

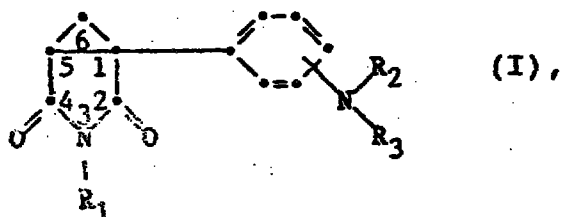
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Substituted azabicycloalkanes, the use thereof, pharmaceutical compositions containing them, and processes for the preparation of these compounds

The present invention relates to novel aminophenyl-substituted azabicycloalkanes having valuable pharmacological properties and to salts thereof, to the use of these compounds and of pharmaceutical compositions which contain them, to the pharmaceutical compositions themselves and to processes for the preparation of the novel compounds, as well as to intermediates and to processes for the preparation thereof.

1-Phenyl-3-azabicyclo[3.1.0]hexane-2,4-dione compounds which are substituted at the phenyl ring by halogen, C₁-C₆alkylamino or di(C₁-C₆)alkylamino are described as intermediates in German Offenlegungsschrift 32 23 463 without any disclosure of pharmaceutical properties. These compounds are converted by reduction into the corresponding antidepressive 1-phenyl-3-azabicyclo[3.1.0]hexane compounds. The Applicant has voluntarily restricted himself in the light of this German Offenlegungsschrift, which is older but was published later, and the equivalent applications BE 893 707 and AT 377 619, and has introduced separate patent claims for the Contracting States DE and BE, and AT.

The present invention relates to substituted 1-phenyl-3-azabicyclo[3.1.0]hexane-2,4-diones of the formula



wherein R_1 is hydrogen, R_2 is hydrogen, sulfo or acyl and R_3 is hydrogen, or R_1 is a saturated or unsaturated aliphatic, cycloaliphatic or cycloaliphatic-aliphatic hydrocarbon radical of up to and including 18, preferably of up to and including 12, carbon atoms, R_2 is hydrogen, lower alkyl, sulfo or acyl and R_3 is hydrogen or lower alkyl, and to salts thereof.

The present invention also relates to pharmaceutical compositions which contain compounds of formula I wherein R_1 is hydrogen, R_2 is hydrogen or lower alkyl, and R_3 is lower alkyl, and to the use of these compounds in a method of treating humans or animals.

Throughout this specification, the term "lower" used to qualify groups or radicals, e.g. lower alkyl, lower alkoxy, lower alkanoyl and the like, will be understood as meaning that, unless otherwise explicitly indicated, the groups and radicals so defined contain up to and including 7, preferably up to and including 4, carbon atoms.

The terms and expressions generally employed throughout this specification will be understood as having preferably the following meanings.

A saturated or unsaturated aliphatic, cycloaliphatic or cycloaliphatic-aliphatic hydrocarbon radical R_1 is alkyl, alkenyl, lower alkynyl, cycloalkyl, cycloalkenyl, cycloalkyl-lower alkyl, cycloalkyl-lower alkenyl or cycloalkenyl-lower alkyl.

Alkyl R_1 contains 1 to 12 carbon atoms and is lower alkyl of 1 to 7 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, neopentyl, n-hexyl or n-heptyl, as well as n-octyl, n-

nonyl, n-decyl, n-undecyl or n-dodecyl.

Alkenyl R_1 contains 2 to 12 carbon atoms and is lower alkenyl of 2 to 7 carbon atoms, e.g. vinyl, allyl or 2- or 3-butenyl, as well as 1-octenyl, 1-nonenyl, 1-decenyl, 1-undecenyl or 1-dodecenyl, in which the double bond can also be in a position other than the 1-position.

Lower alkynyl R_1 contains e.g. 2 to 7, especially 2 to 4, carbon atoms, and is e.g. ethynyl, 1-propynyl or 2-propynyl.

Cycloalkyl R_1 contains e.g. 3 to 10, especially 3 to 6, carbon atoms, and is e.g. cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

Cycloalkenyl R_1 contains e.g. 3 to 10, especially 3 to 6, carbon atoms, and is e.g. 1-cyclohexenyl or 1,4-cyclohexadienyl.

Cycloalkyl-lower alkyl R_1 contains e.g. 4 to 10, especially 4 to 7, carbon atoms, and is e.g. cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl or cyclohexylmethyl, as well as 2-cyclopropylethyl, 2-cyclobutylethyl, 2-cyclopentylethyl or 2-cyclohexylethyl.

Cycloalkyl-lower alkenyl R_1 contains e.g. 5 to 10, especially 4 to 9, carbon atoms, and is e.g. cyclohexylvinyl or cyclohexylallyl.

Cycloalkenyl-lower alkyl R_1 contains e.g. 4 to 10, especially 4 to 8, carbon atoms, and is e.g. 1-cyclohexenylmethyl or 1,4-cyclohexadienylmethyl, as well as 2-(1-cyclohexenyl)ethyl or 2-(1,4-cyclohexadienyl)ethyl.

Lower alkyl R_2 or R_3 is as defined for R_1 and is

preferably methyl or ethyl.

Acyl R₂ is preferably lower alkanoyl, e.g. formyl or acetyl, or is lower alkanesulfonyl, e.g. methanesulfonyl or ethanesulfonyl.

Salts of compounds of the formula I according to the invention which contain a salt-forming group are, in particular, pharmaceutically acceptable non-toxic salts.

Such salts are formed e.g. from the amino group at the phenyl ring by addition of an inorganic acid, e.g. hydrochloric acid, sulfuric acid or phosphoric acid, and are e.g. hydrochlorides, hydrogen sulfates, hydrogen phosphates or dihydrogen phosphates.

Further acid addition salts are formed e.g. from carboxylic acids and are, for example, formates, acetates, trifluoroacetates, benzoates or salicylates.

The compounds of formula I may also be obtained in the form of hydrates.

The present invention relates especially to compounds of formula I wherein R₁ is hydrogen, R₂ is hydrogen, sulfo, C₁-C₇alkanoyl or C₁-7alkanesulfonyl, and R₃ is hydrogen, or R₁ is C₁-C₁₂alkyl, C₂-C₁₂alkenyl, C₂-C₇alkynyl, C₃-C₁₀cycloalkyl, C₃-C₁₀cycloalkenyl, C₃-C₆cycloalkyl-C₁-C₄alkyl, C₃-C₆cycloalkyl-C₂-C₄alkenyl or C₃-C₆-cycloalkenyl-C₁-C₄alkyl, R₂ is hydrogen, C₁-C₇alkyl, sulfo, C₁-C₇alkanoyl or C₁-C₇alkanesulfonyl, and R₃ is hydrogen or C₁-C₇alkyl, and salts thereof, in particular pharmaceutically acceptable salts thereof.

