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Novel 1,2,4-triaminobenzene derivatives and processes for their preparation

In Chemiker Zeitung 103 (1979), pages 6-13 there is described a process for the preparation of 1-amino-2-carbethoxyamino-6-(2,4,6-trimethyl)benzylaminopyridine and of its hydrochloride (compound 81). There is no disclosure or teaching in this literature reference of any pharmacological activity of this compound.

The invention relates to items defined in the claims.

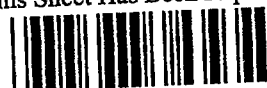
The compounds of the invention are pharmacologically active. In particular, the compounds of the invention have anticonvulsive, antipyretic and muscle-relaxant activity. In addition they also have a specific peripheral analgesic activity.

It is thus an object of the invention to provide compounds with favourable pharmacological properties which can for example be used as anti-epileptic, muscle-relaxing, fever reducing and peripherally analgesically acting medicaments.

The following explanations provide information on important examples:

The alkyl groups, halogenalkyl groups, alkenyl groups, alkynyl groups, alkoxy groups, alkylamino groups, alkanoyl amino groups, alkanoyloxy groups and alkanoyl groups in general in Formula I can be straight or branched. The same also applies to alkyl and alkyloxy groups (= alkoxy groups) if these are components of more complicated radicals for example in the form of a monoalkyl- or dialkylamino group, alkanoylamino group, alkoxycarbonylamino group, carbalkoxy group, alkylcarbonyl group and analogous groups. In the case of the C₃-C₇-cycloalkyl group this is preferably cyclopentyl or cyclohexyl. C₂-C₆-alkenyl preferably represents allyl. C₂-C₆-alkynyl preferably represents propargyl.

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The halogen atoms are chlorine, bromine or fluorine, in particular chlorine or fluorine. The alkyl and alkoxy groups as such or as components of groups of more complicated radicals consist in particular of 1-4 carbon atoms, preferably 1 or 2 carbon atoms. Alkanoyl groups, such as alkanoylamino groups or alkanoyloxy groups consist in particular of 2-4, preferably 2-3 carbon atoms. Alk consists in particular of 1-3, preferably 1 or 2 carbon atoms.

Particularly favourable properties are displayed by those compounds of formula I where R_1 represents hydrogen, C_1 - C_6 -alkyl or C_2 - C_6 -alkanoyl, R_2 hydrogen or C_1 - C_6 -alkyl, R_4 and R_5 hydrogen, R_3 C_1 - C_6 -alkoxy, the alkylene group Alk is directly bound to the nitrogen atom ($n=0$) and represents CH_2 and Ar represents a halogenphenyl radical preferably fluorophenyl (for example 4-fluorophenyl) or a trifluoromethyl radical (for example 4-trifluoromethylphenyl).

Those compounds of formula I which contain asymmetrical carbon atoms and generally occur as racemates can be split into the optically active isomers in a manner known per se, for example using an optically active acid. It is, however, also possible to use an optically active starting material from the outset, the end product then being obtained in a correspondingly optically active or diastereomeric form. The present invention thus also comprises the D- and L-form as well as the DL mixture in the event of the compound of formula I also containing an asymmetrical carbon atom and in the event of 2 and more asymmetrical carbon atoms also the corresponding diastereomeric form.

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Depending on the reaction conditions and on the starting materials, the end products of formula I are obtained in free form or in the form of their salts. The salts of the end substances can be transferred back into the bases in a manner known per se, for example with alkali or ion exchangers. Salts can be obtained from the latter by reaction with organic or inorganic acids, in particular those which are suitable for forming therapeutically useful salts.

The compounds of the invention are suitable for the preparation of pharmaceutical compositions. The pharmaceutical compositions or medicaments may contain one or more compounds of the invention. The conventional carriers and auxiliary substances can be used to prepare the pharmaceutical formulations.

With regard to process a) (Reduction of the nitro group)

Catalytic hydrogenation has been found particularly suitable for reduction according to process a). The following catalysts may, for example, be used: Raney-nickel, precious metals such as palladium and platinum as well as compounds thereof, with and without carriers, such as for example barium sulphate, calcium sulphate and the like. It is advisable to carry out the hydrogenation of the nitro group at temperatures between 20 and 100°C and a pressure of about 1 to 70 bar in a solvent.

Particularly suitable solvents are for example C₁-C₄-alkanols, C₂-C₄-diols and their lower alkyl ethers, cyclic ethers such as dioxan, tetrahydrofuran, methoxy ethanol, water, aromatic hydrocarbons (benzene, toluenes, xylenes) as well as mixtures of these agents. It may in some cases be of advantage for the subsequent isolation of the reduced compounds if drying agents such as anhydrous sodium or magnesium sulphate are added to the mixture to be hydrogenated at the outset.



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The reduction may, however, also be carried out with nascent hydrogen for example zinc/hydrochloric acid, tin/hydrochloric acid, iron/hydrochloric acid or with salts of hydrogen sulfide in alcohol/water at about 70 to about 120°C or with activated aluminium in aqueous ether at 20 to 40°C or with tin II-chloride/hydrochloric acid or with ammonium formate. If a starting material is used which contains an oxo group (for example alkyl carbonyl) it may be appropriate to protect this oxo group by conventional acetal formation (for example in the form of the ethylene acetal). This applies in particular to catalytic hydrogenation.

