved by Fieser and Fieser, *Steroids* (1959), at page 336, in which the enantiomer of 13β configuration is considered as the *d*-form and its antipode the enantiomer of 13α configuration is designated the *l*-13 β form, so that the racemate is the *dl*-13 β or $(\pm)$ -13 β compound. This invention is not concerned with the 13α antipodes and where in this specification a designation is used indicating a 13β compound, either inherently as in "17 α - ethynyl - 18 - homo - 19 - nortestosterone", or expressly, as in the structures (I) to (VIII) above, where the group R^1 is shown in the β -position, or as in "18,19 - bisnor - 17 α - ethyl - 13 β - *n* - propyltestosterone", without any symbol indicating a state of resolution, there is meant the compound itself without reference to its state of resolution, and excluding the resolved 13α enantiomer.

The compounds of this invention are useful as pharmaceuticals having anabolic, progestational, or other valuable steroidal hormone properties, or are useful as intermediates for conversion to other steroid compounds, for example the corresponding 4,9(10)-dien-3-ones: moreover the hormonal properties are exhibited on oral administration. It has been discovered that in general these steroidal hormone properties are superior to, or different from, those of the corresponding compounds having a 13-methyl group, and the difference of these properties from those of the corresponding 13-methyl compounds is, moreover, not only a difference of degree, but also a qualitative one.

In particular, it has been observed that homologation with one additional carbon atom at the 18-position (giving a 13-ethyl group) generally results in retention and enhancement of the valuable properties of the corresponding 13-methyl compounds. Compounds of the invention with *n*-propyl or *n*-butyl at the

13-position in general show less potency, but are still valuable because they show a separation of activities different from that shown by the corresponding 13-methyl compounds. The concept of homologation of the angular group in 17-alkyl-19-nortestosterones which is the basis of this invention in its broadest aspects is therefore important, for it extends the possibilities of achieving a particular single hormone action without causing an unwanted secondary action would result if a corresponding 13-methyl steroid was used under similar conditions. This is particularly true so far as anabolic properties, and a separation of anabolic and androgenic activities, are concerned, as anabolic activity is known to be closely dependent on chemical structure.

Anabolic and androgenic activity

The anabolic (myotrophic) activity of some of the compounds of the invention has been investigated using the test of Hershberger *et al.*, *Proc. Soc. Exp. Biol. Med.*, 1953, 83, 175, in which weanling rats of 45-50 g. body weight are castrated and treated daily for seven days. On the eighth day the rats are sacrificed, the levator ani muscles removed and weighed, the increase in weight being taken as a measure of anabolic activity. A dose-response curve was calculated from a series of tests using the method of least-squares, the line obtained plotted on a graph and the dose of compound required to produce a doubling of muscle weight was estimated graphically. In this way potency relative to that of a standard anabolic material, testosterone propionate, was determined, relative potency being defined as one hundred times the dose of testosterone propionate required to produce doubling of weight, divided by the dose of the compound under test required to do the same. Simultaneously with the determination of anabolic potency in the Hershberger tests, the androgenicity of the materials was measured by growth of the ventral prostate gland. A dose-response curve was calculated as before and potencies relative to testosterone propionate determined. From the anabolic and androgenic potencies obtained, the ratio of anabolic to androgenic activities was calculated.

On this basis the anabolic and androgenic potencies, and anabolic/androgenic ratios of various materials, including $(+)\text{-}17\alpha\text{-ethyl-19-nortestosterone}$ (a commercial anabolic agent) determined were as follows:

	Anabolic potency	Androgenic potency	Ratio
(+) - 19-Nortestosterone	60	4	15
17 α -Substituted 19-nortestosterones			
(+) - 17 α -Ethyl	85	12	7
($\pm$) - 18-Homo-17 α -methyl	110	89	1
($\pm$) - 17 α -Ethyl-18-homo	340	17	20
($\pm$) - 18-Homo-17 α - <i>n</i> -propyl	13	0.7	19
($\pm$) - 17 α -Methyl-18-nor-13 β - <i>n</i> -propyl	270	34	8
($\pm$) - 17 α -Ethyl-18-nor-13 β - <i>n</i> -propyl	54	11	5

- 5 The anabolic and androgenic potencies of the active (+)-enantiomers in the racemates are of course correspondingly higher. 19-Nortestosterone is orally inactive, while the other compounds listed are orally active: for example, ($\pm$) - 17 α - ethyl - 18 - homo - 19 - nortestosterone is 10% as potent orally as it is parenterally. The remarkable anabolic potency and separation of activities shown by ($\pm$) - 17 α - ethyl - 18 - homo - 19 - nortestosterone are evident. On the other hand the ($\pm$) - 18-homo - 17 α - methyl compound has remarkable androgenic potency.
- 10 In estimating anabolic and androgenic potencies it is in practice found that the dose-response curves are often not parallel with the curve for the standard material, testosterone propionate, and the above method of estimating potencies does not take this into account.
- 15 In order to account for this factor, dose-response curves have been analysed in the
- 20 following way. It is assumed that (a) all doses of compound above the point where the levator ani dose-response curve intersects the control level are anabolic, and (b) all doses above the point where the ventral prostate dose-response curve intersects the control level are androgenic. Where, for a specific compound, the intercept on the levator ani curve is at a lower dose than the intercept on the ventral prostate curve, the compound is more anabolic than androgenic, and the levator ani weight at the intercept on the ventral prostate curve gives the maximum amount of growth possible at non-androgenic doses.

The following table gives these intercepts, (VP and LA), the levator ani muscle weight (W) at the ventral prostate intercept, and the myotrophic potential, which is defined as the possible percentage increase (%) of levator ani muscles at non-androgenic doses of the compounds.

	VP	LA	W	%
Testosterone propionate	3.5	15.5	<33	
19-Nortestosterone	83	33	48	45.5
17 α -Substituted 19-nortestosterones				
(+) - 17 α -Ethyl	17	8.6	42.2	28
($\pm$) - 18-Homo-17 α -methyl	2.3	2.1	34	3
($\pm$) - 17 α -Ethyl-18-homo	20	7.7	48	46
($\pm$) - 18-Homo-17 α - <i>n</i> -propyl	290	250	36	9
($\pm$) - 17 α -Methyl-18-nor-13 β - <i>n</i> -propyl	12	7.5	40	21
($\pm$) - 17 α -Ethyl-18-nor-13 β - <i>n</i> -propyl	25	39	<33	

The outstanding properties of ($\pm$) - 17 α -ethyl - 18 - homo - 19 - nortestosterone are again apparent. Further tests on the effect of this 18-homo compound on the growth of seminal vesicles of male rats showed it had about 15% of the androgenic activity of testosterone propionate measured in this way.

Oestrogen-antagonist activity

The oestrogen-antagonistic potency of a compound can be measured by the mouse vaginal smear test of Edgren, *Proc. Soc. Exp. Biol. Med.*, 1960, 105, 252, in which test material is mixed with a total dose of 2 μ g. of oestrone and the mixture administered in four equal daily injections. The potency is measured in terms of the activity of progesterone. Results of this test using various compounds are given in the following table.

20	Progesterone	100
	19-Nortestosterone	200
	17 α -Substituted 19-nortestosterones	
	(+)-17 α -Methyl	1800
	(+)-17 α -Ethyl	2100
25	($\pm$)-17 α -Ethinyl	910
	($\pm$)-18-Homo-17 α -methyl	5000
	($\pm$)-18-Homo-17 α -ethyl	3160
	($\pm$)-17 α -Ethinyl-18-homo	5370

Moreover ($\pm$) - 17 α - ethyl - 18 - homo - 17 β - hydroxy - oestr - 5(10) - en - 3 - one is 5 times as active as (+) 17 α - ethyl - 17 β - hydroxy - oestr - 5(10) - en - 3 - one as an oestrogen antagonist.

Progestational activity

Measurement of progestational activity by the Clauberg method of Elton and Edgren, *Endocrinology*, 1958, 63, 464, has given the following results.

