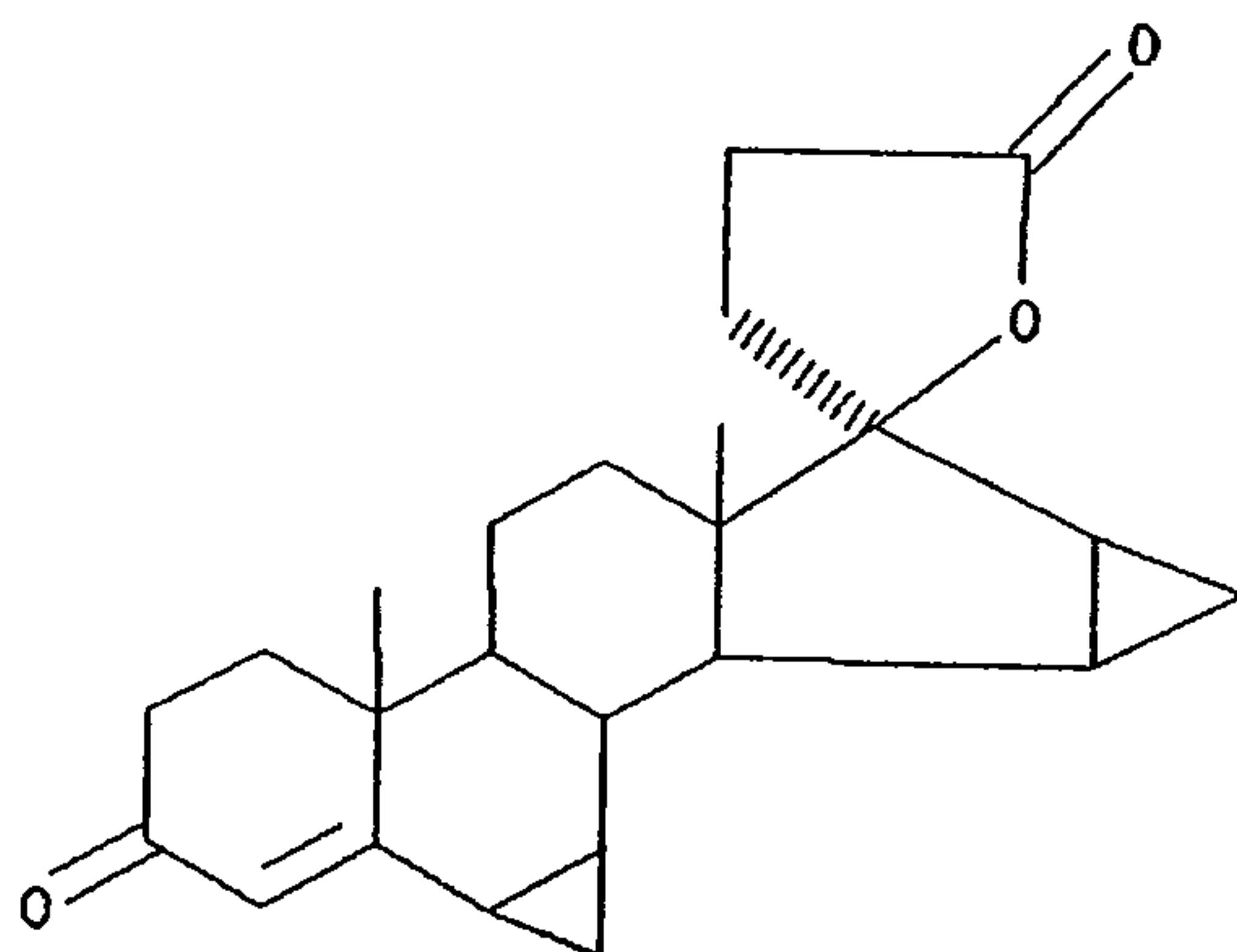




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(54) **DIHYDROSPIRORENONE ANTIANDROGENIQUE**
(54) **DIHYDROSPIRORENONE AS AN ANTIANDROGEN**

