Description

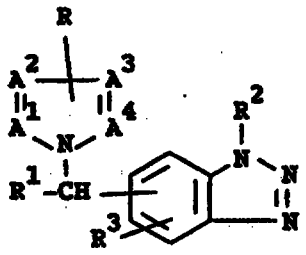
A large number of azole derivatives are known in the art as antifungal agents. Recently miconazole, clotrimazole and ketoconazole, members of a class of imidazole agents with a broad spectrum activity against a variety of yeasts, dermatophytes and dimorphous fungi, have been reported to inhibit the action of the enzyme aromatase in Biochemical Pharmacology, 34, 1087 (1985).

Related azole derivatives have been described in U.S. Pat. Nos. 4,602,025 and 4,609,666 and in the Published European Patent Application 0,165,781 as aromatase inhibitors useful for treating estrogen dependent disease.

In U.S. Patent No. 4,410,539 there are further described a number of (1H-imidazol-1-ylmethyl) substituted indole derivatives which compounds are useful as thromboxane synthetase inhibitors.

The compounds of the present invention differ therefrom by the fact that they contain invariably a benzotriazole moiety and by their capability to inhibit the action of the enzyme aromatase. The compounds of the present invention are therefore useful in therapeutically treating and preventing estrogen hormone dependent disorders in mammals.

The present invention is concerned with benzotriazole derivatives of formula



(I),

and pharmaceutically acceptable acid addition salts and stereoisomeric forms thereof, wherein

$A^1=A^2-A^3=A^4$ is a bivalent radical having the formula

-CH=N-CH=CH- (a-1),

-CH=N-CH=N- (a-2), or

-CH=N-N=CH- (a-3);

R is a hydrogen or C_{1-6}alkyl;

R^1 is hydrogen, C_{1-10}alkyl, C_{3-7}cycloalkyl, Ar^1, Ar^2-C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl;

R^2 is hydrogen; C_{1-10}alkyl optionally substituted with Ar^1, C_{3-7}cycloalkyl, hydroxy or C_{1-6}alkoxy; Ar^1; C_{2-6}alkenyl; C_{2-6}alkynyl; C_{3-7}cycloalkyl; bicyclo[2.2.1]heptan-2-yl; 2,3-dihydro-1H-indenyl; 1,2,3,4-tetrahydronaphthalenyl; hydroxy; C_{2-6}alkenyloxy optionally substituted with Ar^2; C_{2-6}alkynyloxy; pyrimidinyloxy; di(Ar^2) methoxy; (1-C_{1-4}alkyl-4-piperidinyl)oxy; or C_{1-10}alkyloxy optionally substituted with halo, hydroxy, C_{1-6}alkyloxy, amino, mono- and di(C_{1-6}alkyl)amino, trifluoromethyl, carboxyl, C_{1-6}alkyloxycarbonyl, Ar^1, Ar^2-O-, Ar^2-S-, C_{3-7}cycloalkyl, 2,3-dihydro- 1,4-benzodioxinyl, 1H-benzimidazolyl, C_{1-4}alkyl substituted 1H-benzimidazolyl, (1,1'-biphenyl)-4-yl or with 2,3-dihydro-2-oxo-1H-benzimidazolyl;

R^3 is hydrogen, nitro, amino, mono- and di(C_{1-6}alkyl) amino, halo, C_{1-6}alkyl, hydroxy or C_{1-6}alkyloxy;

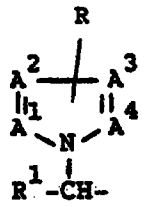
wherein Ar^1 is phenyl, substituted phenyl, naphthalenyl, pyridinyl, aminopyridinyl, imidazolyl, triazolyl, thienyl, halothienyl, furanyl, C_{1-6}alkylfuranyl, halofuranyl or thiazolyl; and

Ar^2 is phenyl, substituted phenyl or pyridinyl, said substituted phenyl being phenyl substituted with up to 3 substituents each independently selected from halo, hydroxy, hydroxymethyl, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, formyl, (hydroxyimino)methyl, cyano, amino, mono- and di(C_{1-6}alkyl) amino and nitro;

As used in the foregoing definitions the term halo is generic to fluoro, chloro, bromo and iodo; the term "C_{1-6}alkyl" is meant to include straight and branch chained saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as, for example, methyl, ethyl, 1-methylethyl, 1,1-dimethylethyl, propyl, 2-methylpropyl, butyl, pentyl, hexyl and the like; "C_{1-10}alkyl" is meant to include C_{1-6}alkyl radicals, as defined hereinabove, and the higher homologs thereof having from 7 to 10 carbon atoms; the term "C_{3-7}cycloalkyl" is generic to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. "C-

$_{2-6}$alkenyl" defines straight and branch chained hydrocarbon radicals containing one double bond and having from 2 to 6 carbon atoms such as, for example, ethenyl, 2-propenyl, 3-butenyl, 2-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl and the like; "C_{2-6}alkynyl" defines straight and branch chained hydrocarbon radicals containing one triple bond and having from 2 to 6 carbon atoms such as, for example, 2-propynyl, 2-butynyl, 3-butynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl and the like; and when a C_{2-6}alkenyl or a C_{2-6}alkynyl is substituted on a heteroatom, then the carbon atom of said C_{2-6}alkenyl or said C_{3-6}alkynyl connected to said heteroatom preferably is saturated.

It is to be understood that the



moiety, hereinafter refered as the 1H-azol-1-ylmethyl moiety, may be substituted on either the 4,5,6 or 7 position of the benzotriazole heterocyclic ring. In addition, the compounds of formula (I) may also contain in their structure a tautomeric system and consequently these compounds can be present in each of their tautomeric forms. Also within the scope of the invention are the compounds of formula (I) in the form of hydrates or in solvent addition forms.

An interesting group among the compounds of formula (I) comprises those compounds of formula (I) wherein $A^1 = A^2\text{-}A^3 = A^4$ is a bivalent radical having the formula (a-1).

Another interesting group among the compounds of formula (I) comprises those compounds of formula (I) wherein $A^1 = A^2\text{-}A^3 = A^4$ is a bivalent radical having a formula (a-2) or (a-3), with (a-2) being the most interesting subgroup.

Preferred compounds within the present invention are those compounds of formula (I) wherein R is hydrogen or C_{1-4}alkyl; R^1 is hydrogen; C_{1-6}alkyl optionally substituted with phenyl or substituted phenyl; C_{3-7}cycloalkyl; phenyl; substituted phenyl; pyridinyl; naphthalenyl; thienyl; furanyl; imidazolyl; triazolyl; C_{2-6}alkenyl or C_{2-6}alkynyl; R^2 is hydrogen; C_{1-6}alkyl optionally substituted with phenyl, substituted phenyl, naphthalenyl, thienyl, furanyl, C_{1-4}alkylfuranyl, C_{3-7}cycloalkyl, hydroxy or C_{1-4}alkyloxy; phenyl; substituted phenyl; C_{2-6}alkenyl; C_{2-6}alkynyl; C_{3-7}cycloalkyl; bicyclo[2.2.1]heptan-2-yl; 2,3-dihydro-1H-indenyl; 1,2,3,4-tetrahydronaphthalenyl; hydroxy; C_{2-6}alkenyloxy optionally substituted with phenyl; C_{2-6}alkynyloxy; pyrimidinyloxy; di(phenyl)methoxy; (1-C_{1-4}alkyl-4-piperidinyl)oxy; or C_{1-6}alkyloxy optionally substituted with halo, hydroxy, amino, mono-and di(C_{1-4}alkyl)amino, trifluoromethyl, carboxyl, C_{1-6}alkyl oxy-carbonyl, phenyl, substituted phenyl, thienyl, furanyl, pyridinyl, phenoxy, phenylthio, C_{3-7}cycloalkyl, 2,3-dihydro-1,4-benzodioxinyl, 1H-benzimidazolyl, C_{1-4}alkyl substituted 1H-benzimidazolyl, (1,1'-biphenyl)-4-yl, or with 2,3-dihydro-2-oxo-1H-benzimidazolyl; and R^3 is hydrogen or nitro.

Particularly preferred compounds within the present invention are those preferred compounds wherein the 1H-azol-1-ylmethyl moiety is substituted on either the 5 or 6 position of the benzotriazole heterocyclic ring.

More particularly preferred compounds within the present invention are those particularly preferred compounds wherein R is hydrogen; R^1 is hydrogen, C_{1-6}alkyl, phenyl or substituted phenyl; and R^2 is hydrogen; C_{3-7}cycloalkyl; bicyclo[2.2.1]heptan-2-yl; 2,3-dihydro-1H-indenyl; 1,2,3,4-tetrahydronaphthalenyl; C_{1-6}alkyl optionally substituted with phenyl, substituted phenyl or C_{3-7}cycloalkyl; or C_{1-6}alkyloxy optionally substituted with phenoxy, phenylthio, C_{3-7}cycloalkyl, phenyl or substituted phenyl.

Especially preferred compounds within the invention are those more particularly preferred compounds of formula (I) wherein R^1 is phenyl optionally substituted with halo, C_{1-4}alkyl, C_{1-4}alkyloxy or trifluoromethyl; and R^2 is C_{1-6}alkyl.

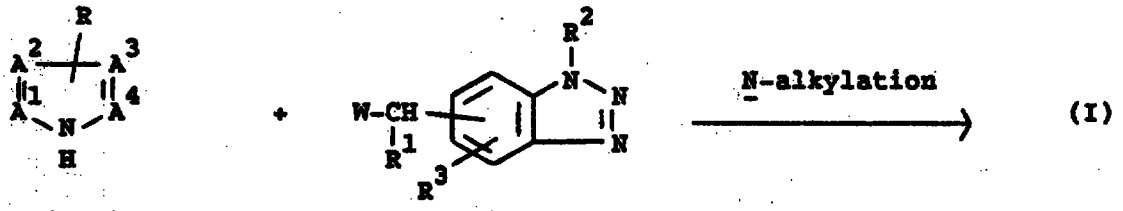
More especially preferred compounds within the invention are those especially preferred compounds of formula (I) wherein R^1 is phenyl or halophenyl and R^2 is C_{1-4}alkyl.

The most preferred compounds within the invention are selected form the group consisting of 6-[(1H-imidazol-1-yl)phenylmethyl]-1-methyl-1H-benzotriazole, 6-[(4-chlorophenyl)(1H-1,2,4-triazol-1-yl)methyl]-1-methyl-1H-benzotriazole, the pharmaceutically acceptable acid addition salts and possible stereochemically isomeric forms thereof.

A particular subgroup of compounds of formula (I) comprises those compounds, preferred, particularly preferred and more particularly preferred compounds of formula (I) wherein R^2 is connected to the nitrogen atom of the benzotriazole ring on a carbon atom or wherein R^2 is hydrogen. Said compounds of formula (I) being represented hereinafter by compounds of formula (I-b).

Another particular subgroup of compounds of formula (I) comprises those compounds, preferred, particularly preferred and more particularly preferred compounds of formula (I) wherein R^2 is connected to the nitrogen atom of the benzotriazole ring on an oxygen atom. Said compounds of formula (I) being represented hereinafter by compounds of formula (I-c).

The compounds of formula (I) can generally be prepared by N-alkylating an azole of formula (III) or an alkali metal salt thereof with a benzotriazole of formula (II).



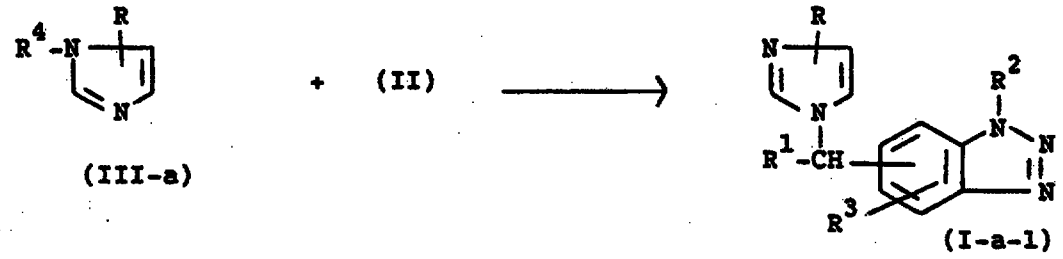
(III) (II) (I)

W as used in the reaction of (II) with (III) and in the following reaction schemes is an appropriate leaving group such as, for example, halo, preferably chloro, bromo or iodo, a sulfonyloxy group, e.g., methylsulfonyloxy or 4-methylbenzenesulfonyloxy.

The above described N-alkylation is conveniently carried out by stirring the reactants in the presence of a suitable organic solvent such as, for example, an aromatic hydrocarbon. e.g., benzene. methylbenzene, dimethylbenzene, and the like; a ketone, e.g., 2-propanone, 4-methyl-2-pentanone and the like; an ether, e.g., 1,4-dioxane, 1,1'-oxybisethane, tetrahydrofuran and the like; a polar aprotic solvent, e.g., N,N-dimethylformamide (DMF), N,N-dimethyl-acetamide (DMA), dimethyl sulfoxide (DMSO), 1-methyl-2-pyrrolidinone, acetonitrile, hexamethylphosphor triamide (HMPT), 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU), 1,3-dimethyl-2-imidazolidinone (DMEU), benzonitrile and the like; and mixtures of such solvents. Somewhat elevated temperatures may be appropriate to enhance the rate of the reaction and in some cases the reaction may even be carried out at the reflux temperature of the reaction mixture.

The addition of an appropriate base such as, for example, an alkali or an earth alkaline metal carbonate, hydrogen carbonate, hydroxide, amide or hydride, e.g., sodium hydroxide, potassium hydroxide, potassium carbonate, sodium hydride and the like or an organic base, such as, for example, N,N-dimethyl-4-pyridinamine, pyridine, N,N-diethylethanamine or N-(1-methylethyl)-2-propanamine may be employed to pick up the acid which is liberated during the course of the reaction. In some instances it may be advantageous to use an excess of the azole (III) or to convert it to its metal salt form, in particularly its alkali metal salt form following art-known procedures such as, e.g., by treatment of the azole with an alkali metal hydroxide, alkoxide, or hydride.

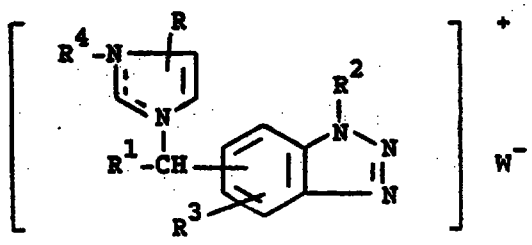
Compounds of formula (I) wherein $A^1=A^2-A^3=A^4$ is a bivalent radical of formula (a-l), said compounds being represented by formula (I-a-1), may also be prepared by reacting a benzotriazole of formula (II) with a 1-protected imidazole of formula (III-a) following the N-alkylation procedures described hereinabove for the preparation of compounds of formula (I) starting from (II) and (III).



(III-a) (II) (I-a-1)

In (III-a) R^4 represents a protective group such as, for example, C_{1-6}alkylcarbonyl, C_{1-6}alkyloxycarbonyl, arylcarbonyl or a tri(C_{1-6}alkyl)silyl group. In some instances the reaction of (III-a) with (II) first yields a 1-

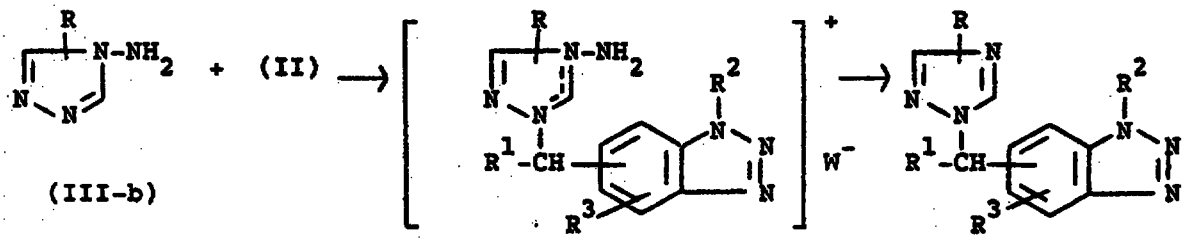
protected-imidazolium salt of formula (IV) which may in situ, or if desired, after isolating and further purifying it, be deprotected by stirring it in an aqueous basic solution.



(IV)

In (IV) W^- is an anion arising from an acid such as, for example, hydrochloric acid, hydrobromic acid, methanesulfonic acid, 4-methyl-benzenesulfonic acid and the like acids.

Particular compounds of formula (I) wherein $A^1=A^2-A^3=A^4$ is a bivalent radical of formula (a-2), said compounds being represented by formula (I-a-2), can also be prepared by N-alkylation of a triazolamine of formula (III-b) with a benzotriazole of formula (II) and subsequent deamination of the thus prepared triazolium salt of formula (V).

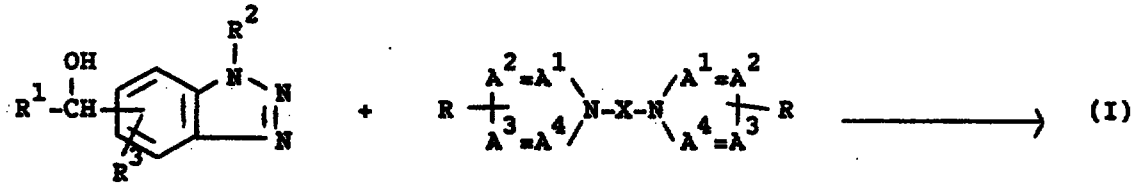


(III-b) (V) (I-a-2)

In (V) W^- is an anion arising from an acid such as, for example, hydrochloric acid, hydrobromic acid, methanesulfonic acid, 4-methylbenzenesulfonic acid and the like acids.

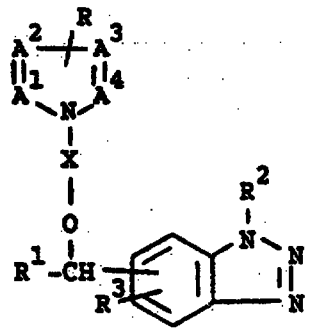
The N-alkylation reaction of (III-b) with (II) is carried out according to similar procedures as described hereinabove for the preparation of a compound of formula (I) starting from (III) and (II). The said deamination reaction is conveniently conducted by means of an acidic nitrite solution in the presence of an appropriate reductant. Preferably, the said deamination reaction is conducted with an aqueous solution of nitrous acid or of a nitrite salt in a suitable acid in the presence of a reducing agent such as, for example, hypophosphorous acid, formic acid, at a lower temperature.

The compounds of formula (I) may also be prepared by reacting an alcohol of formula (VI) with a reagent of formula (VII), such as, for example, a 1,1'-carbonylbis[1H-imidazole].



(VI) (VII) (I)

In (VII) X represents $>C=O$, S or $>C=O$. In some instances the reaction of (VI) with (VII) first yields an intermediate of formula (VIII) which may in situ or, if desired, after isolating and further purifying it, be converted to the desired compound of formula (I).

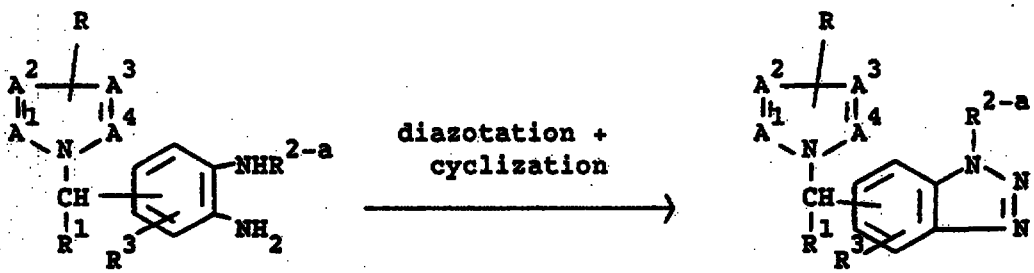


(VIII)

Said reaction may conveniently be conducted in a suitable solvent such as, for example, an ether, e.g., 1,4-dioxane, tetrahydrofuran; a halogenated hydrocarbon, e.g., di- or trichloromethane; a hydrocarbon, e.g., benzene, methylbenzene; a ketone, e.g., 2-propanone, 4-methyl-2-pentanone; N,N-dimethylformamide, N,N-dimethylacetamide, or mixtures of such solvents. In order to enhance the reaction rate, it may be advantageous to heat the reaction mixture.

The compounds of formula (I) can alternatively be prepared under similar conditions as are described in the literature for the preparation of benzotriazoles starting from appropriate benzenediamines or halonitrobenzene derivatives. Depending on the nature of the substituent R^2 in the compounds of formula (I) to be prepared, the following procedures may, for example, be utilized.

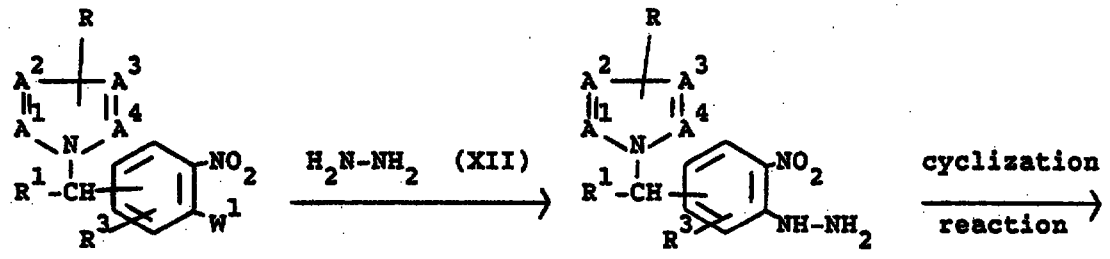
The compounds of formula (I) wherein R^2 is hydrogen; C_{1-10} alkyl optionally substituted with Ar^1, C_{3-7}cycloalkyl, hydroxy or C_{1-6}alkyloxy; Ar^1; C_{2-6}alkenyl; C_{2-6}alkynyl; C_{3-7}cycloalkyl; bicyclo[2.2.1]-heptan-2-yl; 2,3-dihydro-1H-indenyl; or 1,2,3,4-tetrahydronaphthalenyl, said radical being represented by R^{2-a} and said compounds by (I-b), may be derived from an appropriately substituted diamine of formula (IX) by diazotation and subsequent cyclization.



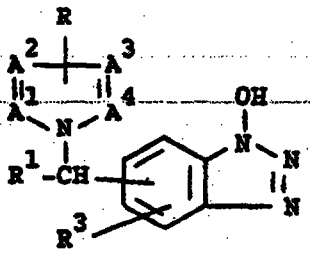
(IX) (I-b)

Said diazotative cyclization reaction can be carried out by stirring the diamine of formula (IX) in an acidic nitrite solution. Preferably the said reaction is conducted with an aqueous solution of nitrous acid or of a nitrite salt, e.g., sodium nitrite in the presence of a suitable acid such as, for example, hydrochloric acid, hydrobromic acid, formic acid, acetic acid, propanoic acid and the like acids, at a low temperature.

The compounds of formula (I), wherein R^2 is hydroxy, said compounds being represented by formula (I-c-1), can be prepared by cyclizing an appropriately substituted azole of formula (X), which in situ may be formed by reacting an intermediate of formula (XI) with hydrazine (XII) or a hydrate thereof.



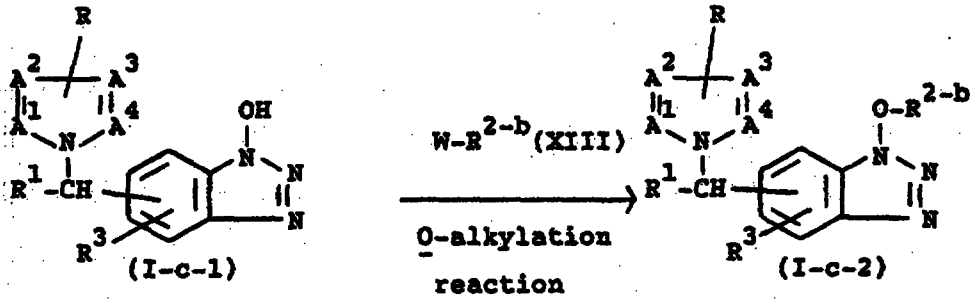
(XI) (X)



(I-c-1)

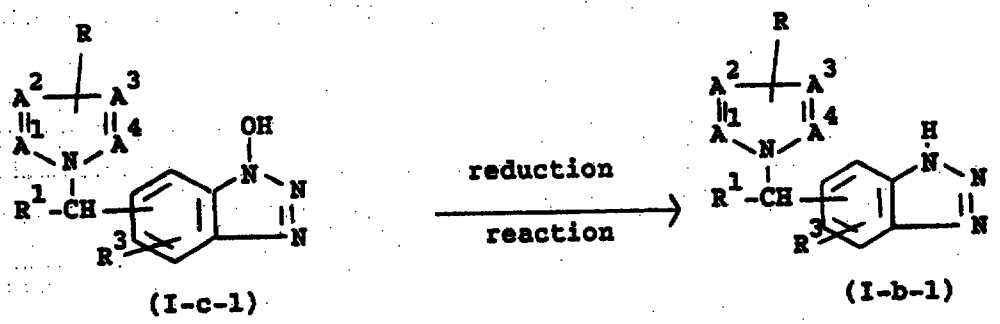
In (XI) W^1 represents an appropriate leaving group such as, for example, halo, preferably fluoro, chloro or bromo, a sulfonyloxy group, e.g., methylsulfonyloxy or 4-methylbenzenesulfonyloxy, or a C_{1-6}alkyloxy or C_{1-6}alkylthio group. The cyclization reaction may be carried out by stirring an intermediate of formula (XI) with hydrazine in a suitable reaction-inert solvent such as, for example, an alcohol, e.g., methanol, ethanol, 2-propanol, 1-butanol and the like or an aromatic hydrocarbon, e.g., benzene, methylbenzene, dimethylbenzene and the like. Somewhat elevated temperatures may be appropriate to enhance the rate of the reaction and preferably the reaction is carried out at the reflux temperature of the reaction mixture. After completion, the reaction mixture is preferably cooled and acidified with an acidic solution such as, for example, a hydrochloric acid solution.

The compounds of formula (I-c-1) can further be O-alkylated with a reagent of formula (XIII) following art-known procedures, thus preparing the corresponding compounds of formula (I-c-2) wherein R^2 is optionally substituted C_{1-10} alkyloxy, optionally substituted C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, pyrimidinyloxy, di(Ar^2)methoxy or (1-C_{1-4}alkyl-4-piperidinyl)oxy, the said radical being represented by O-R^{2-b}.