40	Progesterone	100
	17 α -Substituted 19-nortestosterones	
	(+)-17 α -Ethyl	750
	(+)-17 α -Ethinyl	10
	($\pm$)-17 α -Ethyl-18-homo	500
	($\pm$)-17 α -Ethinyl-18-homo	100
45	($\pm$)-17 α -Ethinyl-18-nor-13 β -n-propyl	250
	($\pm$)-13 β -n-Butyl-17 α -ethinyl	25

Moreover it has been found that the ($\pm$)-17 α - ethinyl - 18 - homo and ($\pm$) - 17 α -ethinyl - 18 - nor - 13 β - n - propyl compounds will maintain pregnancy in spayed while the (+)-17 α -ethinyl compound will not do this.

(+) - 17 α - Ethinyl - 17 β - hydroxy - oestr - 5(10) - en - 3 - one is an important commercial progestational agent, but has a disadvantage in that it exhibits 7% of the oestrogenic activity of oestrone. It has been discovered that the valuable progestational agent

($\pm$) - 17 α - ethinyl - 18 - homo - 17 β -hydroxy - oestr - 5(10) - en - 3 - one has only 0.3% of the oestrogenic-metrotropic activity of oestrone, but has greater progestational activity than (+) - 17 α - ethinyl - 17 β - hydroxy - oestr - 5(10) - en - 3 - one.

Hypocholesterolemic activity

The injection of groups of adult male rats daily for 9 days with doses of 100, 300 and 1000 μ g. of ($\pm$) - 17 α - ethyl - 18 - homo - 19 - nortestosterone, followed by blood analysis on the 10th day showed cholesterol blood levels of 44, 39.6, and 42 mg.%, representing depression of blood cholesterol content by 87, 78 and 83% respectively as compared with controls.

Studies with ($\pm$) - 17 α - ethyl - 18 - homo - 19 - nortestosterone have demonstrated that it exhibits remarkably low toxicity when administered to animals. In this respect it shows advantages over the important commercial anabolic agent (+) - 17 α - ethyl - 19 - nortestosterone: the latter has an LD₅₀ of 430 mg./kg., while the 18-homo compound has been administered to mice in quantities up to 5 g./kg., either by oral or by intraperitoneal routes, without killing any. The administration of the 18-homo compound to rats over a period of 8 oestrous cycles resulted in no adverse effects on the reproductive potential (fertility and fecundity) of the rats.

It has thus been demonstrated that ($\pm$) - 17 α - ethyl - 18 - homo - 19 - nortestosterone is an outstanding anabolic agent with a very high anabolic potency, high anti-oestrogenic activity, low androgenic activity, strong progestational activity and blood-lipid concentration-reducing properties, and very low toxicity. It has also been found to exhibit no appreciable oestrogenic activity.

The invention is illustrated by the following Examples, in which temperatures are in $^{\circ}$ C., infrared absorption data (IR) refer to the positions of maxima given in cm.⁻¹, and ultraviolet absorption data (UV) refer to positions of maxima given in m μ , with figures in parentheses denoting molecular extinction coefficients at these wavelengths.

EXAMPLE 1

($\pm$) - 1,4 - Dihydro - 17 α - ethyl - 18 - homo - oestradiol 3 - methyl ether (5 g.) was stirred in methanol (430 cc.) containing water (87 cc.) and oxalic acid dihydrate (6.6 g.) until the solid had completely dissolved. Isolation by means of ether gave a crystalline product (4.55 g.), m.p. 126—34 $^{\circ}$, which after repeated recrystallisation from ethyl acetate gave ($\pm$) - 17 α - ethyl - 18 - homo - oestr - 5(10) - en - 17 β - ol - 3 - one, m.p. 142—3.5 $^{\circ}$; IR: 3450, 1710; (Found: C, 79.6; H, 10.1. C₂₁H₃₂O₂ requires C, 79.9; H, 10.2%).

EXAMPLE 2

To ($\pm$) - 1,4 - dihydro - 17 α - ethynyl-18 - homo - oestradiol 3 - methyl ether (0.6 g.) in methanol (30 cc.) was added a solution of oxalic acid dihydrate (0.46 g.) in water (6 cc.). After standing at room temperature for 45 minutes, ether (60 cc.) was added and the ether solution washed, dried and evaporated. The residual gum was dissolved in benzene (5 cc.) and chromatographed on an activated fuller's earth (50 g.): elution with light petroleum containing first a small and then a gradually increasing proportion of benzene gave a crystalline by-product, followed by the desired ($\pm$) - 17 α - ethynyl - 18 - homo-oestr - 5(10) - en - 17 β - ol - 3 - one, recrystallised from a mixture of light petroleum and ethyl acetate, as the pure compound (0.15 g.), m.p. 169—73°; IR: 3351, 3241, 1706.

EXAMPLE 3

($\pm$) - 17 α - Allyl - 1,4 - dihydro - 18 - homo - oestradiol 3 - methyl ether (1.5 g.) was suspended in methanol (50 cc.) and water (5 cc.). Oxalic acid (1 g.) was added followed by dioxan (20 cc.), and the mixture stirred until dissolution was complete and then for a further 20 minutes. Water was added gradually, and the precipitated material filtered, washed with water and dried. Recrystallisation from a mixture of ethyl acetate and *n*-hexane gave ($\pm$) - 17 α - allyl - 18 - homo - oestr - 5(10) - en - 17 β - ol - 3 - one (1 g.); UV: no selective absorption beyond 220; IR: 3400, 1640, 1610.

EXAMPLE 4

($\pm$) - 1,4 - Dihydro - 18 - homo - 17 α - propynyloestradiol 3 - methyl ether (4 g.) was suspended in methanol (200 cc.) and water (20 cc.). Oxalic acid (4 g.) was added, followed by dioxan (100 cc.) and the mixture stirred until dissolution was complete and then for a further 20 minutes. Water was added and the precipitated product filtered, washed with water and dried. Recrystallisation from a mixture of ethyl acetate and *n*-hexane gave ($\pm$) - 18 - homo - 17 α - (1 - propynyl)estr - 5(10) - en - 17 β - ol - 3 - one, m.p. 156—9°; UV: no selective absorption beyond 220; IR: 2200, 1710.

EXAMPLE 5

($\pm$) - 1,4 - Dihydro - 18 - homo - 17 α - (2 - methallyl) - oestradiol 3 - methyl ether (1.5 g.) was suspended in methanol (50 cc.) and water (5 cc.). Oxalic acid (1 g.) was added, followed by dioxan (20 cc.), and the mixture stirred until dissolution was complete and then for a further 30 minutes. Water was added and the product extracted with ether, the ethereal solution washed, dried and evaporated, and the residue recrystallised from a mixture of ethyl acetate and *n*-hexane to give ($\pm$) - 18 - homo - 17 α - (2 - methallyl)estr - 5(10) - en - 17 β - ol - 3 - one; U.V: no selective absorption beyond 220; IR: 3450, 1710, 1640, 970.

EXAMPLE 6

To ($\pm$) - 1,4 - dihydro - 17 α - methyl-18 - nor - 13 β - *n* - propyloestradiol 3 - methyl ether (0.3 g.) in methanol (30 cc.) was added a solution of oxalic acid dihydrate (0.46 g.) in water (6 cc.). After stirring at room temperature for 20 minutes solution was still not complete, and isopropanol (30 cc.) was added and stirring continued for 80 minutes: the product was then worked up with ether and recrystallised from a mixture of ether and hexane, giving ($\pm$) - 17 α - methyl - 18 - nor-13 β - *n* - propyloestr - 5(10) - en - (17 β -ol - 3 - one (0.2 g.), m.p. 158—63°; UV: no selective absorption beyond 220; IR: 1695 (carbonyl group).

EXAMPLE 7

To ($\pm$) - 1,4 - dihydro - 17 α - ethynyl-18 - nor - 13 β - *n* - propyloestradiol 3-methyl ether (0.24 g.) in methanol (40 cc.) was added a solution of oxalic acid dihydrate (0.58 g.) in water (7.6 cc.) and the mixture stirred for 90 minutes at room temperature under nitrogen. Water was added, the product was worked up with ether and the residue obtained purified by chromatography on a fuller's earth, and crystallised from cyclohexane and then from ethyl acetate, giving ($\pm$) - 17 α - ethynyl - 18 - nor-13 β - *n* - propyloestr - 5(10) - en - (17 β -ol) - 3 - one (0.037 g.), m.p. 201—5°; IR: 3440, 3250, 1710; (Found: C, 80.5; H, 8.6. C₂₂H₂₈O₂ requires C, 80.9; H, 9.3%).

