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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.



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 formiate. 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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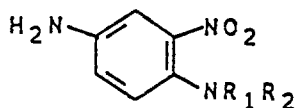
Agents of this kind that may for example be considered are: inorganic condensation agents such as ammonia, alkali metal or alkaline earth hydroxides, alkali metal- or alkaline earth-carbonates or organic basis such as pyridine, tertiary amines (triethylamine), piperidine, alkali metal alcoholates, alkali 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.

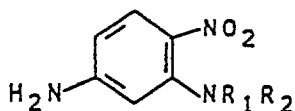
The additionally available amino groups can for example contain a conventional amino protection group. Protection groups of this kind can be split by solvolysis or hydrogenolysis after completion of the reaction.

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

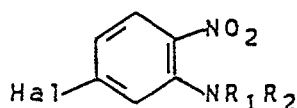
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with an aldehyde Ar-Alk'-CHO where Alk has the meanings given and Alk' is a corresponding straight or branched alkylene group with 0 - 8 carbon atoms, reduction of the Schiff's base obtained in conventional manner and optionally introducing the radicals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

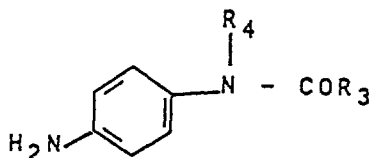


IX

where Hal represents fluorine, chlorine or bromine with an amine of formula Ar-Alk-NH₂, 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 .

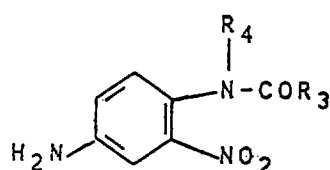
Starting materials of formula III may for example also be obtained as follows:

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 phthalyl 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, phosphoroxychloride, 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.



The alkylation or acylation occurs for example by reaction with compounds of formulae $R\text{-Hal}$, ArSO_2OR and $\text{SO}_2(\text{OR})_2$, 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 $\text{C}_1\text{-C}_6\text{-alkyl}$, $\text{Ar-C}_1\text{-C}_6\text{-alkyl}$, $\text{Ar-C}_1\text{-C}_6\text{-alkyl}$ where the $\text{C}_1\text{-C}_6\text{-alkyl}$ group contains a further radical Ar or represents Ar. Examples are p-toluenesulfonic acid- $\text{C}_1\text{-C}_6\text{-alkyl}$ esters, $\text{C}_1\text{-C}_6\text{-dialkyl}$ sulfates, $\text{C}_1\text{-C}_6\text{-alkyl}$ 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



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-ethoxycarbonylamino benzene.

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



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 %

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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)

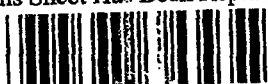
2-ethoxycarbonylamino-5-(4-fluorobenzylamino)-nitrobenzene are obtained as dark red crystals.

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-propyloxycarbonylamino
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.

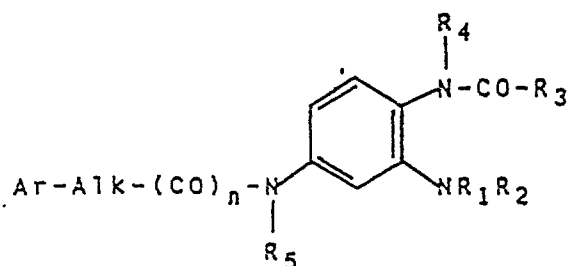
M.p. 152 - 156°C

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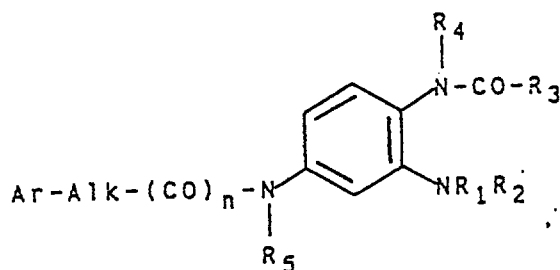
-CON(C₁-C₆-alkyl)₂, -CONHAr,
-NH-CO-C₁-C₆-alkyl, -NHCO-Ar,
-NHCO-C₁-C₆-alkoxy, -NH-CO-OAr, -NHCO-NH₂,
-NHCO-N(C₁-C₆-alkyl)₂, -NHCO-NHAr,
-NH-SO₂-C₁-C₆-alkyl, -NH-SO₂Ar,
-NH-SO₂-nitrophenyl, -SO₂-OH,
-SO₂-C₁-C₆-alkyl, -SO₂-Ar,
-SO₂-C₁-C₆-alkoxy, -SO₂-OAr, -SO₂-NH₂,
-SO₂-NH-C₁-C₆-alkyl,
-SO₂-N(C₁-C₆-alkyl)₂,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



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

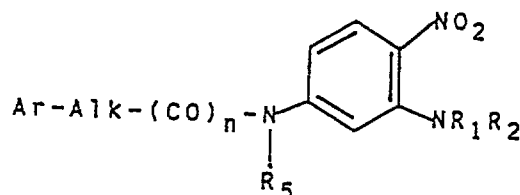
1-amino-2-carbethoxyamino-6-(2,4,6-trimethyl)-benzyl amino)-pyridine and its hydrochloride, characterized in that

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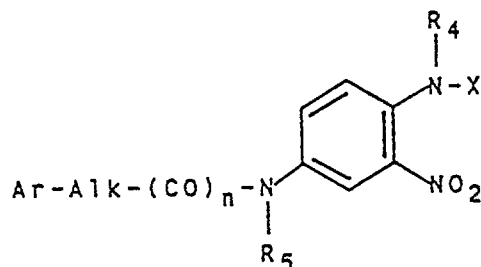


a) in a compound of formula



II

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

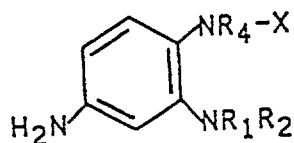


III

where X is hydrogen or the group $-COR_3$ and R_3 , R_4 , R_5 , Alk, Ar and n have the given meanings,

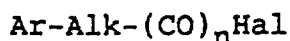
the nitro group is reduced in known manner to an amino group, the group $-COR_3$ is introduced by acylation if this is not present in the starting materials II or III and the radical R_2 , R_2 , R_5 is introduced optionally before or after introduction of the group $-COR_3$ by alkylation, arylation and/or acylation or

b) a compound of formula



IV

where X is hydrogen or the group $-COR_3$ 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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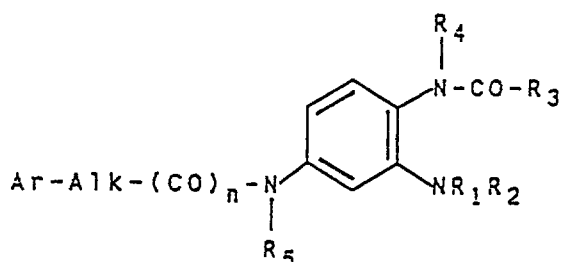
where Ar, -Alk and n have the given meanings and Hal is chlorine, bromine or iodine or a compound of formula



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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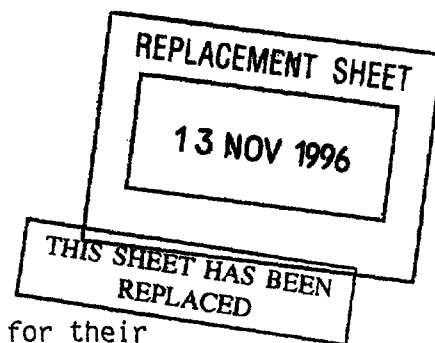


4. A process for the preparation of a medicament characterized in that at least one compound of formula I including the compound
1-amino-2-carbethoxyamino-6-(2,4,6-trimethyl)benzylamino)-pyridine and its hydrochloride is processed with conventional pharmaceutical carriers and/or diluents or other auxiliary 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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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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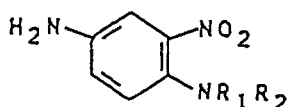
Agents of this kind that may for example be considered are: inorganic condensation agents such as ammonia, alkali metal or alkaline earth hydroxides, alkali metal- or alkaline earth-carbonates or organic basis such as pyridine, tertiary amines (triethylamine), piperidine, alkali metal alcoholates, alkali 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.