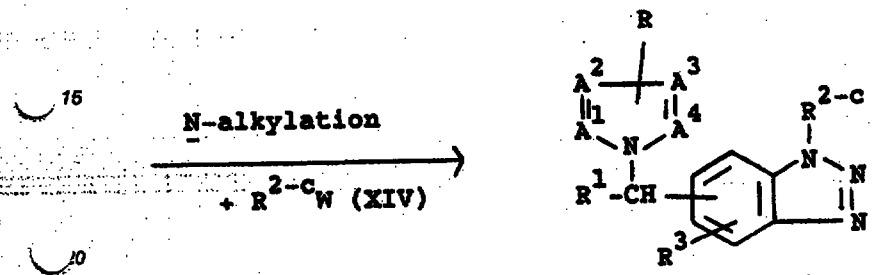


Said O-alkylation is conveniently conducted in a suitable reaction-inert solvent or a mixture of such solvents. Suitable reaction-inert solvents are, for example, an aromatic hydrocarbon, e.g., benzene, methylbenzene, dimethylbenzene, and the like; a lower alkanol, e.g., methanol, ethanol, 1-butanol and the like; a polar aprotic solvent, e.g., N,N-dimethyl-formamide, N,N-dimethylacetamide, hexamethylphosphoric triamide, dimethyl sulfoxide; and the like. Preferably in the presence of an appropriate base such as, for example, an alkali or an earth alkaline metal hydride, alkoxide, hydroxide, hydrogen carbonate, carbonate or amide. It may be advantageous previously to convert (I-c-1) into a metal salt form thereof, preferably the sodium salt, in the usual manner, e.g., by the reaction of (I-c-1) with a metal base such as sodium hydroxide and the like, and thereafter to use said metal salt in the reaction with (XIII).

The compounds of formula (I-b) may alternatively be prepared by reducing a compound of formula (I-c-1), thus preparing a compound of formula (I-b) wherein R^2 is hydrogen and, if further desired, reacting the thus obtained compound of formula (I-b-1) with a reagent $R^{2-c}W$ (XIV), thus preparing compounds of formula (I-b-2).



(I-c-1) (I-b-1)

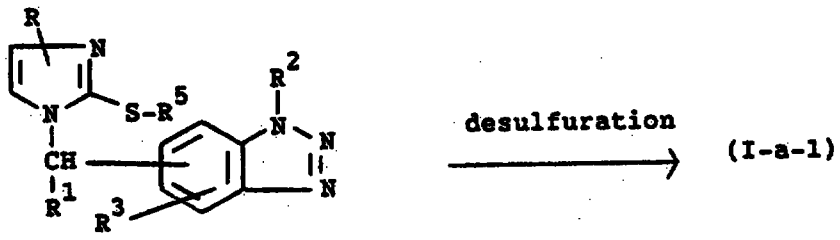


(I-b-2)

In (XIV) W has the previously defined meanings and R^{2-c} has the previously defined meaning of R^{2-a}, provided that it is not hydrogen. Said reduction reaction may for example be conducted by contacting the compounds of formula (I-c-1) with hydrogen in the presence of an appropriate catalyst such as, for example, Raney-nickel, platinum, palladium, platinum(IV) oxide, and the like, in the presence of a reaction-inert organic solvent such as, a lower alkanol, e.g. methanol, ethanol and the like. Said reduction may alternatively be conducted by reacting the starting material (I-c-1) with titanium(III) chloride or tin(II) chloride in hydrochloric acid, optionally in the presence of a reaction inert solvent. Preferably said reduction is carried out by O-alkylating (I-c-1) with a readily oxidizeable group such as, for example, C_{1-6}alkyloxycarbonylmethyl and the like groups and stirring the thus obtained intermediates in a suitable organic solvent, e.g., dimethyl sulfoxide, N,N-dimethylformamide and the like in the presence of a base such as, for example, an alkali or an earth alkaline metal carbonate, hydrogen carbonate, hydroxide, alkoxide or amide.

The N-alkylation reaction of (I-b-1) with (XIV) can be carried out in the usual manner, e.g., by stirring the reactants preferably at somewhat elevated temperatures in an appropriate organic solvent such as, for example, a polar aprotic solvent, e.g., dimethyl sulfoxide, dimethylformamide and the like in the presence of an appropriate base such as, for example, an alkali metal hydride, hydroxide, carbonate or amide.

The compounds of formula (I-a-1) can also be obtained by desulfurating an intermediate of formula (XV) in the usual manner, e.g., by treating the latter with Raney-nickel in the presence of an alcohol, e.g., ethanol or by treating the starting compounds with sodium nitrite in the presence of nitric acid in an aqueous medium.



(XV) (I-a-1)

R^5 in (XV) is C_{1-6}alkyl.

The compounds of formula (I) may also be converted into each other following art-known functional group transformation procedures. A number of such procedures will be described hereinafter in more detail.

The compounds of formula (I) containing an ester group may be converted into the corresponding acids following art-known saponification procedures, e.g., by treating the starting compound with an aqueous alkaline or an aqueous acidic solution. Vice versa, the carboxylic acid group may be converted into the corresponding ester group following art-known esterification procedures. For example, the carboxylic acid may be converted into a reactive derivative which subsequently is reacted with the corresponding alkanol; or by reacting the carboxylic acid and the alkanol with a suitable reagent capable of forming esters, e.g., dicyclohexylcarbodiimide, 2-chloro-1-methylpyridinium iodide and the like.

Compounds of formula (I) containing a formyl group may be converted into the corresponding oxime following art-known procedures, e.g., by treating the starting compound with hydroxylamine or an acid addition salt form thereof in a suitable solvent, e.g., water, a lower alkanol, an ether, in the presence of a base, e.g., an alkali metal hydroxide, carbonate or hydrogen carbonate.

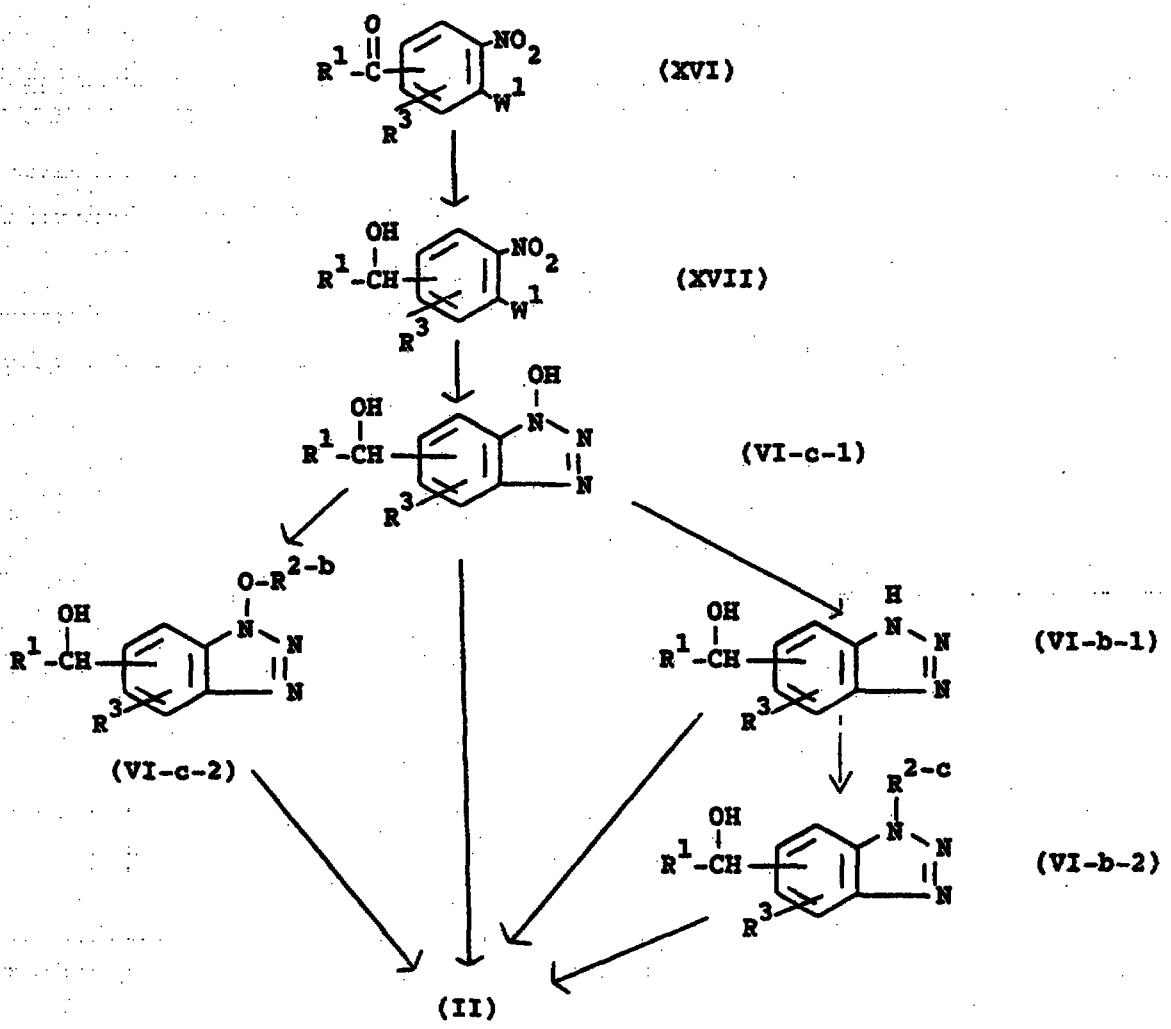
Compounds of formula (I) containing an alkynyl group may be converted into the corresponding compounds having an alkenyl group by catalytically hydrogenating the starting compound in a suitable reaction-inert solvent according to art-known catalytic hydrogenation procedures. Suitable catalysts are for example palladium-on-charcoal, platinum-on-charcoal and the like.

Compounds of formula (I) wherein R^3 is hydrogen may by converted into compounds wherein R^3 is nitro by stirring the starting compound in a solution of nitrous acid in the presence of an appropriate acid, e.g., sulfuric acid, or a mixture of acetic acid and acetic acid anhydride.

The compounds of formula (I) have basic properties and, consequently, they may be converted to their therapeutically active non-toxic acid addition salt forms by treatment with appropriate acids, such as, for example, inorganic acids, such as hydrohalic acid, e.g. hydrochloric, hydrobromic and the like, and sulfuric acid, nitric acid, phosphoric acid and the like; or organic acids, such as, for example, acetic, propanoic, hydroxyacetic, 2-hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, 2-hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids.
The compounds of formula (I) containing an acidic proton may also be converted to their therapeutically active non-toxic metal or amine substitution salts, by treatment with appropriate organic or inorganic bases. Conversely the metal or amine substitution salt form can be converted into the free acidic form by treatment with an acid.

A number of intermediates and starting materials in the foregoing preparation are known compounds which may be prepared according to art-known methodologies of preparing said or similar compounds and some intermediates are news. A number of such preparation methods will be described hereinafter in more detail.

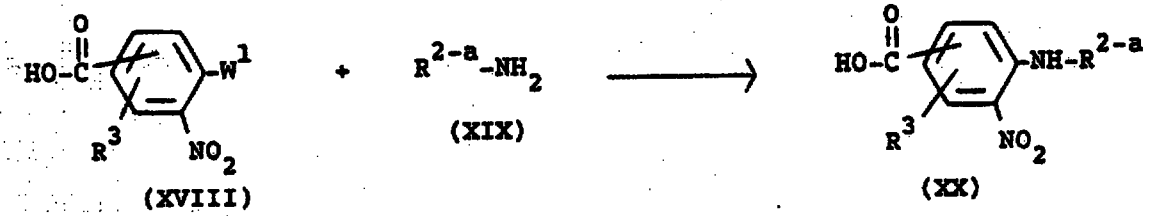
Starting materials of formula (II) can conveniently be prepared by the following reaction sequence. An aldehyde or ketone of formula (XVI) is reduced with an appropriate reductant such as, for example an aluminum or boron hydride or a complex hydride, e.g., lithium aluminum hydride, sodium borohydride, yielding an alcohol of formula (XVII), and is subsequently converted into a benzotriazole of formula (VI-c-1) following the cyclization procedure described hereinabove for the conversion of (XI) to (I-c-1). If desired, the thus obtained benzotriazole may further be converted into an appropriate intermediate of formula (VI-c-2), (VI-b-1) or (VI-b-2) following the same procedures as described for the conversion of (I-c-1) to (I-c-2), (I-c-1) to (I-b-1) and (I-b-1) to (I-b-2). The desired starting materials of formula (II) wherein W represents a leaving group may then be obtained by converting the hydroxy moiety of the benzotriazoles of formulae (VI) into a reactive ester following standard procedures as known in the art. Halides are generally prepared by the reaction of (VI) with an appropriate halogenating agent such as, for example, thionyl chloride, sulfuryl chloride, pentachlorophoshorane, pentabromophoshorane, phosphoryl chloride, hydrochloric acid, hydrobromic acid and the like. When the leaving group is a iodide it is preferably prepared from the corresponding chloride or bromide by the replacement of that halogen with iodine. Other reactive esters such as methanesulfonates and 4-methylbenzenesulfonates are obtained by the reaction of the alcohol with an appropriate sulfonyl halide such as, for example, methanesulfonyl chloride and 4-methylbenzenesulfonyl chloride.



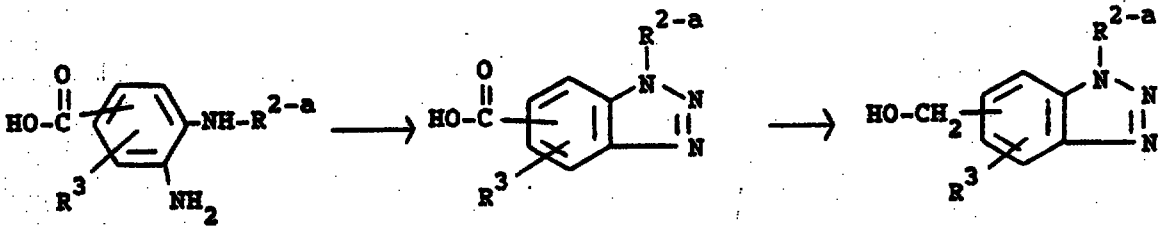
In the above reaction scheme R^1, R^{2-b} and R^{2-c} are the same as previously described.

In addition to the above described procedure the intermediates of formula (II), wherein R^2 *is a radical of* formula R^{2-a}, may also be prepared from an appropriately substituted benzoic acid of formula (XVIII) *according to the following reaction sequence.*

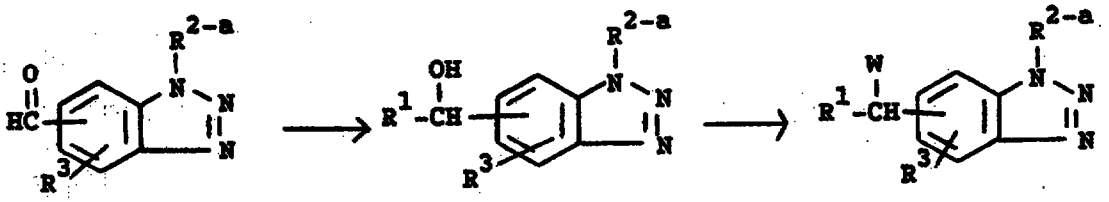
An intermediate of formula (XVIII) is reacted with an appropriate amine of formula (XIX) following art-known N-arylation procedures and is subsequently subjected to a nitro-to-amine reduction reaction yielding an intermediate of formula (XXI). The latter is converted into a benzotriazole derivative of formula (XXII) according to similar cyclization procedures as described hereinabove for the preparation of (I-b). The carboxylic acid function of the benzotriazole (XXII) is then converted into the corresponding alcohol (VI-b-3) in the usual manner, e.g. by reduction with an appropriate reducing agent, e.g., lithium tetrahydroaluminate, in a suitable solvent, e.g. tetrahydrofuran. If further desired, an appropriate substituent R^1 may be introduced by converting the hydroxymethyl moiety of formula (VI-b-3) into a formyl moiety with a suitable oxidizing agent, e.g., manganese (IV) oxide or potassium permanganate, and reacting the thus obtained aldehyde (XXIII) with a metal alkyl, e.g., methyllithium, butyllithium, metal aryl, e.g., phenyllithium, or with a complex metal alkyl or aryl in a suitable solvent, e.g., tetrahydrofuran. The desired intermediates of formula (II-b) may then be obtained by converting the alcohol function of formula (VI-b-3) or (VI-b) into an appropriate leaving group following standard procedures described hereinabove.



(XVIII) (XIX) (XX)

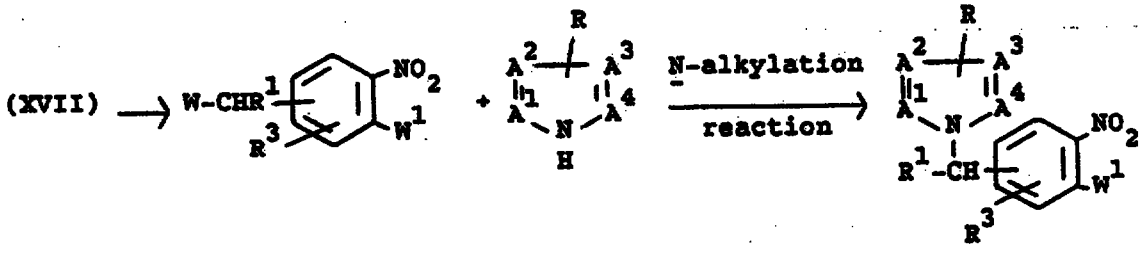


(XXI) (XXII) (VI-b-3)

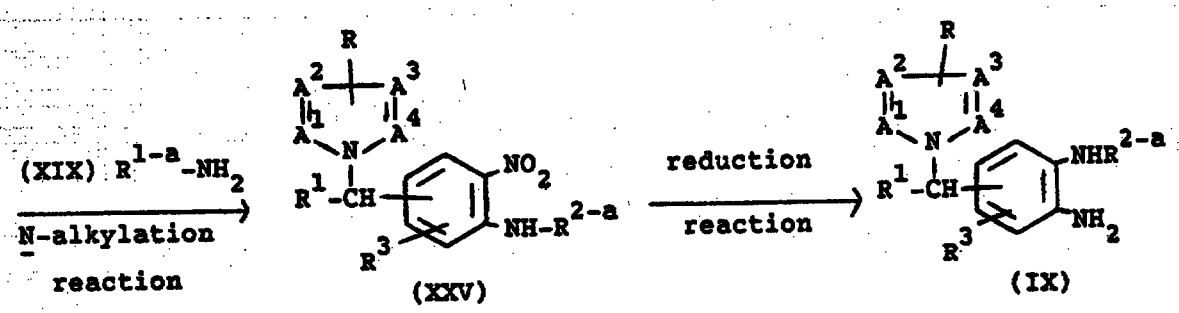


(XXIII) (VI-b) (II-b)

The intermediates of formula (IX) can be synthesized by various methodologies. For example, they may be prepared by the following sequence of reactions. An intermediate of formula (XVII) is converted into a reactive ester of formula (XXIV) and reacted with an 1H-azole of formula (III) following the same procedures as described hereinabove for the preparation of (I) starting from (II) and (III), yielding an intermediate of formula (XI). The latter is reacted with an appropriate amine of formula (XIX) following art-known N-arylation procedures and is subsequently subjected to a standard nitro-to-amine reduction reaction to yield the desired starting materials of formula (IX).

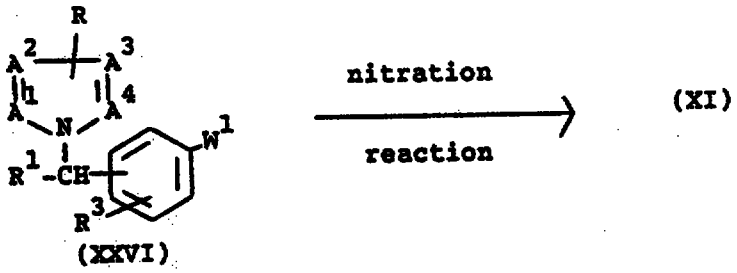


(XXIV) (III) (XI)

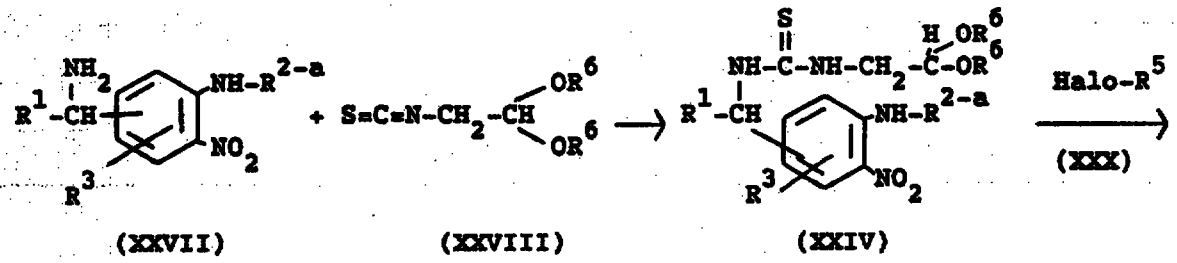


In formula (XXIV) W^1 and W have the previously described meanings. The above mentioned nitro-to amine reduction reactions are generally carried out by stirring the starting compounds in a hydrogen containing medium in the presence of a suitable amount of an appropriate catalyst such as, for example, platinium-on-charcoal, palladium-on-charcoal, Raney-nickel and the like. In addition, the reduction may also be carried out by stirring the starting compound with sodium sulfide or sodium dithionite in a suitable solvent such as, for example water, methanol, ethanol and the like.

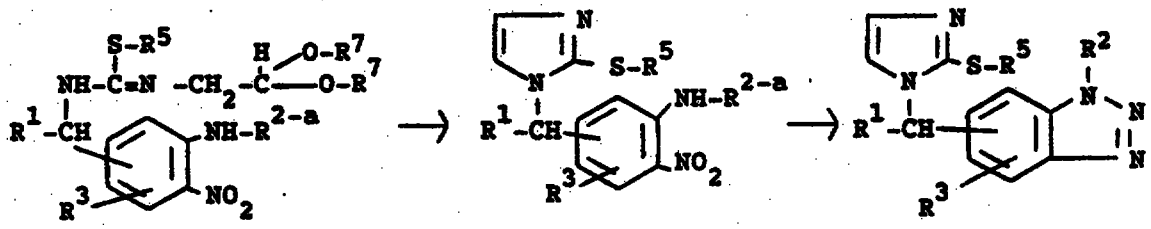
Intermediates of formula (XI) may also be prepared by nitration of a intermediate of formula (XXVI). The nitration reaction is conveniently conducted in a suitable solvent such as, for example, a halogenated hydrocarbon, e.g., trichloromethane and the like in the presence of an appropriate acid, such as, for example, sulfuric acid, or a mixture of acetic acid and acetic acid anhydride.



Intermediates of formula (XV-a) can be prepared by stirring and heating an appropriate isothiocyanate (XXVIII), wherein R^6 is C_{1-6}alkyl or Ar^2-C_{1-6}alkyl, with an appropriately substituted amine (XXVII) in the presence of a suitable reaction-inert organic solvent such as, for example, a halogenated hydrocarbon, e.g., dichloromethane; subsequently by converting the thus obtained thiourea (XXIV) to the corresponding carbamimidothioate (XXXI) with a halogenide (XXX), wherein R^5 is C_{1-6}alkyl and Halo is preferably chloro, bromo or iodo, by stirring the reactants in the presence of an appropriate reaction-inert solvent, e.g., propanone; cyclizing the thus obtained carbamimidothioate (XXXI) by stirring and heating the latter in an aqueous acidic solvent, e.g., in aqueous sulfuric acid; and finally condensing the benzotriazole moiety following the cyclizing procedures described hereinabove.



(XXVII) (XXVIII) (XXIV)



(XXXI) (XXXII) (XV-a)

In all of the foregoing preparations, the reaction products may be isolated from the reaction mixture and, if necessary, further purified according to methodologies generally known in the art.

Starting materials and intermediates used in all of the preceding procedures for which no specific preparations are given herein, are generally known and/or may all be prepared following art-known methodologies described in the literature for the preparation of similar known compounds.

The compounds of formula (I) and some of the intermediates in this invention may have an asymmetric carbon atom in their structure. This chiral center may be present in a R- and a S-configuration, this R- and S-notation being in correspondence with the rules described by R.S. Cahn, C. Ingold and V. Prelog in Angew. Chem., Int. Ed. Engl., 5,385;511 (1966).

The compounds of formula (I) containing an alkene moiety may be present in a "E" or "Z" form, said E- and Z-notation having the meanings described in J. Org. Chem., 35, 2849-2868 (1970).

Pure stereochemically isomeric forms of the compounds of this invention may be obtained by the application of art-known procedures. Diastereoisomers may be separated by physical separation methods such as selective crystallization and chromatographic techniques, e.g.: counter current distribution, and enantiomers may be separated from each other by the selective crystallization of their diastereomeric salts with optically active acids. They may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically.

The compounds of formula (I), the pharmaceutically acceptable acid-addition salts and possible stereochemically isomeric forms thereof have very interesting pharmacological properties. They inhibit the action of the enzyme aromatase which catalyses the formation of estrogens from androgenic steroids in mammals.

As generally accepted, estrogens are synthesized from androgens by the loss of the C-19 angular methyl group and the formation of the aromatic A ring. These reactions require NADPH and the enzyme aromatase. The inhibition of estrogen formation from androstenedione and testosterone can be demonstrated by in vitro-tests or in vivo-tests in mammals such as dogs, rats, mice and cats. The in vitro-inhibition of the aromatase activity can, for example, be demonstrated by analyzing the effects of the compounds of the present invention on the conversion of [1,2^{3}H]-androstenedione or[4^{14}C]-androstenedione into estrone and estradiol in the presence of human placental microsomes. The in vivo-inhibition of the aromatase activity can, for example, be demonstrated by measuring the suppression of the plasma estrogen concentration in female rats. The "In vitro-inhibition of the aromatase activity"-test and the "In vivo-inhibition of the aromatase activity"-test described hereinafter illustrate the estrogen inhibiting properties of the compounds of formula (I) and are based on the above principles.

In view of their capability to inhibit the biosynthesis of estrogens the subject compounds can be used in the treatment of estrogen dependent disorders such as, for example, breast cancer, endometriosis, endometrial cancer, polycystic ovarian disease, benign breast disease, gynecomastia, leyomyoma and the like.

