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NEW CONTRACEPTIVE KIT

(a) Field of the Invention

The invention is in the field of hormonal contraception and pertains to a contraceptive kit comprising means for the daily administration of a contraceptive agent. The invention also pertains to certain steroid compounds having an outstanding profile of biological properties with respect to use as contraceptive agents. More particularly, the invention pertains to compounds having such a profile as to make them suitable for use in anticonception by "monotherapy," i.e. by administering to a female of child-bearing age a single active substance which on its own possesses the required activity for preventing pregnancy.

(b) Background of the Invention

Many conventional contraceptive kits provide for the administration to a female of child-bearing age of two different agents, usually a progestagen and an estrogen. Depending on the specific kit, these agents can be administered in various ways and according to various regimens. Most customary are kits providing a contraceptive regimen of the so-called "combined contraceptive" type, in which daily dosage units comprising both the progestagen and the estrogen are administered for usually 21 consecutive days, in one or more phases distinguished by different amounts and ratio's of both active substances, while in the remaining days of the 28 days' cycle placebo's are administered or a "pill-free" interval is provided.

Contraceptive kits in which a single active substance is provided, are known. These are usually of the "progestagen only" type. While such "progestagen-only-pills" (POPs) have the advantage of avoiding the administration of an estrogen, they have a drawback in that cycle control frequently is unsatisfactory, as can be seen from irregular bleeding as well as from inherent amenorrhoe.

Hence, it is desired to include an estrogenic component, for which usually ethinyl estradiol is taken. In the art, several less-desired properties (on haemostasis and a risk of cancer) of combined contraceptives are mainly attributed to this estrogenic component. It is an object of the invention to provide, by taking a single compound having an activity profile including both the required progestagenic and the required estrogenic activity, a contraceptive which leads to good cycle control without exposing the above-identified less-desired properties. Further, it is an object of the invention to provide a contraceptive which has the advantages of excluding ethinyl estradiol, but at the same time retains the favourable effect of ethinyl estradiol on the lipid profile.

In the art, estrogenic receptor binding is usually described in relation to steroids which, just as estradiol, have an aromatic A-ring. Thus, e.g. a review paper by Anstead et al. in Steroids, 1997, vol. 62, pages 269-303, describes the *in vitro* estrogen receptor binding of a great many of such steroid structures, carrying various substituents. Such a disclosure, apart from not relating to *in vivo* activity, does not allow making any prediction on the estrogenic receptor binding of other, non-aromatic structures, let alone with respect to mixed estrogenic/progestagenic activity.

(c) Disclosure of the Invention:

1. Summary

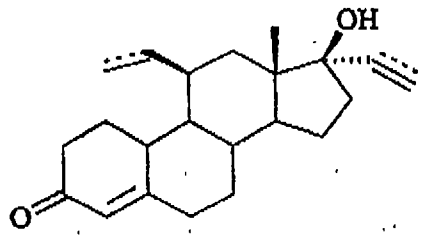
The present invention now provides a contraceptive kit comprising means for the daily administration of a contraceptive agent, characterised in that the single contraceptive agent is a steroid compound having an activity profile inherently combining progestagenic and estrogenic activity. The invention also resides in the use of a steroid compound having an activity profile inherently combining progestagenic and estrogenic activity for the manufacture of a contraceptive pharmaceutical preparation in which said compound is the single contraceptive agent. More particularly, the invention is in the use of a steroid compound selected from the group

consisting of steroids satisfying structural formula I given below, prodrugs thereof, and pharmaceutically acceptable salts thereof for the manufacture of a contraceptive pharmaceutical preparation.

2. Detailed Description

The present invention is made possible in particular by the unexpected finding of a type of compounds which possess a rare activity profile in that they are at the same time progestagenic (P) and estrogenic (E), and both activities are at a relatively high level. Thus, the single contraceptive agent to be used in the kit according to the invention is a steroid compound having an activity profile inherently combining progestagenic and estrogenic activity to such an extent that the Minimum Active Dose (MAD) in both the Allen-Doisy test for estrogenic activity and the McPhail test for progestagenic activity is ≤ 250 µg/kg. It will be apparent to the person skilled in the art that the term "single contraceptive agent" does not preclude said steroids from being combined with any other progestogen and/or estrogen, in a minor amount that is not contraceptively active, to the extent that such is desired for fine-tuning of the activity profile. It is preferred that the mixed-profile steroid is the only active compound present.