The reaction product obtained in this manner is usually immediately reacted in the reaction mixture obtained with a compound suitable to replace a hydrogen atom of the amino group obtained by the reduction by the group $-COR_3$ without it being necessary to isolate the reduced compound. This applies in particular in the case of catalytic hydrogenation. The compound obtained by reduction of the nitro group can of course also be isolated and the $-COR_3$ group can then be introduced. Introduction of the $-COR_3$ group can be effected in the manner conventional herefor using conventional reagents in particular halides of formula $Hal-COR_3$ ($Hal = Cl, Br, I$). Examples of such reagents are: C_1-C_6 -alkylhaloformates (for example ethyl esters such as chlorine, bromine or iodo ethyl formates), -phenyl esters or $Hal-CO-OAr$. If R_3 is a C_1-C_6 -alkyl group, acylating agents that may for example be considered are the halides (chlorine, bromine, iodine) or anhydrides of C_1-C_6 -alkyne carboxylic acids, C_2-C_6 -alkene carboxylic acids, C_2-C_6 -alkyne carboxylic acids or acids of the formula $ArCO_2H$. It is also possible to use as acylating agents halides of the following formulae $Hal-CO-NH_2$, $Hal-CO-NH-C_1-C_6$ -alkyl, $Hal-CO-N(C_1-C_6$ -alkyl) $_2$ or $Hal-CO-NHAr$, if the radical R_3 has one of the given amine functions.

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The latter compounds may, however, also be obtained in conventional manner from compounds of Formula I where R_3 is C_1 - C_6 -alkoxy or phenoxy by reaction with ammonia, C_1 - C_6 -alkylamines, C_1 - C_6 -dialkylamines or amines NH_2 -Ar.

These reactions preferably occur under pressure (10-50 bar) at temperatures between 0 and 220°C, preferably 100 to 200°C in an inert solvent or dispersing agent. Agents of this kind that may for example be considered are: lower aliphatic alcohols (1-6 carbon atoms such as propanol, isopropanol, butanol, methoxyethanol), lower aliphatic ethers (diethyl ether, diisopropyl ether), aromatic hydrocarbons (benzene, toluene, xylene), cyclic ethers (dioxan, tetrahydrofuran), esters of lower aliphatic carboxylic acids with lower aliphatic alcohols, amides and N-alkyl-substituted amides of aliphatic C_1 - C_4 -carboxylic acids (dimethylformamide, dimethylacetamide), C_1 - C_6 -dialkylsulfones (dimethylsulfone, tetramethylenesulfone), C_1 - C_6 -dialkylsulfoxides (dimethylsulfoxide) as well as other aprotic agents such as n-methylpyrrolidone, tetramethylurea, hexamethylphosphoric acid triamide, acetonitrile as well as mixtures of these agents. This acylation may optionally also occur without the use of a solvent or dispersing agent. Without such an agent the reaction occurs for example between 0 and 200°C, preferably between 100 and 200°C.

Since the free amines of formula I where the group $-COR_3$ is hydrogen are sensitive to oxygen, working is preferably in a nitrogen atmosphere.

In general the reaction components are reacted in molar amounts. It may, however, optionally be appropriate to use one reaction component in slight excess. The reaction may optionally be carried out in the presence of basic or acid-binding agents.

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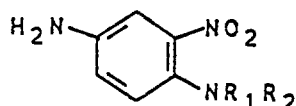
Agents of this kind that may for example be considered are: inorganic condensation agents such as ammonia, alkali metal or alkaline earth hydroxides, alkali metal- or alkaline earth-carbonates or organic basis such as pyridine, tertiary amines (triethylamine), piperidine, alkali metal alcoholates, alkali metal acetates or also triethylphosphate. The alkali metals are in particular sodium or potassium. It is also possible to work under phase-transfer conditions i.e. with the addition of one or more long-chain amines such as a benzyl tributylammonium halide, a tetrabutyl ammonium halide or benzyl triphenyl phosphonium chloride.

Particularly when haloformates or derivatives thereof are employed, the basic condensation agents used may be tertiary amines, alkali metal hydroxides, alkali metal acetates or alkali metal bicarbonates.

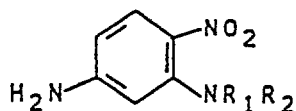
The additionally available amino groups can for example contain a conventional amino protection group. Protection groups of this kind can be split by solvolysis or hydrogenolysis after completion of the reaction.

Starting materials of general formula II or III may for example be obtained as follows.

1. By reacting a compound of formula VII or VIII



VII



VIII

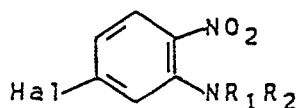
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with an aldehyde $\text{Ar-Alk}'\text{-CHO}$ where Alk has the meanings given and Alk' is a corresponding straight or branched alkylene group with 0 - 8 carbon atoms, reduction of the Schiff's base obtained in conventional manner and optionally introducing the radicals R_1 , R_2 and R_5 .

2. By acylating compounds of formula VII or VIII with a compound Ar-Alk-COHal , where Ar and Alk have the meanings given above and Hal represents chlorine, bromine or iodine and optionally introducing of the radicals R_1 , R_2 and R_5 .

It is also possible to obtain starting materials of formula II where $n = 0$ (CO is absent) by reacting a compound of formula IX

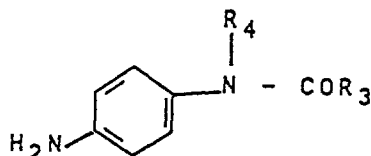


IX

where Hal represents fluorine, chlorine or bromine with an amine of formula Ar-Alk-NH_2 , where Ar and Alk have the meanings given, appropriately in the presence of a basic substance (tertiary amine) and optionally subsequent introduction of the radicals R_1 , R_2 and R_5 .

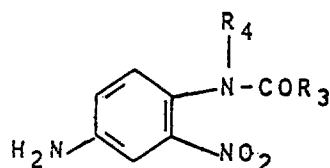
Starting materials of formula III may for example also be obtained as follows:

A compound of formula



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is reacted in conventional manner with phthalic acid anhydride (for example in glacial acetic acid at 90°C) the reaction product obtained, in which the free amino group in the 4-position is only protected by the phthalyl radical, is then nitrated in known manner in the 3-position to the phthalyl group, for example with fuming nitric acid in glacial acetic acid at 90-100°C. The pthalyl radical is then split off in known manner (for example with hydrazine hydrate) in an inert agent such as 1,2-dimethoxyethane, a compound of the following formula being obtained:



It is now possible to successively introduce the radicals Ar-Alk-(CO)_n- and R₅ in a conventional manner into the free amino group (for example as stated under procedure b) and optionally split off the radical -COR₃ in known manner (replacement of -COR₃ by hydrogen).

