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1,041,280

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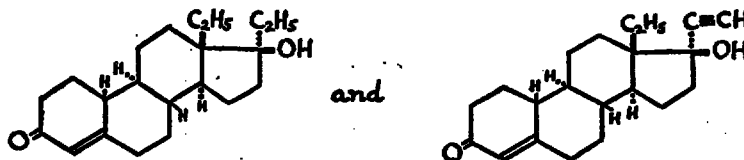
COMPLETE SPECIFICATION

17 α -Ethyl- and 17 α -Ethynyl-18-Homo-19-Nortestosterones

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 relates to steroid ketones having a 13-ethyl group, and to pharmaceutical preparations containing them.

The steroid ketones of this invention are two specific compounds that are members of the class of steroid ketones described and claimed in Patent Specification 37618/61 (Serial No. 1041279). The compounds concerned are 17 α -ethyl-18-homo-19-nortestosterone and 17 α -ethynyl-18-homo-19-nortestosterone, which have the structures



respectively.

These substances, which have the 9 α ,8 β ,14 α ,13 β ,17 β -OH, 17 α -ethyl or -ethynyl configuration, can be prepared by the process described and claimed in Specification 37618/61 (Serial No. 1041279) and in the product of their total synthesis which has not included a suitable resolution stage will be present in equimolecular mixture or racemate form with the corresponding 13 α enantiomers. 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 13 β configuration is considered as the *d*-form and its antipode the enantiomer of 13 α 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 13 α antipodes and where in this specification a designation is used indicating a 13 β compound, either inherently, as in the names of the compounds given above, or expressly, as in the above structures, 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 13 α enantiomer.

($\pm$)-17 α -Ethyl-18-homo-19-nortestosterone has a melting point of 144—5°C. and ($\pm$)-17 α -ethynyl-18-homo-19-nortestosterone has one of 203—6°C. in the purified state. Typical methods for their preparation are as follows, but others are also described in Specification 37618/61 (Serial No. 1041279).

Preparation of 17 α -ethyl-18-homo-19-nortestosterone

($\pm$)-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,

[Price 4s. 6d.]

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°; ultraviolet absorption: 240 m μ (ϵ 15,680); infrared absorption: 3420, 1670, 1610 cm⁻¹.

Preparation of 17 α -ethynyl-18-homo-19-nortestosterone

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 absorbed 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°; infrared absorption: 3370, 3300, 1660 cm⁻¹.

17 α -Ethyl-18-homo-19-nortestosterone is a highly potent anabolic agent with high anti-oestrogenic activity, low androgenic activity, no appreciable oestrogenic activity, strong progestational activity and blood-lipid concentration reducing properties, and very low toxicity. 17 α -Ethynyl-18-homo-19-nortestosterone is a highly potent progestational agent with high anti-oestrogenic activity and blood-lipid concentration reducing properties.

Anabolic and androgenic activity

The anabolic (myotrophic activity of ($\pm$)-17 α -ethyl-18-homo-19-nortestosterone and, for comparison, of (+)-17 α -ethyl-19-nortestosterone (a commercial anabolic agent) have 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 compound 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 ($\pm$)-17 α -ethyl-18-homo-19-nortestosterone and (+)-17 α -ethyl-19-nortestosterone determined were as follows:

	Anabolic potency	Androgenic potency	Ratio
(+)-19-Nortestosterone	60	4	15
(+)-17 α -Ethyl-19-nortestosterone	85	12	7
($\pm$)-17 α -Ethyl-18-homo-19-nortestosterone	340	17	20

The anabolic and androgenic potencies of the active (+)-enantiomers in the racemates are of course correspondingly higher. 19-Nortestosterone is orally inactive, while ($\pm$)-17 α -ethyl-18-homo-19-nortestosterone is 10% as potent orally as it is parenterally.

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. In order to account for this factor, dose-response curves have been analysed in the following way. It is assumed that (a) all doses of compound above the point where the levator and 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 and 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 -Ethyl-19-nortestosterone	17	8.6	42.2	28
($\pm$)-17 α -Ethyl-18-homo-19-nortestosterone	20	7.7	48	46

Further tests on the effect of ($\pm$)-17 α -ethyl-18-homo-19-nortestosterone 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.