Suitable compounds according to the invention include those satisfying the following structural formula I:

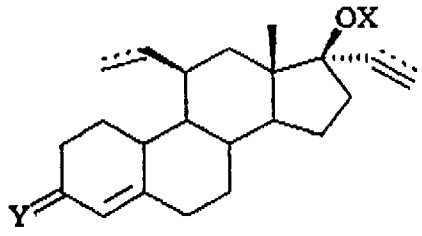


formula I

wherein the dotted lines each independently indicate an optional additional bond.

In one embodiment, the invention pertains to the use of these compounds for the manufacture of a contraceptive pharmaceutical preparation. In another embodiment, the invention is a contraceptive kit comprising means for the daily administration of any one of the above steroids as a contraceptive agent. In yet another embodiment, the invention provides a method of contraception comprising administering, to a female of child-bearing age, an effective amount of a steroid compound as described above.

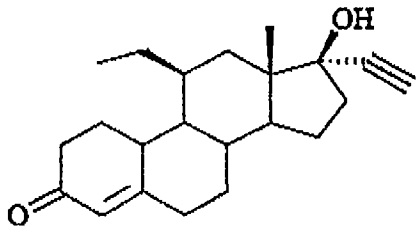
It is intended to include in the invention the compounds of formula I, as well as prodrugs thereof, i.e. related compounds the substituents of which are easily metabolised to the active compound according to formula I, or are readily cleaved to such a compound upon being administered. Together with the most regular prodrugs, the invention thus pertains to the compounds satisfying formula II, and pharmaceutically acceptable salts thereof.



formula II

wherein wherein the dotted lines each independently indicate an optional additional bond, Y stands for (H,H), (O), (N-OH), or (H,OH); and X stands for (-H) or (-C_2-C_7 acyl), such as -C(=O)CH_3. The 3-keto compounds, i.e. with Y being (O), are preferred. The other possibilities for the substituent at carbon atom number 3 have as their main property according to the invention that they are precursors (prodrugs) of the preferred 3-keto compounds. Similar considerations hold for the X substituent, in which the optional ester group is a precursor for the preferred active compound, in which the OX group is OH. For the sake of clarity, the invention is described hereinafter with reference to the active compounds according to formula I, but is intended to include at least the prodrugs described with reference to formula II.

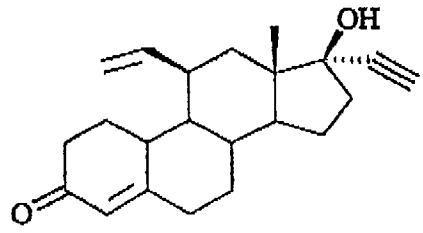
In a preferred embodiment, the compound used in the present invention is (11β,17α)-11-ethyl-17-hydroxy-19-norpregn-4-en-20-yn-3-one (Org 4060), which has the following structural formula III:



formula III

This compound, which is known from US 3,325,520 as a component of a mixture, from US 5,710,144 as a medicament in the treatment of menopausal complaints, and from GB 1,190,240 as a starting compound for the synthesis of other steroids, surprisingly has properties which make it highly favourable for use in contraception.

A yet further preferred embodiment of the invention, is the compound satisfying the structural formula IV.



formula IV

This compound (11β,17α)-11-Ethenyl-17-hydroxy-19-norpregn-4-en-20-yn-3-one (Org 4325) is within a class of steroid compounds known in general from US 4,292,251. This document describes a group of compounds with a range of possible properties. The document does not pertain to compounds having a specific mixed E/P profile, nor to monotherapy contraception. In this preferred embodiment, the invention now provides a compound which shows a marked difference with respect to the profile of biological properties compared with structurally related compounds known from US 4,292,251. This very difference, i.e. the unexpected mixed E/P profile, makes Org 4325, as well as prodrugs thereof and pharmaceutically acceptable salts thereof, highly suitable for use in monotherapy contraception.

According to the invention it is preferred to use the above steroids in contraception by monotherapy. However, it will be clear to the person skilled in the art that the outstanding biological properties of the steroids according to the invention can also be benefited from if one were to combine any one of these steroids with another active substance, e.g. a progestagenic or an estrogenic steroid.

