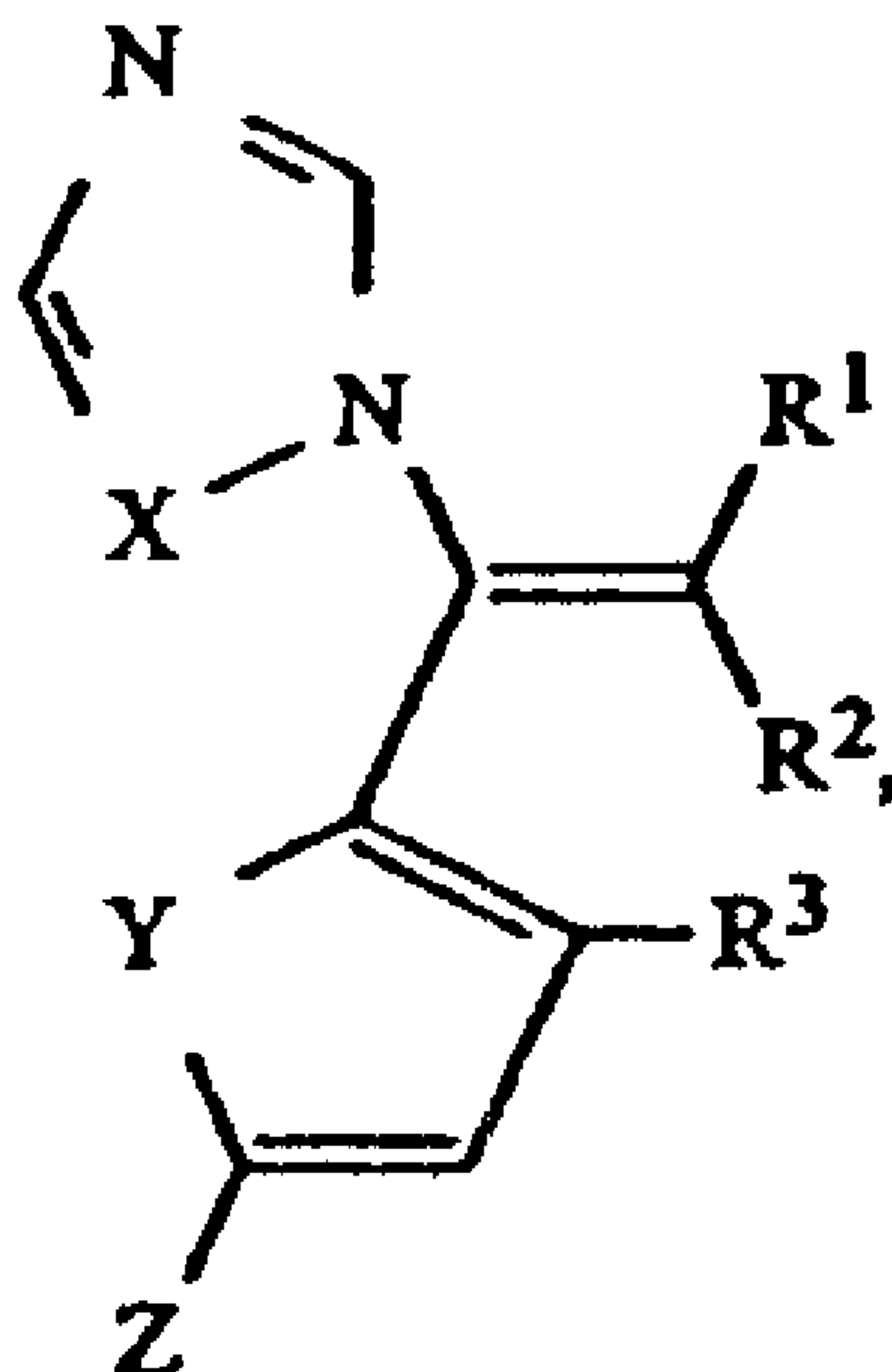




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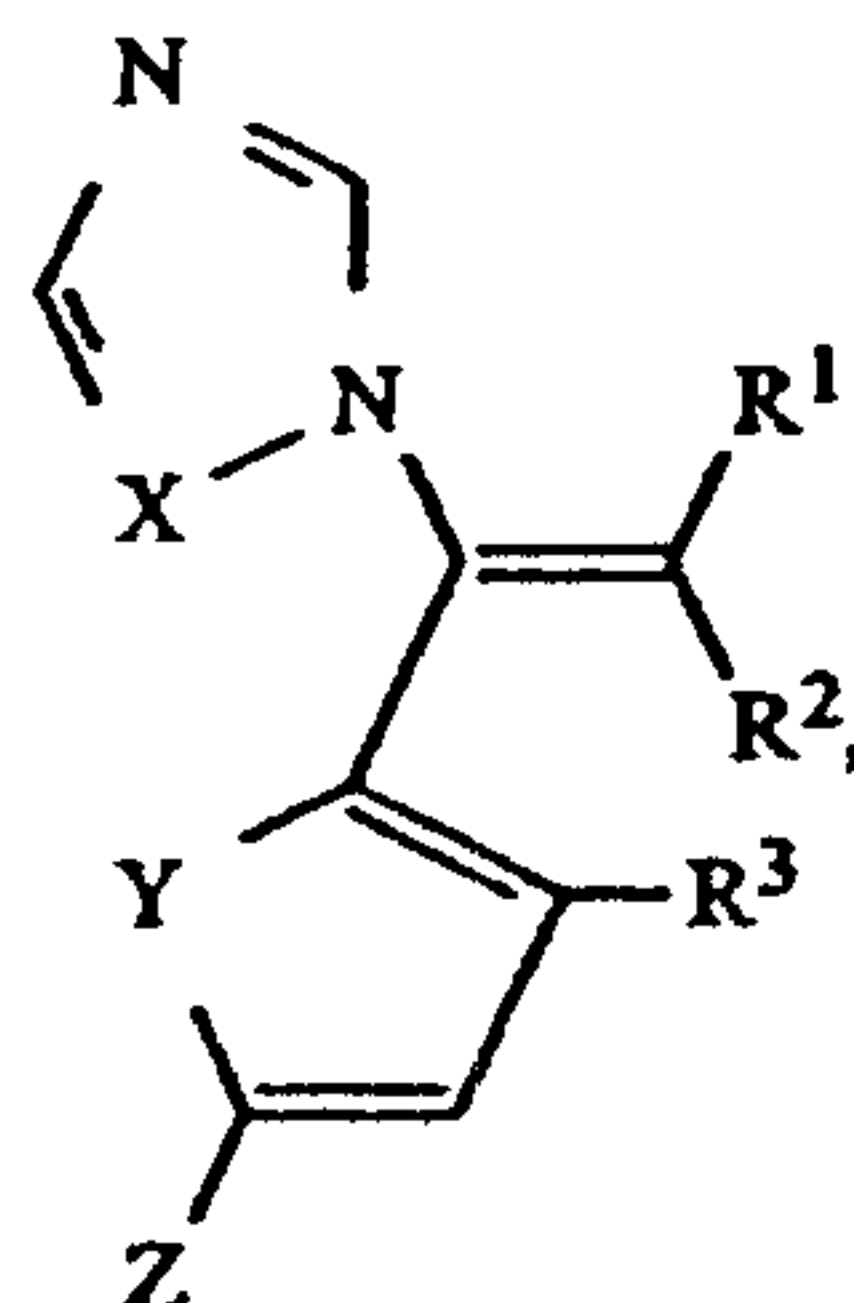


(57) **Abrégé/Abstract:**

Pharmaceutical compositions that contain vinylazoles having general formula (I) (see above formula) are disclosed, as well as new vinylazoles having general formula (Ia), contained within the scope of formula (I). In the formulas, X stands for an N atom or for a CH group; Y stands for a S atom or for a CH=CH group; Z stands for a cyano group, a fluorine, chlorine or bromine atom; and R¹ or R² stand for a carboxyl group that may be esterified, for a carboxylic acid amide group that may be substituted, for an aldehyde group, for an alkyl or aryl ketone group, for a sulfonamide group that may be substituted, or for a nitrile group; whereas the other group represented by R¹ or R² stands for a hydrogen atom, a lower alkyl group of a cycloalkyl group, an aryl group that may be substituted; an aralkyl group, a carboxyl group that may be esterified, a carboxylic acid amide group that may be substituted, an aldehyde group, an alkyl or aryl ketone group or a nitrile group. The compounds having general formulas (I) or (Ia) are effective inhibitors of estrogen biosynthesis (aromatase inhibitors) and are useful for treating diseases mediated by or dependent on estrogens. Processes for producing the compounds having general formula (I) are also disclosed.

ABSTRACT OF THE DISCLOSURE

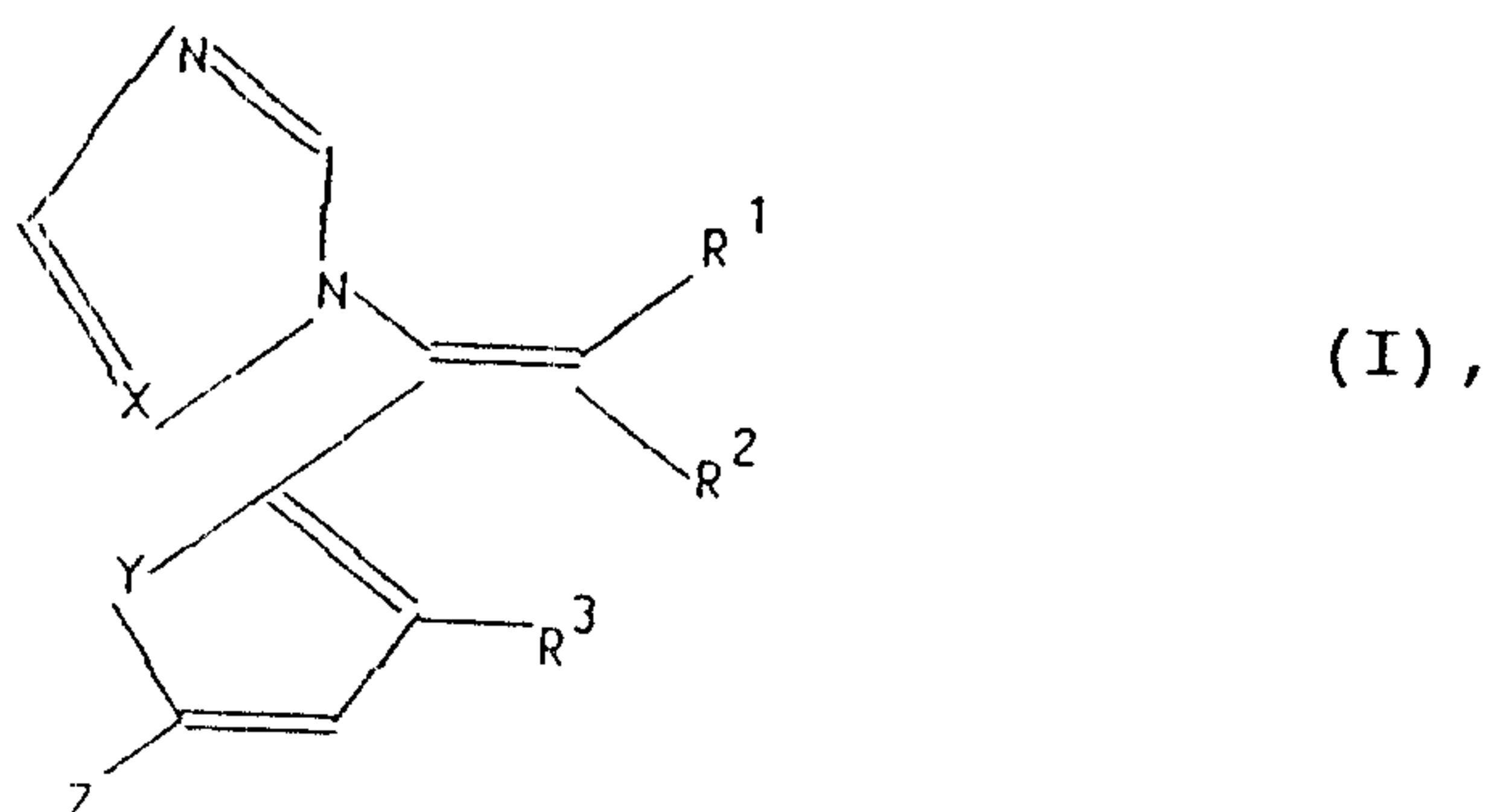
Pharmaceutical compositions that contain vinylazoles having general formula (I)



are disclosed, as well as new vinylazoles having general formula (Ia), contained within the scope of formula (I). In the formulas, X stands for an N atom or for a CH group; Y stands for a S atom or for a CH=CH group; Z stands for a cyano group, a fluorine, chlorine or bromine atom; and R¹ or R² stand for a carboxyl group that may be esterified, for a carboxylic acid amide group that may be substituted, for an aldehyde group, for an alkyl or aryl ketone group, for a sulfonamide group that may be substituted, or for a nitrile group; whereas the other group represented by R¹ or R² stands for a hydrogen atom, a lower alkyl group of a cycloalkyl group, an aryl group that may be substituted; an aralkyl group, a carboxyl group that may be esterified, a carboxylic acid amide group that may be substituted, an aldehyde group, an alkyl or aryl ketone group or a nitrile group. The compounds having general formulas (I) or (Ia) are effective inhibitors of estrogen biosynthesis (aromatase inhibitors) and are useful for treating diseases medicated by or dependent on estrogens. Processes for producing the compounds having general formula (I) are also disclosed.

FUNCTIONALIZED VINYL AZOLES AND THEIR USE

This invention relates to functionalized vinyl azoles of general formula I



in which

X means an N atom or a CH group,

Y means an S atom or a CH=CH group,

Z means a cyano group, a fluorine, chlorine or bromine atom

and R^1 or R^2 means

an optionally esterified carboxyl group,

an optionally substituted carboxylic acid amide group,

an aldehyde group,

an alkylketone or arylketone group,

an optionally substituted sulfonamide group or a nitrile

group

and the respective other group R^1 or R^2 means

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a hydrogen atom,
a low-alkyl group or cycloalkyl group,
an optionally substituted aryl group,
an aralkyl group,
an optionally esterified carboxyl group,
an optionally substituted carboxylic acid amide group,
an aldehyde group,
an alkylketone or arylketone group as well as
a nitrile group

or

R^1 and R^2 together with the carbon atom, on which they are bound, mean a 5-, 6- or 7-membered ring, which contains a ketone, ester, lactone, lactam or imide grouping placed so that at least one carbonyl group is conjugated with a vinyl double bond, and

R^3 means a hydrogen atom or R^3 together with R^2 means an $-O-C=O$ grouping or an $-N-C=O$ grouping optionally substituted on the N atom whose carbonyl group is conjugated with a vinyl double bond,

as well as pharmaceutical preparations containing a pharmaceutically compatible vehicle,

use of these vinyl azoles for the production of pharmaceutical agents, vinyl azoles themselves as well as process for their production.

Substituent Z preferably stands for a fluorine atom or a cyano group.

