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(54) Titre : METHYLENE-4-AZASTEROIDES

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(57) **Abrégé/Abstract:**

Novel 17-methylene-4-azasteroids of general formula (I), where R²⁰ and R^{20a} independently = fluoro, chloro, bromo and cyano groups; R⁴ and R¹⁰ = H or methyl; R¹ and R² = each an H atom or together an additional bond, are disclosed. Said compounds are inhibitors of 5- α -reductase and are thus suitable for the treatment of diseases which are the result of increased testosterone and hence dihydrotestosterone levels in blood and tissue.



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Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

(54) Title: METHYLENE-4-AZASTEROIDS

(54) Bezeichnung: METHYLEN-4-AZASTEROIDE

(57) **Abstract:** Novel 17-methylene-4-azasteroids of general formula (I), where R²⁰ and R^{20a} independently = fluoro, chloro, bromo and cyano groups; R⁴ and R¹⁰ = H or methyl; R¹ and R² = each an H atom or together an additional bond, are disclosed. Said compounds are inhibitors of 5- α -reductase and are thus suitable for the treatment of diseases which are the result of increased testosterone and hence dihydrotestosterone levels in blood and tissue.

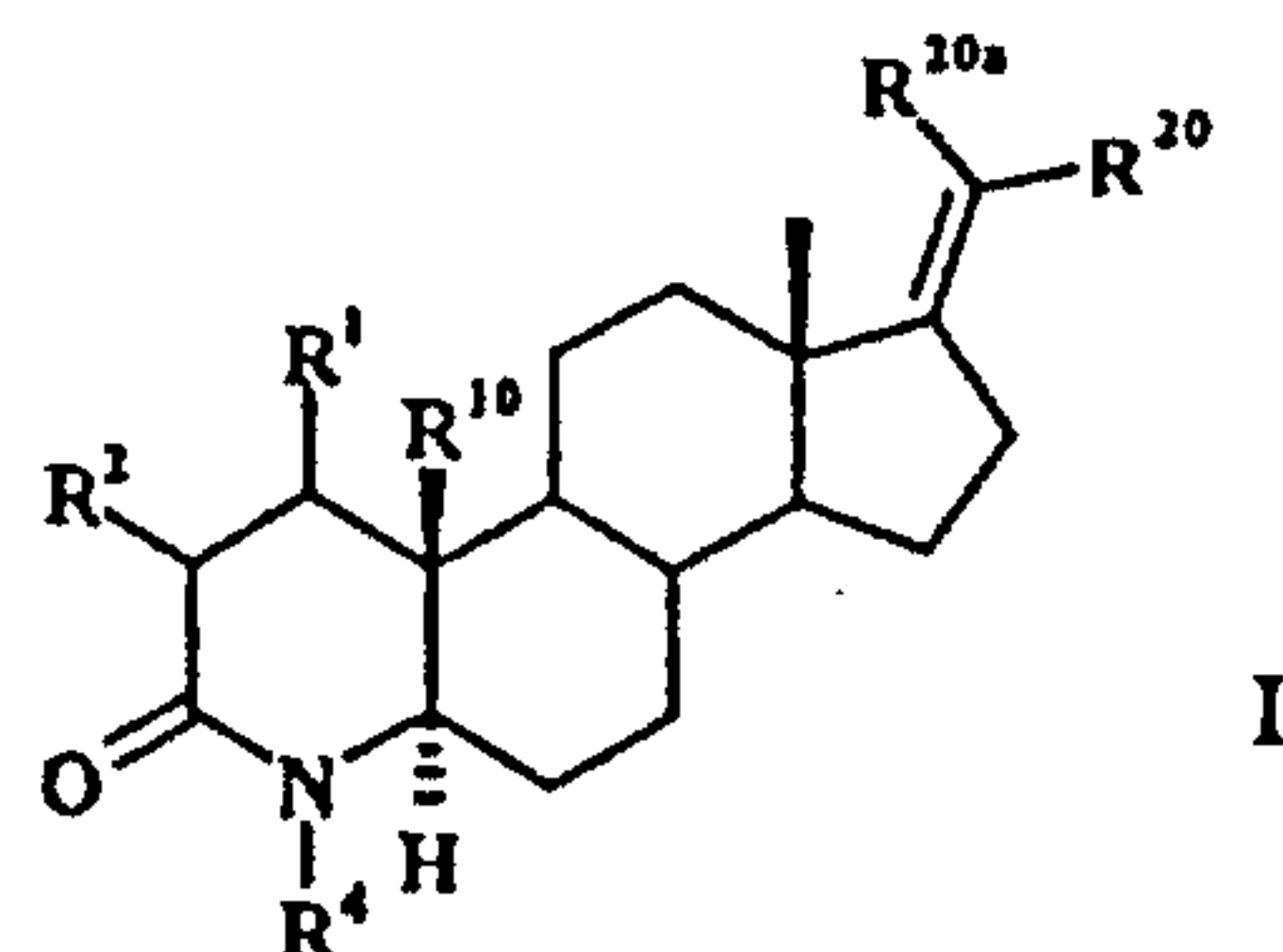
(57) **Zusammenfassung:** Es werden neue 17-Methylen-4-azasteroide der allgemeinen Formel (I), worin R²⁰ und R^{20a} getrennt Fluoro-, Chloro-, Bromo- und Cyanogruppen darstellen; R⁴ und R¹⁰ stehen jeweils für ein Wasserstoffatom oder eine Methylgruppe; R¹ und R² gemeinsam jeweils ein Wasserstoffatom oder eine zusätzliche Bindung sind, beschrieben. Die erfindungsgemässen Verbindungen sind Inhibitoren der 5- α -Reduktase und eignen sich daher zur Behandlung von Erkrankungen, die Folge erhöhter Testosteron- und letztlich Dihydrotestosteronspiegel im Blut und Gewebe sind.



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Methylene-4-azasteroids

The invention relates to novel 17-methylene-4-azasteroids of general formula I



wherein

R^{20} and R^{20a} separately denote fluoro, chloro, bromo and cyano groups,

R^4 and R^{10} denote a hydrogen atom or a methyl group, and

R^1 and R^2 together denote a hydrogen atom or an additional bond.

Methods for preparing novel compounds and for producing pharmaceutical compositions thereof are described.

The compounds of the invention, 17-methylene-4-azasteroids, are new; their preparation and their biological activity have thus far not been described.

Compounds preferred according to the invention are indicated in Claim 3. Another object of the present invention are pharmaceutical compositions containing as the active ingredient at least one 17-methylene-4-azasteroid of general formula I, said compositions optionally containing appropriate auxiliary agents and carriers.

The compounds of the invention are 5α -reductase inhibitors. Hence, they are suitable for the treatment of diseases caused by elevated testosterone levels and finally dihydrotestosterone levels in the blood and tissues.

Diseases induced by excessive androgen effects can also occur at normal blood testosterone levels if the conversion of testosterone to dihydrotestosterone in the tissues is elevated. This is the case, for example, in idiopathic forms of hirsutism (REF).

Progesterone plays an important role in the tight closing of the os of uterus (Mahendroo). The softening thereof before giving birth is a result of local 5α -reductase-induced degradation of progesterone to dihydroprogesterone, which is a very weak gestagen. By inhibiting the progesterone catabolism in this part of the uterus, the substances of the invention are therefore also

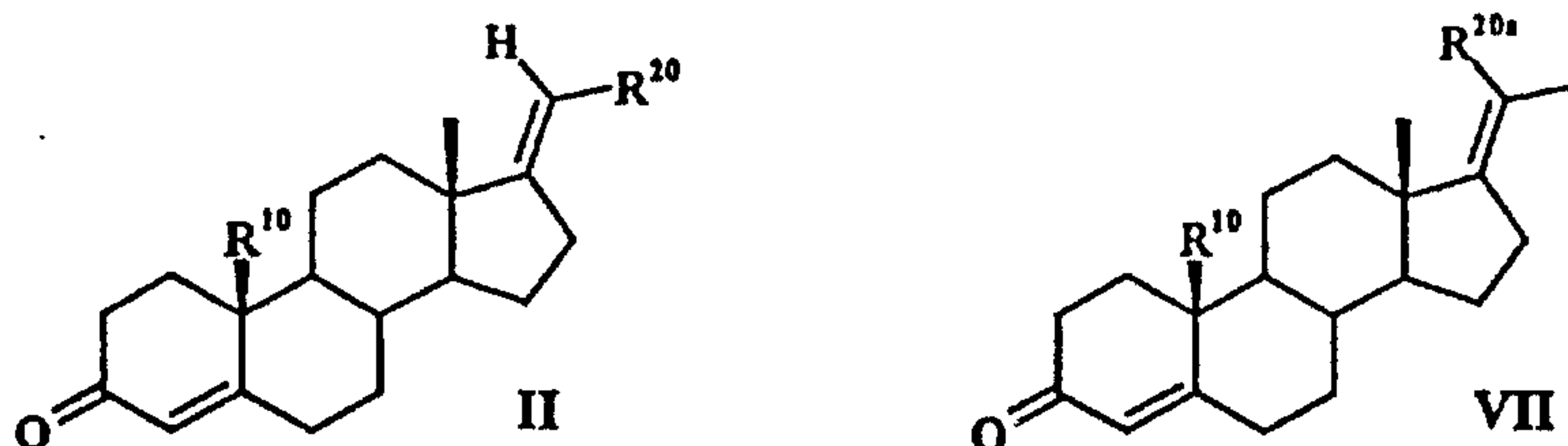
suitable for preventing premature maturation and opening of the os of uterus.

5 α -Reduced metabolites of progesterone (REF from Lancet) and other C21-steroids and the metabolites thereof formed in the body, for example allo-pregnanolone, can act as neurosteroids and can interact with neurosteroids. Disorders of this function can result in depression. Possible indications for the substances of the invention are prostate diseases, alopecia of the masculine type, acne and hirsutism as well as various gynecological clinical conditions such as the premenstrual syndrome. The appearance of 5 α -reduced metabolites of progesterone in the CNS plays an important role in the onset of such conditions. Premature opening of the os of uterus can be induced by increased degradation of progesterone to dihydroprogesterone in this tissue. The substances of the invention are suitable for preventing this catabolism and thus the premature maturation of the cervix uteri. The substances of the invention can exert their action by inhibiting the 5 α -reduction of testosterone or progesterone in the organs and tissues affected by this disorder. In addition, the blood levels of the 5 α -reduced metabolites are lowered.

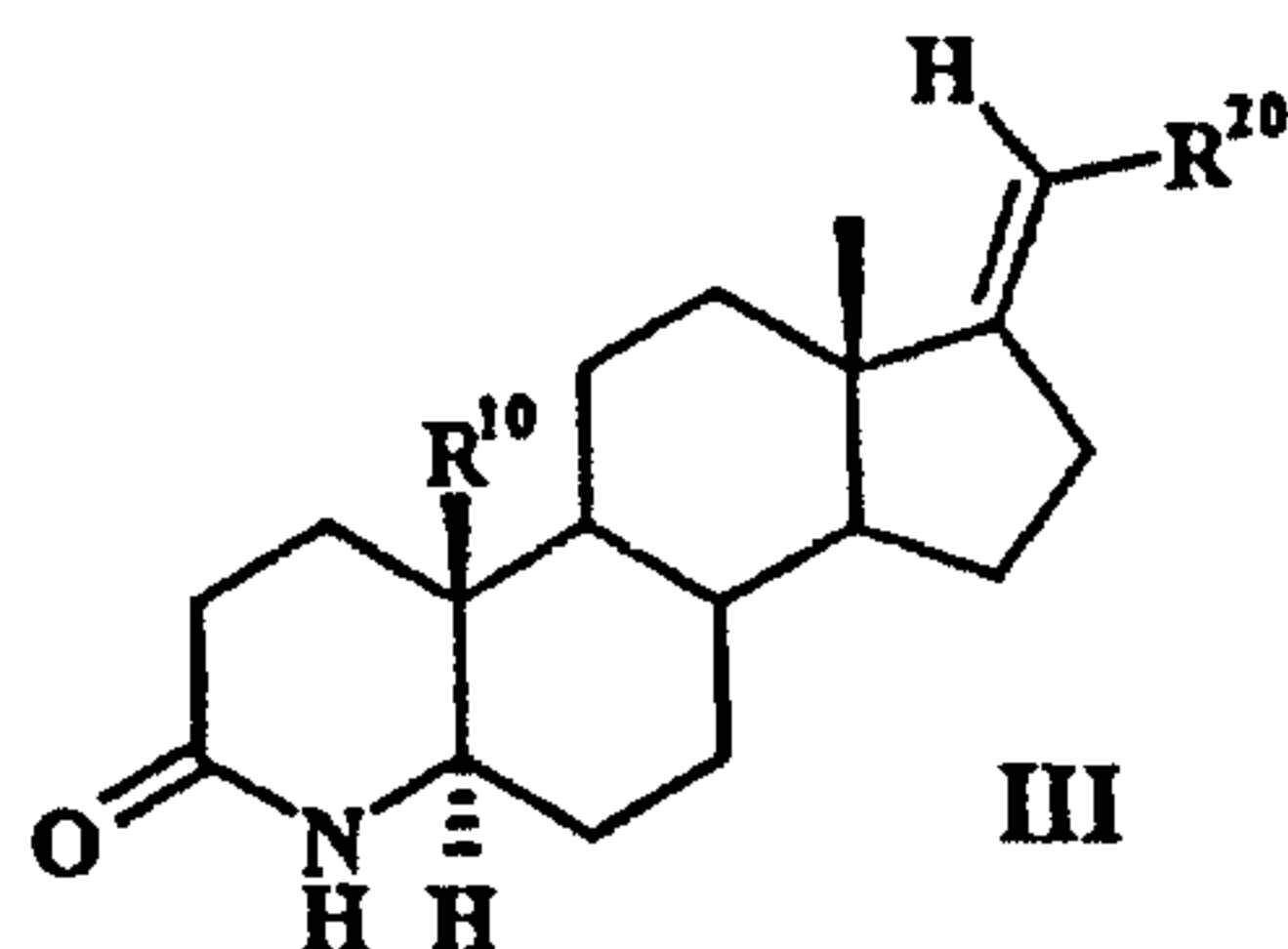
Moreover, the compounds of the invention constitute intermediates for the synthesis of other pharmacologically highly active steroid products.

The compounds of the invention are prepared as indicated in Claims 4 and 5.