The present invention further provides for a contraceptive kit in which a single active substance having both progestagenic and estrogenic properties is administered for e.g. 18 to 30, and preferably 21 to 25 days, the remaining days of the cycle being a "pill-free" or placebo interval. In principle, any other number of days is possible, but for practical reasons this is less desired. It is also possible to refrain from a pill-free or placebo interval, i.e. to provide for the continuous (daily) administration of the aforementioned mixed estrogen/progestagen compound. Thus several advantages of the above compounds may be enjoyed, but as such a continuous regimen will lead to inherent amenorrhoe, it is preferred to include a pill-free or placebo interval.

The kits according to the invention provide contraception by "monotherapy" rather than by combination of components having separate activities, but include an estrogenic component so as attain contraceptive efficacy and cycle control comparable to that of combined contraceptives. The pill-free or placebo interval will make for a withdrawal bleeding, which is generally considered desirable, *inter alia* because thus the natural cycle is mimicked as much as possible, and because it gives the certainty that no pregnancy has occurred.

The instant steroids can be administered in various ways. E.g., a means for sustained release can be chosen, but it is preferred if the means for administration is in the form of sequential daily dosage units, particularly tablets for oral administration.

The term "dosage unit" generally refers to physically discrete units suitable as unitary dosages for humans, each containing a predetermined quantity of active material

calculated to produce the desired effect, for instance tablets, pills, powders, suppositories, capsules and the like.

Methods and compositions for making such dosage units are well-known to those skilled in the art. For example, conventional techniques for making tablets and pills, containing active ingredients, are described in the standard reference, Gennaro et al., Remington's Pharmaceutical Sciences, (18th ed., Mack Publishing Company, 1990, see especially Part 8: Pharmaceutical Preparations and Their Manufacture).

For making dosage units, e.g. tablets, the use of conventional additives, e.g. fillers, colourants, polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used in one or more of the compositions.

Suitable carriers with which the compositions can be administered include lactose, starch, cellulose derivatives and the like used in suitable amounts. Lactose is a preferred carrier. Mixtures of carriers can also be used.

A process of manufacturing the kit of the invention comprises mixing a predetermined quantity of one or more of the aforementioned steroid compounds having progestagenic and estrogenic activity, optionally together with another estrogenic or progestagenic steroid, with predetermined quantities of excipients, and converting the mixture into dosage units. The resulting kits may contain any number of daily dosage units, but will generally be adapted to a defined length of the menstrual cycle by having 18-30, and preferably 20-28 daily dosage units. Preferred kits are in a form adapted to the normal length of the human menstrual cycle and contain 21-25, most preferably 21 of said daily sequential dosage units and optionally further placebo dosage units to make up a total of 28-32 daily dosage units.

Converting the mixture into dosage units generally involves moulding the mixture into a tablet, filling a capsule with a dried mixture, or filling a capsule with a wet mixture.

As indicated above, the means for administration of the steroids according to the invention may also be in a form other than that of a daily tablet, e.g an implant or an intravaginal article, such as a vaginal ring, or another type of sustained-release device.

Methods of making sustained-release devices such as implants and vaginal rings are known in the art. In this respect, reference is made to Jorge Heller Drug Delivery in the Plastics Age, in "Innovations in Drug Delivery", Tom Sam and Jasper Fokkens ed., pages 134-145. For a preferred contraceptive implant, EP 303 306 is referred to. Many designs of a vaginal ring releasing two substances are known to the person skilled in the art. The preferably ring-shaped drug delivery system that can be used in the present invention comprises at least one compartment comprising a thermoplastic polymer core containing the mixed-profile steroid compound in an amount which allows a direct release of the compound in physiologically required amounts.

The daily dosage of the steroids according to the invention, which may be up to 1 mg, generally is in the range of from 50 to 500 μg, preferably of from 100 to 300 μg. For the compounds according to formula III and IV, the amount to be administered preferably is 50-250 μg per day and more preferably 100-200 μg per day. The most preferred daily dosage in the case of monotherapy contraception is 140-160 μg. For Org 37678, which is the compound satisfying formula I wherein both of the optional additional bonds are absent, the doses typically are 1,5 to 2 times higher, 200-300 μg being chosen by preference.

The steroids used in the present invention can be prepared in accordance with the general teachings of US 5,710,144 and US 4,292,251.

The invention will be explained further with reference to the following examples.