EXAMPLE 8

($\pm$) - 1,4 - Dihydro - 18 - nor - 13 β - *n* - propyl - 17 α - propynyloestradiol 3 - methyl ether (2.5 g.) was stirred for 2 hours in methanol (80 cc.) containing water (10 cc.), oxalic acid dihydrate (1.75 g.) and tetrahydrofuran (60 cc.). The mixture was added to brine and the product extracted with ether. The washed and dried extracts were evaporated to give a residue, which was recrystallised from a mixture of ethyl acetate and *n*-hexane, yielding ($\pm$) - 18 - nor - 13 β - *n* - propyl - 17 α - (1 - propynyl)estra - 5(10)-en - 17 β - ol - 3 - one, m.p. 147—50°; (Found: C, 80.8; H, 9.4. C₂₃H₃₂O₂ requires C, 81.1; H, 9.5%).

EXAMPLE 9

($\pm$) - 13 β - *n* - Butyl - 1,4 - dihydro-17 α - ethynyl - 18 - noroestradiol 3 - methyl-ether (2 g.) was stirred in methanol (50 cc.) containing oxalic acid dihydrate (0.9 g.) and water (12 cc.) under nitrogen for 2 hours. The mixture was poured into water and extracted with ether. The washed and dried extracts were evaporated to a residue which was purified by chromatography on an activated fuller's earth and recrystallised from a mixture of ethyl acetate and *n*-hexane to give ($\pm$) - 13 β - *n* - butyl - 17 α - ethynyl - 18 - noroestr - 5(10) - en - 17 β - ol - 3 - one (0.75 g.), m.p. 160—4°; IR: 3480, 3250, 1720.

EXAMPLE 10

A solution of ($\pm$) - 1,4 - dihydro - 18-homo - 17 α methyl - oestradiol 3 - methyl ether (0.5 g.) in methanol (55 cc.) was heated under nitrogen to boiling and 3N hydrochloric acid (0.6 cc.) was added. The solution was allowed to cool to room temperature and kept under nitrogen for 3 hours: water was then added and the mixture ether-extracted. The washed and dried extracts were evaporated and the residue crystallised from a mixture of ether and hexane, and subsequently from benzene, yielding ($\pm$) - 18 - homo - 17 α - methyl - 19 - nortestosterone as a benzene solvate, which was freed from benzene by drying at 100° for 7 hours; giving the free compound (0.2 g.), m.p. 128—9°; UV: 240 (16,200); IR: 3390, 1663.

EXAMPLE 11

($\pm$) - 1,4 - Dihydro - 17 α - ethyl - 18-homo - oestradiol 3 - methyl ether (0.29 g.) was added to 15 cc. of a solution prepared by mixing concentrated hydrochloric acid (2.4 cc.), water (1.6 cc.) and methanol (36 cc.). The mixture was shaken for 10 minutes, during which the solid dissolved. After 2 hours the solution was poured into water (50 cc.) and the mixture ether-extracted. The washed, dried and evaporated extracts gave a crystalline residue (0.255 g.) which was recrystallised from a mixture of ethyl acetate and light petroleum, yielding ($\pm$) - 17 α - ethyl - 18-homo - 19 - nortestosterone (0.196 g.), m.p. 139—41°; UV: 240 (15,000); IR: 3500, 1665.

EXAMPLE 12

To ($\pm$) - 1,4 - dihydro - 17 α - ethynyl - 18 - homo - oestradiol 3 - methyl ether (0.7 g.) in methanol (36 cc.) was added water (1.6 cc.) and concentrated hydrochloric acid (2.4 cc.). After standing at room temperature for 2 hours ether was added, and the washed and dried ethereal solution was evaporated, yielding a gum which was dissolved in benzene (5 cc.) and the solution adsorbed on an activated fuller's earth (50 g.). Elution with light petroleum containing increasing proportions of benzene gave a crystalline by-product: further elution with benzene containing a small proportion of ether gave a crystalline product which was recrystallised from ethyl acetate, yielding ($\pm$) - 17 α - ethynyl - 18 - homo - 19 - nortestosterone (0.11 g.), m.p. 203—6°; IR: 3370, 3300, 1660.

EXAMPLE 13

A solution of ($\pm$) - 1,4 - dihydro - 18-homo - 17 α - *n* - propylloestradiol 3 - methyl ether (0.53 g.) in a mixture of methanol (22.5 cc.), 12N hydrochloric acid (1.5 cc.), and water (1.5 cc.) was kept under nitrogen for 2½ hours at room temperature: ice-water (75 cc.) was then added, the precipitated solid filtered off and dissolved in ether (50 cc.):

the ether solution was washed, dried and evaporated, giving a solid residue which was recrystallised repeatedly from ethyl acetate, yielding ($\pm$) - 18 - homo - 19 - nor - 17 α - *n* - propyltestosterone (0.23 g.), m.p. 132—4.5°; UV: 240 (15,900); IR: 3425, 1660, 1618; (Found: C, 79.8; H, 10.2. C₂₁H₃₀O₂ requires C, 79.5; H, 10.4%).

EXAMPLE 14

($\pm$) - 17 α - Allyl - 1,4 - dihydro - 18-homo - oestradiol 3 - methyl ether (2 g.) was suspended in a mixture of methanol (72 cc.), concentrated hydrochloric acid (4.8 cc.) and water (3.2 cc.), in an atmosphere of nitrogen. Dioxan (20 cc.) was added and the mixture stirred until dissolution was complete, and then for a further 20 minutes, after which water was added and the mixture extracted with ether. The ethereal solution was washed with saturated sodium bicarbonate solution and water, and dried. Evaporation of the solvent gave ($\pm$) - 17 α - allyl - 18 - homo - 19 - nortestosterone; UV: 240 (15,600); IR: 3400, 1660, 1610.

EXAMPLE 15

($\pm$) - 1,4 - Dihydro - 18 - homo - 17 α - propynyloestradiol 3 - methyl ether (1.5 g.) was suspended in methanol (36 cc.) and stirred with concentrated hydrochloric acid (2.4 cc.), water (1.6 cc.) and dioxan (10 cc.) until dissolution was complete, and then for a further 20 minutes. The product was precipitated by the addition of water, filtered, washed and dried. Recrystallisation from a mixture of ethyl acetate and *n*-hexane gave ($\pm$) - 18 - homo - 19 - nor - 17 α - (1 - propynyl)testosterone, m.p. 124—5°; UV: 240 (15,600); IR: 3300, 2190, 1660.

EXAMPLE 16

($\pm$) - 1,4 - Dihydro - 18 - homo - 17 α - (2 - methyl)loestradiol 3 - methyl ether (1.5 g.) was suspended in a mixture of methanol (36 cc.), concentrated hydrochloric acid (2.4 cc.), water (1.6 cc.) and dioxan (10 cc.). When the material had dissolved, water was added and the precipitate filtered and again stirred with methanol (36 cc.), concentrated hydrochloric acid (2.4 cc.) and water (1.6 cc.) for 20 minutes. Water was then added gradually and the precipitate filtered, washed with water, dried and recrystallised from a mixture of ethyl acetate and *n*-hexane and then from acetonitrile to give ($\pm$) - 18 - homo - 17 α - (2 - methyl) - 19 - nortestosterone (2 g.); UV: 240 (16,800); IR: 3450, 1670, 1610, 880.

EXAMPLE 17

($\pm$) - 1,4 - Dihydro - 17 α - methyl - 18-nor - 13 β - *n* - propylloestradiol 3 - methyl ether (1.0 g.) was shaken with 44 cc. of an aqueous methanolic hydrochloric acid solution similar to that of Example 2, and stirred for 2 hours: the mixture was then poured into

water and the product isolated by means of ether; purification by chromatography on silica gel (elution with ether) and recrystallisation from a mixture of ethyl acetate and hexane gave ($\pm$) - 18,19 - bisnor - 17 α - methyl-13 β - *n* - propyltestosterone (0.35 g.), m.p. 134—5.5°; UV: 240 (18,100); IR: 1660.