The beneficial effect of aromatase inhibitors and/or anti estrogens in these disorders, especially in the treatment of breast cancer, is described in e.g. Cancer Research, 42, Suppl. 8: 3261s (1982).

The anti-tumour activity, especially in estrogen-dependent tumours, may in vivo be demonstrated. for example, by DMBA induced Mamma tumours in female Sprague-Dawley-rats.

In view of the usefulness of the subject compounds in the treatment of estrogen dependent disorders it is evident that the present invention Provides a method of treating mammals suffering from said estrogen dependent disorders. Said method comprises the systemic administration to the latter of an amount, effective to treat estrogen dependent disorders, of a compound of formula (I), a pharmaceutically acceptable acid-addition salt, or a possible stereochemically isomeric form thereof. In particular there is provided a method of inhibiting estrogen synthesis in mammals which comprises the systemic administration to said mammals of an estrogen synthesis inhibitory amount, more particularly an aromatase inhibitory amount, of a compound of formula (I).

In addition to the above, some compounds of formula (I) show an inhibitory action or the biosynthesis of thromboxane A_2.

In view of their useful pharmacological properties, the subject compounds may be formulated into various pharmaceutical forms for administration purposes.

To prepare the pharmaceutical compositions of this invention, an effective amount of the particular compound, in base or acid addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions: or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deletorious effect to the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a transdermal patch, as a spot-on, as an ointment.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and segregated multiples thereof.

Those of skill in treating the estrogen dependent disorders could easily determine the effective amount from the test results presented hereinafter. In general it is contemplated that an effective amount would be from 0.0001 mg/kg to 10 mg/kg body weight, and more preferably from 0.001 mg/kg to 0.5 mg/kg body weight.

The following examples are intended to illustrate and not to limite the scope of the invention. Unless otherwise stated all parts therein are by weight.

EXPERIMENTAL PART

A. Preparation of Intermediates

Example 1

a) A solution of 14 parts of (4-chloro-3-nitrophenyl)(4-fluorophenyl)methanone in 69 parts of 2-propanamine was stirred overnight at reflux temperature. The reaction mixture was poured into water. The precipitate was filtered off and washed with water, dried, filtered and evaporated, yielding 14.7 parts (97.2%) of (4-fluorophenyl) [4-[(1-methylethyl)amino]-3-nitrophenyl]methanone as a residue (int. 1).

b) A solution of 14.7 parts of (4-fluorophenyl) [4-[(1-methylethyl)amino]-3-nitrophenyl]methanone in 120 parts of ethanol was hydrogenated at 2.10^5 Pa with 3 parts of Raney nickel catalyst. After the calculated amount of hydrogen was taken up, the catalyst was filtered off over diatomaceous earth and the filtrate was evaporated, yielding 12.3 parts (92.1%) of [3-amino-4-[(1-methylethyl)amino]phenyl] (4-fluorophenyl)methanone as a residue (int. 2).

c) To a stirred and cooled (5 °C) solution of 12.3 parts of [3-amino-4-[(1-methylethyl)amino]phenyl] (4-fluorophenyl)methanone in 150 parts of a hydrochloric acid solution 6 N were added 4.7 parts of sodium nitrite. Upon complete addition, stirring was continued for 1 hour at room temperature. The mixture was treated with a potassium carbonate solution to pH 9 and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated, yielding 17 parts (100%) of (4-fluorophenyl) [1-(1-methylethyl)-1H-benzotriazol-5-yl]methanone as a residue (int. 3).

d) To a stirred solution of 17 parts of (4-fluorophenyl) [1-(1-methyl-ethyl)-1H-benzotriazol-5-yl]methanone in 80 parts of ethanol were added 3.4 parts of sodium tetrahydroborate. After stirring for 1 hour at room temperature, the reaction mixture was neutralized to pH 7. The reaction mixture was concentrated and the product was extracted with ethyl acetate. The extract was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of dichloromethane and methanol (98:2 by volume) as eluent. The pure fractions were collected and the eluent was evaporated, yielding 10.7 parts (62.5%) of α-(4-fluorophenyl)-1-(1-methylethyl)-1H-benzotriazole-5-methanol as a residue (int. 4).

In a similar manner there were also prepared:
1-cyclopropyl-α-(4-fluorophenyl)-1H-benzotriazole-5-methanol as a residue (int. 5); and
1-cyclohexyl-α-(4-fluorophenyl)-1H-benzotriazole-5-methanol as a residue (int. 6).

Example 2

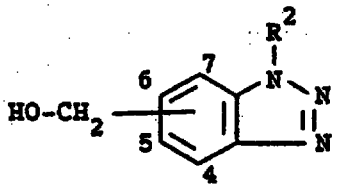
a) A mixture of 50 parts of 4-chloro-3-nitrobenzoic acid and 222 parts of 1-butanamine was stirred for 3 hours at reflux temperature. After cooling and evaporation of the excess of 1-butanamine, the reaction mixture was acidified with a sulfuric acid solution 2 N to pH 1. The precipitated product was filtered off and dried, yielding 59 parts (100%) of 4-(butylamino)-3-nitrobenzoic acid (int. 7).

b) A mixture of 50 parts of 4-(butylamino)-3-nitrobenzoic acid and 240 parts of methanol was hydrogenated in a Parr apparatus at 3.10^5 Pa and at room temperature with 40 parts of Raney Nickel catalyst under nitrogen atmosphere. After the calculated amount of hydrogen was taken up, the catalyst was filtered off over diatomaceous earth and the filtrate was evaporated to dry, yielding 43.7 parts (100%) of 3-amino-4-(butylamino)benzoic acid; mp. 158 °C (int. 8).

c) To a stirred and cooled mixture of 43.7 parts of 3-amino-4-(butyl-amino)benzoic acid and 200 parts of a hydrochloric acid solutin 6 N was added dropwise a solution of 22 parts of sodium nitrite in a small amount of water. Upon complete addition, the reaction mixture was stirred for 4 hours at 10-20 °C. The product was filtered off, washed with 30 parts of water and crystallized from a mixture of 2-propanone and ethyl acetate. The product was filtered off and dried, yielding 33.3 parts (72.6%) of 1-butyl-1H-benzotriazole-5-carboxylic acid; mp. 192.5 °C (int. 9).

d) To a stirred and cooled (0 °C) suspension of 23.4 parts of lithium tetrahydroaluminate in 270 parts of dry tetrahydrofuran were added portionwise 45 parts of 1-butyl-1H-benztriazole-5-carboxylic acid. Upon complete addition, stirring was continued for 1 hour at 0 °C. The reaction mixture was hydrolysed with 50 parts of water. The whole was filtered and washed with a mixture of dichloromethane and methanol (90:10 by volume). The filtrate was evaporated to dry and the residue was purified by column chromatography over silica gel using a mixture of dichloromethane and methanol (98:2 by volume) as eluent. The pure fractions were collected and the eluent was evaporated, yielding 18 parts (42.7%) of 1-butyl-1H-benzotriazole-5-methanol as an oily residue (int. 10).

In a similar manner there were also prepared:



Int. No.	R^2	P	base/salt	mp (°C)
11	$-CH_3$	7	base	106
12	$-(CH_2)_3-CH_3$	7	base	residue
13	$-(CH_2)_3-CH_3$	6	base	residue
14	$-CH_3$	4	base	residue
15	$-CH_3$	5	base	residue
16	$-CH_3$	6	base	oil
17	$-(CH_2)_3-CH_3$	4	base	residue

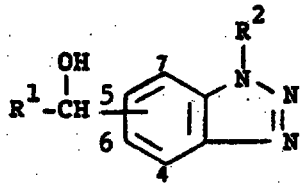
In the foregoing and following tables of the experimental part "P" represents the position of the substitution on the benzene moiety of the benzotriazole heterocycle.

Example 3

a) To a stirred mixture of 7.4 parts of potassium permanganate, 0.6 parts of 2-(2-methoxyethoxy)-N,N-bis[2-(2-methoxyethoxy)ethyl]ethanamine and 130 parts of dichloromethane was added dropwise a solution of 7.6 parts of 1-methyl-1H-benzotriazole-7-methanol in dichloromethane. Upon complete addition, stirring was continued for 2 hours. The reaction mixture was filtered over diatomaceous earth and washed with dichloromethane. The organic layer was washed with 30 parts of a hydrochloric acid solution 2 N and then with a sodium carbonate solution, dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of dichloromethane and methanol (98:2 by volume) as eluent. The pure fractions were collected and the eluent was evaporated, yielding 3.5 parts (46.6%) of 1-methyl-1H-benzotriazole-7-carboxaldehyde; mp. 126 °C (int. 18).

b) To a stirred and refluxed Grignard complex, previously prepared starting from 8.15 parts of 1-bromo-3-fluorobenzene, 1.2 parts of magnesium and a small amount of 1,1'-oxybisethane was added a solution of 5 parts of 1-methyl-1H-benzotriazole-7-carboxaldehyde in 80 parts of 1,1'-oxybisethane. After stirring for 2 hours at room temperature, the reaction mixture was poured into 300 parts of water. The product was extracted three times with 65 parts of dichloromethane. The combined extracts were dried, filtered and evaporated. The residue was stirred for 15 minutes in 100 parts of water and 13 parts of petroleum ether at room temperature. The product was filtered off and dried, yielding 7.6 parts (95.2%) of α-(3-fluorophenyl)-1-methyl-1H-benzotriazole-7-methanol; mp. 152 °C (int. 19).

In a similar manner there were also prepared:



Int. No.	R^1	R^2	P	base/ salt	mp (°C)
20	phenyl	$-(CH_2)_3-CH_3$	7	base	125°C
21	phenyl	$-CH_3$	7	base	residue
22	H_3C-	$-CH_3$	7	base	126°C
23	H_3C-	$-(CH_2)_3-CH_3$	7	base	residue
24	$3-Cl-C_6H_4-$	$-(CH_2)_3-CH_3$	7	base	112.0°C
25	$4-Cl-C_6H_4-$	$-(CH_2)_3-CH_3$	6	base	residue
26	$4-F-C_6H_4-$	$-(CH_2)_3-CH_3$	6	base	residue

Int. No.	R^1	R^2	P	base/ salt	mp (°C)
27	3-F-C_6H_4-	-$(CH_2)_3$-CH_3	6	base	residue
28	3-F-C_6H_4-	-$(CH_2)_3$-CH_3	7	base	116°C
29	3-Cl-C_6H_4-	-CH_3	7	base	128°C
30	3-Cl-C_6H_4-	-$(CH_2)_3$-CH_3	6	base	residue
31	3-F-C_6H_4-	-CH_3	5	base	residue
32	CH_3-$(CH_2)_2$-	-CH_3	5	base	residue
33	3-Cl-C_6H_4-	-CH_3	5	base	residue
34	3-Cl-C_6H_4-	-CH_3	6	base	residue
35	4-F-C_6H_4-	-CH_3	6	base	residue
36	4-Cl-C_6H_4-	-CH_3	6	base	residue
37	CH_3-$(CH_2)_2$-	-CH_3	6	base	residue
38	3-Br-C_6H_4-	-CH_3	5	base	oil
39	3-F-C_6H_4-	-CH_3	6	base	residue
40	3-Cl-C_6H_4-	-$(CH_2)_3$-CH_3	5	base	residue
41	H_3C-	-$(CH_2)_3$-CH_3	5	base	residue
42	H_3C-	-CH_3	6	base	residue
43	3-F-C_6H_4-	-$(CH_2)_3$-CH_3	5	base	residue
44	4-F-C_6H_4-	-$(CH_2)_3$-CH_3	5	base	82°C
45	4-Cl-C_6H_4-	-$(CH_2)_3$-CH_3	5	base	residue
46	4-Br-C_6H_4-	-$(CH_2)_3$-CH_3	5	base	residue
47	4-Cl-C_6H_4-	-CH_3	5	base	residue
48	3-Br-C_6H_4-	-CH_3	6	base	residue
49	4-Br-C_6H_4-	-CH_3	6	base	residue
50	4-Br-C_6H_4-	-CH_3	5	base	residue
51	4-CF_3-C_6H_4-	-CH_3	6	base	residue
52	2-Cl-C_6H_4-	-CH_3	6	base	residue
53	4-CH_3-C_6H_4-	-CH_3	6	base	residue
54	2-naphthalenyl	-CH_3	6	base	residue
55	4-H_3CO-C_6H_4-	-CH_3	6	base	residue

and α-[4-(4,5-dihydro-4,4-dimethyl-2-oxoazolyl)phenyl]-1-methyl-1H-benzotriazole-6-methanol as a residue (int. 56).

Example 4

a) A mixture of 36.5 parts of 1-butyl-1H-benzotriazole-5-methanol, 35 parts of manganese(IV) oxide and 390 parts of dichloromethane was stirred for 12 hours at room temperature. The manganese(IV) oxide was filtered off over diatomaceous earth and another portion of 35 parts of manganese(IV) oxide was added to the filtrate. After stirring for 12 hours at room temperature, the whole was filtered and the filtrate

was evaporated. The residue was purified by column chromatography over silica gel using dichloromethane as eluent. The pure fractions were collected and the eluent was evaporated, yielding 15.3 parts (42.2%) of 1-butyl-1H-benzotriazole-5-carboxaldehyde as a residue (int. 57).

b) To a stirred and cooled (-78 °C) solution of 7.2 parts of 3-bromothiophene in 70 parts of 1,1'-oxybisethane were added 30 parts of a 1-butyllithium solution 1.6 M in hexane. After stirring for 20 minutes at this low temperature, a solution of 6 parts of 1-butyl-1H-benzotriazole-5-carboxaldehyde in 1,1'-oxybisethane was added to the previous mixture. The reaction mixture was stirred for 2 hours at -78~ -40 °C. The whole was poured into 200 parts of ice water and the product was extracted three times with 56 parts of 1,1'-oxybisethane. The combined extracts were dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of dichloromethane and methanol (98:2 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from 2,2'-oxybispropane. The product was filtered off and dried, yielding 5 parts (58.9%) of 1-butyl-α-(3-thienyl)-1H-benzotriazole-5-methanol; mp. 80 °C (int. 58).

In a similar manner there were also prepared:

1-butyl-α-(2-thienyl)-1H-benzotriazole-5-methanol as a residue (int. 59);
1-methyl-α-(2-thienyl)-1H-benzotriazole-6-methanol as a residue (int. 60); and
1-methyl-α-(3-thienyl)-1H-benzotriazole-6-methanol as a residue (int 61).

Example 5

a) To a stirred mixture of 496 parts of aluminum chloride in 900 parts of benzene was added dropwise a solution of 256 parts of 4-fluoro-3-nitrobenzoyl chloride in 225 parts of benzene at ±10 °C. Upon complete addition, stirring was continued first for 1.5 hours in an ice bath and then for 8 hours at room temperature. The mixture was heated to 60 °C, cooled again and poured into crushed ice and 180 parts of concentrated hydrochloric acid. The separated organic layer was dried, filtered and concentrated. The concentrate was dissolved in 2100 parts of 2,2'-oxybispropane, the solution was treated with diatomaceous earth and activated charcoal. After filtration, the filtrate was concentrated. The crystallized product was filtered off and dried, yielding 223 parts (73%) of (4-fluoro-3-nitrophenyl) phenylmethanone; mp. 59 °C (int. 62).

b) To a cooled (ice bath) solution of 24.5 parts of (4-fluoro-3-nitrophenyl) phenylmethanone in 120 parts of methanol were added portionwise 1.5 parts of sodium tetrahydroborate. Upon complete addition, stirring was continued for 15 minutes at 0 °C. A solution of 3 parts of acetic acid in 25 parts of water was added dropwise to the mixture. Upon completion, the mixture was concentrated. Water was added to the residue and the product was extracted with dichloromethane. The extract was dried, filtered and concentrated, yielding 25.1 parts (100%) of 4-fluoro-3-nitro-α-phenylbenzenemethanol as an oily residue (int. 63).

c) A mixture of 25 parts of 4-fluoro-3-nitro-α-phenylbenzenemethanol, 20 parts of hydrazine monohydrate and 80 parts of ethanol was stirred for 1.5 hours at reflux temperature. After cooling, 20 parts of a hydrochloric acid solution 10 N were added. After concentration, the residue was washed twice with 50 parts of water and dissolved in a solution of 300 parts methanol (10%) in trichloromethane. The organic layer was dried, filtered and concentrated, yielding 23.8 parts (98.6%) of 1-hydroxy-α-phenyl-1H-benzotriazole-6-methanol as a residue (int. 64).

d) To a stirred solution of 1.2 parts of sodium hydroxide in 40 parts of methanol were added 7.8 parts of 1-hydroxy-α-phenyl-1H-benzotriazole-6-methanol. After concentration, 18 parts of methylbenzene were added to the concentrate. The solvent was evaporated again and the residue was dissolved in 27 parts of N,N-dimethylformamide. 5.52 Parts of 1-iodobutane were added at once and the whole was stirred for 30 minutes at 50 °C. After concentration, 30 parts of water were added. The solidified product was filtered off, washed with water and dissolved in dichloromethane. The organic layer was dried, filtered and evaporated. The residue was crystallized from 17.5 parts of 2,2'-oxybispropane. The product was filtered off and dried, yielding 7.8 parts (87.4%) of 1-butoxy-α-phenyl-1H-benzotriazole-6-methanol; mp. 89.2 C (int. 65).

In a similar manner there were also prepared:

1-ethoxy-α-phenyl-1H-benzotriazole-6-methanol; mp. 102.5 °C (int. 66);
1-(1-methylethoxy)-α-phenyl-1H-benzotriazole-6-methanol; mp. 109.6 °C (int. 67);
1-methoxy-α-phenyl-1H-benzotriazole-6-methanol; mp. 89.4 °C; and (int. 68)
α-phenyl-1-propoxy-1H-benzotriazole-6-methanol; mp. 104.1 °C (int. 69).

Example 6

a) To a stirred solution of 5.2 parts of 1-hydroxy-α-phenyl-1H-benzotriazole-6-methanol in 30 parts of dimethyl sulfoxide were added 0.96 parts of a sodium hydride dispersion 50%. The reaction mixture was stirred till no more hydrogen escapted. After the addition of 3.34 parts of ethyl 2-bromoacetate, the whole was stirred for 30 minutes at room temperature. 1.38 Parts of potassium carbonate were added and stirring was continued for 3 hours at 50 °C. The dimethyl sulfoxide layer was evaporated and the residue was taken up in water and 20 parts of a hydrochloric acid solution 1 N. The product was extracted with a mixture of trichloromethane and methanol (90:10 by volume). The extract was dried, filtered and concentrated. The concentrate was crystallized from 32.5 parts of dichloromethane. The product was filtered off and dried, yielding 3.1 parts (68.8%) of α-phenyl-1H-benzotriazole-5-methanol; mp. 143.0 °C (int. 70).

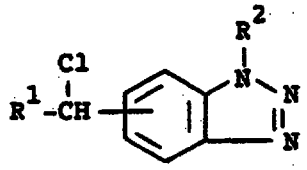
b) A mixture of 22.5 parts of α-phenyl-1H-benzotriazole-5-methanol, 4.8 parts of a sodium hydride dispersion 50% and 90 parts of N,N-dimethylformamide was stirred till hydrogen production had ceased. After the addition of 14.2 parts of iodomethane, stirring was continued for 30 minutes at room temperature. The mixture was concentrated. The concentrate was taken up in 50 parts of water and the product was extracted with dichloromethane. The extract was dried, filtered and concentrated. The concentrate was purified by filtration over silica gel using a mixture of trichloromethane and methanol (99:1 by volume) as eluent. The desired fraction was collected and the eluent was evaporated. The two isomers were separated by crystallization from ethyl acetate. The first isomer was further purified by crystallisation from ethyl acetate. The product was filtered off and dried, yielding 3 parts (12.5%) of 1-methyl-α-phenyl-1H-benzotriazole-6-methanol; mp. 145 °C (int. 71).

The other isomer was collected and crystallized three times from ethyl acetate. The product was filtered off and dried, yielding 3.3 parts (13.8%) of 1-methyl-α-phenyl-1H-benzotriazole-5-methanol; mp. 129 °C (int. 72).

Example 7

To a stirred solution of 6.5 parts of 1-butyl-α-(3-chlorophenyl)-1H-benzotriazole-6-methanol in 45 parts of tetrahydrofuran were added 3.7 parts of thionyl chloride at room temperature. After stirring for 1 hour, the reaction mixture was concentrated. The product was extracted with ethyl acetate. The extract was washed with a diluted sodium hydrogen carbonate solution, dried, filtered and evaporated, yielding 6.2 parts (88.3%) of 1-butyl-6-[chloro(3-chlorophenyl)methyl]-1H-benzotriazole as a residue (int. 73).

In a similar manner there were also prepared:



Comp. No.	R^1	R^2	P	base/ salt	mp (°C)
74	phenyl	$-O-CH-(CH_3)_2$	6	HCl	oil
75	phenyl	$-OCH_3$	6	HCl	residue
76	phenyl	$-O-CH_2-CH_3$	6	HCl	residue

Comp. No.	R^1	R^2	P	base/ salt	mp (°C)
77	phenyl	$-O-(CH_2)_2-CH_3$	6	HCl	oil
78	phenyl	$-CH_3$	6	base	oil
79	phenyl	$-O-(CH_2)_3-CH_3$	6	HCl	oil
80	phenyl	$-CH_3$	5	base	oil
81	H-	$-(CH_2)_3-CH_3$	7	base	residue
82	phenyl	$-(CH_2)_3-CH_3$	7	base	residue
83	H-	$-CH_3$	7	base	residue
84	phenyl	$-CH_3$	7	base	residue
85	H_3C-	$-CH_3$	7	base	residue
86	H_3C-	$-(CH_2)_3-CH_3$	7	base	residue
87	$3-Cl-C_6H_4-$	$-(CH_2)_3-CH_3$	7	base	residue
88	$4-Cl-C_6H_4-$	$-(CH_2)_3-CH_3$	6	base	residue
89	H-	$-CH_3$	4	base	residue
90	$4-F-C_6H_4-$	$-(CH_2)_3-CH_3$	6	base	residue
91	$3-F-C_6H_4-$	$-(CH_2)_3-CH_3$	6	base	residue
92	$3-F-C_6H_4-$	$-(CH_2)_3-CH_3$	7	base	residue
93	$H_3C-(CH_2)_2-$	$-(CH_2)_3-CH_3$	6	base	oil
94	$3-F-C_6H_4-$	$-CH_3$	7	base	residue
95	$3-Cl-C_6H_4-$	$-CH_3$	7	base	residue
96	$3-F-C_6H_4-$	$-CH_3$	5	base	residue
97	$H_3C-(CH_2)_2-$	$-CH_3$	5	base	residue
98	$3-Cl-C_6H_4-$	$-CH_3$	5	base	residue
99	$4-F-C_6H_4-$	$-CH_3$	5	base	residue
100	$3-Cl-C_6H_4-$	$-CH_3$	6	base	residue
101	$4-F-C_6H_4-$	$-CH_3$	6	base	residue
102	$4-Cl-C_6H_4-$	$-CH_3$	6	base	residue
103	$H_3C-(CH_2)_2-$	$-CH_3$	6	base	residue
104	$3-Br-C_6H_4-$	$-CH_3$	5	base	residue
105	$3-F-C_6H_4-$	$-CH_3$	6	base	residue
106	$3-Cl-C_6H_4-$	$-(CH_2)_3-CH_3$	5	base	residue
107	H_3C-	$-(CH_2)_3-CH_3$	5	base	residue

Comp. No.	R	R^1	P	base/ salt	mp (°C)
108	H_3C-	$-CH_3$	6	base	residue
109	3-F-C_6H_4-	$-(CH_2)_3-CH_3$	5	base	residue
110	4-F-C_6H_4-	$-(CH_2)_3-CH_3$	5	base	residue
111	H-	$-(CH_2)_3-CH_3$	4	base	residue
112	4-Cl-C_6H_4-	$-(CH_2)_3-CH_3$	5	base	residue
113	3-thienyl	$-(CH_2)_3-CH_3$	5	base	residue
114	4-Br-C_6H_4-	$-(CH_2)_3-CH_3$	5	base	residue
115	2-thienyl	$-(CH_2)_3-CH_3$	5	base	residue
116	4-Cl-C_6H_4-	$-CH_3$	5	base	residue
117	4-F-C_6H_4-	$-CH-(CH_3)_2$	5	base	residue
118	3-Br-C_6H_4-	$-CH_3$	6	base	residue
119	4-Br-C_6H_4-	$-CH_3$	6	base	residue
120	4-Br-C_6H_4-	$-CH_3$	5	base	residue
121	4-F-C_6H_4-	-cyclopropyl	5	base	residue
122	4-F-C_6H_4-	-cyclohexyl	5	base	residue
123	4-CF_3-C_6H_4-	$-CH_3$	6	base	residue
124	2-Cl-C_6H_4-	$-CH_3$	6	base	residue
125	4-CH_3-C_6H_4-	$-CH_3$	6	base	residue
126	2-naphthalenyl	$-CH_3$	6	base	residue
127	4-CH_3O-C_6H_4-	$-CH_3$	6	base	residue

and 6-(bromophenylmethyl)-1-methyl-1H-benzotriazole monohydrobromide (int. 128); and 6-[chloro[4-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)phenyl]methyl]-1-methyl-1H-benzotriazole as a residue (int.129)

Example 8

A mixture of 245 parts of α-(4-chlorophenyl)-1-methyl-1H-benzotriazole-6-methanol and 1500 parts of a hydrobromic acid solution in acetic acid was stirred for 2.5 hours at 40 °C. The reaction mixture was evaporated at 60 °C and the residue was stirred in dichloromethane. After cooling to 10 °C, the precipitated product was filtered off and dried, yielding 285 parts (76.6%) of 6-[bromo(4-chlorophenyl)methyl]-1-methyl-1H-benzotriazole monohydrobromide (int. 130).

