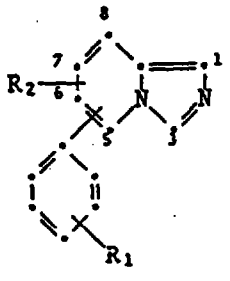
The use of substances that inhibit the enzyme aromatase as medicaments is known. The object of so doing is to suppress oestrogen production in the body and thus have a beneficial effect on oestrogen-dependent diseases, for example breast cancer. There are known up to now both steroidal aromatase inhibitors [see, for example, A.M.H. Brodie et al., Endocrinology 104, 118 (1979)] and also individual non-steroidal aromatase inhibitors, especially aminoglutethimide and derivatives thereof [see, for example, A.M. Camacho et al., J. Am. Med. Assoc. 202, 20 (1967); A.B. Foster et al., J. Med. Chem. 26, 50 (1983) or EP-A-114 033].

Certain 5-(substituted phenyl)-imidazo[1,5-a]pyridines and 5,6,7,8-tetrahydro derivatives thereof, which have an inhibiting effect on thromboxane synthetase, are furthermore known from EP-A-114 573.

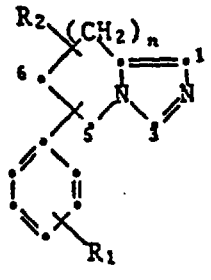
The invention relates to the use of substituted imidazo-[1,5-a]pyridine derivatives of formula I



(I)

wherein R_1 represents hydrogen, lower alkyl; lower alkyl substituted by hydroxy, lower alkoxy, lower alkanoyloxy, lower alkanoyl, amino, lower alkylamino, di-lower alkylamino, halogen, sulfo, carboxy, lower alkoxy-carbonyl, carbamoyl or cyano; nitro, halogen, hydroxy, lower alkoxy, lower alkanoyloxy, phenylsulfonyloxy, lower alkylsulfonyloxy, mercapto, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, lower alkanoylthio, amino, lower alkylamino, di-lower alkylamino, lower

alkyleneamino, N-morpholino, N-thiomorpholino, optionally 4-lower alkyl-substituted N-piperazino, tri-lower alkylammonio, sulfo, lower alkoxysulfonyl, sulfamoyl, lower alkylsulfamoyl, di-lower alkylsulfamoyl, formyl; iminomethyl optionally N-substituted by hydroxy, lower alkoxy, lower alkanoyloxy, lower alkyl, phenyl or amino; C_2-C_7alkanoyl, benzoyl, carboxy, lower alkoxycarbonyl, carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl, cyano, 5-tetrazolyl, optionally lower alkyl-substituted 4,5-dihydro-2-oxazolyl or hydroxycarbamoyl; and R_2 represents hydrogen, lower alkyl, phenyl-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, halogen, hydroxy, lower alkoxy, lower alkanoyloxy, mercapto, lower alkylthio, phenyl-lower alkylthio, phenylthio, lower alkanoylthio, carboxy, lower alkoxycarbonyl or lower alkanoyl; of the 7,8-dihydro derivatives thereof; or of compounds of formula I*



(I*)

wherein n denotes 0, 1, 2, 3 or 4; and R_1 and R_2 are as defined above under formula I; it being possible for the phenyl ring within the radicals phenylsulfonyloxy, phenyliminomethyl, benzoyl, phenyl-lower alkyl, phenyl-lower alkylthio and phenylthio to be unsubstituted or substituted by lower alkyl, lower alkoxy or halogen; and in a compound of formula I* it being possible for the two substituents C_6H_4-R_1 and R_2 to be attached to any of the saturated carbon atoms of the saturated ring, either both to the same carbon atom or to different carbon atoms; radicals designated "lower" containing up to 7 carbon atoms; of stereoisomers, mixtures of these stereoisomers,

or of pharmaceutically acceptable salts thereof for the manufacture of pharmaceutical compositions for the treatment of diseases responsive to aromatase inhibition.

The invention further relates to pharmaceutical compositions containing such compounds, to novel compounds of this kind, processes for the manufacture of the latter, pharmaceutical compositions containing the latter and the use of the latter as pharmaceutical active ingredients or for the manufacture of pharmaceutical compositions.

Organic radicals designated by the term "lower" usually contain up to and including 7, and preferably up to and including 4, carbon atoms.

The compounds of formula I* and certain 7,8-dihydro derivatives of formula I contain at least one asymmetric carbon atom. They can be found as R- or S-enantiomers and as enantiomeric mixtures thereof, such as a racemate. The present invention includes all these forms and also all those further isomers, and mixtures of at least two isomers, for example diastereoisomeric mixtures or enantiomeric mixtures, that may exist if one or more further centres of asymmetry are present within the molecule.

Lower alkyl is, for example, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or tert-butyl, also n-pentyl, isopentyl, neopentyl, n-hexyl, isohexyl or n-heptyl, but preferably ethyl and especially methyl.

Halogen is, for example, bromine or iodine, preferably fluorine and especially chlorine.

In an aza-lower alkyleneamino radical, the aza-nitrogen atom is optionally substituted, for example by lower

alkyl. Examples of oxa-, thia- or aza-lower alkylene-amino are N-morpholino, N-thiomorpholino or optionally 4-lower alkyl-substituted N-piperazino.

Tri-lower alkylammonio comprises, for example, quaternary ammonium salts derived from di-lower alkylamino groups and containing as quaternary substituent lower alkyl. Tri-lower alkylammonio is, for example, trimethylammonio. The ammonium salts correspond to the salts defined hereinafter, especially the salts mentioned as being pharmaceutically acceptable, non-toxic acid addition salts, and more especially to those salts formed with hydrohalic acids, sulfuric acid or phosphoric acid.

Sulfo is a $-SO_3H$ group.

Iminomethyl is a -CH=NH group.

C_1Alkanoyl corresponds to formyl.

Lower alkoxy is preferably methoxy or ethoxy, also, for example, n-propoxy, isopropoxy, n-butoxy, isobutoxy or tert-butoxy.

Lower alkanoyloxy is, for example, formyloxy, acetoxy, propionyloxy or pivaloyloxy.

Lower alkanoyl is, for example, formyl, acetyl, propionyl or pivaloyl. Halo-C_2-C_7alkanoyl is preferably trifluoroacetyl. Lower alkanoylamino is preferably acetylamino or propionylamino, but may also be, for example, formylamino.

Lower alkoxycarbonyl is preferably methoxycarbonyl or ethoxycarbonyl. Lower alkoxycarbonyloxy is, for example, methoxycarbonyloxy or ethoxycarbonyloxy.

Lower alkylamino is, for example, methylamino, ethylamino, n-propylamino or isopropylamino. Di-lower alkylamino is, for example, dimethylamino, ethylmethylamino or diethylamino. Lower alkyleneamino contains, for example, from 2 to 7, preferably 4 to 6, ring carbon atoms and is, for example, N-pyrrolidino or N-piperidino.

Lower alkylthio is, for example, methylthio, ethylthio, n-propylthio or isopropylthio, while lower alkylsulfinyl is, for example, methylsulfinyl, and lower alkylsulfonyl is, for example, methylsulfonyl or ethylsulfonyl. Lower alkanoylthio is preferably formylthio or acetylthio.

Lower alkoxysulfonyl is, for example, methoxysulfonyl or ethoxysulfonyl. Lower alkylsulfamoyl is, for example, N-methyl- or N-ethyl-sulfamoyl, while di-lower alkylsulfamoyl is, for example, dimethyl- or diethylsulfamoyl.

Lower alkylcarbamoyl is, for example, N-methylcarbamoyl or N-ethylcarbamoyl, while di-lower alkylcarbamoyl is, for example, dimethyl- or diethyl-carbamoyl.

The compounds of the invention form acid addition salts. These are preferably formed with those inorganic or organic acids that produce pharmaceutically acceptable acid addition salts. Such acids are, for example, strong mineral acids, such as hydrochloric acid, sulfuric acid or phosphoric acid, or organic acids, especially aliphatic or aromatic carboxylic or sulfonic acids, for example formic, acetic, propionic, succinic, glycolic, lactic, hydroxysuccinic, tartaric, citric, maleic, fumaric, hydroxymaleic, pyruvic, phenylacetic, benzoic, 4-aminobenzoic, anthranilic, 4-hydroxybenzoic, salicylic, 4-aminosalicylic, pamoic, gluconic, nicotinic, methane-

sulfonic, ethanesulfonic, halobenzenesulfonic, p-toluenesulfonic, naphthalenesulfonic, sulfanilic or cyclohexylsulfamic acid; or other acidic organic substances, for example ascorbic acid. Salts may also be formed, for example, with amino acids, such as arginine or lysine.

Compounds of the invention that contain acidic groups, for example a free carboxy or sulfo group, form especially metal or ammonium salts, such as alkali metal or alkaline earth metal salts, for example sodium, potassium, magnesium or calcium salts, and also ammonium salts which are derived from ammonia or suitable organic amines. There come into consideration especially aliphatic, cycloaliphatic, cycloaliphatic-aliphatic or araliphatic primary, secondary or tertiary mono-, di- or poly-amines, such as lower alkylamines, for example di- or tri-ethylamine, hydroxy-lower alkylamines, for example 2-hydroxyethylamine, bis(2-hydroxyethyl)amine or tris(2-hydroxyethyl)amine, basic aliphatic esters or carboxylic acids, for example 4-aminobenzoic acid 2-diethylaminoethyl ester, lower alkyleneamines, for example 1-ethylpiperidine, cycloalkylamines, for example dicyclohexylamine, benzylamines, for example N,N'-dibenzylethylenediamine; or heterocyclic bases, for example of the pyridine type, for example pyridine, collidine or quinoline.

When several acidic or basic groups are present, mono- or poly-salts may be formed. Compounds of the invention that have an acidic group and a basic group may also be in the form of internal salts, i.e. in zwitterionic form, or part of the molecule may be in the form of an internal salt and another part of the molecule may be in the form of a normal salt. The pharmaceutically acceptable salts mentioned above are preferred. For isolation or purification it is also possible to use pharmaceutically

unsuitable salts, for example the picrates.

The compounds of the invention have valuable pharmacological properties: for example, they inhibit aromatase in mammals, including humans. For example, these compounds inhibit the metabolic conversion of androgens to oestrogens. The compounds of formula I and I* are therefore useful, for example, in the treatment of gynaecomastia, i.e. male breast development, by inhibiting the aromatisation of the steroids in such males. Compounds of formulae I and I* are useful, for example, in the treatment of oestrogen-dependent diseases, including oestrogen-dependent breast cancer, especially in post-menopausal females, by inhibiting oestrogen synthesis. These effects are demonstrable by *in vitro* tests or *in vivo* animal tests, preferably using mammals, for example guinea pigs, mice, rats, cats, dogs or monkeys.

The *in vitro* inhibition of aromatase activity can be demonstrated, for example, by applying the method described in J. Biol. Chem. 249, 5364 (1974). Furthermore, IC_{50} values for aromatase inhibition can be obtained, for example, *in vitro* from enzyme kinetic studies concerning the inhibition of the conversion of 4-^{14}C-androstenedione to 4-^{14}C-oestrone in human placental microsomes. The IC_{50} values of the compounds of the invention are between about 10^{-6} and about 10^{-9} mol/l. *In vivo*, aromatase inhibition can be demonstrated, for example, by the suppression of the ovarian oestrogen content of female rats that are first injected with mare's serum gonadotrophin and two days later with human chorionic gonadotrophin, and treated p.o. the following day with a compound of the invention and 1 hour later with androstenedione. The minimum effective dose of the compounds of the invention is between about 0.01 and

about 10 mg/kg or less. The antitumour activity, especially in oestrogen-dependent tumours, can be demonstrated in vivo, for example, in DMBA-induced mammary tumours in female Sprague-Dawley rats. The use of compounds of the invention brings about almost total regression of the tumours and furthermore suppresses the occurrence of new tumours at daily doses of about 1 to about 20 mg/kg p.o. or less.

Surprisingly, the compounds of the invention, which act as effective aromatase inhibitors in vitro and in vivo, do not have an inhibiting effect on cholesterol side-chain cleavage in vivo, since they do not induce adrenal hypertrophy, as can be demonstrated by endocrine organ investigations.

On account of their pharmacological properties as aromatase inhibitors, the compounds of the invention can be used as medicaments, for example in the form of pharmaceutical compositions, for example for the treatment of hormonal diseases, such as oestrogen-dependent tumours, in specific mammary carcinoma, and anomalies, for example gynaecomastia, in warm-blooded animals including humans. The novel compounds are also valuable intermediates for the manufacture of other pharmaceutically active compounds.

The invention relates especially to the above-mentioned use of compounds of formula I wherein R_1 represents lower alkyl; lower alkyl substituted by hydroxy, amino, di-lower alkylamino, 1 to 5 fluorine atoms, carboxy, lower alkoxycarbonyl, carbamoyl or cyano; nitro, halogen, hydroxy, lower alkoxy, amino, lower alkylamino, di-lower alkylamino, sulfo, sulfamoyl, formyl, iminomethyl; iminomethyl N-substituted by hydroxy, lower alkoxy, lower alkanoyloxy, lower alkyl or phenyl; carboxy, lower

alkoxycarbonyl, carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl or cyano; and R_2 is hydrogen, lower alkyl, lower alkoxy or halogen; or of compounds of formula I* wherein n denotes 1, 2 or 3; R_1 is as defined above under formula I and R_2 represents hydrogen, lower alkyl, phenyl-lower alkyl, carboxy-lower alkyl, lower alkoxy-carbonyl-lower alkyl, halogen, lower alkoxy, lower alkylthio, phenyl-lower alkylthio, phenylthio, carboxy, lower alkoxycarbonyl or lower alkanoyl; in a compound of formula I* it being possible for the two substituents C_6H_4-R_1 and R_2 to be attached to any of the saturated carbon atoms of the saturated ring, either both to the same carbon atom or to different carbon atoms; of stereoisomers, mixtures of these stereoisomers, or of pharmaceutically acceptable salts thereof.

The invention relates more especially to the above-mentioned use of compounds of formula I wherein R_1 represents lower alkyl, hydroxy-lower alkyl, halogen, amino, formyl, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl or cyano; and R_2 is hydrogen; or of compounds of formula I* wherein n denotes 1, 2 or 3; R_1 is as defined above under formula I and R_2 represents hydrogen, lower alkylthio, lower alkoxycarbonyl, phenyl-lower alkyl, carboxy-lower alkyl or lower alkoxycarbonyl-lower alkyl; in a compound of formula I* it being possible for the two substituents C_6H_4-R_1 and R_2 to be attached to any of the saturated carbon atoms of the saturated ring, either both to the same carbon atom or to different carbon atoms; of stereoisomers, mixtures of these stereoisomers, or of pharmaceutically acceptable salts thereof.

The invention relates further to pharmaceutical compositions containing a compound of formula I wherein R_1 represents halogen, hydroxy, mercapto, or lower alkyl

substituted by lower alkoxy, lower alkanoyloxy or halogen; and R_2 is hydrogen, lower alkyl, lower alkoxy or halogen; or a compound of formula I* wherein n denotes 2, R_1 is as defined above under formula I and R_2 represents hydrogen, lower alkyl, phenyl-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, halogen, lower alkoxy, lower alkylthio, phenyl-lower alkylthio, phenylthio, carboxy, lower alkoxycarbonyl or lower alkanoyl; in a compound of formula I* it being possible for the two substituents C_6H_4-R_1 and R_2 to be attached to any of the saturated carbon atoms of the saturated ring, either both to the same carbon atom or to different carbon atoms; radicals designated "lower" containing up to 7 carbon atoms; a stereoisomer, a mixture of these stereoisomers or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable carriers.

The invention relates further to compounds of formula I wherein R_1 represents hydrogen, lower alkyl; C_2-C_7alkyl substituted by hydroxy, lower alkoxy, halogen or lower alkanoyloxy; lower alkyl substituted by lower alkanoyl, amino, lower alkylamino, di-lower alkylamino, sulfo, lower alkoxycarbonyl, carbamoyl or cyano; nitro, lower alkoxy, lower alkanoyloxy, phenylsulfonyloxy, lower alkylsulfonyloxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, lower alkanoylthio, amino, lower alkylamino, di-lower alkylamino, lower alkyleneamino, N-morpholino, N-thiomorpholino, optionally 4-lower alkyl-substituted N-piperazino, tri-lower alkylammonio, sulfo, lower alkoxysulfonyl, sulfamoyl, lower alkylsulfamoyl, di-lower alkylsulfamoyl; iminomethyl optionally N-substituted by hydroxy, lower alkoxy, lower alkanoyloxy, lower alkyl, phenyl or amino; C_2-C_7alkanoyl or benzoyl; and R_2 represents hydrogen, lower alkyl, phenyl-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower

alkyl, halogen, hydroxy, lower alkoxy, lower alkanoyloxy, mercapto, lower alkylthio, phenyl-lower alkylthio, phenylthio, lower alkanoylthio, carboxy, lower alkoxycarbonyl or lower alkanoyl; the 7,8-dihydro derivatives thereof and also such 7,8-dihydro derivatives wherein R_1 is hydroxymethyl, lower alkoxymethyl, halomethyl, lower alkanoyloxymethyl, carboxy-lower alkyl, halogen, hydroxy, mercapto, formyl, carboxy, lower alkoxycarbonyl, carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl, cyano, 5-tetrazolyl, optionally lower alkyl-substituted 4,5-dihydro-2-oxazolyl or hydroxycarbamoyl and R_2 is as defined above under formula I; and compounds of formula I* wherein n denotes 0, 1, 2, 3 or 4; R_1 is as defined above under formula I or R_1 may be, in addition, hydroxymethyl, lower alkoxymethyl, halomethyl, lower alkanoyloxymethyl, carboxy-lower alkyl, halogen, hydroxy, mercapto, formyl, carboxy, lower alkoxycarbonyl, carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl, cyano, 5-tetrazolyl, optionally lower alkyl-substituted 4,5-dihydro-2-oxazolyl or hydroxycarbamoyl if n represents 0, 1, 3 or 4 or if n represents 2 and R_2 is phenyl-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, lower alkanoyloxy, mercapto, lower alkylthio, phenyl-lower alkylthio, phenylthio, lower alkanoylthio, carboxy, lower alkoxycarbonyl or lower alkanoyl; and R_2 is as defined above under formula I; it being possible for the phenyl ring within the radicals phenylsulfonyloxy, phenyliminomethyl, benzoyl, phenyl-lower alkyl, phenyl-lower alkylthio and phenylthio to be unsubstituted or substituted by lower alkyl, lower alkoxy or halogen; and in a compound of formula I* it being possible for the two substituents C_6H_4-R_1 and R_2 to be attached to any of the saturated carbon atoms of the saturated ring, either both to the same carbon atom or to different carbon atoms; radicals designated "lower" containing up to 7 carbon atoms; stereoisomers, mixtures

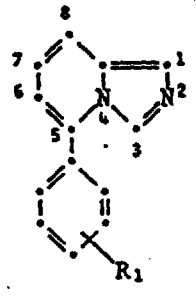
of these stereoisomers, and salts thereof.

The invention relates especially to compounds of formula I wherein R_1 represents lower alkyl, hydroxy-C_2-C_7alkyl; lower alkyl substituted by amino, di-lower alkylamino, 2 to 5 fluorine atoms, lower alkoxycarbonyl, carbamoyl or cyano; nitro, lower alkoxy, amino, lower alkylamino, di-lower alkylamino, sulfo, sulfamoyl, iminomethyl or iminomethyl N-substituted by hydroxy, lower alkoxy, lower alkanoyloxy, lower alkyl or phenyl; and R_2 is hydrogen, lower alkyl, lower alkoxy or halogen; and compounds of formula I* wherein n denotes 1, 2 or 3; R_1 is as defined above under formula I or R_1 may be, in addition, hydroxymethyl, carboxy-lower alkyl, halogen, hydroxy, formyl, carboxy, lower alkoxycarbonyl, carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl or cyano if n represents 1 or 3 or if n represents 2 and R_2 is phenyl-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, lower alkylthio, phenyl-lower alkylthio, phenylthio, carboxy, lower alkoxycarbonyl or lower alkanoyl; and R_2 represents hydrogen, lower alkyl, phenyl-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, halogen, lower alkoxy, lower alkylthio, phenyl-lower alkylthio, phenylthio, carboxy, lower alkoxycarbonyl or lower alkanoyl; in a compound of formula I* it being possible for the two substituents C_6H_4-R_1 and R_2 to be attached to any of the saturated carbon atoms of the saturated ring, either both to the same carbon atom or to different carbon atoms; stereoisomers, mixtures of these stereoisomers, and pharmaceutically acceptable salts thereof.

The invention relates most especially to compounds of formula I* wherein n denotes 1, 2 or 3; R_1 represents lower alkyl, amino, lower alkylamino or di-lower alkylamino, or R_1 may be, in addition, hydroxymethyl, halogen,

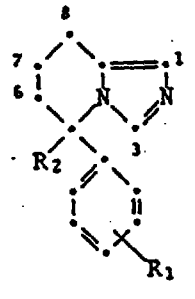
formyl, carboxy, lower alkoxycarbonyl, carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl or cyano if n represents 1 or 3 or if n represents 2 and R_2 is phenyl-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, lower alkylthio, carboxy or lower alkoxycarbonyl; and R_2 is hydrogen, lower alkyl, phenyl-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, lower alkylthio, carboxy or lower alkoxycarbonyl; it being possible for the two substituents C_6H_4-R_1 and R_2 to be attached to any of the saturated carbon atoms of the saturated ring, either both to the same carbon atom or to different carbon atoms; stereoisomers, mixtures of these stereoisomers, and pharmaceutically acceptable salts thereof.