If R^1 and/or R^2 stands for an esterified carboxyl group, the latter is esterified first with a straight-chain or branched-

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chain or cyclic O-alkyl radical with up to 10 carbon atoms, with an O-aryl radical, and aryl is a phenyl or naphthyl radical optionally substituted by one or three low-alkyl groups (1-4 carbon atoms) or halogen atoms (F, Cl, Br, I) or an O-aralkyl radical, and in the latter, the aryl and the alkyl fragments have the above-indicated meaning. In this case, the methoxy, ethoxy, propoxy, isopropoxy, isobutoxy, tert-butoxy, cyclohexyloxy, cyclopentyloxy, phenyloxy or 2,6-dichlorophenoxy radical is especially preferred.

If R^1 and/or R^2 is a substituted carboxylic acid amide group, the latter above all is substituted with one or two, in the latter case same or different, radicals. These radicals can be straight-chain or branched-chain alkyl radicals with 1 to 10 carbon atoms, or aryl radicals with 6 to 10 carbon atoms optionally substituted by one to three alkyl groups or halogen atoms. Further, the amidic nitrogen atom can also be part of a 5- to 8-membered ring, which also can contain the grouping $\text{N}-R^6$ with R^6 meaning a hydrogen atom or a straight-chain or branched-chain alkyl group with 1 to 6 carbon atoms, an oxygen or sulfur atom as a ring member.

Quite especially to be emphasized is the substitution of the carboxylic acid amide group with a methyl, ethyl, propyl, phenyl, benzyl radical, two methyl, ethyl, propyl radicals, a phenyl and a methyl, a phenyl and an ethyl, and a benzyl and a methyl radical or a pyrrolidine, piperidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine ring formed together with the amidic nitrogen atom.

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The preferred substituents suitable for the substituted sulfonamide group are identical with the preferred N-substituents for the carboxylic acid amide group. First of all, R^9 and R^{10} each mean an alkyl substituent with 1 to 10 carbon atoms.

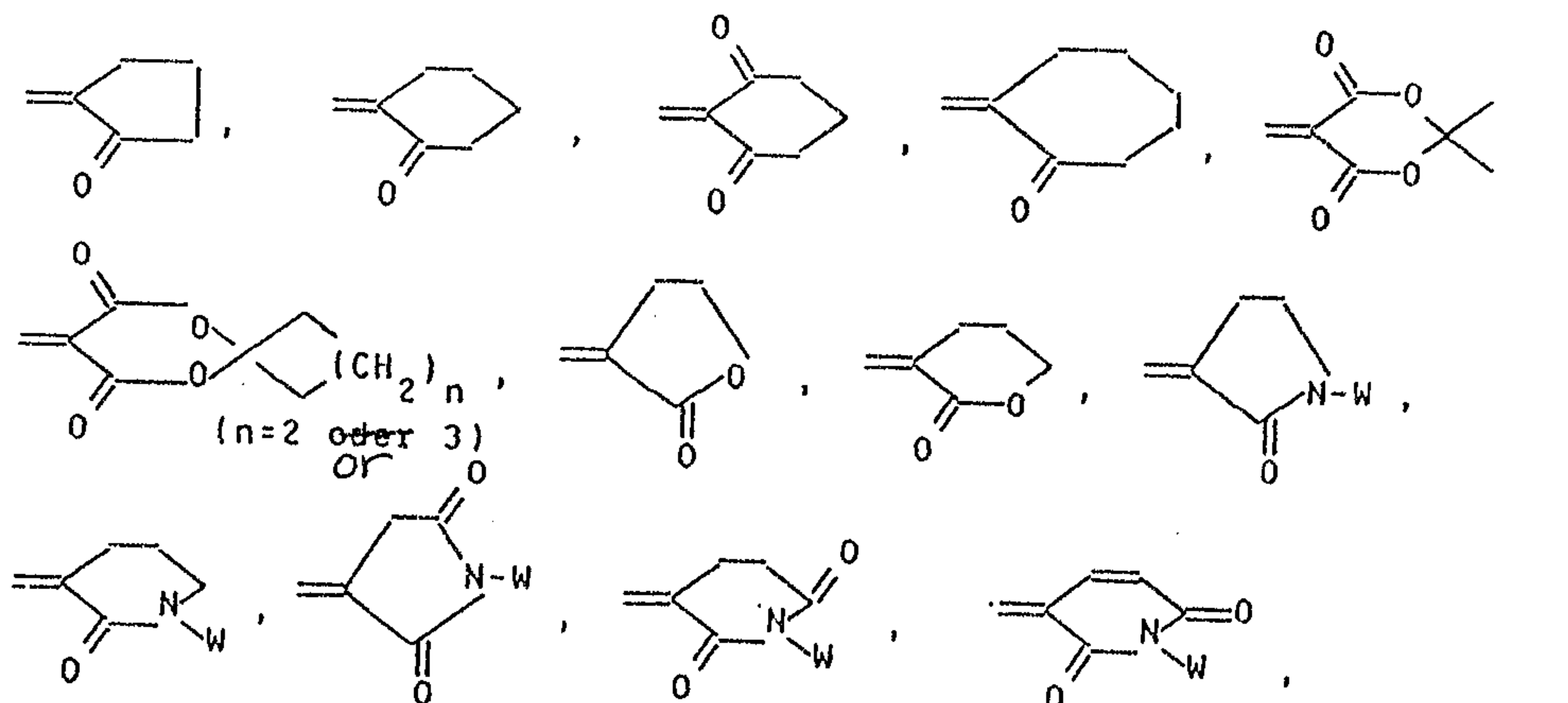
As alkylketone group R^1 and/or R^2 , radical $-CO-R^7$ is preferred, and R^7 means a straight-chain or branched-chain alkyl radical with 1 to 10 carbon atoms or a cycloalkyl radical with 3 to 12 carbon atoms, and as an arylketone group, radical $-CO-R^8$ is preferred, and R^8 means a phenyl, naphthyl or heteroaryl radical, optionally substituted by one or more alkyl, halogen, hydroxy or alkoxy radicals, such as, e.g., a thiophene, furan, pyridine, thiazole, oxazole or diazine ring.

In particular, R^7 is a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, isopentyl, neopentyl, cyclopentyl or cyclohexyl radical and R^8 is a phenyl, hydroxyphenyl, methoxyphenyl or chlorophenyl radical.

If R^1 and R^2 together with the carbon atom, on which they are bound, form a cyclic system, which should contain at least one carbonyl group, the following ring systems are to be

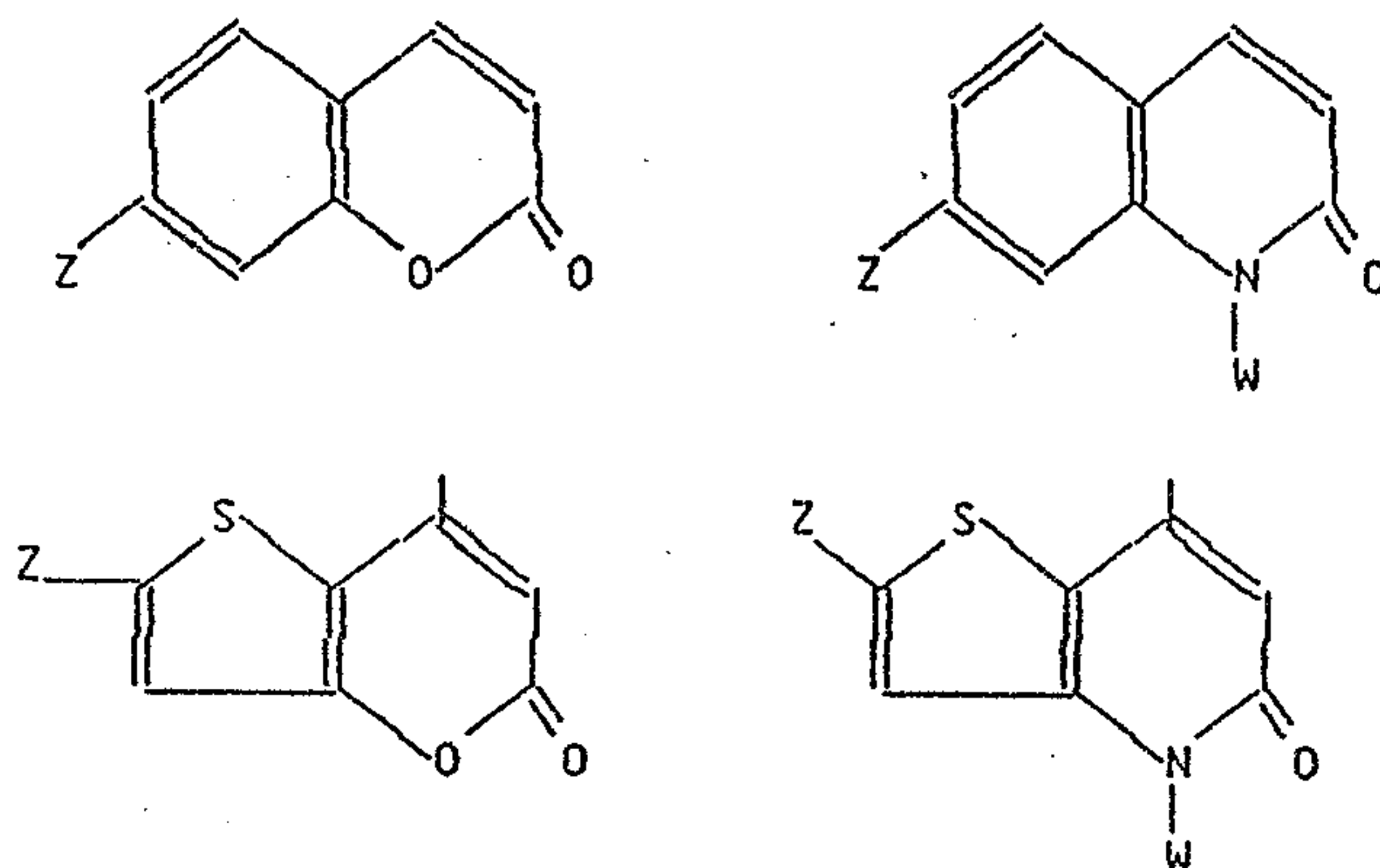
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emphasized:



and W means a hydrogen atom or an alkyl group with 1-10 C atoms.

With the bridge formed from R^2 and R^3 , the following partial structures result together with the aromatic ring containing Y:



If R^1 and R^2 in formula I are different, Z- and E-isomeric compounds are produced (except in the case of the cyclical structures above). The invention therefore also comprises the pure Z- or E-compounds as well as any mixtures of both.

The separation of the isomers takes place with standard methods, such as crystallization or chromatography.

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The following compounds are preferred:

3-(4-Cyanophenyl)-3-(1-imidazolyl)-acrylic acid methyl ester

3-(4-cyanophenyl)-3-(1-imidazolyl)-acrylic acid-tert-butyl ester

E-3-(4-cyanophenyl)-3-(1-imidazolyl)-acrylic acid

E-3-(4-cyanophenyl)-3-(1-imidazolyl)-acrylic acid piperidide

E-3-(4-cyanophenyl)-3-(1-imidazolyl)-acrylic acid methylamide

3-(4-cyanophenyl)-3-(1-imidazolyl)-acrylonitrile

4-[1-(1-imidazolyl)-3-oxo-1-butenyl]-benzonitrile

3-[(4-cyanophenyl)-(1-imidazolyl)-methylene]-dihydro-2(3H)-furanone

3-(5-cyano-2-thienyl)-3-(1-imidazolyl)-acrylic acid-tert-butyl ester

3-(5-cyano-2-thienyl)-3-(1-imidazolyl)-acrylonitrile

3-(4-cyanophenyl)-3-(1,2,4-triazol-1-yl)-acrylic acid-tert-butyl ester

3-(4-cyanophenyl)-3-(1,2,4-triazol-1-yl)-acrylonitrile

7-cyano-4-(1-imidazolyl)-coumarin

3-(4-fluorophenyl)-3-(1-imidazolyl)-acrylic acid-tert-butyl ester

3-(4-chlorophenyl)-3-(1-imidazolyl)-acrylic acid-tert-butyl ester

3-(4-bromophenyl)-3-(1-imidazolyl)-acrylic acid-tert-butyl ester

3-(4-fluorophenyl)-3-(1,2,4-triazol-1-yl)-acrylic acid-tert-butyl ester

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The compounds of general formula I are inhibitors of estrogen biosynthesis (aromatase inhibitors). Thus, they are suitable for the treatment of diseases which are caused by estrogens or are dependent on estrogens. Thus, they are suitable for the treatment of estrogen-induced or estrogen-stimulated tumors, such as, for example, breast cancer, endometrial cancer, melanoma or prostatic hyperplasia (The Lancet, 1984, 1237-1239).

Said compounds are also valuable for influencing fertility. Thus, a male infertility, which results from increased estrogen levels, can be overcome with the new active ingredients. Further, the compounds can be used in females of child-bearing age as a means of birth control, to inhibit ovulations by removal of estrogen. Aromatase inhibitors probably are also suitable for treatment of impending myocardial infarction, since increased estrogen levels in the male can precede a myocardial infarction (US Patent 4,289,762).

This invention therefore also relates to the use of compounds of general formula I for the production of pharmaceutical agents for treating estrogen-induced and estrogen-dependent diseases.

Phenylalkenones of general formula $R^aC(O)CH=CR^bR^c$, in which R^a means an optionally substituted alkyl or cycloalkyl radical, R^b means a 1,2,4-triazolyl or 1-imidazolyl radical and R^c means a phenyl or naphthyl ring, which optionally can be substituted, among others, with a fluorine, chlorine or bromine atom or a cyano group, can already be seen from EP-A-0 003 884. These

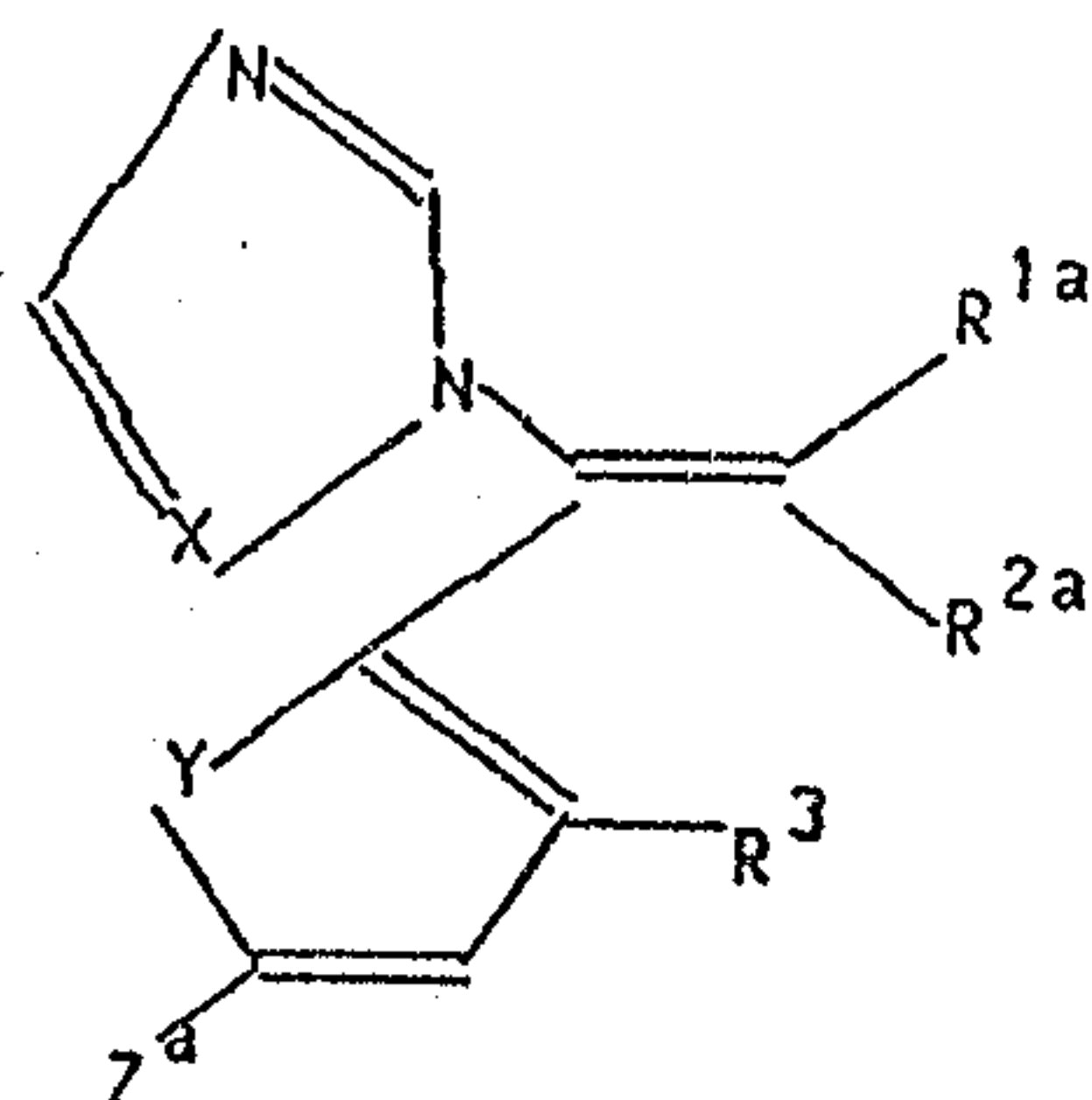
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phenylalkenones are described as compounds with herbicidal activity.