EXAMPLE 18

A mixture of ($\pm$) - 1,4 - dihydro - 17 α - ethyl - 18 - nor - 13 β - *n* - propyltestosterone (0.8 g.) in tetrahydrofuran (20 cc.), methanol (50 cc.), 12N hydrochloric acid (3.3 cc.) and water (2.2 cc.) was kept with stirring at room temperature for 2½ hours and then poured into sodium chloride solution: the mixture was extracted with ether and the extracts washed, dried and evaporated. The crystalline residue obtained (0.8 g.) was dissolved in a mixture (25 cc.) of equal volumes of benzene and hexane and chromatographed on silica gel: elution with a mixture of equal volumes of benzene and chloroform gave a crystalline material which was recrystallised from a mixture of benzene and light petroleum, giving a benzene solvate, m.p. 93—5°; recrystallisation of this material from a mixture of hexane and ethyl acetate gave the solvent free product, ($\pm$) - 18,19 - bisnor - 17 α - ethyl - 13 β - *n* - propyltestosterone (0.2 g.), m.p. 98—100°; UV: 240 (15,700); IR: 3415, 1660, 1619.

EXAMPLE 19

($\pm$) - 1,4 - Dihydro - 17 α - ethynyl - 18 - nor - 13 β - *n* - propyltestosterone 3 - methyl ether (0.31 g.) was shaken with a solution prepared by mixing concentrated hydrochloric acid (0.81 cc.), water (0.54 cc.) and methanol (12.15 cc.) until the solid dissolved. After addition of water, isolation with ether, purification by chromatography on neutral alumina and recrystallisation from cyclohexane gave ($\pm$) - 18,19 - bisnor - 17 α - ethynyl - 13 β - *n* - propyltestosterone (0.1 g.), m.p. 149—50.5°; UV: 240 (15,700); IR: 3345, 3265, 1655, 1623; (Found: C, 81.0; H, 9.3. C₂₂H₃₀O₂ requires C, 80.9; H, 9.3%).

EXAMPLE 20

($\pm$) - 13 β ,17 α - Bis - *n* - propyl - 1,4 - dihydro - 18 - noroestradiol 3 - methyl ether (1.07 g.) was stirred under nitrogen in methanol (50 cc.) containing water (2.5 cc.) and 11N hydrochloric acid (3.8 cc.) at room temperature for 2 hours. Water was then added and the product extracted with ether. Evaporation of the washed and dried extracts gave a residue which was purified by chromatography on alumina, followed by repeated recrystallisation from ethyl acetate, and by sublimation at 145°/0.003 mm. to give ($\pm$) - 18,19 - bisnor - 13 β ,17 α - bis - *n* - propyltestosterone (0.34 g.), m.p. 147—9°; UV: 241 (16,600); IR: 3440, 1660, 1610.

EXAMPLE 21

($\pm$) - 17 α - Allyl - 1,4 - dihydro - 19 - nor - 13 β - *n* - propyltestosterone (0.77 g.) was stirred under nitrogen in isopropyl alcohol (25 cc.) containing 11N hydrochloric acid (2.4 cc.) and water (1.6 cc.) for 2½ hours. The mixture was filtered, added to brine and the product then extracted with ether. The washed and dried extracts were evaporated to a residue which was purified by chromatography on an activated fuller's earth and then by recrystallisation from ethyl acetate to give ($\pm$) - 17 α - allyl - 18,19 - bisnor - 13 β - *n* - propyltestosterone, m.p. 135—7°; UV: 241 (17,500); IR: 3390, 1660, 1620; (Found: C, 80.4; H, 9.8. C₂₃H₃₁O₂ requires C, 80.65; H, 10.0%).

EXAMPLE 22

($\pm$) - 1,4 - Dihydro - 18 - nor - 13 β - *n* - propyl - 17 α - propynyltestosterone 3 - methyl ether (2.5 g.) was stirred under nitrogen with methanol (135 cc.) containing 11N hydrochloric acid (9 cc.) and water (6 cc.). After 2 hours isopropyl alcohol (35 cc.) was added and the stirring was continued for a further 30 minutes. The mixture was added to brine and the product extracted with ether. The washed and dried extracts were evaporated to a glassy residue which was taken up in benzene and chromatographed on an activated fuller's earth. Benzene containing 5% ether eluted a product which on recrystallisation from a mixture of ethyl acetate and *n*-hexane gave ($\pm$) - 18,19 - bisnor - 13 β - *n* - propyl - 17 α - (1 - propynyl)testosterone, m.p. 182—4°; UV: 240 (16,700); (Found: C, 80.95; H, 9.4. C₂₃H₃₂O₂ requires C, 81.1; H, 9.5%).

EXAMPLE 23

Using the procedure of Example 20, ($\pm$) - 1,4 - dihydro - 17 α - (2 - methallyl) - 18 - nor - 13 β - *n* - propyltestosterone 3 - methyl ether was hydrolysed with hydrochloric acid and the product was purified by chromatography on an activated fuller's earth and recrystallised from ethyl acetate to give ($\pm$) - 18,19 - bisnor - 17 α - (2 - methallyl) - 13 β - *n* - propyltestosterone, m.p. 141.5—3.5°; UV: 241 (16,700); IR: 3480, 1660, 1620; (Found: C, 80.8; H, 9.9. C₂₄H₃₀O₂ requires C, 80.85; H, 10.2%).

EXAMPLE 24

($\pm$) - 1,4 - Dihydro - 17 α - (1 - methallyl) - 18 - nor - 13 β - *n* - propyltestosterone 3 - methyl ether (1.5 g.) was stirred under nitrogen with methanol (90 cc.) containing 11N hydrochloric acid (9 cc.) and water (6 cc.). The mixture was added to brine and the product extracted with ether. The washed and dried extracts were evaporated to give ($\pm$) - 18,19 - bisnor - 17 α - (1 - methallyl) - 13 β - *n* - propyltestosterone; UV: 240 (13,500); IR: 910.

EXAMPLE 25

A solution of ($\pm$) - 13 β - *n* - butyl - 1,4-dihydro - 17 α - ethyl - 18 - nor - oestradiol 3 - methyl ether (1.05 g.) in a mixture of tetrahydrofuran (15 cc.), methanol (54 cc.), 12N hydrochloric acid (3.6 cc.) and water (2.4 cc.) was kept for 2 hours at room temperature and then poured into brine (350 cc.). Working up with ether gave a gum (1.0 g.), which was taken up in a mixture of light petroleum and benzene (25 cc.) and chromatographed on silica gel. Elution with benzene containing a small proportion of ether gave a crystalline by-product (0.1 g.); subsequent elution with a mixture of ether, benzene and chloroform (in the proportions 5:4:1 by volume) gave a crystalline product which was recrystallised from hexane, and subsequently from hexane containing a little ethyl acetate, yielding ($\pm$) - 18,19 - bisnor - 13 β - *n* - butyl - 17 α - ethyltestosterone (0.23 g.), m.p. 78–80°; UV: 240 (14,700); IR: 3470, 1668, 1619.

EXAMPLE 26

($\pm$) - 13 β - *n* - Butyl - 1,4 - dihydro - 17 α - ethynyl - 18 - noroestradiol 3 - methyl ether (2 g.) was hydrolysed using the procedure of Example 24 and the product was purified by chromatography on an activated fuller's earth and then by recrystallisation from a mixture of ether and *n*-hexane to give 13 β - *n* - butyl - 17 α - ethynyl - 18,19 - bisnortestosterone (0.71 g.), m.p. 159–63°; UV: 240 (15,900); IR: 1670; (Found: C, 80.8; H, 9.3. C₂₅H₃₂O₂ requires C, 81.1; H, 9.5%).

EXAMPLE 27

A mixture (0.05 g.) of ($\pm$) - 17 α - ethyl - 3,3 - ethylenedioxy - 18 - homo - oestr - 5 - en - 17 β - ol and ($\pm$) - 17 α - ethyl - 3,3 - ethylenedioxy - 18 - homo - oestr - 5(10) - en - 17 β - ol was hydrolysed in methanol with hydrochloric acid using the procedure of Example 11, and the product isolated with ether and recrystallised, yielding ($\pm$) - 17 α - ethyl - 18 - homo - 19 - nortestosterone (0.04 g.), m.p. 138–9°, undepressed on admixture with the product of Example 11; UV: 240 (16,100).