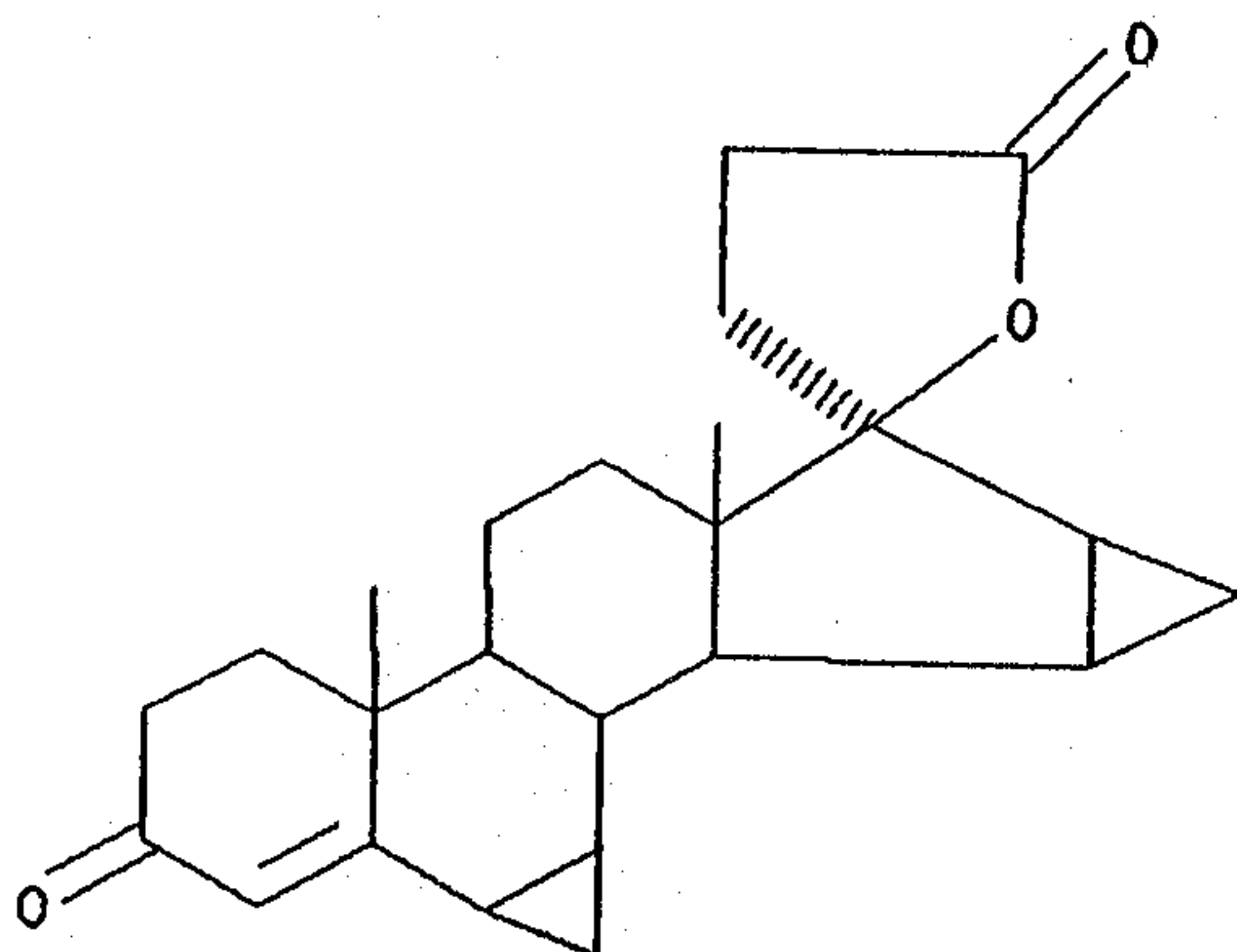


(I)

(57) Dihydrospirorenone, (see formula I) preferably together with an estrogen, can be used for the production of a pharmaceutical agent suitable for treatment of hormonal irregularities during premenopause (menstruation stabilization), for hormonal substitution therapy during menopause, for treatment of androgen-induced disorders and/or for contraception.