Accordingly, the invention relates, for example, to compounds of formula I wherein R₁ is hydrogen or C₁-C₇-

alkyl, R_2 is hydrogen, C_1 - C_7 alkyl, sulfo, C_1 - C_7 alkanoyl or C_1 - C_7 alkanesulfonyl, and R_3 is hydrogen or C_1 - C_7 alkyl, and salts thereof.

The present invention relates principally to compounds of formula I wherein R_1 , R_2 and R_3 are hydrogen or wherein R_1 is C_1 - C_{12} alkyl, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, neopentyl, n-hexyl or n-heptyl, as well as n-octyl, n-nonyl or n-decyl, C_2 - C_7 alkenyl, e.g. vinyl or allyl, C_2 - C_7 alkynyl, e.g. ethynyl, 1-propynyl or 2-propynyl, C_3 - C_{10} cycloalkyl, e.g. cyclopropyl, cyclopentyl or cyclohexyl, or C_3 - C_6 cycloalkyl- C_1 - C_4 alkyl, e.g. cyclopentylmethyl or cyclohexylmethyl, R_2 is hydrogen or C_1 - C_7 alkyl, e.g. methyl, and R_3 is hydrogen or C_1 - C_7 alkyl, e.g. methyl, and salts thereof, especially pharmaceutically acceptable salts thereof.

The present invention relates especially to compounds of formula I wherein R_1 is hydrogen or C_1 - C_7 alkyl, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, n-pentyl, neopentyl, n-hexyl or n-heptyl, and R_2 and R_3 are hydrogen, and salts thereof.

The present invention relates most especially to compounds of formula I wherein R_1 is hydrogen, C_1 - C_7 alkyl, e.g. methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or tert-butyl, C_2 - C_7 alkenyl, e.g. vinyl or allyl, C_2 - C_7 alkynyl, e.g. ethynyl or 1- or 2-propynyl, C_3 - C_6 cycloalkyl- C_1 - C_4 alkyl, e.g. cyclohexylmethyl; the group $-N(R_2)(R_3)$ is in the 4-position of the phenyl radical and R_2 and R_3 are hydrogen, and pharmaceutically acceptable salts thereof.

Accordingly, the invention relates, for example, to compounds of formula I wherein R_1 is hydrogen or

C₁-C₇alkyl, the group -N(R₂)(R₃) is in the 4-position of the phenyl radical and R₂ and R₃ are hydrogen, and pharmaceutically acceptable salts thereof.

Most particularly, the present invention relates to the compounds referred to in the Examples.

The novel compounds of formula I and their pharmaceutically acceptable salts have, for example, valuable pharmacological properties as aromatase inhibitors. The suitability of compounds of formula I as aromatase inhibitors can be demonstrated in the aromatase assay according to P.E. Graves and H.A. Salhanick, Endocrinology, Vol. 105, page 52 (1979), by using human placental microsomes in vitro. In this experimental method, the formation of water with tritium isotopes and 17 β -oestradiol obtained from [1 β ,2 β -³H]-testosterone is measured as a result of the action of a compound of the formula I on the formation of the hydrogenated form of the aromatase coenzyme, nicotinamide adenine dinucleotide phosphate (NADPH). The addition of a compound of the formula I according to the invention, e.g. of 1-(4-aminophenyl)-3-cyclohexylmethyl-3-azabicyclo[3.1.0]-hexane-2,4-dione, substantially reduces the enzyme activity (NADPH content), resulting in a markedly lower content of water with radioactive tritium isotopes than with measurements made without the addition of a compound of the formula I according to the invention. Comparison measurements show, moreover, that the diminution of enzyme activity resulting from the addition of a compound of the formula I according to the invention, e.g. of 1-(4-aminophenyl)-3-cyclohexylmethyl-3-azabicyclo[3.1.0]-hexane-2,4-dione, at the same concentrations is substantially greater than with the addition of other known aromatase inhibitors, e.g. aminoglutethimide.

On account of their activity as aromatase inhibitors, the compounds of the formula I, wherein R_1 is hydrogen, C_1 - C_{12} alkyl, C_2 - C_{12} alkenyl, C_2 - C_7 alkynyl, C_3 - C_{10} cycloalkyl, C_3 - C_{10} cycloalkenyl, C_3 - C_6 cycloalkyl- C_1 - C_4 alkyl, C_3 - C_6 cycloalkyl- C_2 - C_4 alkenyl or C_3 - C_6 cycloalkenyl- C_1 - C_4 alkyl, R_2 is hydrogen, C_1 - C_7 alkyl, sulfo, C_1 - C_7 alkanoyl or C_1 - C_7 alkanesulfonyl, and R_3 is hydrogen or C_1 - C_7 alkyl, or salts thereof, can be used as medicaments, for example in the form of pharmaceutical compositions, for the treatment of hormonal diseases, e.g. hormonal tumours, especially mammary carcinoma, and anomalies, e.g. gynecomastia, in warm-blooded animals (humans and animals), by enteral, e.g. oral, or parenteral administration of therapeutically effective doses.

The use of these compounds as medicaments, especially with carcinostatic activity, in one of the methods referred to above for treatment of the human or animal body, also falls within the scope of the present invention.

The daily doses of such compounds are from about 1 mg to about 100 mg, especially from 5 mg to about 50 mg/kg of body weight for mammals, depending on the species, and also for persons, depending on age, individual condition and mode of application. For parenteral administration, e.g. intramuscular or subcutaneous injection, or intravenous infusion, the doses within this range are in general lower than in enteral, i.e. oral or rectal, administration. The compounds of formula I and pharmaceutically acceptable salts of such compounds with salt-forming properties are administered orally or rectally, preferably in dosage unit formulations such as tablets, dragées, capsules or suppositories, and parenterally in particular in the form of injectable solutions, emulsions or suspensions, or in the form of infusion solutions,

suitable solutions being in particular salt solutions.

The invention further relates to pharmaceutical compositions for enteral, e.g. oral or rectal, or for parenteral administration, which compositions contain a therapeutically effective amount of a compound of the formula I, or of a pharmaceutically acceptable salt of such a compound having a salt-forming group, optionally together with a pharmaceutically acceptable carrier or mixture of carriers, there being used as carriers solid or liquid inorganic or organic substances. Appropriate dosage unit formulations, especially for peroral administration, e.g. dragées, tablets or capsules, preferably contain about 50 mg to about 500 mg, especially about 100 mg to about 400 mg, of a compound of the formula I or of a pharmaceutically acceptable salt of such a compound which is capable of salt formation, together with pharmaceutically acceptable carriers.