EXAMPLE 1

(11β,17α)-11-Ethenyl-17-hydroxy-19-norpregn-4-en-20-yn-3-one was prepared from (11β)-11-ethenylestr-5-ene-3,17-dione cyclic 3-(1,2-ethanediyl acetal) as follows:

i) - A suspension of 57.5 g of potassium *tert*-butoxide in 585 ml of dry THF was ice-cooled to 0 °C and subsequently acetylene was passed through this mixture for 2 hours, at which point the ice-bath was removed. Next, a solution of 15.0 g of (11β)-11-ethenylestr-5-ene-3,17-dione cyclic 3-(1,2-ethanediyl acetal) in 156 ml of dry THF was added dropwise and acetylene was passed through the resulting mixture at room temperature. After 2 hours, 350 ml of a saturated aqueous solution of ammonium chloride was slowly added and the resulting mixture was extracted twice with ethyl acetate containing ca. 2% of pyridine. The combined extracts were washed twice with a saturated aqueous solution of sodium hydrogen carbonate and once with a saturated aqueous solution of sodium chloride (brine), dried over sodium sulfate, and concentrated under reduced pressure to afford 16.2 g of (11β,17α)-11-ethenyl-17-hydroxy-19-norpregn-5-en-20-yn-3-one cyclic (1,2-ethanediyl acetal).

ii) - To a solution of 16.2 g of (11β,17α)-11-ethenyl-17-hydroxy-19-norpregn-5-en-20-yn-3-one cyclic (1,2-ethanediyl acetal) in 870 ml of acetone, 44 ml of 4N HCl was added and the resulting mixture was stirred at room temperature and under a nitrogen atmosphere for 3½ hours. Subsequently, the reaction mixture was poured into 3½ l of water, which was extracted three times with ethyl acetate. The combined extracts were washed once with a saturated aqueous solution of sodium hydrogen carbonate, twice with water and once with a saturated aqueous solution of sodium chloride (brine), dried over sodium sulfate, and concentrated under reduced pressure to afford 14.0 g of crude material. This crude product was crystallised twice from a mixture of methylene chloride and acetone (K_1: 1.2 g, K_2: 4.8 g). The mother liquor of the second crystallisation was concentrated under reduced pressure and the residue was purified by flash chromatography (toluene:ethyl acetate = 8:2) to afford another 3.8 g of product. This material was combined with K_1 and K_2 and 50 ml of diethyl ether was added. The resulting suspension was refluxed for 4 hours, cooled for 60 hours at 5 °C and the crystals, after washing with 3 ml of cold diethyl ether, collected by filtration (9.0 g). Since repeating this procedure twice did not improve the purity of the product,

flash chromatography (heptane:acetone = 7:3) was used as a final purification step to afford 6.3 g of pure (11β,17α)-11-ethenyl-17-hydroxy-19-norpregn-4-en-20-yn-3-one. M.p. 186.8 °C. $[\alpha]_D^{20}$ = + 29.5° (c=1, ethanol).

EXAMPLE 2

(11β,17α)-17-Acetyloxy-11-ethenyl-19-norpregn-4-en-20-yn-3-one was prepared from (11β,17α)-11-ethenyl-17-hydroxy-19-norpregn-4-en-20-yn-3-one as follows:

- To a solution of 460 mg of (11β,17α)-11-ethenyl-17-hydroxy-19-norpregn-4-en-20-yn-3-one in 4.6 ml of acetic anhydride, 156 mg of *para*-toluenesulfonic acid was added and the resulting mixture was stirred at room temperature and under a nitrogen atmosphere for 4½ hours. Subsequently, 0.4 ml of 36% HCl was added and the mixture was stirred overnight. The crude mixture was then poured into 46 ml of water, which was extracted four times with methylene chloride. The combined extracts were washed with a saturated aqueous solution of sodium hydrogen carbonate, water and a saturated aqueous solution of sodium chloride (brine), dried over sodium sulfate, and concentrated under reduced pressure to afford the crude product which was still contaminated with the corresponding 3-acetyloxy-3,5-diene.

The crude product was dissolved in a mixture of 28 ml of acetone and 0.2 ml of 36% HCl and the resulting solution was stirred for 24 hours at room temperature (after 3 and 7½ hours, 0.7 ml of water was added). Next, another 0.2 ml of 36% HCl was added and the resulting mixture was once more stirred overnight at room temperature. Finally, the crude mixture was poured into 275 ml of water, which was extracted three times with ethyl acetate. The combined extracts were washed with a saturated aqueous solution of sodium hydrogen carbonate, water and a saturated aqueous solution of sodium chloride (brine), dried over sodium sulfate, and concentrated under reduced pressure to afford 550 mg of crude product. Purification by flash chromatography (toluene:ethyl acetate = 4:6) yielded 165 mg of pure (11β,17α)-17-acetyloxy-11-ethenyl-19-norpregn-4-en-20-yn-3-one as an amorphous solid.