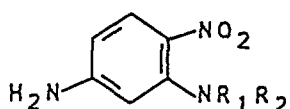
The additionally available amino groups can for example contain a conventional amino protection group. Protection groups of this kind can be split by solvolysis or hydrogenolysis after completion of the reaction.

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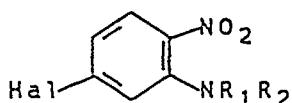
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with an aldehyde $\text{Ar-Alk}'\text{-CHO}$ where Alk has the meanings given and Alk' is a corresponding straight or branched alkylene group with 0 - 8 carbon atoms, reduction of the Schiff's base obtained in conventional manner and optionally introducing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

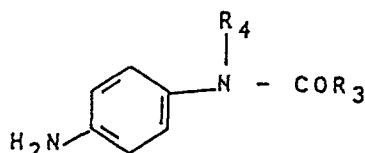


IX

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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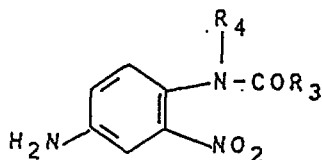


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is reacted in conventional manner with phthalic acid anhydride (for example in glacial acetic acid at 90°C) the reaction product obtained, in which the free amino group in the 4-position is only protected by the phthalyl radical, is then nitrated in 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 phthalyl 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 $\text{Ar-Alk}(\text{CO})_n-$ and R_5 in a conventional manner into the free amino group (for example as stated under procedure b) and optionally split off the radical $-\text{COR}_3$ in known manner (replacement of $-\text{COR}_3$ 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 R_1 , R_2 and R_5 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, phosphoroxychloride, 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

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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

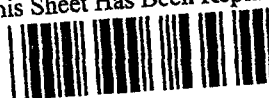
2 mg/kg oral
0.5 mg/kg intravenous.

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.

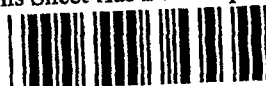
The individual dose of the active components of the invention can for example lie

- 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 %

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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.

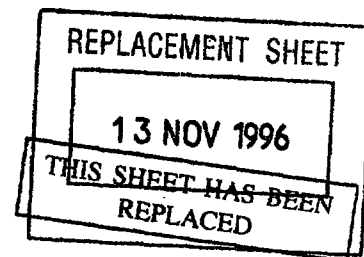
M.p. 180°C

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)

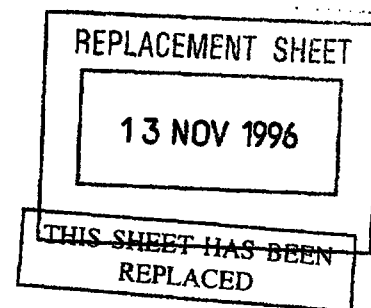
2-ethoxycarbonylamino-5-phthalimido-nitrobenzene in 700 ml

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

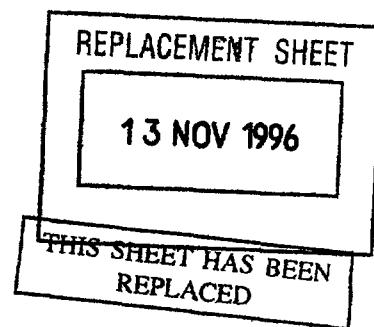
A suspension of 15.5 g (50 mmol)

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-propyloxycarbonylamino
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-(diethylcarbamoylelamino)
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-dimethylcarbamoyle chloride. 6.5 g of
the end product are obtained as colourless to pale pink
crystals.
M.p. 153 - 155°C.

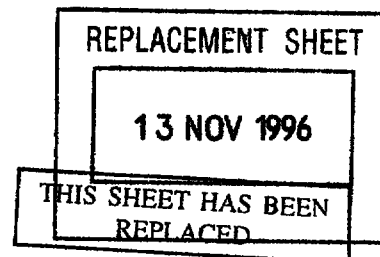
Example 7

2-Amino-4-(2,4-dichlorobenzylamino)-1-(dimethylcarbamoylelamino)
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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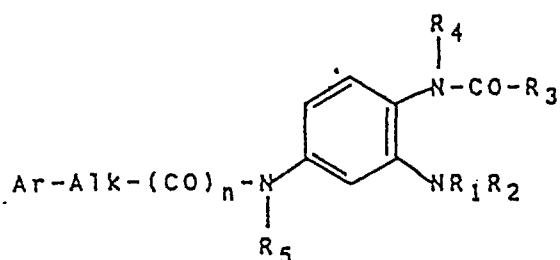
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Novel 1,2,4-triaminobenzene derivatives and processes for their preparation
Claims

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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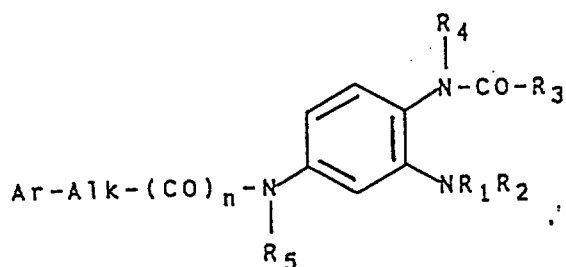
-CON(C₁-C₆-alkyl)₂, -CONHAr,
-NH-CO-C₁-C₆-alkyl, -NHCO-Ar,
-NHCO-C₁-C₆-alkoxy, -NH-CO-OAr, -NHCO-NH₂,
-NHCO-N(C₁-C₆-alkyl)₂, -NHCO-NHAr,
-NH-SO₂-C₁-C₆-alkyl, -NH-SO₂Ar,
-NH-SO₂-nitrophenyl, -SO₂-OH,
-SO₂-C₁-C₆-alkyl, -SO₂-Ar,
-SO₂-C₁-C₆-alkoxy, -SO₂-OAr, -SO₂-NH₂,
-SO₂-NH-C₁-C₆-alkyl,
-SO₂-N(C₁-C₆-alkyl)₂, -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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- 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 -halogen alkyl, $-CN$, $-NH_2$, $-NH-C_1-C_6$ -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, $-CON(C_1-C_6-alkyl)_2$, $-CONHAr$, $-NH-CO-C_1-C_6$ -alkyl, $-NHCO-Ar$, $-NHCO-C_1-C_6$ -alkoxy, $-NH-CO-OAr$, $-NHCO-NH_2$, $-NHCO-N(C_1-C_6-alkyl)_2$, $-NHCO-NHAr$, $-NH-SO_2-C_1-C_6$ -alkyl, $-NH-SO_2Ar$, $-NH-SO_2$ -nitrophenyl, $-SO_2-OH$, $-SO_2-C_1-C_6$ -alkyl, $-SO_2-Ar$, $-SO_2-C_1-C_6$ -alkoxy, $-SO_2-OAr$, $-SO_2-NH_2$, $-SO_2-NH-C_1-C_6$ -alkyl, $-SO_2-N(C_1-C_6-alkyl)_2$, $-SO_2-NHAr$, $-SO_2-C_1-C_6$ -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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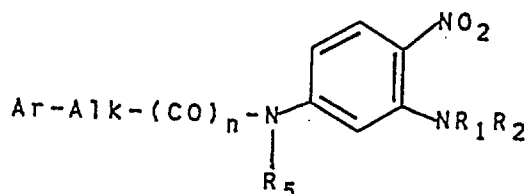
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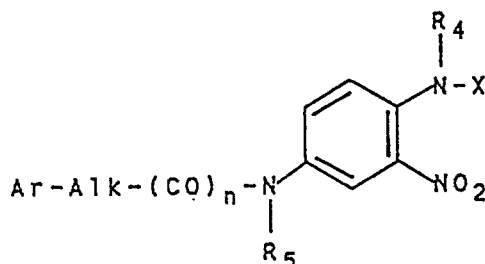
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II