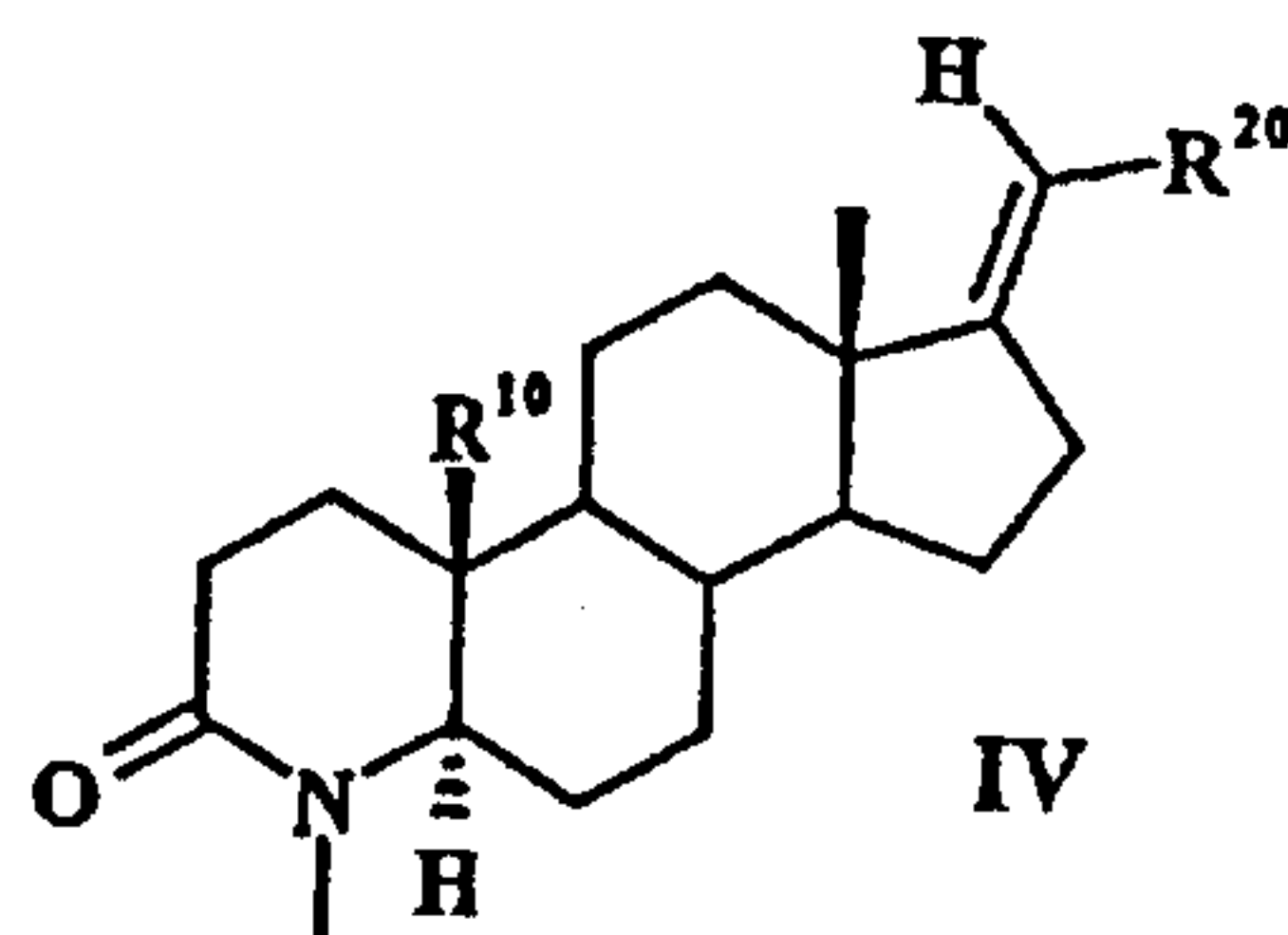
According to the invention, the compounds of Claim 1 can be derived from the 17-methylenesteroids of general formula II and general formula VII.



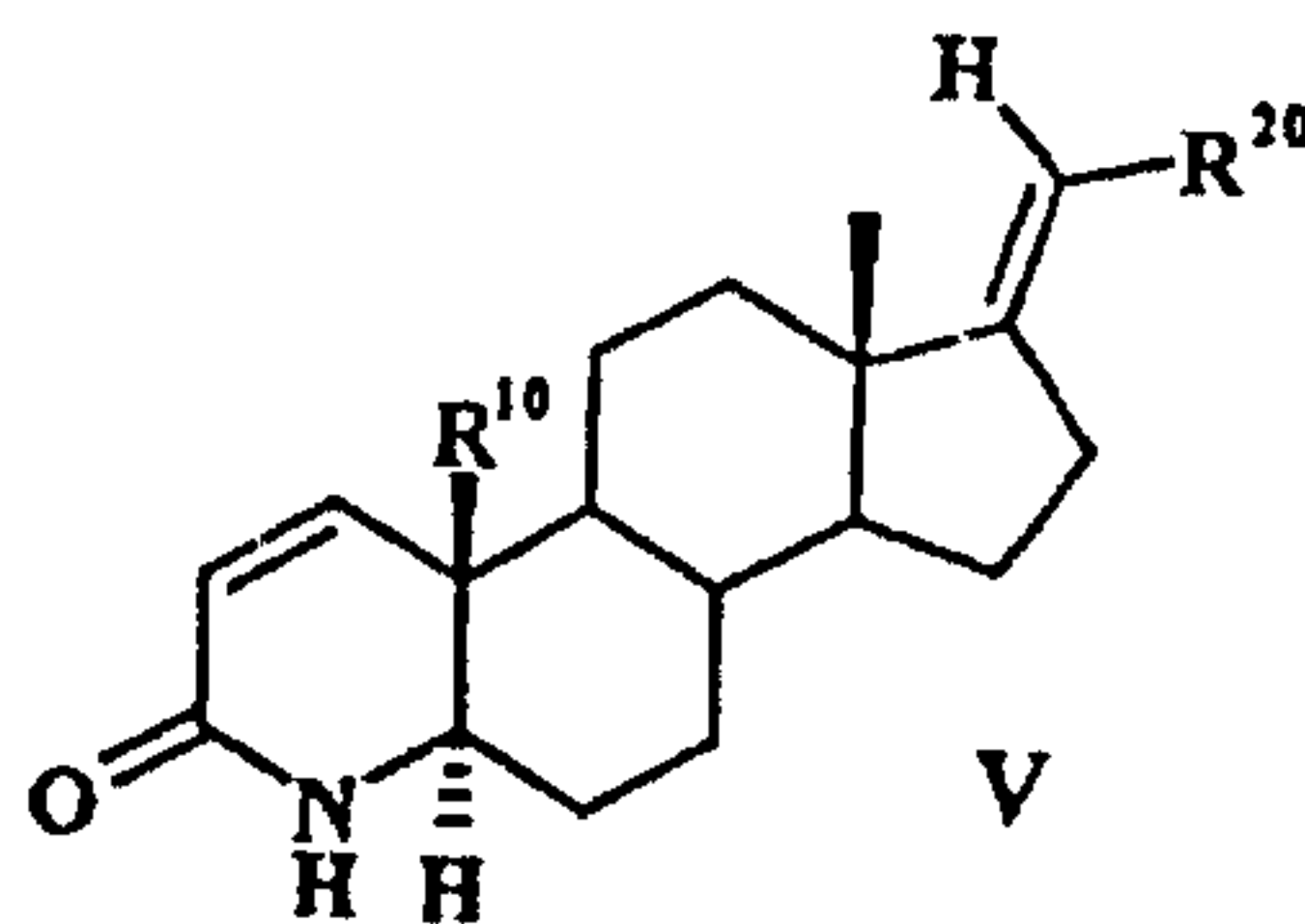
Compounds according to Claim 1 are obtained by reacting compounds of general formula II in a known manner with NaIO₄ with catalytic mediation of KMnO₄ in a protic solvent, preferably tert.BuOH, to form the 3,5-seco keto acid, cyclizing this acid with NH₄OAc in glacial acetic acid to form the unsaturated lactam and then reducing said lactam to the saturated lactam of general formula III with HCOOH/K₂CO₃ in DMF



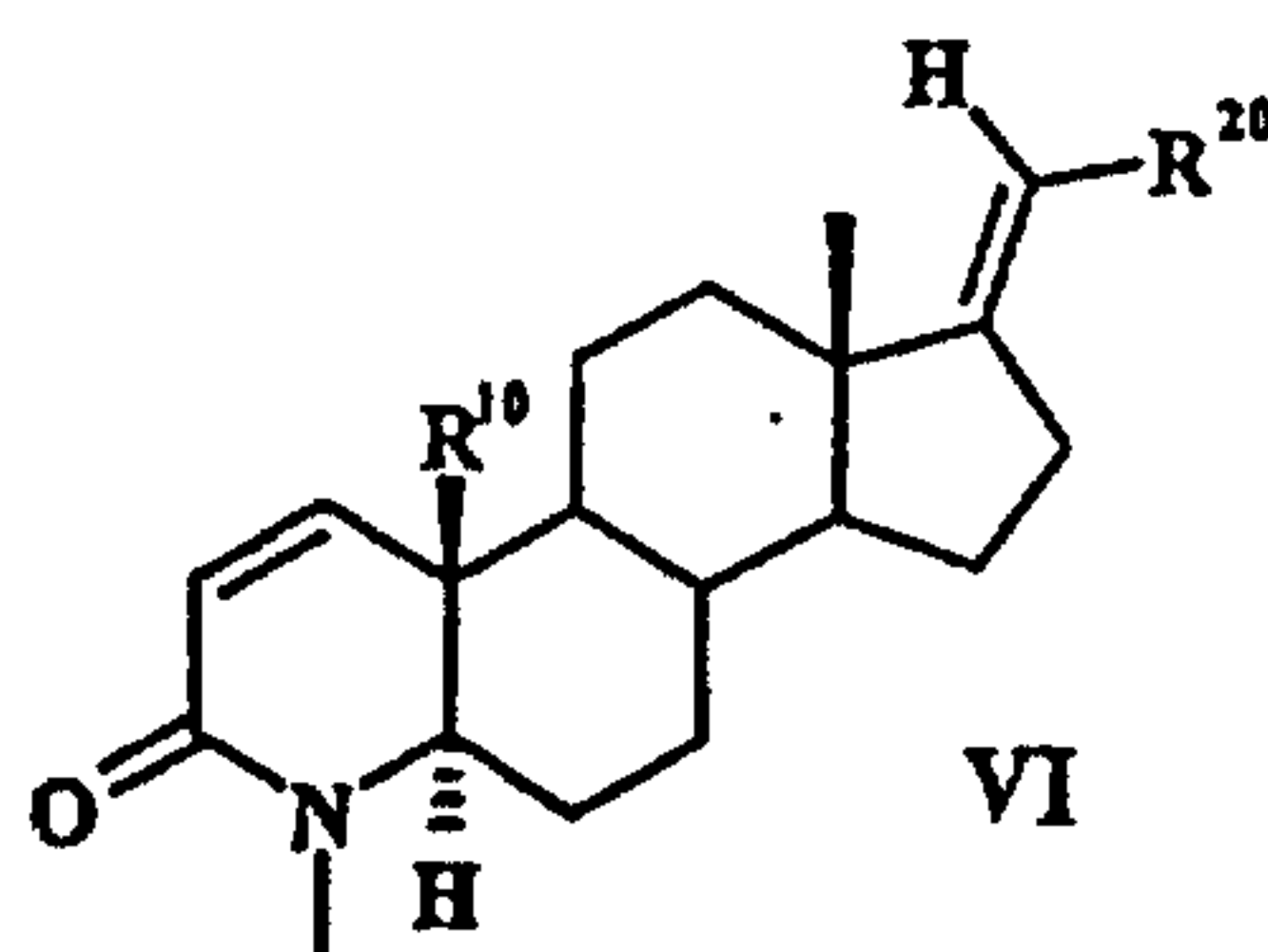
furthermore reacting the compounds of general formula III with MeI and NaH in a dipolar aprotic solvent, preferably DMF, to form the 4-methyl-substituted compounds of general formula IV