Suitable carriers are in particular fillers, such as sugar, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, e.g. tricalcium phosphate or calcium biphosphate, and also binders, such as starch pastes using e.g. maize, corn, rice or potato starch, gelatin, tragacanth, methyl cellulose and/or, if desired, disintegrators, such as the above-mentioned starches, also carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate. Adjuncts are in particular glidants and lubricants, for example silica, talc, stearic acid or salts thereof such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Dragée cores can be provided with suitable coatings which may be resistant to gastric juices, there being used, inter alia, concentrated sugar solutions which may contain gum

arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or shellac solutions in suitable organic solvents or mixtures of solvents or, for the preparation of coatings which are resistant to gastric juices, solutions of suitable cellulose preparations, such as acetyl cellulose phthalate or hydroxypropyl-methylcellulose phthalate. Dyes or pigments can be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of active ingredient.

Further pharmaceutical compositions for oral administration are dry-filled capsules made of gelatin and also soft sealed capsules consisting of gelatin and a plasticiser, such as glycerol or sorbitol. The dry-filled capsules can contain the active ingredient in the form of granules, for example in admixture with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and optionally stabilisers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, to which stabilisers can also be added.

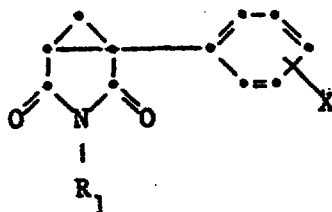
Suitable pharmaceutical compositions for rectal administration are e.g. suppositories, which consist of a combination of the active ingredient with a suppository base. Examples of suitable suppository bases are natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols and higher alkanols. It is also possible to use gelatin rectal capsules which contain a combination of the active ingredient with a base material. Suitable base materials are e.g. liquid triglycerides, polyethylene glycols and paraffin hydrocarbons.

Particularly suitable for parenteral administration are aqueous solutions of an active ingredient in water-soluble form, for example a water-soluble salt, and also suspensions of the active ingredient, such as corresponding oily injection suspensions, for which there are used suitable lipophilic solvents or vehicles, such as fatty oils, for example sesame oil, or synthetic fatty acid esters, for example ethyl oleate or triglycerides, or aqueous injection suspensions which contain substances which increase the viscosity, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and optionally also stabilisers.

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

The present invention also relates to processes for the preparation of compounds of the formula I. These compounds can be prepared by methods which are known per se, e.g.

a) by converting X into the $\begin{array}{c} \text{R}_2 \\ \diagup \\ \text{-N} \\ \diagdown \\ \text{R}_3 \end{array}$ group in a compound of the formula

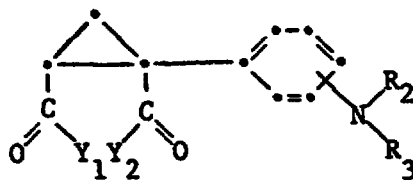


(II)

wherein R_1 is as defined for formula I and X is a group

which can be converted into the $\begin{array}{c} R_2 \\ | \\ -N \\ | \\ R_3 \end{array}$ group, or a salt thereof, or

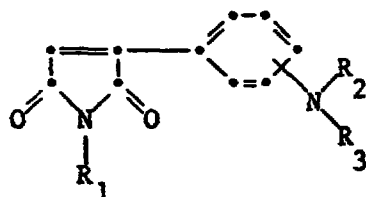
b) cyclising a compound of the formula



(III)

wherein R_2 and R_3 are as defined for formula I, Y_1 and Y_2 are leaving groups, or a salt thereof, by reaction with a compound which introduces the group $>N-R_1$, or

c) by addition of $-CH_2-$ (methylene) to the double bond of the maleimide in a compound of the formula



(IV)

wherein R_1 , R_2 and R_3 are as defined for formula I, or a salt thereof,

and, if desired, converting a compound of the formula I obtained in accordance with the invention into another compound of the formula I according to the definition,

and/or converting a resultant salt into the free compound or into another salt, and/or converting a resultant free compound into a salt and/or separating a resultant mixture of isomers into the individual isomers.

Process a)

In a compound of the formula II, a group X which can be

converted into the $\begin{array}{c} \text{R}_2 \\ \diagup \\ \text{-N} \\ \diagdown \\ \text{R}_3 \end{array}$ group is e.g. a nitrogen-

containing reducible group, e.g. the nitro, nitroso, hydroxylamino or azido group, a replaceable group, e.g. halogen, such as chlorine, bromine or iodine, or a derived carboxyl group, or a protected amino group from which the protective group is removed and replaced by hydrogen.

A nitrogen-containing reducible group, e.g. the nitro, nitroso, hydroxylamino or azido group, is converted into the amino group by a conventional reducing agent which, if desired, is used in the presence of a suitable catalyst and/or carrier.

A suitable reducing agent is in particular: catalytically activated hydrogen, the hydrogenation catalyst being e.g. a noble metal catalyst, such as a palladium, platinum, rhodium or nickel catalyst, or a noble metal compound, e.g. platinum dioxide, and which is used, if desired, with a suitable carrier, such as carbon, barium sulfate or barium carbonate or calcium carbonate, a reducing tin(II) or iron(II) salt, which are used e.g. in the form of the chloride and, in the latter case, also in the form of the sulfate, a reducing dithionite or sulfite salt, e.g. sodium dithionite, sodium sulfite or sodium bisulfite, an optionally activated base metal, e.g. activated iron, tin, zinc or aluminium, which may be

activated in the presence of the corresponding metal salt or of a neutral salt, e.g. calcium, magnesium, potassium or sodium chloride, and also a sulfide, e.g. hydrogen sulfide, a di- or polysulfide, e.g. sodium disulfide or sodium polysulfide, an alkali metal sulfide or alkali metal bisulfide, e.g. sodium sulfide or sodium bisulfide, ammonium sulfide or ammonium polysulfide, a reducing hydrogen donor, e.g. unsubstituted or substituted hydrazine, for example hydrazine or phenylhydrazine, which may be added in the form of an acid addition salt, e.g. in the form of the hydrochloride, or molecular hydrogen from which the charge is removed by electrolytic reduction at the cathode.

The reduction with catalytically activated hydrogen is carried out under normal or elevated pressure, e.g. up to about 6 bar (5 atmos). The reduction with the above-mentioned reducing agents is carried out in acid medium, e.g. in acetic acid medium, or in neutral medium. The reduction with iron(II) salts is carried out under basic conditions, in which reaction the reducing iron(II) hydroxide precipitates. The reductions with dithionite salts and sulfides also take place under basic conditions.