a) in a compound of formula



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

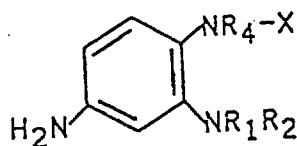


III

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,

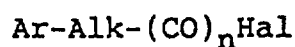
the nitro group is reduced in known manner to an amino group, the group $-\text{COR}_3$ is introduced by acylation if this is not present in the starting materials II or III and the radical R_2 , R_2 , R_5 is introduced optionally before or after introduction of the group $-\text{COR}_3$ by alkylation, 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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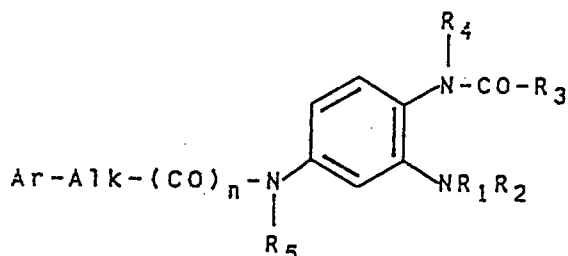
where Ar, -Alk and n have the given meanings and R₃ is chlorine, bromine or iodine or a compound of formula

Ar-Alk'-CHO

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



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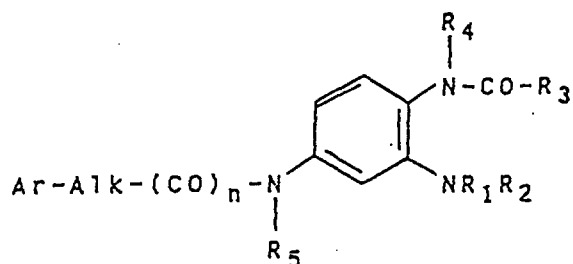
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Novel 1,2,4-triaminobenzene derivatives and processes for their preparation

Abstract:

Pharmacologically active 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;

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Alk: a straight or branched alkylene group with 1-6 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.

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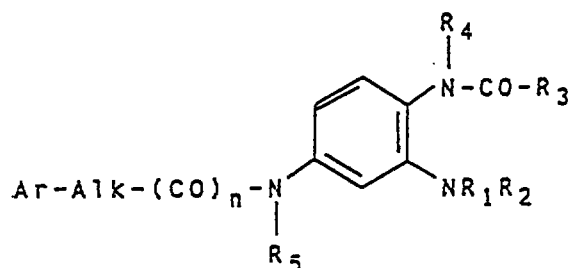
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Novel 1,2,4-triaminobenzene derivatives and processes for their preparation

Abstract:

Pharmacologically active 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;

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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 -halogen alkyl, -CN, -NH₂, -NH- C_1 - C_6 -alkyl, -N(C_1 - C_6 -alkyl)₂, -CO₂H, -CO- C_1 - C_6 -alkyl, -CO-O- C_1 - C_6 -alkyl, -COAr, -CO-OAr, -CONH₂, -CONH- C_1 - C_6 -alkyl, -CON(C_1 - C_6 -alkyl)₂, -CONHAr, -NH-CO- C_1 - C_6 -alkyl, -NHCO-Ar, -NHCO- C_1 - C_6 -alkoxy, -NH-CO-OAr, -NHCO-NH₂, -NHCO-N(C_1 - C_6 -alkyl)₂, -NHCO-NHAr, -NH-SO₂- C_1 - C_6 -alkyl, -NH-SO₂Ar, -NH-SO₂-nitrophenyl, -SO₂-OH, -SO₂- C_1 - C_6 -alkyl, -SO₂-Ar, -SO₂- C_1 - C_6 -alkoxy, -SO₂-OAr, -SO₂-NH₂, -SO₂-NH- C_1 - C_6 -alkyl, -SO₂-N(C_1 - C_6 -alkyl)₂, -SO₂-NHAr, -SO₂- C_1 - C_6 -alkoxy;

n: 0 or 1;

and pharmaceutically acceptable acid addition salts thereof

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NOVAL 1,2,4-TRIAMINOBENZENE DERIVATIVES AND PROCESSES
FOR THEIR PREPARATION

The production of 2-carbethoxyamino-5-(2,4,6-trimethyl-benzylamino)aniline or the hydrochloride thereof (compound 81) is described in the journal *Chemiker Zeitung* 103 (1979) on page 390. This reference contains no data relating to any pharmacological action of this compound.

This invention relates to the subject matter defined by the patent claims.

The compounds according to the invention are pharmacologically active. In particular, the compounds according to the invention have anticonvulsive, antipyretic and muscle-relaxing effects. They furthermore have a specific peripheral analgesic action.

The object of the invention is thus to provide compounds with favourable pharmacological properties which may, for example, be exploited as pharmaceutical preparations having antiepileptic, muscle-relaxing, antipyretic and peripheral analgesic action.

The following explanations are important exemplifications:

The alkyl groups, halogenoalkyl groups, alkenyl groups, alkynyl groups, alkoxy groups, alkylamino groups, alkanoylamino groups, alkanoyloxy groups or, generally, alkanoyl groups occurring in the formula I may be linear or branched. The same also applies to alkyl and alkyloxy groups (= alkoxy groups) if these are a constituent of groups of another composition (for example in the form of a monoalkyl- or dialkylamino group, alkanoylamino group, alkoxycarbonylamino group, carbalkoxy group, alkylcarbonyl group and analogous groups. The C₃-C₇ cycloalkyl group is preferably cyclopentyl or cyclohexyl. C₂-C₆ alkenyl preferably means allyl. C₂-C₆ alkynyl preferably means propargyl.

The halogen atoms are chlorine, bromine or fluorine, in particular chlorine and fluorine. As such or as a

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constituent of groups of another composition, the alkyl and alkoxy groups in particular consist of 1-4 C atoms, preferably 1 or 2 C atoms. Alkanoyl groups, such as for example alkanoylamino groups or alkanoyloxy groups in particular consist of 2-4, preferably 2-3 C atoms. Alk in particular consists of 1-3, preferably 1 or 2 C atoms.

Compounds of the formula I having particularly favourable properties are those in which R_1 denotes hydrogen, C_1-C_6 alkyl or C_2-C_6 alkanoyl, R_2 denotes hydrogen or C_1-C_6 alkyl, R_4 and R_5 denote hydrogen, R_3 denotes C_1-C_6 alkoxy, the alkylene group Alk is directly attached to the nitrogen atom ($n = 0$) and means CH_2 and Ar denotes a halogenophenyl residue, preferably fluorophenyl (for example 4-fluorophenyl) or a trifluoromethyl residue (for example 4-trifluoromethylphenyl).

Those compounds of the formula I which contain asymmetrical carbon atoms and generally occur as racemates may be resolved 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, wherein the final product obtained is then a corresponding optically active or diastereomeric form. The present invention thus also includes the D- and L-form and the DL-mixture in the event that an asymmetrical C atom occurs in the compound of the formula I and, in the event of 2 and more asymmetrical C atoms, also the corresponding diastereomeric forms.

Depending upon the process conditions and starting substances, the final substances of the formula I are obtained in free form or in the form of the salts thereof. The salts of the final substances may be reconverted into bases in a manner known *per se*, for example with alkali or ion exchangers. Salts may be obtained from these bases by reaction with organic or inorganic acids, in particular

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such acids as are suitable for the formation of therapeutically usable salts.