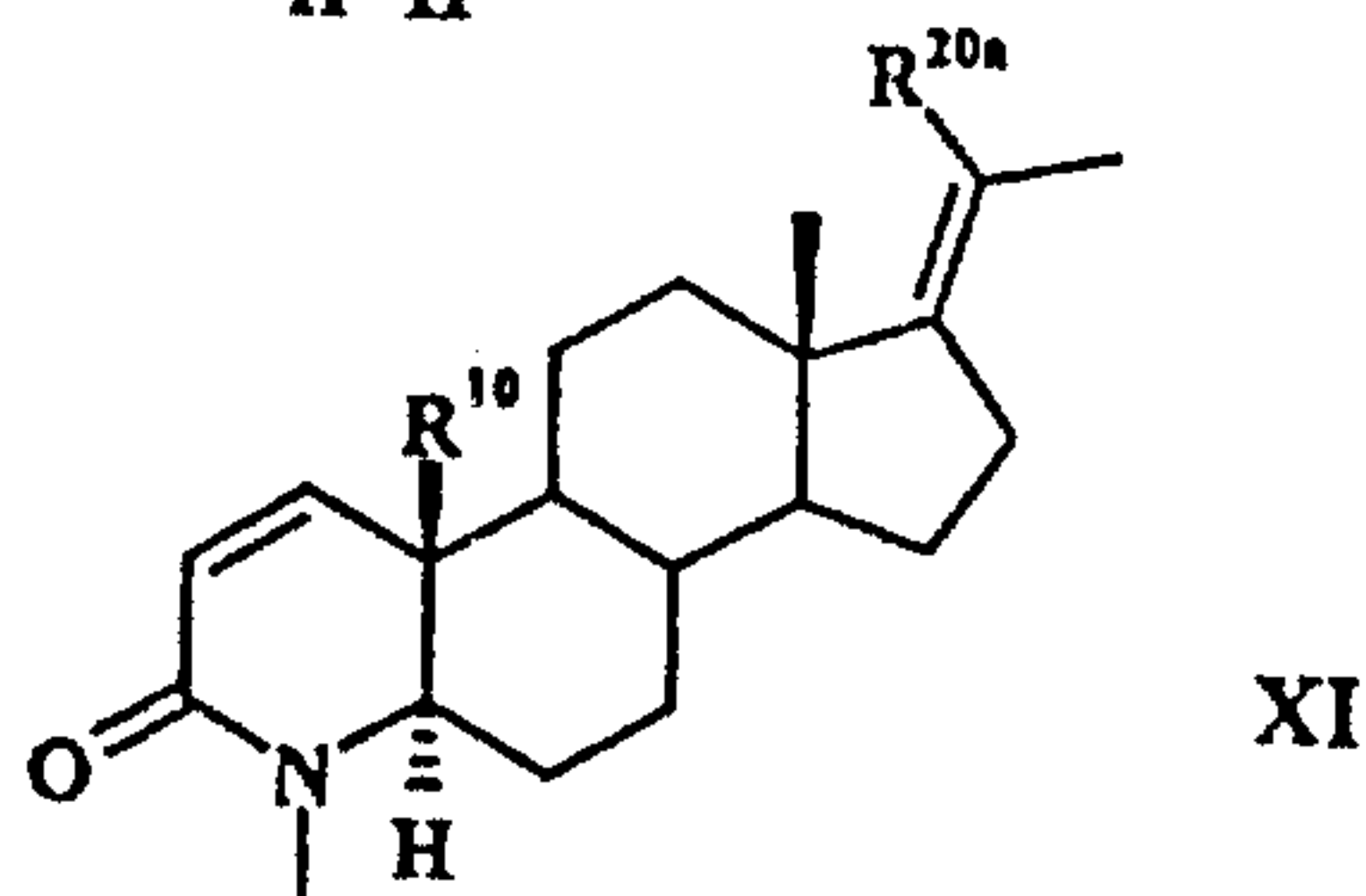
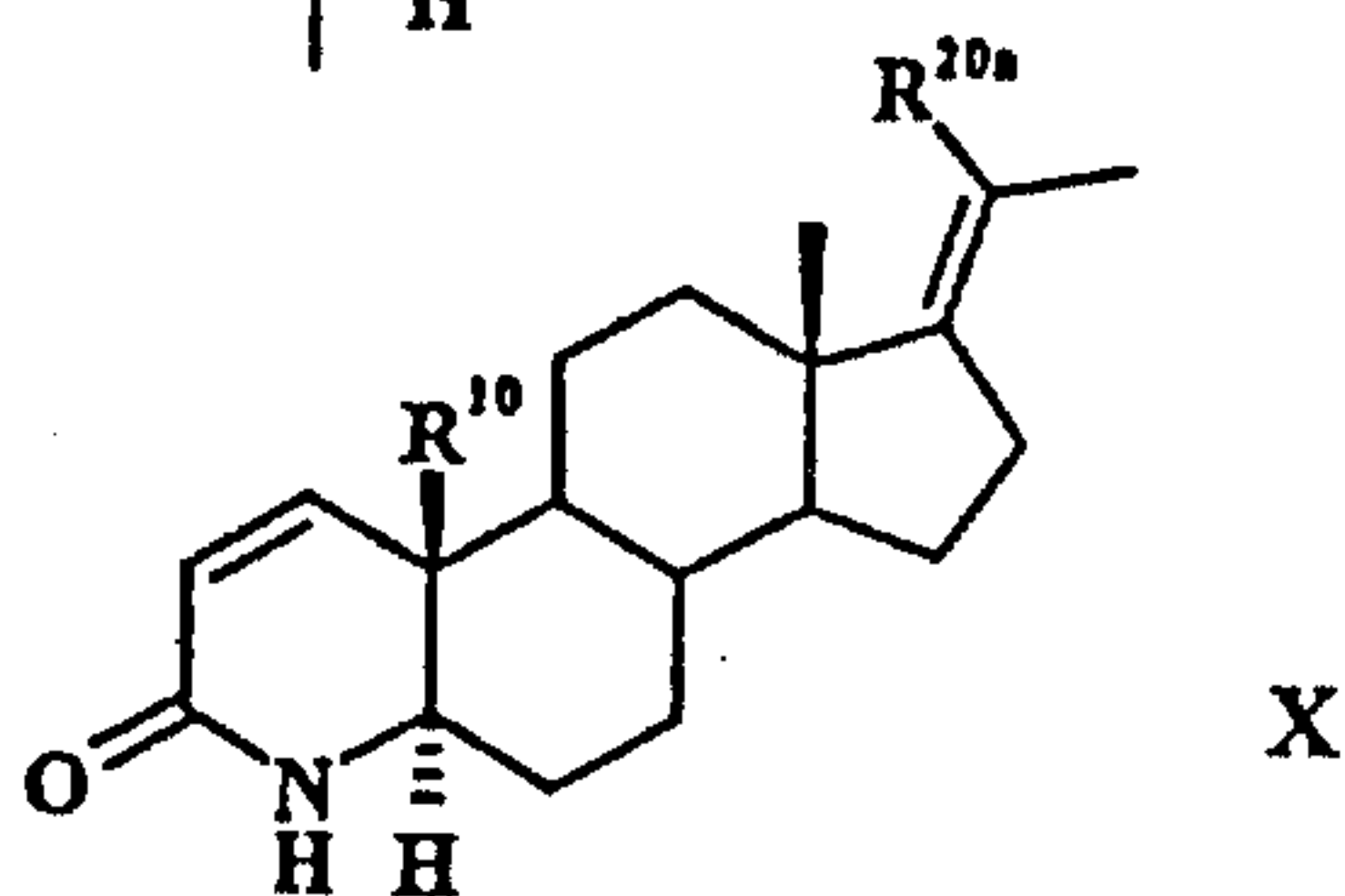
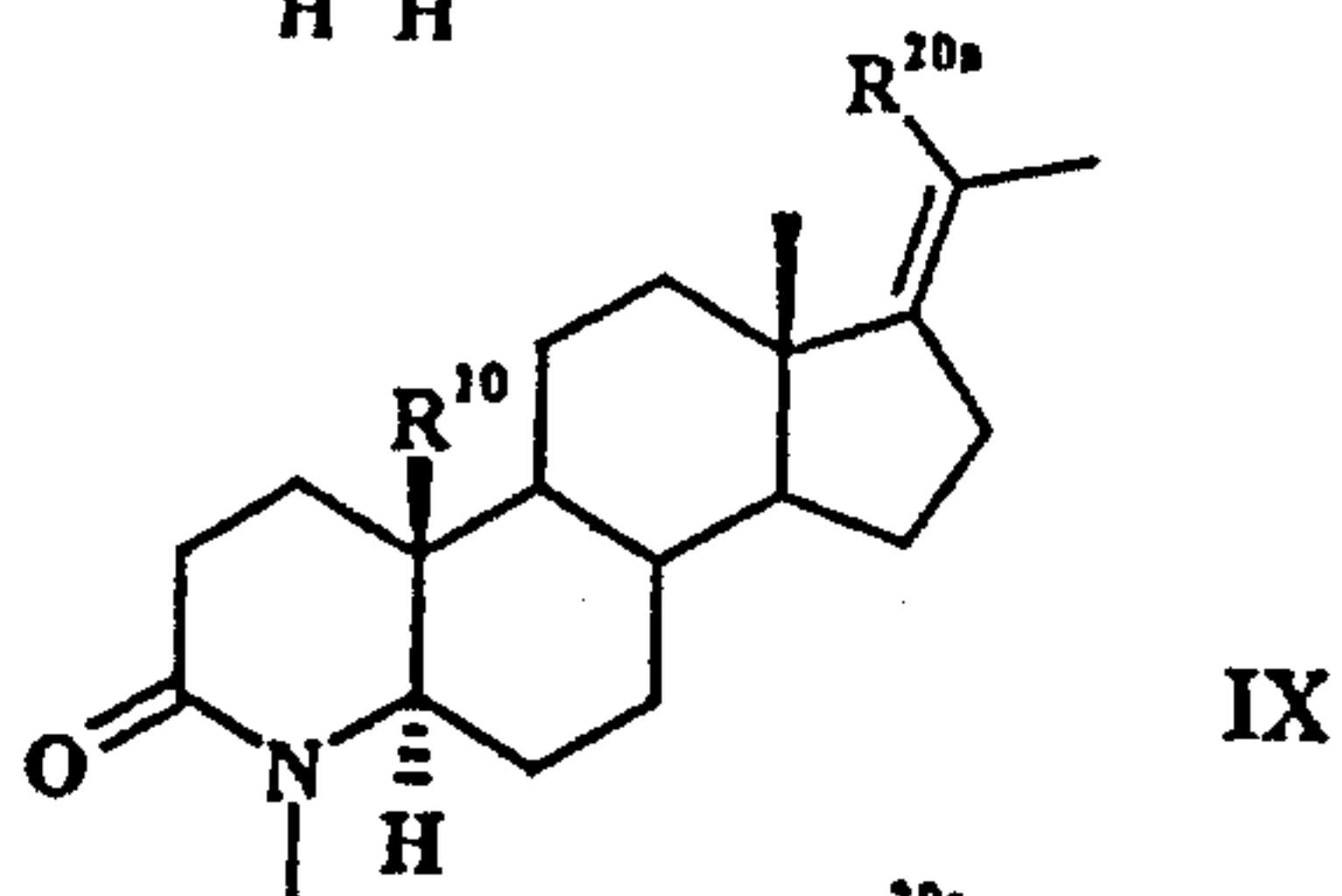
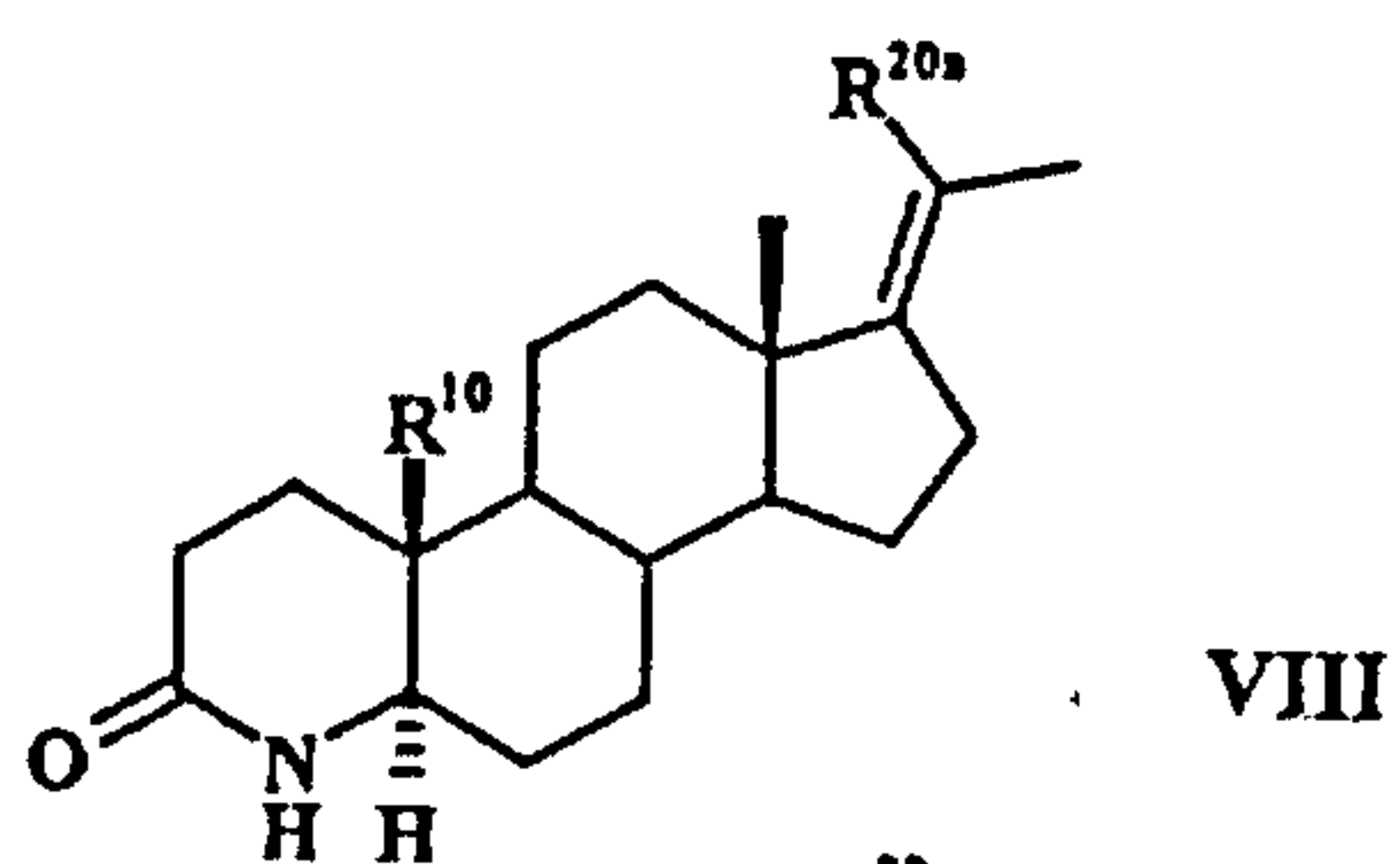
and reacting other compounds of general formula III by a silyl-mediated DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) oxidation in a dipolar aprotic solvent such as dioxane to form the dehydrogenated lactams of general formula V



The compounds of general formula V, like the compounds of general formula III, are reacted with MeI and NaH to form the 4-methyl-substituted lactams of general formula VI



Moreover, compounds according to Claim 1 are obtained by subjecting compounds of general formula VII to the same chemistry as the compounds of general formula II thus forming compounds of general formulas VIII, IX, X and XI.