M.p. 141.1-161.1 °C. $[\alpha]_D^{20}$ = -1° (c=0.5, dioxane).

EXAMPLE 3

(3E/Z,11β,17α)-11-Ethenyl-17-hydroxy-19-norpregn-4-en-20-yn-3-one oxime was prepared from (11β,17α)-11-ethenyl-17-hydroxy-19-norpregn-4-en-20-yn-3-one as follows:

- To a solution of 500 mg of (11β,17α)-11-ethenyl-17-hydroxy-19-norpregn-4-en-20-yn-3-one in 2.6 ml of pyridine, 1.18 g of hydroxylamine.HCl was added and the resulting mixture was stirred at room temperature and under a nitrogen atmosphere for 1 hour. Subsequently, the reaction mixture was poured into 46 ml of water, which was extracted three times with methylene chloride. The combined extracts were washed with water and a saturated aqueous solution of sodium chloride (brine), and concentrated under reduced pressure to yield 480 mg of crude (3E/Z,11β,17α)-11-ethenyl-17-hydroxy-19-norpregn-4-en-20-yn-3-one oxime.

Crystallisation from methylene chloride afforded 260 mg of a 85:15 mixture of the 3E- and 3Z-oxime.

M.p. 257 °C. $[\alpha]_D^{20} = +58.4°$ (c=0.5, dioxane).

EXAMPLE 4

(11β,17α)-11-Ethenyl-17-hydroxy-19-norpregna-4,20-dien-3-one was prepared from (11β,17α)-11-ethenyl-17-hydroxy-19-norpregn-4-en-20-yn-3-one as follows:

- To a suspension of 175 mg Lindlar catalyst in 15 ml of ethanol, pre-treated with hydrogen gas for 25 minutes, a solution of 500 mg (11β,17α)-11-ethenyl-17-hydroxy-19-norpregn-4-en-20-yn-3-one in 5 ml of ethanol was added and the resulting mixture was hydrogenated at atmospheric pressure for 1 hour. Subsequently, the catalyst was removed by filtration of the crude mixture over dicalite and the filtrate concentrated under reduced pressure. Purification of the crude product by flash chromatography with toluene/ethyl acetate (4/6), using silver nitrate impregnated silica as the stationary phase, gave 162 mg of pure (11β,17α)-11-ethenyl-17-hydroxy-19-norpregna-4,20-dien-3-one as an amorphous solid.

M.p. 62.9-70.3 °C. $[\alpha]_D^{20} = +74.1°$ (c=0.5, dioxane).

EXAMPLE 5

(3α,11β,17α)-11-Ethenyl-19-norpregn-4-en-20-yne-3,17-diol and (3β,11β,17α)-11-ethenyl-19-nor-pregn-4-en-20-yne-3,17-diol were prepared from (11β,17α)-11-ethenyl-17-hydroxy-19-norpregn-4-en-20-yn-3-one as follows:

- To a solution of 2.0 g of (11β,17α)-11-ethenyl-17-hydroxy-19-norpregn-4-en-20-yn-3-one in 25 ml of dry THF, 3.14 g of Li(O^{t}Bu)$_3$AlH was added and the resulting mixture was stirred at room temperature and under a nitrogen atmosphere for 2 hours. Subsequently, the reaction mixture was poured into a saturated aqueous solution of ammonium chloride, which was extracted with ethyl acetate. The extract was washed with water and a saturated aqueous solution of sodium chloride (brine), and concentrated under reduced pressure. Purification of the crude mixture by flash-chromatography with dichloromethane/acetone (95/5) gave, after crystallisation from diisopropyl ether, 100 mg of pure (3α,11β,17α)-11-ethenyl-19-norpregn-4-en-20-yne-3,17-diol and 700 mg of pure (3β,11β,17α)-11-ethenyl-19-norpregn-4-en-20-yne-3,17-diol.

3α–isomer: M.p. 178.5 - 179.1 °C.

3β–isomer: M.p. 147.6 - 148.2 °C.