The compounds according to the invention are suitable for the production of pharmaceutical preparations. The pharmaceutical preparations or medicaments may contain one or more of the compounds according to the invention. Conventional excipients and auxiliary substances may be used to produce the pharmaceutical preparations.

Re process a) (reduction of the nitro group)

Catalytic hydrogenation has proved particularly suitable for reduction in accordance with process a). Catalysts which may, for example, be considered are: Raney nickel, noble metals such as palladium and platinum together with compounds thereof, with and without supports, such as for example barium sulphate, calcium sulphate etc.. It is advisable to perform hydrogenation of the nitro group at temperatures of between 20 and 100°C and a pressure of approximately 1 to 70 bar in a solvent. Suitable solvents are, for example, C₁-C₄ alkanols, C₂-C₄ diols and the lower alkyl ethers thereof, cyclic ethers such as dioxane, tetrahydrofuran, methoxyethanol, water, aromatic hydrocarbons (benzene, toluenes, xylenes) together with mixtures of these solvents. In many cases, for the purpose of subsequent isolation of the reduced compounds, it may be advantageous at the beginning to add desiccating agents, such as anhydrous sodium sulphate or magnesium sulphate, to the mixture to be hydrogenated.

Reduction may, however, also be performed by nascent hydrogen, for example zinc/hydrochloric acid, tin/hydrochloric acid, iron/hydrochloric acid or with hydrogen sulphide salts in alcohol/water at 70 to 120°C or with activated aluminium in hydrous ether at 20 to 40°C or

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with tin(II) chloride/hydrochloric acid or with ammonium formate.

In the event that a starting compound containing an oxo group is used (for example alkylcarbonyl), it may be convenient to protect this oxo group by conventional acetal formation (for example in the form of the ethylene acetal). This applies particularly to catalytic hydrogenation.

The reaction product obtained in this manner is conveniently immediately reacted in the resultant reaction mixture with a compound which is capable of replacing one hydrogen atom of the amino group obtained by the reduction with the group $-COR_3$, without the reduced compound having to be isolated. This particularly applies in the event of catalytic hydrogenation. Naturally, the compound obtained by reduction of the nitro group may also be isolated and the $-COR_3$ group then introduced. The COR_3 group may be introduced in the conventional manner with the reagents customary for this purpose, in particular halides of the formula $Hal-COR_3$ ($Hal = Cl, Br, I$). Examples of such reagents are: haloformic acid C_1-C_6 alkyl esters (for example ethyl esters such as ethyl chloroformate, bromoformate or iodoformate), phenyl esters or $Hal-CO-OAr$. If R_3 is a C_1-C_6 alkyl group, acylating agents which may for example be considered are the halides (chlorides, bromides, iodides) or anhydrides of C_1-C_6 alkanecarboxylic acids, C_2-C_6 -alkenecarboxylic acids, C_2-C_6 alkynecarboxylic acids or acids of the formula $ArCO_2H$. Further acylating agents are halides of the following formula $Hal-CO-NH_2$, $Hal-CO-NH-C_1-C_6$ alkyl, $Hal-CO-N(C_1-C_6$ alkyl) $_2$, $Hal-CO-NHAr$, if the residue R_3 has one of the stated amine functional groups. The latter compounds may, however, also be obtained in the conventional manner from compounds of the formula I, in which 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 .

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These reactions preferably proceed under pressure (10 to 50 bar) at temperatures of between 0 and 220°C, preferably of 100 to 200°C in an inert solvent or dispersant. Examples of such agents which may be considered are: lower aliphatic alcohols (1-6 C atoms such as propanol, isopropanol, butanol, methoxyethanol), lower aliphatic ethers (diethyl ether, diisopropyl ether), aromatic hydrocarbons (benzene, toluene, xylene), cyclic ethers (dioxane, tetrahydrofuran), esters of lower aliphatic carboxylic acids with lower aliphatic alcohols, amides and N-alkyl-substituted amides of aliphatic C₁-C₄ carboxylic acids (dimethylformamide, dimethylacetamide), C₁-C₆ dialkyl sulphones (dimethyl sulphone, tetramethylene sulphone), C₁-C₆ dialkyl sulphoxides (dimethyl sulphoxide) together with further aprotic agents such as N-methylpyrrolidone, tetramethylurea, hexamethylphosphoric acid triamide, acetonitrile together with mixtures of these agents. This acylation may optionally also proceed without using a solvent or dispersant. Without such an agent, the reaction proceeds, for example, at between 0 and 200°C, preferably between 100 and 200°C.

Since the free amines of the formula I, in which the -COR₂ group is hydrogen, are sensitive to oxygen, the reaction is conveniently performed under a nitrogen atmosphere.

The reaction components are generally reacted in molar quantities. It may, however, optionally be convenient to use one reaction component in slight excess. The reaction is optionally performed in the presence of basic or acid-binding agents.

Examples of such agents which may be considered are: inorganic condensing agents such as ammonia, alkali metal or alkaline earth metal hydroxides, alkali metal or alkaline earth metal carbonates or organic bases such as pyridine, tertiary amines (triethylamine), piperidine,

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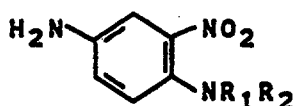
alkali metal alkoxides, alkali metal acetates or also triethyl phosphate. The alkali metals are in particular sodium or potassium. The reaction may also be performed under phase-transfer conditions (i.e. with the addition of one or more long-chain amines such as a benzyltributylammonium halide, a tetrabutylammonium halide or benzyltriphenylphosphonium chloride).

In particular, if haloformic acid esters or haloformic acid derivatives are used, tertiary amines, alkali metal hydroxides, alkali metal acetates or alkali metal hydrogen carbonates are used as basic condensing agents.

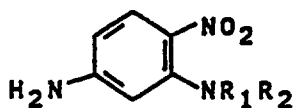
The additionally present amino groups may, for example, contain a conventional amino protective group. Once the reaction is complete, such protective groups may be eliminated solvolytically or by hydrogenation.

Starting substances of the general formula II or III may, for example, be obtained as follows.

1. By reacting a compound of the formula VII or VIII



VII



VIII

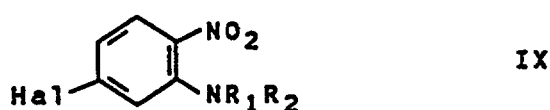
with an aldehyde Ar-Alk'-CHO, wherein Alk has the stated meanings and Alk' is a corresponding linear or branched alkylene group with 0 to 8 C atoms, reducing the resultant Schiff's base in the conventional manner and optionally introducing residues R₁, R₂ and R₅.

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2. By acylating compounds of the formula VII or VIII with a compound Ar-Alk-COHal, wherein Ar and Alk have the stated meanings and Hal means chlorine, bromine or iodine and optionally introducing residues R_1 , R_2 and R_5 .

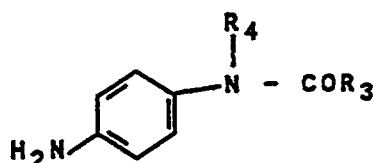
Starting substances of the formula II in which $n = 0$ (CO not present) may also be obtained by reacting a compound of the formula IX



in which Hal means fluorine, chlorine or bromine with an amine of the formula Ar-Alk-NH₂, in which Ar and Alk have the stated meanings, conveniently in the presence of a basic substance (tertiary amine) and optionally subsequently introducing the residues R_1 , R_2 and R_5 .