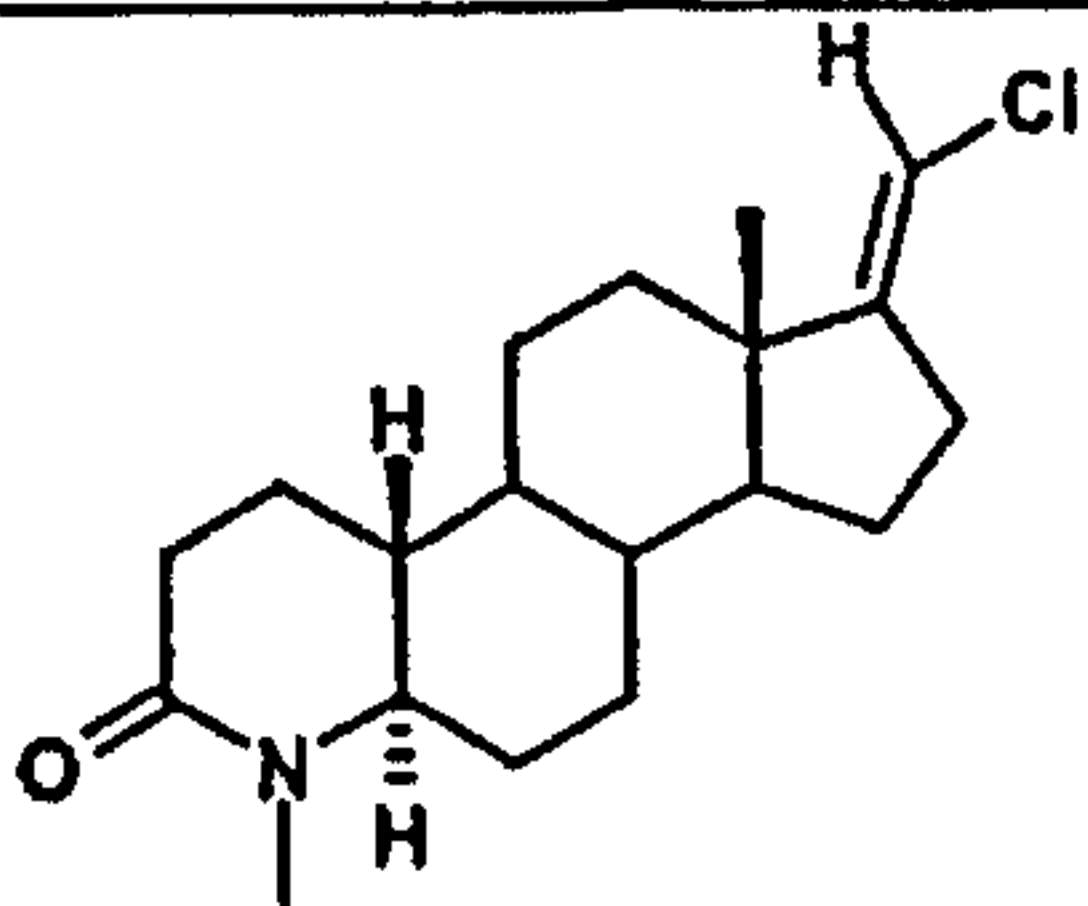
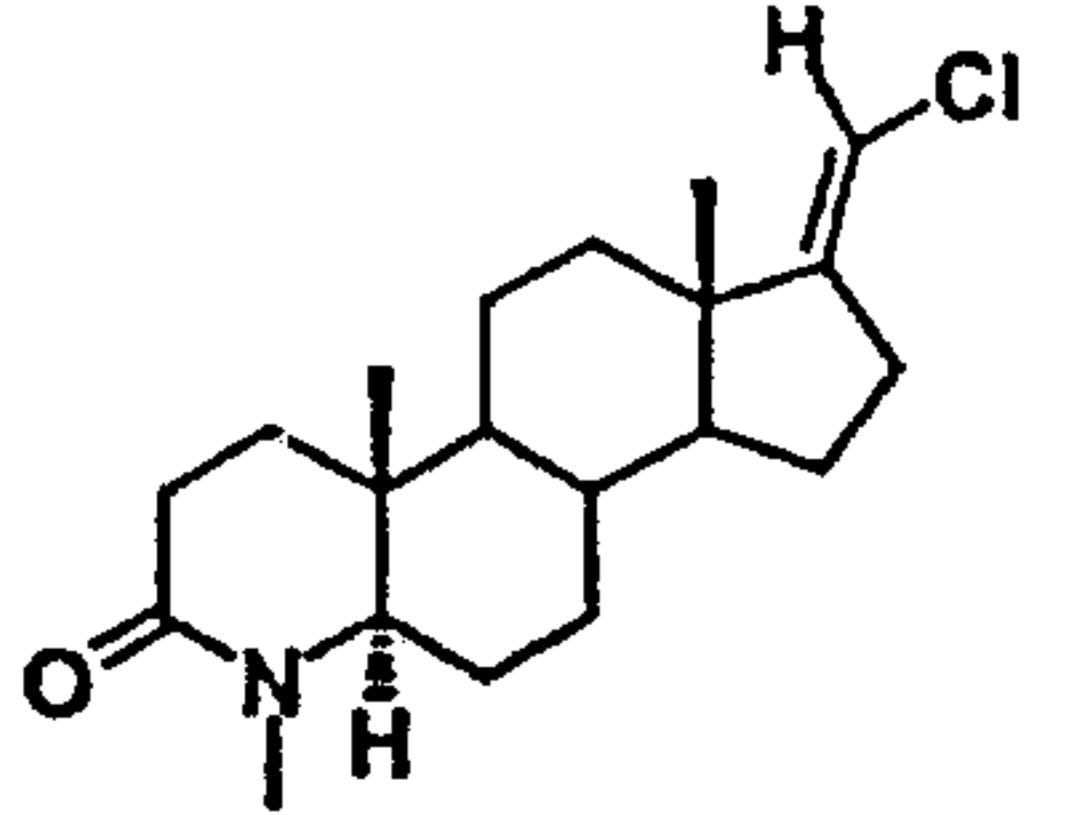
RESULTS

Evaluation of antiandrogenic activity in castrated male rats (see figures/table). Castrated immature male rats were treated for 7 days with testosterone propionate (TP) and the substances of the invention (0.1 mg of TP alone and/or 1 mg of 5 α -reductase inhibitor/animal/day, s.c., n = 5 - 10/group). The treatment with TP caused a severe increase in weight of the accessory genital glands (prostate and seminal vesicle). In the animals treated with the vehicle and with 5 α -reductase inhibitor alone, the weights of the examined organs remained at low values. We found that the substances of the invention exerted an inhibitory effect in the test systems selected.

Table XX [sic] shows that the compounds J 1879 and J 1924 weakened appreciably the effects of TP on the prostate and seminal vesicle.

Table:

Inhibition of the action of testosterone propionate (TP) on the growth of the seminal vesicle and prostate. Test on sexually immature, castrated male rats, n = 5 - 10/group, dosage: TP: 0.1 mg/animal/day s.c., 5 α -reductase inhibitor: 1 mg/animal/day s.c., difference vehicle controls and TP controls = 100%.

ET 01.31:	Prostate	Seminal vesicle
 TP + J 1879	34	25
 TP + J 1924	39	41

The studies to determine the IC₅₀ values of the steroids J 1879 and J 1924 for the 5 α -reductase outside the genital tract were carried out in four different human bone cell lines (hOB cells). The cells were incubated for 6 hours with 0.5 μ M androstendione (0.1 μ M [³H] androstendione; 0.4 μ M androstendione) with or without adding increasing concentrations of the inhibitor (10⁻¹¹ - 10⁻⁸ M).

After the incubation, the medium was extracted with chloroform : methanol (2 : 1, vol : vol), the steroids (substrate and 5 α -reduced metabolites) were separated by thin-layer chromatography, and the DNA content of the cells of the samples was determined. The 5 α -reductase activity (sum of the 5 α -reduced metabolites formed: 5 α -androstandione, 5 α -dihydrotestosterone, 5 α -androstan-3 α ,17 β -diol, 5 α -androstan-3 β ,17 β -diol expressed in pmol/ μ g DNA/h) was determined in duplicate samples. The relative 5 α -reductase activity (5 α -reductase activity of the samples with added inhibitor compared to the corresponding control values, namely those for the samples without added

inhibitor) is shown in the figure always as a mean $\pm$ SEM. The IC₅₀ values of J 1879 and J 1924 for the 5 α -reductase in bone cells amounted to $< 10^{-10}$ M in all cases.

In addition, within the framework of studies to determine the IC₅₀ values of J 1879 and J 1924, the inhibiting action of LY 191704, a nonsteroidal specific inhibitor of type-1 5 α -reductase, finasteride, a 4-azasteroid with inhibiting action mainly on type-2 5 α -reductase, and progesterone, a physiological substrate of 5 α -reductase, was determined for comparative purposes in all four cell lines at a concentration of 10^{-8} M. It can be seen from the figures that the substances of the invention inhibited the 5 α -reductase in the cell types studied more strongly and at substantially lower concentrations than did the said natural substrates and reference substances.

The invention will be illustrated in greater detail by the following examples.

EXAMPLE 1**E-17-Chloromethylene-4-aza-5 α -androstan-3-one**

To a solution of 3.1 mmol (1.0 g) of E-17-chloromethylene-4-aza-androst-5-en-3-one in 140 mL of dimethylformamide were added with stirring 59 mL of formic acid (85%) and 115.8 mmol (16 g) of potassium carbonate, and the reaction mixture was heated at reflux for 8 hours. Toluene was then added to the reaction solution, and the mixture was evaporated under vacuum. The residue was taken up in water, and the resulting mixture was extracted with methylene chloride. The combined extracts were treated with saturated sodium carbonate solution, washed neutral with water, dried over sodium sulfate and evaporated. The resulting crude product was crystallized from acetone/n-hexane, which gave 543 mg of solid product (54%).

M.p. = 148 - 151 °C; $[\alpha]_D^{20} = +16^\circ$ (CHCl₃).

EXAMPLE 2**E-17-Chloromethylene-4-methyl-4-aza-5 α -androstan-3-one**

To a suspension of 1.06 mmol (340 mg) of E-17-chloromethylene-4-aza-5 α -androstan-3-one in 9 mL of dimethylformamide were added at room temperature and under an argon atmosphere 3.08 mmol (123 mg) of sodium hydride (60% in oil). The reaction mixture was stirred 30 min, and to it was then added dropwise a solution of 5.3 mmol (0.33 mL) of methyl iodide in 3.0 mL of dimethylformamide. After about 60 minutes, 2 mL of methanol was added followed after another 10 min by 9 mL of saturated aqueous ammonium chloride solution. The reaction mixture was diluted with water and extracted with toluene. The combined extracts were washed with water, dried over sodium sulfate and evaporated. The resulting crude product was crystallized from acetone/n-hexane, which gave 154 mg of solid product (43%).

M.p. = 150 - 162 °C; $[\alpha]_D^{20} = -7^\circ$ (CHCl₃).

EXAMPLE 3**E-17-Chloromethylene-4-aza-5 α -androst-1-en-3-one**

1.34 mmol (430 mg) of E-17-chloromethylene-4-aza-5 α -androstan-3-one was suspended in 9 mL of dioxane at room temperature and under an argon atmosphere and to the suspension were then added 1.5 mmol (340 mg) of 2,3-dichloro-5,6-dicyano-p-benzoquinone and 6.4 mmol (1.7 mL) of bis-

(trimethylsilyl)trifluoroacetamide. The mixture was stirred first 3 hours at room temperature and then 3 hours in an oil bath at about 100 - 110 °C. The reaction solution was diluted with methylene chloride and then washed first with 2% aqueous sodium hydrogen sulfite solution, then with 2N hydrochloric acid and finally with water. The remaining extract was dried over sodium sulfate and evaporated. Crystallization from acetone gave 243 mg of solid product (57%).
M.p. = 275 - 282 °C; $[\alpha]_D^{20} = -41^\circ$ (CHCl₃).

EXAMPLE 4

E-17-Chloromethylene-4-methyl-4-aza-5 α -androst-1-en-3-one

To a suspension of 0.87 mmol (279 mg) of E-17-chloromethylene-4-aza-5 α -androst-1-en-3-one in 7 mL of dimethylformamide were added at room temperature and under an argon atmosphere 2.4 mmol (98 mg) of sodium hydride (60% in oil). The reaction mixture was stirred for 30 minutes, after which a solution of 7.5 mmol (0.47 mL) of methyl iodide in 3 mL of dimethylformamide was added dropwise. After about 60 minutes, 2 mL of methanol was added followed after an additional 10 min by 9 mL of saturated aqueous ammonium chloride solution. The reaction mixture was diluted with water and extracted with toluene, and the extract was washed with water, dried over sodium sulfate and evaporated. The resulting crude product was crystallized from ethyl acetate, which gave 122 mg of solid product (42%).
M.p. = 160 - 165 °C; $[\alpha]_D^{20} = -47^\circ$ (CHCl₃).

EXAMPLE 5

E-17-Chloromethylene-4-aza-5 α -estran-3-one

To a suspension of 3.27 mmol (1 g) of E-17-chloromethylene-4-aza-estr-5-en-3-one in 150 mL of dimethylformamide were added with stirring 73.3 mL of formic acid (85%) and 121.55 mmol (16.8 g) of potassium carbonate, and the reaction mixture was heated at reflux for 12 hours. Toluene was then added to the reaction solution, and the mixture was evaporated under vacuum. The residue was taken up in water and extracted with methylene chloride. The combined extracts were treated with saturated sodium carbonate solution, washed neutral with water, dried over sodium sulfate and evaporated. The resulting crude product was crystallized from acetone/n-hexane, which gave 461 mg of solid product (46%).
M.p. = (178 - 200) 262 - 282 °C; $[\alpha]_D^{20} = -21^\circ$ (CHCl₃).

EXAMPLE 6**E-17-Chloromethylene-4-methyl-4-aza-5 α -estran-3-one**

To a suspension of 0.65 mmol (200 mg) of E-17-chloromethylene-4-aza-5 α -estran-3-one in 5.8 mL of dimethylformamide were added at room temperature and under an argon atmosphere 1.7 mmol (73 mg) of sodium hydride (60% in oil). The reaction mixture was stirred 30 min after which a solution of 3.2 mmol (0.2 mL) of methyl iodide in 2 mL of dimethylformamide was added dropwise. After about 60 minutes, 1 mL of methanol was added followed after an additional 10 min by 4 mL of saturated aqueous ammonium chloride solution. The reaction mixture was diluted with water and extracted with methylene chloride. The combined extracts were washed with water, dried over sodium sulfate and evaporated. The resulting crude product was purified by chromatography on Silica Gel 60 (eluent; methylene chloride/acetone 8/2). Crystallization from ethyl acetate then gave 131 mg of solid product (62%).

M.p. = 161-171 °C; $[\alpha]_D^{20} = -88^\circ$ (CHCl₃).

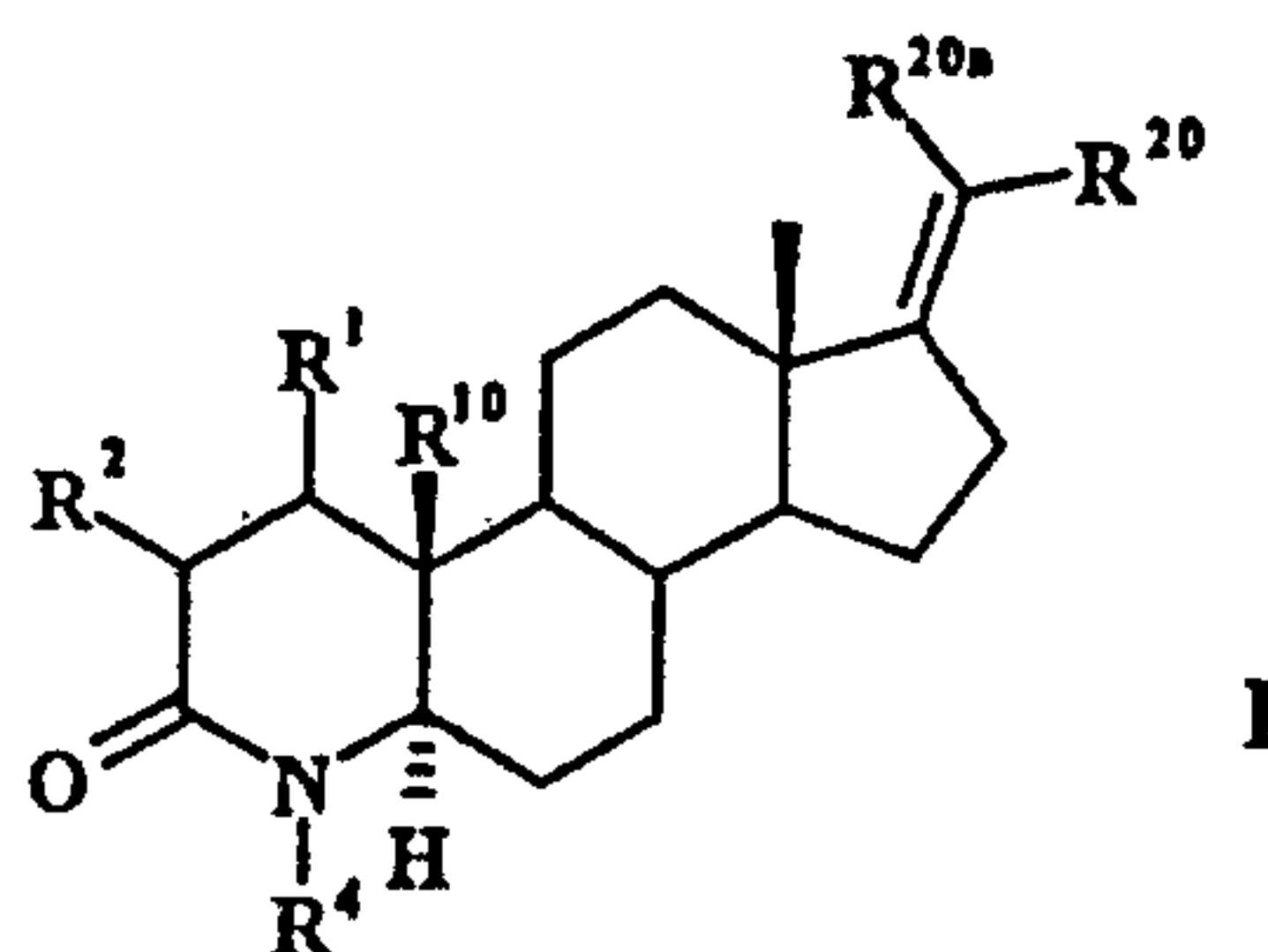
EXAMPLE 7**E-17-Chloromethylene-4-aza-5 α -estr-1-en-3-one**