Other herbicidal 1,2,4-triazolylvinyl and imidazolyl vinyl compounds, which, in geminal position in the heterocycle, have a phenyl ring chlorosubstituted in p-position, are known from DE-A-27 38 640.

Finally, the objects of DE-A 28 26 760 are 3-(4-chlorophenyl)-3-(1,2,4-triazolyl)-acrylic acid alkyl esters for use as fungicides and plant-growth regulators.

The above-named compounds, whose medicinal applicability was previously unknown, are comprised by general formula I. On the other hand, the compounds of general formula Ia



(Ia),

in which

X means an N atom or a CH group,

Y means an S atom or a CH=CH group,

Z^a means a cyano group or a fluorine or bromine atom and

R^{1a} or R^{2a} means

an optionally esterified carboxyl group,

an optionally substituted carboxylic acid amide group,

an aldehyde group,

an arylketone group,

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an optionally substituted sulfonamide group or a nitrile group

and the respective other group R^{1a} or R^{2a} means

a hydrogen atom,

a low-alkyl group or cycloalkyl group,

an optionally substituted aryl group,

an aralkyl group,

an optionally esterified carboxyl group,

an optionally substituted carboxylic acid amide group,

an aldehyde group,

an alkylketone group as well as

a nitrile group

or

R^{1a} and R^{2a} together with the carbon atom, on which they are bound, mean a 5-, 6- or 7-membered ring, which contains a ketone, ester, lactone, lactam or imide grouping placed so that at least one carbonyl group is conjugated with a vinyl double bond, and

R^3 means a hydrogen atom or R^3 together with R^{2a} means an $-O-C=O$ grouping or an $-N-C=O$ grouping optionally substituted on an N atom whose carbonyl group is conjugated with a vinyl double bond,

are new.

The compounds of general formula Ia therefore also belong to the object of this invention.

The radicals possibly or preferably standing for substituents R^{1a} , R^{2a} and R^3 in the compounds of general formula Ia are the same as those of formula I mentioned as possibly or

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preferably standing for substituents R^1 , R^2 and R^3 , with the difference that in the compounds of general formula Ia, no chlorine atom can stand for Z^a and no alkylketone group can stand for R^{1a} or R^{2a} .

Known substances exhibiting an aromatase-inhibiting effect are in addition to steroids also nonsteroidal substances, for example, the various nitrogen heterocycles described in European patent applications EP-A 0165777 to 0165784, the substituted glutaric acid imides described in J. Med. Chem. 1986, 29, pages 1362-1369, the substituted imidazobenzenes described in European patent application EP 0165904, the substituted heterocyclically-substituted toluenenitriles described in European patent application EP-A 0236940 and the imidazo- and 5,6,7,8-tetrahydroimidazo[1,5a]pyridines having an optionally substituted phenyl ring, seen from US Patent US-A-4,728,465, from which in particular 5-(p-cyanophenyl)5,6,7,8-tetrahydroimidazo[1,5a]pyridine, hydrochloride stands out as a greatly effective aromatase inhibitor (Cancer Res. 48, pp. 834-838, 1988).

The compounds of general formula I are distinguished relative to the previously known compounds in that they inhibit the enzyme system of the aromatase more strongly and at the same time more selectively. The selective action is shown in that other enzyme systems are affected to a smaller extent.

The concentrations, in which the aromatase activity is inhibited in vitro by the compounds of general formula I, are in the range of 10^{-7} to 10^{-10} mol/l.

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In comparison with the compounds of EP-A 0236940 that are structurally very close, by the introduction of the double bond the compounds of general formula I no longer have a chirality center on the carbon atom, on which both the cyanoaryl and the N-heteroaryl radical are present. An enantioselective synthesis or the expensive separation of the enantiomers is avoided by the elimination of the chirality center.

The amount of the compounds to be administered fluctuates within a wide range and can cover every effective amount. As a function of the condition to be treated and the type of administration, the amount of the administered compounds can be 0.0001-10 mg/kg of body weight, preferably 0.001-1 mg/kg of body weight daily.

For oral administration, capsules, pills, tablets, coated tablets, etc. are suitable. In addition to the active ingredient, the dosage units can contain a pharmaceutically compatible vehicle, such as, for example, starch, sugar, sorbitol, gelatin, lubricants, silicic acids, talc, etc. The individual dosage units for oral administration can contain, for example, 0.05-50 mg of the active ingredient (aromatase inhibitor).

For parenteral administration, the active ingredients can be dissolved or suspended in a physiologically compatible diluent. As a diluent, very often oils are used with or without adding a solubilizer, a surfactant, a suspension mixture or an emulsifying mixture. As examples for oils used, there can be mentioned:

olive oil, peanut oil, cottonseed oil, soybean oil, castor oil and sesame oil.

The compounds can also be used in the form of a depot injection or an implantation preparation, which can be formulated so that a delayed release of active ingredient is made possible.

Implantations can contain as inert materials, for example, biodegradable polymers or synthetic silicones, such as, for example, silicone rubber. The active ingredients can further be worked into, for example, plasters for percutaneous administration.

The tumor-inhibiting action of imidazole derivatives is based on an inhibition of P-450-dependent enzyme systems (cf., e.g., J. P. Van Wanne and P. A. J. Janssen; J. Med. Chem. 32 (1989) 2231). Also, the action of antifungal therapeutic agents of the series of imidazole and triazole derivatives is based on a blocking of P-450-dependent biochemical reactions.

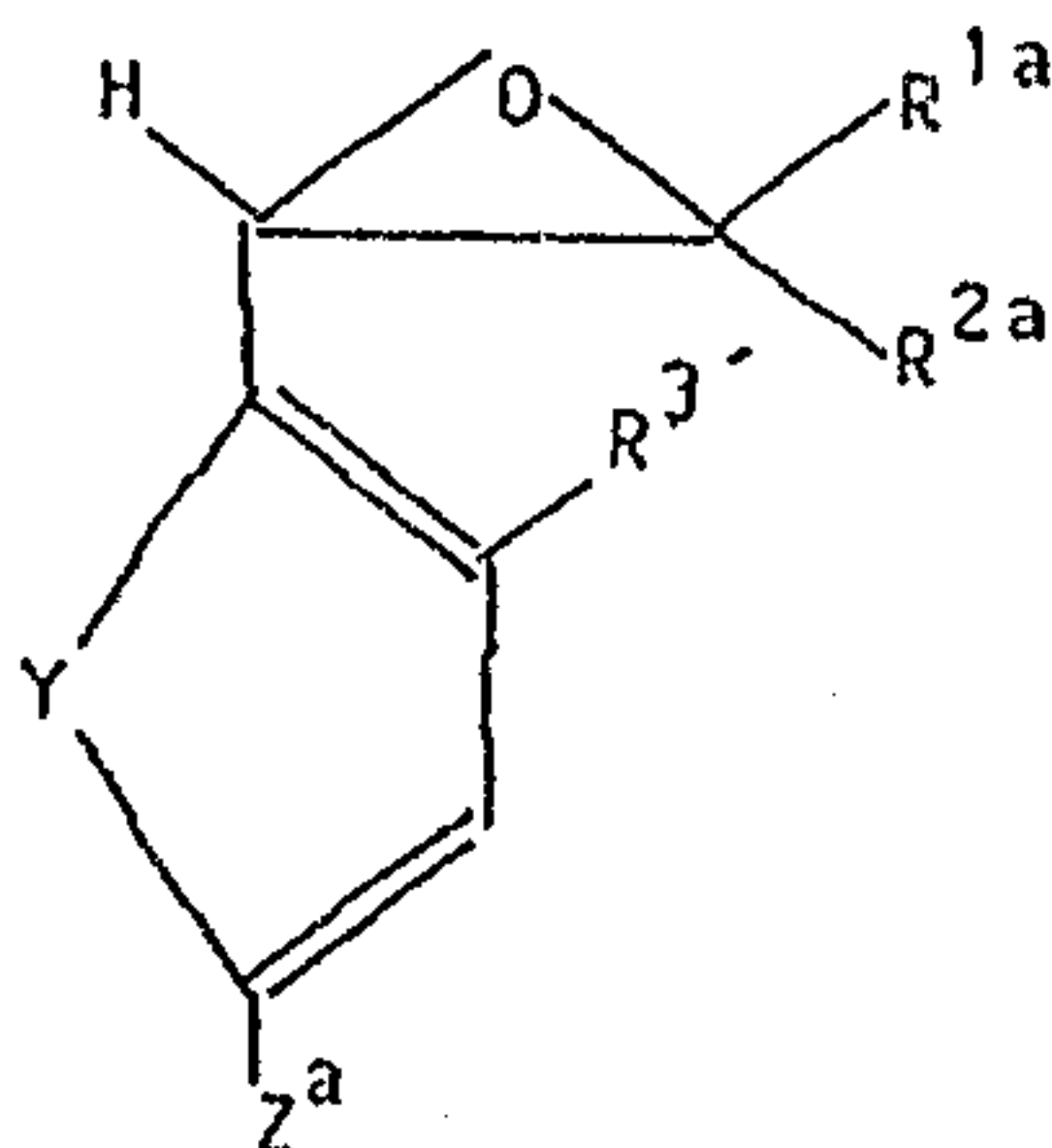
Further, it is known from the patent literature that azole derivatives have both antifungal and tumor-inhibiting action at the same time (in this connection, see European Patent Application 165,777 (Dec. 27, 1985)). The compounds according to the invention should therefore also comprise an antifungal action against human-, animal- and plant-pathogenic organisms.

The invention further relates to processes for the production of compounds of general formula Ia as well as a process for the production of certain compounds of general formula I, identified below as compounds of general formula I'.

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For the production of the compounds of general formula Ia,
either

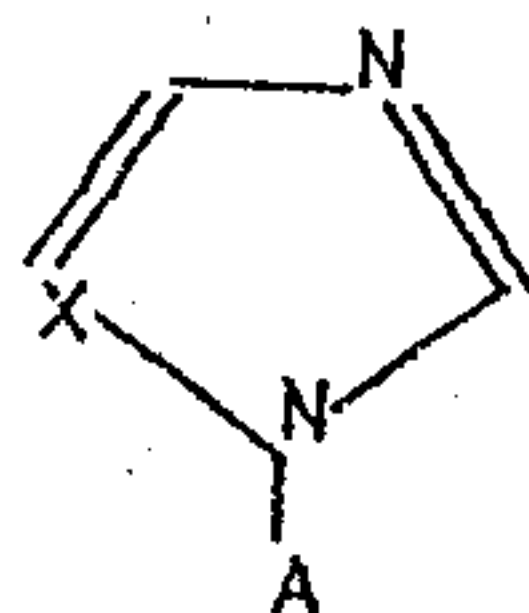
i) a compound of general formula II



(II),

in which

R^{1a} , R^{2a} , Y and Z^a have the meaning indicated in formula Ia
and $R^{3'}$ means a hydrogen atom or $R^{3'}$ together with R^{2a} forms a ring
of the above-indicated partial structures, reacts with a compound
of general formula VII



(VII),

in which

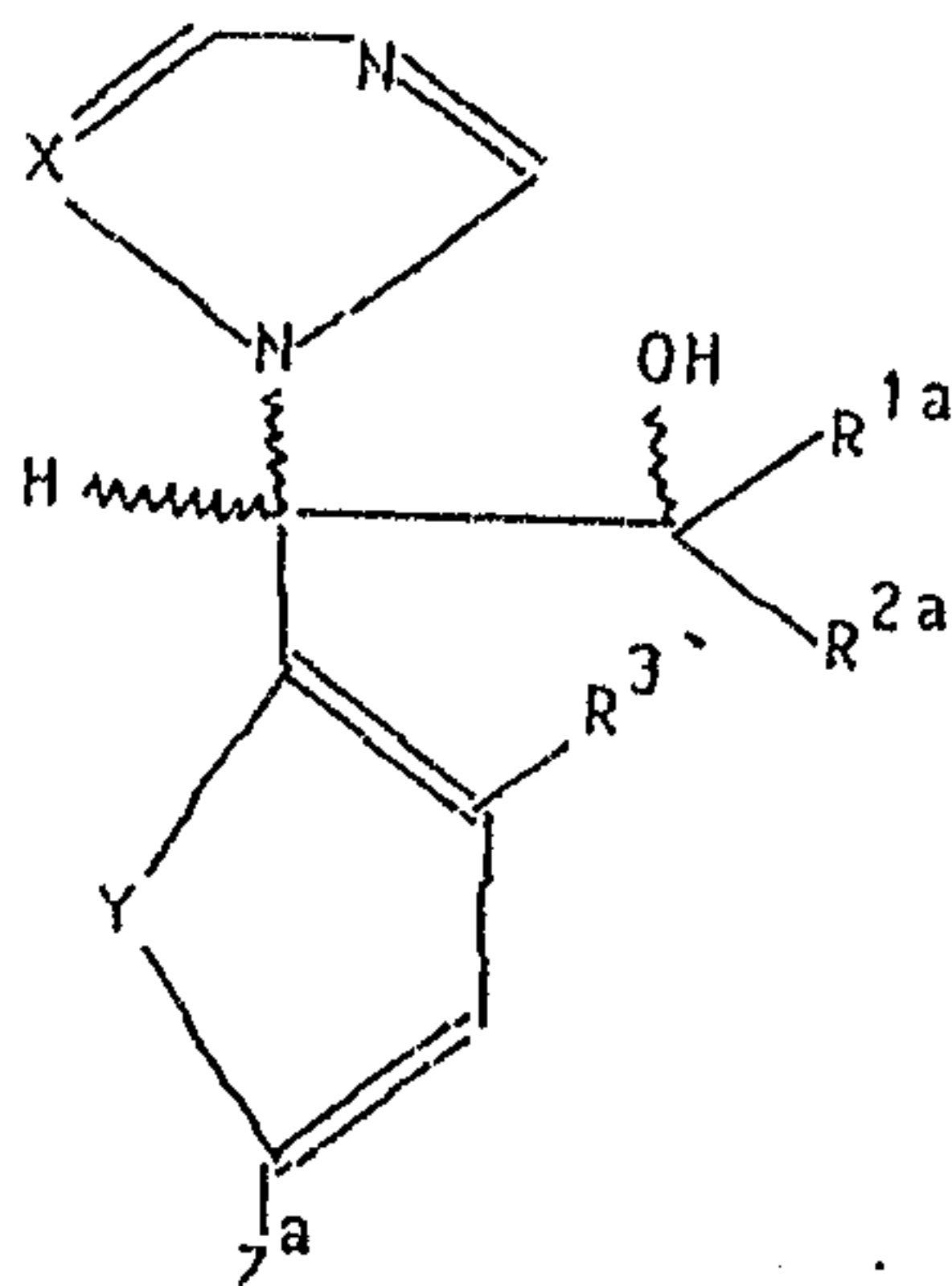
X means an N atom or a CH group and

A means a hydrogen atom, an alkali metal or a trialkylsilyl
radical with the same or different straight-chain or branched C_1 -
 C_8 alkyl groups,

in an inert solvent at a temperature between room temperature and
boiling temperature of the solvent or without solvent, optionally