Starting substances of the formula III may, for example, also be obtained as follows:

A compound of the formula

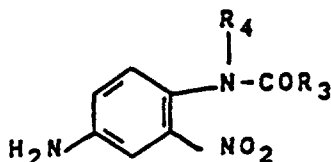


is reacted in a conventional manner with phthalic anhydride (for example in glacial acetic acid at 90°C), the resultant reaction product, in which the free amino group in position 4 is protected only by the phthalyl residue, is then nitrated in position 3 relative to the phthalyl group in a known manner (for example with fuming nitric acid in

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glacial acetic acid at 90-100°C). The phthalyl residue is then eliminated in a known manner (for example with hydrazine hydrate) in an inert agent such as 1,2-dimethoxyethane and the compound of the formula



is obtained.

The residues Ar-Alk-(CO)_n- and R₅ may then be introduced in succession into the free amino group in this compound in the conventional manner (for example as stated in process b) and the residue -COR₃ may optionally be eliminated in a known manner (replacement of -COR₃ with hydrogen).

The reactions described above for production of the starting substances are performed in the conventional manner as described in example 1 or in an analogous manner. Residues R₁, R₂ and R₅ are also introduced in the conventional manner and as is stated in the application (specification).

Re process b), reaction of a compound of the formula IV with a compound of the formula V or VI

Process b) is conveniently performed at temperatures of between 0 and 250°C, in particular of 20 to 140°C.

Examples of solvents or suspending agents which may be considered for the process are: water, aliphatic alcohols (ethanol, propanol, butanol), aromatic hydrocarbons (benzene, xylene, toluene), lower aliphatic acid amides (dimethylformamide), alicyclic and cyclic saturated ethers (diethyl ether, dioxane), N-methylpyrrolidone, dimethyl

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sulphoxide, sulpholane, tetramethylurea and mixtures of these agents.

Examples of condensing agents which may be considered for process b) in the event of a compound of the formula IV reacting with a compound of the formula V are primarily sodium acetate, sodium amide, alkali metal carbonates and tertiary amines. Zinc chloride, phosphorus oxychloride, p-toluenesulphonic acid, iodine and the like may optionally also act as condensing agents.

The process is performed in the presence of hydrogen if a compound of the formula VI is used. Catalysts which may be considered here are conventional hydrogenation catalysts, preferably metallic hydrogenation catalysts such as Raney nickel, platinum, palladium. Alkali metal borohydrides (NaBH_4), lithium borohydride, sodium cyanoborohydride may, however, also be used.

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

Starting substances of the formula V or VI are known. Introduction of the residues R_1 , R_2 , R_4 and R_5 , including the group COR_3 , according to process a) and/or b), proceeds in the conventional manner, for example by the following reactions:

By alkylation or acylation:

This relates in particular to the acylation or alkylation of amino groups.

Alkylation or acylation proceeds, for example, by reaction with compounds of the formula R-Hal , ArSO_2OR and $\text{SO}_2(\text{OR})_2$, wherein Hal is a halogen atom (in particular chlorine, bromine or iodine) and Ar is an aromatic residue (for

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example a phenyl or naphthyl residue optionally substituted by one or more lower alkyl residues) and R means the residues 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 additionally contains a further residue Ar or means Ar. Examples are p-toluenesulphonic acid C_1-C_6 alkyl esters, C_1-C_6 dialkyl sulphates, C_1-C_6 alkyl halides and the like. In the above-stated compounds, the aryl group may in each case be substituted in accordance with the meaning of Ar. The alkylation and acylation reaction is performed at temperatures of between 0 and 200°C, preferably of between 40 and 140°C in inert solvents or suspending agents, optionally 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 metal carbonates, alkaline earth metal acetates, tertiary amines (for example trialkylamine, such as triethylamine), pyridine or also alkali metal hydrides. Examples of solvents or dispersants which may be considered are: aromatic hydrocarbons such as, for example, benzene, toluene, xylene; aliphatic ketones such as, for example, acetone, methyl ethyl ketone; halogenated hydrocarbons such as, for example, chloroform, tetrachloromethane, chlorobenzene, methylene chloride; aliphatic ethers such as, for example, butyl ether; cyclic ethers such as, for example, tetrahydrofuran, dioxane; sulphoxides such as, for example, dimethyl sulphoxide; tertiary acid amides such as, for example, dimethylformamide, N-methylpyrrolidone, hexamethylphosphoric acid triamide; aliphatic alcohols such as methanol, ethanol, isopropanol, amyl alcohol, tert.-butanol, cycloaliphatic hydrocarbons such as cyclohexane. Aqueous mixtures of the stated solvents may also be used. The reaction is frequently performed at the refluxing temperature of the solvents or dispersants used. The alkylation reaction components are frequently introduced in excess. Alkylation may also be performed in the presence of tetraalkylammonium salts (in particular

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halides) in combination with alkali metal hydroxides at temperatures of between 0 and 100°C, preferably of 20-80°C, in an aprotic solvent or also in chloroform or methylene chloride. Aprotic solvents which may, in particular, be considered are: tertiary amides (dimethylformamide, N-methylpyrrolidone, hexamethylphosphoric acid triamide), dimethyl sulphoxide, acetonitrile, dimethoxyethane, acetone, tetrahydrofuran.

During acylation, the following are, for example, introduced into amino groups, the group $-\text{COR}_3$, the group $-\text{CO}-\text{C}_1-\text{C}_6$ alkyl, $-\text{CO}-\text{C}_2-\text{C}_6$ alkenyl, $-\text{CO}-\text{C}_2-\text{C}_6$ alkynyl, the C_1-C_6 alkoxy carbonyl group or the following groups: $-\text{COAr}$, $-\text{CO-OAr}$, $-\text{CONH}_2$, $-\text{CONH}-\text{C}_1-\text{C}_6$ alkyl, $-\text{CON}(\text{C}_1-\text{C}_6 \text{ alkyl})_2$, $-\text{CONHAr}$, $-\text{SO}_2-\text{C}_1-\text{C}_6$ alkyl, $-\text{SO}_2\text{Ar}$, $-\text{SO}_2$ -nitrophenyl.

The reaction is performed in a manner known *per se*, for example the corresponding acid halides (chlorides, bromides) are used, such as for example carb- C_1-C_6 -alkoxy halides or the corresponding anhydrides. Reaction temperatures are preferably between 20 and 120°C.

The alkylation and acylation may optionally also be performed in such a manner that an alkali metal compound (for example sodium, potassium or also lithium salt) of the compound to be alkylated or acylated is first produced by reacting the compound in an inert solvent such as dioxane, dimethylformamide, benzene or toluene with an alkali metal, alkali metal hydride or alkali metal amides (in particular sodium or sodium compounds) or butyllithium at temperatures of between 0 and 150°C and then adding the alkylating agent.

Other common chemically equivalent agents may also be used instead of the listed alkylating and acylating agents (see, for example, also L.F. & Mary Fieser *Reagents for Organic*

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Synthesis, John Wiley & Sons Inc., New York, 1967, volume 1, pages 1303-4 and volume 2, page 471.

Any acyl groups present such as, for example, carb- C_1 - C_6 alkoxy groups, C_2 - C_6 alkanoyl groups and similar groups may be eliminated solvolytically. This elimination proceeds in a known manner, for example by saponification with acids (mineral acids such as hydrochloric acid, sulphuric acid, in particular concentrated halohydric acids such as HBr/glacial acetic acid) or by means of basic substances (potash, soda, aqueous alkali solutions, alcoholic alkali solutions, aqueous NH_3) at temperatures of between 10 and 150°C, in particular of 20-100°C.

The compounds according to the invention exhibit good antiepileptic action, for example in the maximum electrospasm test (MES).

For example, using the above-stated test method, 50% inhibition of the spasms induced by electrical stimulation is achieved at a dose of 6 mg/kg of body weight in rats.

The lowest effective dose in the above-stated animal test is, for example

2 mg/kg oral

0.5 mg/kg intravenous.