The reactions described above for the preparation of the starting materials are carried out in conventional manner as described in Example 1 or by analogy thereto. Introduction of the radicals R₁, R₂ and R₅ also occurs in a conventional manner and as stated in the application (specification).

With regard to process b) reaction of a compound of formula IV with a compound of formula V or VI

Process b) is appropriately carried out at temperatures between 0 to 250°C, in particular 20 to 140°C.

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Solvents or suspension agents that may for example be considered for the process are: water, aliphatic alcohols (ethanol, propanol, butanol), aromatic hydrocarbons (benzene, xylene, toluene), lower aliphatic acid amides (dimethylformamide), alicyclic and cyclically saturated ethers (diethyl ether, dioxan), N-methylpyrrolidone, dimethylsulfoxide, sulfolane, tetramethyl urea and mixtures of these agents.

Condensation agents that may be considered for process b) in the event of the reaction of a compound of formula IV with a compound of formula V are primarily for example sodium acetate, sodium amide, alkali metal carbonates and tertiary amines. Zinc chloride, phosphoroxchloride, p-toluenesulfonic acid, iodine and the like may also serve as condensation agents.

The process is carried out in the presence of hydrogen if a compound of formula VI is used. Catalysts that may be considered are conventional hydrogenation catalysts, preferably metallic hydrogenation catalysts such as Raney nickel, platinum, palladium. It is, however, also possible to use alkali metal borohydrides (NaBH_4) lithium borohydride, sodium cyanoborohydride.

Starting materials of formula IV may for example be obtained by conventional reduction of the corresponding nitro compounds (for example of formula VIII). This reduction may for example be carried out as stated in process a) and in the examples.

Starting materials of formula V or VI are known.

Introduction of the radicals R_1 , R_2 , R_4 and R_5 including the group COR_3 according to process a) and/or b) is carried out in a conventional manner for example by the following reactions:

By alkylation or acylation: in this case particularly the acylation or alkylation of amino groups.



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The alkylation or acylation occurs for example by reaction with compounds of formulae $R-Hal$, $ArSO_2OR$ and $SO_2(OR)_2$, where Hal is a halogen atom (in particular chlorine, bromine or iodine) and Ar is an aromatic radical (for example a phenyl or naphthyl radical optionally substituted by one or more lower alkyl radicals and R represents the radicals C_1-C_6 -alkyl, $Ar-C_1-C_6$ -alkyl, $Ar-C_1-C_6$ -alkyl where the C_1-C_6 -alkyl group contains a further radical Ar or represents Ar . Examples are p-toluenesulfonic acid- C_1-C_6 -alkyl esters, C_1-C_6 -dialkyl sulfates, C_1-C_6 -alkyl halides and the like. In the previously mentioned compounds the aryl group may in each case be substituted according to the meaning of Ar . The alkylation and or acylation reaction is optionally carried out with the addition of conventional acid-binding agents, such as alkali metal hydroxides, alkali metal carbonates, alkali metal hydrocarbonates, alkali metal hydrogen carbonates, alkaline earth carbonates, alkaline earth acetates, tertiary amines (for example trialkylamines such as triethylamine), pyridine or also alkali metal hydrides at temperatures between 0 and 200°C, preferably 40 and 140°C in inert solvents or suspension agents. Solvents or dispersing agents that may be considered are for example: aromatic hydrocarbons such as benzene, toluene, xylene; aliphatic ketones such as acetone, methylethyl ketone; halogenated hydrocarbons such as chloroform, carbon tetrachloride, chlorobenzene, methylene chloride; aliphatic ethers such as butyl ether; cyclic ethers such as tetrahydrofuran, dioxan; sulfoxides such as dimethylsulfoxide; tertiary acid amides such as dimethyl formamide, N-methylpyrrolidone, hexamethylphosphoric acid triamide; aliphatic alcohols such as methanol, ethanol, isopropanol, amyl alcohol, tert.-butanol, cycloaliphatic hydrocarbons such as cyclohexane and the like. It is also possible to use aqueous mixtures of the solvents mentioned. Working is often at the reflux temperature of the solvents or dispersing agents used. The alkylation reaction components are frequently used in

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excess. The alkylation can also occur in the presence of tetraalkylammonium salts (in particular the halides) in combination with alkali hydroxides at temperatures between 0-100°C, preferably 20-80°C, in an aprotic solvent or also in chloroform or methylene chloride. Aprotic solvents that may in particular be used are: tertiary amides (dimethylformamide, N-methyl-pyrrolidone, hexamethylphosphoric acid triamide), dimethylsulfoxide, acetonitrile, dimethoxyethane, acetone, tetrahydrofuran.

During acylation the amino groups for example have introduced in them the group $-\text{COR}_3$, the group $-\text{CO}-\text{C}_1-\text{C}_6\text{-alkyl}$, $-\text{CO}-\text{C}_2-\text{C}_6\text{-alkenyl}$, $-\text{CO}-\text{C}_2-\text{C}_6\text{-alkynyl}$, the $\text{C}_1-\text{C}_6\text{-alkoxycarbonyl}$ group or the following groups:
 $-\text{COAr}$, $-\text{CO-OAr}$, $-\text{CONH}_2$
 $-\text{CONH}-\text{C}_1-\text{C}_6\text{-alkyl}$, $-\text{CON}(\text{C}_1-\text{C}_6\text{-alkyl})_2$, $-\text{CONHAr}$,
 $-\text{SO}_2-\text{C}_1-\text{C}_6\text{-alkyl}$, $-\text{SO}_2\text{Ar}$, $-\text{SO}_2\text{-nitrophenyl}$.