ABSTRACT OF THE DISCLOSURE

Dihydrospirorenone,



(1)

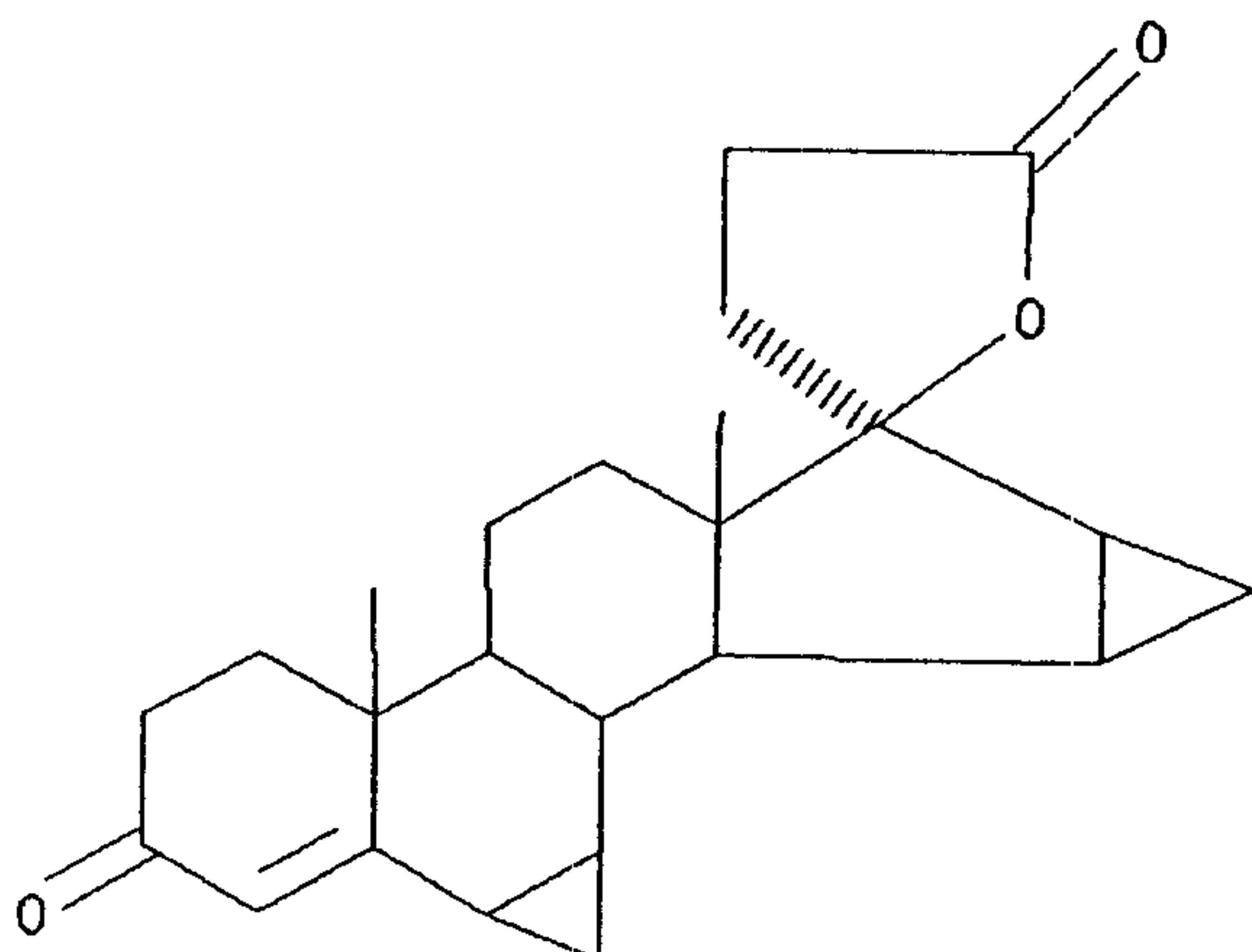
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DIHYDROSPIRORENONE AS AN ANTIANDROGEN

Background of the Invention

This invention relates to the use of the compound of formula I



5 for the production of a pharmaceutical agent.

Compound I (dihydrospirorenone) is described in DE A-26 52 761, among others, as a diuretic of the aldosterone-antagonist type.

10 It can be seen from DE-A 30 22 337 that compound I, at doses at which the antialdosterone effect already appears, also exhibits a marked gestagen effect. Therefore, compound I can be used alone or in combination with estrogens in contraceptive preparations.

15 According to DE-A 30 22 137, these preparations are to be used for women who desire contraception and suffer from

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high blood pressure or in whom blood pressure rises when they take oral contraceptives. Thus, also for women predisposed to increased blood pressure, hormonal contraception is possible.

5 A combined preparation for substitution therapy and contraception for women before menopause (starting at about age 40) is known from EP-A 0253 607. This combined preparation contains an estrogen from the group

17beta-estradiol,
10 ethynylestradiol and
 mestranol

and a gestagen from the group

levonorgestrel,
gestodene,
15 desogestrel,
 3 ketodesogestrel and
 norethindrone.