A special embodiment of the invention comprises compounds of formula Ia



(Ia)

wherein R_1 represents cyano, nitro or C_1-C_4alkyl, the 7,8-dihydro derivatives thereof and the 5,6,7,8-tetrahydro derivatives thereof of formula Ib



(Ib)

wherein R_1 is as defined above under formula Ia and R_2 is hydrogen, C_1-C_4alkyl, benzyl, halogen, C_1-C_4alkoxy,

C_1-C_4alkylthio, benzylthio, 2-phenylethylthio, diphenylmethylthio, phenylthio, C_1-C_4alkanoyloxy, C_1-C_4alkanoylthio, carboxy-C_1-C_4alkyl, C_1-C_4alkoxycarbonyl-C_1-C_4alkyl or C_1-C_4alkanoyl, stereoisomers, mixtures of these stereoisomers, and salts of these compounds.

The 5,6,7,8-tetrahydro derivatives of formula Ib have a chiral carbon atom in the 5-position. The 5R- and 5S-enantiomers and the 5(R,S)-racemates fall within the scope of the present invention.

The general terms used to define the compounds of formulae Ia and Ib have preferably the following meanings:

C_1-C_4alkyl R_1 or R_2 is, for example, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl or tert-butyl, and preferably methyl.

Halogen R_2 is, for example, fluorine or bromine or, preferably, chlorine.

C_1-C_4alkoxy is, for example, methoxy or ethoxy, and C_1-C_4alkylthio is, for example, methyl- or ethyl-thio.

Carboxy-C_1-C_4alkyl R_2 is, for example, carboxymethyl or 2-carboxyethyl.

C_1-C_4alkoxycarbonyl-C_1-C_4alkyl R_2 is, for example, methoxy- or ethoxy-carbonylmethyl.

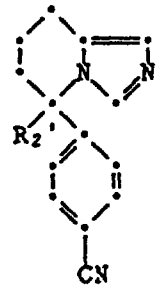
C_1-C_4alkanoyl R_2 is, for example, formyl, acetyl or propionyl.

The invention relates especially to the compounds of formula Ia wherein R_1 represents cyano, the 7,8-dihydro

derivatives thereof, and the 5,6,7,8-tetrahydro derivatives thereof of formula Ib wherein R_1 is cyano and R_2 is hydrogen, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4alkylthio, benzylthio, 2-phenylethylthio, diphenylmethylthio, phenylthio or C_1-C_4alkanoyl, and pharmaceutically acceptable acid addition salts of compounds of formulae Ia and Ib.

Preferred above all are the compounds of formula Ia wherein R_1 is cyano, the 7,8-dihydro derivatives thereof, and the 5,6,7,8-tetrahydro derivatives thereof of formula Ib wherein R_1 is as defined above under formula Ia and R_2 is hydrogen, and pharmaceutically acceptable acid addition salts thereof.

The invention relates especially to the compounds of formula Ic



(Ic)

wherein R_2' is hydrogen, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4-alkylthio, benzylthio, 2-phenylethylthio, diphenylmethylthio, phenylthio or C_1-C_4alkanoyl, and pharmaceutically acceptable acid addition salts thereof.

Especially preferred is the compound of formula Ic wherein R_2' is hydrogen, named 5-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine, and pharmaceutically acceptable acid addition salts thereof.

The invention relates further to compounds of formula Ia wherein R_1 represents hydrogen, p-toluenesulfonyloxy,

benzenesulfonyloxy, methylsulfonyloxy, sulfo, amino, carbamoyl, C_1-C_4alkylcarbamoyl or hydroxyiminomethyl; and the 5,6,7,8-tetrahydro compounds of formula Ib wherein R_1 is as defined above under formula Ia or is halogen, and R_2 is hydrogen, C_1-C_4alkyl, benzyl, halogen, C_1-C_4-alkoxy, C_1-C_4alkanoyloxy, C_1-C_4alkylthio, benzylthio, 2-phenylethylthio, diphenylmethylthio, phenylthio, C_1-C_4-alkanoylthio, carboxy-C_1-C_4alkyl, C_1-C_4alkoxycarbonyl-C_1-C_4alkyl or C_1-C_4alkanoyl; and pharmaceutically acceptable salts thereof.

Among the last-mentioned compounds of formulae Ia and Ib the compounds of formulae Ia and Ib wherein R_1 represents carbamoyl, and the compounds of formula Ib wherein R_1 represents halogen are most especially of interest.

Also preferred among the last-mentioned compounds of formulae Ia and Ib are the compounds of formula Ia wherein R_1 is hydrogen, p-toluenesulfonyloxy, benzene-sulfonyloxy, methylsulfonyloxy, sulfo, amino or hydroxy-iminomethyl; and the 5,6,7,8-tetrahydro compounds of formula Ib wherein R_1 is as defined above under formula Ia and R_2 is hydrogen; or wherein R_1 is hydrogen, halogen, p-toluenesulfonyloxy, benzenesulfonyloxy, methylsulfonyloxy, sulfo, amino, carboxy, carbamoyl, C_1-C_4alkylcarbamoyl, formyl or hydroxyiminomethyl and R_2 represents C_1-C_4-alkyl, benzyl, halogen, C_1-C_4alkoxy, C_1-C_4alkanoyloxy, C_1-C_4alkylthio, benzylthio, 2-phenyl-ethylthio, diphenylmethylthio, phenylthio, C_1-C_4alkanoyl-thio, carboxy-C_1-C_4alkyl, C_1-C_4alkoxycarbonyl-C_1-C_4alkyl or C_1-C_4alkanoyl; and pharmaceutically acceptable salts thereof.

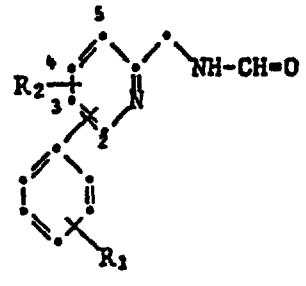
Generally preferred are those compounds of the invention wherein the substituent C_6H_4-R_1 is attached in the 5- or 7-position of the bicyclic ring system, and of particular

interest are the compounds wherein C_6H_4-R_1 is attached in the 5-position. In compounds of the invention, the substituent R_1 is preferably attached in the para- or meta-position, especially in the para-position, of the phenyl ring. The integer n in a compound of formula I* is preferably 1, 2 or 3, especially 1 or 2 and more especially 2. Of the compounds of the invention, the aromatic ones, for example of formula I or Ia, are preferred to the corresponding 7,8-dihydro derivatives. Most preferred are the compounds with a totally hydrogenated ring, for example of formula I* or Ib.

Preferred above all are the compounds of the invention described in the Examples and pharmaceutically acceptable salts thereof, pharmaceutical compositions containing those compounds and their use as pharmaceutical active ingredients or for the manufacture of pharmaceutical compositions.

The compounds of formula I or I*, which comprise the compounds of formulae Ia and Ib, are prepared in a manner known per se, preferably by

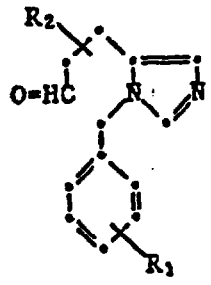
a) cyclising a compound of formula II



(II)

or a 4,5-dihydro derivative thereof in order to obtain a compound of formula I or a 7,8-dihydro derivative thereof, respectively, or

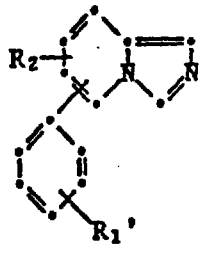
b) cyclising a compound of formula III



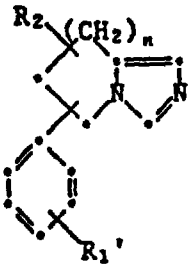
(III),

wherein R_2 may, as indicated, be attached to any of the carbon atoms including the carbonyl carbon, in order to obtain a 7,8-dihydro derivative of a compound of formula I wherein the substituent C_6H_4-R_1 is attached in the 5-position, or

c)/f) in a compound of formula IV or VII



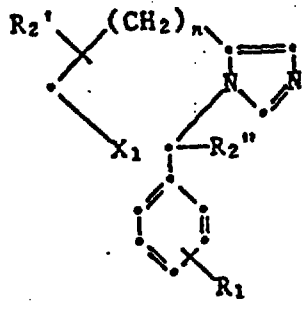
(IV)



(VII)

or in a 7,8-dihydro derivative of formula IV, in each of which R_1' is a group that can be converted into cyano, converting R_1' into cyano, in order to obtain a compound of formula I, a 7,8-dihydro derivative thereof or a compound of formula I*, respectively, wherein R_1 represents cyano, or

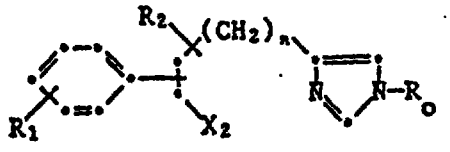
d) cyclising a compound of formula V



(V),

wherein at least one of the radicals R_2' and R_2'' is hydrogen and the other represents a radical R_2 as defined under formula I*, and X_1 is a leaving group, and R_2' may, as indicated, be attached to any of the carbon atoms, in order to obtain a compound of formula I* wherein the substituent C_6H_4-R_1 is attached in the 5-position; or X_1 represents a =CH-COOH group or a lower alkyl ester thereof, R_2' is hydrogen and R_2'' is as defined under formula I*, in order to obtain a compound of formula I* wherein the substituent C_6H_4-R_1 is attached in the 5-position and the 6-position is substituted by carboxymethyl or lower alkoxycarbonylmethyl, or

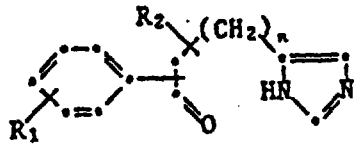
e) cyclising a compound of formula VI



(VI)

wherein the substituents C_6H_4-R_1 and R_2 may, as indicated, be attached to any of the carbon atoms, either both radicals to the same carbon atom or to different carbon atoms, R_o is an NH-protecting group or hydrogen, and X_2 is a leaving group, in order to obtain a compound of formula I*; or

g) cyclising a compound of formula IX



(IX)

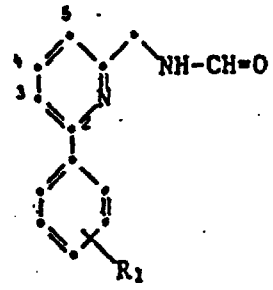
wherein the substituents C_6H_4-R_1 and R_2 may, as indicated, be attached to any of the carbon atoms including the carbonyl carbon, either both radicals to the same carbon atom or to different carbon atoms, optionally under reductive conditions, in order to obtain a 7,8-dihydro derivative of a compound of formula I or, in the

case of reductive conditions, a compound of formula I*, or

h) decarboxylating a compound analogous to formula I, or a 7,8-dihydro derivative thereof, or a compound analogous to formula I*, each of which contains an additional carboxy group in the 1- or 3-position, in order to obtain a compound of formula I, a 7,8-dihydro derivative thereof or a compound of formula I*; wherein, in the starting materials of formulae II to VII and IX, the symbols n, R_1 and R_2 have the meanings given under formulae I and I*, respectively; and/or reducing a compound of formula I or a 7,8-dihydro derivative thereof to a corresponding 5,6,7,8-tetrahydro derivative of formula I* optionally with simultaneous reduction of the substituent(s) R_1 and/or R_2 to (an)other substituent(s) R_1 and/or R_2; and/or decarboxylating a compound of formula I* wherein R_2 is carboxy, in order to obtain a compound of formula I* wherein R_2 is hydrogen; and/or converting a compound obtained into another compound of the invention and/or converting a salt obtained into the free compound or into another salt and/or converting a free compound obtained into a salt and/or separating a mixture of isomers or racemates obtained into the individual isomers or racemates and/or resolving an enantiomeric mixture, such as a racemate, into the optical antipodes.

The compounds of formula Ia or Ib are preferably manufactured by

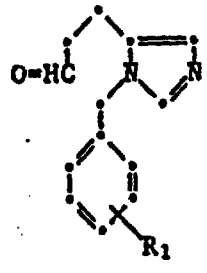
a) cyclising a compound of formula IIa



(IIa),

wherein R_1 is as defined above under formula Ia, or a 4,5-dihydro derivative thereof, under acidic conditions, in order to obtain a compound of formula Ia or a 7,8-dihydro derivative thereof, or

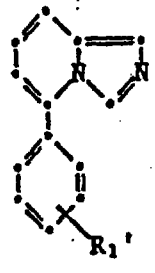
b) for the manufacture of a 7,8-dihydro derivative of a compound of formula Ia, cyclising a compound of formula IIIa



(IIIa),

wherein R_1 is as defined above under formula Ia, under basic conditions, or

c) in a compound of formula IVa

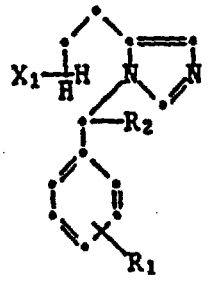


(IVa),

wherein R_1' is a radical that can be converted into cyano, or in a 7,8-dihydro derivative thereof, converting R_1' into cyano, in order to obtain a compound of

formula Ia, or a 7,8-dihydro derivative thereof, or

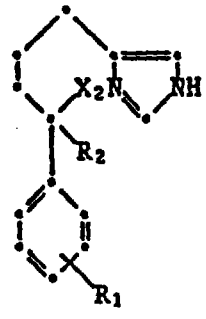
d) cyclising a compound of formula Vb



(Vb),

wherein R_1 and R_2 are as defined above under formula Ib and X_1 is a leaving group, in the presence of a base, in order to obtain a compound of formula Ib, or

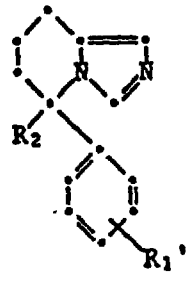
e) cyclising a compound of formula VIb



(VIb),

wherein R_1 and R_2 are as defined above under formula Ib and X_2 is a leaving group, in the presence of a base, in order to obtain a compound of formula Ib, or

f) in a compound of formula VIIb



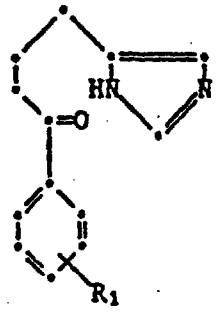
(VIIb),

wherein R_1' is a radical that can be converted into cyano, and wherein R_2 is as defined above under formula

Ib, converting the radical R_1' into cyano, in order to obtain a compound of formula Ib wherein R_1 is cyano; and/or reducing a compound of formula Ia, or a 7,8-dihydro derivative thereof, with hydrogen in the presence of a hydrogenation catalyst to the corresponding 5,6,7,8-tetrahydro derivative of formula Ib, and/or converting a compound obtained into another compound of the invention and/or converting a salt obtained into the free compound or into another salt and/or converting a free compound having a salt-forming group into a salt and/or separating a racemic mixture obtained into the individual enantiomers.

Compounds of formula Ia or Ib can also be manufactured, for example, by using, in a variant of process e), compounds of formula VIb wherein the free NH group is protected by an NH-protecting group as defined hereinafter, or

g) cyclising a compound of formula IXb



(IXb),

optionally under reductive conditions, in order to obtain a 7,8-dihydro derivative of a compound of formula Ia or, in the case of reductive conditions, a compound of formula Ib, or

h) decarboxylating a compound analogous to formula Ia, or a 7,8-dihydro derivative thereof, or a compound analogous to formula Ib, each of which contains an additional carboxy group in the 1- or 3-position, in order to obtain

a compound of formula Ia, a 7,8-dihydro derivative thereof or a compound of formula Ib.

Process a): The cyclisation of the formylamino compound of formula II or IIa is advantageously carried out under conditions such as those described for the cyclisation of 6-methyl-2-methylaminopyridine to 5-methylimidazo[1,5-a]-pyridine in J. Org. Chem. 40, 1210 (1975). The cyclisation under acid conditions may be achieved advantageously with a Lewis acid, such as polyphosphoric acid, phosphorus oxychloride or polyphosphate ester.

Process b): The cyclisation of the formyl compound of formula III or IIIa is carried out, for example, under basic conditions. The base employed may be any base that rapidly accepts protons, for example an amine, such as a tertiary amine, for example a tri-lower alkylamine, such as trimethylamine or triethylamine, a cyclic tertiary amine, for example N-methylmorpholine, a bicyclic amidine, such as a diazabicycloalkene, for example 1,5-diazabicyclo[4.3.0]non-5-ene or 1,5-diazabicyclo[5.4.0]-undec-5-ene (DBU), or, for example, a base of the pyridine type, such as pyridine. Also suitable are inorganic bases, for example an alkali metal hydroxide or alkaline earth metal hydroxide, e.g. sodium, potassium or calcium hydroxide. Preferred bases are alcoholates, for example an alkali metal alcoholate, such as sodium or potassium methanolate, ethanolate or tert-butanolate.

The cyclisation according to processes a) and b) is generally carried out in inert organic solvents, such as suitable alcohols, for example methanol, ethanol or isopropanol, ketones, for example acetone, ethers, for example dioxane or tetrahydrofuran, nitriles, for example acetonitrile, hydrocarbons, for example benzene or toluene, halogenated hydrocarbons, for example

methylene chloride, chloroform or tetrachloromethane, esters, for example ethyl acetate, or amides, for example dimethylformamide or dimethylacetamide, and the like. The reaction temperature is between room temperature and the boiling point of the reaction mixture, preferably between 60°C and the boiling temperature of the reaction mixture. Furthermore, the cyclisation is preferably carried out under an inert gas atmosphere, especially a nitrogen atmosphere.

Process c)/f): A radical R_1' in a compound of formula IV, IVa, VII or VIIb that can be converted into cyano is, for example, hydrogen, esterified hydroxy, for example halogen, especially chlorine, bromine or iodine, or a sulfonyloxy group, for example p-toluenesulfonyloxy, benzenesulfonyloxy or mesyloxy, sulfo, amino, carboxy, carboxy in the form of a functional derivative, for example carbamoyl, lower alkylcarbamoyl, such as tert-butylcarbamoyl, or haloformyl, for example chloro- or bromo-formyl, formyl, formyl in the form of a functional derivative, for example hydroxyiminomethyl, or a halo-magnesium group, for example iodo-, bromo- or chloro-magnesium.

Compounds of formula I, Ia, I* or Ib wherein R_1 is cyano can be obtained, for example, by carrying out the following conversions:

The conversion of a compound of formula IV, IVa, VII or VIIb wherein R_1' is hydrogen into a compound of formula I, Ia or I* or Ib is performed, for example, according to the known method of C. Friedel, F.M. Crafts and P. Karrer by reacting with cyanogen chloride (ClCN) or cyanogen bromide or according to the method of J. Houben and W. Fisher by reacting with, for example, trichloroaceto-nitrile. Advantageously, the standard catalyst aluminium

trichloride is used in these reactions, with hydrogen chloride or hydrogen bromide being split off, which can be bound by adding a base, preferably an amine, for example triethylamine or pyridine.

The conversion of a compound of formula IV, IVa, VII or VIIb wherein R_1' is halogen, for example chlorine, bromine or iodine, into a compound of formula I, Ia, I* or Ib is performed, for example, by reacting the former with a cyanide, preferably sodium or potassium cyanide or, especially, copper(I) cyanide. Preferred solvents for this reaction are pyridine, quinoline, dimethylformamide, 1-methyl-2-pyrrolidinone and hexamethylphosphoric acid triamide. High temperatures, especially the reflux temperature of the reaction mixture, are preferred.

The conversion of compounds of formula IV, IVa, VII or VIIb wherein R_1' is a sulfonyloxy group, for example p-toluenesulfonyloxy, benzenesulfonyloxy or mesyloxy, into a compound of formula I, Ia, I* or Ib is performed, for example, by reaction with an alkali metal cyanide, preferably sodium or potassium cyanide. High temperatures, especially the reflux temperature of the reaction mixture, are preferred.

The conversion of a compound of formula IV, IVa, VII or VIIb wherein R_1' is amino into a compound of formula I, Ia, I* or Ib proceeds over several steps. First, a diazonium salt is formed, for example by reaction of the amino compound with an alkali metal nitrite, preferably potassium nitrite. The diazonium salt can be reacted according to the known Sandmeyer reaction <u>in situ</u>, for example, with copper(I) cyanide or a cyanide complex with labile cyano groups, preferably potassium cuproammonium cyanide, or with catalytic amounts of freshly precipi-

tated copper powder in the presence of an alkali metal cyanide, for example sodium or potassium cyanide. Details of this reaction are given, for example, in Houben-Weyl, Methoden der Organischen Chemie, Thieme Stuttgart 1952, vol. VIII.

A carboxy group R_1' can be converted into cyano, for example, by reaction with chlorosulfonyl isocyanate according to the method of R. Graf, Angew. Chem. 80, 183 (1968). Dimethylformamide is the preferred solvent; in this reaction CO_2 is evolved and the chlorosulfonic acid dimethylformamide addition salt is precipitated.

The conversion of a compound of formula IV, IVa, VII or VIIb wherein R_1' is carboxy in the form of a functional derivative, for example carbamoyl, lower alkylcarbamoyl, for example tert-butylcarbamoyl, into a compound of formula I, Ia, I* or Ib is performed, for example, with a strong dehydrating agent, such as phosphorus pentoxide, phosphorus oxychloride, thionyl chloride, phosgene or oxalyl chloride.