The procedure is conducted in a manner known per se, for example using the corresponding acid halides (chloride, bromide) such as Carb- $\text{C}_1-\text{C}_6\text{-alkoxyhalide}$ or corresponding anhydrides). The reaction temperatures are preferably between 20 and 120°C.

It is optionally also possible to carry out the alkylation and acylation by first preparing an alkali metal compound (sodium, potassium or also lithium salt for example) from the compound to be alkylated or acylated by reacting it in an inert solvent such as dioxan, dimethylformamide, benzene or toluene with an alkali metal, alkali metal hydride or alkali metal amide (in particular sodium or sodium compounds) or butyl lithium at temperatures between 0 and 150°C and then adding the alkylating agent.

Instead of the alkylating and acylating agents listed, it is also possible to use other chemically equivalent agents conventionally used in chemistry, see for example also L.F. and



Mary Fieser "Reagents for Organic Synthesis", John Wiley and Sons Inc., New York, 1967, Vol. 1, pages 1303-4 and Vol. 2, page 471.

Acyl groups present, such as Carb-C₁-C₆-alkoxy groups, C₂-C₆-alkanoyl groups and similar groups can be split off solvolytically. This splitting occurs in known manner, for example by saponification with acids (mineral acids such as hydrochloric acid, sulphuric acid, in particular concentrated hydrohalic acids such as HBr/glacial acetic acid) or using base substances (potashes, soda, aqueous alkali solutions, alcoholic alkali solutions, aqueous NH₃) at temperatures between 10 and 150°C, in particular 20-100°C.

The compounds of the invention display a good anti-epileptic action for example in the maximal electrocramp test (MES). For example in the above-mentioned test method, a dose of 6 mg/kg body weight rat achieves a 50% inhibition of the cramps provoked by electric stimulation.

The lowest already effective dose in the above-mentioned animal experiment is for example

2 mg/kg oral
0.5 mg/kg intravenous.

The general dose range that may for example be used for the effect (animal experiment as above) is:

2 - 20 mg/kg oral, in particular 10 mg/kg
0.5 - 5 mg/kg intravenous, in particular 2 mg/kg.

Generally speaking the activity of the compounds of the invention is comparable with the effect of the known medicinally active substance diazepam, although the compounds of the invention have a broader therapeutic spectrum.



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The compounds of the invention may in particular be considered to be effective anti-epileptic agents.

The pharmaceutical formulations contain in general between 10 to 100, preferably 30 to 60 mg of the active component(s) of the invention.

Administration may for example be in the form of tablets, capsules, pills, coated tablets, suppositories, ointments, gels, creams, powders, dusting powders, aerosols or in liquid form. Liquid application forms that may for example be considered are: oils or alcoholic or aqueous solutions as well as suspensions and emulsions. Preferred forms of application are tablets that contain between 30 and 60 mg or solutions that contain between 0.1 to 5 percent by weight of active substance.

The individual dose of the active components of the invention can for example lie

- a) in the case of oral medicinal forms between 20 and 80 mg, preferably 30 - 60 mg
- b) in the case of parenteral medicinal forms (for example intravenous, intramuscular) between 5 - 20 mg, preferably 8 - 16 mg.

-(The doses are in each case related to the free base)-

It is for example possible to recommend 3 times daily 1 to 3 tablets containing 30 - 60 mg of active substance or for example in the case of intravenous injection 1 to 3 times daily one ampoule of 3 to 5 ml content with 8 to 16 mg substance. In the case of oral administration the minimum daily dose is for example 90 mg; the maximum daily dose in oral administration should not exceed 270 mg.

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For the treatment of dogs and cats the oral individual dose is generally between about 2 and 20 mg/kg body weight; the parenteral dose about between 1 and 5 mg/kg body weight.

The medicament can be used in human medicine, in veterinary medicine and in agriculture, alone or mixed with other pharmacologically active substances.

Examples:

Example 1

2-Amino-4-(4-fluorobenzylamino)-1-ethoxycarbonylaminobenzene.

Variant A

A suspension of 5.2 g (20 mmol)
2-amino-5-(4-fluorobenzylamino)-nitrobenzene or 5.2 g (20 mmol)
2-amino-4-(4-fluorobenzylamino)-nitrobenzene in 100 ml dioxan is hydrogenated at 55 - 60°C under normal pressure in the presence of 2 g Raney nickel. When hydrogen uptake is completed the catalyst is filtered off under an inert gas and the filtrate is reacted with 3.2 g (25 mmol) di-isopropylethylamine. A solution of 2.3 g (21 mmol) ethyl chloroformate in 15 ml dioxan is added dropwise to the solution obtained with stirring and an inert gas atmosphere (for example nitrogen) at 10 - 20°C. When all has been added, the mixture is then stirred for 1 hour at room temperature and 10 ml 6N ethanolic hydrochloric acid is then added dropwise with stirring and ice cooling. A colourless solid material gradually crystallizes out. The mixture is then stirred for 2 more hours at room temperature and the precipitated product is suction filtered. After recrystallization from ethanol/ether 5.5 g (73 % of theory) of
2-amino-4-(4-fluorobenzylamino)-1-ethoxycarbonylamino-benzene is

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obtained as dihydrochloride in the form of colourless to slightly pink crystals.

M.p. of the dihydrochloride 182 - 186°C

Preparation of the starting materials.