1 mmol (310 mg) of E-17-chloromethylene-4-aza-5 α -estran-3-one was suspended in 6.3 mL of dioxane at room temperature and under an argon atmosphere. Thereafter, 2.3 mmol (522 mg) of 2,3-dichloro-5,6-dicyano-p-benzoquinone and 9.8 mmol (2.6 mL) of bis-(trimethylsilyl)trifluoroacetamide were added. The mixture was stirred first 3 hours at room temperature and then 15 hours in an oil bath at 100 - 110 °C. The reaction solution was diluted with methylene chloride and then washed first with 2% aqueous sodium hydrogen sulfite solution, then with 2N hydrochloric acid and finally with water. The remaining residue was dried over sodium sulfate and evaporated. Purification by chromatography on Silica Gel 60 (eluent: methylene chloride/methanol 98/2) gave 57 mg of solid product (18.5%).

$[\alpha]_D^{20} = 37^\circ$ (CHCl₃).

PATENT CLAIMS

1. Halogen-substituted and pseudohalogen-substituted 17-methylene-4-azasteroids of general formula I



wherein

R^{20} and R^{20a} separately denote fluoro, chloro, bromo, azido, cyano, isocyano, rhodano, isothiocyano, C_1 - C_4 -alkyl or hydroxy- C_1 - C_4 -alkyl groups,

R^{10} denotes a hydrogen atom or methyl group,

R^4 is selected from the group consisting of hydrogen and a C_1 - C_4 -alkyl group and

R^1 and R^2 together denote a hydrogen atom or an additional bond.

2. Halogen-substituted and pseudohalogen-substituted 17-methylene-4-azasteroids according to Claim 1,

wherein

$R^4 = H, Me$ and

$R^{20}/R^{20a} = F, Cl, Br, CN$.

3. 17-Methylene-4-azasteroids according to Claim 1, namely

E-17-chloromethylene-4-aza-5 α -estran-3-one,

E-17-chloromethylene-4-aza-5 α -androstan-3-one,

E-17-chloromethylene-4-methyl-4-aza-5 α -estran-3-one,

E-17-chloromethylene-4-methyl-4-aza-5 α -androstan-3-one,

E-17-chloromethylene-4-aza-5 α -estr-1-en-3-one,

E-17-chloromethylene-4-aza-5 α -androst-1-en-3-one,

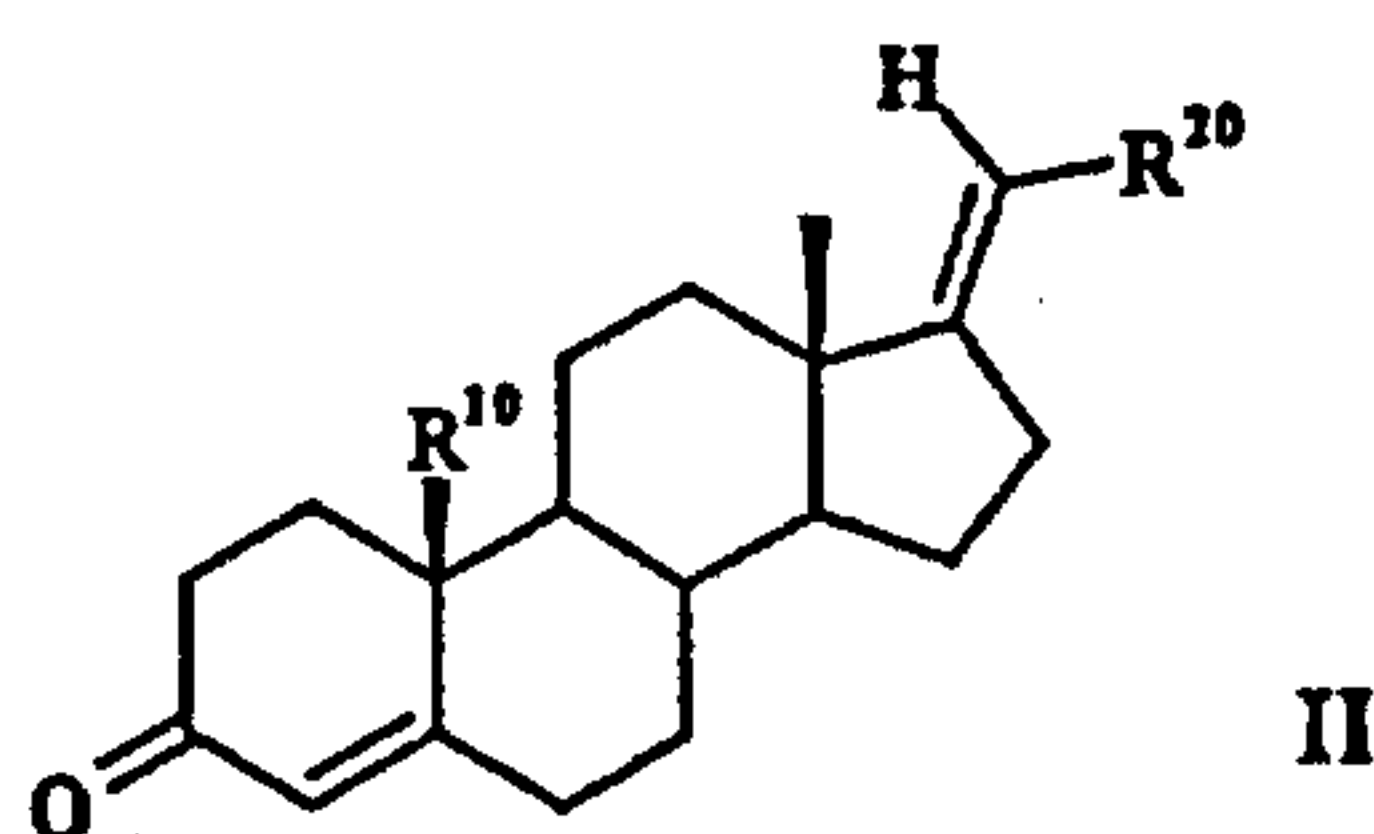
E-17-chloromethylene-4-methyl-4-aza-5 α -androst-1-en-3-one,

E-17-bromomethylene-4-methyl-4-aza-5 α -estran-3-one,

E-17-bromomethylene-4-methyl-4-aza-5 α -estran-3-one [sic],

E-17-cyanomethylene-4-methyl-4-aza-5 α -estran-3-one,
 E-17-cyanomethylene-4-methyl-4-aza-5 α -estran-3-one [sic],
 Z-17-(1')-chloroethylidene-4-methyl-4-aza-5 α -androstan-3-one,
 Z-17-(1')-chloroethylidene-4-methyl-4-aza-5 α -estran-3-one,
 Z-17-(1')-bromoethylidene-4-methyl-4-aza-5 α -androstan-3-one,
 Z-17-(1')-bromoethylidene-4-methyl-4-aza-5 α -estran-3-one.

4. Process for preparing compounds of Claim 1, characterized in that a 17-methylenesteroid of general formula II

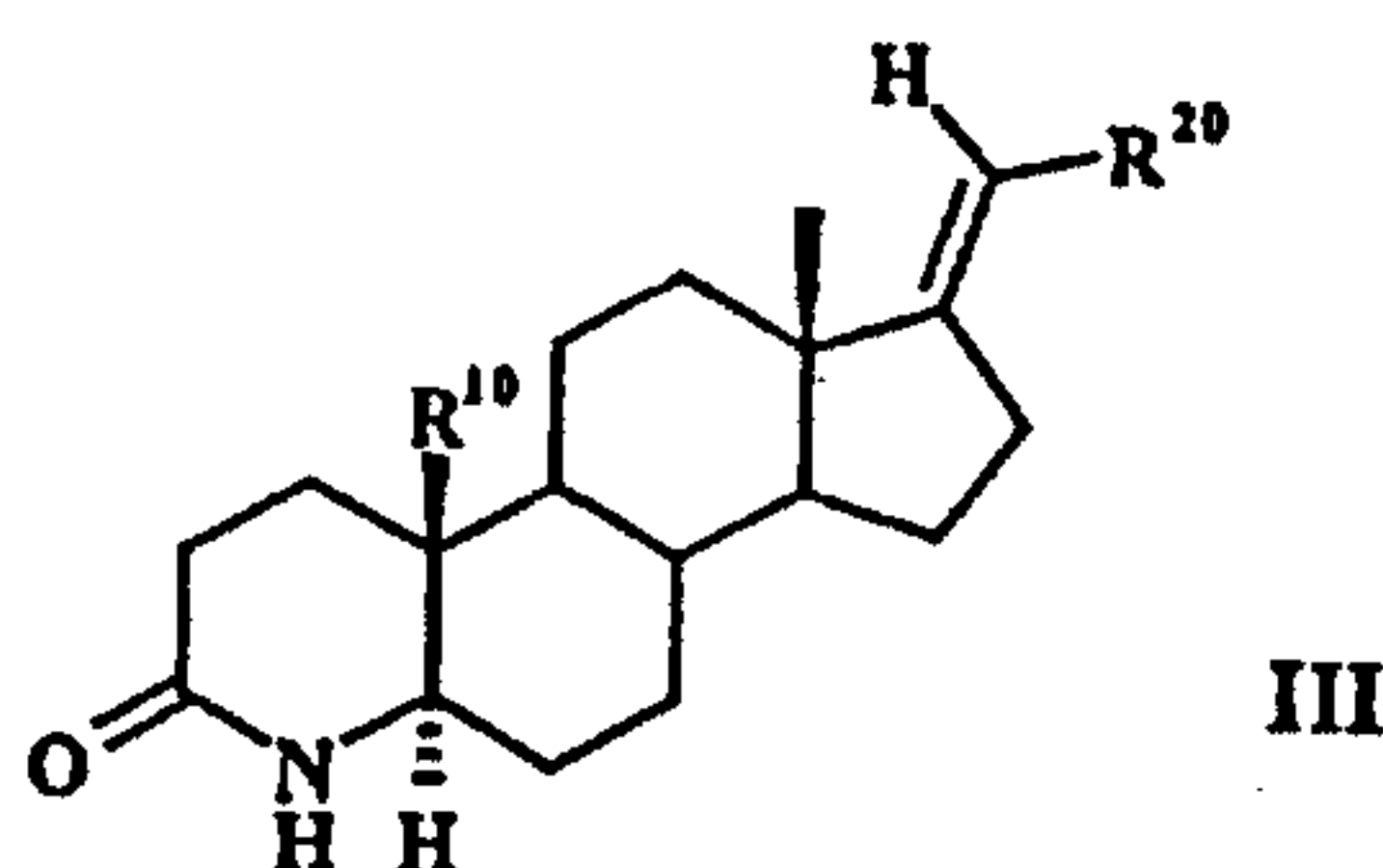


wherein

R^{20} denotes a fluoro, chloro, bromo or cyano function and

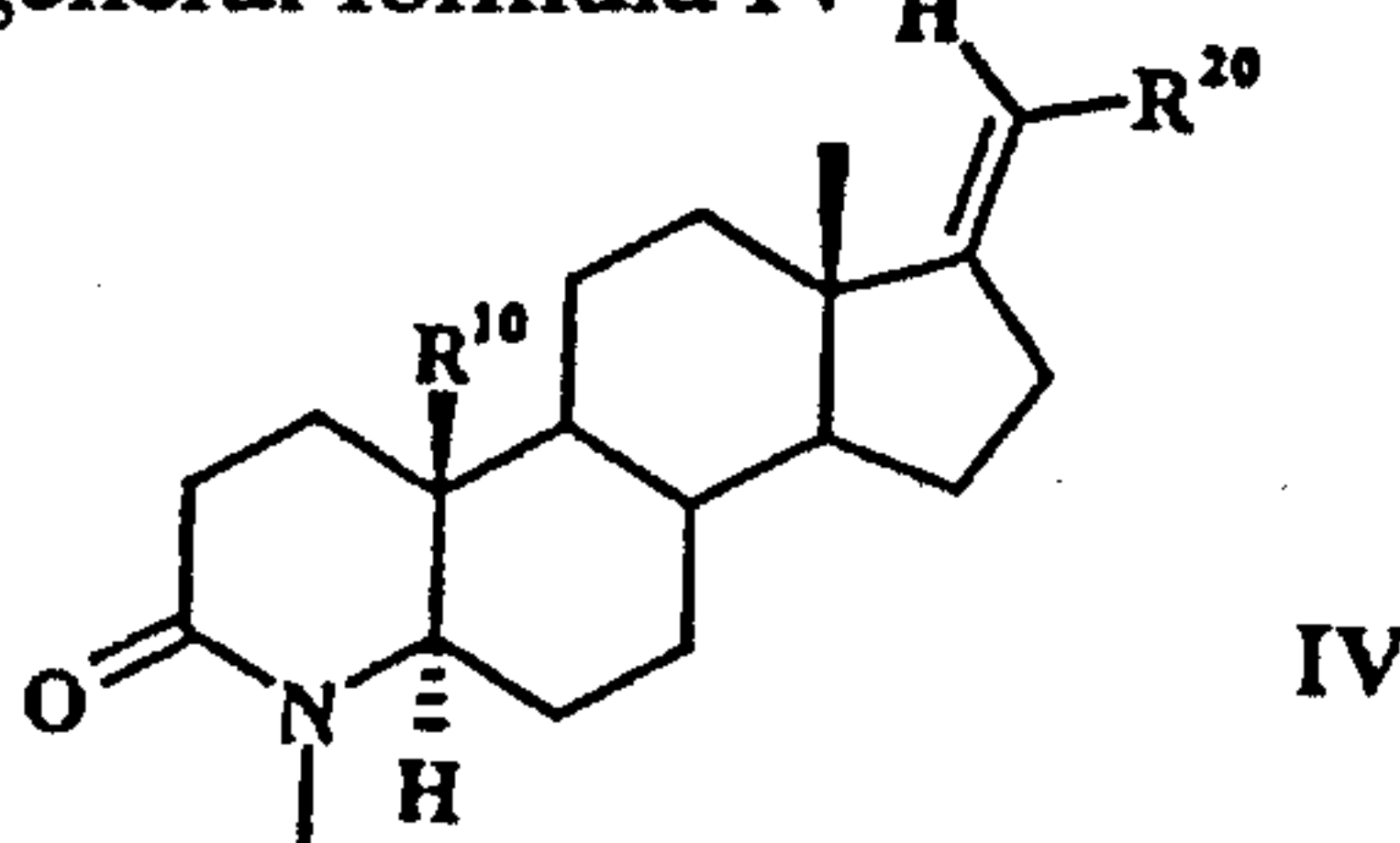
R^{10} is a hydrogen atom or a methyl group,

is made to react in a known manner with NaIO_4 under catalytic mediation of KMnO_4 in a protic solvent to form the 3,5-seco keto acid, said acid is cyclized with NH_4OAc in glacial acetic acid to form the unsaturated lactam and said lactam is then reduced with HCOOH in DMF to the saturated lactam of general formula III