A haloformyl (= halocarbonyl) radical R_1', for example chloro- or bromo-formyl, is reacted, for example, with ammonia or a primary or secondary amine, such as methyl- or dimethyl-amine. The amide so obtained is converted into the nitrile of formula I, Ia, I* or Ib, optionally in situ, using one of the dehydrating agents mentioned above, for example phosphorus pentachloride in the case of the unsubstituted amides or phosphorus oxychloride in the case of mono- or di-lower alkylamides.

The dehydration is preferably carried out in the presence of a suitable base. A suitable base is, for example, an amine, for example a tertiary amine, such as a tri-lower alkylamine, for example trimethylamine, triethylamine or

ethyldiisopropylamine, or an N,N-di-lower alkylaniline, for example N,N-dimethylaniline, or a cyclic tertiary amine, for example N-lower alkylmorpholine, for example N-methylmorpholine, or, for example, a base of the pyridine type, such as pyridine or quinoline.

The conversion of a formyl group into cyano is carried out, for example, by converting the formyl group into a reactive functional derivative, for example hydroxyiminomethyl, and dehydrating that group to cyano. Suitable dehydrating agents are the inorganic dehydrating agents mentioned above, for example phosphorus pentachloride, or, preferably, anhydrides of organic acids, for example the anhydrides of lower alkanecarboxylic acids, for example acetic anhydride.

The conversion of formyl into hydroxyiminomethyl is carried out, for example, by reacting with an acid addition salt of hydroxylamine, preferably the hydrochloride.

A compound of formula IV, IVa, VII or VIIb wherein R_1' is formyl can be converted directly into a compound of formula I, Ia, I* or Ib by reacting it, for example, with O,N-bis(trifluoroacetyl)-hydroxylamine in the presence of a base, for example pyridine, according to the method of D.T. Mowry, Chem. Rev. 42, 251 (1948).

The conversion of a compound of formula IV, IVa, VII or VIIb wherein R_1' is halomagnesium, for example iodo-, bromo- or chloro-magnesium, into a compound of formula I, Ia, I* or Ib is achieved, for example, by reacting the magnesium halide with cyanogen halide or dicyanogen. Magnesium halide, for example magnesium chloride, or magnesium cyanohalide, for example magnesium cyanochloride, is produced during this reaction. The

"Grignard" compound wherein R_1' is halomagnesium is prepared in known manner, for example by reacting a compound of formula IV, IVa, VII or VIIb wherein R_1' is halogen, for example chlorine, bromine or iodine, with magnesium, for example in dry ether.

Unless stated otherwise, the conversion of a compound of formula IV, IVa, VII or VIIb into a compound of formula I, Ia, I* or Ib is preferably carried out in an inert, especially anhydrous, solvent or solvent mixture, for example in a carboxylic acid amide, for example a formamide, such as dimethylformamide, a halogenated hydrocarbon, for example methylene chloride, tetrachloromethane or chlorobenzene, a ketone, for example acetone, a cyclic ether, for example tetrahydrofuran, an ester, for example ethyl acetate, or a nitrile, for example acetonitrile, or in mixtures thereof, optionally in the presence of an alcohol, for example methanol or ethanol, or water, optionally at reduced or elevated temperature, for example in a temperature range of approximately from -40°C to +100°C, preferably from room temperature to the boiling point of the reaction mixture, and optionally under an inert gas atmosphere, for example a nitrogen atmosphere.

Process d): In a starting material of formula V or Vb, a leaving group X_1 is preferably esterified hydroxy, for example lower alkanoyloxy, such as acetoxy, mesyloxy, benzenesulfonyloxy or toluenesulfonyloxy, or, especially, halogen, for example chlorine or bromine.

A suitable base is, for example, an alkali metal or alkaline earth metal hydroxide, for example sodium, potassium or calcium hydroxide, a bicyclic amidine, for example 1,5-diazabicyclo[5.4.0]undec-5-ene, preferably an alcoholate, for example sodium or potassium methanolate,

ethanolate or tert-butanolate, an alkali metal amide, for example lithium diisopropylamide, or an alkali metal hydride, for example sodium hydride. If R_2 represents free or functionally modified carboxy or acyl, the reaction is remarkably facilitated and weaker bases, for example tertiary amines, such as tri-lower alkylamines, for example triethylamine, can be used.

The cyclisation is carried out in an aprotic organic solvent, for example an ether, for example diethyl ether, dioxane or tetrahydrofuran, or a ketone, for example acetone, an amide, for example dimethylformamide or hexamethylphosphoric acid triamide, or in mixtures of those solvents, optionally also in a mixture of the mentioned solvents with an alkane, for example n-hexane or petroleum ether. The reaction temperature is between approximately -50° and +50°C, preferably between -10° and room temperature. The reaction is preferably carried out under an inert gas atmosphere, for example argon or nitrogen.

Process e): In a starting material of formula VI or VIb, the leaving group X_2 is preferably defined as a leaving group X_1 in process d). The cyclisation is carried out preferably by using a base, such as a tertiary amine as defined above, for example triethylamine, or even using no base. NH-protecting groups (or blocking groups) R_o are preferably tri-lower alkylsilyl, for example trimethylsilyl, lower alkanoyl, for example acetyl, dialkylcarbamoyl, for example dimethylcarbamoyl, or tripheylmethyl.

Process g): The non-reductive reaction is preferably performed in the presence of an acidic catalyst, for example p-toluenesulfonic acid. The reductive amination reaction is performed, for example, with hydrogen in the

presence of a customary hydrogenation catalyst, for example Raney nickel, platinum or palladium-on-carbon, or with a hydrogen-yielding agent, for example sodium cyanoborohydride.

Process hl: The decarboxylation reaction can be performed with customary decarboxylation agents, for example with acids, such as hydrochloric acid, preferably at elevated temperature.

Subsequent operations

A compound of formula I or Ia, or a 7,8-dihydro derivative thereof, can be converted to the further hydrogenated derivative of formula I*, for example the corresponding 5,6,7,8-tetrahydro derivative of formula Ib, by reduction, for example with hydrogen in the presence of a hydrogenation catalyst, such as platinum or palladium, under acidic conditions, for example in a mineral acid, such as hydrochloric acid, or with palladium-on-carbon at atmospheric pressure in an inert solvent, for example ethanol or ethyl acetate.

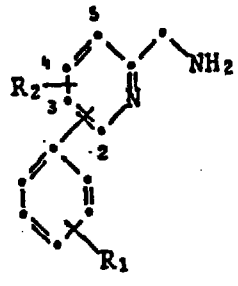
Furthermore, compounds of formula I* or Ib wherein R_2 is carboxy can be decarboxylated in order to obtain different compounds of formula I* or Ib, wherein R_2 is hydrogen, using customary decarboxylation methods, for example those described above for process h). In the mentioned compounds of formula I*, the carboxy substituent R_2 is preferably bonded to the same carbon atom as is the substituent C_6H_4-R_1.

A compound of formula I* in which the 5-position is monosubstituted by the substituent C_6H_4-R_1, for example a compound of formula Ib or Ic wherein R_2 represents hydrogen, can be additionally substituted at that carbon atom by a group R_2 by reacting it under basic conditions

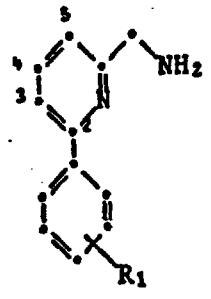
with a reactive derivative of R_2, for example a lower alkyl halide, an aryl-lower alkyl halide or a lower alkyl disulfide. Suitable bases are, for example, alkali metal alkoxides, for example potassium tert-butoxide, alkali metal amides, for example lithium diisopropylamide, or alkali metal hydrides, for example sodium hydride.

Preparation of the starting compounds

Compounds of formulae II and IIa are known or, if they are novel, they can be prepared in a manner known per se, for example by reacting a compound of formula VIII or VIIIa



(VIII),



(VIIIa),

wherein R_1 and R_2 are as defined above under formula I or Ia, with formic acid or a reactive, functional derivative thereof, for example formic acetic anhydride.

Compounds of formulae III and IIIa are prepared, for example, by reacting a compound of formula V wherein X_1 is hydroxy, n is 2, R_2' is as defined under formula V and preferably represents hydrogen, and R_2'' is hydrogen, or a compound of formula Vb wherein X_1 is hydroxy and R_2 is hydrogen, with, for example, dimethyl sulfoxide in the presence of dehydrating agents, for example acid anhydrides, such as anhydrides of organic carboxylic acids, for example aliphatic or aromatic carboxylic acids or dicarboxylic acids, for example anhydrides of lower alkanecarboxylic acids, especially acetic anhydride, mixed anhydrides of lower alkanecarboxylic or dicar-

boxylic acids with mineral acids, for example acetyl or oxalyl chloride, and also anhydrides of inorganic acids, especially of phosphoric acid, for example phosphorus pentoxide. The above-mentioned anhydrides, above all those of organic carboxylic acids, for example oxalyl chloride, are preferably used in a ratio of approximately 1:1 with dimethyl sulfoxide. Further dehydrating or water-absorbing agents are, for example, carbodiimides, above all dicyclohexylcarbodiimide, and also diisopropylcarbodiimide, or keteneimides, for example diphenyl-N-p-tolylketeneimine. These reagents are preferably used in the presence of acidic catalysts, such as phosphoric acid, pyridinium trifluoroacetate or pyridinium phosphate. Sulfur trioxide can also be used as a dehydrating or water-absorbing agent; it is customarily employed in the form of a complex, for example with pyridine. A base is subsequently added, preferably a base that has been mentioned above under process c), for example triethylamine.

The compounds of formulae IV and IVa are preferably prepared analogously to process a) mentioned above.

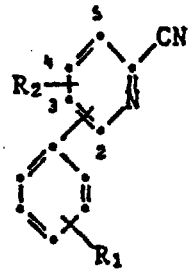
Compounds of formulae V and Va are known or, if they are novel, they can be prepared in a manner known per se, for example by reacting another compound of formula V or Vb, wherein X_1 is hydroxy and wherein both R_2' and R_2'' are, or R is, preferably hydrogen, with a halogenating agent or by esterifying the hydroxy group with a reactive functional derivative of a sulfonic or carboxylic acid. The reaction with a halogenating agent, for example thionyl chloride or phosphorus pentachloride, is carried out, for example, analogously to the halogenation process described in US Patent 4 089 955. The reaction with a reactive functional derivative of a sulfonic or carboxylic acid, for example a mixed anhydride with a

mineral acid, for example mesyl chloride, benzenesulfonyl chloride or p-toluenesulfonyl chloride, or acetyl chloride, is carried out according to known esterification methods.

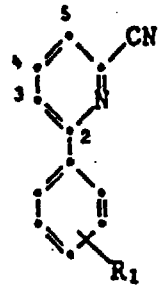
Compounds of formulae VI and VIb are known or, if they are novel, they can be prepared in a manner known per se, for example by reacting another compound of formula VI or VIb, wherein X_2 is hydroxy, R_1 and R_2 are as defined above under formula I* or Ib, and the imidazole NH group is optionally protected by a conventional amino-protecting group, for example tri-lower alkylsilyl, such as trimethylsilyl, with a halogenating agent or by esterifying the hydroxy group with a reactive functional derivative of a sulfonic or carboxylic acid. R_2 is preferably lower alkyl and especially hydrogen. The halogenation reaction is carried out, for example, analogously to the process described in US Patent 4 089 955. The reaction with a reactive functional derivative of a sulfonic or carboxylic acid, for example a mixed anhydride with a mineral acid, for example mesyl chloride, benzenesulfonyl chloride or p-toluenesulfonyl chloride, or acetyl chloride, is carried out according to known esterification methods.

The compounds of formula VII or VIIb are preferably prepared in a manner analogous to that of processes d) and e), and also g) and h).

Compounds of formula VIII or VIIIa are known or, if they are novel, they can be prepared in a manner known per se, for example by hydrogenation of a compound of formula XV or XVa



(XV)

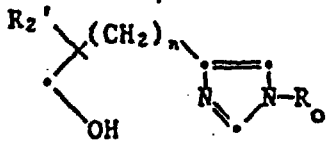


(XV),

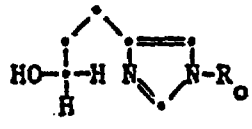
wherein R_1 and R_2 are as defined above under formula I or Ia.

The hydrogenation is preferably carried out in the presence of a catalyst, for example platinum or palladium-on-carbon, and in the presence of a mineral acid, for example hydrochloric acid.

Compounds of formula V or Vb wherein X_1 is hydroxy are known or, if they are novel, they can be prepared in a manner known <u>per se</u>, for example by reacting a compound of formula XVII or XVIIa

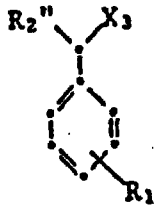


(XVII)

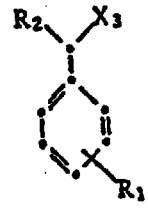


(XVIIa),

wherein n and R_2' are defined as n and R_2 under formula I*, R_o is a NH-blocking group as defined above, for example dialkylcarbamoyl, such as dimethylcarbamoyl, and the hydroxy group is protected by a conventional hydroxy-protecting group, for example trimethylsilyl, with a compound of formula XVIII or XVIIIa



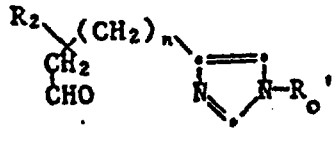
(XVIII)

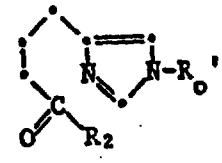


(XVIIIa),

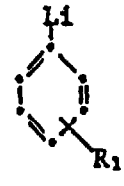
wherein R_1 is as defined above under formula I or Ia, R_2 is as defined under formula Ib and is preferably hydrogen, R_2" is defined as R_2 under formula I*, and X_3 is a leaving group, for example esterified hydroxy, such as halogen, for example chlorine or bromine, or sulfonyloxy, for example mesyloxy or p-toluenesulfonyloxy.

Compounds of formulae VI and VIb wherein X_2 is hydroxy, R_2 is preferably lower alkyl and especially hydrogen, and the radical C_6H_4-R_1 is bonded to the same carbon atom as is the group X_2 are known or, if they are novel, they can be prepared in a manner known <u>per se</u>, for example by reacting a compound of formula XIX or XIXa


(XIX),

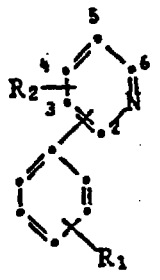

(XIXa),

wherein n and R_2 are as defined above under formula I* or Ib, and R_2 is preferably lower alkyl and especially hydrogen, wherein in formula XIX the group R_2 may, as indicated, be attached to any carbon atom including the carbonyl carbon, and wherein R_O' is preferably a conventional NH-protecting group as defined above, for example tri-lower alkylsilyl, such as trimethylsilyl, in a reaction with an organometal compound of formula XX

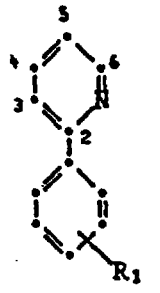

(XX),

wherein R_1 is as defined above under formula I or Ia.

Compounds of formulae XV and XVa can be prepared, for example, by first of all reacting a compound of formula XXI or XXIa



(XXI)



(XXIa)

with an oxidising agent, for example peracetic acid, to give the corresponding N-oxide, then treating the N-oxide with a methylating agent, for example dimethyl sulfate, substituting the 6-position with a cyanide ion, for example using potassium cyanide, and converting the N-oxide back into the pyridine derivative.

Compounds of formulae XVII-XXI, XVIIa-XIXa and XXIa are known or can be prepared using conventional chemical methods.

Compounds of formulae IX and IXb can be prepared, for example, by the following synthesis sequence: First of all, a compound of formula XIX - or of formula XIXa wherein R_2 is hydrogen - is oxidised with customary oxidising agents, for example $KMnO_4$, to produce the corresponding acid which can optionally be converted further into the corresponding lower alkyl ester. Reaction of the latter - or of the free acid - with a compound of formula XX, or a suitable organometal equivalent thereof, and splitting-off of the NH-protecting group results in compounds of formulae IXb and IX, in the latter of which the substituent C_6H_4-R_1 is bonded to the carbonyl carbon.

Compounds of formula VI and IX wherein the substituent C_6H_4-R_1 is not bonded to the same carbon atom as is the group X_2 or to the carbonyl carbon, respectively, can be obtained, for example, from compounds analogous to

formula XVII that additionally have a radical C_6H_4-R_1 in the side chain. This can be achieved by known methods, for example by esterification of the hydroxy group or its oxidation to formyl, respectively. The starting compounds analogous to formula XVII can be prepared by using known chemical methods.

The starting compounds for process h) which contain a carboxy group in the 3- or 1-position of the bicyclic ring system can be obtained, for example, by reaction of a compound of formula VIII or VIIIa, or a compound analogous thereto that contains an additional carboxy group in the α-position, with, for example, oxalic acid lower alkyl ester halide, for example ethyl oxalyl chloride, or with formic acid or a derivative thereof, for example formic acetic anhydride, respectively, and subsequent ring-closure with a Lewis acid, for example phosphorus oxychloride.

If any of the intermediates mentioned contain interfering reactive groups, for example carboxy, hydroxy, amino, sulfo or mercapto groups, such groups may be protected, preferably temporarily, at any stage by readily removable protecting groups. The choice of protecting group for a particular reaction depends upon various factors, for example the nature of the functional group to be protected, the structure and stability of the molecule in which the functional group is located, and the reaction conditions. Protecting groups that meet these conditions and their introduction and removal are known per se and described, for example, in J.F.W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London, New York 1973. Thus, carboxy and also sulfo groups can be protected, for example, as esters, for example as unsubstituted or substituted lower alkyl esters, such as methyl or benzyl ester, it being possible to remove such

ester groups again under mild conditions, especially alkaline conditions. Amino- and hydroxy-protecting groups that can be removed again under mild conditions are, for example, acyl radicals, for example unsubstituted or halo-substituted lower alkanoyl, for example formyl or trichloroacetyl, or organic silyl groups, for example tri-lower alkylsilyl, such as trimethylsilyl.

Salts of compounds of the invention can be prepared in a manner known per se. For example, they may be prepared in accordance with the methods described in the Examples. Acid addition salts are obtained in customary manner, for example by treating the free compound with an acid or a suitable anion-exchange reagent. Salts can be converted in customary manner into the free compounds, for example by treating an acid addition salt with a suitable base, for example an alcoholate, such as potassium tert-butoxide. On the other hand, compounds of the invention that contain acid groups, for example carboxy, can be converted into salts in a manner known per se, for example by treating them with a base, for example an alkali metal hydroxide or alkoxide, an alkali metal or alkaline earth metal salt, for example sodium hydrogen carbonate, ammonia or a suitable organic amine. Free compounds can be obtained by treating such salts with an acid. In view of the close relationship between the compounds in free form and the compounds in the form of their salts, any reference hereinbefore and hereinafter to the free compounds or their salts is to be understood as including also the corresponding salts or free compounds, respectively, provided that such is possible or appropriate under the circumstances.

Depending upon the starting materials and method chosen, the novel compounds may be in the form of one of the possible isomers or in the form of mixtures of isomers.

Thus, depending on the presence and number of chiral carbon atoms, they may be in the form of optical isomers, i.e. antipodes, or in the form of mixtures of optical isomers, for example racemates, or in the form of mixtures of diastereoisomers.

Resulting mixtures of diastereoisomers can be separated on the basis of the physico-chemical differences of their components in a manner known per se, for example by chromatography and/or fractional crystallisation.

Resulting racemates can furthermore be separated into the optical antipodes in a manner known per se, for example by chromatography using an optically active stationary phase, by recrystallisation from an optically active solvent, with the aid of microorganisms or, for example, by reaction of an acidic intermediate or end product with an optically active base that forms a salt with the racemic acid, and separation of the salts so obtained, for example on the basis of their different solubilities, into the diastereoisomers, from which the antipodes can be liberated by the action of suitable agents. Basic racemic end products can be separated into the antipodes in the same manner, for example by separating diastereoisomeric salts thereof, for example by fractional crystallisation of the d- or l-tartrates.

The reactions mentioned above are carried out according to methods that are known per se, in the presence or absence of diluents, preferably in those which are inert towards the reactants and are solvents thereof, catalysts, condensing agents or other agents mentioned above, and/or in an inert atmosphere, while cooling, at room temperature or at elevated temperature, for example in a temperature range of from -20° to +200°C, preferably at the boiling point of the solvent used, at normal or

elevated pressure. The preferred solvents, catalysts and reaction conditions are disclosed in the accompanying Examples.

The compounds, including their salts, may also be obtained in the form of their hydrates, or their crystals may, for example, include the solvent used for crystallisation.

The invention relates also to variants of the present process, in which an intermediate obtained at any stage of the process is used as starting material and the remaining process steps are carried out, or the process is discontinued at any stage, or in which a starting material is formed under the reaction conditions, or in which one or more of the starting materials is or are used in the form of a salt or an optically pure antipode. The starting materials used in the process of this invention are preferably those which result in the compounds described above as being especially valuable. The invention relates also to novel starting materials and processes for the preparation thereof.

The invention further relates to pharmaceutical compositions for enteral or parenteral administrations. These compositions contain a therapeutically effective amount of a compound of the invention, on its own or in combination with one or more pharmaceutically acceptable carriers. Solid or liquid, inorganic or organic substances are used as carriers. Suitable unit dose forms, especially for peroral administration, for example dragées, tablets or capsules, contain preferably approximately 5-100 mg, especially approximately 10 to 50 mg, of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with pharmaceutically acceptable carriers.