2-Amino-5-(4-fluorobenzylamino)-nitrobenzene

A solution of 25.9 g (100 mmol) 2-amino-5-(4-fluorobenzylidene amino)-nitrobenzene in 250 ml dioxan/methanol mixture (4:1) is reacted in portions with stirring with 5.7 g (150 mmol) sodium tetrahydroborate. When all has been added the mixture is stirred at room temperature for 2 hours more, the reaction solution then being concentrated under a vacuum until dry. The remaining dark red residue is taken up in 100 ml water and the resulting suspension is extracted four times with in each case 200 ml dichloromethane. The combined organic phases are dried with sodium sulfate and then concentrated in a vacuum. The remaining dark red oil is crystallized from 100 ml toluene. After drying in a vacuum 21.0 g (80 % of theory)

2-amino-5-(4-fluorobenzylamino)-nitrobenzene are obtained as dark red crystals.

M.p. 111 - 112°C

2-Amino-5-(4-fluorobenzylideneamino)-nitrobenzene can for example be obtained as follows:

A solution of 15.3 g (100 mmol) 2-nitro-p-phenylenediamine and 13.6 g (110 mmol) 4-fluorobenzaldehyde in 400 ml xylene is heated under reflux in the presence of 0.5 g of an acid ion exchanger (for example Nafion) for 3 hours in a water separator. Insoluble constituents are filtered out hot and the mixture is allowed to stand overnight at room temperature. An orange-yellow solid crystallizes out. This is suction filtered, washed with a little toluene and dried in a vacuum. 22.0 g (85 %



of theory) 2-amino-5-(4-fluorobenzylideneamino)-nitrobenzene are obtained as orange-yellow crystals.

M.p. 136 - 139°C

2-Amino-4-(4-fluorobenzylideneamino)-nitrobenzene

A solution of 15.6 g (100 mmol) 2-amino-4-fluoro-nitrobenzene, 22.5 g (180 mmol) 4-fluorobenzylamine and 20.2 g (220 mmol) triethylamine in 150 ml dimethylsulfoxide is heated under stirring and an inert gas atmosphere for 30 hours to 60 - 70°C. When the reaction time is completed, the solvent is distilled off in a vacuum, the residue is taken up in 500 ml 0.5 N hydrochloric acid and the mixture stirred intensively at room temperature for 30 minutes. The precipitated solid is suction filtered and subjected to hot steam extraction with toluene. The product crystallizing out of the toluene after the mixture has been allowed to stand for twelve hours at 0 - 4°C is suction filtered and dried in a vacuum. 22.2 g (85 % of theory) are obtained. After being left to stand for 12 hours at 0 - 4°C 2-amino-4-(4-fluorobenzylamino)-nitrobenzene crystallizes out of the toluene phase as orange-yellow crystals.

M.p. 180°C

Variant B

A suspension of 13.3 g (40 mmol) of 2-ethoxycarbonylamino-5-(4-fluorobenzylamino)-nitrobenzene in 150 ml 1,2-dimethoxyethane is hydrogenated at 55 - 60°C under normal pressure in the presence of 2 g Raney nickel. After hydrogen uptake has finished, the catalyst is filtered off under an inert gas and the filtrate is concentrated in a vacuum. The remaining residue is taken up in 150 ml ethanol and 20 ml 6 N ethanolic hydrochloric acid are added dropwise to the solution obtained under stirring and an inert gas atmosphere. After



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addition has finished the mixture is stirred for a further 1 hour, the precipitated solid is suction filtered and washed with ethanol. After drying in a vacuum 13.5 g (89 % of theory) of the named compound are obtained as colourless to slightly pink crystals.

M.p. 186 - 189°C

Preparation of the starting substance

2-Ethoxycarbonylamino-5-(4-fluorobenzylamino)-nitrobenzene 39.8 g (120 mmol)

2-ethoxycarbonylamino-5-(4-fluorobenzylideneamino)-nitrobenzene (prepared from 33.8 g (150 mmol)

5-amino-2-ethoxycarbonylamino-nitrobenzene and 19.2 g (155 mmol) 4-fluorobenzaldehyde) are reacted as stated above with 3.8 g (100 mmol) sodiumtetrahydridoborate. After appropriate working up 31.3 g (78 % of theory)

2-ethoxycarbonylamino-5-(4-fluorobenzylamino)-nitrobenzene are obtained as dark red crystals.

M.p. 85 - 87°C

The 5-amino-2-ethoxycarbonylamino-nitro-benzene may for example be obtained as follows:

21.0 g (0.42 mol) hydrazine hydrate is added dropwise with stirring under reflux to a suspension of 142.1 g (0.4 mol) 2-ethoxycarbonylamino-5-phthalimido-nitrobenzene in 700 ml 1,2-dimethoxyethane and the mixture is allowed to react for a further 2 hours. After cooling to room temperature, precipitated phthalyl hydrazide is filtered off and the dark red filtrate in the vacuum is evaporated to dryness. The remaining solid residue is recrystallized from about 150 ml toluene. 84.4 g 5-amino-2-ethoxycarbonylaminonitrobenzene are obtained as dark red crystals.

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M.p. 105 - 107°C

2-Ethoxycarbonylamino-5-phthalimido-nitrobenzene is for example obtained as follows:

75.7 g phthalic acid anhydride are added in portions to a solution of 90.1 g (0.5 mol) N-ethoxycarbonyl-p-phenylene diamine in 1.5 l glacial acetic acid with stirring and an inert gas atmosphere at 90°C. When addition is completed the mixture is left to react for a further 60 minutes. 27.5 ml fuming nitric acid are then added dropwise to the resulting suspension and the mixture is allowed to continue to react for 2 hours at 100°C. After cooling to room temperature the precipitated solid substance is filtered off and washed neutral several times with a total of 2.5 l water. After drying in a vacuum 149.9 g of the phthalimido compound are obtained as yellow crystals.

M.p. 215 - 216°C

Example 2

2-Amino-4-(4-trifluoromethylbenzylamino)-1-ethoxycarbonylamino-benzene

Variant A

A suspension of 9.3 g (30 mmol)

2-amino-5-(4-trifluoromethylbenzylamino)-nitrobenzene is hydrogenated by analogy with Example 1 (variant A) and then reacted with 3.4 g (31 mmol) ethyl chloroformate. 5.8 g (45 % of theory) of the named end product is obtained as dihydrochloride in the form of colourless to weakly pink crystals.