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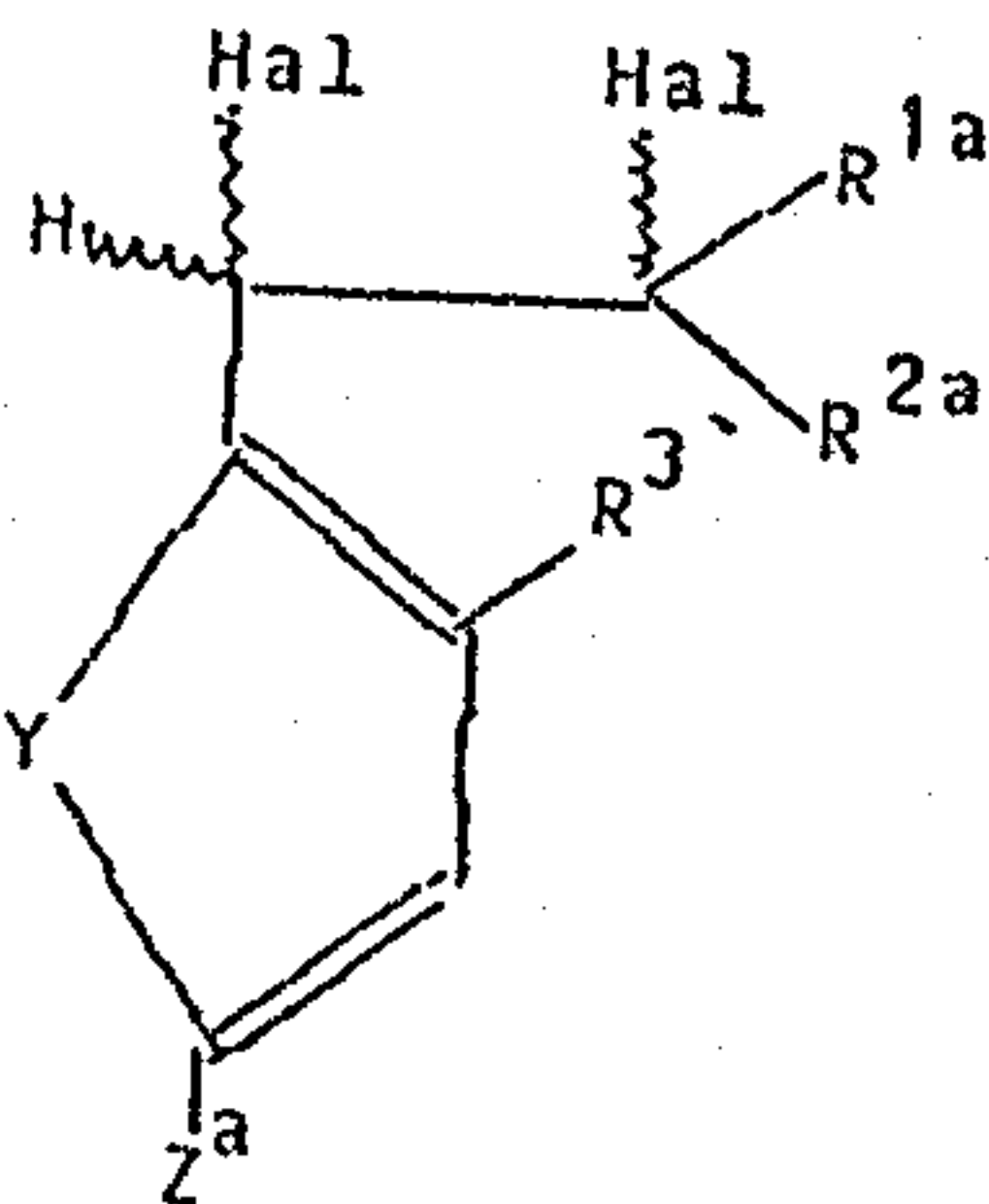
by adding a catalyst first to a compound of general formula IIIi



(IIIi),

in which R^{1a} , R^{2a} , $R^{3'}$, X, Y and Z^a have the meaning already indicated in formula II or VII, and the latter is allowed to further react by dehydration above 60°C , optionally in a solvent and optionally by using a catalyst, to a compound of general formula Ia, or

ii) a compound of general formula III



(III),

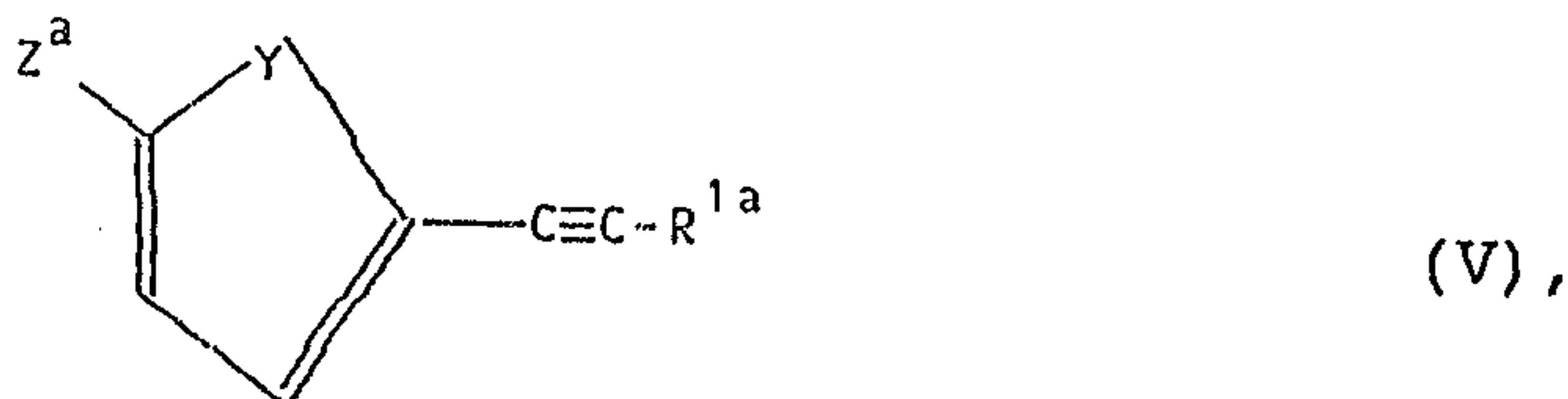
in which

R^1 , R^2 and Y have the meaning indicated in formula 1, $R^{3'}$ means a hydrogen atom or, together with R^2 , forms a ring of the above-indicated partial structures, and Hal means halogen atoms, in particular one bromine atom each,

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reacts with a compound of general formula VII according to conventional processes with or without adding a foreign base to a compound of general formula I or

iii) to an acetylene compound of general formula V



in which Y and Z^a have the meaning indicated in formula I and R^{1a} means an esterified carboxyl group,

an optionally substituted carboxylic acid amide group,

an aldehyde group,

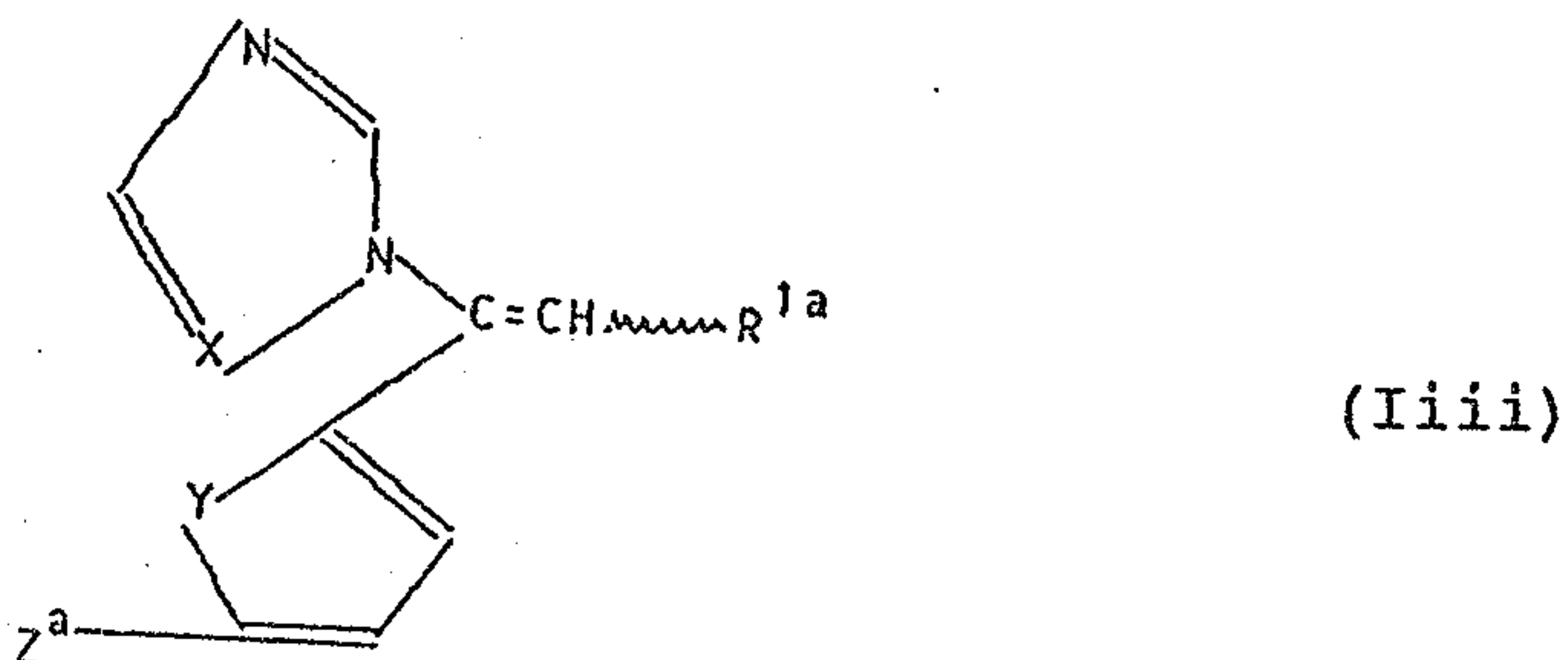
an arylketone group,

an optionally substituted sulfonamide group or

a nitrile group,

and the optionally possible substituents and the alkoxy radicals of the esterified carboxyl group correspond to the definitions already indicated in more detail,

is added a compound of general formula VII in a solvent between room temperature and boiling temperature of this solvent with forming a compound of general formula Iiii



The production of the compounds of general formula I according to the invention takes place according to variant i) starting from an epoxide of general formula II and an azole of formula VII in a way known in the art.

The addition of the azole is performed in an inert solvent, such as, for example, benzene, toluene, xylene, tetrahydrofuran, dioxane, acetonitrile or dimethylformamide, preferably at a temperature between 60°C and the boiling temperature of the solvent or without solvent, preferably between 60°C and 150°C. If necessary, a catalyst, e.g., a metal salt, such as lithium, magnesium, sodium perchlorate, zinc chloride or calcium chloride, can be added (Tetrahedron Letters 31 (1990) 4661).

The dehydration takes place thermally, preferably at temperatures between 100°C and 200°C or the boiling temperature of an optionally used solvent, such as, e.g., toluene, chlorobenzene or xylene. As catalysts, inorganic or organic acids, such as, for example, sulfuric acid or p-toluenesulfonic acid are suitable.

The dehydration can also be performed by using dehydrating agents such as thionyl chloride or phosphorus oxychloride with or without a solvent (e.g., dichloromethane, acetonitrile, tetrahydrofuran) at room temperature to boiling temperature of the solvent, preferably between 20°C and 50°C.

In the reaction of the dihalide of general formula III with an azole of general formula VII according to ii), methods familiar to one skilled in the art are also involved. Possibly,

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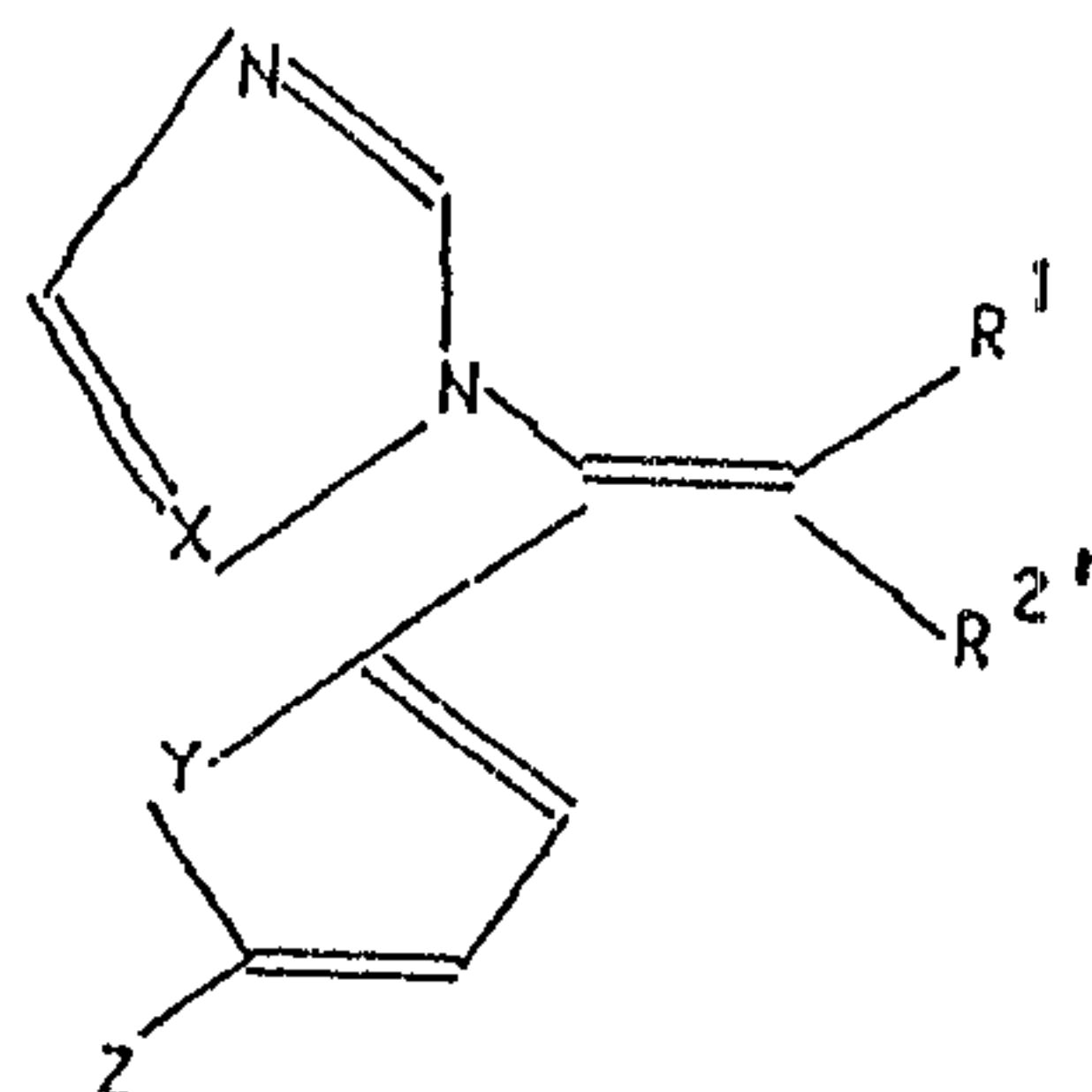
the additional use of a foreign base (Heterocycles 15 (1981), 961) can be useful in facilitating the reaction.