Example 9

a) To a stirred and cooled solution of 58.1 parts of (4-chloro-3-nitrophenyl)phenylmethanone in 240 parts of methanol were added portionwise 4.4 parts of sodium tetrahydroborate. Upon complete addition, stirring was continued for 30 minutes at room temperature. The reaction mixture was evaporated. The residue was taken up in water and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated, yielding 58 parts (99.9%) of 4-chloro-3-nitro-α-phenylbenzenemethanol as a residue (int. 131).

b) A mixture of 58 parts of 4-chloro-3-nitro-α-phenylbenzenemethanol and 450 parts of a hydrobromic acid solution 48% in water was stirred for 45 minutes at reflux temperature. After cooling, the product

was extracted with dichloromethane. The extract was dried, filtered and evaporated, yielding 71.4 parts (99.3%) of 4-(bromophenylmethyl)-1-chloro-2-nitrobenzene as a residue (int. 132).

c) A mixture of 31.9 parts of 4-(bromophenylmethyl)-1-chloro-2-nitrobenzene, 49.3 parts of 4-methyl-1H-imidazole and 120 parts of acetonitrile was stirred for 24 hours at reflux temperature. The reaction mixture was concentrated and the concentrate was taken up in 150 parts of water. The product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane, methanol and methanol, saturated with ammonia, (98:1:1 by volume) as eluent. The desired fractions were collected and the eluent was evaporated. The residue was converted into the ethanedioate salt in 80 parts of 2-propanol. The salt was filtered off, washed with 2-propanol and dried, yielding 22.8 parts (54.5%) of 1-[(4-chloro-3-nitrophenyl)phenylmethyl]-4-methyl-1H-imidazole ethanedioate(1:1); mp. 105 °C (int. 133).

In a similar manner there were also prepared:

1-[(4-chloro-3-nitrophenyl)methyl]-1H-imidazole; mp. 81.7 °C (int. 134);
1-[(3-chloro-4-nitrophenyl)phenylmethyl]-1H-imidazole (int. 135);
1-[(4-chloro-3-nitrophenyl)Phenylmethyl]-1H-imidazole (int. 136);
1-[(4-chloro-3-nitrophenyl)methyl]-2-methyl-1H-imidazole; mp. 102 °C (int. 137);
1-[(4-chloro-3-nitrophenyl)phenylmethyl]-5-methyl-1H-imidazole; mP. 164 °C (int. 138);
1-[(3-chlorophenyl)(4-methoxy-3-nitrophenyl)methyl]-1H-imidazole as a residue (int. 139); and
1-[(3-chloro-4-nitrophenyl)(4-chlorophenyl)methyl]-1H-imidazole ethanedioate(1:1) (int. 140).

Example 10

To a stirred solution of 10 parts of 4-chloro-α-methyl-3-nitrobenzenemethanol in 90 parts of tetrahydrofuran were added 8 parts of 1,1'-carbonylbis[1H-imidazole]. After stirring for 4 hours at reflux temperature, the tetrahydrofuran layer was evaporated. After the addition of 90 parts of methylbenzene, the reaction mixture was stirred for 75 hours at reflux. The reaction mixture was evaporated and the residue was taken up in water. The whole was treated with an ammonium hydroxide solution and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol, saturated with ammonia, (95:5 by volume) as eluent. The first fraction was collected and the eluent was evaporated. The residue was crystallized from 84 parts of 1,1'-oxybisethane. The product was filtered off and dried, yielding 4.2 parts (33.3%) of 1-[1-(4-chloro-3-nitrophenyl)ethyl]-1H-imidazole (int. 141).

Example 11

A mixture of 2.52 parts of 4H-1,2,4-triazol-4-amine, 8 parts of 4-chloro-3-nitrobenzenemethanol methanesulfonate(ester) and 40 parts of acetonitrile was stirred for 3 hours at reflux temperature. After cooling, the product was filtered off, washed with acetonitrile and dried, yielding 9.9 parts (94%) of 4-amino-1-[(4-chloro-3-nitrophenyl)-methyl]-1,2,4-triazolium methanesulfonate; mp. 163.9 °C (int. 142).

b) To a stirred solution of 8.75 parts of 4-amino-1-[(4-chloro-3-nitrophenyl)methyl]-1,2,4-triazolium methanesulfonate in 85 parts of a hydrochloric acid solution 1N were added 7.15 parts of phosphinic acid 50%. After cooling in ice, a solution of 3.5 parts of sodium nitrite in 15 parts of water was added. The mixture was stirred for 2 hours at room temperature. An excess of concentrated ammonium hydroxide was added and stirring was continued for 15 minutes. The product was filtered off, washed with water, 2-propanol and 2,2'-oxybispropane and crystallized from 8 parts of 2-propanol. The product was filtered off and dried, yielding 5 parts (83.8%) of 1-[(4-chloro-3-nitrophenyl)methyl]-1H-1,2,4-triazole; mp. 98.9 °C (int. 143).

In a similar manner there was also prepared:

1-[(4-chloro-3-nitrophenyl)phenylmethyl]-1H-1,2,4-triazole as an oily residue (int. 144).

Example 12

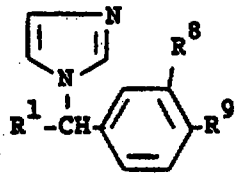
To 184 parts of cold (10 °C, ice bath) concentrated sulfuric acid were added portionwise 75 parts of 1-[(3-methoxyphenyl)methyl]-1H-imidazole mononitrate during 1 hour. Upon complete addition, stirring was continued for 30 minutes at 10 °C. 15 parts of concentrated nitric acid were added dropwise during 30 minutes at 15 °C. Upon completion, the whole was stirred for 30 minutes at 10 °C. The reaction mixture was poured into 1500 parts of crushed ice and the whole was treated with an ammonium hydroxide solution. The product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue

was purified by column chromatography over silica gel using a mixture of ethyl acetate, methanol and methanol, saturated with ammonia, (95:2.5:2.5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated in vacuo. The residue was stirred in 45 parts of ethyl acetate. The precipitated product was filtered off, washed with 2,2'-oxybispropane and dried, yielding 28.2 parts (40.3%) of 1-[(3-methoxy-4-nitrophenyl)methyl]-1H-imidazole (int. 145).

Example 13

A mixture of 8 parts of 1-[(4-chloro-3-nitrophenyl)methyl]-1H-imidazole and 42 parts of cyclohexanamine was stirred for 2 hours at reflux temperature. The mixture was evaporated and the residue was stirred in 2,2'-oxybispropane. The precipitated product was filtered off, washed with water and 2,2'-oxybispropane and purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (90:10 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was stirred in a mixture of 2,2'-oxybispropane and ethyl acetate. The product was filtered off, washed with ethyl acetate and 2,2'-oxybispropane and dried in vacuo at 60 °C, yielding 9.5 parts (93.8%) of N-cyclohexyl-4-(1H-imidazol-1-ylmethyl)-2-nitrobenzenamine; mp.121.1 °C (int. 146).

In a similar manner there were also prepared:



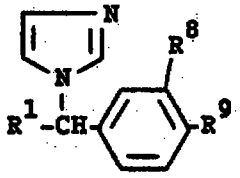
Comp. No.	R^1	R^8	R^9	base/ salt	mp (°C)
147	H-	$-NH-(CH_2)_3-CH_3$	$-NO_2$	base	117.5°C
148	H-	$-NO_2$	$-NH-(CH_2)_3-CH_3$	base	89.1°C
149	H-	-NH-cyclohexyl	$-NO_2$	base	134.7°C
150	H-	$-NH-C_6H_5$	$-NO_2$	base	150.8°C
151	H_3C-	$-NO_2$	$-NH-(CH_2)_3-CH_3$	HNO_3/H_2O	84.7°C
152	phenyl	$-NO_2$	$-NH-(CH_2)_3-CH_3$	base	residue
153	phenyl	$-NH-(CH_2)_3-CH_3$	$-NO_2$	base	oil
154	phenyl	$-NH-CH-(CH_3)_2$	$-NO_2$	base	oil
155	H-	-NH-cyclopropyl	$-NO_2$	base	111.6°C
156	H-	$-NH-CH-(CH_3)_2$	$-NO_2$	base	101.6°C
157	H-	$-NH-(CH_2)_2-CH_3$	$-NO_2$	base	98.9°C
158	phenyl	$-NH-CH_3$	$-NO_2$	base	residue
159	H-	$-NH-CH_2-(4-Cl-C_6H_4)$	$-NO_2$	base	124.7°C
160	H-	$-NH-(CH_2)_2CH(CH_3)_3$	$-NO_2$	base	75.4°C
161	H-	$-NO_2$	$-NH-(CH_2)_2-CH_3$	base	98.4°C

Comp. No.	R^1	R^8	R^9	base/ salt	mp (°C)
162	H-	$-NO_2$	$-NH-CH-(CH_3)_2$	base	98.3
163	H-	$-NO_2$	$-NH-(CH_2)_2-C_6H_5$	base	100.5
164	H-	$-NH-CH_2-(4-F-C_6H_4)$	$-NO_2$	base	111.0
165	H-	$-NH-CH_2-CH_3$	$-NO_2$	base	106.2
166	H-	$-NH-CH_2-(3-F-C_6H_4)$	$-NO_2$	base	95.4
167	H-	$-NH-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-CH_2-CH_3$	$-NO_2$	base	residue
168	H-	-NH-bicyclo[2.2.1] heptan-2-yl	$-NO_2$	base	130.7
169	phenyl	-NH-cyclohexyl	$-NO_2$	base	residue
170	H-	-NH-cyclopentyl	$-NO_2$	base	81.9
171	H-	-NH-1,2,3,4-tetra-hydro-1-naphthalenyl	$-NO_2$	base	118.0
172	H-	$-NH-CH_2-CH=CH_2$	$-NO_2$	base	86.4
173	H-	$-NO_2$	$-NH-CH_2-C_6H_5$	base	residue
174	H-	$-NH-CH_2$-cycopropyl	$-NO_2$	base	101.4
175	H-	$-NH-CH_2$-2-thienyl	$-NO_2$	base	residue
176	H-	$-NH-(CH_2)_3-OH$	$-NO_2$	base	107.0
177	H-	$-NH-CH_2-C-(CH_3)_3$	$-NO_2$	base	113.7
178	H-	$-NH-(CH_2)_2-N-(CH_3)_2$	$-NO_2$	base	111.6
179	H-	-NH-2,3-dihydro-1H-inden-1-yl	$-NO_2$	base	200.2
180	$4-Cl-C_6H_4-$	$-NH-CH-(CH_3)_2$	$-NO_2$	$(COOH)_2$	110.9
181	$4-Cl-C_6H_4-$	-NH-cyclohexyl	$-NO_2$	$(COOH)_2$	114.4
182	$4-Cl-C_6H_4-$	-NH-phenyl	$-NO_2$	base	oil
183	$4-Cl-C_6H_4-$	$-NH-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-C_6H_5$	$-NO_2$	base	residue
184	$4-Cl-C_6H_4-$	$-NH-CH_2-(4-Cl-C_6H_4)$	$-NO_2$	base	residue
185	$4-Cl-C_6H_4-$	$-NH-CH_2-C_6H_5$	$-NO_2$	base	residue

Example 14

A mixture of 7.9 parts of N-cyclohexyl-4-(1H-imidazol-1-ylmethyl)-2-nitrobenzenamine, 22.9 parts of sodium dithionite, 288 parts of ethanol and 240 parts of water was stirred at room temperature. Upon complete reaction, the ethanol layer was evaporated. The aqueous layer was diluted with a potassium carbonate solution. The whole was extracted twice: first with dichloromethane and then with a mixture of trichloromethane and methanol (90:10 by volume). The combined extracts were dried, filtered and evaporated. The residue was taken up in methylbenzene and the solvent was evaporated again, yielding 7 parts

(98.0%) of N¹-cyclohexyl-4-(1H-imidazol-1-ylmethyl)-1,2-benzenediamine as a residue (int. 186).
In a similar manner there were also prepared:



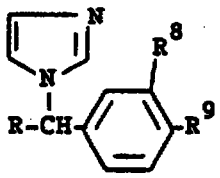
Comp. No.	R^1	R^8	R^9	base/ salt	mp (°C)
187	-H	$-NH_2$	$-NH-CH_3$	base	residue
188	-H	$-NH-(CH_2)_3-CH_3$	$-NH_2$	base	residue
189	-H	$-NH_2$	$-NH-(CH_2)_3-CH_3$	base	residue
190	-H	-NH-cyclohexyl	$-NH_2$	base	residue
191	-H	$-NH-C_6H_5$	$-NH_2$	base	residue
192	-H	$-NH-CH_2-C_6H_5$	$-NH_2$	base	residue
193	$-C_6H_5$	$-NH_2$	$-NH-(CH_2)_3-CH_3$	base	residue
194	$-CH_3$	$-NH_2$	$-NH-(CH_2)_3-CH_3$	base	residue
195	$-C_6H_5$	$-NH-(CH_2)_3-CH_3$	$-NH_2$	base	residue
196	$-C_6H_5$	$-NH-CH(CH_3)_2$	$-NH_2$	base	residue
197	-H	-NH-cyclopropyl	$-NH_2$	base	residue
198	-H	$-NH-CH(CH_3)_2$	$-NH_2$	base	residue
199	-H	$-NH_2$	$-NH-CH_2-C_6H_5$	base	residue
200	-H	$-NH-(CH_2)_2-CH_3$	$-NH_2$	base	residue
201	-H	$-NHCH_2(4-Cl-C_6H_4)$	$-NH_2$	base	residue
202	-H	$-NH(CH_2)_2CH(CH_3)_2$	$-NH_2$	base	residue
203	-H	$-NH_2$	$-NH-(CH_2)_2C_6H_5$	base	residue
204	-H	$-NH-CH_2(4-F-C_6H_4)$	$-NH_2$	base	residue

Comp. No.	R^1	R^8	R^9	base/ salt	mp (°C)
205	-H	$-NH-CH_2-(3-F-C_6H_4)$	$-NH_2$	base	residue
206	-H	$-NH-\underset{\displaystyle CH_3}{\underset{\vert}{CH}}-CH_2-CH_3$	$-NH_2$	base	residue
207	-H	-NH-bicyclo-[2.2.1]hept-2-yl	$-NH_2$	base	residue
208	-H	-NH-cyclopentyl	$-NH_2$	base	residue
209	-H	-1,2,3,4-tetrahydro-1-naphthalenyl	$-NH_2$	base	residue
210	-H	$-NH-CH_2-CH=CH_2$	$-NH_2$	base	residue
211	-H	$-NH-CH_2-c-C_3H_5$	$-NH_2$	base	residue
212	-H	$-NH-(CH_2)_3-OH$	$-NH_2$	base	residue
213	$4-Cl-C_6H_4-$	(5-methyl-2-furanyl)-methylamino	$-NH_2$	base	residue
214	$4-Cl-C_6H_4-$	$-NH-CH_2-(4-Cl-C_6H_4)$	$-NH_2$	base	residue
215	$4-Cl-C_6H_4-$	$-NH-C_3H_5-c$	$-NH_2$	base	residue

Example 15

A mixture of 9 parts of 2,3-dihydro-N-[5-(1H-imidazol-1-ylmethyl)-2-nitrophenyl]-1H-inden-1-amine, 2 parts of a solution of thiophene in methanol 4% and 200 parts of methanol was hydrogenated at normal pressure and at room temperature with 2 parts of platinum-on-charcoal catalyst 5%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated, yielding 8 parts (97.3%) of N^2-(2,3-dihydro-1H-inden-1-yl)-4-(1H-imidazol-1-ylmethyl)-1,2-benzenediamine as a residue (int. 216).

In a similar manner there were also prepared:



Comp. No.	R	R^8	R^9	base/ salt	mp (°C)
217	-phenyl	$-NH-CH_3$	$-NH_2$	base	residue
218	-H	$-NH_2$	$-NH-(CH_2)_2-CH_3$	base	residue
219	-H	$-NH_2$	$-NH-CH-(CH_3)_2$	base	residue
220	-H	$-NH-CH_2-CH_3$	$-NH_2$	base	residue
221	-phenyl	$-NH-c-C_6H_{11}$	$-NH_2$	base	residue
222	-phenyl	$-NH_2$	$-NH-CH_2-C_6H_5$	base	residue
223	-H	$-NH-CH_2$-2-thienyl	$-NH_2$	base	residue
224	-H	$-NH-CH_2-C-(CH_3)_3$	$-NH_2$	base	residue
225	4-Cl-C_6H_4-	$-NH-CH-(CH_3)_2$	$-NH_2$	base	residue
226	4-Cl-C_6H_4-	$-NH-c-C_6H_{11}$	$-NH_2$	base	residue
227	-H	$-NH(CH_2)_2-N(CH_3)_2$	$-NH_2$	base	residue
228	4-Cl-C_6H_4-	$-NH-C_6H_5$	$-NH_2$	base	residue
229	4-Cl-C_6H_4-	$-NH(CH_2)_2CH(CH_3)_2$	$-NH_2$	base	residue
230	4-Cl-C_6H_4-	$-NH-\underset{\displaystyle CH_3}{\overset{\displaystyle |}{CH}}-C_6H_5$	$-NH_2$	base	residue

Example 16

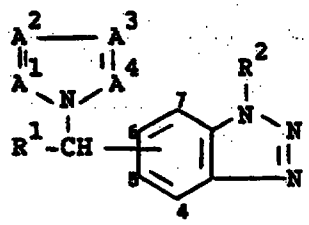
A solution of 10 parts of 6-[chloro[4-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)phenyl]methyl]-1-methyl-1H-benzotriazole and 10 parts of 1H-imidazole in 80 parts of acetonitrile was stirred for 4 hours at reflux temperature. The reaction mixture was evaporated and the product was extracted with ethyl acetate. The extract was washed with a diluted potassium carbonate solution, dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of dichloromethane and methanol (98:2 by volume) as eluent. The pure fractions were collected and the eluent was evaporated, yielding 7.1 parts (65.6%) of 6-[[4-(4,5-dihydro-4,4-dimethyl-2-oxazolyl)phenyl] (1H-imidazol-1-yl)methyl]-1-methyl-1H-benzotriazole as a residue (int. 231).

B. Preparation of Final compounds

Example 17

A mixture of 4 parts of 5-(chlorophenylmethyl)-1-methyl-1H-benzotriazole, 5.65 parts of 1H-imidazole and 20 parts of acetonitrile was stirred for 1.5 hours at reflux temperature. After concentration, 50 parts of water were added and the product was extracted with dichloromethane. The extract was dried, filtered and concentrated. The residue was purified by filtration over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was converted into the nitrate salt in 45 parts of tetrahydrofuran. The salt was filtered off, washed with tetrahydrofuran and dried, yielding 3.9 parts (80.2%) of 5-[(1H-imidazol-1-yl)phenylmethyl]-1-methyl-1H-benzotriazole mononitrate; mp. 111.9 °C (compound 1).

In a similar manner there were also prepared:



Comp. No.	R^1	R^2	$-A^1=A^2-A^3=A^4-$	P	base/salt	mp (°C)
2	phenyl	$-O-CH-(CH_3)_2$	-CH=CH-N=CH-	6	HNO_3	103.4
3	phenyl	$-O-CH_3$	-CH=CH-N=CH-	6	HNO_3	93.1
4	phenyl	$-O-CH_2-CH_3$	-CH=CH-N=CH-	6	HNO_3	98.1
5	phenyl	$-O-CH_2-CH_2-CH_3$	-CH=CH-N=CH-	6	HNO_3	120.2
6	phenyl	$-O-(CH_2)_3-CH_3$	-CH=CH-N=CH-	6	HNO_3	86.0
7	phenyl	$-CH_3$	-CH=CH-N=CH-	6	$(COOH)_2$	112.6
8	H-	$-(CH_2)_3-CH_3$	-CH=CH-N=CH-	7	base	109.7
9	phenyl	$-(CH_2)_3-CH_3$	-CH=CH-N=CH-	7	HCl	225.2
10	H-	$-CH_3$	-CH=CH-N=CH-	7	0.5 H_2O	175.8
11	phenyl	$-CH_3$	-CH=CH-N=CH-	7	base	192.2
12	H_3C-	$-CH_3$	-CH=CH-N=CH-	7	base	180.1
13	H_3C-	$-(CH_2)_3-CH_3$	-CH=CH-N=CH-	7	$(COOH)_2$	85.8

Comp. No.	R^1	R^2	$-A^1=A^2-A^3=A^4-$	P	base/salt	mp (°C)
14	3-Cl-C_6H_4-	-$(CH_2)_3$-CH_3	-CH=CH-N=CH-	7	$(COOH)_2$	144.3
15	4-Cl-C_6H_4-	-$(CH_2)_3$-CH_3	-CH=CH-N=CH-	6	$(COOH)_2$	99.4
16	H-	-CH_3	-CH=CH-N=CH-	4	base	132.7
17	4-F-C_6H_4-	-$(CH_2)_3$-CH_3	-CH=CH-N=CH-	6	$(COOH)_2$	91.2
18	3-F-C_6H_5-	-$(CH_2)_3$-CH_3	-CH=CH-N=CH-	6	$(COOH)_2$	89.8
19	3-F-C_6H_4-	-$(CH_2)_3$-CH_3	-CH=CH-N=CH-	7	HCl	212.0
20	CH_3-$(CH_2)_2$-	-$(CH_2)_3$-CH_3	-CH=CH-N=CH-	6	$(COOH)_2$	124.5
21	3-F-C_6H_4-	-CH_3	-CH=CH-N=CH-	7	base	182.3
22	3-Cl-C_6H_4-	-CH_3	-CH=CH-N=CH-	7	base	195.1
23	3-Cl-C_6H_4-	-$(CH_2)_3$-CH_3	-CH=CH-N=CH-	6	$(COOH)_2$	71.5
24	3-F-C_6H_4-	-CH_3	-CH=CH-N=CH-	5	base	150.1
25	CH_3-$(CH_2)_2$-	-CH_3	-CH=CH-N=CH-	5	base	112.4
26	3-Cl-C_6H_4-	-CH_3	-CH=CH-N=CH-	5	base	146.1
27	4-F-C_6H_4-	-CH_3	-CH=CH-N=CH-	5	$(COOH)_2$	152.4
28	3-Cl-C_6H_4-	-CH_3	-CH=CH-N=CH-	6	$(COOH)_2$	90.5
29	4-F-C_6H_4-	-CH_3	-CH=CH-N=CH-	6	$(COOH)_2$	96.5
30	4-Cl-C_6H_4-	-CH_3	-CH=CH-N=CH-	6	$(COOH)_2$/ 0.5 H_2O	90.2
31	H_3C-$(CH_2)_2$-	-CH_3	-CH=CH-N=CH-	6	base	95.0
32	3-Br-C_6H_4-	-CH_3	-CH=CH-N=CH-	5	base	143.2
33	3-F-C_6H_4-	-CH_3	-CH=CH-N=CH-	6	$(COOH)_2$	189.9
34	3-Cl-C_6H_4-	-$(CH_2)_3$-CH_3	-CH=CH-N=CH-	5	$(COOH)_2$	120.8
35	H_3C-	-$(CH_2)_3$-CH_3	-CH=CH-N=CH-	5	*(1:1)	100.5
36	H_3C-	-CH_3	-CH=CH-N=CH-	6	base	116.8
37	3-F-C_6H_4-	-$(CH_2)_3$-CH_3	-CH=CH-N=CH-	5	$(COOH)_2$	131.2
38	4-F-C_6H_4-	-$(CH_2)_3$-CH_3	-CH=CH-N=CH-	5	$(COOH)_2$	166.4
39	H-	-$(CH_2)_3$-CH_3	-CH=CH-N=CH-	4	$(COOH)_2$	95.8
40	4-Cl-C_6H_4-	-$(CH_2)_3$-CH_3	-CH=CH-N=CH-	5	$(COOH)_2$/ 0.5 H_2O	135.7
41	3-thienyl	-$(CH_2)_3$-CH_3	-CH=CH-N=CH-	5	$(COOH)_2$	168.9
42	4-Br-C_6H_4-	-$(CH_2)_3$-CH_3	-CH=CH-N=CH-	5	$(COOH)_2$/ 0.5 H_2O	152.9

* = (E)-2-butenedioate

Comp. No.	R^1	R^2	$-A^1=A^2-A^3=A^4-$	P	base/ salt	mp (°C)
43	3-Cl-C_6H_4-	$-CH_3$	-CH=CH-N=C(-CH_3)-	6	base	177.4
44	2-thienyl	$-(CH_2)_3-CH_3$	-CH=CH-N=CH-	5	$(COOH)_2$	143.5
45	4-Cl-C_6H_4-	$-CH_3$	-N=CH-N=CH-	6	$(COOH)_2$	104.2
46	4-Cl-C_6H_4-	$-CH_3$	-CH=N-N=CH-	6	0.5 H_2O	119.8
47	4-Cl-C_6H_4-	$-CH_3$	-CH=CH-N=CH-	5	base	172.4
48	4-Cl-C_6H_4-	$-CH_3$	-CH=CH-N=CH-	6	HCl/H_2O	151.2
49	4-F-C_6H_4-	$-CH-(CH_3)_2$	-CH=CH-N=CH-	5	base	155.3
50	3-Br-C_6H_4-	$-CH_3$	-CH=CH-N=CH-	6	$(COOH)_2$/ 0.5 H_2O	107.7
51	4-Br-C_6H_4-	$-CH_3$	-CH=CH-N=CH-	6	$(COOH)_2$	136.2
52	4-Br-C_6H_4-	$-CH_3$	-CH=CH-N=CH-	5	base	180.1
53	4-F-C_6H_4-	c-C_3H_5-	-CH=CH-N=CH-	5	base	94.6
54	4-F-C_6H_4-	c-C_6H_{11}-	-CH=CH-N=CH-	5	base	157.6
55	4-CF_3-C_6H_4-	$-CH_3$	-CH=CH-N=CH-	6	$(COOH)_2$/ 0.5 H_2O	89.9
56	2-Cl-C_6H_4-	$-CH_3$	-CH=CH-N=CH-	6	$(COOH)_2$/ 0.5 H_2O	132.6
57	4-CH_3-C_6H_4-	$-CH_3$	-CH=CH-N=CH-	6	$(COOH)_2$/ 0.5 H_2O	140.9
58	2-naphthalenyl	$-CH_3$	-CH=CH-N=CH-	6	0.5 H_2O	148.8
59	4-CH_3O-C_6H_4-	$-CH_3$	-CH=CH-N=CH-	6	$(COOH)_2$	144.2
60	C_6H_5-CH_2-	$-CH_3$	-CH=CH-N=CH-	5	base	159.9
61	CN-C_6H_5-	$-CH_3$	-CH=CH-N=CH-	5	base	176.5

Example 18

A mixture of 12.8 parts of 6-(bromophenylmethyl)-1-methyl-1H-benzotriazole monohydrobromide, 14.8 parts of 4-methyl-1H-imidazole and 80 parts of acetonitrile was stirred for 8 hours at reflux temperature. The mixture was concentrated and the residue was stirred in 100 parts of water. The product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified twice by column chromatography over silica gel using a mixture of trichloromethane and methanol (99:1 by volume) as eluent. The desired fraction was collected and the eluent was evaporated. The residue was purified by reversed phase chromatography (HPLC) over Li Chroprep RP 18 using a mixture of methanol, tetrahydrofuran and ammonium acetate (30:5:65 by volume) as eluent. The pure fraction was collected and the eluent was evaporated. The residue was converted into the ethanedioate salt in tetrahydrofuran. The salt was filtered off and dried, yielding 1.6 parts (13.5%) of 1-methyl-6-[(4-methyl-1H-imidazol-1-yl)-phenylmethyl]-1H-benzotriazole ethanedioate(1:1); mp. 203.1 °C (compound 62).