EXAMPLE 6

(11β,17α)-11-Ethyl-17-hydroxy-19-norpregn-4-en-20-yn-3-one was prepared as follows from (11β)-11-ethenylestr-5-ene-3,17-dione cyclic bis-(1,2-ethanediyl acetal):

i) - To a solution of 100 g of the bisacetal mentioned above in 3.5 l of dry tetrahydrofuran was added 5 g of platinum(IV) oxide, and the mixture was hydrogenated at room temperature until no more hydrogen was taken up. The mixture was filtered over celite, the residue washed twice with tetrahydrofuran, and the combined filtrates concentrated under reduced pressure to afford 93 g of crude cristalline (11β)-11-ethylestr-5-ene-3,17-dione cyclic bis-(1,2-ethanediyl acetal), which was used in the subsequent step without further purification.

ii) - The diketal from the previous step (10 g) was suspended in 50 ml of acetone. To this suspension was cautiously added a solution of 6,7 ml of water and 3,3 ml of sulfuric acid. The mixture was stirred at room temperature for 1 hour, and then poured into a solution of 20 g of sodium acetate in 100 ml of water. The mixture was cooled in an ice bath; the resulting precipitate was filtered off and the residue washed with water until the washings were neutral; the residue was then collected and dried, giving 7.5 g of crude (11β)-11-ethylestr-4-ene-3,17-dione which was used in the subsequent step without further purification.

iii) - Acetylene gas was passed through a suspension of 16.5 g of potassium *tert*-butoxide in 100 ml of dry tetrahydrofuran for 2 hours. To this suspension a solution of 10 g of the diketone from the previous step in 50 ml of dry tetrahydrofuran was added dropwise. The mixture was stirred at room temperature for 2 hours while acetylene was continuously passed through. Subsequently, a solution of 15 ml of sulfuric acid in 30 ml of water was cautiously added and the mixture stirred for a further 2 hours. Thereafter, a sulution of 40 g of sodium acetate in 250 ml of water was slowly added, and the mixture heated at 75 °C for 15 minutes. The organic solvents were then distilled of and the residue cooled to room temperature. A precipitate was formed, which was removed by filtration and taken up in 600 ml of toluene. Active charcoal was added and the mixture heated to 65 °C, filtered and concentrated under reduced pressure. The crude product was recrystallized from ethanol/water to afford 6.5 g of (11β,17α)-11-Ethyl-17-hydroxy-19-norpregn-4-en-20-yn-3-one.

M.p. 222 °C. $[\alpha]_D^{20}$ = -16.1° (c = 1, dioxane).

COMPARATIVE EXAMPLE

(A) Identical with Example II(b) of US 4,292,251.

(B) Identical with Example XIII of US 4,292,251 (including the procedures of Example VI(a) and (b) therein).

EXAMPLE OF PHARMACEUTICAL FORMULATION

Pharmaceutical compositions are prepared containing a steroid in accordance with the present invention. By way of illustration, the compound of Example 6 (Org 4060) is chosen. The compound is mixed with the other ingredients in a standard way, and the mixture is subjected to granulation. The composition is as follows, the same formulation being applicable to other compounds including Org 4325:

Org 4060 (active)	1-10 wt.%;
Corn Starch (disintegrant)	15 wt.%;
Hydroxy Propyl Cellulose (binder)	3 wt.%;
Lactose 200 M (diluent) up to	100 wt.%;

TEST EXAMPLE A

Several steroids, compounds according to the invention as well as compounds not according to the invention, were subjected to testing for relevant biological properties, viz. progestagenic activity and estrogenic activity. The progestagenic activity was determined by means of the McPhail test, the estrogenic activity by means of the Allen-Doisy test. Both tests are known in the art, and can be described as follows:

McPhail test:

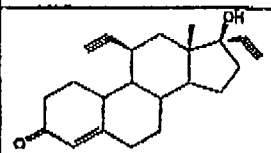
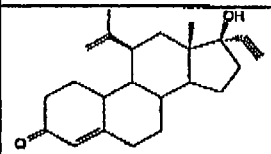
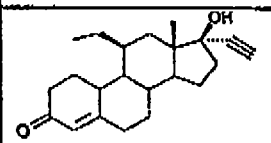
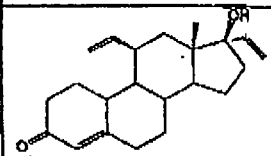
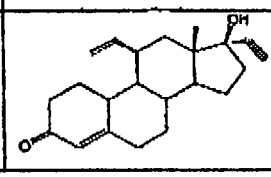
In vivo test in rabbit used to evaluate test compounds for their progestational activity by histologically scoring the differentiation of endometrial tissue. Rabbits are primed with estradiol for 8 days and, subsequently, the progestagenic compound is orally administered for 5 days. The animals are euthanized (60 mg pentobarbitone/rabbit i.v.) and transverse haematoxylin-eosin-stained sections of two different parts of each uterine horn are prepared. The progestin-dependent endometrium development is evaluated microscopically and rated on a scale from 0-4 (Van der Vies J., and De Visser, J. 1983. Endocrinological studies with desogestrel. *Drug Res.* 33: 231-236).