EXAMPLE 28

A mixture (0.15 g.) of ($\pm$) - 3,3 - ethylenedioxy - 17 α - ethynyl - 18 - homo - oestr - 5 - en - 17 β - ol and ($\pm$) - 3,3 - ethylenedioxy - 17 α - ethynyl - 18 - homo - oestr - 5(10) - en - 17 β - ol was hydrolysed in methanol with hydrochloric acid using the procedure of Example 11, and the product isolated with ether and recrystallised, yielding ($\pm$) - 17 α - ethynyl - 18 - homo - 19 - nortestosterone (0.09 g.), m.p. 206°, undepressed on admixture with the product of Example 12, UV: 240 (16,900).

EXAMPLE 29

($\pm$) - 3 - Ethoxy - 17 α - ethynyl - 18 - homo - oestra - 3,5 - dien - 17 β - ol (0.1 g.)

was stirred with methanol (10 cc.) containing concentrated hydrochloric acid (1 cc.) and the mixture allowed to stand at room temperature for 1 hour. Water was then added and the precipitate filtered off and recrystallised from a mixture of ethyl acetate and *n*-hexane, giving ($\pm$) - 17 α - ethynyl - 18 - homo - 19 - nortestosterone.

EXAMPLE 30

($\pm$) - 17 α - Ethyl - 18 - homo - oestr - 5(10) - en - 17 β - ol - 3 - one (12.2 g.) was stirred with a solution of methanol (442 cc.), water (22 cc.) and concentrated hydrochloric acid (30 cc.) and the mixture allowed to stand at room temperature for 2 hours. The product was precipitated by the addition of water and the reaction mixture extracted with ether. The washed and dried extracts were evaporated and the residue recrystallised from acetonitrile to give ($\pm$) - 17 α - ethyl - 18 - homo - 19 - nortestosterone (7.9 g.), m.p. 144–5°; UV: 240 (15,680); IR: 3420, 1670, 1610; (Found: C, 79.85; H, 10.05. C₂₁H₃₂O₃ requires C, 79.7; H, 10.2%).

EXAMPLE 31

($\pm$) - 17 α - Ethynyl - 18 - homo - oestr - 5(10) - en - 17 β - ol - 3 - one (0.1 g.) was stirred with a mixture of methanol (36 cc.), water (1.6 cc.) and concentrated hydrochloric acid (2.4 cc.) for 1 hour. Water was added, the product isolated with ether and recrystallised from a mixture of ether and *n*-hexane to give ($\pm$) - 17 α - ethynyl - 18 - homo - 19 - nortestosterone, m.p. 203–6°; IR: 3280, 2860, 1650, 1060.

EXAMPLE 32

($\pm$) - 17 α - Ethynyl - 18 - homo - 19 - nortestosterone (0.5 g.) in pyridine (20 cc.) containing a 2% palladium on calcium carbonate catalyst (0.15 g.) was shaken with hydrogen at atmospheric pressure until one molecular equivalent of hydrogen had been absorbed. Isolation with ether gave a product which was recrystallised from a mixture of ether and *n*-hexane and dried for 4 hours at 65°/0.005 mm. to give ($\pm$) - 18 - homo - 19 - nor - 17 α - vinyltestosterone, m.p. 108–11°; UV: 240 (15,200); IR: 920; (Found: C, 80.4; H, 9.7. C₂₁H₃₀O₂ requires C, 80.2; H, 9.6%).

EXAMPLE 33

($\pm$) - 17 α - Ethynyl - 18 - homo - 19 - nortestosterone (1 g.) in benzene (15 cc.) and ethanol (5 cc.) was added to a pre-reduced suspension of 2% palladium on calcium carbonate (0.3 g.) in benzene (10 cc.) and the mixture shaken in an atmosphere of hydrogen until 163 cc. (2.1 mols) of hydrogen had been absorbed. The catalyst was filtered, the solvent removed and the product (0.55 g.) in methanol (10 cc.) was shaken with a solution of sodium metabisulphite (1.7 g.) in water (8 cc.) for 5 minutes. Water was added and the product was

isolated with ether and recrystallised from acetone to give ($\pm$) - 17 α - ethyl - 18 - homo - 19 - nortestosterone (0.4 g.), m.p. 144°; UV: 241 (17,250); IR: 3440, 1670, 1620.

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EXAMPLE 34

($\pm$) - 17 α - Ethynyl - 18,19 - bisnor - 13 β - *n* - propyltestosterone (0.5 g.) was hydrogenated using the procedure of Example 32, and the product isolated and recrystallised in the same way as ($\pm$) - 18,19 - bisnor - 13 β - *n* - propyl - 17 α - vinyltestosterone (0.425 g.), m.p. 94—7°; UV: 240 (15,600); IR: 920; (Found: C, 81.1; H, 9.9. $C_{22}H_{32}O_2$ requires C, 80.4; H, 9.8%).

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EXAMPLE 35

($\pm$) - 17 α - Ethyl - 18 - homo - oestr - 5 - ene - 3,17 β - diol (0.1 g.), m.p. 178—82°; IR: 3330, 1640, 830, was dissolved in acetone (30 cc.) and some small pieces of solid carbon dioxide added. 8N Chromic acid solution was added dropwise until the colour of the acetone solution remained orange (3 drops): isopropanol (1 cc.) was then added. The mixture was shaken for 5 minutes with 10% aqueous sodium hydroxide (50 cc.), benzene (30 cc.) was added and the organic layer separated, washed, dried and evaporated. The residue was triturated with ether and the crystalline material remaining was recrystallised from ether to give ($\pm$) - 17 α - ethyl - 18 - homo - 19 - nortestosterone, m.p. 138—42°, undepressed on admixture with the substance prepared as in Example 11.

The pharmaceutical preparations of the invention are ones comprising a compound of the invention in association with a pharmaceutically acceptable carrier. Accordingly such a preparation is prepared by a process in which a compound of the invention is mixed or otherwise brought into association with a pharmaceutically acceptable carrier.

The pharmaceutically acceptable carrier can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. A solid carrier can be one or more substances which may also act as flavouring agents, solubilisers, lubricants, suspending agents, binders, or tablet-disintegrating agents: it can also be an encapsulating material. In powders the carrier is a finely divided solid which is in admixture with the finely divided compound. In the tablets the compound is mixed with carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from 5 or 10 to 99% of the active ingredient. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low melting wax, and cocoa butter. The term "preparation"

is intended to include the formulation of the compound with encapsulating material as carrier providing a capsule in which the compound (with or without other carriers) is surrounded by carrier, which is thus in association with it. Similarly, cachets are included. Tablets, powders, cachets and capsules can be used for oral administration.

Liquid form preparations include solutions, suspensions, and emulsions. The compounds are insoluble in water but can be dissolved in aqueous propylene glycol solutions for parenteral injection. They can also be formulated in solution in aqueous solutions of polythene glycol of molecular weight 400. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided compound in water with sodium carboxymethyl cellulose as suspending agent. Oily suspensions can be prepared by dispersing the finely-divided compound in arachis oil.

Preferably the pharmaceutical preparation is in unit dosage form. In such form, the preparation is sub-divided in unit doses containing appropriate quantities of the compound: the unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, for example packeted powders or vials or ampoules. The unit dosage form can be a capsule, cachet or tablet itself, or it can be the appropriate number of any of these in packaged form. The quantity of compound in a unit dose of preparation may be varied or adjusted from 1 mg. to 100 mg. (generally within the range of 2.5 to 25 mg.) according to the particular application and the potency of the active ingredient.

The invention is further illustrated by the following Examples describing pharmaceutical preparations.

EXAMPLE 36

A pharmaceutical tablet for use as an oral anabolic agent consists of the following ingredients:

	mg.	
($\pm$)-18-Homo-19-nor-17 α - <i>n</i> -propyltestosterone	10	
Carboxymethyl cellulose (viscosity 400 cps)	15	110
Lactose powder	25	
Redried corn starch	25	
Magnesium stearate powder	4	
Calcium silicate powder	q.s.	115
	200	

The tablet is prepared by dissolving the steroid in benzene, mixing the solution with the right proportion of starch, drying the mix in a current of air, adding the remaining ingredients in the correct proportions, mixing them and compressing the composition obtained into slugs, and finally regranulating and compress-

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ing into tablets such that each contains 10 mg. of steroid.