Example 19

A solution of 203 parts of 6-[bromo(4-chlorophenyl)methyl]-1-methyl-1H-benzotriazole monohydrobromide and 170 parts of 1H-imidazole in 1350 parts of methylbenzene was stirred for 28 hours at reflux temperature. The reaction mixture was allowed to cool to 80 °C and then evaporated. The oily residue was dissolved in dichloromethane. The organic layer was washed with a diluted hydrochloric acid solution. The separated aqueous layer was treated with a sodium hydroxide solution and extracted with dichloromethane. The combined dichloromethane layers were washed with water, dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of dichloromethane and methanol (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. To the residue were added 210 parts of 1,1'-oxybisethane and the whole was allowed to stand over weekend. The solid product was filtered off and dried at 50 °C, yielding 48.1 parts (29.7%) of 6-[(4-chlorophenyl)(1H-imidazol-1-yl)methyl]1-methyl-1H-benzotriazole; mp. 87.7 °C (compound 63).

Example 20

To a stirred solution of 28.4 parts of 1H-1,2,4-triazole in 135 parts of N,N-dimethylformamide were added 11.4 parts of a sodium hydride dispersion 80% under nitrogen atmosphere. After stirring for 1 hour at room temperature, a solution of 40 parts of 6-[chloro(4-chlorophenyl)methyl]-1-methyl-1H-benzotriazole in 90 parts of N,N-dimethylformamide was added to the mixture. The whole was stirred for 1 hour at 60 °C. The reaction mixture was diluted with 50 parts of water and the whole was evaporated. The residue was extracted with ethyl acetate. The extract was washed with water, dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of dichloromethane and methanol (99:1 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from a mixture of 2-propanone and 1,1'-oxybisethane. The product was filtered off and dried, yielding 13 parts (29.2%) of 6-[(4-chlorophenyl)-(1H-1,2,4-triazol-1-yl)methyl]-1-methyl-1H-benzotriazole; mp. 178.9 °C (compound 64).

Example 21

To a stirred solution of 4.25 parts of 1H-1,2,4-triazole in 47 parts of N,N-dimethylformamide were added 2 parts of a sodium hydride dispersion 50% under nitrogen atmosphere. The whole was stirred for 10 minutes at room temperature and a solution of 6 parts of 6-[chloro(3-chlorophenyl)methyl]-1-methyl-1H-benzotriazole in 47 parts of N,N-dimethylformamide was added to the mixture. The whole was stirred for 1 hour at 50 °C and then cooled to room temperature. The product was extracted with ethyl acetate. The extract was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of dichloromethane and methanol (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was converted into the ethanedioate salt in 2-propanone. The salt was filtered off and crystallized from a mixture of acetonitrile and 1,1'-oxybisethane. The product was filtered off and dried, yielding 2.8 parts (33.7%) of 6-[(3-chlorophenyl)(1H-1,2,4-triazol-1-yl)methyl]-1-methyl-1H-benzotriazole ethanedioate(1:1); mp. 125.0 °C (compound 65).

Example 22

A mixture of 9.1 parts of 6-(bromophenylmethyl)-1-methyl-1H-benzotriazole monohydrobromide, 10.25 parts of (4-methyl-1H-imidazol-1-yl)phenylmethanone and 64 parts of acetonitrile was stirred for 3 hours at reflux temperature. The acetonitrile layer was evaporated and the residue was stirred overnight at room temperature in a mixture of 16.6 parts of potassium carbonate and 80 parts of water. The product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The desired fraction was collected and the eluent was evaporated. The residue was Purified by reversed phase chromatography (HPLC) over Li Chroprep RP 18 using a mixture of methanol, tetrahydrofuran and ammonium acetate (30:5:65 by volume) as eluent. The pure fraction was collected and the eluent was evaporated. The residue was further purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was converted into the ethanedioate salt in tetrahydrofuran. The salt was filtered off and dried in vacuo at 80 °C, yielding 3.1 parts (35.8%) of 1-methyl-6-[(5-methyl-1H-imidazol-1-yl)phenylmethyl]-1H-benzotriazole ethanedioate(1:1); mp. 120.7 °C (compound 66).

Example 23

A mixture of 8.2 parts of 6-(bromophenylmethyl)-1-methyl-1H-benzotriazole monohydrobromide, 3.45 parts of 4H-1,2,4-triazole-4-amine and 64 parts of acetonitrile was stirred first for 2 hours at reflux temperature and then overnight at room temperature. The precipitate was filtered off and the filtrate was concentrated, yielding 4-amino-1-[(1-methyl-1H-benzotriazol-6-yl)phenylmethyl]-4H-1,2,4-triazolium bromide. To a stirred solution of the latter, 7.3 parts of a phosphinic acid solution 50% and 7.3 parts of a hydrochloric acid solution 12 N in 40 parts of methanol and 20 parts of water was added dropwise a solution of 3.45 parts of sodium nitrite in 20 parts of water. Upon complete addition, stirring was continued for 30 minutes at room temperature. The methanol layer was evaporated and the residue was treated with an ammonium hydroxide solution. The product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified twice by column chromatography over silica gel using a mixture of trichloromethane and methanol (98:2 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was converted into the ethanedioate salt in 36 parts of tetrahydrofuran. The salt was filtered off and crystallized from 45 parts of ethyl acetate. The product was filtered off and dried, yielding 3.1 parts (40.7%) of 1-methyl-6-[Phenyl-(1H-1,2,4-triazol-1-yl)methyl]-1H-benzotriazole ethanedioate(1:1); mp. 164.9 °C (compound 67).

Example 24

To a stirred and heated solution of 3.2 parts of 1-methyl-α-(2-thienyl)-1H-benzotriazole-6-methanol in 45 parts of tetrahydrofuran were added 4.2 parts of 1,1'-carbonylbis[1H-imidazole] under nitrogen atmosphere. After stirring for 30 minutes at 50 °C, the reaction mixture was evaporated. The product was extracted with ethyl acetate. The extract was washed with a diluted sodium hydrogen carbonate solution, dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of dichloromethane and methanol (98:2 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from 2-propanone. The product was filtered off and dried, yielding 1.9 parts (49.5%) of 6-[(1H-imidazol-1-yl)(2-thienyl)methyl]-1-methyl-1H-benzotriazole; mp. 157.2 °C (compound 68).

In a similar manner there were also prepared :

6-[(1H-imidazol-1-yl)(3-thienyl)methyl]-1-methyl-1H-benzotriazole; mP. 160.5 °C (compound 69);

5-[bis-(1H-imidazol-1-yl)methyl]-1-butyl-1H-benzotriazole; mp. 180.1 °C (compound 70); and

5-[1-(1H-imidazol-1-yl)-2-butynyl]-1-methyl-1H-benzotriazole; mp. 155.5 °C (compound 71).

Example 25

A mixture of 1.6 parts of 4-(1H-imidazol-1-ylmethyl)-N^2-phenyl-1,2-benzenediamine, 20 parts of acetic acid and 1.08 parts of concentrated hydrochloric acid was cooled in an ice bath at 12-16 °C. A solution of 0.83 parts of sodium nitrite in 7 parts of water was added dropwise. Upon complete addition, the reaction mixture was allowed to reach room temperature while stirring. The reaction mixture was poured into alkaline ice water and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was Purified by column chromatography over silica gel first using a mixture of trichloromethane and methanol, saturated with ammonia, (97.5:2.5 by volume) and then a mixture of ethyl acetate, methanol and methanol, saturated with ammonia (95:2.5:2.5 by volume) as eluents. The pure fractions were collected and the eluent was evaporated. The residue was taken up in a mixture of 2-propanone and 2,2'-oxybispropane. The product was filtered off, washed with 2,2'-oxybispropane and dried in vacuo at 60 °C, yielding 0.81 parts (49.0%) of 6-(1H-imidazol-1-ylmethyl)-1-phenyl-1H-benzotriazole; mp. 110.1 °C (compound 72).

In a similar manner there were also prepared:

1-cyclohexyl-6-(1H-imidazol-1-ylmethyl)-1H-benzotriazole; mp. 109.3 °C (compound 73);

1-butyl-5-[(1H-imidazol-1-yl)phenylmethyl]-1H-benzotriazole; mp. 83.6 °C (compound 74);

1-butyl-6-[(1H-imidazol-1-yl)phenylmethyl]-1H-benzotriazole ethanedioate(1:1; mp. 109.0 °C (compound 75);

6-[(1H-imidazol-1-yl)phenylmethyl]-1-(1-methylethyl)-1H-benzotriazole ethanedioate(1:1); mp. 123.1 °C (compound 76);

6-[(4-chlorophenyl)(1H-imidazol-1-yl)methyl]-1-phenyl-1H-benzotriazole mononitrate; mp. 166.7 °C (compound 77);

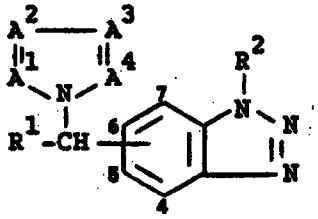
6-[(4-chlorophenyl)(1H-imidazol-1-yl)methyl]-1-(phenylethyl)-1H-benzotriazole mononitrate; mp. 160.7 °C (compound 78); and

6-[(4-chlorophenyl)(1H-imidazol-1-yl)methyl]-1-[(4-chlorophenyl)methyl]-1H-benzotriazole mononitrate; mp. 185.9 °C (compound 79).

Example 26

To a stirred and cooled (0 °C) mixture of 3.9 parts of 4-(1H-imidazol-1-ylmethyl)-N^2-(phenylmethyl)-1,2-benzenediamine and 9.6 parts of concentrated hydrochloric acid was added dropwise a solution of 1.86 parts of sodium nitrite in 8 parts of water. Upon complete addition, stirring was continued for 10-15 minutes at this low temperature. The reaction mixture was allowed to reach room temperature and poured into ice water. The whole was extracted with dichloromethane. The acid aqueous layer was treated with a concentrated ammonium hydroxide solution while cooling and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by filtration over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was further purified by column chromatography over silica gel using a mixture of ethyl acetate, methanol and methanol, saturated with ammonia (95:2.5:2.5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The product was filtered off, washed with 2,2'-oxybispropane and dried in vacuo at 50 °C, yielding 1.6 parts (40.9%) of 6-(1H-imidazol-1-ylmethyl)-1-(phenylmethyl)-1H-benzotriazole; mp. 85.4 °C (compound 80).

In a similar manner there were also prepared:



Comp. No.	R^1	R^2	$A^1=A^2-A^3=A^4$	P	base/ salt	mp (°C)
81	H-	CH_3-	CH=CH-N=CH	5	base	141.6
82	CH_3-	CH_3-	CH=CH-N=CH	5	base	147.5
83	CH_3-	$CH_3-(CH_2)_3$-	CH=CH-N=CH	5	$(COOH)_2$	108.4
84	H-	CH_3-	CH=CH-N=CH	6	base	159.5
85	H-	cyclopropyl	CH=CH-N=CH	6	base	108.4
86	H-	cyclohexyl	CH=CH-N=CH	5	base	149.4
87	H-	$(CH_3)_2$-CH-	CH=CH-N=CH	6	base	188.6
88	H-	$C_6H_5-CH_2$-	CH=CH-N=CH	5	base	130.5

Comp. No.	R^1	R^2	$A^1=A^2-A^3=A^4$	P	base/ salt	mp (°C)
89	H-	$CH_3-CH_2-CH_2-$	CH=CH-N=CH	6	base	113.9
90	phenyl	CH_3-	CH=CH-N=CH	6	base	105.5
91	H-	4-Cl-$C_6H_4-CH_2-$	CH=CH-N=CH	6	base	117.6
92	H-	$C_6H_5-CH_2-CH_2-$	CH=CH-N=CH	6	base	108.5
93	H-	$(CH_3)_2-CH-(CH_2)_2-$	CH=CH-N=CH	6	HNO_3	164.3-165.6
94	H-	$CH_3-CH_2-CH_2-$	CH=CH-N=CH	5	base	89.6
95	H-	$(CH_3)_2-CH-$	CH=CH-N=CH	5	base	163.0
96	H-	$C_6H_5-CH_2-CH_2-$	CH=CH-N=CH	5	base	96.6
97	H-	$C_6H_{11}-CH_2-$	CH=CH-N=CH	6	base	108.3
98	H-	4-F-$C_6H_4-CH_2-$	CH=CH-N=CH	6	base	101.8
99	H-	3-F-$C_6H_4-CH_2-$	CH=CH-N=CH	6	base	110.0
100	H-	cycloheptyl	CH=CH-N=CH	6	base	110.6
101	H-	$CH_3-CH_2-(CH_3)CH-$	CH=CH-N=CH	6	HNO_3	165.3
102	H-	CH_3-CH_2-	CH=CH-N=CH	6	base	96.7
103	H-	bicyclo[2.2.1]-hept-2-yl	CH=CH-N=CH	6	HNO_3	155.5-156.7
104	phenyl	cylcohexyl	CH=CH-N=CH	6	base	119.0
105	H-	1,2,3,4-tetrahydro-1-naphtalenyl	CH=CH-N=CH	6	$(COOH)_2$	166.1
106	H-	$CH_2=CH-CH_2-$	CH=CH-N=CH	6	base	114.2
107	H-	cylcopentyl	CH=CH-N=CH	6	H_2O	108.8-111.7
108	H-	cyclopropyl-CH_2-	CH=CH-N=CH	6	base	150.2
109	H-	$HO-CH_2-CH_2-CH_2-$	CH=CH-N=CH	6	base	122.5
110	phenyl	$C_6H_5-CH_2-$	CH=CH-N=CH	6	HNO_3	177.7
111	H-	2-thienyl-CH_2-	CH=CH-N=CH	6	base	117.6
112	H-	$(CH_3)_3-C-CH_2-$	CH=CH-N=CH	6	HNO_3	170.4
113	4-F-C_6H_4-	H-	CH=CH-N=CH	5	base	98.6
114	H-	$(CH_3)_2-CH-(CH_2)_2-$	CH=CH-N=CH	6	2 HNO_3	162.9
115	H-	2,3-dihydro-1H-inden-1-yl	CH=CH-N=CH	6	HNO_3	131.1
116	4-Cl-C_6H_4-	$(CH_3)_2-CH-$	CH=CH-N=CH	6	base	132.5
117	4-Cl-C_6H_4-	cylcohexyl	CH=CH-N=CH	6	base	162.0
118	3-pyridinyl	H-	CH=CH-N=CH	6	2 HCl	235.2

Comp. No.	R^1	R^2	$A^1=A^2-A^3=A^4$		base/ salt	mp (°C)
119	1H-imidazol-1-yl	H-	CH=CH-N=CH	5	2 HCl	260.4
120	4-Cl-C_6H_4-	$(CH_3)_2$-CH-$(CH_2)_2$-	CH=CH-N=CH	6	HCl 0.5 H_2O	163.8
121	3-Cl-C_6H_4-	H-	CH=CH-N=CH	5	base	110.6
122	3-F-C_6H_4-	H-	CH=CH-N=CH	5	base	170.9
123	4-Cl-C_6H_4-	(5-methyl-2-furanyl)methyl	CH=CH-N=CH	6	base	residue
124	4-Cl-C_6H_4-	H-	CH=CH-N=CH	5	base	164.9
125	i-C_3H_7-	H-	CH=CH-N=CH	5	base	175.3
126	4-Cl-C_6H_4-	C_6H_5-methyl	CH=CH-N=CH	5	HCl/ 0.5 H_2O	188.6
127	4-Cl-C_6H_4-	cyclopropyl	CH=CH-N=CH	5	$(COOH)_2$	117
128	CH_3	C_6H_5-ethyl	CH=CH-N=CH	6	*	
129	4-F-C_6H_4-	H-	-N=CH-N=CH	6		
130	4-Cl-C_6H_4-	H-	-N=CH-N=CH	6		
131	2-thienyl	H-	-N=CH-N=CH	6		
132	4-F-C_6H_4-	CH_3-	-N=CH-N=CH	6		
133	3-F-C_6H_4-	CH_3-	-N=CH-N=CH	6		
134	4-CH_3-C_6H_4-	CH_3-	-N=CH-N=CH	6		
135	4-CH_3O-C_6H_4-	CH_3-	-N=CH-N=CH	6		
136	4-Cl-C_6H_4-	CH_3-CH_2-	-N=CH-N=CH	6		
137	4-Cl-C_6H_4-	CH_3-CH_2-CH_2-	-N=CH-N=CH	6		
138	4-Cl-C_6H_4-	CH_3-(CH_3)CH-	-N=CH-N=CH	6		
139	4-Cl-C_6H_4-	c-C_6H_{11}-	-N=CH-N=CH	6		
140	4-Cl-C_6H_4-	C_6H_5-CH_2-	-N=CH-N=CH	6		
141	1,2,4-triazol-1-yl	CH_3-	-N=CH-N=CH	6		
142	4-F-C_6H_4-	H-	CH=N-N=CH	6		
143	4-Cl-C_6H_4-	H-	CH=N-N=CH	6		
144	4-F-C_6H_4-	CH_3-	CH=N-N=CH	6		
145	4-Cl-C_6H_4-	CH_3-(CH_3)CH-	CH=N-N=CH	6		

* = (±)-2,3-dihydrobutanedioate (1:1)

Example 27

To a stirred and cooled (5°C) solution of 5.2 parts of 4-[(1H-imidazol-1-yl)phenylmethyl]-1,2-benzenediamine in 4.8 parts of acetic acid and 20 parts of water was added a solution of 1.38 parts of sodium nitrite in 10 parts of water. The whole was stirred for 1 hour at room temperature. The reaction mixture was treated with a sodium hydrogen carbonate solution and the product was extracted with dichloromethane.

The extract was dried, filtered and evaporated. The residue was crystallized from 64 parts of ethyl acetate. The product was filtered off and dried, yielding 4.7 parts (85.3%) of 5-[(1H-imidazol-1-yl)phenylmethyl]-1H-benzotriazole; mp. 178.8 °C (compound 146).

In a similar manner there were also prepared:

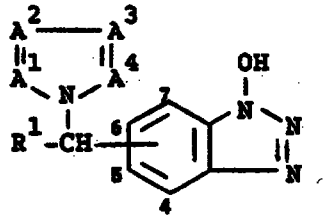
1-butyl-6-(1H-imidazol-1-ylmethyl)-1H-benzotriazole; mp. 49.2 °C (compound 147); and

1-butyl-5-(1H-imidazol-1-ylmethyl)-1H-benzotriazole; mp. 74.3 °C (compound 148).

Example 28

A mixture of 4.3 parts of 1-[1-(4-chloro-3-nitrophenyl)ethyl]-1H-imidazole, 3.42 parts of hydrazine monohydrate and 40 parts of 1-butanol was stirred for 12 hours at reflux temperature. After cooling, 3.4 parts of a hydrochloric acid solution 10 N were added. The separated organic layer was evaporated. The residue was stirred in ethyl acetate. The product was filtered off and dried, yielding 4.5 parts (99.0%) of 6-[1-(1H-imidazol-1-yl)ethyl]-1H-benzotriazol-1-ol monohydrochloride (compound 149).

In a similar manner there was also prepared:



Comp. No.	R^1	$-A^1=A^2-A^3=A^4-$	P	base/salt	mp (°C)
150	phenyl	-CH=CH-N=CH-	5	base	residue
151	H-	-CH=CH-N=C(CH$_3$)-	6	base	157
152	H-	-N=CH-N=CH-	6	base	222
153	phenyl	-N=CH-N=CH-	6	base	185
154	phenyl	-CH=C(CH$_3$)-N=CH-	6	base	200
155	phenyl	-C(CH$_3$)=CH-N=CH-	6	base	residue
156	H-	-CH=CH-N=CH-	5	base	residue
157	phenyl	-CH=CH-N=CH-	6	HCl	residue

Example 29

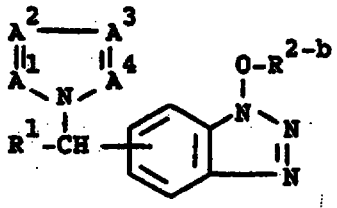
A mixture of 6.5 parts of 1-[(4-fluoro-3-nitrophenyl)methyl]-1H-imidazole, 6.01 parts of hydrazine monohydrate and 80 parts of ethanol was stirred and refluxed for 5 hours. After cooling, 12 parts of a hydrochloric acid solution 5N were added. The whole was evaporated. The residue was stirred with 30 parts of water and the precipitated product was filtered off and boiled in 40 parts of 2-propanol. 2-Propanol, saturated with hydrogen chloride, was added. The salt was allowed to crystallize at room temperature. It was filtered off and dried, yielding 4.1 parts (54.3%) of 6-(1H-imidazol-1-ylmethyl)-1H-benzotriazol-1-ol

monohydrochloride; mp. 207.4 °C (compound 158).

In a similar manner there were also prepared: 6-[(3-chlorophenyl)(1H-imidazol-1-yl)methyl]-1H-benzotriazol-1-ol (compound 159).

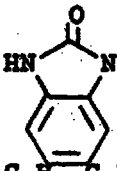
Example 30

A mixture of 3.2 parts of 6-(1H-imidazol-1-ylmethyl)-1H-benzotriazol-1-ol, 1 part of potassium carbonate and 27 parts of N,N-dimethylformamide was stirred for 30 minutes at room temperature. 2.1 parts of 1-(chloromethyl)-3-methylbenzene were added and stirring was continued for 3 hours at room temperature. The mixture was allowed to stand overnight at room temperature and was evaporated. The residue was diluted with water and the product was extracted with dichloromethane. The extract was dried, filtered and concentrated. The concentrate was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The solid residue was crystallized from a mixture of ethyl acetate and 2,2'-oxybispropane (10:20 by volume). The product was filtered off, washed with 2,2'-oxybispropane and dried, yielding 3.4 parts (70.9%) of 6-(1H-imidazol-1-ylmethyl)-1-[(3-methylphenyl)methoxy]-1H-benzotriazole; mp. 120.1 °C (compound 160). In a similar manner there were also prepared:



Comp. No.	R^1	R^{2-b}	$-A^1=A^2-A^3=A^4-$	base/salt	mp (°C)
161	H-	CH_3-CH_2-	-CH=CH-N=CH-	base	108.5
162	H-	$2-CH_3-C_6H_4-CH_2-$	-CH=CH-N=CH-	base	134.6
163	H-	$4-CH_3-C_6H_4-CH_2-$	-CH=CH-N=CH-	base	109.4
164	H-	$2-F-C_6H_4-CH_2-$	-CH=CH-N=CH-	base	105.8
165	H-	$C_6H_5-O-(CH_2)_3-$	-CH=CH-N=CH-	$(COOH)_2$	154.1
166*	H-	$C_6H_5-CH=CH-CH_2-$	-CH=CH-N=CH-	$(COOH)_2$	102.2
167	H-	$C_6H_5-O-CH_2-CH_2-$	-CH=CH-N=CH-	base	124.1
168	H-	$3-CH_3O-C_6H_4-CH_2-$	-CH=CH-N=CH-	base	118.9
169	H-	$4-F-C_6H_4-CH_2-$	-CH=CH-N=CH-	base	126.2
170	H-	$3-F-C_6H_4-CH_2-$	-CH=CH-N=CH-	base	114.4
171	H-	$(C_6H_5)_2-CH-$	-CH=CH-N=CH-	$(COOH)_2$	163.4
172	H-	$2-CH_3O-C_6H_4-CH_2-$	-CH=CH-N=CH-	base	127.2
173	H-	$4-CH_3O-C_6H_4-CH_2-$	-CH=CH-N=CH-	base	92.6
174	H-	2-thienyl-CH_2-	-CH=CH-N=CH-	base	126.5

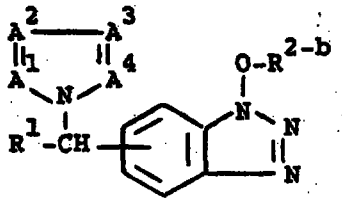
* = E-form

Comp. No.	R^1	R^{2-b}	$-A^1=A^2-A^3=A^4-$	base/salt	mp (°C)
175	H-	$(CH_3)_2-N-CH_2-CH_2-$	-CH=CH-N=CH-	2 HCl	230.1
176	H-	$C_6H_5-S-CH_2-$	-CH=CH-N=CH-	base	118.0
177	H-	1-naphthalenyl-CH_2-	-CH=CH-N=CH-	base	158.0
178	H-	$HO-CH_2-CH_2-CH_2-$	-CH=CH-N=CH-	base	137.0
179	H-	$CH\equiv C-CH_2-$	-CH=CH-N=CH-	base	130.0
180	H-	F_3C-CH_2-	-CH=CH-N=CH-	base	91.7
181	H-	$C_6H_4-S-CH_2-CH_2-$	-CH=CH-N=CH-	base	84.2
182	H-	2-pyrimidinyl	-CH=CH-N=CH-	base	167.7
183	H-	cyclo-$C_3H_5-CH_2-$	-CH=CH-N=CH-	HNO_3	136.5
184	H-	cyclo-$C_6H_{11}-CH_2-$	-CH=CH-N=CH-	HNO_3	149.0
185	H-	CH_3-CH_2-	-CH=CH-N=C(-CH_3)-	base	93.6
186	H-	CH_3-CH_2-	-N=CH-N=CH-	base	116.9
187	H-	$CH_3-CH_2-CH_2-CH_2-$	-CH=CH-N=C(-CH_3)-	HNO_3	95.1
188	phenyl	$C_6H_5-CH_2-$	-CH=CH-N=CH-	$(COOH)_2$	152.5
189	phenyl	$C_6H_5-CH_2-$	-CH=CH-N=CH-	base	113.2
190	H-		-CH=CH-N=CH-	base	210.3
191	H-	$C_6H_5-C_6H_4-CH_2-$	-CH=CH-N=CH-	base	133.0
192	H-	(1H-benzimidazol-2-yl)methyl	-CH=CH-N=CH-	base	212.5
193	H-	(2-methyl-1H-benzimidazol-5-yl)methyl	-CH=CH-N=CH-	base	209.1
194	H-	(2,3-dihydro-1,4-benzodioxin-2-yl)-methyl	-CH=CH-N=CH-	$(COOH)_2$	171.6

Example 31

A mixture of 3.23 parts of 6-(1H-imidazol-1-ylmethyl)-1H-benzotriazol-1-ol, 2.07 parts of potassium carbonate and 20 parts of dimethyl sulfoxide was stirred for 10 minutes at room temperature. Then there were added 2.55 parts of 2-iodopropane and stirring was continued first for 15 minutes at room temperature and then for 1 hour at 50 °C. The reaction mixture was evaporated. 50 Parts of water were added. The product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from 14 parts of 1,1'-oxybisethane. The product was filtered off and dried, yielding 3.3 parts (85.5%) of 6-(1H-imidazol-1-ylmethyl)-1-(1-methylethoxy)-1H-benzotriazole; mp. 114.3 °C (compound 195).