Allen-Doisy test:

In vivo test in rat used to evaluate test compounds for their estrogenic activity by scoring the cornification of the vaginal epithelium on vaginal smears. Mature female rats are ovariectomized and, in the third week thereafter, primed with a single dose of 1 µg oestradiol (day 1). Seven days after priming, test compound is administered once on day 8 and twice on day 9. Vaginal smears are taken in the afternoon of day 10, twice on day 11 and again in the morning of day 12. The smears are stained with Giemsa and the number of positive smears is determined (Van der Vies J., and De Visser, J. 1983. Endocrinological studies with desogestrel. *Drug Res.* 33: 231-236).

Results:

The test results are indicated in the following table.

Compound	Structure	McPhail (µg/kg)	Allen-Doisy (µg/kg)
Comparison A (Org 4433)		63-125	2000
Comparison B (Org 10436)		>1000	>125
Example 6 (Org 4060)		250	63-125
Example 4 (Org 37678)		125	250
Example 1 (Org 4325)		63-125	32

TEST EXAMPLE B

The compound of Example 6 was employed in monkey studies.

Mature female stumptail monkeys (*Macaca Arctoides*) 5-20 years of age with proven regular menstrual cyclicity were used. The monkeys were housed in a colony of approximately 35 females and one vasectomized male. Experiments were approved by the 'Animal Use Committee' (DEC, AEP nr. E97A0801PV E). To three of these monkeys the compound of Example 6 was administered at a dose of 8 µg/kg per day. The first day of menstrual bleeding was considered to be day 1 of the cycle and the experiments started with the pre-treatment control cycle (day 1 of the experiment). Treatment (daily) started on day 2 of the treatment cycle until day 22. Compounds were administered orally via a catheter under light anaesthesia with ketamin® (dose depending on the monkey, i.m. ≤ 10 mg/kg). Following administration animals were housed individually to regain consciousness and to check for regurgitation. After two hours the animals were allowed to return to the colony. The post-treatment cycle started after the (expected time of) menstrual bleeding of the treatment cycle. Blood samples for analysis of estradiol and progesterone levels were taken twice a week (Mondays and Thursdays) throughout the experiment. Blood samples were taken from the vena femoralis using Vacutainer tubes (Venoject). Cyclicity was also monitored by taking daily vaginal swabs with a cotton tip applicator. Vaginal bleedings were divided in clear bleedings (score = +) and minor bleedings (score = ±).

All of the monkeys receiving the compound of Example 6 showed ovulation inhibition; two out of three showed a withdrawal bleeding; none showed intermittent bleedings. These results show that this mixed E/P compound is highly suitable as a contraceptive: ovulation inhibition is excellent and, while a separate estrogen is dispensed with, the bleeding pattern and cycle control is good.

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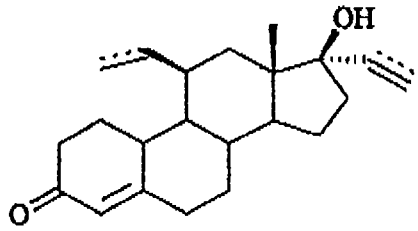
Claims:

1. A contraceptive kit comprising means for the daily administration of a contraceptive agent, characterised in that the single contraceptive agent is a steroid compound having an activity profile inherently combining progestagenic and estrogenic activity.

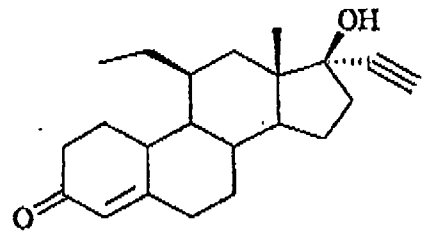
2. A contraceptive kit according to claim 1, characterised in that the steroid compound is selected from the group consisting of steroids satisfying structural formula I, prodrugs thereof and pharmaceutically acceptable salts thereof,



formula I

wherein the dotted lines each independently indicate an optional additional bond.