Alternatively the tablet is prepared by dissolving the steroid in benzene, mixing the solution with the lactose powder and drying the mix in a current of air, then adding the carboxymethyl cellulose, calcium silicate and half the starch. With the powder thus obtained is mixed starch paste prepared from the remainder of the starch, the mixture is wet-granulated, the granules dried, the stearate added and the composition compressed into tablets such that each contains 10 mg. of steroid.

EXAMPLE 37

- 15 A capsule for use as an oral anabolic agent contains, in encapsulating gelatine, the following ingredients:

	mg.
(±)-18-Homo-19-nor-17 α -n-propyl-testosterone	10
Finely divided silica lubricant	5
Magnesium stearate powder	5
Powdered corn starch	113
Lactose powder	q.s.

25 245

This is prepared by mixing the powder ingredients in the correct proportions and filling it into hard gelatine capsules such that each capsule contains 10 mg. of active ingredient.

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EXAMPLE 38

An anabolic agent suspension for oral use consists of the following ingredients per 5 cc.:

	mg.
(±)-18-Homo-19-nor-17 α -n-propyl-testosterone	10.0
Magnesium aluminium silicate (thickening agent)	37.5
Carboxymethyl cellulose of low viscosity	37.5
Polyoxyethylene sorbitan mono-laurate	50.0
Glycerol	250.0
Sucrose	2000.0
Methyl p-hydroxybenzoate	5.0
Propyl p-hydroxybenzoate	1.0
Flavour and distilled water	q.s.

The finely divided steroid is stirred into a vehicle prepared by mixing the other ingredients in correct proportion with water, and the final volume is adjusted so that each cc. contains 2 mg. of steroid.

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EXAMPLE 39

- 55 An anabolic agent suspension for parenteral use consists of the following ingredients per cc.:

	g.	
(±)-18-Homo-19-nor-17 α -n-propyltestosterone	0.001	
Benzyl alcohol	0.01	60
Sodium chloride	0.09	
Sodium carboxymethyl cellulose	0.005	
Polyoxyethylene sorbitan mono-oleate	0.004	
Water for injection	q.s.	65

The benzyl alcohol, sodium chloride, sodium carboxymethyl cellulose and polyoxyethylene sorbitan mono-oleate are mixed with water for injection and the mixture sterilised by autoclaving. The sterile steroid in finely divided form is then mixed with the vehicle in such quantity that each cc. contains 1.0 mg. of it.

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EXAMPLE 40

Pediatric drops for use as an anabolic agent consist of the following ingredients per drop (0.05 cc.):

	mg.	
(±)-18-Homo-19-nor-17 α -n-propyl testosterone	1.000	
Magnesium aluminium silicate (thickening agent)	0.375	80
Polyoxyethylene sorbitan mono-laurate	0.500	
Disodium phosphate heptahydrate	0.375	
Citric acid monohydrate	0.060	85
Glycerol	1.250	
Methyl p-hydroxybenzoate	0.025	
Propyl p-hydroxybenzoate	0.005	
Butyl p-hydroxybenzoate	0.020	
Distilled water	0.015	90
Sodium saccharin	0.013	
Sorbitol and flavour	q.s.	

A vehicle is prepared by mixing together all the ingredients except the steroids: the finely-divided steroid is then added, and the volume adjusted with sorbitol so that each 0.05 cc. contains 1.0 mg. steroid.

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EXAMPLE 41

A long-acting anabolic agent tablet consists of the following ingredients:

	mg.	
(±)-18-Homo-19-nor-17 α -n-propyl-testosterone	10	
Water-insoluble acid carboxy vinyl polymer of acrylic acid copolymerised with 0.75—2% of polyallyl sucrose	150	
Magnesium stearate powder	2	
Lactose	q.s.	
	200	110

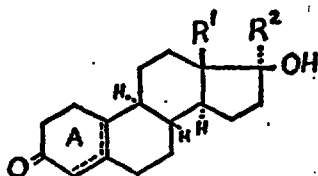
The steroid is compounded with the lactose and carboxy vinyl polymer and compressed into slugs: the composition is then granulated,

the stearate added, and the mixture compressed into tablets such that each contains 10 mg. of steroid.

- I disclaim the substances 17 α - ethyl - 18-homo - 19 - nortestosterone and 17 α - ethynyl - 18 - homo - 19 - nortestosterone except when prepared by the processes claimed below, and I disclaim pharmaceutical preparations containing them: these substances and preparations are described and claimed in Patent Specification No. 20453/66 (Serial No. 1,041,280).

Subject to the foregoing disclaimer, WHAT I CLAIM IS:—

1. A steroid ketone of the structure



- where R¹ is an alkyl group of at least 2 carbon atoms, R² is an unsubstituted alkyl, alkenyl or alkynyl group, or a substituted alkyl, alkenyl or alkynyl group having the essential character of an unsubstituted alkyl, alkenyl or alkynyl group (as hereinbefore defined) and ring A contains an ethylenic bond terminating at the 5-position.

2. A ketone according to Claim 1, in which R¹ and R² each contain not more than 6 carbon atoms.

3. A ketone according to Claim 1 or Claim 2, in which R¹ is an ethyl group.

4. A ketone according to Claim 1 or Claim 2, in which R¹ is an *n*-propyl group.

5. A ketone according to Claim 1 or Claim 2, in which R¹ is an *n*-butyl group.

6. A ketone according to any preceding claim, in which R² is a substituted or unsubstituted alkyl group.

7. A ketone according to any one of Claims 1 to 5, in which R² is a substituted or unsubstituted alkenyl group.

8. A ketone according to any one of Claims 1 to 5, in which R² is a substituted or unsubstituted alkynyl group.

9. A ketone according to any one of Claims 1 to 8, in which R² has from 1 to 4 carbon atoms.

10. A ketone according to any one of Claims 1 to 8, in which R² has 1 or 2 carbon atoms.

11. A ketone according to any preceding claim, in which R² is an unsubstituted alkyl, alkenyl or alkynyl group.

12. A ketone according to any one of Claims 1 to 5, in which R² is an ethyl group.

13. A ketone according to any one of Claims 1 to 3 and 5, in which R² is a substituted or unsubstituted ethynyl group.

14. A ketone according to any one of Claims 1 to 5, in which R² is a methyl, vinyl, *n*-

propyl, allyl, 1-propynyl or 1- or 2-methallyl group.

15. A ketone according to any preceding claim, having the ethylenic bond in the 5(10)-position.

16. A ketone according to any one of Claims 1 to 14, having the ethylenic bond in the 4,5-position.

17. 17 α - Ethyl - 18 - homo - oestr - 5(10)-en - 17 β - ol - 3 - one.

18. 17 α - Ethynyl - 18 - homo - oestr - 5(10) - en - 17 β - ol - 3 - one.

19. 17 α - Allyl - 18 - homo - oestr - 5(10)-en - 17 β - ol - 3 - one.

20. 17 α - (1 - Propynyl) - 18 - homo - oestr - 5(10) - en - 17 β - ol - 3 - one.

21. 17 α - (2 - Methallyl) - 18 - homo - oestr - 5(10) - en - 17 β - ol - 3 - one.

22. 17 α - Methyl - 18 - nor - 13 β - *n*-propyloestr - 5(10) - en - 17 β - ol - 3 - one.

23. 17 α - Ethynyl - 18 - nor - 13 β - *n*-propyloestr - 5(10) - en - 17 β - ol - 3 - one.

24. 18 - Nor - 13 β - *n*-propyl - 17 α - (1-propynyl) oestr - 5(10) - en - 17 β - ol - 3 - one.

25. 13 β - *n*-Butyl - 17 α - ethynyl - 18-nor oestr - 5(10) - en - 17 β - ol - 3 - one.

26. 18 - Homo - 17 α - methyl - 19 - nortestosterone.

27. 18 - Homo - 17 α - vinyl - 19 - nortestosterone.