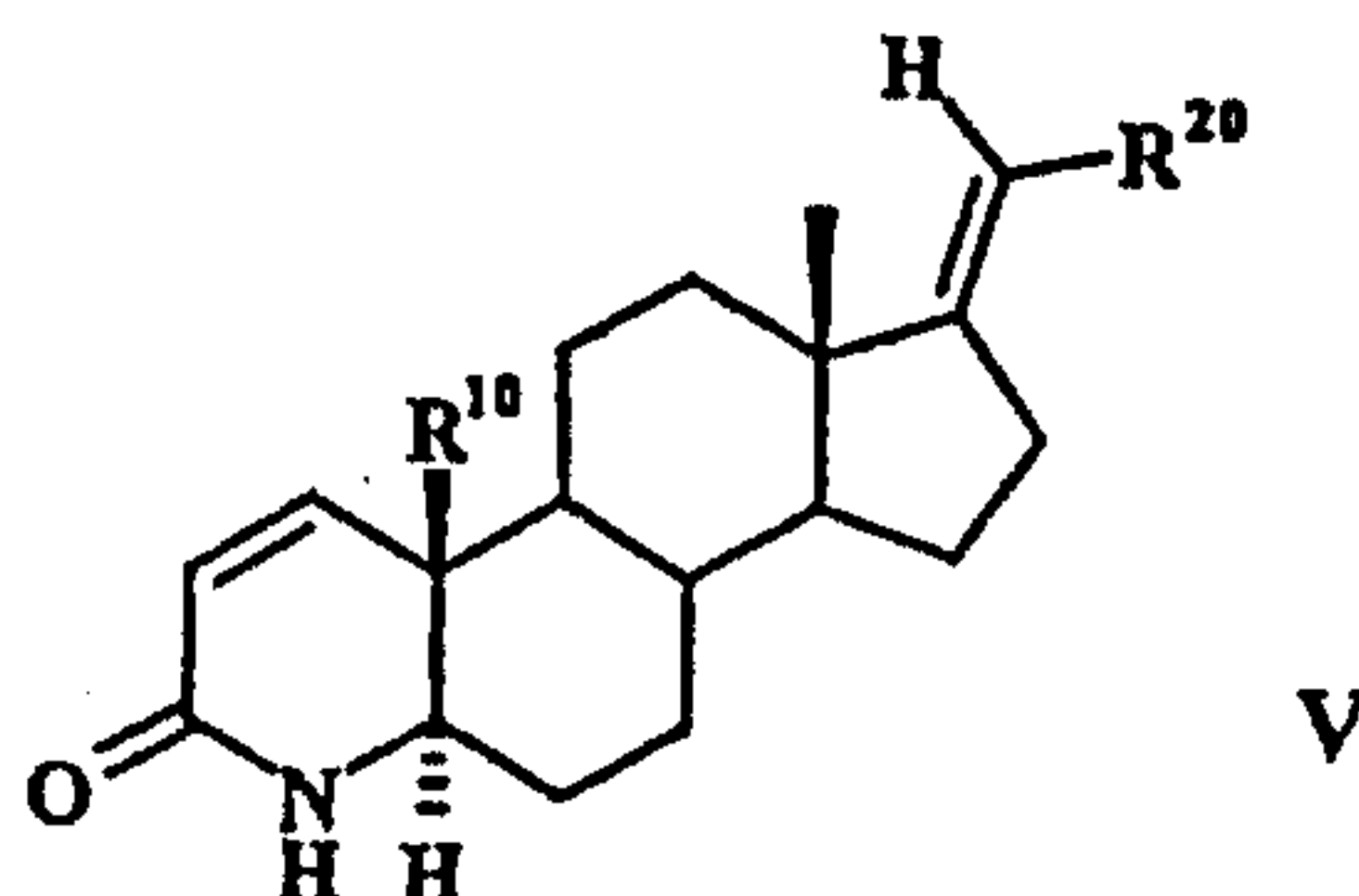
wherein the substituents R^{20} and R^{10} are the same as in formula II,

furthermore reacting the compounds of general formula III with MeI and NaH to form the 4-methyl-substituted compounds of general formula IV



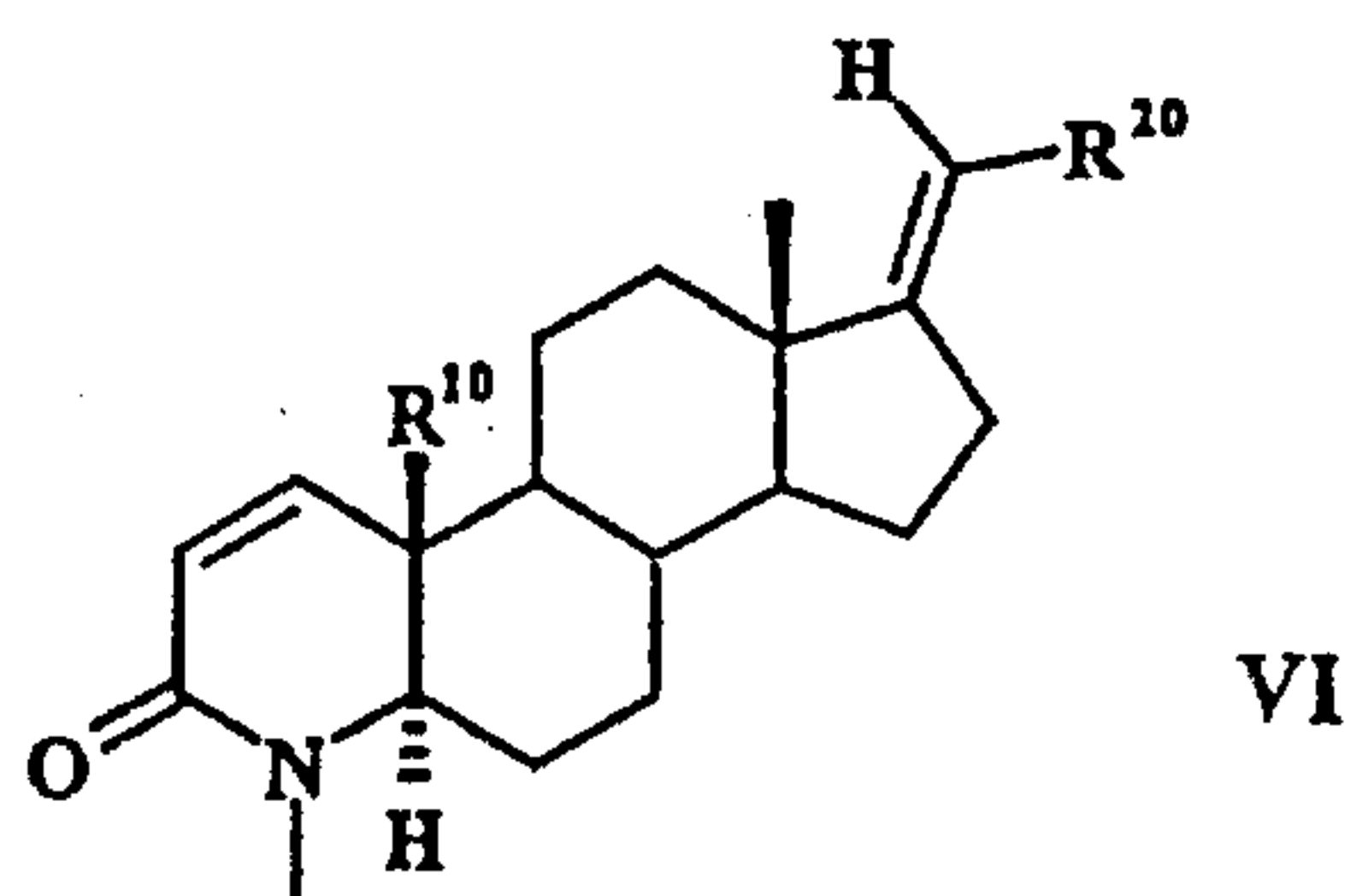
wherein the substituents R^{20} and R^{10} are the same as in formula II,

and reacting other compounds of general formula III by a silyl-mediated oxidation to form the dehydrogenated compounds of general formula V,



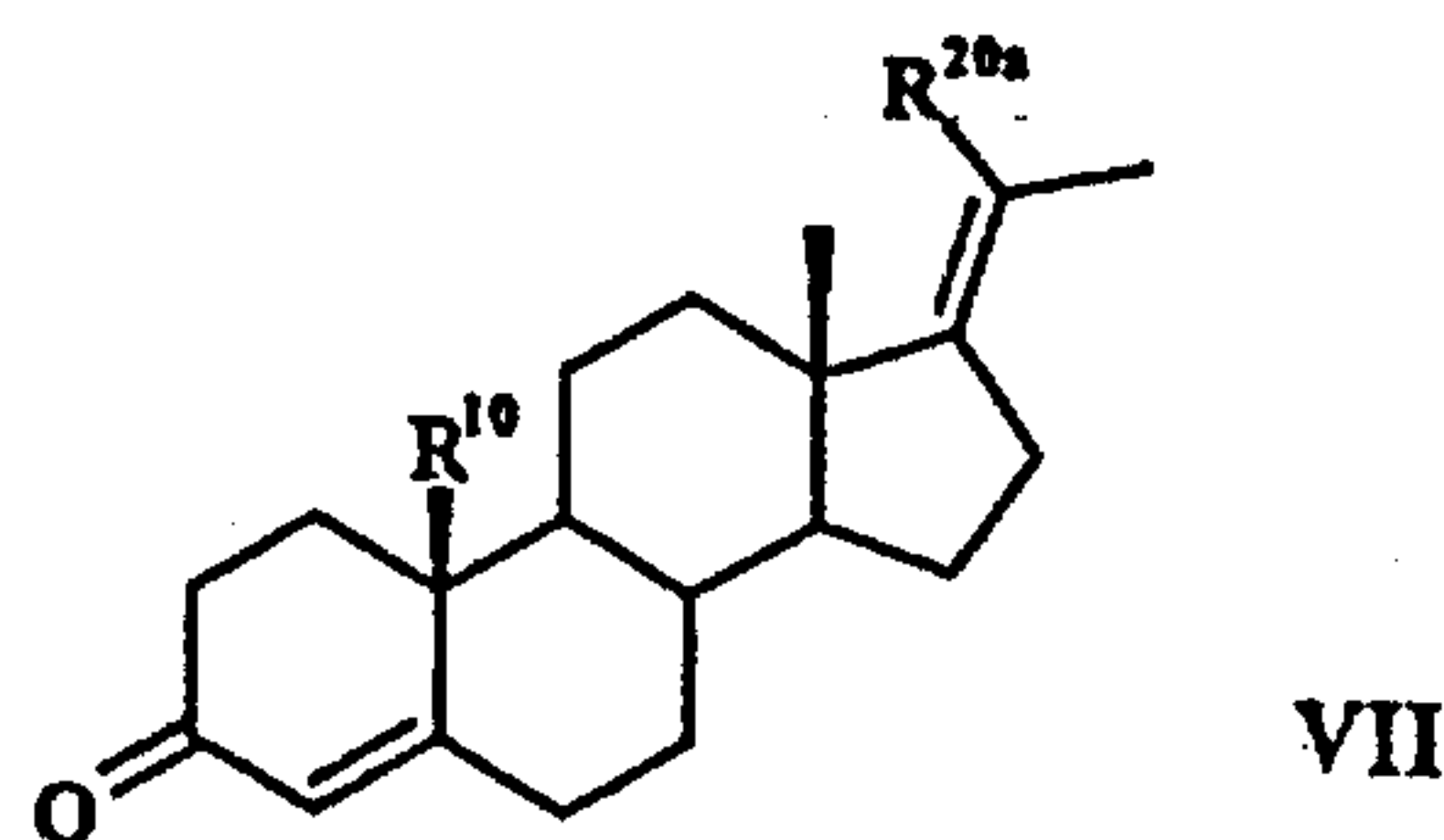
wherein the substituents R^{20} and R^{10} are the same as in formula II

and reacting the compounds of general formula V, like the compounds of general formula III, with MeI and NaH to form the 4-methyl-substituted compounds of general formula VI