The daily doses of the compounds of the invention are approximately from 0.1 to 100 mg/kg, preferably approximately from 0.5 to 50 mg/kg, of body weight for mammals depending on the species, and also for persons depending on age, individual condition and the mode of administration. For parenteral administration, for example intramuscular or subcutaneous injections or intravenous infusions, the doses within the range indicated are generally lower than in the case of enteral, for example oral or rectal, administration. The compounds of the invention are administered orally or rectally preferably in unit dose form, such as tablets, dragées, capsules or suppositories, and parenterally especially in the form of injectable solutions, emulsions or suspensions, or in the form of infusion solutions.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and binders, such as starch pastes using, for example, corn, wheat, rice or potato starch, gelatin, tragacanth, methylcellulose and/or, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate. Adjuncts are especially flow-regulating and lubricating agents, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Dragée cores may be provided with suitable, optionally enteric, coatings, there being used, inter alia, concentrated sugar solutions which may contain gum arabic, talc, polyvinylpyrrolidinone, polyethylene glycol and/or titanium dioxide, or lacquer solutions in suitable

organic solvents or solvent mixtures, or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Dyes or pigments may be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of active ingredient.

Other orally administrable pharmaceutical compositions are dry-filled capsules consisting of gelatin, and also soft sealed capsules consisting of gelatin and a plasticiser, such as glycerol or sorbitol. The dry-filled capsules may contain the active ingredient in the form of a granulate, for example in admixture with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and, if desired, stabilisers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, it being possible also to add stabilisers.

Suitable rectally administrable pharmaceutical compositions are, for example, suppositories that consist of a combination of the active ingredient with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. It is also possible to use gelatin rectal capsules that contain a combination of the active ingredient with a base material; suitable base materials are, for example, liquid triglycerides, polyethylene glycols or paraffin hydrocarbons.

For parenteral administration there are suitable, especially, suspensions of the active ingredient, such as correponding oily injection suspensions or solutions, in

which suitable lipophilic solvents or vehicles, such as fatty oils, for example sesame oil, or synthetic fatty acid esters, for example ethyl oleate or triglycerides, are used, or aqueous injection suspensions or solutions that contain viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran and, if desired, stabilisers.

The pharmaceutical compositions of this invention can be prepared in a manner known per se, for example by means of conventional mixing, granulating, coating, confectioning, dissolving or lyophilising processes. For example, pharmaceutical compositions for oral administration can be obtained by combining the active ingredient with solid carriers, optionally granulating a resulting mixture and processing the mixture or granulate, if desired or necessary, after the addition of suitable adjuncts, to tablets or dragée cores.

The following Examples serve to illustrate the invention and are not to be construed as any limitation of its scope. Temperatures are given in degrees Celsius, and parts are by weight. Unless stated otherwise, evaporation of solvents is carried out under reduced pressure, preferably between approximately 20 and 130 mbar.

Example 1: 5-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo-[1,5-a]pyridine hydrochloride. 7.0 g of potassium tert-butoxide is added as a solid, in several portions, to a solution, cooled to 0°, of 8.1 g of 5-(3-chloropropyl)-1-(p-cyanophenylmethyl)-1H-imidazole in 50 ml of tetrahydrofuran. The mixture is stirred at room temperature for 2 hours, is neutralised with 10 % acetic acid and partitioned between methylene chloride and water. The organic phase is washed with water, dried over magnesium sulfate and concentrated by evaporation to yield an oil,

which is dissolved in a small amount of acetone and neutralised with ethereal hydrogen chloride. Upon cooling, the title compound is obtained in the form of a white solid; m.p. 201-203°.

Preparation of the starting compounds:

a) 1-dimethylcarbamoyl-4-(3-trimethylsilyloxypropyl)-1H-imidazole. 50.0 g of triethylamine are added to a suspension of 51.8 g of 4-(3-hydroxy-n-propyl)-1H-imidazole, obtainable according to Il Farmaco, Ed. Sc. 29, 309 (1973), in 500 ml of acetonitrile. To this mixture, 48.6 g of dimethylcarbamoyl chloride are then added dropwise. When the addition is complete, the mixture is refluxed for 21 hours. The mixture is cooled to 0° whereupon there is precipitation of triethylamine hydrochloride. To this mixture there are added 50.0 g of triethylamine and then 54.0 g of chlorotrimethylsilane. When the addition is complete, stirring is continued for 1 hour. The mixture is then diluted with an equal volume of ether and filtered. The filtrate is concentrated by evaporation to an oil, which is triturated with ether and then filtered again in order to remove further triethylamine hydrochloride. The filtrate is concentrated by evaporation to yield the title compound a) in the form of an oil.

b) 1-(p-cyanophenylmethyl)-5-(3-hydroxypropyl)-1H-imidazole. A solution of 97.0 g of 1-dimethylcarbamoyl-4-(3-trimethylsilyloxypropyl)-1H-imidazole and 72.0 g of 1-bromomethyl-4-cyanobenzene in 500 ml of acetonitrile is refluxed for 10 hours. The solution is cooled in an ice bath to 0° and ammonia gas is bubbled in for a few minutes. The mixture is then evaporated in vacuo to give a semi-solid mass, which is dissolved in 500 ml of 1N hydrochloric acid. The solution is left to stand at room

temperature for 15 minutes and is then extracted with ether. The pH of the aqueous phase is adjusted to 9 with 50 % sodium hydroxide solution and the mixture is then extracted with methylene chloride. The methylene chloride extracts are washed with water, dried over sodium sulfate and concentrated by evaporation to give a semi-solid mass which is triturated with cold acetone. In this manner, title compound b) is obtained in the form of a white solid, m.p. 121-123°.

c) 5-(3-chloropropyl)-1-(p-cyanophenylmethyl)-1H-imidazole. 8.4 g of 1-(p-cyanophenylmethyl)-5-(3-hydroxypropyl)-1H-imidazole are added as a solid, in several portions, to a solution of 5.2 g of thionyl chloride in 80 ml of methylene chloride. The rate of addition is regulated in such a manner that the gas evolution which occurs is kept under control. When the addition is complete, the solution is refluxed for 1.5 hours, cooled with ice and filtered to yield the hydrochloride of the title compound c) in the form of a buff-coloured solid of m.p. 190-191°. The salt is partitioned between methylene chloride and a saturated solution of sodium hydrogen carbonate. The organic extracts are washed with water, dried over sodium sulfate and concentrated by evaporation to yield the free base in the form of an oil.

Example 2: 5-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo-[1,5-a]pyridine hydrochloride. A solution of 2.0 g of 4-[4-chloro-4-(p-cyanophenyl)-n-butyl]-1H-imidazole in 50 ml of chloroform is refluxed under nitrogen for 4 hours, cooled and concentrated by evaporation to yield the title compound.

Preparation of the starting compounds:

a) 4-(3-formyl-n-propyl)-1-trimethylsilylimidazole. A solution of 1.82 g of 4-(3-ethoxycarbonylpropyl)-1H-imidazole in 30 ml of tetrahydrofuran is treated under nitrogen first with 0.5 g of sodium hydride (50 % oil dispersion) for 30 minutes at 0° and then with 1.45 ml of trimethylsilyl chloride for 3 hours at 0°. The reaction mixture is washed with cold 0.5N sodium hydrogen carbonate solution, dried over sodium sulfate and concentrated to dryness by evaporation. The resulting oil is dissolved at -78° under nitrogen in 100 ml of methylene chloride, and 12.82 ml of diisobutylaluminium hydride (1.56 M) are added dropwise thereto. The reaction mixture is stirred at -78° for 5 minutes and the reaction is stopped by adding 1 ml of methanol and then 10 ml of water. The reaction mixture is filtered through Celite®. The organic phase is separated, dried over sodium sulfate and concentrated by evaporation to yield the title compound a).

b) 4-[4-(p-tert-butylaminocarbonylphenyl)-4-hydroxy-n-butyl]-1-trimethylsilylimidazole. A solution of 6.95 g of p-tert-butylaminocarbonyl)-bromobenzene is dissolved in 175 ml of tetrahydrofuran at -70° under nitrogen, and 20.1 ml of a solution of n-butyllithium (2.7 M) in hexane are added dropwise thereto. After a reaction time of 30 minutes, a solution of 5.69 g of 4-(3-formyl-n-propyl)-1-trimethylsilylimidazole in 10 ml of tetrahydrofuran is added slowly. The reaction mixture is allowed to warm slowly to room temperature and 20 ml of a saturated ammonium chloride solution are added thereto. The organic phase is separated, dried over sodium sulfate and concentrated by evaporation to yield the title compound b).

c) 4-[4-chloro-(p-cyanophenyl)-n-butyl]-1H-imidazole. A solution of 4.5 g of 4-[4-(p-tert-butylaminocarbonyl-phenyl)-4-hydroxy-n-butyl]-1-trimethylsilylimidazole in 50 ml of thionyl chloride is refluxed for 1 hour, cooled and concentrated by evaporation. The residue is partitioned between methylene chloride and an aqueous sodium hydrogen carbonate solution. The organic phase is separated, dried over sodium sulfate and concentrated by evaporation to yield the title compound c).

Example 3: 5-(p-cyanophenyl)imidazo[1,5-a]pyridine. A solution of 0.1 g of 5-(p-tert-butylaminocarbonylphenyl)-imidazo[1,5-a]pyridine in 3 ml of toluene is treated with 40 µl of phosphorus oxychloride for 5 hours at 90°. The solvent is evaporated and the residue is dissolved at 0° in 30 ml of chloroform. Ice-cold ammonia solution is added thereto and the organic phase is separated, dried over sodium sulfate and concentrated by evaporation. The residue is chromatographed over silica gel using ethyl acetate to yield the title compound of m.p. 117-118°; the corresponding hydrochloride melts at 255-257°.

Example 4: 5-(p-ethoxycarbonylphenyl)imidazo[1,5-a]-pyridine. A solution of 9.8 g of 2-(p-ethoxycarbonyl-phenyl)-6-formylaminomethylpyridine and 11.15 g of phosphorus oxychloride in 26 ml of toluene is heated at 90° for 15 hours. The solvent is evaporated and the residue is taken up in 50 ml of methylene chloride, cooled to 0° and rendered basic with an excess of ice-cold, saturated ammonia solution. The organic phase is separated, dried and concentrated by evaporation. The solid which remains is passed through 100 g of silica gel using ethyl acetate as eluant to yield, after recrystallisation, the title compound of m.p. 118-119°.

Preparation of the starting compounds:

a) 6-cyano-2-(p-ethoxycarbonylphenyl)pyridine. 8.9 ml of 40 % peracetic acid are added dropwise to 14.08 g of 2-(p-ethoxycarbonylphenyl)pyridine so as to maintain the reaction temperature between 80 and 85°. When the addition is complete, the reaction mixture is heated at 90° for 3 hours, whereupon it is allowed to cool to room temperature. Excess peracetic acid is destroyed with aqueous sodium sulfite solution. The solvent is evaporated and the residue is taken up in methylene chloride and filtered through Celite®. Concentration by evaporation yields 2-(p-ethoxycarbonylphenyl)pyridine N-oxide which is treated with 8.66 g of dimethyl sulfate in 62 ml of toluene at 90° for 3 hours. The solvent is evaporated and the residue is dissolved in an ice-cold mixture of 8 ml of water and 9.3 ml of 1N sodium hydroxide solution. A solution of 13.64 g of potassium cyanide in 10 ml of water is added slowly and the reaction mixture is maintained at 0° for 24 hours. Extraction with methylene chloride, drying over sodium sulfate and evaporation of the solvent yield the title compound a); IR (CH_2Cl_2) 2200 cm^{-1}.

b) 6-aminomethyl-2-(p-ethoxycarbonylphenyl)pyridine. 16.23 g of 6-cyano-2-(p-ethoxycarbonylphenyl)pyridine are hydrogenated under atmospheric pressure in 254 ml of methanol with 12.9 ml of concentrated hydrochloric acid and 2.63 g of 10 % palladium-on-carbon until 2 molar equivalents of hydrogen have been absorbed. 6.9 g of sodium methoxide are added and the catalyst is filtered off. After evaporation of the solvent, the residue is dissolved in 20 ml of methylene chloride and the salts are removed by filtration. Evaporation of the solvent yields a solid which is recrystallised from chloroform. This corresponds to the title compound b), m.p. 141-143°.

c) 2-(p-ethoxycarbonylphenyl)-6-formylaminomethyl-pyridine. A solution of 0.76 g of 6-aminomethyl-2-(p-ethoxycarbonylphenyl)pyridine in 10 ml of formic acid is heated at 90° for 15 hours. The reaction mixture is cooled to 0°, rendered basic with an excess of saturated ammonia solution and extracted with chloroform. The organic extracts are dried and concentrated by evaporation to yield the title compound c) which is recrystallised from toluene; m.p. 119.5-120.5°.

Example 5: 5-(p-carboxyphenyl)imidazo[1,5-a]pyridine. A solution of 1.18 g of 5-(p-ethoxycarbonylphenyl)imidazo-[1,5-a]pyridine in 10 ml of ethanol and 14 ml of 1N sodium hydroxide solution is refluxed for 3 hours, cooled and concentrated by evaporation. The residue is partitioned between water and ethyl acetate. The aqueous phase is separated and adjusted to pH 5. The solid is filtered off, washed with water and dried to yield the title compound of m.p. 308-310° (decomposition).

Example 6: 5-(p-tert-butylaminocarbonylphenyl)imidazo-[1,5-a]pyridine. To a slurry of 0.4 g of 5-(p-carboxy-phenyl)imidazo[1,5-a]pyridine in 40 ml of methylene chloride there are added at room temperature under nitrogen 30 µl of N,N-dimethylformamide followed by 0.16 ml of oxalyl chloride. The reaction mixture is stirred until gas evolution ceases; 0.46 ml of tert-butylamine are then added dropwise. Stirring is discontinued after 90 minutes, and 10 ml of saturated sodium hydrogen carbonate solution are added. The organic phase is separated, dried over sodium sulphate and concentrated by evaporation to yield the title compound of m.p. 128-131°.

Example 7: 5-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo-[1,5-a]pyridine hydrochloride. A solution of 1.13 g of 5-(p-carbamoylphenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]-pyridine and 1.0 ml of phosphorus oxychloride in 30 ml of chloroform is refluxed for 15 hours, cooled and, after the addition of toluene, concentrated by evaporation. The resulting oil is dissolved in 30 ml of methylene chloride, cooled to 0° and 30 ml of ice-cold 50 % ammonia solution are added thereto. The organic phase is separated, dried and concentrated by evaporation to an oil. Filtration through 20 g of silica gel using ethyl acetate as eluant yields the free title compound which is dissolved in 20 ml of acetone and treated with 1.2 ml of 3N ethereal hydrogen chloride to yield the corresponding hydrochloride of m.p. 209-210°.

Example 8: 5-(p-ethoxycarbonylphenyl)-5,6,7,8-tetrahydro-imidazo[1,5-a]pyridine hydrochloride. A solution of 2.0 g of 5-(p-ethoxycarbonylphenyl)imidazo[1,5-a]pyridine in 120 ml of anhydrous ethanol containing 30 ml of concentrated hydrochloric acid is hydrogenated with 1.0 g of 10 % palladium-on-carbon under a hydrogen pressure of 2.76 bar and at a temperature of 60° for 4 hours. The catalyst is filtered off and the solvent is evaporated off to yield a solid which is recrystallised from isopropanol and ether and corresponds to the title compound of m.p. 164-166°.

Example 9: 5-(p-carboxyphenyl)-5,6,7,8-tetrahydroimidazo-[1,5-a]pyridine. A solution of 0.66 g of 5-(p-ethoxy-carbonylphenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine in 8.0 ml of ethanol and 8.0 ml of 1N sodium hydroxide solution is refluxed for 3 hours, cooled and concentrated by evaporation. The residue is partitioned between water and ethyl acetate. The aqueous phase is adjusted to pH 5 with concentrated sulfuric acid, and the solid is

filtered off and dried in air. It corresponds to the title compound, m.p. 309-310° (decomposition).

Example 10: 5-(p-carbamoylphenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine. A solution of 5.42 g of 5-(p-carboxyphenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine in 75 ml of thionyl chloride is refluxed for 30 minutes, cooled and, after the addition of toluene, concentrated by evaporation. The residue is dissolved in methylene chloride, cooled to 0° and treated with ammonia gas until the solution is saturated. The reaction mixture is stirred under an argon atmosphere for 10 minutes and the resulting solid is collected by filtration to yield the title compound of m.p. 181-183°. If this is treated with a molar equivalent of fumaric acid, dissolved in ethanol, the corresponding fumarate of m.p. 164-166° (decomposition) is obtained.

Example 11: 5-(p-tolyl)-5,6,7,8-tetrahydroimidazo[1,5-a]-pyridine hydrochloride. A solution of 0.36 g of 5-(p-hydroxymethylphenyl)imidazo[1,5-a]pyridine in 25 ml of ethanol and 6.4 ml of concentrated hydrochloric acid is hydrogenated with 0.15 g of 10 % palladium-on-carbon at a hydrogen pressure of 2.76 bar and at a temperature of 60° for 4 hours. The reaction mixture is filtered and concentrated by evaporation, and the residue is partitioned between methylene chloride and a sodium hydrogen carbonate solution. The organic phase is dried over sodium sulfate and concentrated by evaporation to an oil which is purified by preparative layer chromatography on silica gel using ethyl acetate. The corresponding hydrochloride, i.e. the title compound, is prepared by treatment with 1.1 molar equivalents of ethereal hydrogen chloride in acetone; m.p. 173-175°.

Example 12: 5-(p-hydroxymethylphenyl)imidazo[1,5-a]-pyridine. 1 g of 5-(p-ethoxycarbonylphenyl)imidazo-[1,5-a]pyridine is dissolved in 26 ml of methylene chloride at -78° under nitrogen, whereupon 6.6 ml of diisobutylaluminium hydride in toluene (11.4 mmol) are added dropwise. After stirring for 1 hour, 1.5 ml of methanol are added, the cooling bath is removed and 15 ml of water are added. The salts are filtered off, and the organic phase is dried over sodium sulfate and concentrated by evaporation to yield the title compound of m.p. 137-138°.

Example 13: 5-(p-cyanophenyl)-7,8-dihydroimidazo[1,5-a]-pyridine. A solution of 0.24 g of 1-(p-cyanophenyl-methyl)-5-(2-formylethyl)-1H-imidazole in 10 ml of anhydrous ethanol is refluxed together with 20 mg of potassium tert-butoxide for 2 hours under nitrogen, cooled and concentrated by evaporation to yield the title compound.

Preparation of the starting compound:

a) 1-(p-cyanophenylmethyl)-5-(2-formylethyl)-1H-imid-azole. A solution of 0.14 ml of dimethyl sulfoxide in 5 ml of methylene chloride is cooled to -78° under nitrogen, then 0.1 ml of oxalyl chloride is added dropwise. After 30 minutes, a solution of 0.24 g of 1-(p-cyanophenylmethyl)-5-(3-hydroxypropyl)-1H-imidazole in 1 ml of methylene chloride and 0.2 ml of dimethyl sulfoxide is added slowly. The reaction mixture is stirred at -78° for 2 hours, then 1 ml of triethylamine is added slowly. The reaction mixture is allowed to warm slowly to room temperature, is diluted with 30 ml of methylene chloride and washed three times with 10 ml of water. The organic phase is dried over sodium sulfate and concentrated by evaporation to yield the title

compound a) in the form of an oil; NMR (60 MHz): δ 5.15 (s, 2H), 9.65 (s, 1H).

Example 14: 5-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo-[1,5-a]pyridine. A solution of 1.6 g of 5-(p-cyanophenyl)-7,8-dihydroimidazo[1,5-a]pyridine in 50 ml of ethyl acetate is hydrogenated at atmospheric pressure with 0.2 g of 5 % palladium-on-carbon until the theoretical amount of hydrogen has been absorbed. The catalyst is filtered off and the solvent is evaporated to yield the title compound of m.p. 117-118°.

Example 15: 5-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo-[1,5-a]pyridine. A solution of 54 mg of 5-(p-cyanophenyl)imidazo[1,5-a]pyridine hydrochloride in 5.0 ml of methanol is hydrogenated for 30 minutes at room temperature under atmospheric pressure with 0.1 g of 10 % palladium-on-carbon. The catalyst is filtered off and 0.21 ml of 1N sodium hydroxide solution is added. The filtrate is concentrated by evaporation, taken up in 10 ml of methylene chloride and filtered through Celite®. Concentration by evaporation yields an oil which is chromatographed on silica gel with ethyl acetate to give the title compound of m.p. 117-118°.

Example 16: 5-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo-[1,5-a]pyridine. A mixture of 85 mg of 5-(p-bromophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine and 74 mg of copper(I) cyanide in 1 ml of N,N-dimethylformamide is heated at 120° for 11 hours under nitrogen. The reaction mixture is cooled, diluted with 10 ml of water and extracted with ethyl acetate. The organic extracts are dried over sodium sulfate and concentrated by evaporation. The resulting oil is chromatographed over silica gel with ethyl acetate to yield the title compound of m.p. 117-118°.