M.p. 159 - 162°C

Variant B

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A suspension of 65.2 g (170 mmol)
2-ethoxycarbonylamino-5-(4-trifluoromethylbenzylamino)-nitro
benzene is hydrogenated by analogy with Example 1 (Variant B)
and worked up appropriately. 52.2 g (72 % of theory) of the
named end product are obtained as dihydrochloride in the form of
colourless crystals.

M.p. 160 - 162°C.

The corresponding starting materials are prepared as described
in Example 1 in analogous manner.

Example 3

2-Amino-4-benzylamino-1-ethoxycarbonylamino-benzene

A suspension of 12.6 g (40 mmol)
5-benzylamino-2-ethoxycarbonyl-amino-nitrobenzene is
hydrogenated by analogy with Example 1 (variant B) and worked up
appropriately. 52.2 g (72 % of theory) of the end product are
obtained: colourless to pale pink crystals.

M.p. 178 - 181°C.

Example 4

2-Amino-4-(3,5-dichlorobenzylamino)-1-ethoxycarbonylamino-benzene

A suspension of 15.5 g (50 mmol)
2-amino-5-(3,5-dichlorobenzylamino)-nitrobenzene is hydrogenated
by analogy with Example 1 (variant A) and worked up
appropriately with 5.5 g (51 mmol) ethyl chloroformate. 10.8 g
(51 % of theory) of the end product are obtained as
dihydrochloride: colourless to pale pink crystals.

M.p. 134 - 136°C.

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Example 5

2-Amino-4-(3,5-dichlorobenzylamino)-1-propyloxy-carbonylamino
benzene

A suspension of 15.5 g (50 mmol)

2-amino-5-(3,5-dichlorobenzylamino)-nitrobenzene is hydrogenated
by analogy with Example 1 (variant A) and worked up
appropriately with 6.2 g (51 mmol) propyl chloroformate. 10.8 g
of the end product are obtained in the form of the
dihydrochloride. This forms colourless to pale pink crystals.
M.p. 154 - 155°C.

Example 6

2-Amino-4-(2-chlorobenzylamino)-1-(diethylcarbamoylamino)
benzene

A suspension of 8.3 g (30 mmol)

2-amino-5-(2-chlorobenzylamino)-nitrobenzene is hydrogenated by
analogy with Example 1 (variant A) and worked up appropriately
with 4.2 g (31 mmol) N,N-dimethylcarbamoyl chloride. 6.5 g of
the end product are obtained as colourless to pale pink
crystals.

M.p. 153 - 155°C.

Example 7

2-Amino-4-(2,4-dichlorobenzylamino)-1-(dimethylcarbamoylamino)
benzene

A suspension of 31.2 g (100 mmol)

2-amino-5-(2,4-dichlorobenzylamino)-nitrobenzene is hydrogenated
by analogy with Example 1 (variant A) and worked up

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appropriately with 13.9 g (101 mmol) N,N-dimethylcarbamoyl chloride. 12.4 g of the end product are obtained in the form of the dihydrochloride. This forms colourless to pale pink crystals.

M.p. 147 - 152°C.

Example 8

1,2-Diacetylamino-4-(4-fluorobenzylamino) benzene

9.4 g (30 mmol)

4-(4-fluorobenzylideneamino)-N,N'-diacetyl-o-phenylene diamine are reduced in 250 ml dioxan/methanol mixture (4:1) as described in Example 1 with 0.9 g (25 mmol) sodiumtetrahydriodoborate. The free base obtained is then transferred into the hydrochloride directly with alcoholic hydrochloric acid. 7.2 g of the end product are obtained in the form of the monohydrochloride. This forms colourless crystals.

M.p. 165 - 168°C.

4-(4-Fluorobenzylideneamino)-N,N'-diacetyl-o-phenylene diamine is for example obtained by reacting 8.3 g (40 mmol) 4-amino-N,N'-diacetyl-o-phenylene diamine with 5.1 g (41 mmol) 4-fluorobenzaldehyde (as described under Example 1). Yield: 11.0 g yellow crystals.

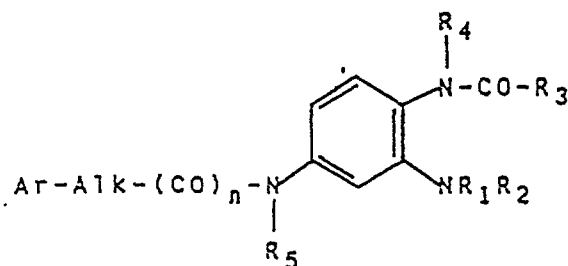
M.p. 152 - 156°C

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Novel 1,2,4-triaminobenzene derivatives and processes for their
preparation
Claims

1. 1,2,4-triaminobenzene derivatives of the general formula



where the symbols R_1 , R_2 , R_3 , R_4 , R_5 , Ar and Alk have the following meanings:

- R_1 : hydrogen, C_1 - C_6 -alkyl, C_2 - C_6 -alkanoyl or the radical Ar;
- R_2 : hydrogen or C_1 - C_6 -alkyl;
- R_3 : C_1 - C_6 -alkoxy, NH_2 , C_1 - C_6 -alkylamino, C_1 - C_6 -dialkylamino, amino substituted by the radical Ar, C_1 - C_6 -alkyl, C_2 - C_6 -alkenyl, C_2 - C_6 -alkynyl, the radical Ar or the radical $ArO-$;
- R_4 : hydrogen, C_1 - C_6 -alkyl or the radical Ar;
- R_5 : hydrogen or C_1 - C_6 -alkyl or the radical Ar;
- Alk: a straight or branched alkylene group with 1 - 9 carbon atoms, which can also be substituted by the radical Ar;
- Ar: a phenyl radical substituted by the radicals R_6 , R_7 and/or R_8 where these radicals R_6 , R_7 and R_8 are the same or different and represent C_1 - C_6 -alkyl, C_3 - C_7 -cycloalkyl, hydroxy, C_1 - C_6 -alkoxy, C_2 - C_6 -alkanoyloxy, halogen, hydroxy, C_1 - C_6 -halogenoalkyl, $-CN$, $-NH_2$, $-NH-C_1-C_6-alkyl$, $-N(C_1-C_6-alkyl)_2$, $-CO_2H$, $-CO-C_1-C_6-alkyl$, $-CO-O-C_1-C_6-alkyl$, $-COAr$, $-CO-OAr$, $-CONH_2$, $-CONH-C_1-C_6-alkyl$,





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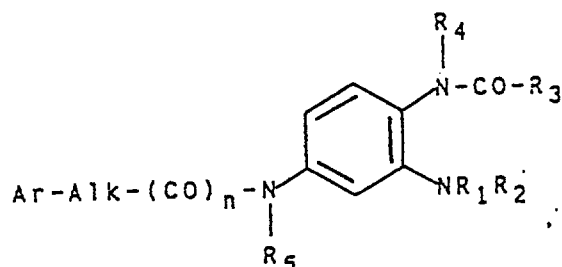
-CON(C₁-C₆-alkyl)₂, -CONHAr,
-NH-CO-C₁-C₆-alkyl, -NHCO-Ar,
-NHCO-C₁-C₆-alkoxy, -NH-CO-OAr, -NHCO-NH₂,
-NHCO-N(C₁-C₆-alkyl)₂, -NHCO-NHAr,
-NH-SO₂-C₁-C₆-alkyl, -NH-SO₂Ar,
-NH-SO₂-nitrophenyl, -SO₂-OH,
-SO₂-C₁-C₆-alkyl, -SO₂-Ar,
-SO₂-C₁-C₆-alkoxy, -SO₂-OAr, -SO₂-NH₂,
-SO₂-NH-C₁-C₆-alkyl,
-SO₂-N(C₁-C₆-alkyl)₂, -SO₂-NHAr, or
-SO₂-C₁-C₆-alkoxy;

n: 0 or 1;

and pharmaceutically acceptable acid addition salts thereof,
except for the compound

1-amino-2-carbethoxyamino-6-(2,4,6-trimethyl)-benzyl
amino)pyridine and the hydrochloride thereof.

2. A process for the preparation of 1,2,4-triaminobenzene
derivatives of the general formula



I

where the symbols R₁, R₂, R₃, R₄, R₅, Ar and Alk
have the following meanings:

- R₁: hydrogen, C₁-C₆-alkyl, C₂-C₆-alkanoyl or the
radical Ar;
R₂: hydrogen or C₁-C₆-alkyl;

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- R₃: C₁-C₆-alkoxy, NH₂, C₁-C₆-alkylamino, C₁-C₆-dialkylamino, amino substituted by the radical Ar, C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, the radical Ar or the radical ArO-;
- R₄: hydrogen, C₁-C₆-alkyl or the radical Ar;
- R₅: hydrogen or C₁-C₆-alkyl or the radical Ar;
- Alk: a straight or branched alkylene group with 1 - 9 carbon atoms, which can also be substituted by the radical Ar;
- Ar: a phenyl radical substituted by the radicals R₆, R₇ and/or R₈ where these radicals R₆, R₇ and R₈ are the same or different and represent C₁-C₆-alkyl, C₃-C₇-cycloalkyl, hydroxy, C₁-C₆-alkoxy, C₂-C₆-alkanoyloxy, halogen, hydroxy, C₁-C₆-halogen alkyl, -CN, -NH₂, -NH-C₁-C₆-alkyl, -N(C₁-C₆-alkyl)₂, -CO₂H, -CO-C₁-C₆-alkyl, -CO-O-C₁-C₆-alkyl, -COAr, -CO-OAr, -CONH₂, -CONH-C₁-C₆-alkyl, -CON(C₁-C₆-alkyl)₂, -CONHAr, -NH-CO-C₁-C₆-alkyl, -NHCO-Ar, -NHCO-C₁-C₆-alkoxy, -NH-CO-OAr, -NHCO-NH₂, -NHCO-N(C₁-C₆-alkyl)₂, -NHCO-NHAr, -NH-SO₂-C₁-C₆-alkyl, -NH-SO₂Ar, -NH-SO₂-nitrophenyl, -SO₂-OH, -SO₂-C₁-C₆-alkyl, -SO₂-Ar, -SO₂-C₁-C₆-alkoxy, -SO₂-OAr, -SO₂-NH₂, -SO₂-NH-C₁-C₆-alkyl, -SO₂-N(C₁-C₆-alkyl)₂, -SO₂-NHAr, -SO₂-C₁-C₆-alkoxy;
- n: 0 or 1;
- and pharmaceutically acceptable acid addition salts thereof, except for the compound
- 1-amino-2-carbethoxyamino-6-(2,4,6-trimethyl)-benzyl amino)-pyridine and its hydrochloride, characterized in that

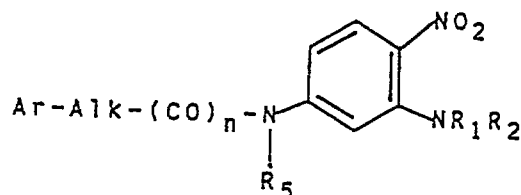
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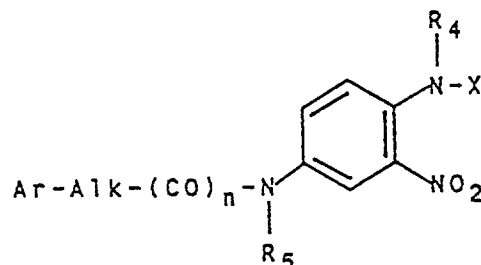
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a) in a compound of formula