28. 17 α - Allyl - 18 - homo - 19 - nortestosterone.

29. 18 - Homo - 17 α - (1 - propynyl) - 19 - nortestosterone.

30. 18 - Homo - 17 α - (2 - methallyl) - 19 - nortestosterone.

31. 18 - Homo - 19 - nor - 17 α - *n*-propyltestosterone.

32. 18,19 - Bisnor - 17 α - methyl - 13 β - *n*-propyltestosterone.

33. 18,19 - Bisnor - 17 α - ethyl - 13 β - *n*-propyltestosterone.

34. 18,19 - Bisnor - 13 β - *n*-propyl - 17 α - vinyltestosterone.

35. 18,19 - Bisnor - 13 β ,17 α - bis - *n*-propyltestosterone.

36. 17 α - Allyl - 18,19 - bisnor - 13 β - *n*-propyltestosterone.

37. 18,19 - Bisnor - 13 β - *n*-propyl - 17 α - (1 - propynyl) testosterone.

38. 18,19 - Bisnor - 17 α - (1 - methallyl) - 13 β - *n*-propyltestosterone.

39. 18,19 - Bisnor - 17 α - (2 - methallyl) - 13 β - *n*-propyltestosterone.

40. 18,19 - Bisnor - 13 β - *n*-butyl - 17 α - ethyltestosterone.

41. 18,19 - Bisnor - 13 β - *n*-butyl - 17 α - ethynyltestosterone.

42. A steroid compound according to Claim 1 substantially as described herein and shown with reference to any one of Examples 2, 6, 7, 10, 13, 17, 18 and 25.

43. A steroid compound according to Claim 1 substantially as described herein and shown with reference to Example 11 or Example 12.

44. A steroid compound according to Claim

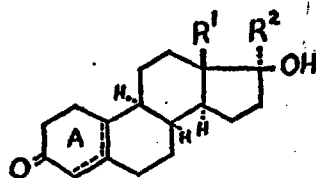


the stearate added, and the mixture compressed into tablets such that each contains 10 mg. of steroid.

- 5 I disclaim the substances 17 α - ethyl - 18-homo - 19 - nortestosterone and 17 α - ethynyl - 18 - homo - 19 - nortestosterone except when prepared by the processes claimed below, and I disclaim pharmaceutical preparations containing them: these substances and preparations
- 10 are described and claimed in Patent Specification No. 20453/66 (Serial No. 1,041,280).

Subject to the foregoing disclaimer, WHAT I CLAIM IS:—

- 15 1. A steroid ketone of the structure



- where R¹ is an alkyl group of at least 2 carbon atoms, R² is an unsubstituted alkyl, alkenyl or alkynyl group, or a substituted alkyl, alkenyl or alkynyl group having the essential character of an unsubstituted alkyl, alkenyl or alkynyl group (as hereinbefore defined) and ring A contains an ethylenic bond terminating at the 5-position.
- 20 2. A ketone according to Claim 1, in which R¹ and R² each contain not more than 6 carbon atoms.
3. A ketone according to Claim 1 or Claim 2, in which R¹ is an ethyl group.
- 30 4. A ketone according to Claim 1 or Claim 2, in which R¹ is an *n*-propyl group.
5. A ketone according to Claim 1 or Claim 2, in which R¹ is an *n*-butyl group.
6. A ketone according to any preceding claim, in which R² is a substituted or unsubstituted alkyl group.
7. A ketone according to any one of Claims 1 to 5, in which R² is a substituted or unsubstituted alkenyl group.
- 40 8. A ketone according to any one of Claims 1 to 5, in which R² is a substituted or unsubstituted alkynyl group.
9. A ketone according to any one of Claims 1 to 8, in which R² has from 1 to 4 carbon atoms.
- 45 10. A ketone according to any one of Claims 1 to 8, in which R² has 1 or 2 carbon atoms.
11. A ketone according to any preceding claim, in which R² is an unsubstituted alkyl, alkenyl or alkynyl group.
- 50 12. A ketone according to any one of Claims 1 to 5, in which R² is an ethyl group.
13. A ketone according to any one of Claims 1 to 3 and 5, in which R² is a substituted or unsubstituted ethynyl group.
- 55 14. A ketone according to any one of Claims 1 to 5, in which R² is a methyl, vinyl, *n*-

propyl, allyl, 1-propynyl or 1- or 2-methallyl group.

15. A ketone according to any preceding claim, having the ethylenic bond in the 5(10)-position.

16. A ketone according to any one of Claims 1 to 14, having the ethylenic bond in the 4,5-position.

17. 17 α - Ethyl - 18 - homo - oestr - 5(10)-en - 17 β - ol - 3 - one.

18. 17 α - Ethynyl - 18 - homo - oestr - 5(10) - en - 17 β - ol - 3 - one.

19. 17 α - Allyl - 18 - homo - oestr - 5(10)-en - 17 β - ol - 3 - one.

20. 17 α - (1 - Propynyl) - 18 - homo - oestr - 5(10) - en - 17 β - ol - 3 - one.

21. 17 α - (2 - Methallyl) - 18 - homo - oestr - 5(10) - en - 17 β - ol - 3 - one.

22. 17 α - Methyl - 18 - nor - 13 β - *n*-propyloestr - 5(10) - en - 17 β - ol - 3 - one.

23. 17 α - Ethynyl - 18 - nor - 13 β - *n*-propyloestr - 5(10) - en - 17 β - ol - 3 - one.

24. 18 - Nor - 13 β - *n*-propyl - 17 α - (1-propynyl)oestr - 5(10) - en - 17 β - ol - 3 - one.

25. 13 β - *n*-Butyl - 17 α - ethynyl - 18-noroestr - 5(10) - en - 17 β - ol - 3 - one.

26. 18 - Homo - 17 α - methyl - 19 - nortestosterone.

27. 18 - Homo - 17 α - vinyl - 19 - nortestosterone.

28. 17 α - Allyl - 18 - homo - 19 - nortestosterone.

29. 18 - Homo - 17 α - (1 - propynyl) - 19-nortestosterone.

30. 18 - Homo - 17 α - (2 - methallyl) - 19-nortestosterone.

31. 18 - Homo - 19 - nor - 17 α - *n*-propyltestosterone.

32. 18,19 - Bisnor - 17 α - methyl - 13 β -*n* - propyltestosterone.

33. 18,19 - Bisnor - 17 α - ethyl - 13 β -*n* - propyltestosterone.

34. 18,19 - Bisnor - 13 β - *n*-propyl - 17 α -vinyltestosterone.

35. 18,19 - Bisnor - 13 β ,17 α - bis - *n*-propyltestosterone.

36. 17 α - Allyl - 18,19 - bisnor - 13 β - *n*-propyltestosterone.

37. 18,19 - Bisnor - 13 β - *n*-propyl - 17 α - (1 - propynyl)testosterone.

38. 18,19 - Bisnor - 17 α - (1 - methallyl)-13 β - *n*-propyltestosterone.

39. 18,19 - Bisnor - 17 α - (2 - methallyl)-13 β - *n*-propyltestosterone.

40. 18,19 - Bisnor - 13 β - *n*-butyl - 17 α -ethyltestosterone.

41. 18,19 - Bisnor - 13 β - *n*-butyl - 17 α -ethynyltestosterone.

42. A steroid compound according to Claim 1 substantially as described herein and shown with reference to any one of Examples 2, 6, 7, 10, 13, 17, 18 and 25.

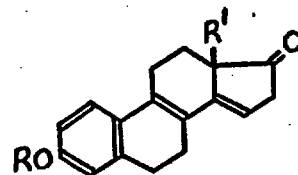
43. A steroid compound according to Claim 1 substantially as described herein and shown with reference to Example 11 or Example 12.

44. A steroid compound according to Claim

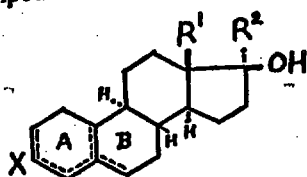
1 substantially as described herein and shown with reference to any one of Examples 1, 3 to 5, 8, 9, 14 to 16, 20 to 24, 26, 32 and 34.