Example 17: 5-(p-bromophenyl)-5,6,7,8-tetrahydroimidazo-[1,5-a]pyridine. A lithium diisopropylamide solution, prepared at 0° from 0.12 ml of diisopropylamine and 0.33 ml of n-butyllithium (2.5 M) in 2 ml of tetrahydrofuran under nitrogen, is added at -78° to a solution of 0.13 ml of N,N,N',N'-tetramethylethylenediamine and 0.124 g of 1-(p-bromobenzyl)-5-(3-chloropropyl)-1H-imidazole in 2 ml of tetrahydrofuran. The reaction mixture is stirred for 3.5 hours, the reaction is stopped at -78° by adding saturated ammonium chloride solution and the mixture is extracted with methylene chloride (3x10 ml). The organic extracts are dried over sodium sulfate and concentrated by evaporation to yield the title compound which is purified by being converted into the corresponding hydrochloride, m.p. 216°.

Preparation of the starting compounds:

a) 1-(p-bromobenzyl)-5-(3-hydroxypropyl)-1H-imidazole. A solution of 11.2 g of 1-dimethylcarbamoyl-4-(3-trimethylsilyloxypropyl)-1H-imidazole and 12.49 g of p-bromobenzyl bromide in 110 ml of acetonitrile is refluxed for 24 hours. The solution is cooled to 0° and ammonia gas is bubbled into the reaction mixture for 5 minutes. After a further 45 minutes at room temperature, the solvent is evaporated. The residue is taken up in 100 ml of 1N hydrochloric acid and extracted with 50 ml of ether. The aqueous phase is adjusted to pH 8 and extracted with ethyl acetate (5x50 ml). The organic extracts are washed with water, dried over sodium sulfate and concentrated by evaporation. The resulting oil is chromatographed over 530 g of silica gel with ethyl acetate:methanol:saturated ammonia solution (90:5:5) to yield the title compound a) in the form of an oil; NMR δ 5.00 (s, 2H).

b) 1-(p-bromobenzyl)-5-(3-chloropropyl)-1H-imidazole. 1-(p-bromobenzyl)-5-(3-hydroxypropyl)-1H-imidazole is treated with thionyl chloride analogously to the method described in Example 1c) to yield the title compound b).

Example 18: 5-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo-[1,5-a]pyridine. A solution of 2.01 g of 5-(p-formyl-phenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine and 0.96 g of hydrazoic acid in 30 ml of benzene is kept at room temperature by external cooling while 0.8 ml of concentrated sulfuric acid is added dropwise. The reaction mixture is stirred for 2 hours and then neutralised. The organic phase is separated, dried over sodium sulfate and concentrated by evaporation to yield an oil which is chromatographed over silica gel with ethyl acetate to give the title compound; m.p. 117-118°.

Example 19: 5-(p-hydroxymethylphenyl)-5,6,7,8-tetrahydro-imidazo[1,5-a]pyridine. A solution of 0.40 g of 5-(p-ethoxycarbonylphenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]-pyridine in 20 ml of methylene chloride is cooled to -70° under nitrogen, and 4.0 ml of 1.53 M diisobutylaluminium hydride solution in toluene are added dropwise thereto. The reaction mixture is allowed to warm to room temperature, the reaction is stopped by adding 3.2 ml of methanol and 15 ml of water and the reaction mixture is filtered through Celite^{R}. The phases are separated, and the organic phase is dried over sodium sulfate and concentrated by evaporation to yield the title compound of m.p. 142-145°.

Example 20: 5-(p-formylphenyl)-5,6,7,8-tetrahydroimidazo-[1,5-a]pyridine. A solution of 0.16 ml of dimethyl sulfoxide in 16 ml of methylene chloride is cooled to -70° under nitrogen and 0.17 g of oxalyl chloride are

added dropwise thereto. The reaction mixture is stirred for 30 minutes, then 0.24 g of 5-(p-hydroxymethylphenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine, dissolved in 4 ml of methylene chloride, is added slowly. The reaction mixture is stirred at -70° for 2 hours, then 0.8 ml of triethylamine is added dropwise, and the reaction mixture is allowed to warm slowly to room temperature. The mixture is diluted with 20 ml of methylene chloride, washed with water, dried over sodium sulfate and concentrated by evaporation to yield the title compound which is purified by being converted into the corresponding fumarate; m.p. 131°.

Example 21: 5-(p-cyanophenyl)-5-methylthio-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine hydrochloride. A solution of lithium diisopropylamide is prepared from 0.6 ml of n-butyllithium (2.5 M) and 0.15 g of diisopropylamine in 5 ml of dry tetrahydrofuran at 0° under nitrogen. It is added at -78° to 0.29 g of 5-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine in 10 ml of tetrahydrofuran. The reaction mixture is stirred for 30 minutes, then 0.14 g of dimethyl sulfide is added dropwise. After 30 minutes, cooling is discontinued, the reaction mixture is allowed to warm to room temperature and the reaction is stopped by adding 10 ml of saturated ammonium chloride solution. The phases are separated, and the organic phase is washed with cold 1N hydrochloric acid. The aqueous phase is neutralised and extracted with ethyl acetate. The organic extracts are dried over sodium sulfate and concentrated by evaporation to an oil which is chromatographed over silica gel with 5 % isopropanol in ethyl acetate. The resulting oil is dissolved in acetone and treated with 0.1 ml of 4N ethereal hydrogen chloride to yield the title compound of m.p. 204-205°.

Example 22: 5-(p-cyanophenyl)-5-ethoxycarbonyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine. In a manner analogous to that described in Example 21, the title compound is obtained by reaction of 5-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine with ethyl chloroformate.

Example 23: 5-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo-[1,5-a]pyridine. A solution of 1.65 g of 5-(p-cyanophenyl)-5-ethoxycarbonyl-5,6,7,8-tetrahydroimidazo-[1,5-a]pyridine in 10 ml of methanol containing 0.2 g of sodium hydroxide is stirred at room temperature for 3 hours whereupon 5 ml of 1N hydrochloric acid are added. The reaction mixture is refluxed for 1 hour, cooled and concentrated by evaporation. The residue is partitioned between water and ethyl acetate. The organic phase is separated, dried over sodium sulfate and concentrated by evaporation to yield the title compound; m.p. 117-118°.

Preparation of the starting compounds:

a) A solution of 1.9 g of ethyl p-cyanophenylacetate in 50 ml of diglyme is added to a mixture of 0.48 g of sodium hydride (50 % oil dispersion) in 10 ml of diglyme. The reaction mixture is stirred at room temperature for 2 hours, cooled to 0°, and 1.75 g of N-bromosuccinimide, divided into several portions, are added thereto. The solvent is evaporated under a high vacuum and the residue is chromatographed over 50 g of silica gel with ether to yield ethyl α-bromo-p-cyanophenylacetate.

b) A solution of 97.0 g of 4-(3-trimethylsilyloxypropyl)-1H-imidazole-1-N,N-dimethyl-carboxamide and 72.0 g of ethyl α-bromo-p-cyanophenylacetate in 500 ml of acetonitrile is refluxed for 10 hours. The solution is cooled to 0° in an ice bath and ammonia gas is bubbled in for a

few minutes. The mixture is concentrated by evaporation in vacuo to give a residue which is dissolved in 500 ml of 1N hydrochloric acid. The solution is left to stand at room temperature for 15 minutes and is then extracted with ether. The pH of the aqueous phase is adjusted to 9 with 50 % sodium hydroxide solution, and the mixture is extracted with methylene chloride. The methylene chloride extracts are washed with water, dried over sodium sulfate and concentrated by evaporation to yield 1-(α-ethoxycarbonyl-p-cyanobenzyl)-1H-imidazole-5-propanol.

c) 8.4 g of 1-(α-ethoxycarbonyl-p-cyanobenzyl)-1H-imidazole-5-propanol are added as a solid, in portions, to a solution of 5.75 g of thionyl chloride in 80 ml of methylene chloride. When the addition is complete, the solution is refluxed for 1.5 hours, cooled in an ice bath and filtered to yield 5-(3-chloropropyl)-1-(α-ethoxycarbonyl-p-cyanobenzyl)-1H-imidazole hydrochloride. The salt is partitioned between methylene chloride and saturated sodium hydrogen carbonate solution. The organic extracts are washed with water, dried over sodium sulfate and concentrated by evaporation to yield the free base.

d) A solution of 8.1 g of 5-(3-chloropropyl)-1-(α-ethoxycarbonyl-p-cyanobenzyl)-1H-imidazole in 50 ml of tetrahydrofuran is cooled to 0° in an ice bath. 8.0 g of potassium tert-butoxide are added as a solid in several portions. The mixture is stirred at room temperature for 2 hours, neutralised with 10 % acetic acid and partitioned between methylene chloride and water. The organic phase is washed with water, dried over magnesium sulfate and concentrated by evaporation to yield an oil which is dissolved in a small volume of acetone and neutralised with ethereal hydrogen chloride. The solid is collected

and 5-(p-cyanophenyl)-5-ethoxycarbonyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine is obtained.

Example 24: 5-(p-cyanophenyl)5,6,7,8-tetrahydroimidazo-[1,5-a]pyridine. A solution of 2.13 g of 5-(p-aminophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine in 4 ml of concentrated hydrochloric acid and 10 ml of water is cooled in an ice bath, whereupon a solution of 0.78 g of sodium nitrite in 2 ml of water is added slowly. This mixture is added via a dropping funnel to an ice-cooled solution of 3.0 g of copper(I) cyanide in 10 ml of water, the temperature being maintained between 30 and 40°. The reaction mixture is heated on a steam bath for 1 hour, cooled and adjusted to pH 9. The organic extracts are dried over sodium sulfate and concentrated by evaporation, and the residue is chromatographed over silica gel with ethyl acetate to yield the title compound.

Example 25: 5-(p-aminophenyl)-5,6,7,8-tetrahydroimidazo-[1,5-a]pyridine. A solution of 2.42 g of 5-(p-carboxyphenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine in 100 ml of ethylene dichloride is treated with 6 ml of concentrated sulfuric acid. The reaction mixture is heated to 40°, then 6 ml of hydrazoic acid (2 M in ethylene dichloride) are added dropwise. When gas evolution has ceased, the reaction mixture is concentrated by evaporation. The residue is dissolved in water and adjusted to pH 10. The aqueous phase is extracted with methylene chloride (3x30 ml). The organic extracts are dried over potassium carbonate and concentrated by evaporation to yield the title compound.

Example 26: 10 000 tablets, each containing 10 mg of the active ingredient, are prepared:

Composition:

5-(p-cyanophenyl)-5,6,7,8-tetrahydro-imidazo[1,5-a]pyridine	100.00 g
lactose	2535.00 g
corn starch	125.00 g
polyethylene glycol 6000	150.00 g
magnesium stearate	40.00 g
purified water	quantum satis

Procedure:

All the pulverulent constituents are sieved through a sieve of 0.6 mm mesh width. Then the active ingredient, lactose, magnesium stearate and half of the starch are mixed in a suitable mixer. The other half of the starch is suspended in 65 ml of water and the suspension is added to a boiling solution of the polyethylene glycol in 260 ml of water. The resulting paste is added to the powders and the mixture is granulated, if necessary with the addition of more water. The granulate is dried overnight at 35°, forced through a sieve of 1.2 mm mesh width and compressed into tablets having a breaking notch.

Example 27: 1000 capsules, each containing 20 mg of the active ingredient, are prepared:

Composition:

5-(p-cyanophenyl)-5,6,7,8-tetrahydro-imidazo[1,5-a]pyridine	20.00 g
lactose	207.00 g
modified starch	80.00 g
magnesium stearate	3.00 g

Procedure:
All the pulverulent constituents are sieved through a sieve of 0.6 mm mesh width. The active ingredient is then mixed, in a suitable mixer, first with magnesium stearate and then with the lactose and the starch until the mixture is homogeneous. Hard gelatin capsules No. 2 are each filled with 310 mg of the resulting mixture using a capsule-filling machine.

In accordance with Examples 26 and 27, tablets and capsules containing approximately from 10 to 100 mg of other compounds of the invention, for example of any other compound described in the Examples, are prepared.

Example 28: A solution of 0.52 g of 5-(p-hydroxymethylphenyl)imidazo[1,5-a]pyridine in 10 ml of methylene chloride is refluxed for 24 hours with 5.2 g of activated manganese dioxide. A further 5.2 g of manganese dioxide are added and the reaction mixture is boiled again for 6 hours, then filtered off. Evaporation of the solvent yields 5-(p-formylphenyl)imidazo[1,5-a]pyridine, m.p. 144-146°.

Example 29: A solution of 0.18 g of 5-(p-carboxyphenyl)-imidazo[1,5-a]pyridine hydrochloride in 5 ml of thionyl chloride is refluxed for 30 minutes and concentrated to dryness by evaporation. The resulting oil is taken up in 10 ml of methylene chloride, and ammonia gas is bubbled into the solution at 0° for 1 hour. The solution is washed with water and dried over sodium sulfate. Concentration by evaporation yields 5-(p-carbamoylphenyl)imidazo[1,5-a]pyridine, m.p. 228-230° (decomp.).

Example 30: A solution of 3.13 g of 4-[3-(4-tert-butylaminocarbonylphenyl)-3-chloroprop-1-yl]-1-tritylimidazole in 150 ml of acetonitrile is refluxed for 15 hours,

cooled and 150 ml of methanol are added thereto. The reaction mixture is boiled for a further 15 hours, then concentrated to dryness by evaporation. The residue is partitioned between ether and water. The ethereal phase is separated and washed with 1N HCl (2x15 ml). The combined aqueous extracts are adjusted to pH 8 and extracted with methylene chloride. The methylene chloride extract is dried over sodium sulfate, filtered and concentrated by evaporation to a white foam. Recrystallisation from ether yields 1.30 g of 5H-5-(4-tert-butylaminocarbonylphenyl)-6,7-dihydropyrrolo[1,2-c]-imidazole, m.p. 136-139°.

Preparation of the starting compounds:

a) A solution of 6.0 g of methyl 3-(1H-imidazol-4-yl)propionate and 11 ml of triethylamine in 31 ml of dimethylformamide is treated with a solution of 9.65 g of triphenylmethyl chloride in 110 ml of dimethylformamide at room temperature under nitrogen for 2 hours. The reaction mixture is poured onto 700 g of ice, and the resulting solid is collected by filtrated and recrystallised from ether to yield 13.83 g of methyl 3-(1-trityl-imidazol-4-yl)propionate; NMR ($CDCl_3$) δ = 2.75 (m, 4H), 3.05 (s, 3H), 6.5-7.5 (m, 17H).

b) A solution of 44.4 mmol of diisobutylaluminium hydride in 29 ml of toluene is added at -72° under nitrogen to a solution of 8.79 g of methyl 3-(1-tritylimidazol-4-yl)propionate in 175 ml of methylene chloride. After 5 minutes, the reaction is stopped by adding 14 ml of methanol and then 90 ml of water. The reaction mixture is allowed to warm to room temperature and is filtered through Celite®. The organic phase is separated, dried over sodium sulfate and concentrated by evaporation to a yellow oil which is chromatographed on 280 g of silica

gel with ether to yield 4.13 g of 3-(1-tritylimidazol-4-yl)propionaldehyde in the form of an oil. IR ($CDCl_3$): 2830, 2740, 1730 cm^{-1}.

c) A solution of 25 mmol of n-butyllithium in 10 ml of hexane is added dropwise at -70° under argon to a solution of 3.19 g of N-tert-butyl-4-bromobenzamide in 250 ml of tetrahydrofuran. After 30 minutes, a solution of 3.74 g of 3-(1-tritylimidazol-4-yl)propionaldehyde in 100 ml of tetrahydrofuran is added slowly. The reaction mixture is stirred at -70° for 30 minutes; it is then allowed to warm to 25° and is stirred at 25° for 2.5 hours, and the reaction is stopped by adding an excess of saturated ammonium chloride solution. The aqueous phase is separated and extracted with methylene chloride (2x100 ml). The combined organic extracts are dried over sodium sulfate and concentrated by evaporation. The residue is chromatographed over 220 g of silica gel with 5:1 ether:ethyl acetate to yield 4-[3-(4-tert-butylaminocarbonylphenyl)-3-hydroxyprop-1-yl]-1-tritylimidazole in the form of an oil. IR (CH_2Cl_2): 1660 cm^{-1}.

d) A solution of 3.21 g of 4-[3-(4-tert-butylaminocarbonylphenyl)-3-hydroxyprop-1-yl]-1-tritylimidazole and 1.5 ml of thionyl chloride in 50 ml of methylene chloride is refluxed for 1 hour, cooled and poured into 50 ml of an ice-cold sodium hydrogen carbonate solution. The organic phase is separated, dried over sodium sulfate and concentrated by evaporation to yield 4-[3-(4-tert-butylaminocarbonylphenyl)-3-chloroprop-1-yl]-1-tritylimidazole in the form of a white foam. NMR ($CDCl_3$): δ = 1.45 (s, 9H), 4.30 (t, J=6.0 Hz, 2H).

Example 31: A solution of 1.25 g of 5H-5-(4-tert-butylaminocarbonylphenyl)-6,7-dihydropyrrolo[1,2-c]-

imidazole in 10 ml of thionyl chloride is refluxed for 1 hour, cooled and concentrated by evaporation. The residue is taken up in 10 ml of chloroform at 0°, and 10 ml of ice-cold aqueous ammonia solution are added slowly. The aqueous phase is separated and extracted with chloroform (3x20 ml), and the combined organic extracts are dried over sodium sulfate. After filtration, concentration by evaporation and chromatography with 5 % aqueous ammonia solution in ethyl acetate over 45 g of silica gel, an oil is obtained which is treated with one molar equivalent of ethereal hydrogen chloride and yields 0.5 g of 5H-5-(4-cyanophenyl)-6,7-dihydropyrrolo[1,2-c]imidazole hydrochloride, m.p. 227-228°.

Example 32: A solution of 1.29 g of 5H-5-(4-tert-butylaminocarbonylphenyl)-6,7,8,9-tetrahydroimidazo[1,5-a]azepine in 10 ml of thionyl chloride is refluxed for 1 hour, cooled and concentrated by evaporation. The residue is partitioned between methylene chloride and an ice-cold sodium hydrogen carbonate solution. The aqueous phase is separated and extracted with methylene chloride (3x15 ml). The combined organic phases are dried over sodium sulfate and concentrated by evaporation. The resulting oil is chromatographed over 26 g of silica gel with 5 % methanol in methylene chloride. The product is treated with 1 molar equivalent of fumaric acid dissolved in ethanol, to yield 5H-5-(4-cyanophenyl)-6,7,8,9-tetrahydroimidazo[1,5-a]azepine fumarate, m.p. 153-155°.

The starting compound is prepared from ethyl 5-(1-tritylimidazol-4-yl)-1-pentanoate analogously to the above-described preparation of 5H-5-(4-tert-butylaminocarbonylphenyl)-6,7-dihydropyrrolo[1,2-c]imidazole from ethyl 3-(1-tritylimidazol-4-yl)propionate. Ethyl 5-(1-tritylimidazol-4-yl)-1-pentanoate is prepared as follows:

a) A solution of 5.6 ml of diisopropylamine in 150 ml of tetrahydrofuran is treated at -70° under nitrogen with 14.5 ml of 2.5 M n-butyllithium solution for 30 minutes; then, 7.2 ml of triethylphosphonoacetate are added dropwise. After 30 minutes, a solution of 10.09 g of 3-(1-tritylimidazol-4-yl)propionaldehyde in 50 ml of tetrahydrofuran is added slowly. The reaction mixture is allowed to warm slowly to room temperature and is stirred for 15 hours, and the reaction is stopped by adding excess saturated ammonium chloride solution. The aqueous phase is separated and extracted with ethyl acetate (2x50 ml). The combined organic extracts are dried over sodium sulfate and concentrated by evaporation to an oil (15.35 g) which is chromatographed over 430 g of silica gel using ether and yields 9.61 g of ethyl 5-(1-trityl-imidazol-4-yl)-1-pent-2-enoate of m.p. 86-88°.

b) A solution of 9.20 g of ethyl 5-(1-tritylimidazol-4-yl)-1-pent-2-enoate in 460 ml of anhydrous ethanol is hydrogenated with 1.88 g of 10 % palladium-on-carbon at atmospheric pressure for 20 minutes. The catalyst is removed by filtration through Celite®. Concentration by evaporation yields a solid which is recrystallised from hexane to yield 8.64 g of ethyl 5-(1-tritylimidazol-4-yl)-1-pentanoate of m.p. 84-86°.

Example 33: A solution of 1.27 g of ethyl 5-[1-(4-cyano-benzyl)imidazol-5-yl]-1-pent-2-enoate in 27 ml of tetrahydrofuran is treated at 5° under nitrogen with 0.52 g of potassium tert-butoxide. The reaction mixture is stirred at 5° for 2 hours, then 10 ml of 1N hydrochloric acid are added. The phases are separated. The organic phase is extracted with 1N hydrochloride acid (2x10 ml). The combined aqueous phases are extracted with ether, adjusted to pH 8 and extracted with methylene chloride (3x15 ml). The organic phase is dried and

concentrated by evaporation to yield an end product which is treated with 1 molar equivalent of ethereal hydrogen chloride. The solid obtained is recrystallised from acetone to yield 5-(4-cyanophenyl)-6-ethoxycarbonyl-methyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine, m.p. 126-127°.