The reduction with hydrogen donors, e.g. hydrazines, is sped up by means of the hydrogenation catalysts referred to above, e.g. Raney nickel, palladium-on-carbon or platinum. The electrolytic reduction of the nitro groups to the amine is carried out at cathodes made of metals with high overpotential, e.g. lead, tin, nickel, copper or zinc. The electrolysis is normally carried out in sulfuric acid or hydrochloric acid solution.

The above-mentioned reducing agents are added in at least equimolar amount and preferably in excess. The addition

of an excess of reducing agent will prevent the formation of intermediates, e.g. nitroso or hydroxylamino compounds.

The reduction is preferably carried out in a solvent, e.g. a lower alkanol, e.g. methanol or ethanol, a lower alkanecarboxylic acid or an ester thereof, e.g. acetic acid and ethyl acetate, and in an ether, e.g. diethyl ether, tetrahydrofuran or dioxan.

To increase the solubility in particular of the salt-like reducing agents in the reaction mixture, water may be added to the reaction mixture, as required. The reaction is normally carried out in the temperature range from about -20° to about 100°C , although it can also be carried out at lower temperatures if highly reactive activators are employed.

In a compound of the formula II, a replaceable group X, e.g. halogen, such as chlorine, bromine or iodine, is

converted into the $\begin{array}{c} \text{R}_2 \\ \diagup \\ \text{-N} \\ \diagdown \\ \text{R}_3 \end{array}$ group with a compound which

introduces the $\begin{array}{c} \text{R}_2 \\ \diagup \\ \text{-N} \\ \diagdown \\ \text{R}_3 \end{array}$ group, e.g. ammonia, or an alkali metal amide, e.g. lithium or sodium amide, a lower alkylamine, e.g. methylamine, a di-lower alkylamine, e.g. dimethylamine, an acid amide wherein one hydrogen atom of the amide group is replaced by an alkali metal, e.g. lithium, e.g. $\text{R}^{\text{a}}\text{-CO-NR}_3\text{Li}$.

The reaction of a compound of the formula II, wherein X is halogen, e.g. chlorine, with a compound which

introduces the $\begin{array}{c} \text{R}_2 \\ \diagup \\ \text{-N} \\ \diagdown \\ \text{R}_3 \end{array}$ group, e.g. with ammonia, takes place preferably in the presence of a catalyst, e.g. copper(I) oxide or copper(II) oxide, copper(I) or copper(II) chloride or copper sulfate. The reaction is conducted in a concentrated aqueous ammonia solution or preferably in liquid ammonia and the reaction conditions described in Houben-Weyl, Methoden der Organischen Chemie (hereinafter referred to as "Houben-Weyl"), Vol. XI/1 "Nitrogen Compounds", pp. 63-67, are observed, e.g. elevated temperature above 100°C and elevated pressure.

The reaction of a compound of the formula II, wherein X is halogen, e.g. chlorine, is preferably carried out with an alkali metal amide, e.g. lithium or potassium amide. The amide is advantageously added in the form of a suspension.

The preferred solvent is benzene or toluene, and the reaction is carried out in an inert gas atmosphere, e.g. under nitrogen. The reaction is most preferably carried out at elevated temperature, e.g. at the boiling temperature of the reaction mixture, analogously to the reaction conditions described in Houben-Weyl, Vol. X/1 "Nitrogen Compounds" on pp. 74-79 for aromatic halogen compounds.

In a compound of the formula II, a derived carboxyl group X, e.g. carbamoyl or azidocarbonyl, can be converted into the amino group under the reaction conditions known for conversions or degradation reactions according to Hofmann (carbamoyl) or Curtius (azidocarbonyl).

The conversion of the carbamoyl compound of the formula II with free halogen, e.g. bromine, into the amino compound of the formula I according to Hofmann is carried out under alkaline conditions.

The conversion of the azidocarbonyl (carboxamide) compound of the formula II into the amino compound of the formula I according to Curtius is carried out at elevated temperature with decomposition of the azidocarbonyl group.

After the rearrangement, saponification is carried out under acid conditions, e.g. in a dilute aqueous mineral acid, e.g. in dilute sulfuric acid.

The reaction conditions for the Hofmann and Curtius degradations are described in the article by P.A. Smith in Org. Reactions 3, 363 (1946).

Protected amino groups from which the protective group can be split off and replaced by hydrogen are described e.g. in "Protective Groups in Organic Chemistry", Plenum Press, London and New York, 1973, in "The Peptides", Vol. I, Schröder and Lubke, Academic Press, London and New York, 1965, and in Houben-Weyl, Vol. 15/1, Georg Thieme Verlag Stuttgart, 1974.

Preferred protective groups are groups which can be removed by acidolysis, for example lower alkoxycarbonyl, e.g. tert-butoxycarbonyl (BOC) or 2-halo-lower alkoxy-carbonyl, e.g. 2-iodoethoxycarbonyl or 2,2,2-trichloroethoxycarbonyl.

It is also possible, however, to use amino protective groups which can be split off reductively or, under mild conditions, with a base, e.g. in particular the

benzyloxycarbonyl group or a benzyloxycarbonyl group wherein the phenyl radical is substituted by halogen atoms, nitro groups and/or lower alkoxy groups, e.g. the p-chloro-, p-nitro- or p-methoxybenzyloxycarbonyl group.

The removal of the protective group is effected in the generally known manner. The acid hydrolysis (acidolysis) is carried out e.g. with trifluoroacetic acid. The groups which can be split off reductively, especially those which contain benzyl radicals, are preferably removed by hydrogenolysis, e.g. by palladium-catalysed hydrogenation.

Process b)

In a compound of the formula III, the leaving groups Y_1 and Y_2 are each independently e.g. hydroxy, halogen, e.g. chlorine, bromine or iodine, lower alkoxy, silyloxy or sulfonyloxy.

Lower alkoxy Y_1 or Y_2 is, for example, methoxy, ethoxy, n-propoxy, branched lower alkoxy, e.g. tert-butoxy, or substituted lower alkoxy, e.g. benzyloxy, 4-nitrobenzyloxy or diphenylmethoxy.

Silyloxy Y_1 or Y_2 is, for example, tri-lower alkyl-silyloxy, such as trimethylsilyloxy.

Sulfonyloxy Y_1 or Y_2 is, for example, lower alkane-sulfonyloxy, such as methanesulfonyloxy, benzene-sulfonyloxy or p-toluenesulfonyloxy.