20 A composition so selected should balance hormonal irregularities in the transition phase of premenopause and help to alleviate the discomfort caused by the hormonal change of the female organism during this phase. Simultaneously, such a composition guarantees the contraceptive protection still necessary at this age.

25 For various, known reasons and because of the increase in the incidence of contraindications with increasing age, the taking of the usual hormonal contraceptives is recommended for women only until about age 35, so that a hormonal treatment during premenopause and a substitution therapy during menopause using doses that simultaneously
30 have a contraceptive effect can be considered problematic.

Besides these circumstances justifying contraindication, in women of such advanced age, symptoms of androgenization such as, for example, beard growth,

deepening of the voice and impure skin are often observed; further, a rise in blood pressure can often be noted.

Thus, there remains a need for good agents for hormonal therapy, especially for such woman, including achievement of one or more of such effects.

Summary of the Invention

It has now been found that the compound of formula I, in addition to its gestagen and antialdosterone effect, surprisingly exhibits a strong antiandrogenic activity component, and specifically at doses that also make possible the formulation of this compound as an oral contraceptive. Dihydrospirorenone acts as an antiandrogen about as strongly as cyproterone acetate, considered the standard compound (same maximum effect). (Animal model: juvenile, castrated and testosterone-substituted male rat.)

This invention thus relates to the use of the compound of formula I for the production of a pharmaceutical agent suitable for treatment of hormonal irregularities during premenopause (e.g., menstruation stabilization) and/or for hormonal substitution therapy during menopause and/or for treatment of androgen-induced disorders and/or for contraception. Conventional protocols can be used to determine antiandrogenic activity, e.g., as disclosed in Methods in Hormone Research, Editor: R.I. Dorfman, Academic Press, New York, London, 1969, pp. 241; or Androgens and Antiandrogens, Editors: L. Martin and M. Motta, Raven Press, New York, 1977, pp. 163.

Thus, in various aspects, this invention relates to a method of achieving an antiandrogenic effect comprising administering I to a patient in need of antiandrogenic treatment; to a method of treating an androgen induced disorder in a female comprising administering I to a method of achieving a contraceptive effect in a female during premenopause or menopause (both terms having their conventional meaning, e.g., as shown in "The Controversial Climacteric," P.A. van Keep et

al., Ed., MTP Press (1981), e.g., page 9) comprising administering to the female an effective amount of I; to a method of treating gestagen-related hormonal irregularities in a female during premenopause comprising administering I; and/or to a method of achieving gestogen-related hormonal substitution therapy in a female in menopause comprising administering I. In preferred aspects, the females are suffering from and/or predisposed to high blood pressure disorders and/or to androgen-related disorders.

10 Preferably an estrogen is used together with the compound of formula I. Whether a synthetic or a natural estrogen is preferably used depends on whether the contraceptive effect or the substitutive effect is emphasized: in the first case, ethynylestradiol or another synthetic estrogen is preferred, in the second case, such a pharmaceutical agent should contain a natural estrogen.

20 But in any case, such a pharmaceutical agent guarantees a woman of middle age (about age 35-55) a stabilization of her menstruation cycle and the contraception still indispensable at this age, with simultaneous, favorable influence on androgen-induced disorders. Of course, this pharmaceutical agent is also suited for younger women, especially for those that have a particular predisposition toward high blood pressure and/or suffer from symptoms of androgenization or are predisposed to one or both of these, e.g., in view of their past medical history, family background, etc., in addition to age.

30 Here such a use is especially effective because the compound of formula I simultaneously combines a gestagen, antialdosterone effect as well as a strong antiandrogen effect. Previously no substance was known that simultaneously exhibited these three properties.

The dose of the compound of formula I can be 0.5 to 50 mg per day, preferably 1-10 mg per day for all uses of this invention.

Suitable as estrogens are all previously known estrogens. The estrogen used preferably for the various purposes of this invention should be administered in doses such that the estrogen amount used according to the invention is equal to that which corresponds to the administration of 0.02 to 0.04 mg of 17alpha-ethynylestradiol or 0.5 to 4.0 mg of estradiol valerate daily. Such amounts can be conventionally determined using fully conventional tests such as described in Dorfman, supra, page 62. As estrogenic components, among others the 17alpha-ethynylestradiol esters and ethers are suitable as well as, for example, esters of 17alpha-ethynyl-7alpha-methyl-1,3,5(10)-estratriene-1,3,17beta-triol (German patent 1 593 509 and German laid-open specification 2 818 164). Further, also the 14,17beta-ethano-14beta-estratrienes described in DE-A 36 28 189 as useful. The estrogenic and gestagenic active components are preferably administered together orally: but they can also be administered separately and/or parenterally or transdermally.