Preparation of the starting compounds:

a) A solution of 2.9 ml of dry dimethyl sulfoxide in 250 ml of methylene chloride is cooled to -78° under nitrogen, and 2.1 ml of oxalyl chloride are added dropwise thereto. After 30 minutes at -78°, a solution of 5.0 g of 3-[1-(4-cyanobenzyl)imidazol-5-yl]-1-propanol in 18 ml of dimethyl sulfoxide is added slowly. The reaction mixture is stirred for 2 hours, then 10.4 ml of triethylamine are added. The reaction mixture is allowed to warm to room temperature and is washed with water (4x100 ml). The organic phase is dried over sodium sulfate and concentrated by evaporation to yield 4.13 g of 3-[1-(4-cyanobenzyl)imidazol-5-yl]-1-propionaldehyde. IR (CH_2Cl_2): 2750, 2250, 1732 cm^{-1}.

b) A solution of 23 mmol of lithium diisopropylamide, prepared from 3.2 ml of diisopropylamine and 9.2 ml of 2.5 M n-butyllithium in 170 ml of tetrahydrofuran at 0° under nitrogen, is cooled to -78°, and 4.2 ml of triethylphosphonoacetate are added dropwise thereto. After 30 minutes, a solution of 4.1 g of 3-[1-(4-cyanobenzyl)-imidazol-5-yl]-1-propionaldehyde in 30 ml of tetrahydrofuran is added slowly. The reaction mixture is stirred at -78° for 2 hours; it is allowed to warm to room temperature and is stirred for a further 15 hours before the reaction is stopped by adding excess saturated ammonium chloride solution. The aqueous phase is separated and extracted with ethyl acetate (2x50 ml).

The combined organic phases are dried over sodium sulfate and concentrated by evaporation to yield a yellow oil which is chromatographed over 20 g of silica gel with ether:ethyl acetate 1:1 and yields 3.56 g of ethyl 5-[1-(4-cyanobenzyl)imidazol-5-yl]-1-pent-2-enoate.
IR (CH_2Cl_2): 2240, 1720 cm^{-1}.

Example 34: A solution of 0.21 g of 5-(4-cyanophenyl)-6-ethoxycarbonylmethyl-5,6,7,8-tetrahydroimidazo[1,5-a]-pyridine hydrochloride in 1.2 ml of ethanol and 1.2 ml of 1N sodium hydroxide solution is stirred at room temperature for 15 hours, then concentrated by evaporation, and the residue is dissolved in water. The aqueous phase is extracted with ethyl acetate, adjusted to pH 2, neutralised and concentrated by evaporation. The residue is triturated with tetrahydrofuran. The organic phase is treated with ethereal hydrogen chloride to yield 0.12 g of 5-(4-cyanophenyl)-6-carboxymethyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine hydrochloride, m.p. 209-211°.

Example 35: A solution of 0.80 mmol of lithium diisopropylamide, prepared from 0.12 ml of diisopropylamine and 0.32 ml of 2.5 M n-butyllithium in 6 ml of tetrahydrofuran at 0°, is slowly added at -78° to a solution of 0.17 g of 5-(4-cyanophenyl)-5,6,7,8-tetrahydroimidazo-[1,5-a]pyridine in 2 ml of tetrahydrofuran. After 0.5 hour, 0.1 ml of benzyl bromide is added dropwise. The reaction mixture is stirred for a further hour, then the reaction is stopped by adding 5 ml of water, and the mixture is acidified with 1N hydrochloric acid and diluted with 20 ml of ether, whereupon the phases are separated. The aqueous phase is adjusted to pH 7 and extracted with ethyl acetate (3x15 ml). The organic extracts are dried over sodium sulfate. Filtration and concentration by evaporation yield a foam which is treated with 1 molar equivalent of ethereal hydrogen

chloride and yields 5-benzyl-5-(4-cyanophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine hydrochloride, m.p. 249-251°.

Example 36: 7-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo-[1,5-a]pyridine hydrochloride, m.p. 253-254°, is prepared from 4-(p-ethoxycarbonylphenyl)pyridine in a manner analogous to that described in Examples 4, 8-10 and 7.

Example 37: 7-(p-carbamoylphenyl)-5,6,7,8-tetrahydro-imidazo[1,5-a]pyridine fumarate, m.p. 193-195°, is prepared from 4-(p-ethoxycarbonylphenyl)pyridine in a manner analogous to that described in Examples 4 and 8-10.

Example 38: A solution of 1.65 g of 5-(p-cyanophenyl)-3-ethoxycarbonyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine in 10 ml of methanol containing 0.2 g of sodium hydroxide is stirred at room temperature for 3 hours. The solution is heated to boiling point and 5 ml of 1N hydrochloric acid are added. After 1 hour, the reaction mixture is cooled and concentrated by evaporation. The residue is partitioned between water and ethyl acetate. The organic phase is separated, dried over sodium sulfate and concentrated by evaporation to yield 5-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine, m.p. 128-131°.

Preparation of the starting compounds:

a) A solution of 2.0 g of 2-aminomethyl-6-(p-cyano-phenyl)pyridine in 20 ml of methylene chloride is treated at -15° under nitrogen with 1.4 g of oxalic acid mono-ethyl ester chloride. The reaction mixture is allowed to warm to room temperature within 2 hours and the solvent is evaporated. The residue is dissolved in 30 ml of phosphorus oxychloride, and the mixture is refluxed for

15 hours and then concentrated to dryness by evaporation. The residue is partitioned between methylene chloride and a sodium hydrogen carbonate solution. The organic phase is separated, dried over sodium sulfate and concentrated by evaporation to yield an oil which is chromatographed over 100 g of silica gel using ethyl acetate as eluant to yield 5-(p-cyanophenyl)-3-ethoxy-carbonyl-imidazo[1,5-a]pyridine.

b) A solution of 1.1 g of 5-(p-cyanophenyl)-3-ethoxy-carbonyl-imidazo[1,5-a]pyridine in 30 ml of ethanol is hydrogenated with 0.1 g of 10 % palladium-on-carbon at a pressure of 1 bar for 2 hours, is filtered and concentrated to dryness by evaporation. The resulting oil is partitioned between water and ethyl acetate. The organic phase is separated, dried over sodium sulfate and concentrated by evaporation. The residue is chromatographed over 40 g of silica gel with ethyl acetate to yield 5-(p-cyanophenyl)-3-ethoxycarbonyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine.

Example 39: A solution of 0.24 g of 1-(p-cyanophenyl)-4-(4-imidazolyl)-1-butanone in 20 ml of methanol at room temperature is treated with 0.2 g of sodium cyanoborohydride. The pH is adjusted to 5.5-6.0, and kept in that range, by adding concentrated hydrochloric acid. The reaction mixture is stirred for 2 hours, adjusted to pH 2 and concentrated to dryness by evaporation. The residue is taken up in methylene chloride and washed with saturated sodium hydrogen carbonate solution. The organic phase is dried over sodium sulfate and concentrated by evaporation to yield 5-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine.

Preparation of the starting compounds:

a) 6.95 g of N-tert-butyl-p-bromobenzamide are dissolved at -70° under nitrogen in 175 ml of tetrahydrofuran, and 20.1 ml of n-butyllithium (2.7 M) are added dropwise thereto. After 30 minutes, a solution of 5.35 g of 4-(1-trityl-4-imidazolyl)-butanoic acid in 10 ml of tetrahydrofuran is added slowly. The reaction mixture is allowed to warm slowly to room temperature and 20 ml of an ammonium chloride solution are added thereto. The organic phase is separated, dried over sodium sulfate and concentrated by evaporation to yield 1-(p-N-tert-butylaminocarbonylphenyl)-4-(1-trityl-4-imidazolyl)-1-butanone.

b) A solution of 0.5 g of 1-(p-N-tert-butylaminocarbonylphenyl)-4-(1-trityl-4-imidazolyl)-1-butanone in 20 ml of thionyl chloride is refluxed for 3 hours, then poured into 100 ml of ice-water. The aqueous phase is extracted with ether (3x20 ml), adjusted to pH 10 and again extracted with methylene chloride. The organic phase is dried and concentrated by evaporation to yield 1-(p-cyanophenyl)-4-(4-imidazolyl)-1-butanone.

Example 40: Racemic 5-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine hydrochloride is chromatographed in 20 mg portions over a 4.6 x 250 mm column packed with silica gel bound to β-cyclodextrin, using a 7:3 mixture of water:methanol as eluant, at a dropping rate of 0.8 ml/min. The fractions are separately concentrated by evaporation in vacuo to yield (-)-5-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine, $[\alpha]_D^{25} = -89.2°$, and (+)-5-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo-[1,5-a]pyridine, $[\alpha]_D^{25} = +85.02°$. Both compounds are dissolved separately in acetone and are each treated with 1 molar equivalent of ethereal hydrogen chloride to yield

the corresponding hydrochlorides of m.p. 82-83° (amorphous) and m.p. 218-220°, respectively.

Example 41: In a manner analogous to that described in the preceding Examples, the following compounds also can be prepared:

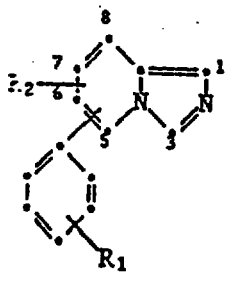
5-(m-cyanophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]-pyridine,
5-(o-cyanophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]-pyridine,
5H-5-(3-cyanophenyl)-6,7-dihydropyrrolo[1,2-c]imidazole,
5H-5-(2-cyanophenyl)-6,7-dihydropyrrolo[1,2-c]imidazole,
5-(m-cyanophenyl)imidazo[1,5-a]pyridine,
5-(o-cyanophenyl)imidazo[1,5-a]pyridine,
6-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]-pyridine,
8-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]-pyridine.

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Patent Claims

for the Contracting States: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE.

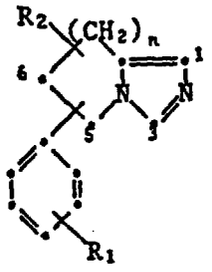
1. The use of substituted imidazo[1,5-a]pyridine derivatives of formula I



(I)

wherein R_1 represents hydrogen, lower alkyl; lower alkyl substituted by hydroxy, lower alkoxy, lower alkanoyloxy, lower alkanoyl, amino, lower alkylamino, di-lower alkylamino, halogen, sulfo, carboxy, lower alkoxycarbonyl, carbamoyl or cyano; nitro, halogen, hydroxy, lower alkoxy, lower alkanoyloxy, phenylsulfonyloxy, lower alkylsulfonyloxy, mercapto, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, lower alkanoylthio, amino, lower alkylamino, di-lower alkylamino, lower alkyleneamino, N-morpholino, N-thiomorpholino, optionally 4-lower alkyl-substituted N-piperazino, tri-lower alkylammonio, sulfo, lower alkoxysulfonyl, sulfamoyl, lower alkylsulfamoyl, di-lower alkylsulfamoyl, formyl; iminomethyl optionally N-substituted by hydroxy, lower alkoxy, lower alkanoyloxy, lower alkyl, phenyl or amino; C_2-C_7alkanoyl, benzoyl, carboxy, lower alkoxycarbonyl, carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl, cyano, 5-tetrazolyl, optionally lower alkyl-substituted 4,5-dihydro-2-oxazolyl or hydroxycarbamoyl; and R_2 represents hydrogen, lower alkyl, phenyl-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, halogen, hydroxy, lower alkoxy, lower alkanoyloxy, mercapto, lower alkylthio, phenyl-lower alkylthio,

phenylthio, lower alkanoylthio, carboxy, lower alkoxycarbonyl or lower alkanoyl; the 7,8-dihydro derivatives thereof; or compounds of formula I*



(I*)

wherein n denotes 0, 1, 2, 3 or 4; and R_1 and R_2 are as defined above under formula I; it being possible for the phenyl ring within the radicals phenylsulfonyloxy, phenyliminomethyl, benzoyl, phenyl-lower alkyl, phenyl-lower alkylthio and phenylthio to be unsubstituted or substituted by lower alkyl, lower alkoxy or halogen; and in a compound of formula I* it being possible for the two substituents C_6H_4-R_1 and R_2 to be attached to any of the saturated carbon atoms of the saturated ring, either both to the same carbon atom or to different carbon atoms; radicals designated "lower" containing up to 7 carbon atoms; stereoisomers, mixtures of these stereoisomers, or pharmaceutically acceptable salts thereof, for the manufacture of pharmaceutical preparations for the treatment of diseases responsive to aromatase inhibition.

2. The use according to claim 1, wherein compounds of formula I wherein R_1 represents lower alkyl; lower alkyl substituted by hydroxy, amino, di-lower alkylamino, 1 to 5 fluorine atoms, carboxy, lower alkoxycarbonyl, carbamoyl or cyano; nitro, halogen, hydroxy, lower alkoxy, amino, lower alkylamino, di-lower alkylamino, sulfo, sulfamoyl, formyl, iminomethyl; iminomethyl N-substituted by hydroxy, lower alkoxy, lower alkanoyloxy, lower alkyl or phenyl; carboxy, lower alkoxycarbonyl, carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl or cyano;



and R_2 is hydrogen, lower alkyl, lower alkoxy or halogen; or compounds of formula I* wherein n denotes 1, 2 or 3; R_1 is as defined above under formula I and R_2 represents hydrogen, lower alkyl, phenyl-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, halogen, lower alkoxy, lower alkylthio, phenyl-lower alkylthio, phenylthio, carboxy, lower alkoxycarbonyl or lower alkanoyl; in a compound of formula I* it being possible for the two substituents C_6H_4-R_1 and R_2 to be attached to any of the saturated carbon atoms of the saturated ring, either both to the same carbon atom or to different carbon atoms; stereoisomers, mixtures of these stereoisomers, or pharmaceutically acceptable salts thereof, are used as specified above.

3. The use according to claim 1, wherein compounds of formula I wherein R_1 represents lower alkyl, hydroxy-lower alkyl, halogen, amino, formyl, carboxy, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl or cyano; and R_2 is hydrogen; or compounds of formula I* wherein n denotes 1, 2 or 3; R_1 is as defined above under formula I and R_2 represents hydrogen, lower alkylthio, lower alkoxycarbonyl, phenyl-lower alkyl, carboxy-lower alkyl or lower alkoxycarbonyl-lower alkyl; in a compound of formula I* it being possible for the two substituents C_6H_4-R_1 and R_2 to be attached to any of the saturated carbon atoms of the saturated ring, either both to the same carbon atom or to different carbon atoms; stereoisomers, mixtures of these stereoisomers, or pharmaceutically acceptable salts thereof, are used.

4. Pharmaceutical preparations containing a compound of formula I as shown in claim 1, wherein R_1 represents halogen, hydroxy, mercapto, or lower alkyl substituted by lower alkoxy, lower alkanoyloxy or halogen; and R_2 is hydrogen, lower alkyl, lower alkoxy or halogen; or a

compound of formula I* as shown in claim 1, wherein n denotes 2, R_1 is as defined above under formula I and R_2 represents hydrogen, lower alkyl, phenyl-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, halogen, lower alkoxy, lower alkylthio, phenyl-lower alkylthio, phenylthio, carboxy, lower alkoxycarbonyl or lower alkanoyl; in a compound of formula I* it being possible for the two substituents C_6H_4-R_1 and R_2 to be attached to any of the saturated carbon atoms of the saturated ring, either both to the same carbon atom or to different carbon atoms; radicals designated "lower" containing up to 7 carbon atoms; a stereoisomer, a mixture of these stereoisomers or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable carriers.

5. Compounds of formula I as shown in claim 1, wherein R_1 represents hydrogen, lower alkyl; C_2-C_7alkyl substituted by hydroxy, lower alkoxy, halogen or lower alkanoyloxy; lower alkyl substituted by lower alkanoyl, amino, lower alkylamino, di-lower alkylamino, sulfo, lower alkoxycarbonyl, carbamoyl or cyano; nitro, lower alkoxy, lower alkanoyloxy, phenylsulfonyloxy, lower alkylsulfonyloxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, lower alkanoylthio, amino, lower alkylamino, di-lower alkylamino, lower alkyleneamino, N-morpholino, N-thiomorpholino, optionally 4-lower alkyl-substituted N-piperazino, tri-lower alkylammonio, sulfo, lower alkoxysulfonyl, sulfamoyl, lower alkylsulfamoyl, di-lower alkylsulfamoyl; iminomethyl optionally N-substituted by hydroxy, lower alkoxy, lower alkanoyloxy, lower alkyl, phenyl or amino; C_2-C_7alkanoyl or benzoyl; and R_2 represents hydrogen, lower alkyl, phenyl-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, halogen, hydroxy, lower alkoxy, lower alkanoyloxy, mercapto, lower alkylthio, phenyl-lower alkylthio,



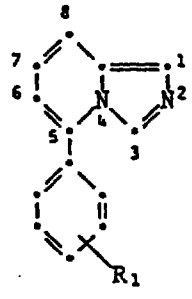
phenylthio, lower alkanoylthio, carboxy, lower alkoxycarbonyl or lower alkanoyl; the 7,8-dihydro derivatives thereof and also such 7,8-dihydro derivatives wherein R_1 is hydroxymethyl, lower alkoxymethyl, halomethyl, lower alkanoyloxymethyl, carboxy-lower alkyl, halogen, hydroxy, mercapto, formyl, carboxy, lower alkoxycarbonyl, carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl, cyano, 5-tetrazolyl, optionally lower alkyl-substituted 4,5-dihydro-2-oxazolyl or hydroxycarbamoyl and R_2 is as defined above under formula I; and compounds of formula I* as shown in claim 1, wherein n denotes 0, 1, 2, 3 or 4; R_1 is as defined above under formula I or R_1 may be, in addition, hydroxymethyl, lower alkoxymethyl, halomethyl, lower alkanoyloxymethyl, carboxy-lower alkyl, halogen, hydroxy, mercapto, formyl, carboxy, lower alkoxycarbonyl, carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl, cyano, 5-tetrazolyl, optionally lower alkyl-substituted 4,5-dihydro-2-oxazolyl or hydroxycarbamoyl if n represents 0, 1, 3 or 4 or if n represents 2 and R_2 is phenyl-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, lower alkanoyloxy, mercapto, lower alkylthio, phenyl-lower alkylthio, phenylthio, lower alkanoylthio, carboxy, lower alkoxycarbonyl or lower alkanoyl; and R_2 is as defined above under formula I; it being possible for the phenyl ring within the radicals phenylsulfonyloxy, phenyliminomethyl, benzoyl, phenyl-lower alkyl, phenyl-lower alkylthio and phenylthio to be unsubstituted or substituted by lower alkyl, lower alkoxy or halogen; and in a compound of formula I* it being possible for the two substituents C_6H_4-R_1 and R_2 to be attached to any of the saturated carbon atoms of the saturated ring, either both to the same carbon atom or to different carbon atoms; radicals designated "lower" containing up to 7 carbon atoms; stereoisomers, mixtures of these stereoisomers, and salts thereof.

6. Compounds according to claim 5 of formula I wherein R_1 represents lower alkyl, hydroxy-C_2-C_7alkyl; lower alkyl substituted by amino, di-lower alkylamino, 2 to 5 fluorine atoms, lower alkoxycarbonyl, carbamoyl or cyano; nitro, lower alkoxy, amino, lower alkylamino, di-lower alkylamino, sulfo, sulfamoyl, iminomethyl or iminomethyl N-substituted by hydroxy, lower alkoxy, lower alkanoyloxy, lower alkyl or phenyl; and R_2 is hydrogen, lower alkyl, lower alkoxy or halogen; and compounds of formula I* wherein n denotes 1, 2 or 3; R_1 is as defined above under formula I or R_1 may be, in addition, hydroxymethyl, carboxy-lower alkyl, halogen, hydroxy, formyl, carboxy, lower alkoxycarbonyl, carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl or cyano if n represents 1 or 3 or if n represents 2 and R_2 is phenyl-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, lower alkylthio, phenyl-lower alkylthio, phenylthio, carboxy, lower alkoxycarbonyl or lower alkanoyl; and R_2 represents hydrogen, lower alkyl, phenyl-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, halogen, lower alkoxy, lower alkylthio, phenyl-lower alkylthio, phenylthio, carboxy, lower alkoxycarbonyl or lower alkanoyl; in a compound of formula I* it being possible for the two substituents C_6H_4-R_1 and R_2 to be attached to any of the saturated carbon atoms of the saturated ring, either both to the same carbon atom or to different carbon atoms; stereoisomers, mixtures of these stereoisomers, and pharmaceutically acceptable salts thereof.

7. Compounds according to claim 5 of formula I* wherein n denotes 1, 2 or 3; R_1 represents lower alkyl, amino, lower alkylamino or di-lower alkylamino, or R_1 may be, in addition, hydroxymethyl, halogen, formyl, carboxy, lower alkoxycarbonyl, carbamoyl, lower alkylcarbamoyl, di-lower

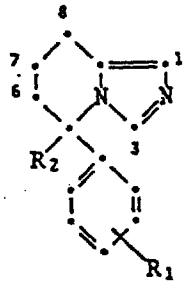
alkylcarbamoyl or cyano if n represents 1 or 3 or if n represents 2 and R_2 is phenyl-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, lower alkylthio, carboxy or lower alkoxycarbonyl; and R_2 is hydrogen, lower alkyl, phenyl-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, lower alkylthio, carboxy or lower alkoxycarbonyl; it being possible for the two substituents C_6H_4-R_1 and R_2 to be attached to any of the saturated carbon atoms of the saturated ring, either both to the same carbon atom or to different carbon atoms; stereoisomers, mixtures of these stereoisomers, and pharmaceutically acceptable salts thereof.