A general effective dosage range (animal test as above) which may, for example, be considered is:

2 - 20 mg/kg oral, in particular 10 mg/kg

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

The type of action of the compounds according to the invention is comparable with that of the action of the known pharmaceutical active ingredient diazepam, but the

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compounds according to the invention have a broader therapeutic spectrum.

The compounds according to the invention are in particular effective antiepileptics.

The pharmaceutical preparations generally contain between 10 and 100, preferably 30 to 60 mg of the active component(s) according to the invention.

The compounds may be administered, for example, in the form of tablets, capsules, pills, coated pills, suppositories, ointments, gels, creams, powders, dusting powders, aerosols or in liquid form. Liquid dosage forms which may, for example, be considered are: oily or alcoholic or aqueous solutions together with suspensions and emulsions. Preferred dosage forms are tablets containing between 30 and 60 mg or solutions containing between 0.1 and 5 wt.% of active substance.

The individual dose for the active components according to the invention may, for example,

- a) for oral dosage forms be between 20 and 80 mg, preferably 30-60 mg,
- b) for parenteral dosage forms (for example intravenous, intramuscular) be between 5 and 20 mg, preferably 8-16 mg.

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

For example, a recommended dose may be 1 to 3 tablets containing 30-60 mg of active substance three times per day or, in the case of intravenous injection, one ampoule with a content of 3 to 5 ml with 8 to 16 mg of active substance

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one to three times per day. In the case of oral administration, the minimum daily dose is, for example, 90 mg; the maximum daily dose in the case of oral administration should not exceed 270 mg.

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

The pharmaceutical preparations may be used in human medicine, veterinary medicine and in agriculture alone or mixed with other pharmacologically active substances.

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Examples:**Example 1**

2-Amino-4-(4-fluorobenzylamino)-1-ethoxycarbonylamino-benzene.

Variant A

A suspension of 5.2 g (20 mmol) of 2-amino-5-(4-fluorobenzylamino)nitrobenzene or 5.2 g (20 mmol) of 2-amino-4-(4-fluorobenzylamino)nitrobenzene in 100 ml of dioxane is hydrogenated at 55 to 60°C under standard pressure in the presence of 2 g of Raney nickel. Once hydrogen absorption has ceased, the catalyst is filtered out under protective gas and the filtrate is combined with 3.2 g (25 mmol) of diisopropylethylamine. A solution of 2.3 g (21 mmol) of ethyl chloroformate in 15 ml of dioxane is added to the resultant solution dropwise with stirring under an inert gas atmosphere (for example nitrogen) at 18-20°C. On completion of addition, stirring is continued for 1 hour at room temperature and 10 ml of 6 N ethanolic hydrochloric acid are then added dropwise with stirring and cooling with ice. A colourless solid gradually crystallises as this is performed. Stirring is continued for 2 hours at room temperature and the precipitated product is separated by suction filtration. After recrystallisation from ethanol/ether, 5.5 g (73% of theoretical) of 2-amino-4-(4-fluorobenzylamino)-1-ethoxycarbonylamino-benzene are obtained as the dihydrochloride in the form of colourless to slightly pink crystals.

Melting point of dihydrochloride: 182-186°C.

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Production of starting substances.

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

A solution of 25.9 g (100 mmol) of 2-amino-5-(4-fluorobenzylideneamino)nitrobenzene in 250 ml of dioxane/methanol mixture (4:1) is combined with stirring in portions with 5.7 g (150 mmol) of sodium tetrahydridoborate. Once addition is complete, stirring is continued for 2 hours at room temperature and the reaction solution is then evaporated to dryness under a vacuum. The remaining dark red residue is taken up to 100 ml of water and the resultant suspension is extracted four times with 200 ml portions of dichloromethane. The combined organic phases are desiccated with sodium sulphate and then evaporated under a vacuum. The remaining dark red oil is crystallised from 100 ml of toluene. After vacuum drying, 21.0 g (80% of theoretical) of 2-amino-5-(4-fluorobenzylamino)nitrobenzene are obtained as dark red crystals.

Melting point: 111-112°C.

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

A solution of 15.3 g (100 mmol) of 2-nitro-p-phenylenediamine and 13.6 g (110 mmol) of 4-fluorobenzaldehyde in 400 ml of xylene is refluxed for 3 hours with a water separator in the presence of 0.5 g of an acidic ion exchanger (for example Nafion). While hot, the mixture is filtered to remove insoluble constituents and is left to stand overnight at room temperature. An orange-yellow solid crystallises out. This solid is separated by suction filtration, washed with a little toluene and dried under a vacuum. 22.0 g (85% of theoretical) of 2-amino-5-(4-fluorobenzylideneamino)nitrobenzene are obtained as orange-yellow crystals.

Melting point: 136-139°C.

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

A solution of 15.6 g (100 mmol) of 2-amino-4-fluoro-nitrobenzene, 22.5 g (180 mmol) of 4-fluorobenzylamine and 20.2 g (200 mmol) of triethylamine in 150 ml of dimethyl sulphoxide is heated for 30 hours to 60-70°C under a protective gas atmosphere while being stirred. On completion of the reaction time, the solvent is distilled off under a vacuum, the residue taken up in 500 ml of 0.5 N hydrochloric acid and vigorously stirred for 30 minutes at room temperature. The precipitated solid is separated by suction filtration and subjected to hot vapour extraction with toluene. The product which crystallises out of the toluene phase after 12 hours' standing at 0-4°C is separated by suction filtration and dried under a vacuum. 22.2 g (85% of theoretical) are obtained. Orange-yellow crystals of 2-amino-4-(4-fluorobenzylamino)nitrobenzene crystallise out of the toluene phase after 12 hours' standing at 0-4°C.

Melting point: 180°C.

Variant B

A suspension of 13.3 g (40 mmol) of 2-ethoxycarbonylamino-5-(4-fluorobenzylamino)nitrobenzene in 150 ml of 1,2-dimethoxyethane is hydrogenated at 55-60°C under standard pressure in the presence of 2 g of Raney nickel. Once hydrogen absorption has ceased, the catalyst is filtered out under protective gas and the filtrate is evaporated under a vacuum. The remaining residue is taken up in 150 ml of ethanol and 20 ml of 6N ethanolic hydrochloric acid are added dropwise to the resultant solution with stirring under a protective gas atmosphere. On completion of addition, stirring is continued for 1 hour, the precipitated solid is separated by suction filtration and washed with ethanol. After drying under a

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vacuum, 13.5 g (89% of theoretical) of the stated compound are obtained as colourless to slightly pink crystals.

Melting point: 186-189°C.

Production of starting substance

2-Ethoxycarbonylamino-5-(4-fluorobenzylamino)nitrobenzene
39.8 g (120 mmol) of 2-ethoxycarbonylamino-5-(4-fluorobenzylideneamino)nitrobenzene (produced from 33.8 g (150 mmol) of 5-amino-2-ethoxycarbonylaminonitrobenzene and 19.2 g (155 mmol) of 4-fluorobenzaldehyde) are reacted as stated previously with 3.8 g (100 mmol) of sodium tetrahydridoborate. After working up in a corresponding manner, 31.3 g (78% of theoretical) of 2-ethoxycarbonylamino-5-(4-fluorobenzylamino)nitrobenzene are obtained as dark red crystals.

Melting point: 85-87°C.

5-Amino-2-ethoxycarbonylaminonitrobenzene may, for example, be obtained as follows:

21.0 g (0.42 mol) of hydrazine hydrate are added dropwise with stirring at boiling temperature to a suspension of 142.1 g (0.4 mol) of 2-ethoxycarbonylamino-5-phthalimidonitrobenzene in 700 ml of 1,2-dimethoxyethane and the reaction is allowed to continue for 2 hours. Once the mixture has cooled to room temperature, the precipitated phthalhydrazide is filtered out and the dark red filtrate is evaporated to dryness under a vacuum. The remaining solid residue is recrystallised from approximately 150 ml of toluene. 84.4 g of 5-amino-2-ethoxycarbonylamino-nitrobenzene are obtained as dark red crystals.