A compound which introduces the $>N-R_1$ group is, for example, an alkali metal amide, e.g. sodium amide or potassium amide, ammonia (R_1 = hydrogen), a lower alkylamine, e.g. methylamine (R_1 = lower alkyl), a carbamide, e.g. urea or 1,3-dimethylurea, or a lower

alkanecarboxamide, e.g. formamide, N-methylformamide, acetamide or N-methylacetamide.

The reaction with a compound which introduces the >N-R_1 group, e.g. with ammonia or methylamine, can be carried out stepwise. For example, it is possible to obtain first a compound of the formula III wherein one of the leaving groups Y_1 and Y_2 is replaced by -NH-R_1 . Such a compound, e.g. the monoamide, can be isolated or converted into a compound of the formula I in situ by removal of HY_1 or HY_2 .

A compound of the formula III wherein e.g. Y_1 and Y_2 are hydroxy, can be converted first into its anhydride, e.g. at elevated temperature or by dehydration with a conventional dehydrating agent, e.g. acetic anhydride or acetyl chloride. This anhydride can be isolated or converted into a compound in which one of the leaving groups Y_1 or Y_2 is replaced by -NH-R_1 in situ by reaction with a compound which introduces the group >N-R_1 e.g. ammonia or methylamine. Such a monoamide can subsequently be cyclised to a compound of the formula I by splitting off water.

During the cyclisation, a total of 2 moles of HY_1 or HY_2 , e.g. HCl or HBr , are set free and are bound, for example, by an excess of the >N-R_1 donor, e.g. ammonia or methylamine.

It is preferred to carry out the reaction in an inert polar solvent, e.g. in benzene, toluene, xylene, methylene chloride, ether or methanol or in a mixture thereof. The reaction temperature is in the range from -20° to about $+80^\circ\text{C}$, preferably from 0° to about 30°C . If an acid halide of the formula III, e.g. the acid dichloride, is reacted with ammonia, the reaction is

preferably carried out with cooling, for example below 0°C.

Process c)

The introduction of the CH₂ group into a compound of the formula IV is effected by addition of a methylene group to the olefinic double bond of the maleimide to form a cyclopropyl ring. CH₂ can be introduced, for example, by reaction with a sulfur ylide compound, e.g. a (dialkylamino)methylsulfoxonium methylide, e.g. (dimethylamino)- or (diethylamino)-methylsulfoxonium methylide, or a dialkylsulfoxonium methylide, e.g. dimethyl- or diethylsulfoxonium methylide, or with dihalomethane, e.g. dichloro-, dibromo- or diiodo-methane, in the presence of a zinc/copper catalyst.

The sulfur ylide compound is advantageously prepared in a solvent (see e.g. C.R. Johnson and P.E. Rogers, J. Org. Chem. Vol. 38, No. 10, 1793-1797, 1978, Preparation of (dimethylamino)methylsulfoxonium methylide in dimethyl sulfoxide, and P.T. Izzo, J. Org. Chem. 1963, pp. 1713-1715, Preparation of dimethylsulfonium methylide in tetrahydrofuran) and then reacted, optionally in situ, with the compound of the formula IV. The reaction is normally carried out at room temperature, with cooling, e.g. to -20°C, or with gentle heating, e.g. to 40°C. The dialkylsulfinamide formed is removed in the course of the subsequent aqueous working up.

The reaction of the maleimide of the formula IV with dihalomethane is carried out under the reaction conditions known for the Simmons-Smith reaction (see Houben-Weyl, Vol. 4/3, pp. 115-126). The compound of the formula IV is reacted with the appropriate dihalomethane, e.g. diiodomethane, in an inert solvent, e.g. in a hydrocarbon, e.g. benzene, an ether, e.g. diethyl ether, or in

an ester, e.g. ethyl acetate, in the presence of a zinc/copper catalyst prepared e.g. from zinc dust and copper(II) acetate in glacial acetic acid, and the reaction product is subsequently washed with ether. The reaction is preferably carried out at room temperature or with gentle heating, e.g. at a temperature above 30°C.

The methylene group $-CH_2-$ can also be introduced with diazomethane, which can be inserted in the maleimide first to form a pyrazoline ring. For example, an ethereal solution of diazomethane which has been prepared in situ (see Houben-Weyl, Vol. X/4, p. 473 et seq.) is combined with an ethereal solution of the maleimide of the formula IV, whereupon the addition compound is formed spontaneously or with gentle heating. The elimination of nitrogen from the pyrazoline ring can be effected at room temperature or with heating, e.g. in the temperature range up to the boiling point of the reaction mixture. The elimination of nitrogen at room temperature can be sped up by the addition of a catalyst, e.g. platinum or copper powder.

It is also possible to decompose diazomethane in an inert solvent, e.g. in hexane or in ether, whereupon the free methylene reacts with the maleimide compound of the formula IV to form directly the cyclopropane ring. The decomposition of diazomethane is preferably carried out catalytically, e.g. in the presence of a noble metal in finely divided form, e.g. copper, or of a metal salt, e.g. copper(I) chloride or copper(II) sulfate.

In compounds of the formula IV wherein R_1 is hydrogen, the imido function is protected by an amino protective group before the reaction with diazomethane. Suitable amino protective groups are described above under process a).

Instead of CH_2 it is also possible to introduce $\text{C}(\text{Hal})_2$, e.g. $\text{C}(\text{Cl})_2$, $\text{C}(\text{Br})_2$ or $\text{C}(\text{I})_2$, which adds on to the olefinic double bond of the maleimide of the formula IV to form a dihalo-substituted cyclopropane ring. The dihalo compound can then be converted by reduction into a compound of the formula I.

Subsequent operations

Within the scope of their definitions, the substituents R_1 , R_2 and R_3 in a compound of the formula I can be converted into other substituents R_1 , R_2 and R_3 . Accordingly, a free amino group can be converted into an acylamino group in which R_2 is acyl and R_3 is hydrogen or lower alkyl. These subsequent operations are carried out in a manner known per se, for example as follows:

Acylation of the amino group at the phenyl ring:

If in a resultant compound of the formula I R_2 and R_3 are hydrogen and R_1 is a hydrocarbon radical, the free amino group at the phenyl ring can be substituted in a manner known per se by an acyl group R_2 or by a lower alkyl radical R_3 . If R_1 is hydrogen, the imido group must be protected by one of the amino protective groups mentioned above.

This substitution can be effected e.g. by acylation with a suitable acylating agent which introduces the corresponding acyl radical R_2 .

The amino group at the phenyl ring is in the free form or in reactive, i.e. acylatable, protected, e.g. silylated, form.