The agents of this invention can be used in the methods of this invention analogously to use of agents known for such purposes, e.g., those of EP 253607 but routinely taking into account the beneficial properties discussed herein.

The formulation of the preparations according to the invention based on 6beta, 7beta; 15beta, 16beta-dimethylene-3-oxo-4-androstene-[17(beta-1')-perhydrofuran-2'-one (I) is performed in a way known in the art by processing the active ingredient, optionally in combination with an estrogen, with the vehicles, diluents, optional flavorings, etc. common in galenicals, and converting it into the desired form of administration. For the preferred oral administration, tablets, coated tablets, capsules, pills, suspensions or solutions are especially suitable. For parenteral administration, in particular oily solutions, such as, for

example, solutions in sesame oil, castor oil and cottonseed oil, are suitable. To increase solubility, solubilizers such as, for example, benzyl benzoate or benzyl alcohol, can be added.

5 Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of
10 the remainder of the disclosure in any way whatsoever.

 In the foregoing and in the following examples, all temperatures are set forth uncorrected in degrees Celsius and unless otherwise indicated, all parts and percentages are by weight.

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E X A M P L E S

Example 1

20.0 mg of 6beta, 7beta; 15beta, 16beta-dimethylene-3-oxo-4-androstene-[17(beta-1')-spiro-5']-perhydrofuran-2'-one and 0.05 mg of 17alpha-ethynylestradiol are mixed homogeneously with 140.45 mg of lactose, 59.5 mg of cornstarch, 2.0 mg of aerosil, 2.5 mg of polyvinylpyrrolidone 25 and 0.5 mg of magnesium stearate and pressed without advance granulation into a tablet of 225 mg final weight.

Example 2

Analogous to example 1, 10 mg of 6beta, 7beta; 15beta, 16beta-dimethylene-3-oxo-4-androstene-[17(beta-1')-spiro-5']-perhydrofuran-2'-one and 0.05 mg of 17alpha-ethynylestradiol with 150.45 mg of 17alpha-ethynylestradiol with 150.45 mg of lactose, 59.5 mg of cornstarch, 2.0 mg of aerosil, 2.5 mg of polyvinylpyrrolidone 25 and 0.5 mg of magnesium stearate are pressed into tablets with a final weight of 225 mg.

Example 3

Analogous to example 1, 20 mg of 6beta, 7beta; 15beta, 16beta-dimethylene-3-oxo-4-androstene-[17(beta-1')-spiro-5']-perhydrofuran-2'-one with 140.5 mg of lactose, 59.5 mg of cornstarch, 2.0 mg of aerosil, 2.5 mg of polyvinylpyrrolidone 25 and 0.5 mg of magnesium stearate are pressed into tablets with a final weight of 225 mg.

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The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the preceding examples.

5 From the foregoing description, one skilled in the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A method of achieving a contraceptive effect in a female during premenopause or menopause, comprising administering to the female an effective amount of dihydrospirorenone.

2. The method of claim 1, wherein the female is suffering from or predisposed to high blood pressure.

3. The method of claim 1 or 2, wherein the female is suffering from or is predisposed to androgen-induced symptoms.

4. The method of claim 1, 2 or 3, further comprising administering an estrogenic compound.

5. The method of claim 4, wherein the estrogenic compound is a synthetic estrogen.

6. The method of claim 4, wherein the estrogenic compound is a natural estrogen.

7. Use of dihydrospirorenone in the preparation of a medicament that is suitable for the simultaneous treatment of

(a) aldosterone-induced disorders,

(b) hormonal irregularities (stabilization of the cycle),

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- (c) for contraception, and
- (d) for the treatment of androgen-induced disorders.

8. Use of dihydrospirorenone in the preparation of a medicament that is suitable for the simultaneous treatment of

- (a) aldosterone-induced disorders,
- (b) androgen-induced disorders, and
- (c) for hormone replacement therapy in the menopause.