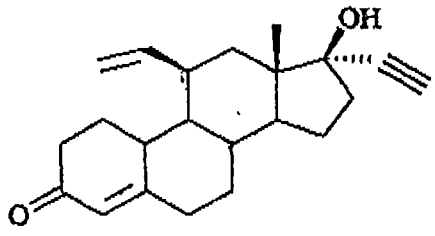
3. A contraceptive kit according to claim 2, characterised in that the steroid compound satisfies structural formula III,



formula III

or is a prodrug or a pharmaceutically acceptable salt thereof.

4. A contraceptive kit according to claim 2, characterised in that the steroid compound satisfies structural formula IV,



formula IV

or is a prodrug or a pharmaceutically acceptable salt thereof.

5. A contraceptive kit according to any one of the preceding claims, characterised in that the means for daily administration is in the form of 18 to 30 sequential daily dosage units each comprising 100-300 µg of the steroid.

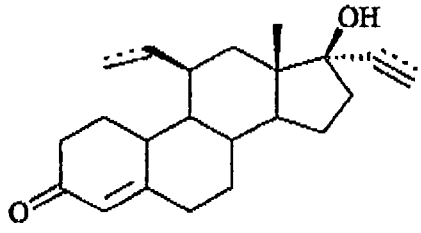
6. A contraceptive kit according to claim 5, characterised in that the number of the daily dosage units is 21-25.

7. A contraceptive kit according to claim 6, characterised by containing placebo dosage units making up a total number of 28-32 daily dosage units.

8. A contraceptive kit according to any one of claims 5-7, characterised in that the sequential daily dosage units are tablets for oral administration.

9. The use of a steroid compound having an activity profile inherently combining progestagenic and estrogenic activity for the manufacture of a contraceptive pharmaceutical preparation in which said compound is the single contraceptive agent.

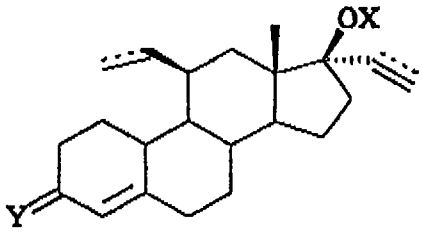
10. The use of a steroid compound selected from the group consisting of steroids satisfying structural formula I, prodrugs thereof, and pharmaceutically acceptable salts thereof,



formula I

wherein the dotted lines each independently indicate an optional additional bond, for the manufacture of a contraceptive pharmaceutical preparation.

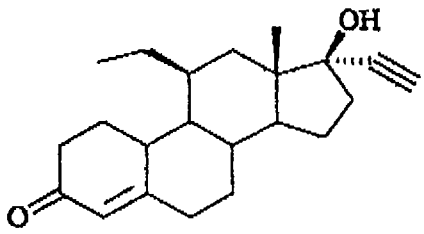
11. A use according to claim 10, characterised in that the steroid compound is one satisfying structural formula II, or a pharmaceutically acceptable salt thereof:



formula II

wherein wherein the dotted lines each independently indicate an optional additional bond, Y stands for (H,H), (O), (N-OH), or (H,OH); and X stands for (-H) or (-C_1-C_7 acyl).

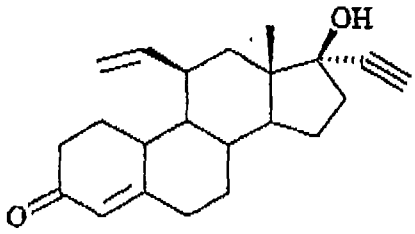
12. A use according to claim 11, characterised in that the steroid compound satisfies structural formula III:



formula III

or is a prodrug or a pharmaceutically acceptable salt thereof.

13. A use according to claim 11, characterised in that the steroid compound satisfies structural formula IV:



formula IV

or is a prodrug or a pharmaceutically acceptable salt thereof.

14. A use according to any of the claims 10-13, characterised in that the pharmaceutical preparation in a monotherapy contraceptive.

15. A use of a steroid compound selected from the group consisting of steroids satisfying structural formula I and prodrugs thereof for the preparation of a contraceptive for administration to a female of child bearing age.

16. The use of claim 15 wherein from 100 to 300 μg of a compound satisfying formula III is administered for 21 to 25 consecutive days, followed by a pill-free or placebo interval of 3 to 7 days.