First, the exchange of the halogen atom on the benzylic carbon atom takes place and then the elimination of the hydrogen halide. The intermediately formed monohalogen compound is not isolated.

The necessary initial compounds of general formula II or formula III are accessible by epoxidation or halogenation, preferably bromation, of the corresponding olefins in a way known in the art; the olefins in turn can be produced, for example, by Wittig or Knoevenagel reaction of the corresponding feedstocks.

In the addition of an azole of formula VII to an acetylene compound of general formula V to be performed in a way known in the art according to variant iii), compounds of general formula Iiii are obtained with $R^2 = H$ as a Z-/E-isomeric mixture. The production of compounds of formula V is known (e.g., Chem. Ber. 94 (1961) 3005; J. Org. Chem. 30 (1965) 1915). The reaction of compounds of formula V with the optionally substituted azoles VII takes place preferably in solvents such as hydrocarbons (benzene, toluene), ethers (ethyl ether, dioxane, tetrahydrofuran), alcohols (tert-butanol) or halogenated hydrocarbons (dichloromethane, chloroform, 1,2-dichloroethane) between room temperature and boiling temperature of the solvent.

Compounds of general formula I'

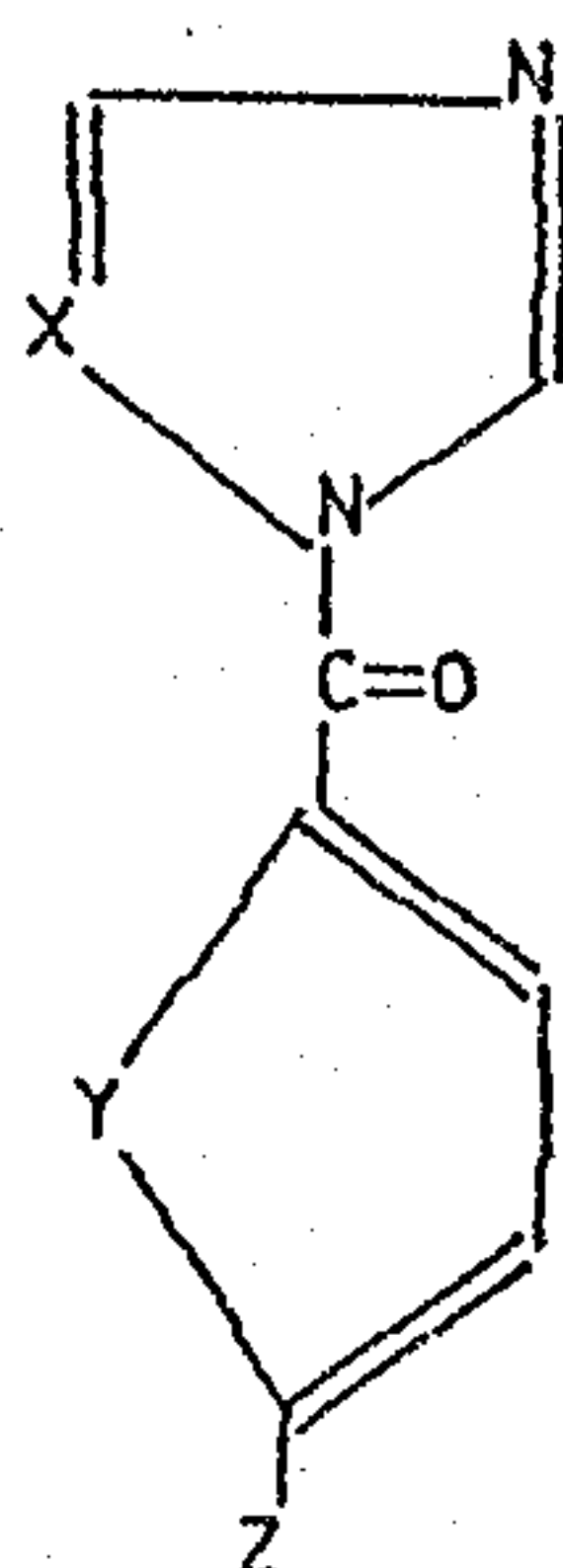


(I'),

in which R¹, X, Y and Z have the meaning indicated in formula I,

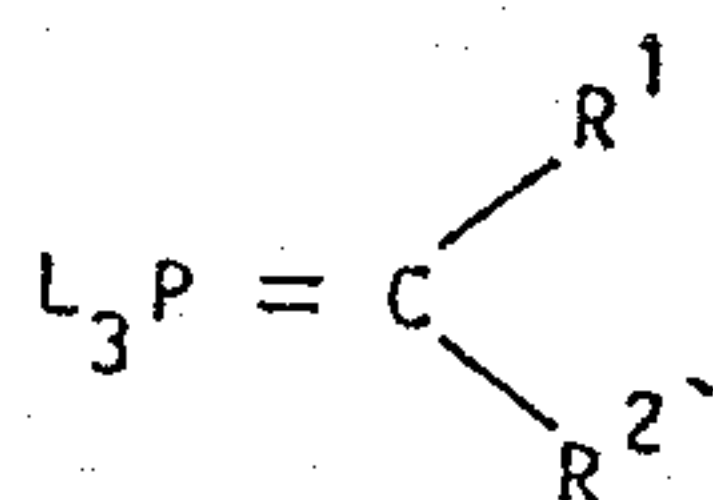
R^{2'} means a hydrogen atom or

R¹ and R^{2'} together with the methylene carbon atom mean a 5-, 6- or 7-membered ring, which contains a ketone, ester, lactone, lactam or imide grouping placed so that at least one carbonyl group is conjugated with a vinyl double bond, are produced, by a compound of general formula IV



(IV),

in which X, Y and Z have the meaning indicated in formula I, being reacted with a phosphorane of formula VIII



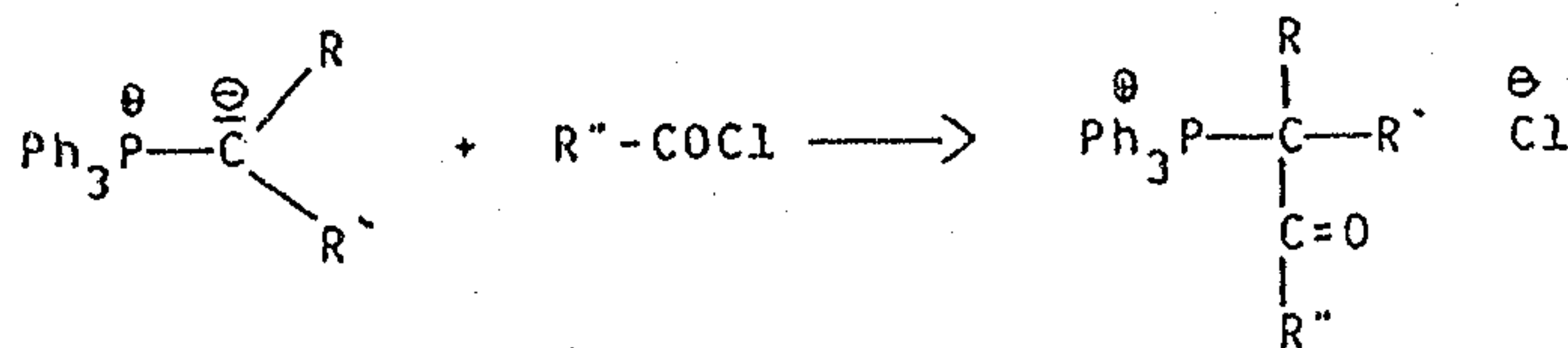
(VIII),

in which

L means an optionally substituted phenyl radical [with low-alkyl(1-6C), low-alkoxy(1-6C), halogen] or a straight-chain or branched low-alkyl radical with 1 to 6 carbon atoms and R¹ and R² have the above-indicated meaning, in an inert solvent between room temperature and boiling temperature of the solvent used.

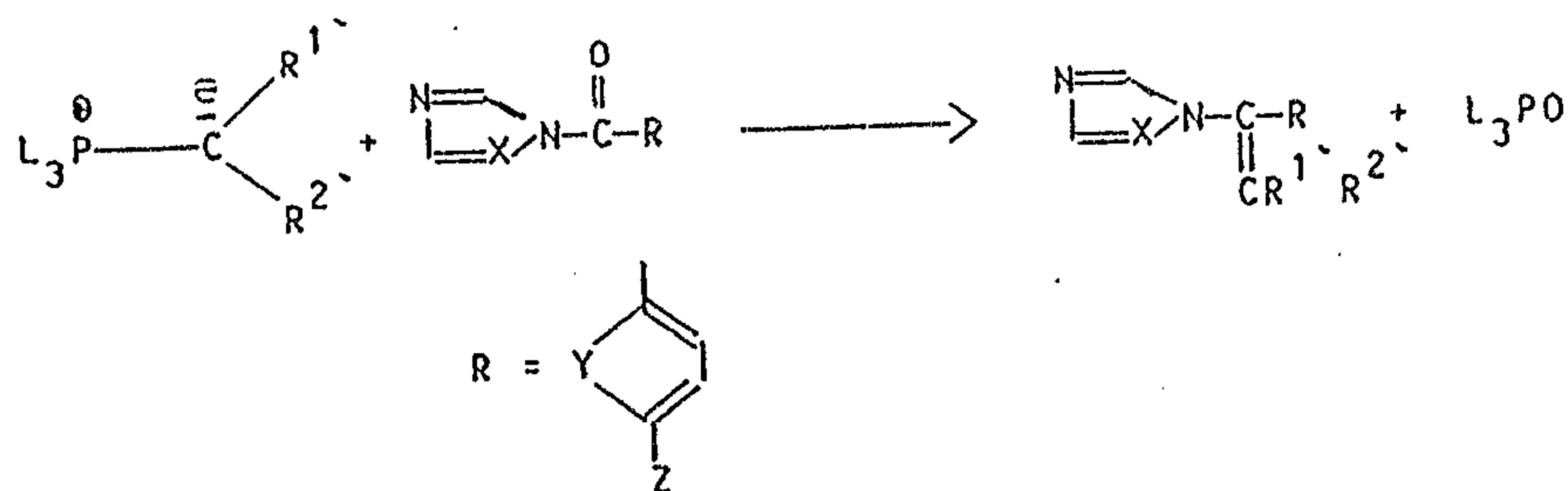
By reaction of an acylazole of general formula IV with a phosphorane of formula VIII, the last-mentioned process variant according to the invention results in the compounds of general formula I' (Wittig reaction). As inert solvents, for example, benzene, toluene, xylene, chlorobenzene, tetrahydrofuran, dioxane, acetonitrile, dimethylformamide or dimethylsulfoxide are used. The reaction temperature is preferably selected above 60°C.

That acylazoles react with a phosphorane in the meaning of a Wittig reaction was not previously known. Rather, it is known that acylimidazoles (generally also acylazoles) are good acylation agents (Comprehensive Heterocyclic Chemistry (Eds. A. R. Katritzky, K. T. Potts) Pergamon Press 1984, Volume 4A, page 451 ff). Accordingly, it was to be expected that a Wittig reagent (phosphorane) is acylated on the carbanion, as it is observed, e.g., in the reaction with acid chlorides:



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In aliphatic acid imidazolides the acylation of triphenylmethylenephosphorane is described (M. Miyano et al., J. Org. Chem. 40 (1975) 2840). It was therefore unexpected and surprising that acylimidazoles or acylazoles enter into a normal Wittig reaction:



The following examples are used to explain the invention in more detail:

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EXAMPLE 1

3-(4-Cyanophenyl)-3-(1-imidazolyl)-acrylic acid methyl ester

2.85 g of 4-cyanobenzoyl chloride, dissolved in 20 ml of ether, is instilled in a solution of 2.4 g of imidazole in 25 ml of tetrahydrofuran and 50 ml of ether. After 10 minutes at room temperature, it is filtered with exclusion of air and the filtrate is concentrated by evaporation in a vacuum. The residue is dissolved in 20 ml of tetrahydrofuran and refluxed with 5.7 g of methoxycarbonylmethylenetriphenylphosphorane for 5 hours. It is added to water, extracted with ethyl acetate and the ethyl acetate phase is washed with water. Then, the ethyl acetate phase is extracted three times with 2 M hydrochloric acid. The hydrochloric acid phase is alkalized with potassium carbonate and extracted with ethyl acetate. After drying the ethyl acetate phase with sodium sulfate and concentration by evaporation, an oil remains, which thoroughly crystallizes. After suctioning off the crystals with ether, 3.5 g (81%) of a Z-/E-mixture of the title compound is obtained. By recrystallization from ethanol, the E-compound is obtained pure. Mp: 144-147°C

EXAMPLE 2

3-(4-Cyanophenyl)-3-(1-imidazolyl)-acrylic acid-tert-butyl ester

Analogously to example 1, with use of tert-butoxycarbonylmethylenetriphenylphosphorane. Yield 37%. After chromatography on silica gel (eluant ethyl acetate) and crystallization from ether, the E-isomer melts at 151-153°C.

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EXAMPLE 3

E-3-(4-Cyanophenyl)-3-(1-imidazolyl)-acrylic acid

100 mg of the E-compound of example 1 is dissolved in 1.5 ml of 10% methanolic potassium hydroxide and left for 15 minutes at room temperature.

Then, it is concentrated by evaporation in a vacuum at 30°C and the residue is dissolved in 2 ml of water. By adding 1 M hydrochloric acid and later 10% acetic acid, it is adjusted to a pH of 5 and extracted with ethyl acetate. After concentration by evaporation of the solvent, 38 mg of the title compound is obtained.

Mp: 230-246°C

The hydrochloride of the title compound is obtained as follows:

200 mg of the E-tert-butyl ester of example 2 is stirred with 20 ml of 6 M hydrochloric acid for 2 hours at room temperature. It is concentrated by evaporation in a vacuum, distilled twice more each with toluene and methylene chloride and 195 mg (100%) of E-3-(4-cyanophenyl)-3-(1-imidazolyl)-acrylic acid, hydrochloride, is obtained.