5 45. The racemate of a ketone according to any one of Claims 1 to 43 and its 13 α enantiomer.

46. A process for preparing a steroid ketone according to any one of Claims 1 to 43 and 45, in which there is hydrolysed a corresponding compound of the structure



where R is an alkyl group, is selectively reduced (a) by hydrogenation in solution in a non-protonic solvent using a palladium or Raney nickel catalyst until sufficient hydrogen has been absorbed for saturation of the 14,15-ethylenic bond, (b) by a carbonyl-reducing ethylenic bond, (c) by the action of a hydroxymethylene group, (d) by the action of alkali metal in liquid ammonia after the catalytic hydrogenation and simultaneously with or after the carbonyl-reducing step, to saturate the 8,9-ethylenic bond, and (e) by the action of alkali metal in liquid ammonia in the presence of a proton donor that is an alcohol having less than 6 carbon atoms, simultaneously with or after the saturation of the 8,9-ethylenic bond, to give a compound of the structure



where X is an acid-hydrolysable protected 3-oxo group which is accompanied by an ethylenic bond terminating at the 5-position, with or without a second ethylenic bond terminating at the 3-position.

47. A process according to Claim 46, where X represents a divalent organic radical linked to ring A by two oxygen or sulphur atoms, or one oxygen and one sulphur atom, and rings A and B have a single ethylenic bond terminating at the 5-position.

48. A process according to Claim 46, where X represents a monovalent organic radical linked to ring A by an oxygen or sulphur atom, or one divalent or two monovalent organic radicals linked to ring A by a nitrogen atom, and rings A and B have two ethylenic bonds, one of which terminates at the 5-position and the other at the 3-position.

49. A process according to Claim 48, in which the compound hydrolysed is a 3-alkoxy-2,5(10)-diene.

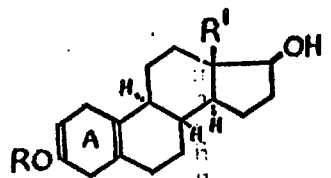
50. A process according to Claim 49, in which hydrolysis is carried out under mild acid conditions and the product is a 5,10-ethylenic 3-ketone.

51. A process according to Claim 49, in which hydrolysis is carried out under vigorous acid conditions and the product is a 4,5-ethylenic 3-ketone.

52. A process according to Claim 47, in which the compound hydrolysed is a 3,3-alkylene-5- or -5(10)-ene.

53. A process according to Claim 47, in which the compound hydrolysed is a 3-alkoxy-3,5(6)- or -3,5(10)-diene.

54. A process for the preparation of a steroid ketone according to any one of Claims

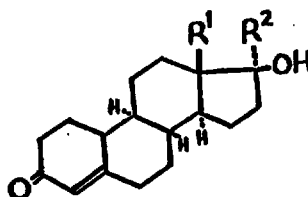


which is then selectively oxidised to convert the hydroxymethylene group to a carbonyl group without rearomatisation of ring A; the resulting ketone and an organometallic reagent containing the group R² are reacted together to introduce the group R² at the 17 α -position with formation of a 17 β -hydroxy group, and the product is finally hydrolysed.

55. A process according to Claim 54, where R is a methyl group.

56. A process according to Claim 54 or Claim 55, in which the carbonyl-reducing reagent is sodium borohydride and the selective oxidation is carried out under Oppenauer conditions.

57. A process for the preparation of a steroid ketone of the structure

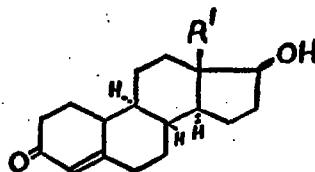
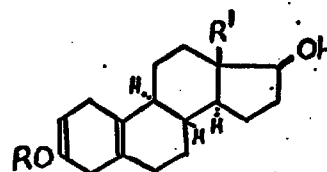




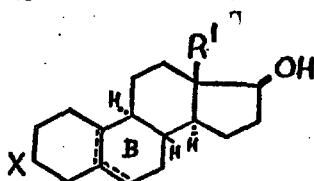
where R^1 is an alkyl group of at least 2 carbon atoms and R^2 is an ethynyl group, in which a

corresponding compound of either of the structures

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where R is an alkyl group, is ketalised with an alkylene glycol to give a compound of the structure



- 10 where X is an alkylendioxy group and ring B has an ethylenic bond terminating at the 5-position, this is then oxidised to convert the hydroxymethylene group to a carbonyl group, the resulting 17-ketone is reacted with an organometallic ethynylating agent to introduce the group R^2 at the 17α -position with formation of a 17β -hydroxy group, and the product is finally hydrolysed.

- 15
20 58. A process according to Claim 57, where the starting material is the 4,5-ethylenic 3-ketone.

59. A process according to Claim 57, where

the starting material is the 3-enol ether in which R is a methyl group.

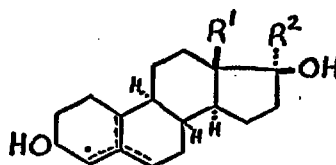
60. A process according to any one of Claims 57 to 59, where R^1 is an ethyl group.

61. A process according to any one of Claims 57 to 60, in which the ketalisation is effected with ethylene glycol and toluene-*p*-sulphonic acid, and the resulting 17-alcohol is oxidised with chromic acid or under Oppenauer conditions.

62. A process for preparing a 4,5-ethylenic steroid ketone according to any one of Claims 1 to 14 and 26 to 43, in which a corresponding 5,10-ethylenic ketone is isomerised.

63. A process for preparing a steroid ketone according to any one of Claims 1 to 7, in which a corresponding ketone whose group R^2 has a greater degree of unsaturation is selectively reduced.

64. A process for preparing a steroid ketone according to any one of Claims 1 to 43 and 45, in which a corresponding diol of the structure



- 50 having an ethylenic bond terminating at the 5-position is oxidised, and where the starting material contains an ethylenic bond at the 5,6-position, the ethylenic bond is conjugated with the carbonyl group formed.

- 55 65. A process according to any one of Claims 46 to 56, and 62 to 64, in which the steroid ketone prepared is 17α -ethyl-18-homo-19-nortestosterone.

66. A process according to any one of Claims 46 to 62 and 64, in which the steroid ketone prepared is 17α -ethynyl-18-homo-19-nortestosterone.

- 60 67. A process for preparing a steroid ketone according to Claim 1 substantially as described in any one of Examples 2, 6, 7, 10 to 13, 17 to 19 and 25.

- 65 68. A process according to any one of Claims 46 to 66, substantially as described herein and shown with reference to any one of Examples 2, 6, 7, 10 to 13, 17 to 19 and 25.

69. A process for preparing a steroid ketone according to Claim 1 substantially as described in any one of Examples 1, 3 to 5, 8, 9, 14 to 16, 20 to 24, and 26 to 35.

70. A process according to any one of Claims 46 to 66, substantially as described herein and shown with reference to any one of Examples 1, 3 to 5, 8, 9, 14 to 16, 20 to 24, and 26 to 35.

71. A steroid ketone according to Claim 1 which has been obtained by a process according to any one of Claims 46 to 68.

72. A steroid ketone according to Claim 1 which has been obtained by a process according to Claim 69 or Claim 70.

73. A pharmaceutical preparation comprising a steroid ketone according to any one of Claims 1 to 16, in association with a pharmaceutically acceptable carrier.

74. A pharmaceutical preparation comprising a steroid ketone of any one of Claims 17 to 25, or the racemate with its 13α enantiomer,

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in association with a pharmaceutically acceptable carrier.

tially as described in any one of Examples 36 to 41.

75. A pharmaceutical preparation comprising a steroid ketone of any one of Claims 26 to 41, or the racemate with its 13 α enantiomer, in association with a pharmaceutically acceptable carrier.

76. A pharmaceutical preparation substan-

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ERRATA

SPECIFICATION No. 1,041,279
Amendment No. 1

Page 2, line 102, for "materals" read
"materials"

Page 2, line 107, for "compounds" read
"compounds")

Page 3, line 53, for "71a" read "17a"

Page 7, line 50, after "spayed" insert "rats"

Page 8, line 17, for "light" read "light"

Page 10, line 110, after "(Found" insert
"colon"

THE PATENT OFFICE
23rd December 1966