Progesterone	100
(+)-19-Nortestosterone	200
(+)-17 α -Ethyl-19-nortestosterone	2100
(+)-17 α -Ethynyl-19-nortestosterone	910
($\pm$)-17 α -Ethyl-18-homo-19-nortestosterone	3160
($\pm$)-17 α -Ethynyl-18-homo-19-nortestosterone	5370

Progestational activity

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

Progesterone	100
(+)-17 α -Ethyl-19-nortestosterone	750
(+)-17 α -Ethynyl-19-nortestosterone	10
($\pm$)-17 α -Ethyl-18-homo-19-nortestosterone	500
($\pm$)-17 α -Ethynyl-18-homo-19-nortestosterone	100

Moreover it has been found that the ($\pm$)-17 α -ethynyl-18-homo-19-nortestosterone will maintain pregnancy in spayed rats, while (+)-17 α -ethynyl-19-nortestosterone will not do this.

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 tenth 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 5g./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.

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 either be 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 polyethylene 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 25 mg. according to the particular application.

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

EXAMPLE 1

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

	mg.
($\pm$)-17 α -Ethyl-18-homo-19-nortestosterone	5
Carboxymethyl cellulose (viscosity 400 cps)	15
Lactose powder	25
Redried corn starch	25
Magnesium stearate powder	4
Calcium silicate powder	q.s.
	<hr/>
	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 com-

position obtained into slugs, and finally regranulating and compressing into tablets such that each contains 5 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 5 mg. of steroid.

EXAMPLE 2

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

	mg.
(±)-17 α -Ethyl-18-homo-19-nortestosterone	5
Finely divided silica lubricant	5
Magnesium stearate powder	5
Powdered corn starch	113
Lactose powder	q.s.
	<hr/> 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 5 mg. of active ingredient.

EXAMPLE 3

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

	mg.
(±)-17 α -Ethyl-18-homo-19-nortestosterone	5.0
Magnesium aluminium silicate (thickening agent)	37.5
Carboxymethyl cellulose of low viscosity	37.5
Polyoxyethylene sorbitan monolaurate	50.0
Glycerol	250.0
Sucrose	2000.0
Methyl <i>p</i> -hydroxybenzoate	5.0
Propyl <i>p</i> -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 1 mg. of steroid.

EXAMPLE 4

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

	g.
(±)-17 α -Ethyl-18-homo-19-nortestosterone	0.0005
Benzyl alcohol	0.01
Sodium chloride	0.09
Sodium carboxymethyl cellulose	0.005
Polyoxyethylene sorbitan mono-oleate	0.004
Water for injection	q.s.

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 0.5 mg. of it.

EXAMPLE 5

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

	mg.
(±)-17 α -Ethyl-18-homo-19-nortestosterone	0.500
Magnesium aluminium silicate (thickening agent)	0.375

		mg.	
	Polyoxyethylene sorbitan monolaurate	0.500	
	Disodium phosphate heptahydrate	0.375	
	Citric acid monohydrate	0.060	
5	Glycerol	1.250	5
	Methyl <i>p</i> -hydroxybenzoate	0.025	
	Propyl <i>p</i> -hydroxybenzoate	0.005	
	Butyl <i>p</i> -hydroxybenzoate	0.020	
	Distilled water	0.015	
10	Sodium saccharin	0.013	10
	Sorbitol and flavour	q.s.	

A vehicle is prepared by mixing together all the ingredients except the steroid: the finely divided steroid is then added, and the volume adjusted with sorbitol so that each 0.05 cc. contains 0.5 mg. steroid.

EXAMPLE 6

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

	(±)-17 α -Ethyl-18-homo-19-nortestosterone	mg.	
		5	
20	Water-insoluble acid carboxy vinyl polymer of acrylic acid copolymerised with 0.75—2% of polyallyl sucrose	150	20
	Magnesium stearate powder	2	
	Lactose	q.s.	
		<hr/> 200	

25 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 5 mg. of steroid. **25**

EXAMPLE 7

30 A tablet for use as a progestational agent is prepared as in Example 1, but using (±)-17 α -ethynyl-18-homo-19-nortestosterone (5 mg.) as the active ingredient instead of the corresponding 17 α -ethyl compound. 30

EXAMPLE 8

A capsule for use as a progestational agent is prepared as in Example 2, but using (±)-17 α -ethynyl-18-homo-19-nortestosterone (5 mg.) as the active ingredient instead of the corresponding 17 α -ethyl compound.