EXAMPLE 4

E-3-(4-Cyanophenyl)-3-(1-imidazolyl)-acrylic acid piperidide

190 mg of the hydrochloride of example 3, 196 mg of 2-chloro-1-methylpyridinium iodide, 57 mg of piperidine, 290 mg of tributylamine and 12 ml of methylene chloride are refluxed for 20 hours. The acid phase is separated and saturated with potassium

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carbonate. It is extracted with ethyl acetate, the ethyl acetate phase is concentrated by evaporation and the low-boiling material is distilled off from the residue at 100°C and 0.01 mbar. The residue is chromatographed on silica gel. With methylene chloride/isopropanol (0.5 - 4% isopropanol), 52 mg of crystalline product is obtained with a melting point of 160-165°C.

EXAMPLE 5

E-3-(4-Cyanophenyl)-3-(1-imidazolyl)-acrylic acid methylamide

1.35 g of methylammonium chloride in 10 ml of toluene is mixed under argon with 7.5 ml of trimethylaluminum in 10 ml of toluene by instillation and stirred for 2 hours at room temperature. 50 mg of the E-methyl ester of example 1 is mixed in 2 ml of toluene with 2 ml of the above-produced reagent. It is stirred for 6 hours at 80°C, then mixed at room temperature with 1 M hydrochloric acid and extracted with ether. The acid phase is alkalized with potassium carbonate and extracted with ethyl acetate. After washing with water and drying, the ethyl acetate phase is concentrated by evaporation. 30 mg of the title compound (50%) remains; melting range: 172-180°C.

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EXAMPLE 6

3-(4-Cyanophenyl)-3-(1-imidazolyl)-acrylonitrile

Analogously to example 1, the title compound is obtained with use of cyanomethylenetriphenylphosphorane. The E-isomer is obtained pure from ethanol; mp: 188-193°C.

EXAMPLE 7

4-[1-(1-Imidazolyl)-3-oxo-1-butenyl]-benzonitrile

a) Analogously to example 1, with use of acetonilidene-triphenylphosphorane. A Z-/E-mixture of the title compound is obtained.

b) By stirring 3.02 g of 4-cyanobenzaldehyde and 7.32 g of acetonilidene-triphenylphosphorane in 50 ml of dichloromethane and then recrystallizing from isopropanol, 3.15 g (80%) of 4-(3-oxobutenyl)-benzonitrile is obtained. 1.71 g of it is mixed in 20 ml of dichloromethane with 20 ml of a 0.5 M solution of bromine in dichloromethane. After decolorization, the solvent is drawn off in a vacuum. The remaining oil is refluxed with 0.95 g of imidazole and 7 ml of triethylamine in 40 ml of toluene for 2 hours. A precipitate is filtered off, the filtrate is distributed in ethyl acetate-2 M hydrochloric acid, the hydrochloric acid phase is alkalized with potassium carbonate and extracted with ethyl acetate. 1.2 g of a crude product is obtained, which, after recrystallization from isopropanol, yields the Z-isomer with mp. 131-135°C. After chromatography of the mother liquor on silica gel (eluant ethyl acetate), the E-isomer

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is obtained from ethyl acetate/ether as crystals of mp: 123-126°C.

EXAMPLE 8

3-[(4-Cyanophenyl)-(1-imidazolyl)-methylene]-dihydro-2(3H)-furanone

Analogously to example 1, with use of 3-(triphenylphosphoranylidene)-dihydro-2(3H)-furanone in the solvent toluene under reflux (20 hours). Chromatography of the crude product on silica gel (eluant dichloromethane/methanol 99:1) and recrystallization from isopropanol produces the title compound in E-form with mp: 194-197°C.

EXAMPLE 9

3-(5-Cyano-2-thienyl)-3-(1-imidazolyl)-acrylic acid-tert-butyl ester

The acid chloride is produced from 2 g of 5-cyanothiophene-2-carboxylic acid by boiling with thionyl chloride and distilling off excess thionyl chloride. The acid chloride is dissolved in 10 ml of ether and mixed with 1.9 ml of N-trimethylsilylimidazole. It is concentrated by evaporation in a vacuum, dissolved in a mixture of 150 ml of tetrahydrofuran and 50 ml of acetonitrile and mixed with 4.9 g of tert-butoxycarbonylmethylene-triphenylphosphorane. It is refluxed for 20 hours and worked up as in example 1. The crude product is chromatographed on silica gel using dichloromethane with 1-2% isopropanol. 2.4 g (63%) of the title compound is obtained as a

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Z-/E-mixture. The E-isomer is obtained pure by recrystallization from isopropanol; mp: 90-91°C

EXAMPLE 10

3-(5-Cyano-2-thienyl)-3-(1-imidazolyl)-acrylonitrile

Analogously to example 9, with use of cyanomethylenetriphenylphosphorane, a Z-/E-mixture of the title compound is obtained. The E-isomer is obtained pure from ethanol; mp: 129-133°C.

EXAMPLE 11

3-(4-Cyanophenyl)-3-(1,2,4-triazol-1-yl)-acrylic acid-tert-butyl ester

Analogously to example 9, with use of 1-trimethylsilyl-1,2,4-triazole and tert-butoxycarbonylmethylenetriphenylphosphorane.

Z-isomer: mp: 132-133°C

E-isomer: mp: 83- 85°C

EXAMPLE 12

3-(4-Cyanophenyl)-3-(1,2,4-triazol-1-yl)-acrylonitrile

Analogously to example 9, with use of 1-trimethylsilyl-1,2,4-triazole and cyanomethylene-triphenylphosphorane.

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EXAMPLE 13

7-Cyano-4-(1-imidazolyl)-coumarin

5 g of 7-hydroxycoumarin in 25 ml of pyridine is mixed by instillation under argon at 0°C with a mixture of 8.1 ml of trifluoromethanesulfonic acid anhydride and 65 ml of pyridine. It is stirred for 20 more hours at room temperature, poured on 400 ml of ice-cold, semiconcentrated hydrochloric acid and extracted with ethyl acetate. After washing the ethyl acetate phase with semiconcentrated hydrochloric acid, water and potassium bicarbonate solution in succession, it is dried and concentrated by evaporation. 6.9 g of 7-hydroxycoumarin-trifluoromethanesulfonic acid ester is obtained; mp: 75-76°C.

3 g of it is refluxed with 960 mg of potassium cyanide, 2.4 g of tetrakis-(triphenylphosphine)-palladium(0) and 30 mg of 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6) in 180 ml of tetrahydrofuran for 5 hours. It is diluted with water, extracted with ethyl acetate and the ethyl acetate phase is washed in succession with 1 M sodium hydroxide solution, water and common salt solution. After concentration by evaporation in a vacuum, it is recrystallized from ethanol and 975 mg of 7-cyanocoumarin is obtained; mp: 217-225°C.

This material is dissolved in 95 ml of dichloromethane, mixed with 10 ml of bromine and stirred under action of light (100 W) for 4 days. Then, it is concentrated by evaporation in a vacuum. The crystals are suctioned off with ether. 1.2 g of 3,4-dibromo-7-cyano-2-chromanone is obtained; mp: 220-230°C.

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The dibromo compound is refluxed with 372 mg of imidazole and 2.52 ml of triethylamine in 20 ml of toluene for 7 hours. The solution is distributed between 1 M hydrochloric acid and ether, the acid water phase is separated and it is alkalized with potassium carbonate. After extraction with ethyl acetate and concentration of the solvent by evaporation, the remaining crystals are suctioned off with ether, dried at 50°C in a vacuum and 140 mg of the title compound of melting point 260-268°C is thus obtained.

EXAMPLE 14

3-(4-Cyanophenyl)-3-(1-imidazolyl)-acrylic acid methyl ester
4-Cyanophenyl-propionic acid methyl ester is obtained from 10 g of 4-cyanobenzoyl chloride and 40 g of methoxycarbonylmethylene-triphenylphosphorane (yield 5.5 g; mp: 103-106°C) analogously to Chem. Ber. 94 (1961) 3005 and further reacted as follows:

a) 185 mg of the ester and 75 mg of imidazole are refluxed in 5 ml of tetrahydrofuran for 20 hours. It is distributed between 1 M hydrochloric acid and ether, the acid water phase is separated, it is alkalized with potassium carbonate and then extracted with ethyl acetate. After drying and concentration by evaporation, 150 mg of crystals, which represent a Z:E mixture in the ratio 5.2:1 of the product produced in example 1, is obtained.

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b) 185 mg of the ester, 75 mg of imidazole and 0.07 mg of triethylamine in 5 ml of tetrahydrofuran are reacted and worked up as in a). 150 mg of product is obtained; Z:E = 6.5:1.

c) 185 mg of ester and 155 mg of N-trimethylsilylimidazole in 5 ml of tetrahydrofuran are treated as in a). 100 mg of product is obtained; Z:E = 4:1.

EXAMPLE 15

3-(4-Fluorophenyl)-3-(1-imidazolyl)-acrylic acid-tert-butyl ester

Analogously to example 9, with use of 4-fluorobenzoic acid, a Z-/E-mixture of the title compound is obtained. After chromatography and recrystallization, the E-isomer is obtained pure.

Mp: 90-93°C

EXAMPLE 16

3-(4-Chlorophenyl)-3-(1-imidazolyl)-acrylic acid-tert-butyl ester

Analogously to example 9, with use of 4-chlorobenzoic acid. The E-isomer melts at 114-121°C (from cyclohexane).

EXAMPLE 17

3-(4-Bromophenyl)-3-(1-imidazolyl)-acrylic acid-tert-butyl ester

Analogously to example 9, with use of 4-bromobenzoic acid. The E-isomer melts at 131-132°C (from isopropanol).

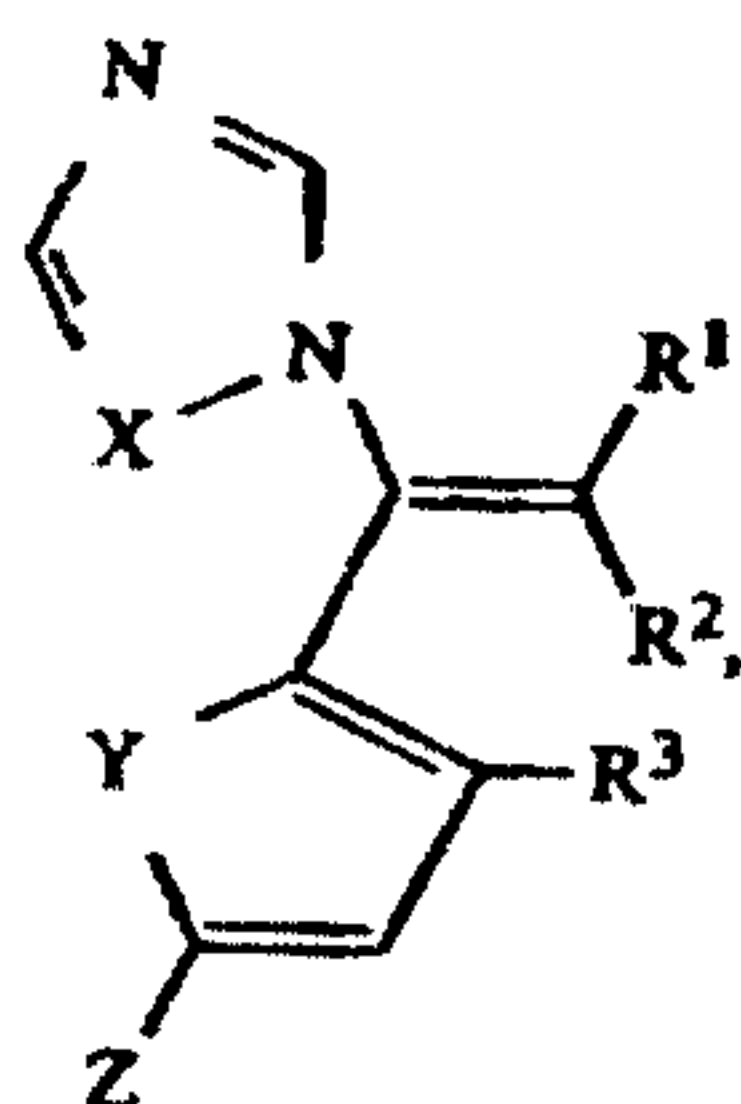
EXAMPLE 18

3-(4-Fluorophenyl)-3-(1,2,4-triazol-1-yl)-acrylic acid-tert-butyl ester

Analogously to example 9, with use of 4-fluorobenzoic acid and 1-trimethylsilyl-1,2,4-triazole. The E-isomer melts at 72-74°C.

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

1. A pharmaceutical composition for the treatment of an estrogen-induced or estrogen-dependent disease, the composition comprising a vinyl azole of formula I:



wherein

X is N or CH;

Y is S or CH=CH;

Z is cyano; and

one of R¹ or R² is carboxyl unesterified, or esterified with C₁₋₁₀ straight-chain, branched-chain or cyclic O-alkyl; or esterified with O-aryl, wherein aryl is phenyl or naphthyl, unsubstituted or substituted 1-3 times by C₁₋₄ alkyl or halogen; or esterified with an O-aralkyl, wherein aryl and alkyl have the indicated meanings;

or said one of R¹ or R² is carboxylic acid amide, wherein the amide N is unsubstituted or substituted 1-2 times by same or different C₁₋₁₀ straight-chain or branched-chain alkyl, or by same or different C₆₋₁₀ aryl optionally substituted 1-3 times by C₁₋₄ alkyl or halogen, or wherein the amide N is part of a 5- to 8-membered heterocyclic ring, either containing no additional heteroatom or containing an additional ring heteroatom N, O or S, and the additional N

is unsubstituted or substituted by R^6 , wherein R^6 is H or C_{1-6} straight-chain or branched-chain alkyl;

or said one of R^1 or R^2 is an aldehyde;

or said one of R^1 or R^2 is an alkylketone $-CO-R^7$, wherein R^7 is a straight-chain or branched-chain C_{1-10} alkyl or C_{3-12} cycloalkyl;

or said one of R^1 or R^2 is an arylketone $-CO-R^8$, wherein R^8 is phenyl, naphthyl or C_3-C_7 heteroaryl, unsubstituted or substituted 1-3 times by C_{1-4} alkyl, halogen, hydroxy or C_{1-4} alkoxy;

or said one of R^1 or R^2 is sulfonamide, unsubstituted or substituted by R^6 as defined above;

or said one of R^1 or R^2 is cyano;

and the respective other R^1 or R^2 is hydrogen, C_{1-4} lower-alkyl or cycloalkyl, unsubstituted or substituted aryl, aralkyl, unesterified or esterified carboxyl, unsubstituted or substituted carboxylic acid amide, aldehyde, alkylketone or arylketone or cyano, each as defined above; or

R^1 and R^2 together with the carbon atom on which they are bound form a 5-, 6- or 7-membered ring, which further contains a ketone, ester, lactone, lactam or imide, wherein at least one carbonyl is conjugated with a vinyl double bond; and

R^3 is hydrogen; or

R^3 together with R^2 are $-O-C(=O)-$, or $-N-C(=O)-$
 $\quad \quad \quad |$
 unsubstituted or substituted on the amide N as defined above, wherein the carbonyl is conjugated with a vinyl double bond;

and a pharmaceutically acceptable excipient.