8. Compounds of formula Ia



(Ia)

wherein R_1 represents cyano, nitro or C_1-C_4alkyl, the 7,8-dihydro derivatives thereof and the 5,6,7,8-tetrahydro derivatives thereof of formula Ib



(Ib)

wherein R_1 is as defined above under formula Ia and R_2 is hydrogen, C_1-C_4alkyl, benzyl, halogen, C_1-C_4alkoxy, C_1-C_4alkylthio, benzylthio, 2-phenylethylthio, diphenylmethylthio, phenylthio, C_1-C_4alkanoyloxy, C_1-C_4alkanoylthio, carboxy-C_1-C_4alkyl, C_1-C_4alkoxycarbonyl-C_1-C_4alkyl

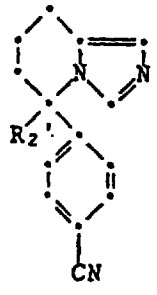
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or C_1-C_4alkanoyl, stereoisomers, mixtures of these stereoisomers, and salts of these compounds.

9. Compounds according to claim 8 of formula Ia wherein R_1 represents cyano, the 7,8-dihydro derivatives thereof, and the 5,6,7,8-tetrahydro derivatives thereof of formula Ib wherein R_1 is cyano and R_2 is hydrogen, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4alkylthio, benzylthio, 2-phenylethylthio, diphenylmethylthio, phenylthio or C_1-C_4alkanoyl, and pharmaceutically acceptable acid addition salts of compounds of formulae Ia and Ib.

10. Compounds according to claim 8 of formula Ia wherein R_1 is cyano, the 7,8-dihydro derivatives thereof, and the 5,6,7,8-tetrahydro derivatives thereof of formula Ib wherein R_1 is as defined above under formula Ia and R_2 is hydrogen, and pharmaceutically acceptable acid addition salts thereof.

11. Compounds according to claim 8 of formula Ic



(Ic)

wherein R_2' is hydrogen, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4-alkylthio, benzylthio, 2-phenylethylthio, diphenylmethylthio, phenylthio or C_1-C_4alkanoyl, and pharmaceutically acceptable acid addition salts thereof.

12. A compound of formula Ic according to claim 11, wherein R_2' is hydrogen, being 5-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine, and pharmaceutically acceptable acid addition salts thereof.

13. Compounds of formula Ia as shown in claim 8, wherein R_1 represents hydrogen, p-toluenesulfonyloxy, benzenesulfonyloxy, methylsulfonyloxy, sulfo, amino, carbamoyl, C_1-C_4alkylcarbamoyl or hydroxyiminomethyl; and the 5,6,7,8-tetrahydro compounds of formula Ib as shown in claim 8, wherein R_1 is as defined above under formula Ia or is halogen, and R_2 is hydrogen, C_1-C_4alkyl, benzyl, halogen, C_1-C_4alkoxy, C_1-C_4alkanoyloxy, C_1-C_4alkylthio, benzylthio, 2-phenylethylthio, diphenylmethylthio, phenylthio, C_1-C_4alkanoylthio, carboxy-C_1-C_4alkyl, C_1-C_4alkoxycarbonyl-C_1-C_4alkyl or C_1-C_4alkanoyl; and pharmaceutically acceptable salts thereof.

14. Compounds of formulae Ia and Ib according to claim 13, wherein R_1 represents carbamoyl, and compounds of formula Ib wherein R_1 represents halogen.

15. Compounds according to claim 13 of formula Ia wherein R_1 is hydrogen, p-toluenesulfonyloxy, benzenesulfonyloxy, methylsulfonyloxy, sulfo, amino or hydroximinomethyl; and the 5,6,7,8-tetrahydro compounds of formula Ib wherein R_1 is as defined above under formula Ia and R_2 is hydrogen; or wherein R_1 is hydrogen, halogen, p-toluenesulfonyloxy, benzenesulfonyloxy, methylsulfonyloxy, sulfo, amino, carboxy, carbamoyl, C_1-C_4alkylcarbamoyl, formyl or hydroxyiminomethyl and R_2 represents C_1-C_4-alkyl, benzyl, halogen, C_1-C_4alkoxy, C_1-C_4alkanoyloxy, C_1-C_4alkylthio, benzylthio, 2-phenylethylthio, diphenylmethylthio, phenylthio, C_1-C_4alkanoylthio, carboxy-C_1-C_4alkyl, C_1-C_4alkoxycarbonyl-C_1-C_4alkyl or C_1-C_4alkanoyl; and pharmaceutically acceptable salts thereof.

16. (-)-(5-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo-[1,5-a]pyridine according to claim 8 and pharmaceutically acceptable salts thereof.



17. (+)-(5-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo-[1,5-a]pyridine according to claim 8 and pharmaceutically acceptable salts thereof.

18. 5-(p-cyanophenyl)-7,8-dihydroimidazo[1,5-a]pyridine according to claim 8 and pharmaceutically acceptable salts thereof.

19. 5-(p-cyanophenyl)imidazo[1,5-a]pyridine according to claim 8 and pharmaceutically acceptable salts thereof.

20. 5-(p-bromophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]-pyridine according to claim 13, a stereoisomer thereof, mixtures of these stereoisomers, and pharmaceutically acceptable salts thereof.

21. 5H-5-(4-cyanophenyl)-6,7-dihydropyrrolo[1,2-c]-imidazole according to claim 5, a stereoisomer thereof, mixtures of these stereoisomers, and pharmaceutically acceptable salts thereof.

22. 5H-5-(4-cyanophenyl)-6,7,8,9-tetrahydroimidazo-[1,5-a]azepine according to claim 5, a stereoisomer thereof, mixtures of these stereoisomers, and pharmaceutically acceptable salts thereof.

23. 5-(4-cyanophenyl)-6-ethoxycarbonylmethyl-5,6,7,8-tetrahydroimidazo[1,5-a]-pyridine according to claim 5, a stereoisomer thereof, mixtures of these stereoisomers, and pharmaceutically acceptable salts thereof.

24. 5-(4-cyanophenyl)-6-carboxymethyl-5,6,7,8-tetra-hydroimidazo[1,5-a]-pyridine according to claim 5, a stereoisomer thereof, mixtures of these stereoisomers, and pharmaceutically acceptable salts thereof.

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25. 5-benzyl-5-(4-cyanophenyl)-5,6,7,8-tetrahydroimidazo-[1,5-a]pyridine according to claim 8, a stereoisomer thereof, mixtures of these stereoisomers, and pharmaceutically acceptable salts thereof.

26. 7-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]-pyridine, a stereoisomer thereof, mixtures of these stereoisomers, and pharmaceutically acceptable salts thereof.

27. Pharmaceutical preparations containing a compound according to claim 5 together with one or more pharmaceutically acceptable carriers.

28. Pharmaceutical preparations containing a compound according to claim 8 together with one or more pharmaceutically acceptable carriers.

29. Pharmaceutical preparations containing a compound according to claim 12 together with one or more pharmaceutically acceptable carriers.

30. Pharmaceutical preparations containing a compound according to claim 13 together with one or more pharmaceutically acceptable carriers.

31. Pharmaceutical preparations containing a compound according to claim 16 together with one or more pharmaceutically acceptable carriers.

32. Pharmaceutical preparations containing a compound according to claim 17 together with one or more pharmaceutically acceptable carriers.

33. A compound according to claim 5 for use in a method

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for the therapeutic treatment of the animal or human body.

34. A compound according to claim 8 for use in a method for the therapeutic treatment of the animal or human body.

35. A compound according to claim 12 for use in a method for the therapeutic treatment of the animal or human body.

36. A compound according to claim 13 for use in a method for the therapeutic treatment of the animal or human body.

37. A compound according to claim 16 for use in a method for the therapeutic treatment of the animal or human body.

38. A compound according to claim 17 for use in a method for the therapeutic treatment of the animal or human body.

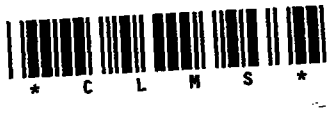
39. A compound according to claim 5 for use as aromatase inhibitor.

40. A compound according to claim 8 for use as aromatase inhibitor.

41. A compound according to claim 12 for use as aromatase inhibitor.

42. A compound according to claim 16 for use as aromatase inhibitor.

43. The use of a compound according to claim 5 for the



manufacture of pharmaceutical preparations.

44. The use of a compound according to claim 8 for the manufacture of pharmaceutical preparations.

45. The use of a compound according to claim 12 for the manufacture of pharmaceutical preparations.

46. The use of a compound according to claim 16 for the manufacture of pharmaceutical preparations.

47. The use of a compound according to claim 17 for the manufacture of pharmaceutical preparations.

48. The use of a compound according to claim 5 for the manufacture of pharmaceutical preparations for the treatment of diseases responsive to aromatase inhibition.

49. The use of a compound according to claim 8 for the manufacture of pharmaceutical preparations for the treatment of diseases responsive to aromatase inhibition.

50. The use of a compound according to claim 12 for the manufacture of pharmaceutical preparations for the treatment of diseases responsive to aromatase inhibition.

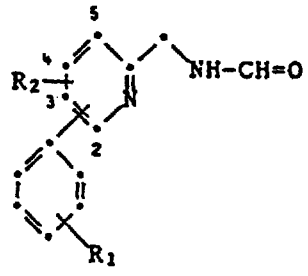
51. The use of a compound according to claim 13 for the manufacture of pharmaceutical preparations for the treatment of diseases responsive to aromatase inhibition.

52. The use of a compound according to claim 16 for the manufacture of pharmaceutical preparations for the treatment of diseases responsive to aromatase inhibition.

53. A process for the manufacture of compounds of formula I or I* according to claim 5, or salts thereof, which

comprises

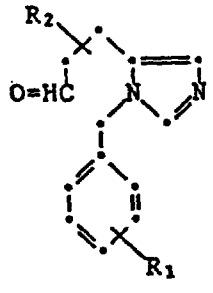
a) cyclising a compound of formula II



(II)

or a 4,5-dihydro derivative thereof in order to obtain a compound of formula I or a 7,8-dihydro derivative thereof, respectively, or

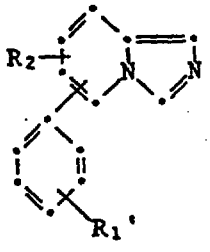
b) cyclising a compound of formula III



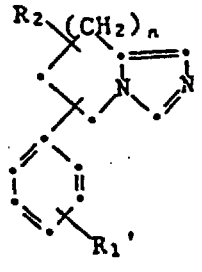
(III),

wherein R_2 may, as indicated, be attached to any of the carbon atoms including the carbonyl carbon, in order to obtain a 7,8-dihydro derivative of a compound of formula I wherein the substituent C_6H_4-R_1 is attached in the 5-position, or

c)/f) in a compound of formula IV or VII



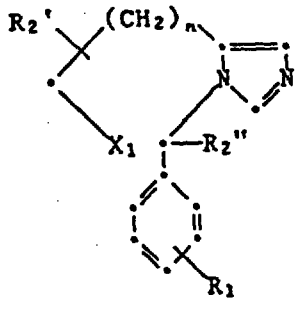
(IV)



(VII)

or in a 7,8-dihydro derivative of formula IV, in each of which R_1' is a group that can be converted into cyano, converting R_1' into cyano, in order to obtain a compound of formula I, a 7,8-dihydro derivative thereof or a compound of formula I*, respectively, wherein R_1 represents cyano, or

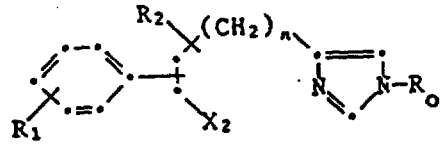
d) cyclising a compound of formula V



(V),

wherein at least one of the radicals R_2' and R_2'' is hydrogen and the other represents a radical R_2 as defined under formula I*, and X_1 is a leaving group, and R_2' may, as indicated, be attached to any of the carbon atoms, in order to obtain a compound of formula I* wherein the substituent C_6H_4-R_1 is attached in the 5-position; or X_1 represents a =CH-COOH group or a lower alkyl ester thereof, R_2' is hydrogen and R_2'' is as defined under formula I*, in order to obtain a compound of formula I* wherein the substituent C_6H_4-R_1 is attached in the 5-position and the 6-position is substituted by carboxymethyl or lower alkoxycarbonylmethyl, or

e) cyclising a compound of formula VI

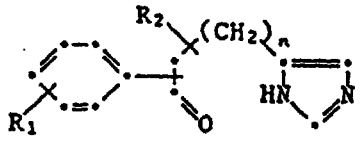


(VI)

wherein the substituents C_6H_4-R_1 and R_2 may, as indicated, be attached to any of the carbon atoms, either both radicals to the same carbon atom or to different

carbon atoms, R_o is an NH-protecting group or hydrogen, and X_2 is a leaving group, in order to obtain a compound of formula I*; or

g) cyclising a compound of formula IX



(IX)

wherein the substituents C_6H_4-R_1 and R_2 may, as indicated, be attached to any of the carbon atoms including the carbonyl carbon, either both radicals to the same carbon atom or to different carbon atoms, optionally under reductive conditions, in order to obtain a 7,8-dihydro derivative of a compound of formula I or, in the case of reductive conditions, a compound of formula I*, or

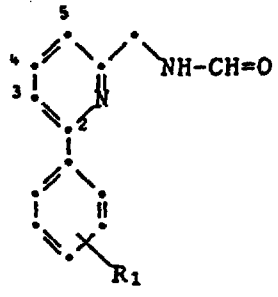
h) decarboxylating a compound analogous to formula I, or a 7,8-dihydro derivative thereof, or a compound analogous to formula I*, each of which contains an additional carboxy group in the 1- or 3-position, in order to obtain a compound of formula I, a 7,8-dihydro derivative thereof or a compound of formula I*; wherein, in the starting materials of formulae II to VII and IX, the symbols n, R_1 and R_2 have the meanings given under formulae I and I*, respectively; and/or reducing a compound of formula I or a 7,8-dihydro derivative thereof to a corresponding 5,6,7,8-tetrahydro derivative of formula I* optionally with simultaneous reduction of the substituent(s) R_1 and/or R_2 to (an)other substituent(s) R_1 and/or R_2; and/or decarboxylating a compound of formula I* wherein R_2 is carboxy, in order to obtain a compound of formula I* wherein R_2 is hydrogen; and/or converting a compound obtained into another compound of the invention and/or converting a salt obtained into the free compound or into

* C L M S *

another salt and/or converting a free compound obtained into a salt and/or separating a mixture of isomers or racemates obtained into the individual isomers or racemates and/or resolving an enantiomeric mixture, such as a racemate, into the optical antipodes.

54. A process for the manufacture of compounds of formula Ia or Ib according to claim 8, or salts thereof, which comprises

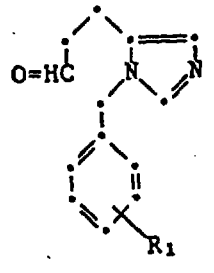
a) cyclising a compound of formula IIa



(IIa),

wherein R_1 is as defined above under formula Ia, or a 4,5-dihydro derivative thereof, under acidic conditions, in order to obtain a compound of formula Ia or a 7,8-dihydro derivative thereof, or

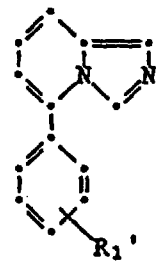
b) for the manufacture of a 7,8-dihydro derivative of a compound of formula Ia, cyclising a compound of formula IIIa



(IIIa),

wherein R_1 is as defined above under formula Ia, under basic conditions, or

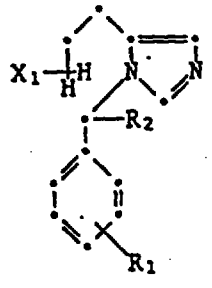
c) in a compound of formula IVa



(IVa),

wherein R_1' is a radical that can be converted into cyano, or in a 7,8-dihydro derivative thereof, converting R_1' into cyano, in order to obtain a compound of formula Ia, or a 7,8-dihydro derivative thereof, or

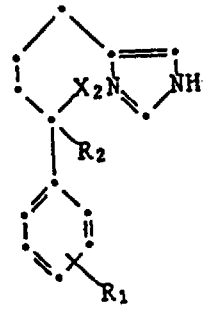
d) cyclising a compound of formula Vb



(Vb),

wherein R_1 and R_2 are as defined above under formula Ib and X_1 is a leaving group, in the presence of a base, in order to obtain a compound of formula Ib, or

e) cyclising a compound of formula VIb

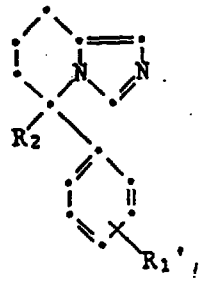


(VIb),

wherein R_1 and R_2 are as defined above under formula Ib and X_2 is a leaving group, and wherein the NH group may be protected by an NH-protecting group, in the presence

of a base, in order to obtain a compound of formula Ib, or

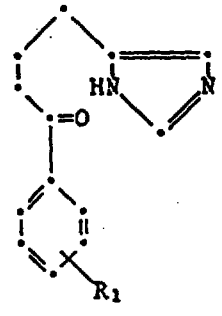
f) in a compound of formula VIIb



(VIIb),

wherein R_1' is a radical that can be converted into cyano, and wherein R_2 is as defined above under formula Ib, converting the radical R_1' into cyano, in order to obtain a compound of formula Ib wherein R_1 is cyano;

g) cyclising a compound of formula IXb



(IXb),

optionally under reductive conditions, in order to obtain a 7,8-dihydro derivative of a compound of formula Ia or, in the case of reductive conditions, a compound of formula Ib, or

h) decarboxylating a compound analogous to formula Ia, or a 7,8-dihydro derivative thereof, or a compound analogous to formula Ib, each of which contains an additional carboxy group in the 1- or 3-position, in order to obtain a compound of formula Ia, a 7,8-dihydro derivative thereof or a compound of formula Ib, and/or decarboxylating a compound of formula Ib wherein R_2 is carboxy in

* C L M S *

order to obtain another compound of formula Ib wherein R_2 is hydrogen, and/or reducing a compound of formula Ia, or a 7,8-dihydro derivative thereof, with hydrogen in the presence of a hydrogenation catalyst to the corresponding 5,6,7,8-tetrahydro derivative of formula Ib, and/or converting a compound obtained into another compound of the invention and/or converting a salt obtained into the free compound or into another salt and/or converting a free compound having a salt-forming group into a salt and/or separating a racemic mixture obtained into the individual enantiomers.

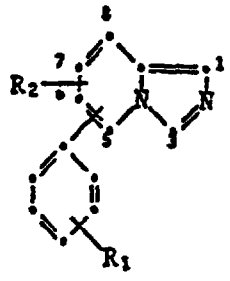
55. The compounds obtainable according to the process of claim 53.

56. The compounds obtainable according to the process of claim 54.

* C L M S *

Patent Claims for the Contracting State: AT.