Melting point: 105-107°C.

2-Ethoxycarbonylamino-5-phthalimidonitrobenzene is obtained, for example, as follows:

75.5 g (0.51 mol) of phthalic anhydride are added in portions with stirring under a protective gas atmosphere at

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90°C to a solution of 90.1 g (0.5 mol) of N-ethoxycarbonyl-p-phenylenediamine in 1.5 l of glacial acetic acid. On completion of addition, the reaction is allowed to continue for 60 minutes. 27.5 ml of fuming nitric acid are thereupon added to the resultant suspension and, once addition is complete, the reaction is allowed to continue for 2 hours at 100°C. Once the mixture has cooled to room temperature, the precipitated solid is filtered out and repeatedly washed until neutral with a total of 2.5 l of water. After drying under a vacuum, 149.9 g of the phthalimido compound are obtained as yellow crystals.

Melting point: 215-216°C.

Example 2

2-Amino-4-(4-trifluoromethylbenzylamino)-1-ethoxycarbonyl-aminobenzene

Variant A

A suspension of 9.3 g (30 mmol) of 2-amino-5-(4-trifluoromethylbenzylamino)nitrobenzene is hydrogenated in a similar manner to example 1 (variant A) and then reacted with 3.4 g (31 mmol) of ethyl chloroformate. 5.8 g (45% of theoretical) of the stated end product are obtained as the dihydrochloride in the form of colourless to slightly pink crystals.

Melting point: 159-162°C.

Variant B

A suspension of 65.2 g (170 mmol) of 2-ethoxycarbonylamino-5-(4-trifluoromethylbenzylamino)nitrobenzene is hydrogenated in a similar manner to example 1 (variant B) and worked up in a corresponding manner. 52.2 g (72% of theoretical) of the stated end product are obtained as the dihydrochloride in the form of colourless crystals.

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Melting point: 160-162°C.

The corresponding starting substances are produced in a similar manner as described in example 1.

Example 3

2-Amino-4-benzylamino-1-ethoxycarbonylaminobenzene.

A suspension of 12.6 g (40 mmol) of 5-benzylamino-2-ethoxycarbonylaminonitrobenzene is hydrogenated in a similar manner to example 1 (variant B) and worked up in a corresponding manner. 52.2 g (72% of theoretical) of the end product are obtained as the dihydrochloride: colourless to slightly pink crystals.

Melting point: 178-181°C.

Example 4

2-Amino-4-(3,5-dichlorobenzylamino)-1-ethoxycarbonylaminobenzene

A suspension of 15.5 g (50 mmol) of 2-amino-5-(3,5-dichlorobenzylamino)nitrobenzene is hydrogenated in a similar manner to example 1 (variant A) and reacted in a corresponding manner with 5.5 g (51 mmol) of ethyl chloroformate. 10.8 g (51% of theoretical) of finished product are obtained as the dihydrochloride: colourless to slightly pink crystals.

Melting point: 134-136°C.

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Example 5

2-Amino-4-(3,5-dichlorobenzylamino)-1-propyloxycarbonyl-aminobenzene

A suspension of 15.5 g (50 mmol) of 2-amino-5-(3,5-dichlorobenzylamino)nitrobenzene is hydrogenated in a similar manner to example 1 (variant A) and reacted in a corresponding manner with 6.2 g (51 mmol) of propyl chloroformate. 10.8 g of end product are obtained in the form of the dihydrochloride. This forms colourless to slightly pink crystals.

Melting point: 154-155°C.

Example 6

2-Amino-4-(2-chlorobenzylamino)-1-(diethylcarbamoyl-amino)benzene

A suspension of 8.3 g (30 mmol) of 2-amino-5-(2-chlorobenzylamino)nitrobenzene is hydrogenated in a similar manner to example 1 (variant A) and reacted in a corresponding manner with 4.2 g (31 mmol) of N,N-dimethylcarbamoyl chloride. 6.5 g of end product are obtained in the form of the dihydrochloride. This forms colourless to slightly pink crystals.

Melting point: 153-155°C.

Example 7

2-Amino-4-(2,4-dichlorobenzylamino)-1-(dimethylcarbamoyl-amino)benzene

A suspension of 31.2 g (100 mmol) of 2-amino-5-(2,4-dichlorobenzylamino)nitrobenzene is hydrogenated in a similar manner to example 1 (variant A) and reacted in a corresponding manner with 13.9 g (101 mmol) of

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N,N-dimethylcarbamoyl chloride. 12.4 g of end product are obtained in the form of the dihydrochloride. This forms colourless to light pink crystals.

Melting point: 147-152°C.

Example 8

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

9.4 g (30 mmol) of 4-(4-fluorobenzylideneamino)-N,N'-diacetyl-o-phenylenediamine are reduced in 250 ml of dioxane/methanol mixture (4:1) with 0.9 g (25 mmol) sodium tetrahydridoborate as described in example 1. The resultant free base is then directly converted into the hydrochloride with alcoholic hydrochloric acid. 7.2 g of end product are obtained in the form of the monohydrochloride. This forms colourless crystals.

Melting point: 165-168°C.

The 4-(4-fluorobenzylideneamino)-N,N'-diacetyl-o-phenylenediamine is obtained, for example, by reacting 8.3 g (40 mmol) of 4-amino-N,N'-diacetyl-o-phenylenediamine with 5.1 g (41 mmol) of 4-fluorobenzaldehyde (in a similar manner to that described in example 1). Yield: 11.0 g of yellow crystals.

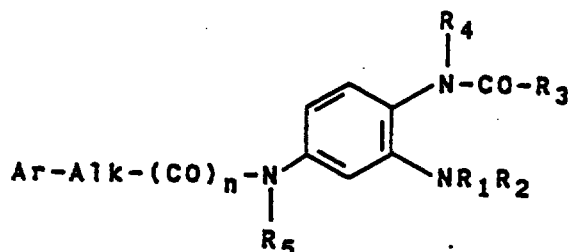
Melting point: 152-156°C.

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Patent Claims

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



in which 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 residue 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 which is substituted by the residue Ar, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, the residue Ar or the residue ArO ;
- R_4 : hydrogen, C_1 - C_6 alkyl or the residue Ar;
- R_5 : hydrogen, C_1 - C_6 alkyl or the residue Ar;
- Alk: a linear or branched alkylene group with 1-9 C atoms, which may also be substituted by the residue Ar;
- Ar: phenyl residue which is substituted by the residues R_6 , R_7 and/or R_8 , wherein these residues R_6 , R_7 and R_8 are identical or different and 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, $-CON(C_1$ - C_6 alkyl) $_2$, $-CONHAr$, $-NH$ -CO- C_1 - C_6 alkyl, $-NHCO$ -Ar, $NCHO$ - C_1 - C_6 alkoxy, $-NH$ -CO-OAr, $-NHCO$ - NH_2 , $-NHCO$ - $N(C_1$ - C_6 alkyl) $_2$,



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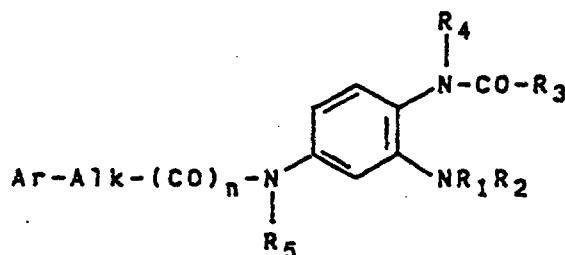
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-NHCO-NHAr, -NH-SO₂-C₁-C₆ alkyl, -NH-SO₂Ar,
 -NH-SO₂-nitrophenyl, -SO₂-OH, -SO₂-C₁-C₆ alkyl,
 -SO₂-Ar, -SO₂-C₁-C₆ alkoxy, -SO₂-OAr, -SO₂-NH₂,
 -SO₂-NH-C₁-C₆ alkyl, -SO₂-N(C₁-C₆ alkyl)₂,
 -SO₂-NHAr, -SO₂-C₁-C₆ alkoxy;

n: 0 or 1;

and the pharmaceutically compatible acid addition salts thereof, with the exception of the compound 2-carbethoxy-amino-5-(2,4,6-trimethylbenzylamino)-aniline and the hydrochloride thereof.