2. A pharmaceutical composition according to claim 1, wherein R^1 or R^2 is hydrogen.
3. A pharmaceutical composition according to claim 1 or 2, wherein R^3 is hydrogen.
4. A pharmaceutical composition according to claim 1, wherein R^1 and R^2 together with the carbon on which they are bound form a 5-, 6- or 7-membered ring and R^3 is hydrogen.
5. A pharmaceutical composition according to claim 1, wherein R^3 together with R^2 are $-O-C(=O)-$ or $-\overset{|}{N}-C(=O)-$.
6. A pharmaceutical composition according to claim 1, wherein R^1 and/or R^2 are carboxyl esterified with a straight-chain or branched-chain or cyclic C_{1-10} O-alkyl, with O-aryl, and aryl is phenyl or naphthyl, unsubstituted or substituted one or more times by C_{1-4} lower-alkyl, F, Cl, Br, I, or by O-aralkyl, wherein aryl and alkyl are as defined above.
7. A pharmaceutical composition according to claim 6, wherein the carboxyl is esterified with methoxy, ethoxy, propoxy, isopropoxy, isobutoxy, tert-butoxy, cyclohexyloxy, cyclopentyloxy, phenyloxy, or 2,6-dichlorophenoxy.
8. A pharmaceutical composition according to claim 1, wherein R^1 and/or R^2 are carboxylic acid amide substituted one or two times by same or different straight-chain or branched-chain C_{1-10} alkyl, or by same or different C_{6-10} aryl

optionally substituted up to three times by C₁₋₄ alkyl or halogen; or

wherein alkyl groups on the amidic nitrogen, together with the amidic nitrogen, form a 5- to 8-membered heterocyclic ring, either containing no additional heteroatoms or containing an additional ring heteroatom N, O or S, and, if there is an additional N in the ring, it is unsubstituted or substituted by R⁶, wherein R⁶ is H or straight-chain or branched-chain C₁₋₆ alkyl.

9. A pharmaceutical composition according to claim 8, wherein the carboxylic acid amide is substituted with methyl, ethyl, propyl, phenyl or benzyl; two methyls, ethyls or propyls; phenyl and methyl; phenyl and ethyl; or benzyl and methyl; or

wherein the substituents on the amidic nitrogen together with the amidic nitrogen form a pyrrolidine, piperidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine ring.

10. A pharmaceutical composition according to claim 1, wherein R¹ and/or R² is alkylketone -CO-R⁷, and R⁷ is straight-chain or branched-chain C₁₋₁₀ alkyl or C₃₋₁₂ cycloalkyl.

11. A pharmaceutical composition according to claim 10, wherein R⁷ is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, cyclopentyl or cyclohexyl.

12. A pharmaceutical composition according to claim 1, wherein R^1 and/or R^2 is arylketone $-\text{CO}-R^8$, and R^8 is phenyl, naphthyl or $\text{C}_3\text{-C}_7$ heteroaryl unsubstituted or substituted by C_{1-4} alkyl, halogen, hydroxy or C_{1-4} alkoxy.

13. A pharmaceutical composition according to claim 12, wherein R^8 is phenyl, hydroxyphenyl, methoxyphenyl or chlorophenyl.

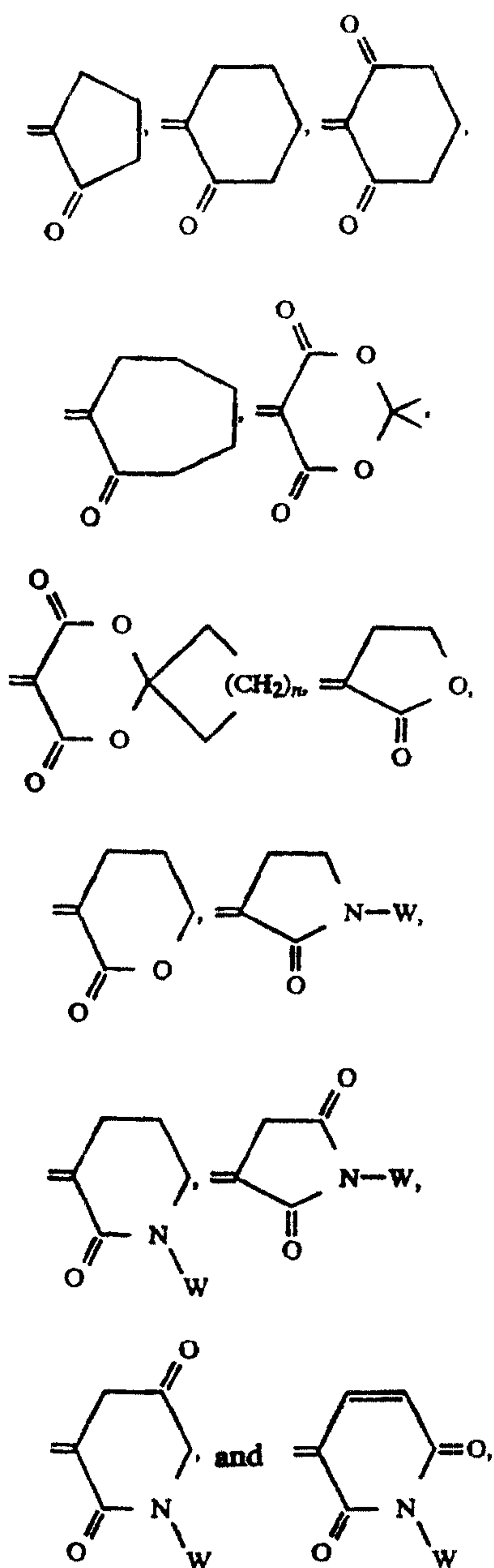
14. A pharmaceutical composition according to claim 1, wherein R^1 or R^2 is sulfonamide $-\text{SO}_2\text{NR}^9\text{R}^{10}$, and R^9 and R^{10} are each, independently, a straight-chain or branched-chain C_{1-10} alkyl, C_{8-10} aryl, unsubstituted or substituted one to three times by alkyl or halogen, or wherein both alkyls on the amidic nitrogen together with the amidic nitrogen form a 5- to 8-membered heterocyclic ring, containing no additional heteroatoms or an additional ring heteroatom N, O or S, and, if there is an additional N in the ring, it is unsubstituted or substituted by R^6 , wherein R^6 is H or straight-chain or branched-chain C_{1-6} alkyl.

15. A pharmaceutical composition according to claim 14, wherein R^9 and R^{10} are methyl, ethyl, propyl, phenyl or benzyl; two methyls, ethyls or propyls; phenyl and methyl; phenyl and ethyl; or benzyl and methyl; or

wherein the substituents on the amidic nitrogen together with the amidic nitrogen form a pyrrolidine, piperidine, piperazine, N-methylpiperazine, morpholine or thiomorpholine ring.

16. A pharmaceutical composition according to claim 15, wherein R^9 and R^{10} is each methyl, ethyl or propyl.

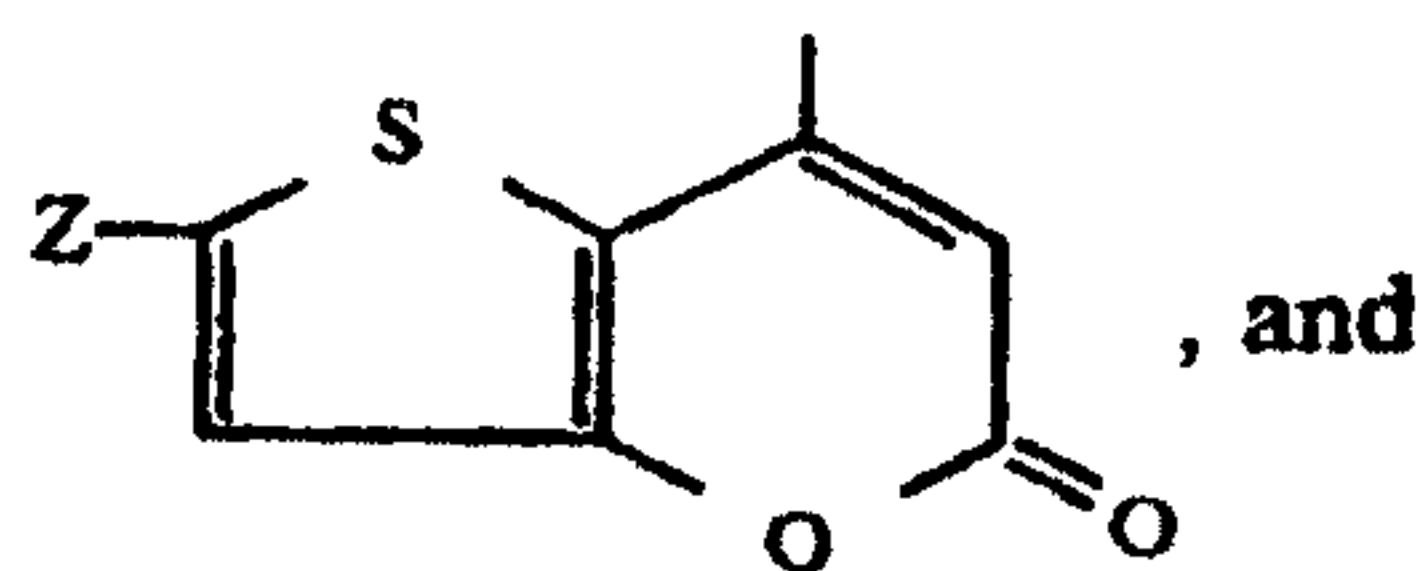
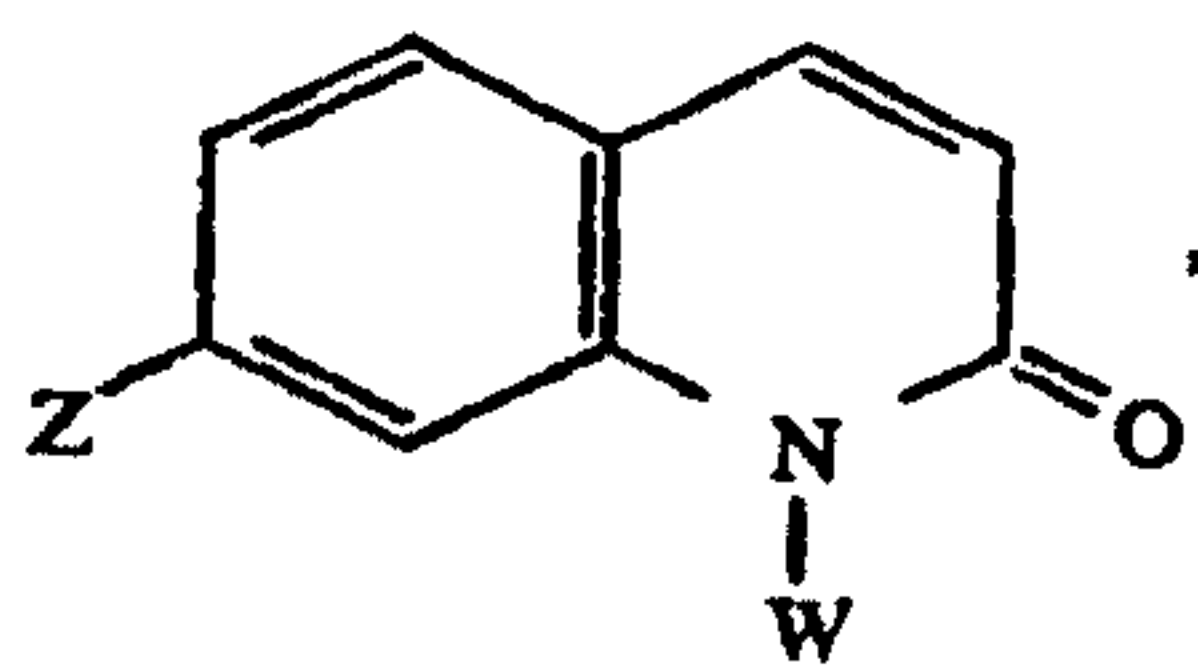
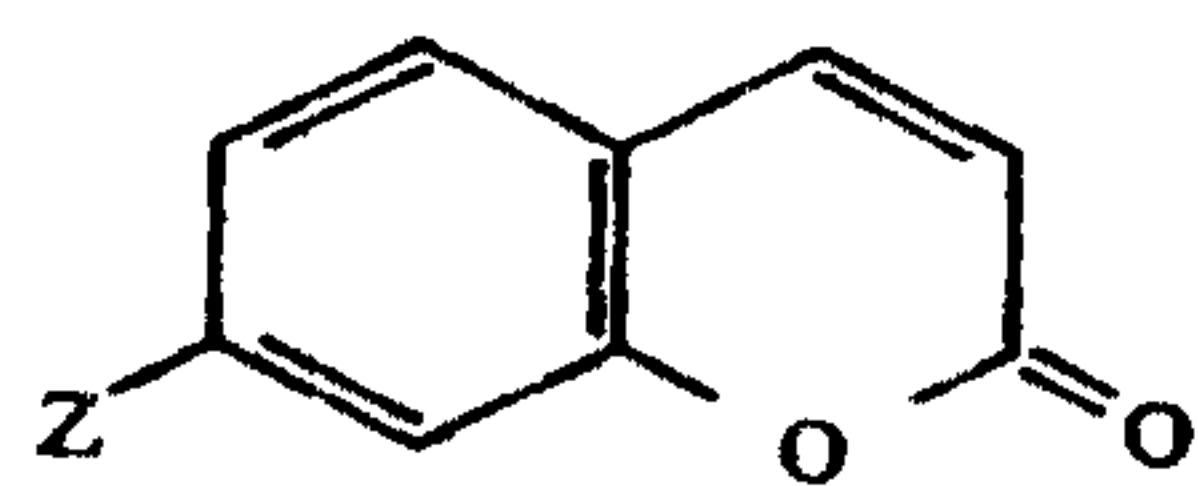
17. A pharmaceutical composition according to claim 4, wherein R^1 and R^2 together with the carbon on which they are bound form a group selected from:



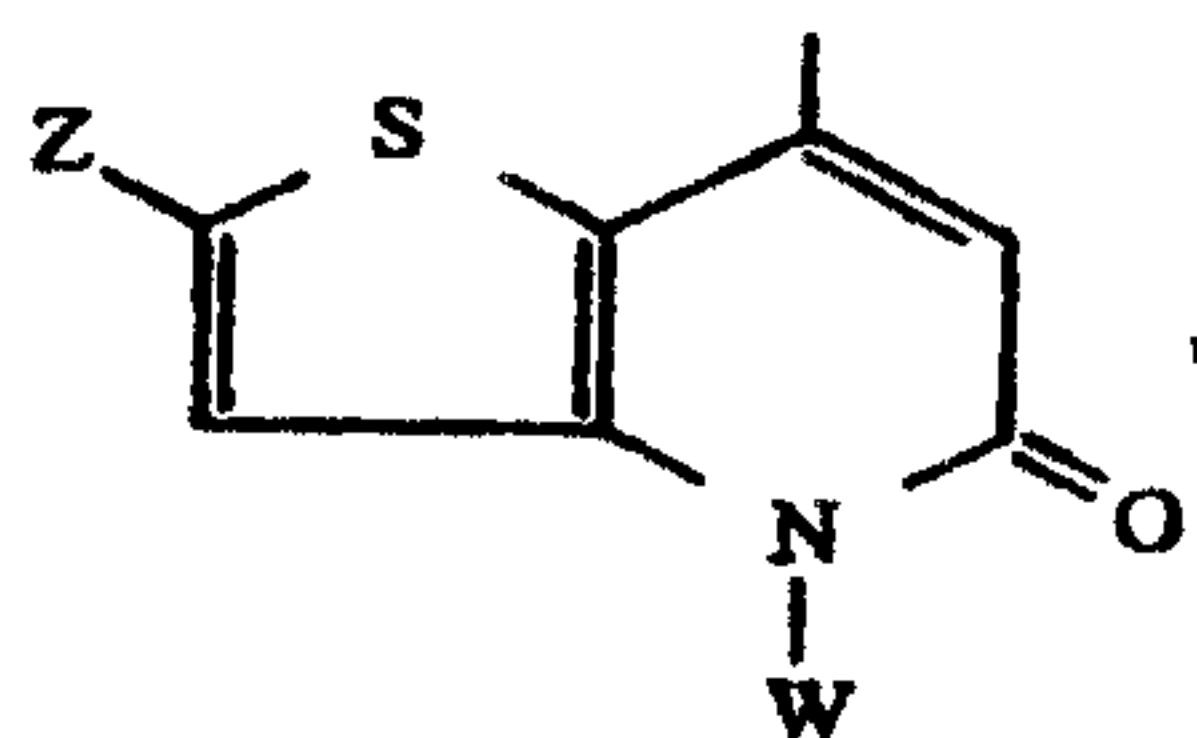
wherein n is 2 or 3, and W is hydrogen or C_{1-6} alkyl.