EXAMPLE 9

An oral suspension for use as a progestational agent is prepared as in Example 3, but using ($\pm$)-17 α -ethynyl-18-homo-19-nortestosterone (5 mg.) as the active ingredient instead of the corresponding 17 α -ethyl compound.

WHAT I CLAIM IS:—

1. 17 α -Ethyl or 17 α -ethynyl-18-homo-19-nortestosterone.
2. 17 α -Ethyl-18-homo-19-nortestosterone.
3. 17 α -Ethynyl-18-homo-19-nortestosterone.
4. The racemate of the steroid ketone of Claim 2 and its 13 α enantiomer.
5. The racemate of the steroid ketone of Claim 3 and its 13 α enantiomer.
6. A pharmaceutical preparation comprising the steroid ketone of Claim 2 or Claim 4 in association with a pharmaceutically acceptable carrier.
7. A pharmaceutical preparation comprising the steroid ketone of Claim 3 or Claim 5 in association with a pharmaceutically acceptable carrier.
8. A pharmaceutical preparation substantially as described herein and shown with reference to any one of Examples 1 to 9.

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		mg.	
	Polyoxyethylene sorbitan monolaurate	0.500	
	Disodium phosphate heptahydrate	0.375	
	Citric acid monohydrate	0.060	
5	Glycerol	1.250	5
	Methyl <i>p</i> -hydroxybenzoate	0.025	
	Propyl <i>p</i> -hydroxybenzoate	0.005	
	Butyl <i>p</i> -hydroxybenzoate	0.020	
	Distilled water	0.015	
10	Sodium saccharin	0.013	10
	Sorbitol and flavour	q.s.	

A vehicle is prepared by mixing together all the ingredients except the steroid: the finely divided steroid is then added, and the volume adjusted with sorbitol so that each 0.05 cc. contains 0.5 mg. steroid.

15 **EXAMPLE 6** 15

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

		mg.	
	(±)-17 α -Ethyl-18-homo-19-nortestosterone	5	
20	Water-insoluble acid carboxy vinyl polymer of acrylic acid copolymerised with 0.75—2% of polyallyl sucrose	150	20
	Magnesium stearate powder	2	
	Lactose	q.s.	
		<hr/> 200	

25 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 5 mg. of steroid. 25

EXAMPLE 7

30 A tablet for use as a progestational agent is prepared as in Example 1, but using (±)-17 α -ethynyl-18-homo-19-nortestosterone (5 mg.) as the active ingredient instead of the corresponding 17 α -ethyl compound. 30

EXAMPLE 8

35 A capsule for use as a progestational agent is prepared as in Example 2, but using (±)-17 α -ethynyl-18-homo-19-nortestosterone (5 mg.) as the active ingredient instead of the corresponding 17 α -ethyl compound. 35

EXAMPLE 9

40 An oral suspension for use as a progestational agent is prepared as in Example 3, but using (±)-17 α -ethynyl-18-homo-19-nortestosterone (5 mg.) as the active ingredient instead of the corresponding 17 α -ethyl compound. 40

WHAT I CLAIM IS:—

1. 17 α -Ethyl or 17 α -ethynyl-18-homo-19-nortestosterone.
2. 17 α -Ethyl-18-homo-19-nortestosterone.
3. 17 α -Ethynyl-18-homo-19-nortestosterone.
4. The racemate of the steroid ketone of Claim 2 and its 13 α enantiomer.
- 45 5. The racemate of the steroid ketone of Claim 3 and its 13 α enantiomer. 45
6. A pharmaceutical preparation comprising the steroid ketone of Claim 2 or Claim 4 in association with a pharmaceutically acceptable carrier.
7. A pharmaceutical preparation comprising the steroid ketone of Claim 3 or Claim 5 in association with a pharmaceutically acceptable carrier.
- 50 8. A pharmaceutical preparation substantially as described herein and shown with reference to any one of Examples 1 to 9. 50

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