If the amino group at the phenyl ring in a compound of the formula I is substituted by an acyl radical $\text{R}^b\text{-SO}_2\text{-}$,

the acylating agent employed is e.g. the corresponding sulfonic acid or a reactive functional derivative thereof, in particular an anhydride thereof, e.g. a mixed anhydride. A mixed anhydride of a sulfonic acid is formed e.g. by condensation with an inorganic acid, for example a hydrohalic acid, e.g. hydrochloric acid, and is e.g. the corresponding sulfonic acid halide, e.g. the sulfonic acid chloride or bromide.

If the amino group is substituted by an acyl group $R^b\text{-CO-}$, the acylating agent employed is e.g. the corresponding carboxylic acid itself or a reactive functional derivative thereof.

A reactive, i.e. carboxamide function forming, functional derivative of a carboxylic acid is an anhydride of this carboxylic acid, preferably a mixed anhydride. A mixed anhydride is formed e.g. by condensation with another acid, e.g. an inorganic acid, such as a hydrohalic acid, and is, for example, the corresponding carboxylic acid halide, e.g. the carboxylic acid chloride or bromide. A reactive functional derivative of a carboxylic acid of the formula III is furthermore formed by condensation with a lower alkyl hemiester of carbonic acid, e.g. the ethyl or isobutyl hemiester of carbonic acid.

If the amino group at the phenyl ring is substituted by an acyl radical R having the meanings $R^b\text{-O-CO-}$, $(R^b)(R^b)\text{N-CO-}$ or $(R^b)(R^b)\text{N-SO}_2$, the acylating agent employed is a reactive derivative of the corresponding carbonic acid hemiester or of the corresponding carbamic acid or amidosulfonic acid. Examples of such reactive derivatives are anhydrides, e.g. mixed anhydrides, which are formed by condensation with inorganic acids, such as hydrohalic acids, e.g. hydrochloric acid, or, if a carbamic acid is used, are also inner anhydrides, e.g.

cyanates.

The acylation reactions are preferably carried out in the presence of a suitable acid-binding agent, e.g. a suitable organic base. A suitable organic base is, for example, an amine, e.g. a tertiary amine, e.g. tri-lower alkylamine, e.g. trimethylamine or triethylamine, a cyclic tertiary amine, e.g. N-methylmorpholine, a bicyclic amidine, e.g. a diazabicycloalkene, e.g. 1,5-diazabicyclo[4.3.0]non-5-ene or 1,5-diazabicyclo[5.4.0]-undec-5-ene (DBU), or is, for example, a base of the pyridine type, e.g. pyridine. A suitable acid-binding agent is also an inorganic base, e.g. an alkali metal or alkaline earth metal hydroxide, e.g. sodium, potassium or calcium hydroxide.

The acylation reactions are preferably carried out in an inert, preferably anhydrous, solvent or mixture of solvents, for example in dimethylformamide, methylene chloride, carbon tetrachloride, chlorobenzene, acetone, tetrahydrofuran, ethyl acetate or acetonitrile, or in mixtures thereof, if desired at low or elevated temperature, e.g. in the temperature range from about -40° to about +100°C, preferably from about -10° to about +50°C, and optionally in an inert gas atmosphere, e.g. under nitrogen.

The acylation of the free amino group at the phenyl ring can be carried out both in the final product of the formula I and in the intermediates of the formulae II, III and IV by the method described above.

Substitution of the amino group at the phenyl ring by sulfo:

If in a resultant compound of the formula I R_2 and R_3 are hydrogen and R_1 is a hydrocarbon radical, the free amino

group at the phenyl ring can be substituted by sulfo in a manner known per se.

This substitution can be effected e.g. by reacting an aminophenyl compound of the formula I with triethylamine in a sulfur trioxide complex.

To prevent the imido function (R_1 =hydrogen) from being substituted by sulfo, it must be protected by one of the amino protective groups mentioned above.

Alkylation of the amino group at the phenyl ring:

If in a resultant compound of the formula I R_2 and R_3 are hydrogen, the free amino group at the phenyl ring can be substituted by two equivalents of a suitable alkylating agent which introduces the lower alkyl radical, e.g. an alkyl halide, such as methyl bromide, to give the di-lower alkyl-substituted amino group (R_2 and R_3 = lower alkyl).

The free amino group at the phenyl ring can also be protected by one of the above-mentioned customary amino protective groups, e.g. by tert-butoxycarbonyl, and, after subsequent metalation of the amino group thus protected with a suitable metalating reagent, alkylated with a reactive alkylating compound corresponding to the lower alkyl radical R_2 or R_3 .

After removal of the amino protective groups, there is obtained a mono-lower alkyl-substituted amino group (R_2 = H and R_3 = lower alkyl or R_2 = lower alkyl and R_3 = H).

Examples of suitable metalating reagents are lithium diisopropylamide or butyllithium. A reactive compound corresponding to the radical R_3 is, for example, a

compound of the formula R_2-X or R_3-X , wherein X is a nucleofugal leaving group, for example a halogen atom, e.g. chlorine, bromine or iodine, or is a sulfonyloxy group, such as mesyloxy or tosyloxy.

If it is not desired to alkylate the imido function ($R_1 =$ hydrogen), then this group must be protected by one of the customary protective groups mentioned above.

The separation of mixtures of diastereoisomers obtained by the process of the invention into optically pure antipodes is effected in a manner known per se, for example by physical or chemical methods, for example by fractional crystallisation. It is also possible, however, to use chromatographic methods, e.g. solid-liquid chromatography. Volatile mixtures of diastereoisomers can also be separated by distillation or by chromatography.

The separation of racemates obtained by the process of the invention into optically pure antipodes is effected in a manner known per se, e.g. by chromatography on optically active adsorption layers, e.g. on raw sugar. It is also possible to dissolve the racemates in optically active solvents and to crystallise the more sparingly soluble optical antipode from the solution so obtained. Use is also made of the different reactivity of the optical antipodes towards biological material, such as microorganisms or isolated enzymes, or the racemates are dissolved and an optical antipode is crystallised by inoculation with a small amount of an optically active product obtained by the above methods.

Instead of the compound of the formula I obtainable according to the invention itself, it is also possible to resolve a precursor obtained in racemic form, for example

an intermediate of the formula III wherein Y_1 or Y_2 is hydroxy, into optically pure antipodes, and then to convert the optically pure antipode of this precursor into an optically pure antipode of the final product of the formula I. The reactions according to processes a), b) and c) do not in general change the configuration of the 1- and 5-C-atom. The addition of methylene to the olefinic double bond of the maleimide of the formula IV according to process c) proceeds in general stereospecifically (cis-addition).

Acid addition salts are obtained in conventional manner, e.g. by treatment with an acid or a suitable anion exchanger reagent.