18. A pharmaceutical composition of claim 1, wherein, when one of R^1 or R^2 is arylketone, the other is cycloalkyl, unsubstituted or substituted aryl, aralkyl, unesterified or esterified carboxyl, unsubstituted or substituted carboxylic acid amide, aldehyde, arylketone or cyano.

19. A pharmaceutical composition according to claim 5, wherein R^2 and R^3 together with the aromatic ring containing Y form a group selected from:



, and



wherein W is hydrogen or C_{1-10} alkyl.

20. A pharmaceutical composition according to claim 1, wherein the vinyl azole is 3-(4-cyanophenyl)-3-(1-imidazolyl)-acrylic acid methyl ester.

21. A pharmaceutical composition according to claim 1, wherein the vinyl azole is 3-(4-cyanophenyl)-3-(1-imidazolyl)-acrylic acid tert-butyl ester.

22. A pharmaceutical composition according to claim 1, wherein the vinyl azole is E-3-(4-cyanophenyl)-3-(1-imidazolyl)-acrylic acid.

23. A pharmaceutical composition according to claim 1, wherein the vinyl azole is E-3-(4-cyanophenyl)-3-(1-imidazolyl)-acrylic acid piperidide.

24. A pharmaceutical composition according to claim 1, wherein the vinyl azole is E-3-(4-cyanophenyl)-3-(1-imidazolyl)-acrylic acid methanamide.

25. A pharmaceutical composition according to claim 1, wherein the vinyl azole is 3-(4-cyanophenyl)-3-(1-imidazolyl)-acrylonitrile.

26. A pharmaceutical composition according to claim 1, wherein the vinyl azole is 4-[1-(1-imidazolyl)-3-oxo-1-butenyl]-benzonitrile.

27. A pharmaceutical composition according to claim 1, wherein the vinyl azole is 3-[(4-cyanophenyl)-(1-imidazolyl)-methylene]dihydro-2(3H)-furanone.

28. A pharmaceutical composition according to claim 1, wherein the vinyl azole is 3-(5-cyano-2-thienyl)-3-(1-imidazolyl)-acrylic acid tert-butyl ester.

29. A pharmaceutical composition according to claim 1, wherein the vinyl azole is 3-(5-cyano-2-thienyl)-3-(1-imidazolyl)-acrylonitrile.

30. A pharmaceutical composition according to claim 1, wherein the vinyl azole is 3-(4-cyanophenyl)-3-(1,2,4-triazol-1-yl)-acrylic acid tert-butyl ester.

31. A pharmaceutical composition according to claim 1, wherein the vinyl azole is 3-(4-cyanophenyl)-3-(1,2,4-triazol-1-yl)-acrylonitrile.

32. A pharmaceutical composition according to claim 1, wherein the vinyl azole is 7-cyano-4-(1-imidazolyl)-coumarin.

33. A pharmaceutical composition according to any one of claims 1 to 32, wherein the composition is in a unit dosage form for oral administration, is sterile for parenteral administration, or is a cream or ointment for topical administration.

34. A pharmaceutical composition of claim 33, which is sterile.

35. A pharmaceutical composition of claim 33, wherein the parenteral administration is in the form of a sterile depot injection.

36. A pharmaceutical composition of claim 33, wherein the parenteral administration is in the form of a sterile implant.

37. A pharmaceutical composition as defined in any one of claims 1 to 36, for inhibiting estrogen biosynthesis.

38. A pharmaceutical composition as defined in any one of claims 1 to 36, for the treatment of an estrogen-induced or estrogen-dependent tumors.

39. A pharmaceutical composition according to claim 38, wherein the tumor represents breast cancer, endometrial cancer, melanoma or prostatic hyperplasia.

40. A pharmaceutical composition according to claim 39, wherein the tumor represents breast cancer.

41. A pharmaceutical composition as defined in any one of claims 1 to 36, for inhibiting ovulation.

42. Use of a pharmaceutical composition as defined in any one of claims 1 to 36, for the manufacture of a medicament for the treatment of an estrogen-induced or estrogen-dependent disease.

43. Use of a pharmaceutical composition as defined in any one of claims 1 to 36, for the manufacture of a medicament for inhibiting estrogen biosynthesis.

44. Use of a pharmaceutical composition as defined in any one of claims 1 to 36, for the manufacture of a medicament for the treatment of an estrogen-induced or estrogen-dependent tumor.

45. A use according to claim 44, wherein the tumor represents breast cancer, endometrial cancer, melanoma or prostatic hyperplasia.

46. A use according to claim 45, wherein the tumor represents breast cancer.

47. Use of a pharmaceutical composition as defined in any one of claims 1 to 36, for the manufacture of a medicament for inhibiting ovulation.

48. Use of a pharmaceutical composition as defined in any one of claims 1 to 36, for the treatment of an estrogen-induced or estrogen-dependent disease.

49. Use of a pharmaceutical composition as defined in any one of claims 1 to 36, for inhibiting estrogen synthesis.

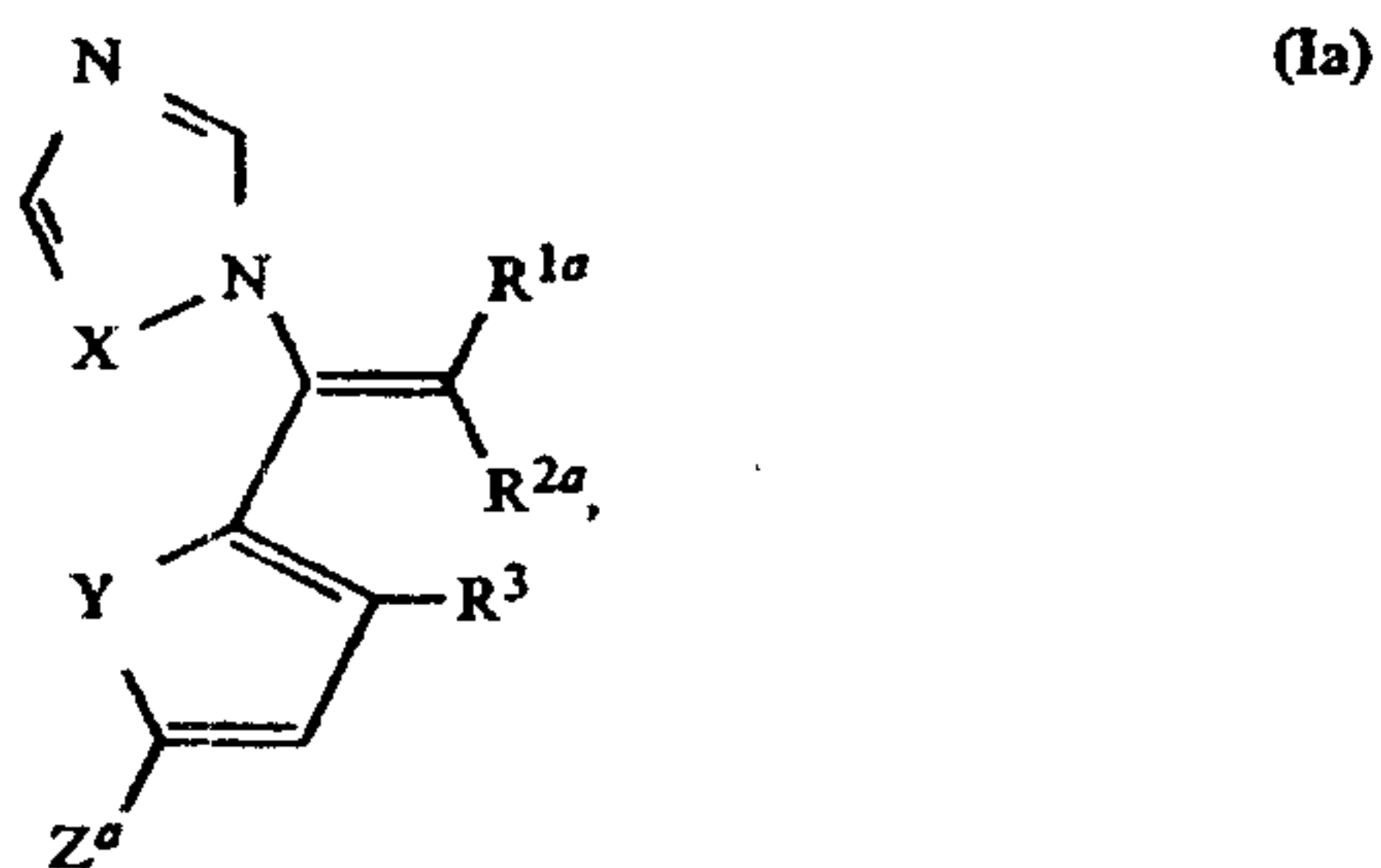
50. Use of a pharmaceutical composition as defined in any one of claims 1 to 36, for the treatment of an estrogen-induced or estrogen-dependent tumor.

51. A use according to claim 50, wherein the tumor represents breast cancer, endometrial cancer, melanoma or prostatic hyperplasia.

52. A use according to claim 51, wherein the tumor represents breast cancer.

53. Use of a pharmaceutical composition as defined in any one of claims 1 to 36, for inhibiting ovulation.

54. A vinyl azole of formula 1a:



wherein

X is N or CH;

Y is S or CH=CH;

Z^a is cyano; and

one of R^{1a} or R^{2a} is carboxyl unesterified, or esterified with C_{1-10} straight-chain or branched-chain or cyclic O-alkyl; or esterified with O-aryl, wherein aryl is phenyl or naphthyl, unsubstituted or substituted 1-3 times by C_{1-4} alkyl or halogen; or esterified with O-aralkyl, wherein aryl and alkyl have the indicated meanings;

or said one of R^{1a} or R^{2a} is carboxylic acid amide, wherein the amide N is unsubstituted or substituted 1-2 times by same or different C_{1-10} straight-chain or branched-chain alkyl, or by same or different C_{6-10} aryl optionally substituted 1-3 times by C_{1-4} alkyl or halogen, or wherein the amide N is optionally part of a 5- to 8-membered heterocyclic ring, either containing no additional heteroatom or containing an additional ring heteroatom N, O or S, and the additional N is unsubstituted or substituted by R^6 , wherein R^6 is H or C_{1-6} straight-chain or branched-chain alkyl;

or said one of R^{1a} or R^{2a} is aldehyde;

or said one of R^{1a} or R^{2a} is arylketone $-CO-R^8$, wherein R^8 is phenyl, naphthyl or C_3-C_7 heteroaryl, unsubstituted or substituted 1-3 times by C_{1-4} alkyl, halogen, hydroxy or C_{1-4} alkoxy;

or said one of R^{1a} or R^{2a} is sulfonamide, unsubstituted or substituted by R^6 ;

or said one of R^{1a} or R^{2a} is cyano;

and the respective other R^{1a} or R^{2a} is hydrogen, lower-alkyl or cycloalkyl, unsubstituted or substituted aryl, aralkyl, unesterified or esterified carboxyl, unsubstituted

or substituted carboxylic acid amide, aldehyde, arylketone or cyano, each as defined above;

with the proviso that R^{1a} and R^{2a} are not simultaneously hydrogen and arylketone; or

R^{1a} and R^{2a} together with the carbon on which they are bound form a 5-, 6- or 7-membered ring, which further contains a ketone, ester, lactone, lactam or imide, wherein at least one carbonyl is conjugated with a vinyl double bond; and

R^3 is hydrogen; or

R^3 together with R^{2a} are $-O-C(=O)-$, or $-N-C(=O)-$ unsubstituted or substituted on the amide N as defined above, wherein the carbonyl group is conjugated with a vinyl double bond.

55. A vinyl azole of claim 54, wherein, when one of R^{1a} or R^{2a} is arylketone, the other is cycloalkyl, unsubstituted or substituted aryl, aralkyl, unesterified or esterified carboxyl, unsubstituted or substituted carboxylic acid amide, aldehyde, arylketone or cyano.

56. A pharmaceutical composition comprising a compound as defined in claim 54 or 55, and a pharmaceutically acceptable excipient, for the treatment of an estrogen-induced or estrogen-dependent disease.

57. A pharmaceutical composition as defined in claim 56, for inhibiting estrogen biosynthesis.

58. A pharmaceutical composition as defined in claim 56, for the treatment of an estrogen-induced or estrogen-dependent tumor.

59. A pharmaceutical composition according to claim 58, wherein the tumor represents breast cancer, endometrial cancer, melanoma or prostatic hyperplasia.

60. A pharmaceutical composition according to claim 59, wherein the tumor represents breast cancer.

61. A pharmaceutical composition as defined in claim 56, for inhibiting ovulation.

62. Use of a compound as defined in claim 54 or 55, for the manufacture of a medicament for the treatment of an estrogen-induced or estrogen-dependent disease.

63. Use of a compound as defined in claim 54 or 55, for the manufacture of a medicament for inhibiting estrogen biosynthesis.

64. Use of a compound as defined in claim 54 or 55, for the manufacture of a medicament for the treatment of an estrogen-induced or estrogen-dependent tumor.

65. A use according to claim 64, wherein the tumor represents breast cancer, endometrial cancer, melanoma or prostatic cancer.

66. A use according to claim 65, wherein the tumor represents breast cancer.

67. Use of a compound as defined in claim 54 or 55, for the manufacture of a medicament for inhibiting ovulation.

68. Use of a compound as defined in claim 54 or 55, for the treatment of an estrogen-induced or estrogen-dependent disease.

69. Use of a compound as defined in claim 54 or 55, for inhibiting estrogen biosynthesis.

70. Use of a compound as defined in claim 54 or 55, for the treatment of an estrogen-induced or estrogen-dependent tumor.

71. A use according to claim 70, wherein the tumor represents breast cancer, endometrial cancer, melanoma or prostatic cancer.

72. A use according to claim 71, wherein the tumor represents breast cancer.

73. Use of a compound as defined in claim 54 or 55, for inhibiting ovulation.