9. Use according to claim 7 or 8, wherein the aldosterone-induced disorder is high blood pressure.

10. Use of dihydrospirorenone according to claim 7 or 8, in combination with an estrogen.

11. Use according to claim 10, wherein the estrogen is a synthetic estrogen.

12. Use according to claim 10, wherein the estrogen is a natural estrogen.

13. Use of the combination according to claim 7 or 10, in the preparation of a medicament for premenopausal women.

14. A composition for simultaneously achieving, during premenopause or menopause, a gestagenic effect, an antiandrogenic effect and an antialdosterone effect in a

female patient in need thereof, comprising an amount of dihydrospirorenone effective to simultaneously achieve a gestagenic effect, an antiandrogenic effect and an antialdosterone effect in said patient, in admixture with a pharmaceutically-acceptable carrier, diluent or excipient.

15. The composition according to claim 14, wherein said patient is in premenopause.

16. The composition according to claim 15, wherein stabilization of menstruation is achieved.

17. The composition according to claim 14, 15 or 16, wherein said female patient is of age 35-55.

18. The composition according to claim 14, wherein said patient is in menopause.

19. The composition according to any one of claims 14 to 18, wherein said patient is predisposed to androgenization symptoms.

20. The composition according to any one of claims 14 to 19, wherein said patient suffers from or is predisposed to high blood pressure.

21. A composition for simultaneously achieving, during premenopause or menopause, a contraceptive effect, an antiandrogenic effect and an anti-aldosterone effect in

a female patient in need thereof, comprising an effective amount of dihydrospirorenone and an effective amount of an estrogenic compound in admixture with a pharmaceutically-acceptable carrier, diluent or excipient, wherein said effective amount of dihydrospirorenone is effective to simultaneously achieve a gestagenic effect, an anti-androgenic effect and an anti-aldosterone effect in said female patient.

22. The composition according to claim 21, wherein said patient suffers from or is predisposed to symptoms of androgenization.

23. The composition according to claim 21 or 22, wherein said patient suffers from or is predisposed to high blood pressure.

24. The composition according to claim 21, 22 or 23, wherein said patient is in premenopause.

25. The composition according to any one of claims 21 to 24, wherein said female patient is of age 35-55.

26. The composition according to any one of claims 20 to 25, wherein said estrogenic compound is a synthetic estrogen.

27. The composition according to any one of claims 20 to 25, wherein said estrogenic compound is a natural estrogen.

28. The composition according to any one of claims 20 to 25, wherein the estrogenic compound is 17 α -ethynylestradiol.

29. The composition according to claim 21, 22 or 23, wherein said patient is in menopause.

30. The composition according to any one of claims 24 to 28, wherein stabilization of menstruation is achieved.

31. Use of an effective amount of dihydrospirorenone to simultaneously achieve a gestagenic effect, an anti-androgenic effect and an anti-aldosterone effect, during premenopause or menopause, in a female patient in need thereof.

32. Use according to claim 31, wherein said patient is in premenopause.

33. Use according to claim 32, wherein stabilization of menstruation is achieved.

34. Use according to claim 31, 32 or 33, wherein said female patient is of age 35-55.

35. Use according to claim 31, wherein said patient is in menopause.

36. Use according to any one of claims 31 to 35, wherein said patient is predisposed to androgenization symptoms.

37. Use according to any one of claims 31 to 36, wherein said patient suffers from or is predisposed to high blood pressure.

38. Use of an effective amount of dihydrospirorenone and an effective amount of an estrogenic compound simultaneously achieve a contraceptive effect, an anti-androgenic effect and an anti-aldosterone effect, during premenopause or menopause, in a female patient in need thereof.

39. Use according to claim 38, wherein said patient suffers from or is predisposed to symptoms of androgenization.

40. Use according to claim 38 or 39, wherein said patient suffers from or is predisposed to high blood pressure.

41. Use according to claim 38, 39 or 40, wherein said patient is in premenopause.

42. Use according to claim 41, wherein stabilization of menstruation is achieved.

43. Use according to claim 38, 39 or 40, wherein said patient is in menopause.

44. Use according to any one of claims 38 to 43, wherein said estrogenic compound is a synthetic estrogen.

45. Use according to any one of claims 38 to 43, wherein said estrogenic compound is a natural estrogen.

46. Use according to any one of claims 38 to 45, wherein said female is of age 35-55.

47. Use according to any one of claims 38 to 46, wherein the estrogenic compound is 17α -ethynylestradiol.