In a similar manner there were also prepared:



Comp. No.	R^1	R^{2-b}	$-A^1=A^2-A^3=A^4-$	base/salt	mp (°C)
196	H-	3-pyridinyl-CH_2-	-CH=CH-N=CH-	base	120.6
197	H-	CH_3-CH_2-(CH_3)CH-	-CH=CH-N=CH-	HNO_3	133.3
198	H-	CH_3-CH_2-O-C(=O)-CH_2-	-CH=CH-N=CH-	HNO_3	143.3
199	H-	CH_3-CH_2-O-C(=O)-(CH_2)$_4$-	-CH=CH-N=CH-	base	oil
200	H-	CH_3-CH_2-O-C(=O)-(CH_2)$_3$-	-CH=CH-N=CH-	base	oil
201	H-	CH_3-(CH_2)$_4$-	-CH=CH-N=CH-	HNO_3	115.2
202	H-	CH_3-(CH_2)$_5$-	-CH=CH-N=CH-	HNO_3	93.9
203	H-	CH_3-(CH_2)$_8$-	-CH=CH-N=CH-	HNO_3	90.0
204	H-	Br-(CH_2)$_2$-	-CH=CH-N=CH-	HNO_3	131.3
205	H-	2-pyridinyl-CH_2-	-CH=CH-N=CH-	base	81.7
206	H-	CH_3-(CH_2)$_6$-	-CH=CH-N=CH-	HNO_3	80.7
207	H-	C_6H_5-(CH_2)$_3$-	-CH=CH-N=CH-	$(COOH)_2$	135.7
208	H-	C_6H_5-(CH_2)$_2$-	-CH=CH-N=CH-	$(COOH)_2$	136.0

Comp. No.	R^1	R^{2-b}	$-A^1=A^2-A^3=A^4-$	base/salt	mp (°C)
209	H-	1-methyl-4-piperidinyl	-CH=CH-N=CH-	2 HNO_3	176.9
210	CH_3-	CH_3-CH_2-O-C(=O)-CH_2-	-CH=CH-N=CH-	base	residue
211	phenyl	CH_3-CH_2-	-N=CH-N=CH-	0.5$(COOH)_2$	92.1
212	phenyl	CH_3-CH_2-	-CH=C(CH_3)-N=CH-	HNO_3	125.8
213	phenyl	C_6H_5-CH_2-	-C(CH_3)=CH-N=CH-	base	156.2
214	phenyl	CH_3-CH_2-CH_2-CH_2-	-CH=C(CH_3)-N=CH-	HNO_3	126.9

Example 32

A mixture of 4.5 parts of 6-[1-(1H-imidazol-1-yl)ethyl]-1H-benzo-triazol-1-ol monohydrochloride, 3.12 parts of iodoethane, 3.7 parts of sodium carbonate and 63 parts of N,N-dimethylformamide was stirred for 4 hours at room temperature. The reaction mixture was evaporated and the residue was taken up in water. The product was extracted with methylbenzene. The extract was dried, filtered and evaporated. The residue was crystallized from a mixture of 27 parts of ethyl acetate and 21 parts of 2,2'-oxybispropane. The product was filtered off and dried, yielding 2.26 parts (51.6%) of 1-ethoxy-6-[1-(1H-imidazol-1-yl)ethyl]-1H-benzotriazole: mp. 81.1 °C (compound 215).

In a similar manner there were also prepared:

5-[(1H-imidazol-1-yl)phenylmethyl]-1-(1-methylethoxy)-1H-benzotriazole; mp. 85.7 °C (compound 216);

1-ethoxy-5-[(1H-imidazol-1-yl)phenylmethyl]-1H-benzotriazole; mp. 85.5 °C (compound 217);

6-[1-(1H-imidazol-1-yl)ethyl]-1-(phenylmethoxy)-1H-benzotriazole; mp. 128.6 °C (compound 218); and

6-[1-[(1H-imidazol-1-yl)ethyl]-1-(2-methoxyethoxy)-1H-benzotriazole (±)-2,3-dihydroxybutanedioate; mp. 140.0 °C (compound 219).

Example 33

To a stirred and heated (50 °C) mixture of 2.81 parts of 6-(1H-imidazol-1-ylmethyl)-1H-benzotriazol-1-ol and 22.5 parts of N,N-dimethylformamide were added 0.69 parts of a sodium hydride dispersion. The reaction mixture was stirred until hydrogen evolution had ceased. 1.28 Parts of 1-chloro-2-methoxyethane were added at room temperature and stirring was continued for a while. 22 Parts of dimethyl sulfoxide and 0.04 parts of 2-(2-methoxyethoxy)-N,N-bis[2-(2-methoxyethoxy)ethyl]ethanamine were added. The reaction mixture was stirred overnight at 50 °C and then poured into water. The product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from a mixture of ethyl acetate and 2,2'-oxybispropane (1:3 by volume). The product was filtered off, washed with a mixture of ethyl acetate and 2,2'-oxybispropane (1:3 by volume) and 2,2'-oxybispropane and dried in vacuo at 50 °C, yielding 1.66 parts (46.7%) of 6-(1H-imidazol-1-ylmethyl)-1-(2-methoxyethoxy)-1H-benzotriazole; mp. 77.0 °C (compound 220).

Example 34

To a stirred mixture of 4.5 parts of 5-(1H-imidazol-1-ylmethyl)-1H-benzotriazol-1-ol and 94 parts of N,N-dimethylformamide was added portionwise 1 part of a sodium hydride dispersion 50%. Upon complete addition, stirring was continued till hydrogen evolution had ceased. 1.3 Parts of iodomethane were added at once and stirring was continued at room temperature. The N,N-dimethylformamide formamide layer was evaporated and the residue was taken up in water and a mixture of trichloromethane, methanol and methanol, saturated with ammonia (90:5:5 by volume). The product was extracted with a mixture of trichloromethane, methanol and methanol, saturated with ammonia (90:5:5 by volume). The extract was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel first using trichloromethane and then a mixture of trichloromethane and methanol (90:10 by volume) as eluents. The pure fractions were collected and the eluent was evaporated. The residue was stirred in 2,2'-oxybispropane. The product was filtered off and dried in vacuo at 50 °C, yielding 3.1 parts (64.3%) of 5-(1H-imidazol-1-ylmethyl)-1-methoxy-1H-benzotriazole; mp. 94.3 °C (compound 221).

In a similar manner there were also prepared:

5-(1H-imidazol-1-ylmethyl)-1-(phenylmethoxy)-1H-benzotriazole; mp. 113.7 °C (compound 222);

6-[(3-chlorophenyl)(1H-imidazol-1-yl)methyl]-1-(phenylmethoxy)-1H-benzotriazole ethanedioate(2:3); mp. 169.3 °C (compound 223); and

1-butoxy-6-[(3-chlorophenyl)(1H-imidazol-1-yl)methyl]-1H-benzotriazole ethanedioate (1:1); mp. 96.5 °C (compound 224).

Example 35

To a stirred solution of 0.46 parts of sodium in 24 parts of methanol were added 4.3 parts of 6-(1H-imidazol-1-ylmethyl)-1H-benzotriazol-1-ol. The mixture was stirred for 10 minutes and then evaporated. 9 Parts of methylbenzene were added to the residue and the whole was evaporated again. To the residue in 9

parts of N,N-dimethylformamide was added a solution of 3.12 parts of iodoethane in 4.5 parts of N,N-dimethylformamide. The whole was stirred for 1 hour at 50 °C and evaporated. 60 Parts of water were added and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was converted into the hydrochloride salt in 2-propanol and 4-methyl-2-pentanone. The salt was filtered off and dried, yielding 4.5 parts (80%) of 1-ethoxy-6-(1H-imidazol-1-ylmethyl)-1H-benzotriazole monohydrochloride; mp. 140.2 °C (compound 225).

In a similar manner there were also prepared:

1-butoxy-6-(1H-imidazol-1-ylmethyl)-1H-benzotriazole monohydrochloride; mp. 124.2 °C (compound 226);

6-(1H-imidazol-1-ylmethyl)-1-propoxy-1H-benzotriazole monohydrochloride. hemihydrate; mp. 130.5 °C (compound 227); and

6-(1H-imidazol-1-ylmethyl)-1-(phenylmethoxy)-1H-benzotriazole; mp. 113.8 °C (compound 228).

Example 36

To a stirred suspension of 4.7 parts of 6-(1H-imidazol-1-ylmethyl)-1H-benzotriazol-1-ol in 60 parts of ethanol were added 22.5 parts of a sodium hydroxide solution 1N. The whole was stirred till a clear solution was obtained. The mixture was evaporated to dry. The residue was dissolved in 18 parts of N,N-dimethylformamide. To the thus obtained solution was added at once a solution of 3.2 parts of iodomethane in 9 parts of N,N-dimethylformamide. After stirring for 30 minutes at room temperature, the whole was evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from 8 parts of 4-methyl-2-pentanone. The product was filtered off and dried, yielding 3.3 parts (65.4%) of 6-(1H-imidazol-1-ylmethyl)-1-methoxy-1H-benzotriazole; mp. 132.4 °C (compound 229).

Example 37

A mixture of 5.85 parts of 6-[phenyl(1H-1,2,4-triazol-1-yl)methyl]-1H-benzotriazol-1-ol, 1.4 parts of potassium carbonate and 27.5 parts of dimethyl sulfoxide was stirred for 30 minutes at 50 °C. After cooling, 3.55 parts of ethyl 2-bromoacetate were added and the whole was stirred for 2 hours at room temperature. Another portion of 1.4 parts of potassium carbonate was added. After stirring for 3 hours at 50 °C, the mixture was cooled and 2.0 parts of concentrated hydrochloric acid were added. The dimethyl sulfoxide layer was evaporated. The residue was taken up in 25 parts of water and 130 parts of dichloromethane. The separated organic layer was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane, methanol and methanol, saturated with ammonia, (92:4:4 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from 20 parts of 4-methyl-2-pentanone. The product was filtered off and dried, yielding 4.4 parts (79.6%) of 5-[phenyl(1H-1,2,4-triazol-1-yl)methyl]-1H-benzotriazole; mp. 182.7 °C (compound 230).

In a similar manner there were also prepared:

5-[1-(1H-imidazol-1-yl)ethyl]-1H-benzotriazole; mp. 165.3 °C (compound 231);

5-[(2-methyl-1H-imidazol-1-yl)methyl]-1H-benzotriazole; mp. 214.3 °C (compound 232); and

5-[(4-methyl-1H-imidazol-1-yl)phenylmethyl]-1H-benzotriazole; mp. 166.7 °C (compound 233).

Example 38

A mixture of 4.3 parts of 6-(1H-imidazol-1-ylmethyl)-1H-benzotriazol-1-ol monohydrochloride and 120 parts of methanol was hydrogenated at normal pressure and at 50 °C with 2 parts of platinium-on-charcoal catalyst 5%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off and the filtrate was evaporated. The residue was crystallized twice from ethanol. The product was filtered off and dried, yielding 2.9 parts (72%) of 5-(1H-imidazol-1-ylmethyl)-1H-benzotriazole monohydrochloride; mp. 230.4 °C (compound 234).

Example 39

2.47 Parts of 5-(1H-imidazol-1-ylmethyl)-1H-benzotriazole were added portionwise to 30 parts of fuming nitric acid while stirring. Upon complete addition, stirring was continued overnight at room temperature. The

reaction mixture was poured into 100 parts of crushed ice and nitrogen was bubbled through the mixture during 30 minutes. The precipitated product was filtered off, washed with water and purified by reversed phase chromatography (HPLC) over Li Chroprep RP 18 using a mixture of methanol, acetonitrile and an ammonium acetate solution 0.5% (17:8:75 by volume) as eluent. The desired fraction was collected and the eluent was evaporated. The residue was stirred in methanol and 2,2'-oxybispropane. The precipitated product was filtered off and boiled in methanol. The product was filtered off, washed with methanol and 2,2'-oxybispropane and dried in vacuo at 50-60 °C, yielding 0.05 parts (1.6%) of 5-(1H-imidazol-1-ylmethyl)-6-nitro-1H-benzotriazole; mp. 286.0 °C (decomp.) (compound 235).

Example 40

A mixture of 3.2 parts of ethyl 4-[[6-(1H-imidazol-1-ylmethyl)-1H-benzotriazol-1-yl]oxy]butanoate, 25 parts of a sodium hydroxide solution 1N and 20 parts of ethanol was stirred for 1.5 hours at room temperature. 25 Parts of a hydrochloric acid solution 1N were added and the whole was concentrated to a volume of about 20 parts. The precipitated product, which was formed during concentration, was filtered off, washed with water, 2-propanol and 1,1'-oxybisethane and dried, yielding 2.1 parts (71%) of 4-[[6-(1H-imidazol-1-ylmethyl)-1H-benzotriazol-1-yl]oxy]butanoic acid; mp. 170.5 °C (compound 236).

In a similar manner there was also prepared:

5-[[6-(1H-imidazol-1-ylmethyl)-1H-benzotriazol-1-yl]oxy]pentanoic acid; mp. 132.7 °C (compound 237).

Example 41

A solution of 7.1 parts of 6-[[4-(4,5-dihydro-4,4-dimethyl-2-oxazolyl) phenyl](1H-imidazol-1-yl)methyl]-1-methyl-1H-benzotriazole in 100 parts of a hydrochloric acid solution 3 N was stirred overnight at reflux temperature. The reaction mixture was evaporated to dry, yielding 8.9 parts (100%) of 4-[(1H-imidazol-1-yl)-(1-methyl-1H-benzotriazol-6-yl) methyl]benzoic acid monohydrochloride as a residue (compound 238).

Example 42

A solution of 8.9 parts of 4-[(1H-imidazol-1-yl)(1-methyl-1H-benzotriazol-6-yl)methyl]benzoic acid monohydrochloride in 32.4 parts of thionyl chloride was stirred for 1 hour at room temperature. The reaction mixture was evaporated. A solution of the residue in 80 parts of ethanol was stirred for 1 hour at 60 °C. The reaction mixture was concentrated. The concentrate was taken up in a diluted potassium carbonate solution and the product was extracted with dichloromethane. The extract was dried, filtered and evaporated. The residue was purified by column chromatography over silica gel using a mixture of dichloromethane and methanol (98:2 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was converted into the ethanedioate salt. The salt was filtered off and dried, yielding 1 part (8.5%) of ethyl 4-[(1H-imidazol-1-yl)(1-methyl-1H-benzotriazol-6-yl)-methyl]benzoate ethanedioate(1:1); mp. 155.5 °C (compound 239).

Example 43

A mixture of 7 parts of 5-[1-(1H-imidazol-1-yl)-2-butynyl]-1-methyl-1H-benzotriazole, 0.1 parts of quinoline, 54 parts of ethyl acetate and 32 parts of ethanol was hydrogenated at 931.00 Pa and at room temperature with 0.3 parts of palladium-on-charcoal catalyst 10%. After the calculated amount of hydrogen was taken up, the catalyst was filtered off over diatomaceous earth and the filtrate was evaporated. The residue was purified by column chromatography over silica gel using a mixture of dichloromethane and methanol (95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from a mixture of dichloromethane and 1,1'-oxybisethane. The product was filtered off and dried, yielding 1.4 parts (19.7%) of 5-[1-(1H-imidazol-1-yl)-2-butenyl]-1-methyl-1H-benzotriazole; mp. 104 °C (compound 240).

Example 44

A mixture of 2.6 parts of 4-[(1H-imidazol-1-yl)(1-methyl-1H-benzotriazol-5-yl)methyl]benzaldehyde, 0.85 parts of hydroxylamine monohydrochloride, 16 parts of ethanol and 3.4 parts of potassium carbonate was stirred for 1 hour at 50 °C. The reaction mixture was filtered and the filtrate was evaporated. The residue was purified by column chromatography over silica gel using a mixture of trichloromethane and methanol

(95:5 by volume) as eluent. The pure fractions were collected and the eluent was evaporated. The residue was crystallized from 2-propanone. The product was filtered off and dried, yielding 1.7 parts (63.9%) of 4-[-(1H-imidazol-1-yl)(1-methyl-1H-benzotriazol-5-yl)methyl]benzaldehyde, oxime; mp. 149.5 °C (compound 241).

C. Pharmacological Examples

The useful inhibition of the aromatase activity of the compounds of formula (I) can be demonstrated in the following test procedures.

Example 45: In Vitro-Inhibition of the Aromatase Activity Test

For example, one may study the effect of the compounds of the present invention on the conversion of 1,2-[3H]androstenedione into estrone and estradiol in the presence of human placental microsomes following procedures analogous to those described in J. Steroid Biochem., 7, 787 (1976).

Human placental microsomes were diluted in potassium phosphate buffer (0.1M, pH 7.4) to give about 50% conversion of androgens to estrogens (protein content: about 0.5 mg). Four ml human placental microsomes were incubated in a final volume of 5 ml with 0.2 μCi1,2[3H]-androstenedione, 2 μg androstendione and 5 μl of test compound and/or dimethyl sulfoxide (DMSO). Further the incubation mixture contained a NADPH-regenerating system consisting of ATP (2,48mM), NADP (0.97mM), glucose-6-phosphate (8.22mM), glucose-6-phosphate dehydrogenase (0.98 units) and $MgCl_2$ (2.46mM). The reaction was initiated by the addition of androstenedione and proceeded for 30 min at 37 °C. During the incubation period, the mixtures were gassed with air. In this assay, aromatization of androstenedione results in the production of [3H]-H_2O which is isolated by extracting the samples with chloroform to remove the free steroid. Samples are counted in a liquid scintillation spectrometer and the percent inhibition is determined by comparing the results with control samples incubated without inhibitor.
The effects of the compounds of the present invention are presented in table I, column (a) as the concentration in μM of the compound required to obtain 50% inhibition of the estrogen synthesis (IC_{50}-values).

Example 46: In vivo-inhibition of the aromatase activity

Immature female Wistar rats weighing 120 g were injected subcutaneously with 200 I.U. of pregnant mare's serum gonadotropin (PMSG). Ninety hours later, 1 mg/kg of the test compound dissolved in 0.5 ml 20% polyethyleneglycol in water was administered by oral gavage. Control animals received 20% polyethyleneglycol only. Two hours following drug or placebo administration the rats were killed by decapitation and trunk blood was collected on heparine. Plasma estradiol concentrations were measured by standard radio-immunological procedures. The percentage recovery estradiol relative to the controls are depicted in column (b) of table (I). The results in this table are not given for the purpose of limiting the invention thereto but only to exemplify the useful pharmacological properties of all the compounds within the scope of formula (I).

Table I

Compound	IC_{50}-values (µM)	% recovery estradiol
225	0.0100	19
226	0.0067	19
227	0.0074	19
228	0.0052	-
195	0.0120	19
196	0.0110	-
197	0.0110	-
198	0.0180	-
201	0.0067	19
202	0.0071	21
203	0.0170	-
204	0.0092	19
206	0.0080	-
2	0.0160	20
4	0.0160	-
6	0.0120	-
207	0.0073	26
208	0.0110	-
7	0.0257	7
147	0.0076	21

Compound	IC_{50}-values (µM)	% recovery estradiol
176	0.0120	-
191	0.0234	-
179	0.0232	-
75	0.0242	27
76	0.0347	9
87	0.0269	5
89	0.0150	5
90	0.0227	5
91	0.0088	-
92	0.0087	15
15	0.0226	2
93	0.0105	8
17	0.0182	7
97	0.0131	10
99	0.0178	11
23	0.0075	-
100	0.0143	3
101	0.0174	7
102	0.0317	2
103	0.0163	5
28	0.0253	6
29	0.0159	7
30	0.0222	7
31	0.0342	8
104	0.0206	9
33	0.0246	5
105	0.0198	14
213	0.0362	-
106	0.0244	8
107	0.0141	6
108	0.0152	3

Compound	IC_{50}-values (μM)	% recovery estradiol
109	0.0262	-
188	0.0182	-
111	0.0143	19
113	0.0188	4
48	0.0166	6
50	0.0183	1
51	0.0222	7
115	0.0144	22
55	0.0188	3
56	0.0215	8
116	0.0249	20
64	0.0257	3
117	0.0125	9
69	0.0290	5
77	0.0176	21
220	0.0200	-
120	0.0089	-
59	0.0180	-

D) Composition Examples

The following formulations exemplify typical pharmaceutical compositions in dosage unit form suitable for systemic administration to animal and human subjects in accordance with the instant invention. "Active ingredient" (A.I.) as used throughout these examples relates to a compound of formula (I) or a pharmaceutically acceptable acid addition salt thereof.

Example 47: ORAL DROPS

500 g of the A.I. was dissolved in 0.5 l of 2-hydroxypropanoic acid and 1.5 l of the polyethylene glycol at 60~80 °C. After cooling to 30~40 °C there were added 35 l of polyethylene glycol and the mixture was stirred well. Then there was added a solution of 1750 g of sodium saccharin in 2.5 l of purified water and while stirring there were added 2.5 l of cocoa flavor and polyethylene glycol q.s. to a volume of 50 l, providing an oral drop solution comprising 10 mg of the A.I. per ml. The resulting solution was filled into suitable containers.

Example 48: ORAL SOLUTION

9 g of methyl 4-hydroxybenzoate and 1 gram of propyl 4-hydroxybenzoate were dissolved in 4 l of boiling purified water. In 3 l of this solution were dissolved first 10 g of 2,3-dihydroxybutanedioic acid and thereafter 20 g of the A.I. The latter solution was combined with the remaining part of the former solution and 12 l 1,2,3-propanetriol and 3 l of sorbitol 70% solution were added thereto. 40 g of sodium saccharin were dissolved in 0.5 l of water and 2 ml of raspberry and 2 ml of gooseberry essence were added. The

latter solution was combined with the former, water was added q.s. to a volume of 20 l providing an oral solution comprising 20 mg of the active ingredient per teaspoonful (5 ml). The resulting solution was filled in suitable containers.

Example 49: CAPSULES

20 g of the A.I., 6 g sodium lauryl sulfate, 56 g starch, 56 g lactose, 0.8 g colloidal silicon dioxide, and 1.2 g magnesium stearate were vigorously stirred together. The resulting mixture was subsequently filled into 1000 suitable hardened gelating capsules, comprising each 20 mg of the active ingredient.

Example 50: FILM-COATED TABLETS

Preparation of tablet core

A mixture of 100 g of the A.I., 570 g lactose and 200 g starch was mixed well and thereafter humidified with a solution of 5 g sodium dodecyl sulfate and 10 g polyvinylpyrrolidone (Kollidon-K 90®) in about 200 ml of water. The wet powder mixture was sieved, dried and sieved again. Then there was added 100 g microcrystalline cellulose (Avicel®) and 15 g hydrogenated vegetable oil (Sterotex ®). The whole was mixed well and compressed into tablets, giving 10.000 tablets, each containing 10 mg of the active ingredient.

Coating

To a solution of 10 g methyl cellulose (Methocel 60 HG®) in 75ml of denaturated ethanol there was added a solution of 5 g of ethyl cellulose (Ethocel 22 cps ®) in 150 ml of dichloromethane. Then there were added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol. 10 g of polyethylene glycol was molten and dissolved in 75 ml of dichloromethane. The latter solution was added to the former and then there were added 2.5 g of magnesium octadecanoate, 5 g of polyvinylpyrrolidone and 30 ml of concentrated colour suspension (Opaspray K-1-2109®) and the whole was homogenated. The tablet cores were coated with the thus obtained mixture in a coating apparatus.

Example 51 : INJECTABLE SOLUTION

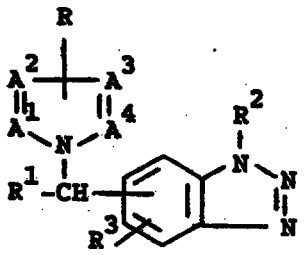
1.8 g methyl 4-hydroxybenzoate and 0.2 g propyl 4-hydroxybenzoate were dissolved in about 0.5 l of boiling water for injection. After cooling to about 50 °C there were added while stirring 4 g lactic acid, 0.05 g propylene glycol and 4 g of the A.I.. The solution was cooled to room temperature and supplemented with water for injection q.s. ad 1 liter volume, giving a solution of 4 mg A.I. per ml. The solution was sterilized by filtration (U.S.P. XVII p. 811) and filled in sterile containers.

Example 52: SUPPOSITORIES

3 g A.I. was dissolved in a solution of 3 g 2,3-dihydroxybutanedioic acid in 25 ml polyethylene glycol 400. 12 g surfactant (SPAN®) and triglycerides (Witepsol 555 ®) q.s. ad 300 g were molten together. The latter mixture was mixed well with the former solution. The thus obtained mixture was poured into moulds at a temperature of 37~38 °C to form 100 suppositories each containing 30 mg of the active ingredient.

Claims

1. A chemical compound having the formula



(I),

* C L M S *

latter solution was combined with the former, water was added q.s. to a volume of 20 l providing an oral solution comprising 20 mg of the active ingredient per teaspoonful (5 ml). The resulting solution was filled in suitable containers.

Example 49: CAPSULES

20 g of the A.I., 6 g sodium lauryl sulfate, 56 g starch, 56 g lactose, 0.8 g colloidal silicon dioxide, and 1.2 g magnesium stearate were vigorously stirred together. The resulting mixture was subsequently filled into 1000 suitable hardened gelating capsules, comprising each 20 mg of the active ingredient.

Example 50: FILM-COATED TABLETS

Preparation of tablet core

A mixture of 100 g of the A.I., 570 g lactose and 200 g starch was mixed well and thereafter humidified with a solution of 5 g sodium dodecyl sulfate and 10 g polyvinylpyrrolidone (Kollidon-K 90®) in about 200 ml of water. The wet powder mixture was sieved, dried and sieved again. Then there was added 100 g microcrystalline cellulose (Avicel®) and 15 g hydrogenated vegetable oil (Sterotex ®). The whole was mixed well and compressed into tablets, giving 10.000 tablets, each containing 10 mg of the active ingredient.