II

where R_1 , R_2 , R_5 , Alk, Ar and n have the given meanings or in a compound of formula

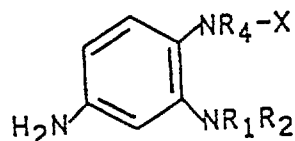


III

where X is hydrogen or the group $-\text{COR}_3$ and R_3 , R_4 , R_5 , Alk, Ar and n have the given meanings,

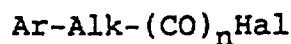
the nitro group is reduced in known manner to an amino group, the group $-\text{COR}_3$ is introduced by acylation if this is not present in the starting materials II or III and the radical R_2 , R_2 , R_5 is introduced optionally before or after introduction of the group $-\text{COR}_3$ by alkylation, arylation and/or acylation or

b) a compound of formula



IV

where X is hydrogen or the group $-\text{COR}_3$ and R_1 , R_2 , R_3 and R_4 have the given meanings is reacted with a compound of formula



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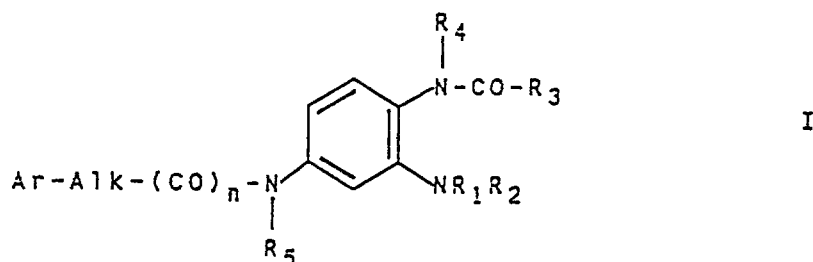
where Ar, -Alk and n have the given meanings and Hal is chlorine, bromine or iodine or a compound of formula



VI

where Ar has the given meanings and Alk' is a straight or branched alkylene group with 0 - 8 carbon atoms, where in the latter case the double bond of the Schiff's base obtained is reduced to the simple bond, that the radicals -COR₃, R₁, R₂, R₄ and R₅ are introduced optionally by alkylation, arylation and/or acylation, the radical R₃ is optionally exchanged for another radical in the compounds obtained according to procedure a) or b) in the context of the definition given for R₃ and the compounds so obtained are converted into acid addition salts.

3. A medicament containing as active substance at least one 1,2,4-triaminobenzene derivative of the general formula



where the symbols R₁, R₂, R₃, R₄, R₅, Ar and Alk have the following meanings:

- R₁: hydrogen, C₁-C₆-alkyl, C₂-C₆-alkanoyl or the radical Ar;
 R₂: hydrogen or C₁-C₆-alkyl;
 R₃: C₁-C₆-alkoxy, NH₂, C₁-C₆-alkylamino, C₁-C₆-dialkylamino, amino substituted by the radical Ar, C₁-C₆-alkyl, C₂-C₆-alkenyl,

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C₂-C₆-alkynyl, the radical Ar or the radical
ArO-;

R₄: hydrogen, C₁-C₆-alkyl or the radical Ar;

R₅: hydrogen, C₁-C₆-alkyl or the radical Ar;

Alk: a straight or branched alkylene group with 1 - 9
carbon atoms, which may also be substituted by the
radical Ar;

Ar: a phenyl radical substituted by the radicals R₆,
R₇ and/or R₈ where these radicals R₆, R₇ and
R₈ are the same or different and represent
C₁-C₆-alkyl, C₃-C₇-cycloalkyl, hydroxy,
C₁-C₆-alkoxy, C₂-C₆-alkanoyloxy, halogen,
hydroxy, C₁-C₆-halogen alkyl, -CN, -NH₂,
-NH-C₁-C₆-alkyl, -N(C₁-C₆-alkyl)₂, -CO₂H,
-CO-C₁-C₆-alkyl, -CO-O-C₁-C₆-alkyl, -COAr,
-CO-OAr, -CONH₂, -CONH-C₁-C₆-alkyl,
-CON(C₁-C₆-alkyl)₂, -CONHAr,
-NH-CO-C₁-C₆-alkyl, -NHCO-Ar,
-NHCO-C₁-C₆-alkoxy, -NH-CO-OAr, -NHCO-NH₂,
-NHCO-N(C₁-C₆-alkyl)₂, -NHCO-NHAr,
-NH-SO₂-C₁-C₆-alkyl, -NH-SO₂Ar,
-NH-SO₂-nitrophenyl, -SO₂-OH,
-SO₂-C₁-C₆-alkyl, -SO₂-Ar,
-SO₂-C₁-C₆-alkoxy, -SO₂-OAr, -SO₂-NH₂,
-SO₂-NH-C₁-C₆-alkyl,
-SO₂-N(C₁-C₆-alkyl)₂, -SO₂-NHAr,
-SO₂-C₁-C₆-alkoxy;

n: 0 or 1;

or pharmaceutically acceptable acid addition salts thereof,
as well as optionally other conventional auxiliary
substances and carriers or diluents.



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4. A process for the preparation of a medicament characterized in that at least one compound of formula I including the compound
1-amino-2-carbethoxyamino-6-(2,4,6-trimethyl)benzylamino)-pyridine and its hydrochloride is processed with conventional pharmaceutical carriers and/or diluents or other auxiliary substances into pharmaceutical formulations or brought into a therapeutically applicable form.
5. The use of compounds of formula I according to claim 1 including the compound
1-amino-2-carbethoxyamino-6-(2,4,6-trimethyl)benzylamino)-pyridine and its hydrochloride for the preparation of medicaments.



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