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



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

- R₁: hydrogen, C₁-C₆ alkyl, C₂-C₆ alkanoyl or the residue Ar;
 R₂: hydrogen or C₁-C₆ alkyl;
 R₃: C₁-C₆ alkoxy, NH₂, C₁-C₆ alkylamino, C₁-C₆ dialkylamino, amino which is substituted by the residue Ar, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, the residue Ar or the residue ArO-;
 R₄: hydrogen, C₁-C₆ alkyl or the residue Ar;
 R₅: hydrogen, C₁-C₆ alkyl or the residue Ar;
 Alk: a linear or branched alkylene group with 1-9 C atoms, which may also be substituted by the residue Ar;
 Ar: phenyl residue which is substituted by the residues R₆, R₇ and/or R₈, wherein these residues



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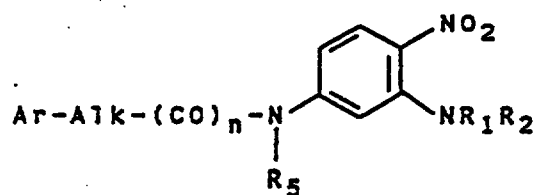
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R_6 , R_7 and R_8 are identical or different and C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, hydroxy, C_1 - C_6 alkoxy, C_2 - C_6 alkanoyloxy, halogen, hydroxy, C_1 - C_6 halogenoalkyl, $-CN$, $-NH_2$, $-NH$ - C_1 - C_6 alkyl, $-N(C_1$ - C_6 alkyl) $_2$, $-CO_2H$, $-CO$ - C_1 - C_6 alkyl, $-CO$ - O - C_1 - C_6 alkyl, $-COAr$, $-CO$ - OAr , $-CONH_2$, $-CONH$ - C_1 - C_6 alkyl, $-CON(C_1$ - C_6 alkyl) $_2$, $-CONHAr$, $-NH$ - CO - C_1 - C_6 alkyl, $-NHCO$ - Ar , $NCHO$ - C_1 - C_6 alkoxy, $-NH$ - CO - OAr , $-NHCO$ - NH_2 , $-NHCO$ - $N(C_1$ - C_6 alkyl) $_2$, $-NHCO$ - $NHAr$, $-NH$ - SO_2 - C_1 - C_6 alkyl, $-NH$ - SO_2 - Ar , $-NH$ - SO_2 -nitrophenyl, $-SO_2$ - OH , $-SO_2$ - C_1 - C_6 alkyl, $-SO_2$ - Ar , $-SO_2$ - C_1 - C_6 alkoxy, $-SO_2$ - OAr , $-SO_2$ - NH_2 , $-SO_2$ - NH - C_1 - C_6 alkyl, $-SO_2$ - $N(C_1$ - C_6 alkyl) $_2$, $-SO_2$ - $NHAr$, $-SO_2$ - C_1 - C_6 alkoxy;

n : 0 or 1;

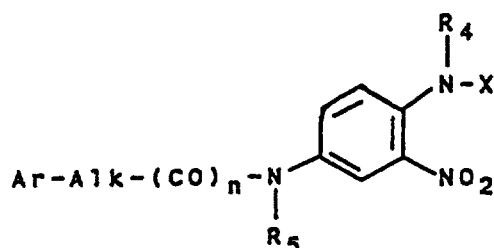
and the pharmaceutically compatible acid addition salts thereof, with the exception of the compound 2-carbethoxy-amino-5-(2,4,6-trimethylbenzylamino)-aniline and the hydrochloride thereof, characterised in that in a manner known per se

a) in a compound of the formula



II

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



III



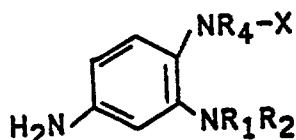
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in which X is hydrogen or the group $-\text{COR}_3$ and R_3 , R_4 , R_5 , Alk, Ar and n have the stated meanings,

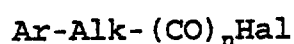
the nitro group is reduced to the amino group, the $-\text{COR}_3$ group is introduced by acylation if it is not present in the starting materials II or III and, optionally after or before introduction of the $-\text{COR}_3$ group, the residues R_1 , R_2 , R_4 and R_5 are introduced by alkylation, arylation and/or acylation, or

b) a compound of the formula



IV

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



V

in which Ar, -Alk and n have the stated meanings and Hal is chlorine, bromine or iodine or with a compound of the formula



VI

in which Ar has the stated meanings and Alk' is a linear or branched alkylene group with 0 - 8 C atoms,

wherein in the latter case the double bond of the resultant Schiff's base is reduced to the single bond, the residues $-\text{COR}_3$, R_1 , R_2 , R_4 and R_5 are optionally introduced by alkylation, arylation and/or acylation, the residue R_3 in the compounds obtained using methods

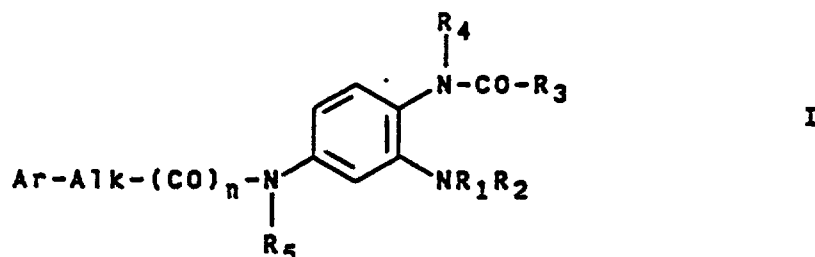


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a) or b) is optionally exchanged for another residue falling within the stated definition for R_3 and the compounds so obtained are converted into acid addition salts.

3. Pharmaceutical preparation containing as active ingredient at least one 1,2,4-triaminobenzene derivative of the general formula



in which 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 residue 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 which is substituted by the residue Ar, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, the residue Ar or the residue ArO -;
- R_4 : hydrogen, C_1 - C_6 alkyl or the residue Ar;
- R_5 : hydrogen, C_1 - C_6 alkyl or the residue Ar;
- Alk: a linear or branched alkylene group with 1-9 C atoms, which may also be substituted by the residue Ar;
- Ar: phenyl residue which is substituted by the residues R_6 , R_7 and/or R_8 , wherein these residues R_6 , R_7 and R_8 are identical or different and 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,



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-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, NCHO-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 the pharmaceutically compatible acid addition salts thereof, optionally together with further conventional auxiliary substances and excipients or diluents.

4. Process for the production of a pharmaceutical preparation, characterised in that at least one compound according to formula I, including the compound 2-carbethoxy-amino-5-(2,4,6-trimethylbenzylamino)aniline and the hydrochloride thereof, is processed into pharmaceutical formulations or converted into a therapeutically usable form with usual pharmaceutical excipients and/or diluents or other auxiliary substances.
5. Use of compounds of the formula 1 according to claim 1, including the compound 2-carbethoxy-amino-5-(2,4,6-trimethylbenzylamino)aniline and the hydrochloride thereof, for the production of pharmaceutical preparations.



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