Coating

To a solution of 10 g methyl cellulose (Methocel 60 HG®) in 75ml of denaturated ethanol there was added a solution of 5 g of ethyl cellulose (Ethocel 22 cps ®) in 150 ml of dichloromethane. Then there were added 75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol. 10 g of polyethylene glycol was molten and dissolved in 75 ml of dichloromethane. The latter solution was added to the former and then there were added 2.5 g of magnesium octadecanoate, 5 g of polyvinylpyrrolidone and 30 ml of concentrated colour suspension (Opaspray K-1-2109®) and the whole was homogenated. The tablet cores were coated with the thus obtained mixture in a coating apparatus.

Example 51 : INJECTABLE SOLUTION

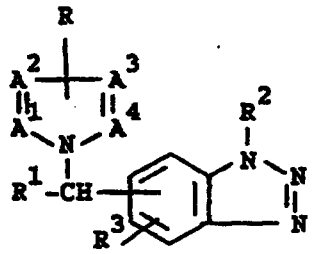
1.8 g methyl 4-hydroxybenzoate and 0.2 g propyl 4-hydroxybenzoate were dissolved in about 0.5 l of boiling water for injection. After cooling to about 50 °C there were added while stirring 4 g lactic acid, 0.05 g propylene glycol and 4 g of the A.I.. The solution was cooled to room temperature and supplemented with water for injection q.s. ad 1 liter volume, giving a solution of 4 mg A.I. per ml. The solution was sterilized by filtration (U.S.P. XVII p. 811) and filled in sterile containers.

Example 52: SUPPOSITORIES

3 g A.I. was dissolved in a solution of 3 g 2,3-dihydroxybutanedioic acid in 25 ml polyethylene glycol 400. 12 g surfactant (SPAN®) and triglycerides (Witepsol 555 ®) q.s. ad 300 g were molten together. The latter mixture was mixed well with the former solution. The thus obtained mixture was poured into moulds at a temperature of 37~38 °C to form 100 suppositories each containing 30 mg of the active ingredient.

Claims

1. A chemical compound having the formula



(I),

a pharmaceutically acceptable acid addition salt or a stereochemically isomeric form thereof, wherein

$A^1 = A^2\text{-}A^3 = A^4$ is a bivalent radical having the formula

-CH = N-CH = CH- (a-1),

-CH = N-CH = N- (a-2), or

-CH = N-N = CH- (a-3);

R is hydrogen or C_{1-6}alkyl;

R^1 is hydrogen, C_{1-10}alkyl, C_{3-7}cycloalkyl, Ar^1, Ar^2-C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl;

R^2 is hydrogen; C_{1-10}alkyl optionally substituted with Ar^1, C_{3-7}cycloalkyl, hydroxy or C_{1-6}alkyloxy; Ar^1; C_{2-6}alkenyl; C_{2-6}alkynyl; C_{3-7}cycloalkyl; bicyclo[2.2.1]heptan-2-yl; 2,3-dihydro-1H-indenyl; 1,2,3,4-tetrahydronaphthalenyl; hydroxy; C_{2-6}alkenyloxy optionally substituted with Ar^2; C_{2-6}alkynyloxy; pyrimidinyloxy; di(Ar^2)methoxy; (1-C_{1-4}alkyl-4-piperidinyl)oxy; or C_{1-10}alkyloxy optionally substituted with halo, hydroxy, C_{1-6}alkyloxy, amino, mono- and di(C_{1-6}alkyl)amino, trifluoromethyl, carboxyl, C_{1-6}alkyloxy-carbonyl, A^1, Ar^2-O-, Ar^2-S-, C_{3-7}cycloalkyl, 2,3-dihydro-1,4-benzodioxinyl, 1H-benzimidazolyl, C_{1-4}alkyl substituted 1H-benzimidazolyl, (1,1'-bi-phenyl)-4-yl or with 2,3-dihydro-2-oxo-1H-benzimidazolyl;

R^3 is hydrogen, nitro, amino, mono- and di(C_{1-6}alkyl)amino,halo, C_{1-6}alkyl, hydroxy or C_{1-6}alkyloxy;

wherein Ar^1 is phenyl, substituted phenyl, naphthalenyl, pyridinyl, aminopyridinyl, imidazolyl, triazolyl, thienyl, halothienyl, furanyl, C_{1-6}alkylfuranyl, halofuranyl or thiazolyl; and

Ar^2 is phenyl, substituted phenyl or pyridinyl, said substituted phenyl being phenyl substituted with up to 3 substituents each independently selected from halo, hydroxy, hydroxymethyl, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkyloxy, C_{1-6}alkyloxycarbonyl, carboxyl, formyl, (hydroxylimino)methyl, cyano, amino, mono- and di(C_{1-6}alkyl)amino and nitro;

2. A chemical compound according to claim 1 wherein R is hydrogen or C_{1-4}alkyl; R^1 is hydrogen; C_{1-6}alkyl optionally substituted with phenyl or substituted phenyl; C_{3-7}cycloalkyl; phenyl; substituted phenyl; pyridinyl; naphthalenyl; thienyl; furanyl; imidazolyl; triazolyl; C_{2-6}alkenyl or C_{2-6}alkynyl; R^2 is hydrogen; C_{1-6}alkyl optionally substituted with phenyl, substituted phenyl, naphthalenyl, thienyl, furanyl, C_{1-4}alkylfuranyl, C_{3-7}cycloalkyl, hydroxy or C_{1-4}alkyloxy; phenyl; substituted phenyl; C_{2-6}alkenyl; C_{2-6}alkynyl; C_{3-7}cycloalkyl; bicyclo[2.2.1]heptan-2-yl; 2,3-dihydro-1H-indenyl; 1,2,3,4-tetrahydronaphthalenyl; hydroxy; C_{2-6}alkenyloxy optionally substituted with phenyl; C_{2-6}alkynyloxy; pyrimidinyloxy; di(phenyl)methoxy; (1-C_{1-4}alkyl-4-piperidinyl)oxy; or C_{1-6}alkyloxy optionally substituted with halo, hydroxy, amino, mono- and di(C_{1-4}alkyl)amino, trifluoromethyl, carboxyl, C_{1-6}alkyloxycarbonyl, phenyl, substituted phenyl, thienyl, furanyl, pyridinyl, phenoxy, phenylthio, C_{3-7}cycloalkyl, 2,3-dihydro-l,4-benzodioxinyl, 1H-benzimidazolyl, C_{1-4}alkyl substituted 1H-benzimidazolyl, (1,1'-biphenyl)-4-yl, or with 2,3-dihydro-2-oxo-1H-benzimidazolyl; and R^3 is hydrogen or nitro.

3. A chemical compound according to claim 2 wherein the



moiety is substituted on either the 5 or 6 position of the benzotriazole ring.

4. A chemical compound according to claim 3 wherein R is hydrogen; R^1 is hydrogen, C_{1-6}alkyl, phenyl or substituted phenyl; and R^2 is hydrogen; C_{3-7}cycloalkyl; bicyclo[2.2.1]heptan-2-yl; 2,3-dihydro-1H-indenyl; 1,2,3,4-tetrahydronaphthalenyl; C_{1-6}alkyl optionally substituted with phenyl, substituted phenyl or C_{3-7}cycloalkyl; or C_{1-6}alkyloxy optionally substituted with phenoxy, phenylthio, C_{3-7}cycloalkyl, phenyl or substituted phenyl.

5. A chemical compound according to claim 1 wherein the compound is 6-[(1H-imidazol-1-yl)-phenylmethyl]-1-methyl-1H-benzotriazole or 6-[(4-chlorophenyl)(1H-1,2,4-triazol-1-yl)methyl]-1-methyl-1H-benzotriazole.

6. A pharmaceutical composition comprising a suitable pharmaceutical carrier and as active ingredient a therapeutically effective amount of a compound as claimed in any one of claims 1 to 5.

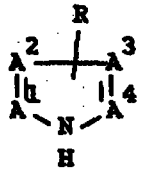
7. An estrogene hormone biosynthesis inhibitory pharmaceutical composition comprising a suitable pharmaceutical carrier and as active ingredient an estrogene hormone biosynthesis inhibitory effective amount of a compound as claimed in any one of claims 1 to 5.

8. A method of preparing a pharmaceutical composition according to claim 6 or 7, characterized in that a therapeutically effective amount of a compound as defined in any of claims 1 to 5 is intimately mixed with suitable pharmaceutical carriers.

9. A compound as claimed in any one of claims 1 to 5 for use as a medicine.

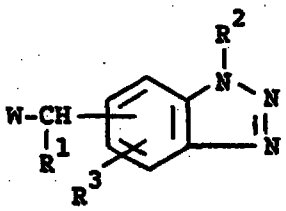
10. A compound as claimed in any one of claims 1 to 5 for use as an estrogene hormone biosynthesis inhibitory medicine.

11. A process for preparing a chemical compound as claimed in any one of claims 1 to 5, characterized by
I.a) N-alkylating an azole of formula



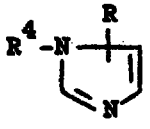
(III)

or an alkali metal salt thereof, with a benzotriazole of formula



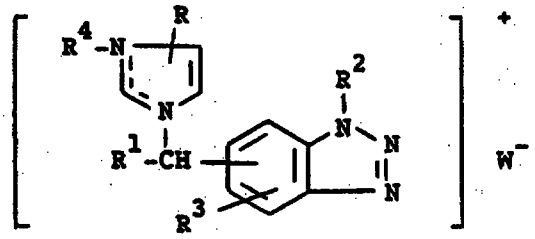
(II)

wherein W represents a reactive leaving group, in a readction-inert medium;
b) N-alkylating a 1-protected imidazole of formula



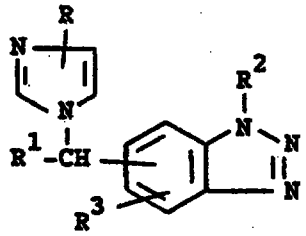
(III-a)

wherein R^4 represents a protective group, with a benzotriazole of formula (II) in a reaction-inert medium, said reaction proceeding in some instances via an intermediate of formula



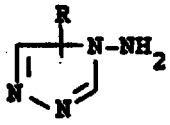
(IV)

wherein W^- is an anion arising from an acid, which may in situ, or if desired, after isolating and further purifying it, be converted to yield a compound of formula



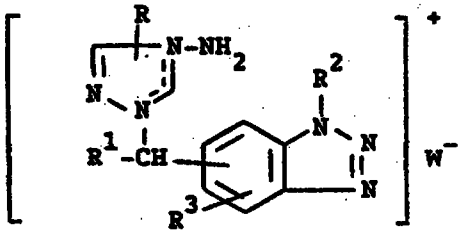
(I-a-1)

c) N-alkylating a triazolamine of formula



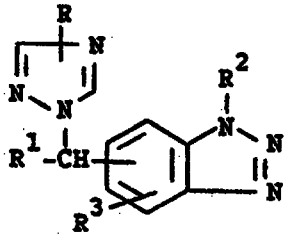
(III-b)

with a benzotriazole of formula (II), in a reaction-inert medium, and subsequently deaminating the thus prepared triazolium salt of formula



(V)

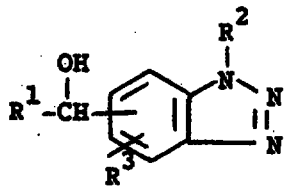
wherein W^- is an anion arising from an acid, in an acidic nitrite solution to yield a compound of formula



(I-a-2)

* C L M S *

II. reacting a benzotriazole of formula



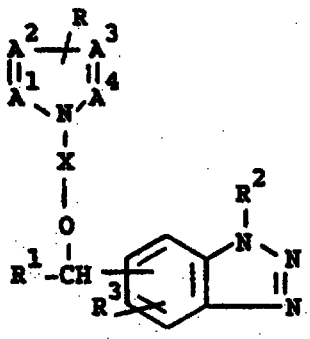
(VI)

with a reagent of formula



(VII)

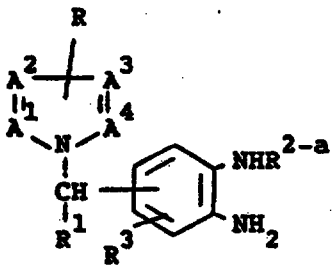
wherein X represents $>C=O$, S or $>S=O$, in a reaction-inert medium, said reaction proceeding in some instances via an intermediate of formula



(VIII)

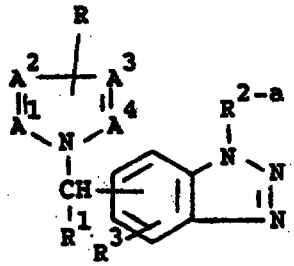
which may in situ, or if desired, after isolating and further purifying it, be converted to yield a compound of formula (I);

III. cyclizing a diamine of formula



(IX)

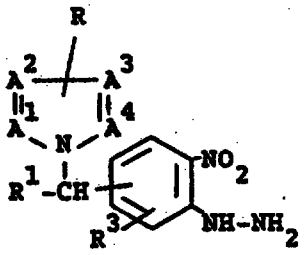
in an acidic nitrite solution, thus preparing a compound of formula



(I-b)

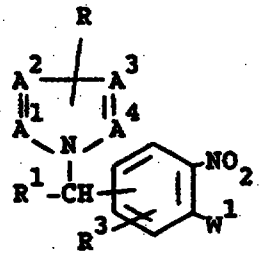
wherein R^{2-a} is hydrogen; C_{1-10}alkyl optionally substituted with Ar^1, C_{3-7}cycloalkyl, hydroxy or C_{1-6}alkyloxy; Ar^1; C_{2-6}alkenyl; C_{2-6}alkynyl; C_{3-7}cycloalkyl; bicyclo[2.2.1]-heptan-2-yl; 2,3-dihydro-1H-indenyl; or 1,2,3,4-tetrahydronaphthalenyl;

IV. cyclizing an intermediate of formula



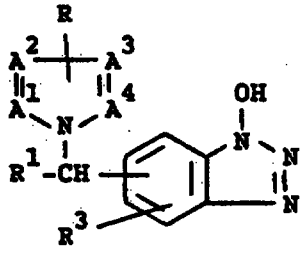
(X)

which in situ may be prepared by N-alkylating an intermediate of formula



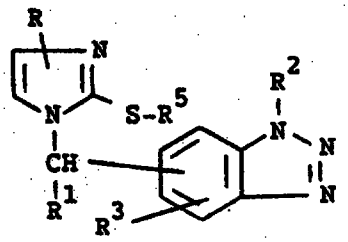
(XI),

wherein W^1 represents a reactive leaving group, with hydrazine (XII) of a hydrate thereof, in a reaction-inert solvent, thus preparing a compound of formula



(I-c-1);

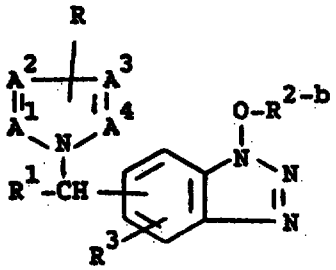
V. desulfurating an intermediate of formula



(XV)

wherein R^5 is C_{1-6}alkyl, in a reaction-inert medium, thus preparing a compound of formula (I-a-1); or

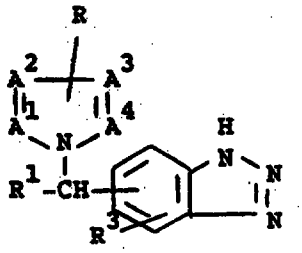
VI.a) O-alkylating a compound of formula (I-c-1) with a reagent of formula W-R^{2-b} (XIII), wherein W represents a reactive leaving group, in a reactive-inert solvent, thus preparing a compound of formula



(I-c-2)

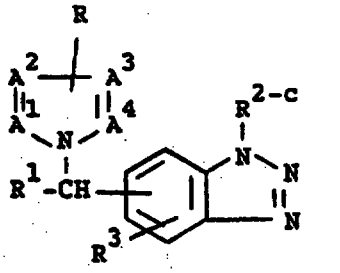
wherein -O-R^{2-b} is optionally substituted C_{1-10}alkyloxy, optionally substituted C_{2-6}alkenyloxy, C_{2-6}alkynyloxy, pyrimidinyloxy, di(Ar^2)methoxy or (1-C_{1-4}alkyl-4-piperidinyl)oxy;

b) reducing a compound of formula (I-c-1) with an reductant in a reaction-inert solvent thus preparing a compound of formula



(I-b-1),

c) N-alkylating a compound of formula (I-b-1) with a reagent of formula W-R^{2-c}, (XIV), wherein W represents a reactive leaving group, in a reaction-inert solvent, thus preparing a compound of formula



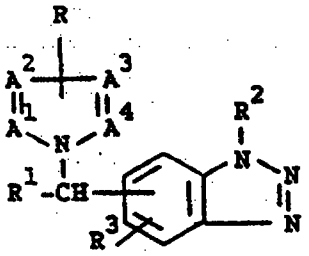
(I-b-2);

wherein R^{2-c} is the same as R^{2-a} provided that is other than hydrogen;

or optionally further converting the compounds of formula (I) into each other following art-known grouptransformation procedures, and, if desired, converting the compounds of formula (I) into a therapeutically active non-toxic acid-addition salt form by treatment with an appropriate acid or, conversely, converting the acid-addition salt into the free base form with alkali; and/or preparing stereochemically isomeric forms thereof.

Patentansprüche

1. Chemische Verbindung mit der Formel



(I),

ein pharmazeutisch annehmbares Säureadditionssalz oder eine stereochemisch isomere Form hievon, worin

$A^1 = A^2\text{-}A^3 = A^4$ ein zweiwertiger Rest mit der Formel

-CH = N-CH = CH- (a-1),

-CH = N-CH = N- (a-2) oder

-CH = N-N = CH- (a-3)

ist;

R für Wasserstoff oder C_{1-6}-Alkyl steht;

R^1 Wasserstoff, C_{1-10}-Alkyl, C_{3-7}-Cycloalkyl, Ar^1, Ar^2-C_{1-6}-Alkyl, C_{2-6}-Alkenyl oder C_{2-6}-Alkinyl darstellt;

R^2 für Wasserstoff; gegebenenfalls durch Ar^1, C_{3-7}-Cycloalkyl, Hydroxy oder C_{1-6}-Alkyloxy substituiertes C_{1-10}-Alkyl; Ar^1; C_{2-6}-Alkenyl; C_{2-6}-Alkinyl; C_{3-7}-Cycloalkyl; Bicyclo[2.2.1]heptan-2-yl; 2,3-Dihydro-1H-indenyl; 1,2,3,4-Tetrahydronaphthalinyl; Hydroxy; gegebenenfalls durch Ar^2 substituiertes C_{2-6}-Alkenyloyy; C_{2-6}-Alkinyloyy; Pyrimidinyloxy; Di(Ar^2)methoxy; (1-C_{1-4}-Alkyl-4-piperidinyl)oxy; oder gegebenenfalls durch Halogen, Hydroxy, C_{1-6}-Alkyloxy, Amino, Mono- und Di(C_{1-6}-alkyl)amino, Trifluormethyl, Carboxyl, C_{1-6}-Alkyloxycarbonyl, Ar^1, Ar^2-O-, Ar^2-S-, C_{3-7}-Cycloalkyl, 2,3-Dihydro-1,4-benzodioxinyl, 1H-Benzimidazolyl, C_{1-4}-Alkyl-substituiertes 1H-Benzimidazolyl, (1,1'-Biphenyl)-4-yl oder durch 2,3-Dihydro-2-oxo-1H-benzimidazolyl substituiertes C_{1-10}-Alkyloxy steht;

R^3 Wasserstoff, Nitro, Amino, Mono- und Di(C_{1-6}-alkyl)amino, Halogen, C_{1-6}-Alkyl, Hydroxy oder C_{1-6}-Alkyloxy darstellt;

worin Ar^1 Phenyl, substituiertes Phenyl, Naphthalinyl, Pyridinyl, Aminopyridinyl, Imidazolyl, Triazolyl, Thienyl, Halogenthienyl, Furanyl, C_{1-6}-Alkylfuranyl, Halogenfuranyl oder Thiazolyl bedeutet; und

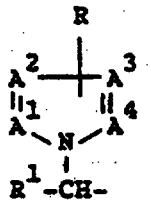
Ar^2 für Phenyl, substituiertes Phenyl oder Pyridinyl steht, worin das erwähnte substituierte Phenyl ein durch bis zu drei Substituenten substituiertes Phenyl ist, welche Substituenten jeweils unabhängig voneinander unter Halogen, Hydroxy, Hydroxymethyl, Trifluormethyl, C_{1-6}-Alkyl, C_{1-6}-Alkyloxy, C_{1-6}-Alkyloxycarbonyl, Carboxyl, Formyl, (Hydroxyimino)methyl, Cyano, Amino, Mono- und Di(C_{1-6}-alkyl)-amino und Nitro ausgewählt sind.

2. Chemische Verbindung nach Anspruch 1, worin R für Wasserstoff oder C_{1-4}-Alkyl steht; R^1 Wasserstoff; gegebenenfalls durch Phenyl oder substituiertes Phenyl substituiertes C_{1-6}-Alkyl; C_{3-7}-Cycloalkyl; Phenyl; substituiertes Phenyl; Pyridinyl; Naphthalinyl; Thienyl; Furanyl; Imidazolyl; Triazolyl; C_{2-6}-Alkenyl oder C_{2-6}-Alkinyl ist; R^2 für Wasserstoff; gegebenenfalls durch Phenyl substituiertes Phenyl, Naphthalinyl, Thienyl, Furanyl, C_{1-4}-Alkylfuranyl, C_{3-7}-Cycloalkyl, Hydroxy oder C_{1-4}-Alkyloxy substi-

* C L M S *

tuiertes C_{1-6}-Alkyl; Phenyl; substituiertes Phenyl; C_{2-6}-Alkenyl; C_{2-6}-Alkinyl; C_{3-7}-Cycloalkyl; Bicyclo-[2.2.1]heptan-2-yl; 2,3-Dihydro-1H-indenyl; 1,2,3,4-Tetrahydronaphthalinyl; Hydroxy; gegebenenfalls durch Phenyl substituiertes C_{2-6}-Alkenyloxy; C_{2-6}-Alkinyloxy; Pyrimidinyloxy; Di(phenyl)methoxy; (1-C_{1-4}-Alkyl-4-piperidinyl)oxy; oder gegebenenfalls durch Halogen, Hydroxy, Amino, Mono- und Di(C_{1-4}-alkyl)amino, Trifluormethyl, Carboxyl, C_{1-6}-Alkyloxycarbonyl, Phenyl, substituiertes Phenyl, Thienyl, Furanyl, Pyridinyl, Phenoxy, Phenylthio, C_{3-7}-Cycloalkyl, 2,3-Dihydro-1,4-benzodioxinyl, 1H-Benzimidazolyl, C_{1-4}-Alkyl-substituiertes 1H-Benzimidazolyl, (1,1'-Biphenyl)-4-yl oder 2,3-Dihydro-2-oxo-1H-benzimidazolyl substituiertes C_{1-6}-Alkyloxy steht; und R^3 Wasserstoff oder Nitro ist.

3. Chemische Verbindung nach Anspruch 2, worin der Rest



an der 5- oder 6-Stellung des Benzotriazolringes als Substituent vorliegt.

4. Chemische Verbindung nach Anspruch 3, worin R Wasserstoff ist; R^1 für Wasserstoff, C_{1-6}-Alkyl, Phenyl oder substituiertes Phenyl steht; und R^2 Wasserstoff; C_{3-7}-Cycloalkyl; Bicyclo[2.2.1]heptan-2-yl; 2,3-Dihydro-1H-indenyl; 1,2,3,4-Tetrahydronaphthalinyl; gegebenenfalls durch Phenyl, substituiertes Phenyl oder C_{3-7}-Cycloalkyl substituiertes C_{1-6}-Alkyl; oder gegebenenfalls durch Phenoxy, Phenylthio, C_{3-7}-Cycloalkyl, Phenyl oder substituiertes Phenyl substituiertes C_{1-6}-Alkyloxy darstellt.

5. Chemische Verbindung nach Anspruch 1, worin die Verbindung 6-[(1H-Imidazol-1-yl)phenylmethyl]-1-methyl-1H-benzotriazol oder 6-[(4-Chlorphenyl) (1H-1,2,4-triazol-1-yl)methyl]-1-methyl-1H-benzotriazol ist.

6. Pharmazeutische Zusammensetzung, umfassend einen geeigneten pharmazeutischen Träger und, als wirksamen Bestandteil, eine therapeutisch wirksame Menge einer Verbindung nach einem der Ansprüche 1 bis 5.

7. Eine die Östrogenhormon-Biosynthese inhibierende pharmazeutische Zusammensetzung, umfassend einen geeigneten pharmazeutischen Träger und, als wirksamen Bestandteil, eine die Östrogenhormon-Biosynthese inhibierende wirksame Menge einer Verbindung nach einem der Ansprüche 1 bis 5.

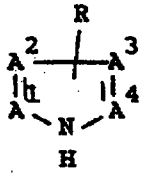
8. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung nach Anspruch 6 oder 7, dadurch gekennzeichnet, daß eine therapeutisch wirksame Menge einer Verbindung nach einem der Ansprüche 1 bis 5 innig mit geeigneten pharmazeutischen Trägern vermischt wird.

9. Verbindung nach einem der Ansprüche 1 bis 5 zur Anwendung als ein Medikament.

10. Verbindung nach einem der Ansprüche 1 bis 5 zur Anwendung als ein die Östrogenhormon-Biosynthese inhibierendes Medikament.