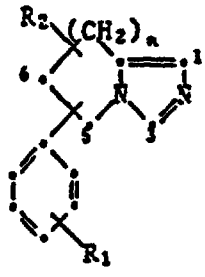
1. A process for the manufacture of compounds of formula I



(I)

wherein R_1 represents hydrogen, lower alkyl; C_2-C_7alkyl substituted by hydroxy, lower alkoxy, halogen or lower alkanoyloxy; lower alkyl substituted by lower alkanoyl, amino, lower alkylamino, di-lower alkylamino, sulfo, lower alkoxycarbonyl, carbamoyl or cyano; nitro, lower alkoxy, lower alkanoyloxy, phenylsulfonyloxy, lower alkylsulfonyloxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, lower alkanoylthio, amino, lower alkylamino, di-lower alkylamino, lower alkyleneamino, N-morpholino, N-thiomorpholino, optionally 4-lower alkyl-substituted N-piperazino, tri-lower alkylammonio, sulfo, lower alkoxysulfonyl, sulfamoyl, lower alkylsulfamoyl, di-lower alkylsulfamoyl; iminomethyl optionally N-substituted by hydroxy, lower alkoxy, lower alkanoyloxy, lower alkyl, phenyl or amino; C_2-C_7alkanoyl or benzoyl; and R_2 represents hydrogen, lower alkyl, phenyl-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, halogen, hydroxy, lower alkoxy, lower alkanoyloxy, mercapto, lower alkylthio, phenyl-lower alkylthio, phenylthio, lower alkanoylthio, carboxy, lower alkoxy-carbonyl or lower alkanoyl; the 7,8-dihydro derivatives thereof and also such 7,8-dihydro derivatives wherein R_1 is hydroxymethyl, lower alkoxymethyl, halomethyl, lower alkanoyloxymethyl, carboxy-lower alkyl, halogen, hydroxy, mercapto, formyl, carboxy, lower alkoxycarbonyl, car-

bamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl, cyano, 5-tetrazolyl, optionally lower alkyl-substituted 4,5-dihydro-2-oxazolyl or hydroxycarbamoyl and R_2 is as defined above under formula I; and compounds of formula I*

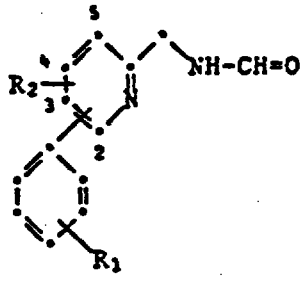


(I*)

wherein n denotes 0, 1, 2, 3 or 4; R_1 is as defined above under formula I or R_1 may be, in addition, hydroxymethyl, lower alkoxymethyl, halomethyl, lower alkanoyloxymethyl, carboxy-lower alkyl, halogen, hydroxy, mercapto, formyl, carboxy, lower alkoxycarbonyl, carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl, cyano, 5-tetrazolyl, optionally lower alkyl-substituted 4,5-dihydro-2-oxazolyl or hydroxycarbamoyl if n represents 0, 1, 3 or 4 or if n represents 2 and R_2 is phenyl-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, lower alkanoyloxy, mercapto, lower alkylthio, phenyl-lower alkylthio, phenylthio, lower alkanoylthio, carboxy, lower alkoxycarbonyl or lower alkanoyl; and R_2 is as defined above under formula I; it being possible for the phenyl ring within the radicals phenylsulfonyloxy, phenyliminomethyl, benzoyl, phenyl-lower alkyl, phenyl-lower alkylthio and phenylthio to be unsubstituted or substituted by lower alkyl, lower alkoxy or halogen; and in a compound of formula I* it being possible for the two substituents C_6H_4-R_1 and R_2 to be attached to any of the saturated carbon atoms of the saturated ring, either both to the same carbon atom or to different carbon atoms; radicals designated "lower" containing up to 7 carbon atoms; stereoisomers, mixtures

of these stereoisomers, and salts thereof, which comprises

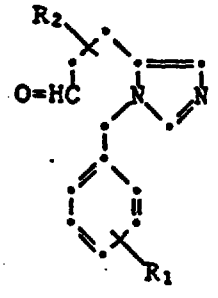
a) cyclising a compound of formula II



(II)

or a 4,5-dihydro derivative thereof in order to obtain a compound of formula I or a 7,8-dihydro derivative thereof, respectively, or

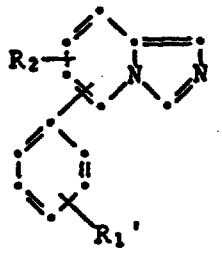
b) cyclising a compound of formula III



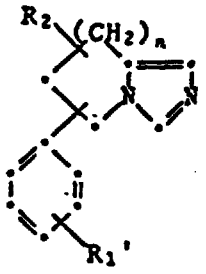
(III),

wherein R_2 may, as indicated, be attached to any of the carbon atoms including the carbonyl carbon, in order to obtain a 7,8-dihydro derivative of a compound of formula I wherein the substituent C_6H_4-R_1 is attached in the 5-position, or

c)/f) in a compound of formula IV or VII



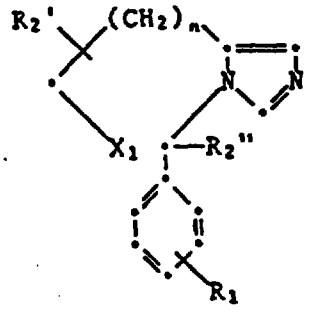
(IV)



(VII)

or in a 7,8-dihydro derivative of formula IV, in each of which R_1' is a group that can be converted into cyano, converting R_1' into cyano, in order to obtain a compound of formula I, a 7,8-dihydro derivative thereof or a compound of formula I*, respectively, wherein R_1 represents cyano, or

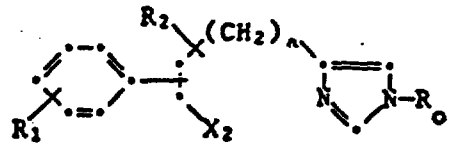
d) cyclising a compound of formula V



(V),

wherein at least one of the radicals R_2' and R_2'' is hydrogen and the other represents a radical R_2 as defined under formula I*, and X_1 is a leaving group, and R_2' may, as indicated, be attached to any of the carbon atoms, in order to obtain a compound of formula I* wherein the substituent C_6H_4-R_1 is attached in the 5-position; or X_1 represents a =CH-COOH group or a lower alkyl ester thereof, R_2' is hydrogen and R_2'' is as defined under formula I*, in order to obtain a compound of formula I* wherein the substituent C_6H_4-R_1 is attached in the 5-position and the 6-position is substituted by carboxymethyl or lower alkoxycarbonylmethyl, or

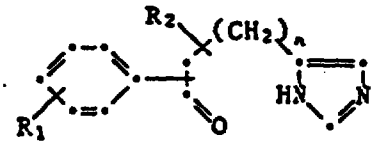
e) cyclising a compound of formula VI



(VI)

wherein the substituents C_6H_4-R_1 and R_2 may, as indicated, be attached to any of the carbon atoms, either both radicals to the same carbon atom or to different carbon atoms, R_o is an NH-protecting group or hydrogen, and X_2 is a leaving group, in order to obtain a compound of formula I*; or

g) cyclising a compound of formula IX



(IX)

wherein the substituents C_6H_4-R_1 and R_2 may, as indicated, be attached to any of the carbon atoms including the carbonyl carbon, either both radicals to the same carbon atom or to different carbon atoms, optionally under reductive conditions, in order to obtain a 7,8-dihydro derivative of a compound of formula I or, in the case of reductive conditions, a compound of formula I*, or

h) decarboxylating a compound analogous to formula I, or a 7,8-dihydro derivative thereof, or a compound analogous to formula I*, each of which contains an additional carboxy group in the 1- or 3-position, in order to obtain a compound of formula I, a 7,8-dihydro derivative thereof or a compound of formula I*; wherein, in the starting materials of formulae II to VII and IX, the symbols n, R_1 and R_2 have the meanings given under formulae I and I*, respectively; and/or reducing a compound of formula I or a 7,8-dihydro derivative thereof to a corresponding 5,6,7,8-tetrahydro derivative of formula I* optionally

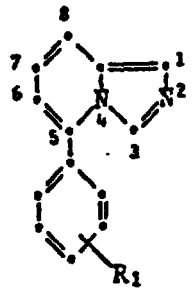
with simultaneous reduction of the substituent(s) R_1 and/or R_2 to (an)other substituent(s) R_1 and/or R_2; and/or decarboxylating a compound of formula I* wherein R_2 is carboxy, in order to obtain a compound of formula I* wherein R_2 is hydrogen; and/or converting a compound obtained into another compound of the invention and/or converting a salt obtained into the free compound or into another salt and/or converting a free compound obtained into a salt and/or separating a mixture of isomers or racemates obtained into the individual isomers or racemates and/or resolving an enantiomeric mixture, such as a racemate, into the optical antipodes.

2. A process according to claim 1, wherein compounds of formula I wherein R_1 represents lower alkyl, hydroxy-C_2-C_7alkyl; lower alkyl substituted by amino, di-lower alkylamino, 2 to 5 fluorine atoms, lower alkoxycarbonyl, carbamoyl or cyano; nitro, lower alkoxy, amino, lower alkylamino, di-lower alkylamino, sulfo, sulfamoyl, iminomethyl or iminomethyl N-substituted by hydroxy, lower alkoxy, lower alkanoyloxy, lower alkyl or phenyl; and R_2 is hydrogen, lower alkyl, lower alkoxy or halogen; or compounds of formula I* wherein n denotes 1, 2 or 3; R_1 is as defined above under formula I or R_1 may be, in addition, hydroxymethyl, carboxy-lower alkyl, halogen, hydroxy, formyl, carboxy, lower alkoxycarbonyl, carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl or cyano if n represents 1 or 3 or if n represents 2 and R_2 is phenyl-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, lower alkylthio, phenyl-lower alkylthio, phenylthio, carboxy, lower alkoxycarbonyl or lower alkanoyl; and R_2 represents hydrogen, lower alkyl, phenyl-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, halogen, lower alkoxy, lower alkylthio, phenyl-lower alkylthio, phenylthio, carboxy, lower alkoxycarbonyl or lower alkanoyl; in a compound of

formula I* it being possible for the two substituents C_6H_4-R_1 and R_2 to be attached to any of the saturated carbon atoms of the saturated ring, either both to the same carbon atom or to different carbon atoms; stereoisomers, mixtures of these stereoisomers, or pharmaceutically acceptable salts thereof, are manufactured.

3. A process according to claim 1, wherein compounds of formula I* wherein n denotes 1, 2 or 3; R_1 represents lower alkyl, amino, lower alkylamino or di-lower alkylamino, or R_1 may be, in addition, hydroxymethyl, halogen, formyl, carboxy, lower alkoxycarbonyl, carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl or cyano if n represents 1 or 3 or if n represents 2 and R_2 is phenyl-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, lower alkylthio, carboxy or lower alkoxycarbonyl; and R_2 is hydrogen, lower alkyl, phenyl-lower alkyl, carboxy-lower alkyl, lower alkoxycarbonyl-lower alkyl, lower alkylthio, carboxy or lower alkoxycarbonyl; it being possible for the two substituents C_6H_4-R_1 and R_2 to be attached to any of the saturated carbon atoms of the saturated ring, either both to the same carbon atom or to different carbon atoms; stereoisomers, mixtures of these stereoisomers, or pharmaceutically acceptable salts thereof, are manufactured.

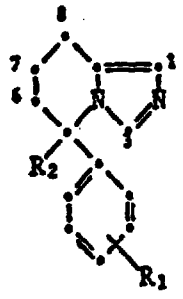
4. A process for the manufacture of compounds of formula Ia



(Ia)

wherein R_1 represents cyano, nitro or C_1-C_4alkyl, the

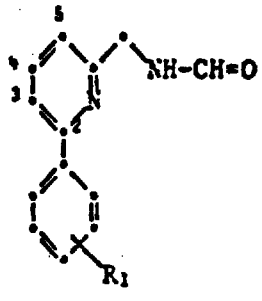
7,8-dihydro derivatives thereof or the 5,6,7,8-tetrahydro derivatives thereof of formula Ib



(Ib)

wherein R_1 is as defined above under formula Ia and R_2 is hydrogen, C_1-C_4alkyl, benzyl, halogen, C_1-C_4alkoxy, C_1-C_4alkylthio, benzylthio, 2-phenylethylthio, diphenylmethylthio, phenylthio, C_1-C_4alkanoyloxy, C_1-C_4alkanoylthio, carboxy-C_1-C_4alkyl, C_1-C_4alkoxycarbonyl-C_1-C_4alkyl or C_1-C_4alkanoyl, stereoisomers, mixtures of these stereoisomers, and salts of these compounds, which comprises

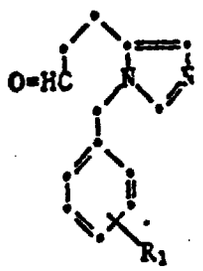
a) cyclising a compound of formula IIa



(IIa),

wherein R_1 is as defined above under formula Ia, or a 4,5-dihydro derivative thereof, under acidic conditions, in order to obtain a compound of formula Ia or a 7,8-dihydro derivative thereof, or

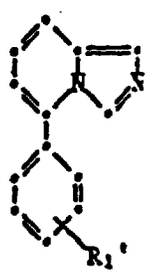
b) for the manufacture of a 7,8-dihydro derivative of a compound of formula Ia, cyclising a compound of formula IIIa



(IIIa),

wherein R_1 is as defined above under formula Ia, under basic conditions, or

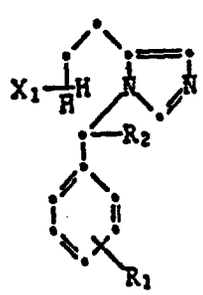
c) in a compound of formula IVa



(IVa),

wherein R_1' is a radical that can be converted into cyano, or in a 7,8-dihydro derivative thereof, converting R_1' into cyano, in order to obtain a compound of formula Ia, or a 7,8-dihydro derivative thereof, or

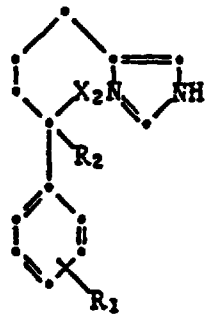
d) cyclising a compound of formula Vb



(Vb),

wherein R_1 and R_2 are as defined above under formula Ib and X_1 is a leaving group, in the presence of a base, in order to obtain a compound of formula Ib, or

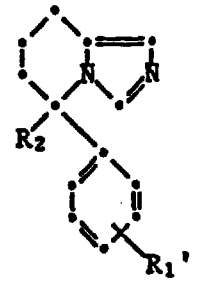
e) cyclising a compound of formula VIb



(VIb),

wherein R_1 and R_2 are as defined above under formula Ib and X_2 is a leaving group, and wherein the NH group may be protected by an NH-protecting group, in the presence of a base, in order to obtain a compound of formula Ib, or

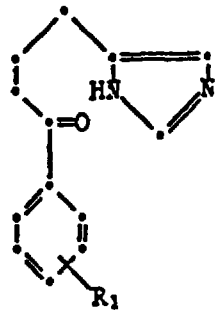
f) in a compound of formula VIIb



(VIIb),

wherein R_1' is a radical that can be converted into cyano, and wherein R_2 is as defined above under formula Ib, converting the radical R_1' into cyano, in order to obtain a compound of formula Ib wherein R_1 is cyano;

g) cyclising a compound of formula IXb



(IXb),

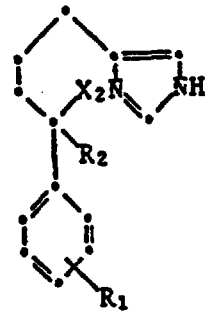
optionally under reductive conditions, in order to obtain a 7,8-dihydro derivative of a compound of formula Ia or,

in the case of reductive conditions, a compound of formula Ib, or

h) decarboxylating a compound analogous to formula Ia, or a 7,8-dihydro derivative thereof, or a compound analogous to formula Ib, each of which contains an additional carboxy group in the 1- or 3-position, in order to obtain a compound of formula Ia, a 7,8-dihydro derivative thereof or a compound of formula Ib, and/or decarboxylating a compound of formula Ib wherein R_2 is carboxy in order to obtain another compound of formula Ib wherein R_2 is hydrogen, and/or reducing a compound of formula Ia, or a 7,8-dihydro derivative thereof, with hydrogen in the presence of a hydrogenation catalyst to the corresponding 5,6,7,8-tetrahydro derivative of formula Ib, and/or converting a compound obtained into another compound of the invention and/or converting a salt obtained into the free compound or into another salt and/or converting a free compound having a salt-forming group into a salt and/or separating a racemic mixture obtained into the individual enantiomers.

5. A process according to claim 4, which comprises carrying out one of the process variants a), b), c), d) or f) specified therein or

e) cyclising a compound of formula VIb



(VIb),

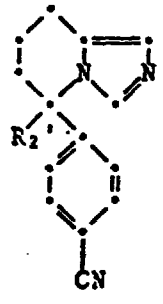
wherein R_1 and R_2 are as defined above under formula Ib and X_2 is a leaving group, in the presence of a base, in

order to obtain a compound of formula Ib, and/or reducing a compound of formula Ia, or a 7,8-dihydro derivative thereof, with hydrogen in the presence of a hydrogenation catalyst to the corresponding 5,6,7,8-tetrahydro derivative of formula Ib, and/or converting a compound obtained into another compound of the invention and/or converting a salt obtained into the free compound or into another salt and/or converting a free compound having a salt-forming group into a salt and/or separating a racemic mixture obtained into the individual enantiomers.

6. A process according to claim 5, wherein compounds of formula Ia wherein R_1 represents cyano, the 7,8-dihydro derivatives thereof, or the 5,6,7,8-tetrahydro derivatives thereof of formula Ib wherein R_1 is cyano and R_2 is hydrogen, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4alkylthio, benzylthio, 2-phenylethylthio, diphenylmethylthio, phenylthio or C_1-C_4alkanoyl, or pharmaceutically acceptable acid addition salts of compounds of formulae Ia and Ib are manufactured.

7. A process according to claim 5, wherein compounds of formula Ia wherein R_1 is cyano, the 7,8-dihydro derivatives thereof, or the 5,6,7,8-tetrahydro derivatives thereof of formula Ib wherein R_1 is as defined above under formula Ia and R_2 is hydrogen, or pharmaceutically acceptable acid addition salts thereof are manufactured.

8. A process according to claim 5, wherein compounds of formula Ic



(Ic)

wherein R_2' is hydrogen, C_1-C_4alkyl, C_1-C_4alkoxy, C_1-C_4-alkylthio, benzylthio, 2-phenylethylthio, diphenylmethylthio, phenylthio or C_1-C_4alkanoyl, or pharmaceutically acceptable acid addition salts thereof are manufactured.

9. A process according to claim 5, wherein a compound of formula Ic wherein R_2' is hydrogen, being 5-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine, or pharmaceutically acceptable acid addition salts thereof are manufactured.

10. A process according to claim 4, wherein a compound of formula Ic wherein R_2' is hydrogen, being 5-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine, or pharmaceutically acceptable acid addition salts thereof are manufactured.

11. A process for the manufacture of compounds of formula Ia as shown in claim 4, wherein R_1 represents hydrogen, p-toluenesulfonyloxy, benzenesulfonyloxy, methylsulfonyloxy, sulfo, amino, carbamoyl, C_1-C_4alkylcarbamoyl or hydroxyiminomethyl; or the 5,6,7,8-tetrahydro compounds of formula Ib as shown in claim 4, wherein R_1 is as defined above under formula Ia or is halogen, and R_2 is hydrogen, C_1-C_4alkyl, benzyl, halogen, C_1-C_4alkoxy, C_1-C_4alkanoyloxy, C_1-C_4alkylthio, benzylthio, 2-phenylethylthio, diphenylmethylthio, phenylthio, C_1-C_4alkanoylthio, carboxy-C_1-C_4alkyl, C_1-C_4alkoxycarbonyl-C_1-C_4alkyl or C_1-C_4alkanoyl; or pharmaceutically acceptable salts thereof, which comprises carrying out the process variants specified in claim 4.

12. A process for the manufacture of compounds of formula Ia as shown in claim 4, wherein R_1 is hydrogen, p-toluenesulfonyloxy, benzenesulfonyloxy, methylsul-

* C L M S *

fonyloxy, sulfo, amino or hydroximinomethyl; or the 5,6,7,8-tetrahydro compounds of formula Ib as shown in claim 4, wherein R_1 is as defined above under formula Ia and R_2 is hydrogen; or wherein R_1 is hydrogen, halogen, p-toluenesulfonyloxy, benzenesulfonyloxy, methylsulfonyloxy, sulfo, amino, carboxy, carbamoyl, C_1-C_4alkylcarbamoyl, formyl or hydroxyiminomethyl and R_2 represents C_1-C_4alkyl, benzyl, halogen, C_1-C_4alkoxy, C_1-C_4alkanoyloxy, C_1-C_4alkylthio, benzylthio, 2-phenylethylthio, diphenylmethylthio, phenylthio, C_1-C_4alkanoylthio, carboxy-C_1-C_4alkyl, C_1-C_4alkoxycarbonyl-C_1-C_4alkyl or C_1-C_4alkanoyl; or pharmaceutically acceptable salts thereof, which comprises carrying out the process variants specified in claim 5.

13. A process according to claim 12, wherein compounds of formulae Ia and Ib wherein R_1 represents carbamoyl, or compounds of formula Ib wherein R_1 represents halogen are manufactured.

14. A process according to claim 4, wherein (-)-(5-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine or pharmaceutically acceptable salts thereof are manufactured.

15. A process according to claim 4, wherein (+)-(5-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine or pharmaceutically acceptable salts thereof are manufactured.

16. A process according to claim 5, wherein 5-(p-cyanophenyl)-7,8-dihydroimidazo[1,5-a]pyridine or pharmaceutically acceptable salts thereof are manufactured.

17. A process according to claim 5, wherein 5-(p-cyanophenyl)imidazo[1,5-a]pyridine or pharmaceutically

acceptable salts thereof are manufactured.

18. A process according to claim 11, wherein 5-(p-bromophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine, a stereoisomer thereof, mixtures of these stereoisomers, or pharmaceutically acceptable salts thereof are manufactured.

19. A process according to claim 1, wherein 5H-5-(4-cyanophenyl)-6,7-dihydropyrrolo[1,2-c]imidazole, a stereoisomer thereof, mixtures of these stereoisomers, or pharmaceutically acceptable salts thereof are manufactured.

20. A process according to claim 1, wherein 5H-5-(4-cyanophenyl)-6,7,8,9-tetrahydroimidazo[1,5-a]azepine, a stereoisomer thereof, mixtures of these stereoisomers, or pharmaceutically acceptable salts thereof are manufactured.

21. A process according to claim 1, wherein 5-(4-cyanophenyl)-6-ethoxycarbonylmethyl-5,6,7,8-tetrahydroimidazo-[1,5-a]pyridine, a stereoisomer thereof, mixtures of these stereoisomers, or pharmaceutically acceptable salts thereof are manufactured.

22. A process according to claim 4, wherein 5-(p-cyanophenyl)imidazo[1,5-a]pyridine or pharmaceutically acceptable salts thereof are manufactured.

23. A process according to claim 12, wherein 5-(p-bromophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine, a stereoisomer thereof, mixtures of these stereoisomers or pharmaceutically acceptable salts thereof are manufactured.

* C L M S *

24. A process according to claim 1, wherein 5-(4-cyanophenyl)-6-carboxymethyl-5,6,7,8-tetrahydroimidazo[1,5-a]-pyridine, a stereoisomer thereof, mixtures of these stereoisomers, or pharmaceutically acceptable salts thereof are manufactured.

25. A process according to claim 4, wherein 5-benzyl-5-(4-cyanophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine, a stereoisomer thereof, mixtures of these stereoisomers, or pharmaceutically acceptable salts thereof are manufactured.

26. A process for the manufacture of 7-(p-cyanophenyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyridine, a stereoisomer thereof, mixtures of these stereoisomers or pharmaceutically acceptable salts thereof, which comprises carrying out the process variants specified in claim 1.

27. A process for the manufacture of pharmaceutical preparations, which comprises mixing a compound obtained by the process according to any one of claims 1, 4, 10, 11, 14 and 15, or a pharmaceutically acceptable salt of such a compound, with a pharmaceutically acceptable carrier.

28. A process for the manufacture of pharmaceutical preparations, which comprises mixing a compound obtained by the process according to any one of claims 5, 9 and 12, or a pharmaceutically acceptable salt of such a compound, with a pharmaceutically acceptable carrier.