The process also comprises those embodiments in which compounds obtained as intermediates are used as starting materials and the remaining process steps are carried out therewith, or the process is interrupted at any stage; in addition, starting materials may be used in the form of derivatives or formed during the reaction.

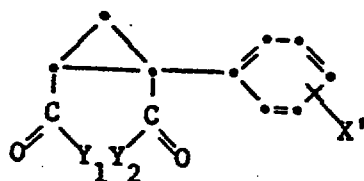
The starting materials employed and the reaction conditions chosen are preferably those which result in the compounds described above as being especially preferred.

Starting materials

The starting materials employed in the process for the preparation of the compounds of the formula I of the present invention are known or, if they are novel, can be prepared in a manner known per se.

Starting materials of the formula II wherein X is halogen or nitro, are described in German Offenlegungsschrift 27 40 562.

Starting materials of the formula II wherein X is e.g. nitroso or hydroxylamino, or a replaceable group, such as carbamoyl or azidocarbonyl, or is protected amino, are novel, and the present invention relates also to them. They can be prepared e.g. in a manner known per se, by cyclising a compound of the formula



(VI)

wherein Y_1 and Y_2 are leaving groups and X' is nitroso or hydroxylamino, carboxyl or protected amino, or a salt thereof, by reaction with a compound which introduces the group $-NH-R_1$ and, in a resultant compound, converting the carboxyl group into a replaceable group, e.g. carbamoyl or azidocarbonyl, and/or, if desired, converting a compound of the formula II obtained according to the invention into another compound of the formula II according to the definition, and/or converting a resultant salt into the free compound or into another salt, and/or converting a resultant free compound into a salt and/or separating a resultant mixture of isomers into the individual isomers.

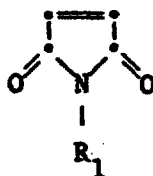
The process can be carried out analogously to the reaction conditions described above under process b). The conversion of the carboxyl group X' in a compound of the formula II into an azidocarbonyl or carbamoyl group can be carried out in accordance with the methods for obtaining derivatives of aromatic carboxyl groups described in Organikum, VEB Deutscher Verlag der Wissenschaften, latest edition.



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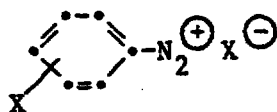
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defined for formula I, R_2 is hydrogen, lower alkyl or sulfo, and R_3 is hydrogen or lower alkyl, are prepared e.g. by reacting a maleimide compound of the formula



(IX)

wherein R_1 is as defined for formula I, with a diazonium salt of the formula



(X)

wherein X is as defined for formula II and Hal is chlorine or bromine, and, in a compound so obtained, converting X into the group of the partial formula $-NR_2(R_3)$, and/or, if desired, converting a resultant salt into the free compound or into another salt, and/or converting a resultant free compound into a salt.

The reaction of a compound of the formula IX with a diazonium salt of the formula IX¹ is carried out analogously to the procedure of Ch.S. Rondestvedt and O. Vogel in J. Am. Chem. Soc. 77, 2313-2315 (1955). The conversion of X into the group of the partial formula $-NR_2(R_3)$ is described above under process a) and in the section "Subsequent operations".

¹ Translator's note: Although "IX" appears here in the German text, "X" was presumably intended.

Compounds of the formula VI can be prepared analogously to compounds of the formula III in accordance with the procedures mentioned by L.L. McCoy in J. Am. Chem. Soc. 1958, 80, 6258 and 1962, 84, 2246, and in J. Org. Chem. 1960, 25, 2078.

Starting materials of the formulae VII, VIII, IX and X are known or, if they are novel, can be prepared in a manner known per se.

The following Examples serve to illustrate the invention. Temperatures are given in degrees Celsius.

Abbreviations

m.p. = melting point

b.p. = boiling point

Example 1: 1-(4-Aminophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione

To a solution of 25.9 g of 1-(4-nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione (preparation as described in DE-A 2 740 562) in 700 ml of ethanol are added 1.4 g of 5% palladium/carbon catalyst. Hydrogenation is carried out under normal pressure and at room temperature in a hydrogen atmosphere. When the absorption of hydrogen is complete (theoretical amount: 7500 ml), the reaction mixture is diluted with 1 ml of ethanol and concentrated after removal of the catalyst. The product so obtained is recrystallised from ethanol, affording the title compound with m.p. 183°-185°.

Example 2:

a) 1-(3-Aminophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione

Analogously to Example 1, 600 mg of 1-(3-nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione are dissolved in 30 ml of ethanol and reduction is carried out with hydrogen in

the presence of 60 mg of 5% palladium/carbon. When the hydrogenation is complete, the mixture is diluted with ethanol and the catalyst is removed by filtration over HYFLO-Super-Cel[®]. The solvent is evaporated off in vacuo and the residue is recrystallised from a mixture of ethyl acetate/petroleum ether, affording the title compound in the form of pale pink crystals with m.p. 135°-137° and an Rf value of 0.47 on thin-layer silica gel plates in the system methylene chloride/methanol (10:1), or 0.52 in the system methylene chloride/methanol/glacial acetic acid (40:5:1).

Preparation of the starting material:

b) Ethyl 2-chloro-2-(3-nitrophenyl)acetate

A mixture of 97 g of ethyl 3-nitromandelate and 69 ml of thionyl chloride is stirred overnight at room temperature. Then a few drops of pyridine are added. After the evolution of gas has ceased, the mixture is stirred for about 2 hours at 100°. Excess thionyl chloride is evaporated off in a water jet vacuum and the reaction mixture is then distilled in a high vacuum. The title compound b) is obtained in the form of a yellow oil with b.p. 134° at 0.06 mbar and with an Rf value of 0.5 on thin-layer silica gel plates in a methylene chloride system.

c) Diethyl 1-(3-nitrophenyl)-1,2-cyclopropane dicarboxylate

With stirring and under nitrogen, a mixture of 68.2 g of ethyl 1-chloro-1-(3-nitrophenyl)acetate and 30.5 ml of ethyl acrylate is slowly added dropwise, with the internal temperature of the reaction vessel at about 50°, to a suspension of 12.3 g of sodium hydride (55-60% in paraffin oil) in 67 ml of toluene. To initiate and speed up the reaction, a few drops of a 1:1 mixture of alcohol/ether are added to the reaction mixture from

time to time. When the reaction is complete, 350 ml of water are carefully added dropwise. After two extractions with ether, the organic phases are washed twice with water and once with a dilute solution of sodium chloride. After drying over magnesium sulfate and filtration, the solution is evaporated to dryness and the residue is chromatographed over 1 kg of silica gel (0.063 to 0.280 mm). The title compound c) is obtained in the form of a brown oil with an Rf value of 0.15 on thin-layer silica gel plates in a methylene chloride system.