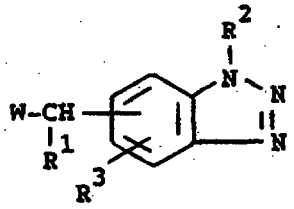
11. Verfahren zur Herstellung einer chemischen Verbindung nach einem der Ansprüche 1 bis 5, gekennzeichnet durch

I.a) N-Alkylieren eines Azols der Formel



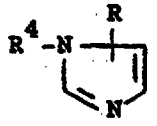
(III)

oder eines Alkalimetallsalzes hievon mit einem Benzotriazol der Formel



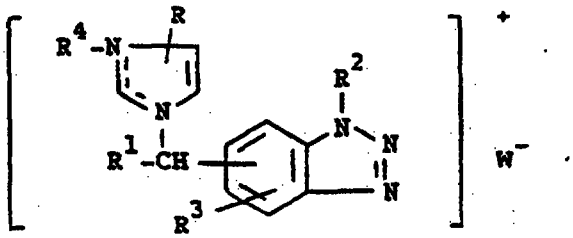
(II) ,

worin W eine reaktive Leaving-Gruppe darstellt, in einem reaktionsinerten Medium;
b) N-Alkylieren eines 1-geschützten Imidazols der Formel



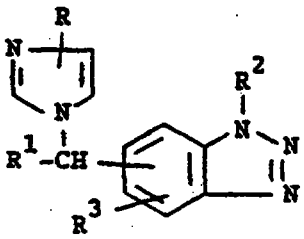
(III-a) ,

worin R^4 eine Schutzgruppe darstellt, mit einem Benzotriazol der Formel (II) in einem reaktionsinerten Medium, welche Reaktion in einigen Fällen über eine Zwischenverbindung der Formel



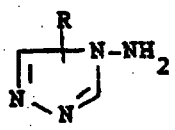
(IV)

verläuft, worin W^- ein aus einer Säure stammendes Anion ist, welche in situ oder gewünschtenfalls nach ihrer Isolierung und weiteren Reinigung umgewandelt werden kann, um eine Verbindung der Formel



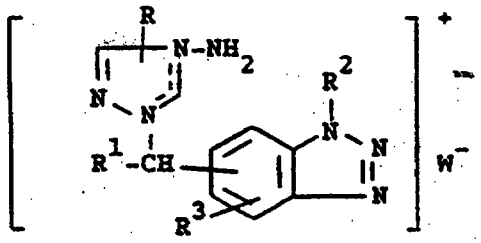
(I-a-1)

zu erhalten;
c) N-Alkylieren eines Triazolamins der Formel



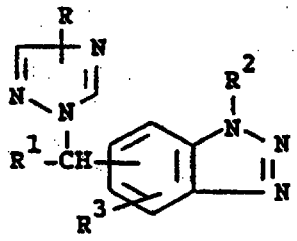
(III-b)

mit einem Benzotriazol der Formel (II) in einem reaktionsinerten Medium, und anschließendes Deaminieren des so hergestellten Triazoliumsalzes der Formel



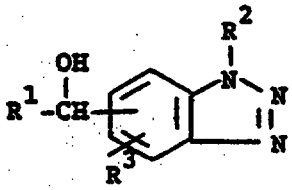
(V) ,

worin W^- ein von einer Säure stammendes Anion bedeutet, in einer sauren Nitritlösung unter Ausbildung einer Verbindung der Formel



(I-a-2) ;

II. Umsetzen eines Benzotriazols der Formel



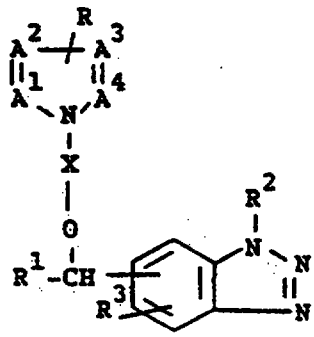
(VI)

mit einem Reagens der Formel



(VII) ,

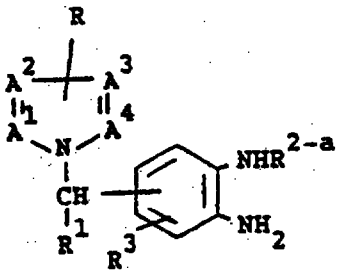
worin X für $>C=O$, S oder $>S=O$ steht, in einem reaktionsinerten Medium, welche Umsetzung in einigen Fällen über ein Zwischenprodukt der Formel



(VIII)

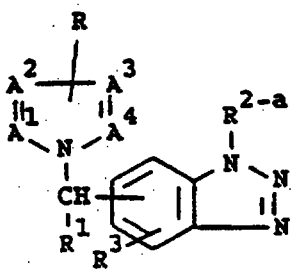
verläuft, das in situ oder gewünschtenfalls nach einem Isolieren und weiteren Reinigen zu einer

Verbindung der Formel (I) übergeführt werden kann;
III. Cyclisieren eines Diamins der Formel



(IX)

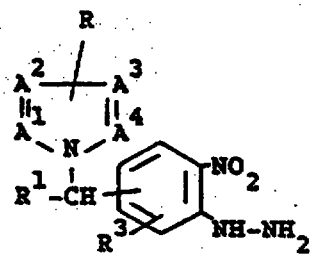
in einer sauren Nitritlösung unter Ausbildung einer Verbindung der Formel



(I-b),

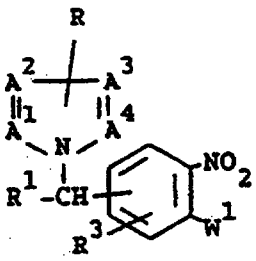
(I-b)

worin R^{2-a} für Wasserstoff; gegebenenfalls durch Ar^1, C_{3-7}-Cycloalkyl, Hydroxy oder C_{1-6}-Alkyloxy substituiertes C_{1-10}-Alkyl; Ar^1; C_{2-6}-Alkenyl; C_{2-6}-Alkinyl; C_{3-7}-Cycloalkyl; Bicyclo[2.2.1]heptan-2-yl; 2,3-Dihydro-1H-indenyl; oder 1,2,3,4-Tetrahydronaphthalinyl steht;
IV. Cyclisieren eines Zwischenprodukts der Formel



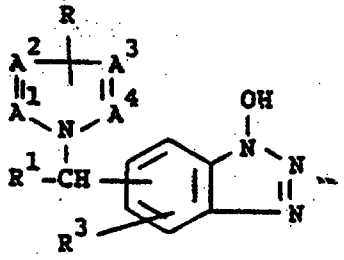
(X),

das in situ durch N-Alkylieren eines Zwischenprodukts der Formel



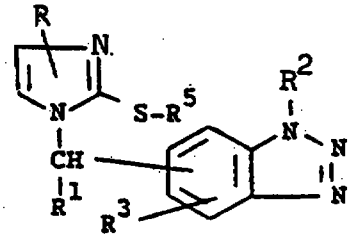
(XI),

worin W^1 eine reaktionsfähige Leaving-Gruppe bedeutet, mit Hydrazin (XII) oder einem Hydrat hievon ausgebildet werden kann, in einem reaktionsinerten Lösungsmittel unter Herstellung einer Verbindung der Formel



(I-c-1);

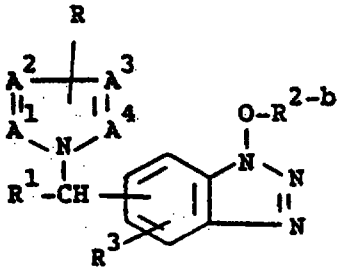
V. Desulfurieren eines Zwischenprodukts der Formel



(XV),

worin R^5 für C_{1-6}-Alkyl steht, in einem reaktionsinerten Medium unter Ausbildung einer Verbindung der Formel (I-a-1); oder

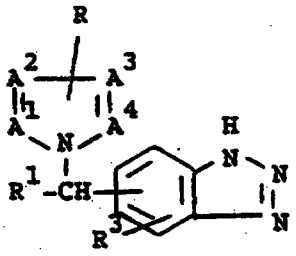
VI.a) O-Alkylieren einer Verbindung der Formel (I-c-1) mit einem Reagens der Formel $W\text{-}R^{2-b}$ (XIII), worin W eine reaktionsfähige Leaving-Gruppe bedeutet, in einem reaktionsinerten Lösungsmittel unter Ausbildung einer Verbindung der Formel



(I-c-2),

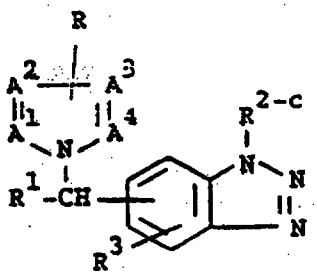
worin $-O\text{-}R^{2-b}$ gegebenenfalls substituiertes C_{1-10}-Alkyloxy, gegebenenfalls substituiertes C_{2-6}-Alkenyloxy, C_{2-6}-Alkinyloxy, Pyrimidinyloxy, Di(Ar^2)methoxy oder (1-C_{1-4}-Alkyl-4-piperidinyl)oxy bedeutet;

b) Reduzieren einer Verbindung der Formel (I-c-1) mit einem Reduktionsmittel in einem reaktionsinerten Lösungsmittel unter Ausbildung einer Verbindung der Formel



(I-b-1);

c) N-Alkylieren einer Verbindung der Formel (I-b-1) mit einem Reagens der Formel $W\text{-}R^{2-c}$ (XIV), worin W eine reaktionsfähige Leaving-Gruppe bezeichnet, in einem reaktionsinerten Lösungsmittel unter Ausbildung einer Verbindung der Formel



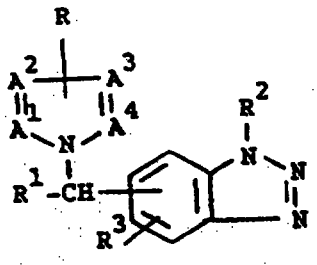
(I-b-2) ,

worin R^{2-c} die gleiche Bedeutung wie R^{2-a} hat, mit der Maßgabe, daß sie von Wasserstoff verschieden ist;

oder gewünschtenfalls weiter Umwandeln der Verbindungen der Formel (I) ineinander nach bekannten Gruppentransformationsverfahren und gewünschtenfalls Überführen der Verbindungen der Formel (I) in eine therapeutisch wirksame, nicht-toxische Säureadditionssalzform durch Behandlung mit einer entsprechenden Säure, oder umgekehrt Überführen des Säureadditionssalzes in die freie Basenform mit Alkali; und/oder Bereiten stereochemisch isomerer Formen hievon.

Revendications

1. Composé chimique ayant la formule



(I),

ou un sel d'addition avec un acide pharmaceutiquement acceptable ou une forme isomère stéréochimiquement de celui-ci, dans lesquels

$A^1 = A^2\text{-}A^3 = A^4$ est un radical bivalent de formule

-CH = N-CH = CH- (a-1),

-CH = N-CH = N- (a-2), ou

-CH = N-N = CH- (a-3);

R est l'hydrogène ou un groupe alkyle en C_{1-6};

R^1 est l'hydrogène ou un groupe alkyle en C_{1-10}, cycloalkyle en C_{3-7}, Ar^1, Ar^2-alkyle en C_{1-6}, alcényle en C_{2-6} ou alcynyle en C_{2-6};

R^2 est l'hydrogène ou un groupe alkyle en C_{1-10} éventuellement substitué par des groupes Ar^1, cycloalkyle en C_{3-7}, hydroxy ou alkyl(C_{1-6})oxy; Ar^1; alcényle en C_{2-6}; alcynyle en C_{2-6}; cycloalkyle en C_{3-7}; bicyclo[2.2.1]heptane-2-yle; 2,3-dihydro-1H-indenyle; 1,2,3,4-tétrahydronaphtalényle; hydroxy; alcényl(C_{2-6})oxy, éventuellement substitué par un groupe Ar^2; alcynyl(C_{2-6})oxy; pyrimidinyloxy; di-(Ar^2)méthoxy; (alkyl(C_{1-4})-4-pipéridinyl)oxy; ou alkyl(C_{1-10})oxy, éventuellement substitué par des groupes halogéno, hydroxy, alkyl(C_{1-6})oxy, amino, mono- et di(alkyl en C_{1-6})amino, trifluoro-méthyle, carboxyle, alkyl(C_{1-6})oxycarbonyle, Ar^1, Ar^2-O-, Ar^2-S-, cycloalkyle en C_{3-7}, 2,3-dihydro-1,4-benzodioxinyle, 1H-benzimidazolyle,1H-benzimidazolyle substitué par des groupes alkyle en C_{1-4}, (1,1'-biphényl)-4-yle ou par un groupe 2,3-dihydro-2-oxo-1H-benzimidazolyle;

R^3 est l'hydrogène ou un groupe nitro, amino, mono- ou di(alkyl en C_{1-6})amino, halogéno, alkyle en C_{1-6}, hydroxy ou alkyl(C_{1-6})oxy;

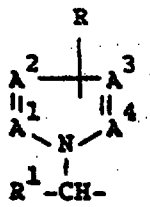
où Ar^1 est un groupe phényle, phényle substitué, naphtalényle, pyridinyle, aminopyridinyle, imidazolyle, triazolyle, thiényle, halogénothiényle, furannyle, alkyl(C_{1-6})furannyle, halogénofurannyle ou thia-

zolyle; et

Ar^2 est un groupe phényle, phényle substitué ou pyridinyle, ledit groupe phényle substitué étant un groupe phényle substitué par jusqu'à 3 substituants choisis, chacun indépendamment l'un de l'autre, parmi les groupes halogéno, hydroxy, hydroxyméthyle, trifluorométhyle, alkyle en C_{1-6}, alkyl(C_{1-6})oxy, alkyl(C_{1-6})oxycarbonyle, carboxyle, formyle, (hydroxyimino)méthyle, cyano, amino, mono- et di(alkyl en C_{1-6})amino et nitro.

2. Composé chimique selon la revendication 1, dans lequel R est l'hydrogène ou un groupe alkyle en C_{1-4}; R^1 est l'hydrogène ou un groupe alkyle en C_{1-6} éventuellement substitué par des groupes phényle ou phényle substitué; cycloalkyle en C_{3-7}; phényle; phényle substitué; pyridinyle; naphtalényle; thiényle; furannyle; imidazolyle; triazolyle; alcényle en C_{2-6} ou alcynyle en C_{2-6}; R^2 est l'hydrogène ou un groupe alkyle en C_{1-6} éventuellement substitué par un groupe phényle, phényle substitué, naphtalényle, thiényle, furannyle; alkylfurannyle en C_{1-4}, cycloalkyle en C_{3-7}, hydroxy ou alkyl(C_{1-4})-oxy; phényle; phényle substitué; alcényle en C_{2-6}; alcynyle en C_{2-6}; cycloalkyle en C_{3-7}; bicyclo-[2.2.1]heptan-2-yl; 2,3-dihydro-1H-indényle; 1,2,3,4-tétrahydronaphtalényle; hydroxy; alcényl(C_{2-6})oxy éventuellement substitué par un groupe phényle; alcynyl(C_{2-6})oxy; pyrimidinyloxy; di(phényl)méthoxy; (1-alkyl(C_{1-4})-4-pipéridinyl)oxy; ou alkyl(C_{1-6})oxy éventuellement substitué par des groupes halogéno, hydroxy, amino, mono- et di(alkyl en C_{1-4})amino, trifluorométhyle, carboxyle, alkyl(C_{1-6})oxycarbonyle, phényle, phényle substitué, thiényle, furannyle, pyridinyle, phénoxy, phénylthio, cycloalkyle en C_{3-7}, 2,3-dihydro-1,4-benzodioxinnyle, 1H-benzimidazolyle, alkyle en C_{1-4} substitué par un groupe 1H-benzimidazolyle, (1,1'-biphényl)-4-yle, ou 2,3-dihydro-2-oxo-1H-benzimidazolyle; et R^3 est l'hydrogène ou un groupe nitro.

3. Composé chimique selon la revendication 2, dans lequel la fraction



est substituée sur l'une des positions 5 ou 6 du cycle benzotriazole.

4. Composé chimique selon la revendication 3, dans lequel R est l'hydrogène; R^1 est l'hydrogène ou un groupe alkyle en C_{1-6}, phényle ou phényle substitué; et R^2 est l'hydrogène ou un groupe cycloalkyle en C_{3-7}; bicyclo-[2.2.1]heptane-2-yl; 2,3-dihydro-1H-indényle; 1,2,3,4-tétrahydronaphtalényle; alkyl en C_{1-6} éventuellement substitué par un groupe phényle, phényle substitué ou cycloalkyle en C_{3-7}; ou alkyl(C_{1-6})oxy éventuellement substitué par un groupe phénoxy, phénylthio, cycloalkyle en C_{3-7}, phényle ou phényle substitué.

5. Composé chimique selon la revendication 1, dans lequel le composé est le 6-[(1H-imidazole-1-yl)-phénylméthyl]-1-méthyl-1H-benzotriazole ou le 6-[(4-chlorophényl)(1H-1,2,4-triazole-1-yl)méthyl]-1-méthyl-1H-benzotriazole.

6. Composition pharmaceutique comprenant un support pharmaceutique approprié et comme constituant actif une quantité thérapeutiquement efficace d'un composé selon l'une quelconque des revendications 1 à 5.

7. Composition pharmaceutique pour l'inhibition de la biosynthèse d'hormones oestrogènes comprenant un support pharmaceutique approprié et comme constituant actif une quantité efficace pour l'inhibition de la biosynthèse des hormones oestrogènes d'un composé selon l'une quelconque des revendications 1 à 5.

8. Procédé pour la préparation d'une composition pharmaceutique selon l'une des revendications 6 ou 7, caractérisé en ce qu'une quantité thérapeutiquement efficace d'un composé selon l'une quelconque

* C L M S *

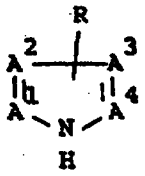
des revendications 1 à 5 est intimement mélangée avec des supports pharmaceutiques appropriés.

9. Composé selon l'une quelconque des revendications 1 à 5 pour une utilisation comme médicament.

10. Composé selon l'une quelconque des revendications 1 à 5 pour une utilisation comme médicament pour l'inhibition de la biosynthèse des hormones oestrogènes.

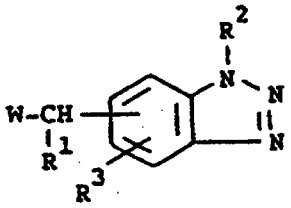
11. Procédé pour la préparation d'un composé chimique selon l'une quelconque des revendications 1 à 5, caractérisé en ce qu'il comprend

I.a) la N-alkylation d'un azole de formule



(III)

ou d'un sel de métal alcalin de celui-ci, avec un benzotriazole de formule



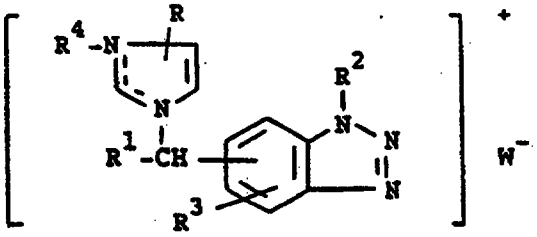
(II)

où W représente un groupe éliminable réactif, dans un milieu inerte vis-à-vis de la réaction;
b) la N-alkylation d'un imidazole protégé en 1 de formule



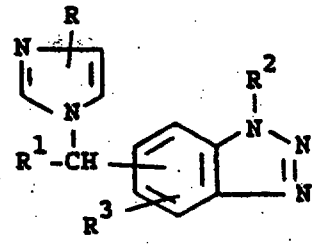
(III-a)

où R^4 représente un groupe protecteur, avec un benzotriazole de formule (II) dans un milieu inerte vis-à-vis de la réaction, ladite réaction se déroulant dans certains cas via un intermédiaire de formule



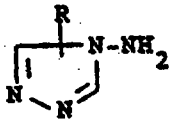
(IV)

où W^- est un anion provenant d'un acide, qui peut in situ, ou si on le souhaite après isolement et ensuite purification, être converti pour donner un composé de formule



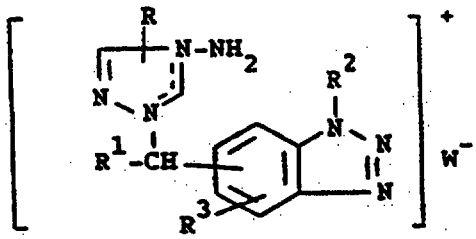
(I-a-1)

c) la N-alkylation d'une triazolamine de formule



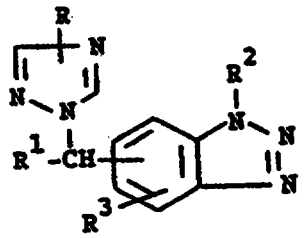
(III-b)

avec un benzotriazole de formule (II), dans un milieu inerte vis-à-vis de la réaction, et ensuite la désamination du sel de triazolium ainsi préparé de formule



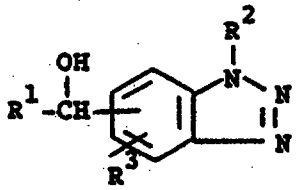
(V)

où W^- est un anion provenant d'un acide, dans une solution de nitrite acide pour donner un composé de formule



(I-a-2)

II. la réaction d'un benzotriazole de formule



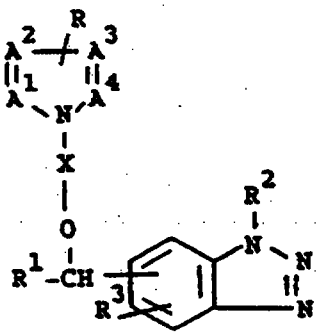
(VI)

avec un corps réagissant de formule



(VII)

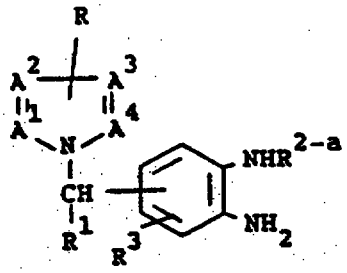
où X représente $>C=O$, S ou $>S=O$, dans un milieu inerte vis-à-vis de la réaction, ladite réaction se déroulant dans certains cas via un intermédiaire de formule



(VIII)

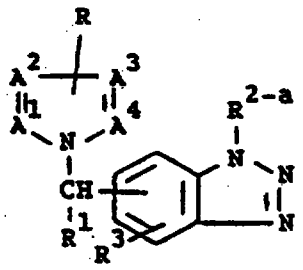
qui peut in situ, ou si on le souhaite après isolement et ensuite purifi-cation, être converti pour donner un composé de formule (I);

III. la cyclisation d'une diamine de formule



(IX)

dans une solution de nitrite acide, préparant ainsi un composé de formule

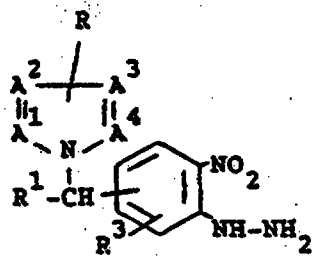


(I-b)

(I-b)

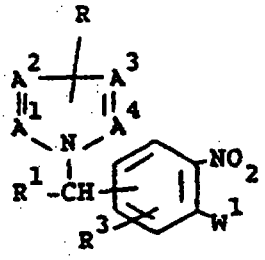
où R^{2-a} est l'hydrogène ou un groupe alkyle en C_{1-10} éventuellement substitué par des groupes Ar^1, cycloalkyle en C_{3-7}, hydroxy ou alkyl(C_{1-6})oxy; Ar^1; alcényle en C_{2-6}; alcynyle en C_{2-6}; cycloalkyle en C_{3-7}; bicyclo[2.2.1]-heptane-2-yle; 2,3-dihydro-1H-indényle; ou 1,2,3,4-tétrahydro-naphténylé;

IV. la cyclisation d'un intermédiaire de formule



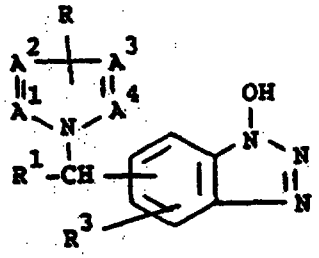
(X)

qui in situ peut être préparé par N-alkylation d'un intermédiaire de formule



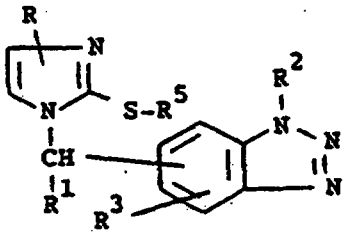
(XI),

où W^1 représente un groupe éliminable réactif, avec de l'hydrazine (XII) ou un hydrate de celle-ci, dans un solvant inerte vis-à-vis de la réaction, préparant ainsi un composé de formule



(I-c-1);

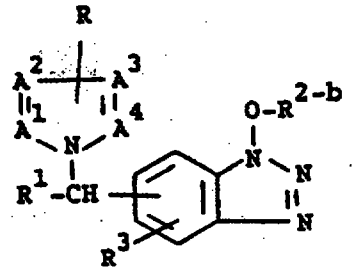
V. la désulfuration d'un intermédiaire de formule



(XV)

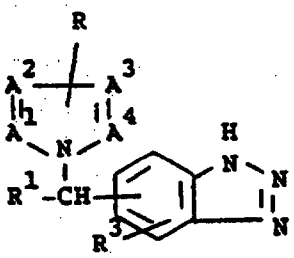
où R^5 est un groupe alkyle en C_{1-6}, dans un milieu inerte vis-à-vis de la réaction, préparaant ainsi un composé de formule (I-a-1); ou

VI.a) la O-alkylation d'un composé de formule (I-c-1) avec un corps réagissant de formule $W\text{-}R^{2-b}$ - (XIII), où W représente un groupe éliminable réactif, dans un solvant inerte vis-à-vis de la réaction, préparant ainsi un composé de formule



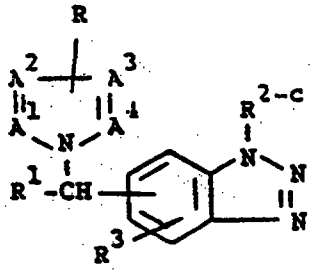
(I-c-2)

où $-O-R^{2-b}$ est un groupe alkyl(C_{1-10})oxy éventuellement substitué, alcényl(C_{2-6})oxy éventuellement substitué, alcynyl(C_{2-6})oxy, pyrimidinyloxy, di(Ar^2)méthoxy ou (1-alkyl(C_{1-4})-4-pipéridinyl)oxy;
b) la réduction d'un composé (I-c-1) avec un réducteur dans un solvant inerte vis-à-vis de la réaction, préparant ainsi un composé de formule



(I-b-1),

c) la N-alkylation d'un composé de formule (I-b-1) avec un réactif de formule WR^{2-c}, (XIV), où W représente un groupe éliminable réactif, dans un solvant inerte vis-à-vis de la réaction, préparant ainsi un composé de formule



(I-b-2);

où R^{2-c} est le même que R^{2-a}, à condition qu'il ne soit pas de l'hydrogène;
ou en option en outre la conversion mutuelle des composés de formule (I) selon des techniques connues de l'homme du métier, et, si on le désire, la conversion des composés de formule (I) en une forme sel d'addition avec un acide non-toxique thérapeutiquement actif par traitement avec un acide approprié ou, à l'inverse, la conversion du sel d'addition avec un acide en la formebase libre avec un alcali; et/ou la préparation de leurs formes stéréochimiquement isomères.