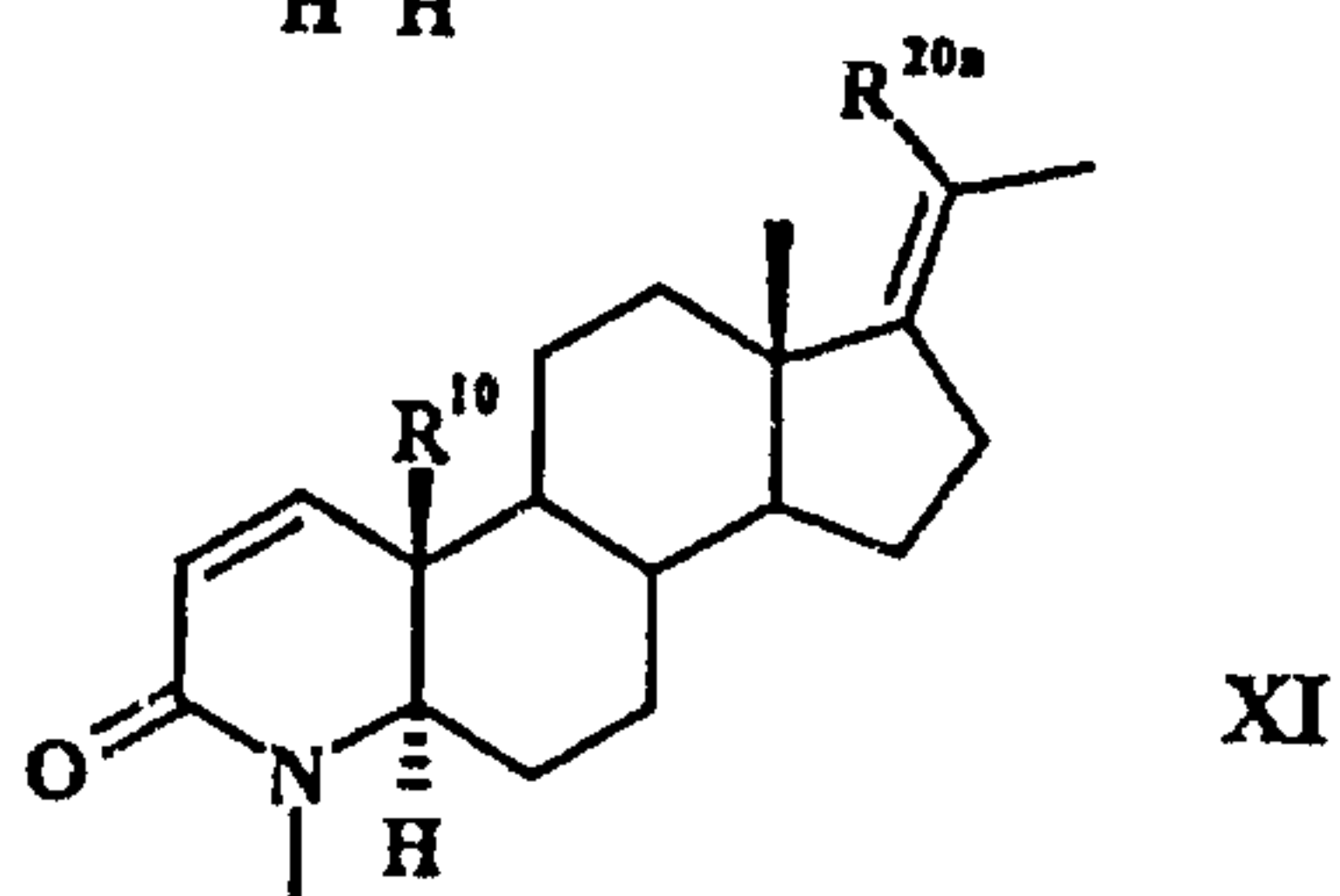
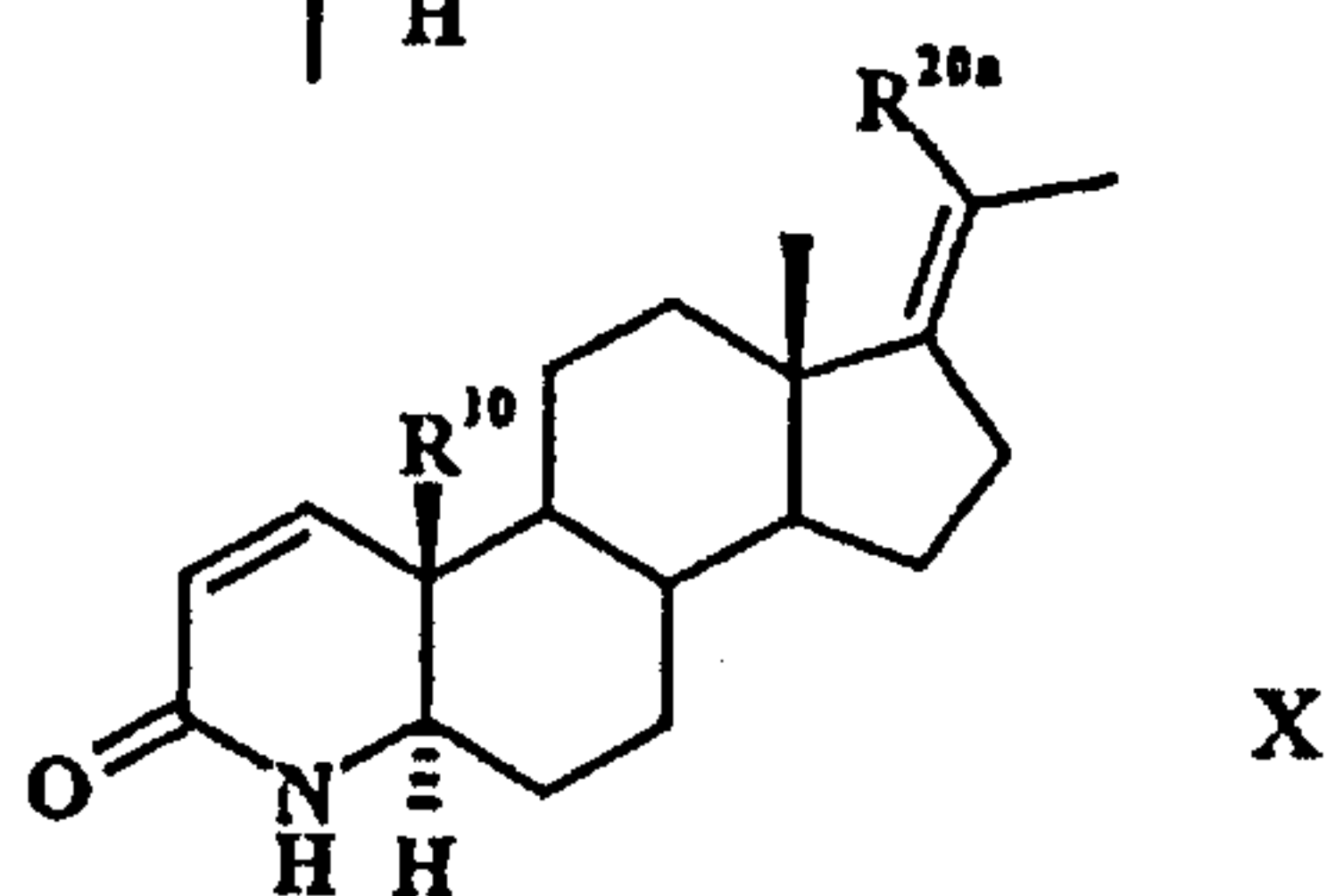
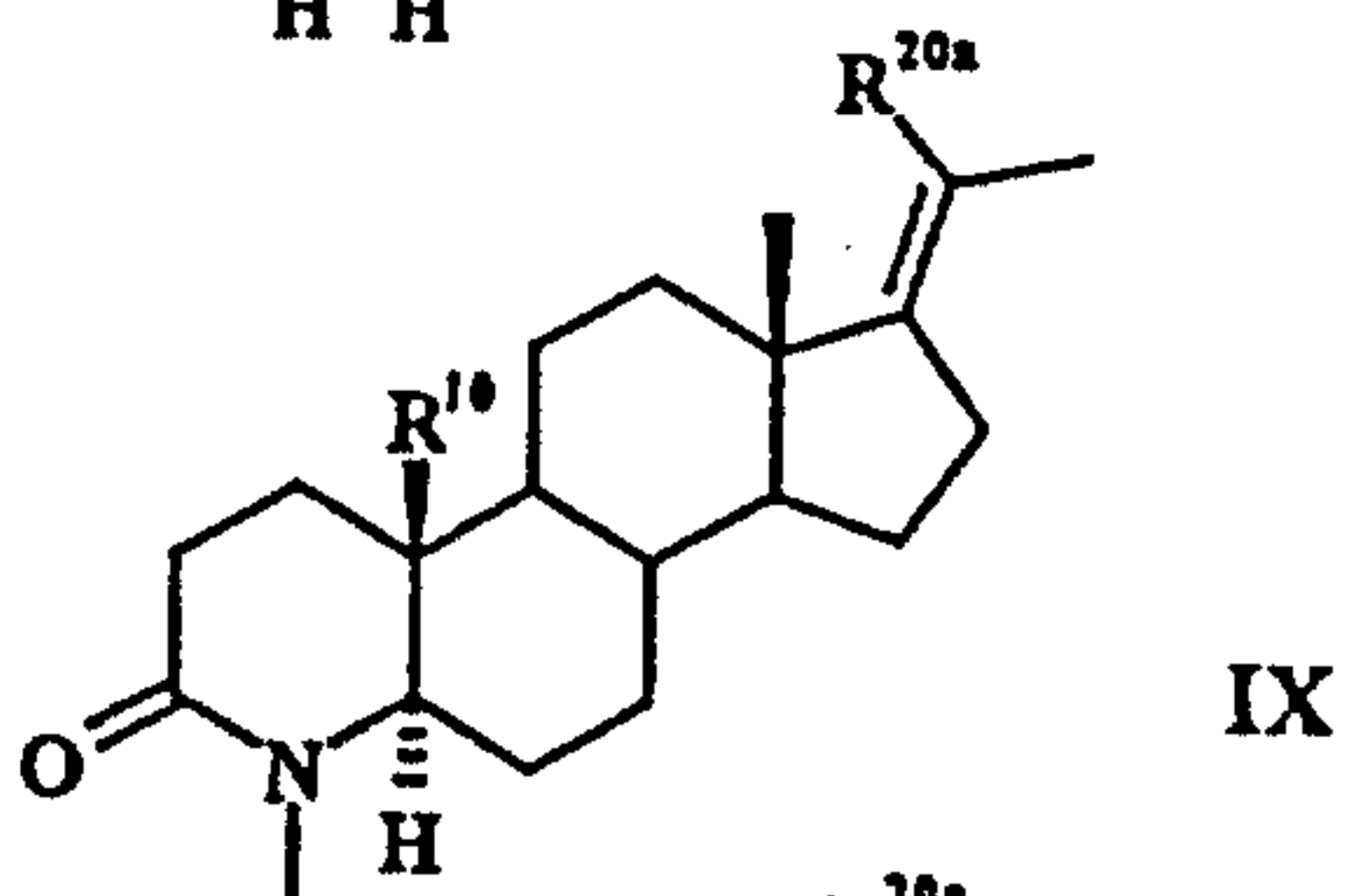
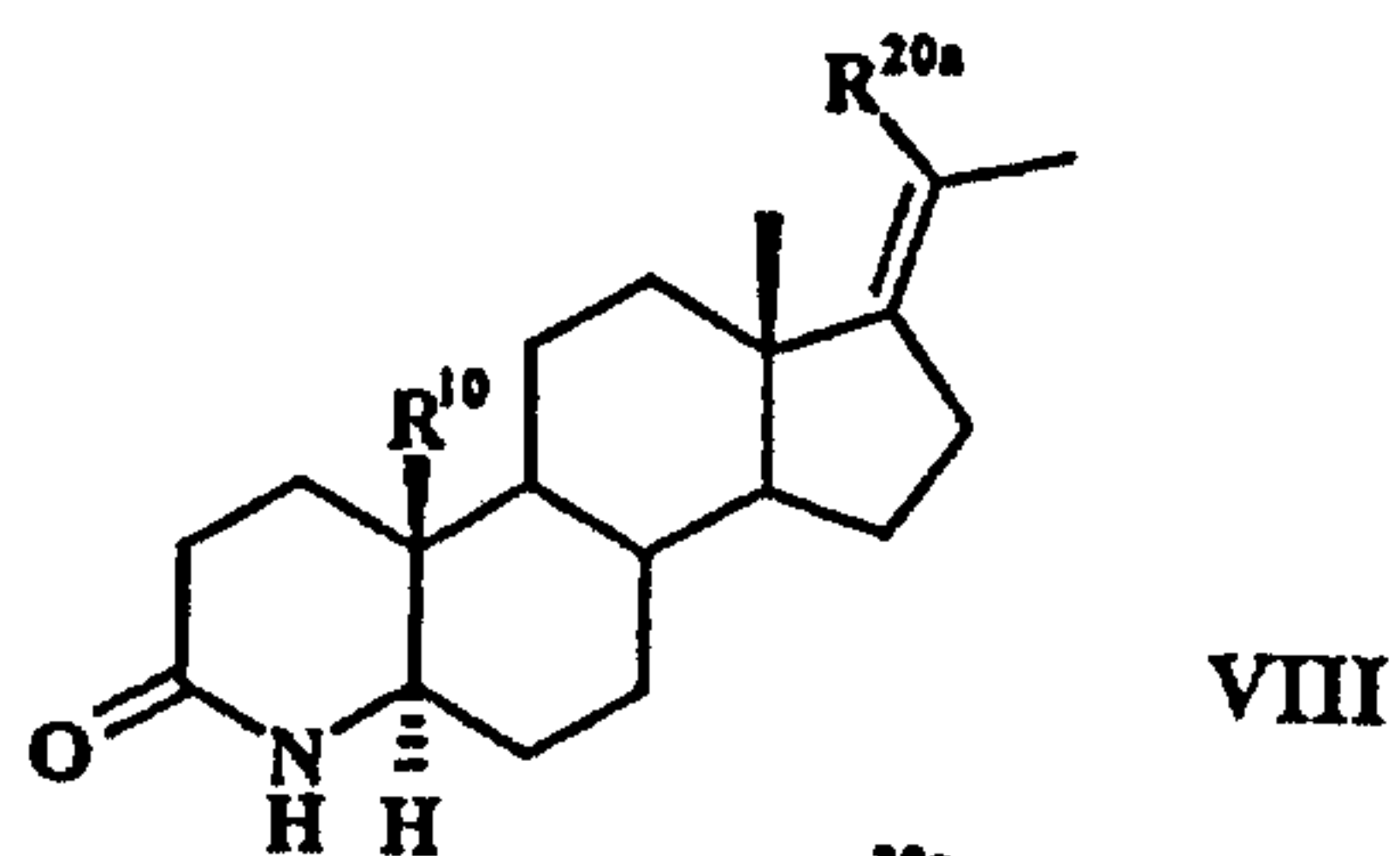
wherein the substituents R^{20} and R^{10} are the same as in formula II.

5. Process for preparing 17-methylene-4-azasteroids according to Claims 1, 2, 3, and 4, characterized in that a 17-methylenesteroid of general formula VII



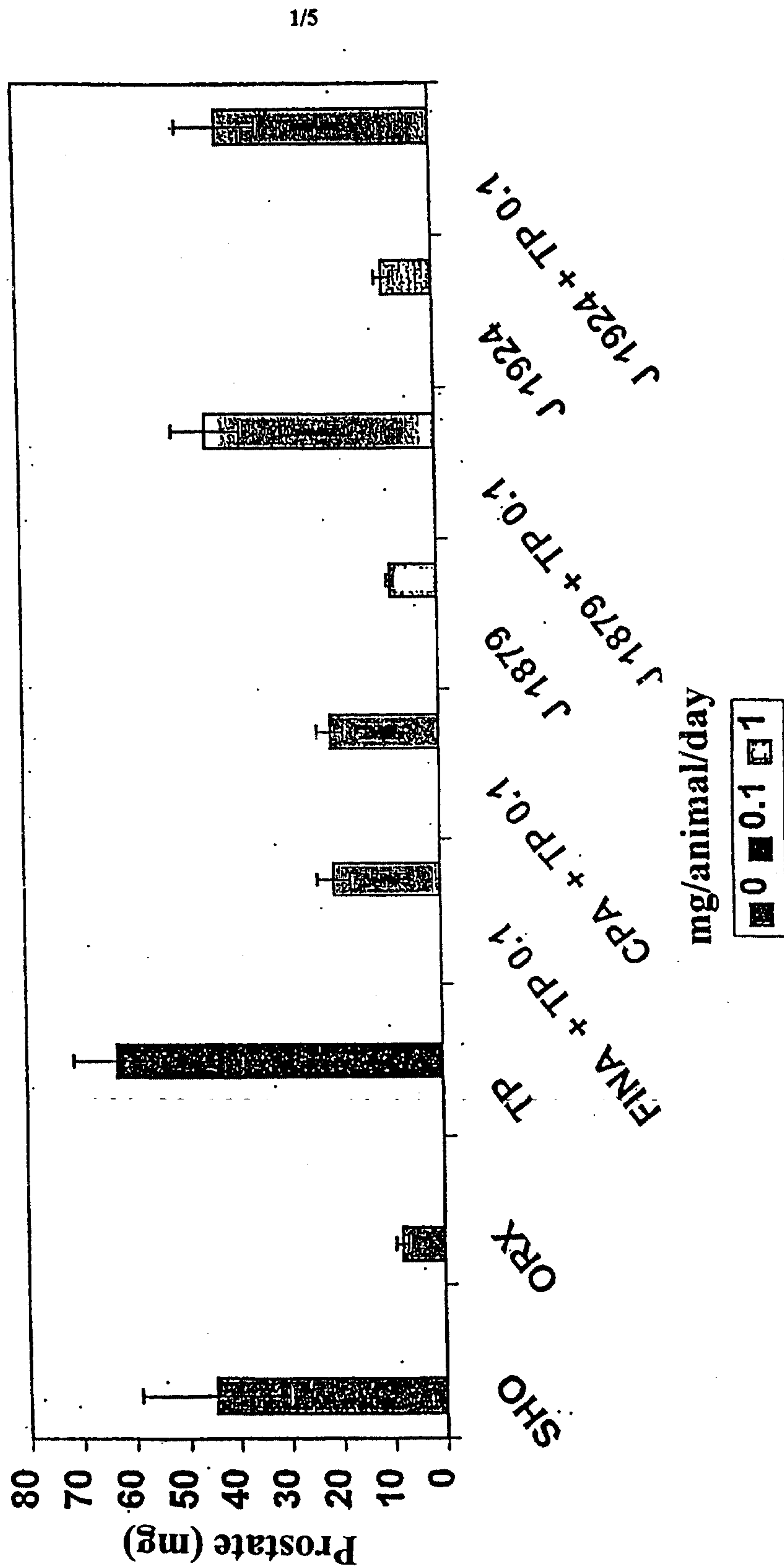
wherein

R^{20a} denotes a fluoro, chloro, bromo or cyano function and R^{10} denotes a hydrogen atom of methyl group is made to react as described in Claim 4 to form the compounds of general formulas VIII, IX, X and XI.

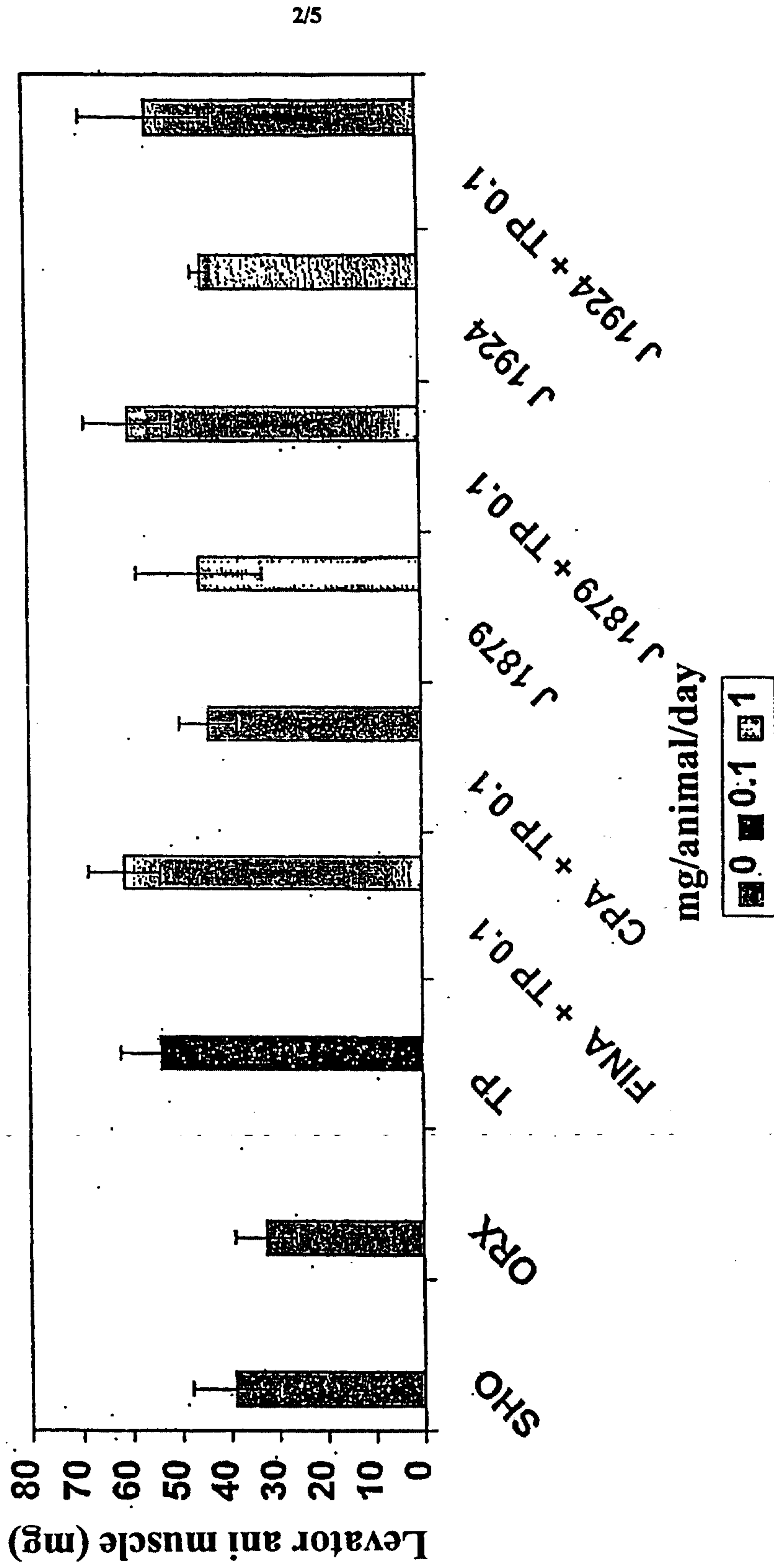


6. Pharmaceutical compositions containing at least one 7-methylene-4-azasteroid [sic] according to Claim 1, optionally together with pharmaceutically compatible auxiliary agents and carriers.

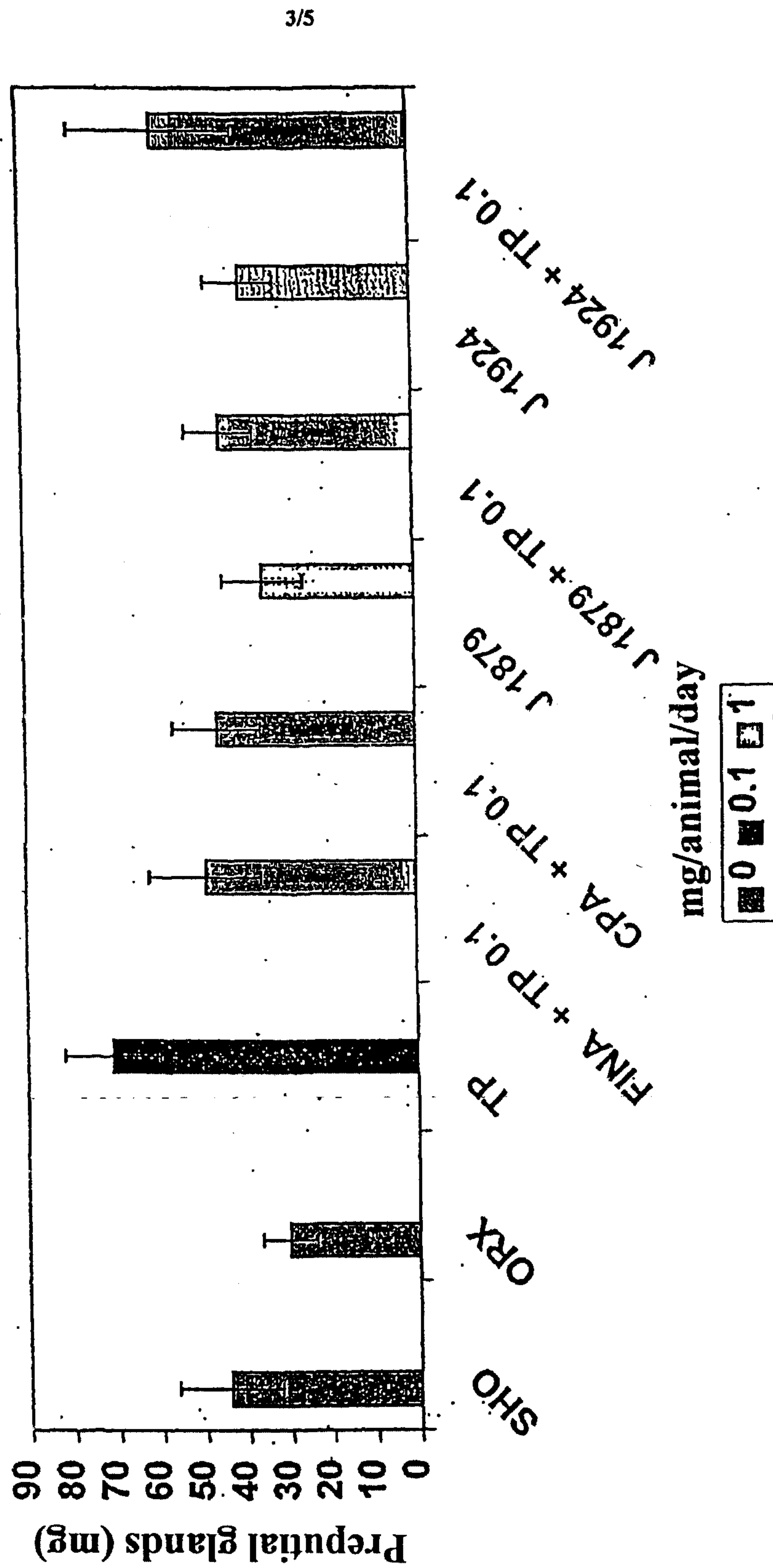
**Evaluation of J 1879 and J 1924 Versus CPA and Finasterides
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Infantile Male Rats After s.c. Administration; ET 01.31**



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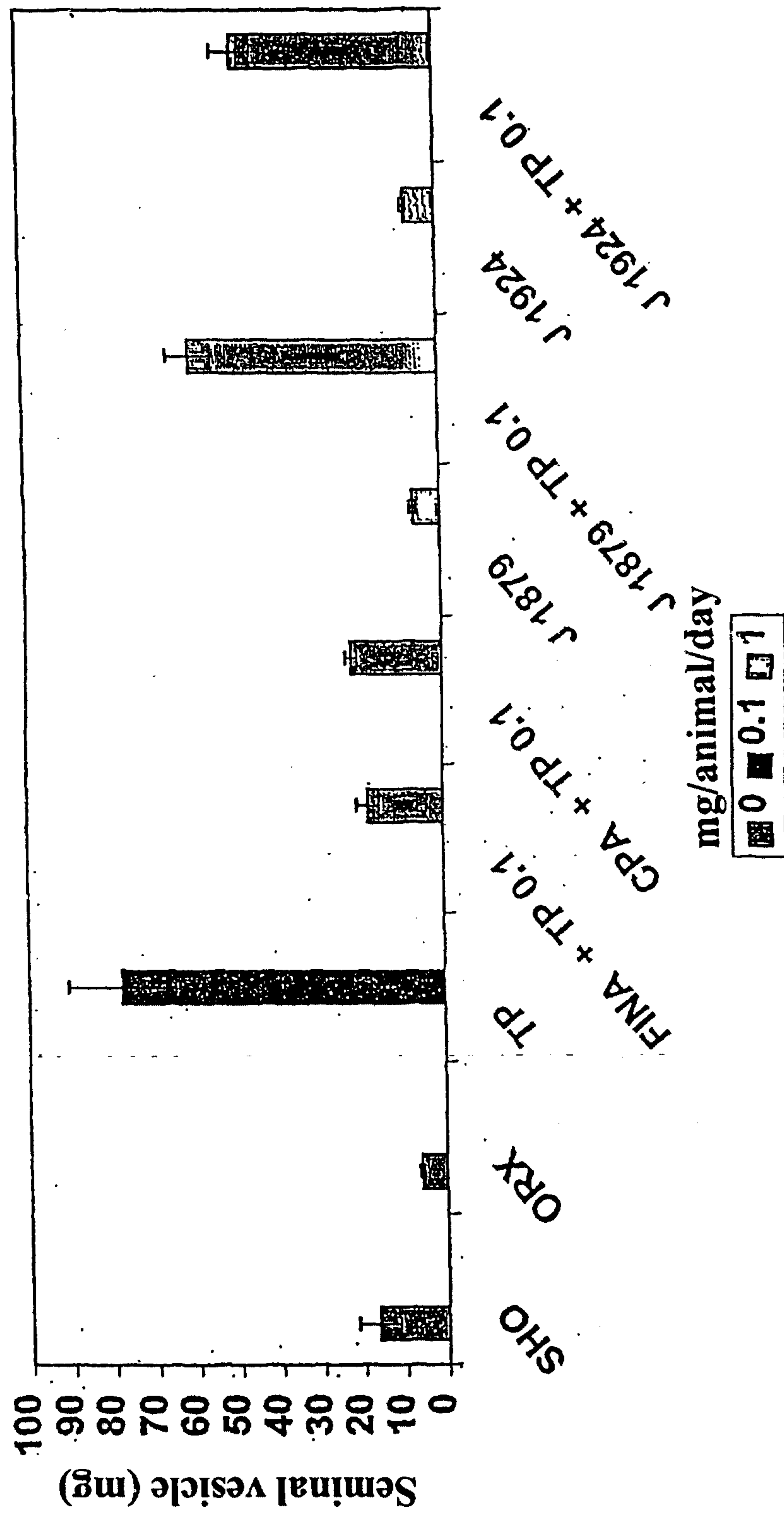


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