d) 1-(3-Nitrophenyl)-1,2-cyclopropanedicarboxylic acid
14.2 g of diethyl 1-(3-nitrophenyl)-1,2-cyclopropanedicarboxylate are dissolved in 150 ml of methanol and to this solution are added 100 ml of 1N sodium hydroxide solution. The mixture is stirred overnight and the solvent is then removed from the dark brown solution. While cooling to 0°, 50 ml of 2N hydrochloric acid are added to the mixture, and then the whole is extracted twice with ether. The ethereal phases are washed repeatedly with a small amount of water, dried over magnesium sulfate, filtered and concentrated by evaporation. The crystals so obtained are recrystallised from boiling ethyl acetate by adding petroleum ether. The title compound d) is obtained in the form of pale beige crystals with m.p. 167°-170° and Rf = 0.2 on thin-layer silica gel plates in the system methylene chloride/methanol/glacial acetic acid (40:5:1).

e) 1-(3-Nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione
A mixture of 9.8 g of 1-(3-nitrophenyl)-1,2-cyclopropanedicarboxylic acid and 4.9 g of urea in 250 ml of xylene (mixture of isomers) is stirred for about 16 hours at a bath temperature of about 150°. The xylene is then evaporated off in vacuo and the residue is partitioned

twice between ethyl acetate and water. The organic phases are combined, dried over MgSO_4 , filtered, and concentrated by evaporation in vacuo. Recrystallisation from ethyl acetate/petroleum ether gives the title compound e) in the form of pale yellow crystals with m.p. 173° - 174° and $R_f = 0.3$ on thin-layer silica gel plates in the system hexane/ethyl acetate (4:6).

Example 3:

a) 1-(4-Aminophenyl)-3-methyl-3-azabicyclo[3.1.0]hexane-2,4-dione

A solution of 1.5 g of 3-methyl-1-(4-nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione in 50 ml of ethanol is hydrogenated in the presence of 0.1 g of 5% palladium/-carbon. When the hydrogenation is complete, the catalyst is removed, the filtrate is concentrated by evaporation, and the residue is recrystallised from ethyl acetate/-petroleum ether. The title compound is obtained in the form of pale pink crystals with m.p. 137° - 139° and an R_f value of 0.47 on thin-layer silica gel plates in the system methylene chloride/methanol (15:1).

Preparation of the starting material:

b) 3-Methyl-1-(4-nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione

2.32 g of 1-(4-nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione are dissolved in 25 ml of dimethylformamide and 0.3 g of sodium hydride (pract. Fluka) is added under nitrogen. After the mixture has been stirred for 30 minutes at room temperature, it is cooled to 0° and then a solution of 0.93 ml of methyl iodide in 5 ml of dimethylformamide is added dropwise. The reaction mixture is stirred for another 5 hours and then excess sodium hydride is destroyed by the addition of methanol. The solvent is then stripped off in vacuo and the residue is partitioned between ethyl acetate/water and a

concentrated aqueous solution of sodium chloride. The aqueous phases are washed once with ethyl acetate. The organic phases are dried over magnesium sulfate, filtered and concentrated by evaporation. Recrystallisation from ethyl acetate/petroleum ether yields the title compound b) in the form of colourless crystals with m.p. 148°-150° and an R_f value of 0.7 on thin-layer silica gel plates in the system methylene chloride/methanol/glacial acetic acid (40:5:1).

Example 4:

3-Ethyl-1-(4-aminophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione

Analogously to Example 3, 4.1 g of 3-ethyl-1-(4-nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione are dissolved in 120 ml of ethanol and the solution is hydrogenated in the presence of 0.2 g of 5% palladium-on-carbon and worked up, affording the title compound which melts at 116°-118° after recrystallisation from ethyl acetate/-petroleum ether.

The starting material used is synthesised analogously to Example 3 starting from 4.6 g of 1-(4-nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione, 0.72 g of sodium hydride (pract. Fluka) and 2 ml of ethyl iodide, m.p. 155°-157° (ethyl acetate/petroleum ether).

Example 5:

1-(4-Aminophenyl)-3-n-propyl-3-azabicyclo[3.1.0]hexane-2,4-dione

Analogously to Example 3, 3.4 g of 1-(4-nitrophenyl)-3-n-propyl-3-azabicyclo[3.1.0]hexane-2,4-dione are dissolved in 120 ml of ethanol and the solution is hydrogenated in the presence of 0.2 g of 5 % palladium-on-carbon and worked up, affording the title compound which melts at 114°-115°C after recrystallisation from ethyl acetate/-

petroleum ether.

The starting material used is synthesised analogously to Example 3 starting from 4.6 g of 1-(4-nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione, 0.72 g of sodium hydride (pract. Fluka) and 2.44 ml of propyl iodide, m.p. 97° (ether).

Example 6:

1-(4-Aminophenyl)-3-isopropyl-3-azabicyclo[3.1.0]hexane-2,4-dione

Analogously to Example 3, 3.4 g of 3-isopropyl-1-(4-nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione are dissolved in 100 ml of ethanol and the solution is hydrogenated in the presence of 0.17 g of 5% palladium-on-carbon and worked up, affording the title compound which melts at 160°-163°C after recrystallisation from ethyl acetate/petroleum ether.

The starting material used is synthesised analogously to Example 3 starting from 4.6 g of 1-(4-nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione, 0.72 g of sodium hydride (pract. Fluka) and 2.5 ml of isopropyl iodide, m.p. 115°-118° (ethyl acetate/petroleum ether).

Example 7

1-(4-Aminophenyl)-3-n-butyl-3-azabicyclo[3.1.0]hexane-2,4-dione

Analogously to Example 3, 4.0 g of 3-n-butyl-1-(4-nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione are dissolved in 120 ml of ethanol and the solution is hydrogenated in the presence of 0.2 g of 5% palladium-on-carbon and worked up, affording the title compound which melts at 95°-98° after recrystallisation from ether/petroleum ether.

The starting material used is synthesised analogously to Example 3 starting from 4.6 g of 1-(4-nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione, 0.72 g of sodium hydride (pract. Fluka) and 2.9 ml of n-butyl iodide; yellow oil with an R_f value of 0.2 on thin-layer silica gel plates in the system hexane/ethyl acetate (2:1).

Example 8

1-(4-Aminophenyl)-3-isobutyl-3-azabicyclo[3.1.0]hexane-2,4-dione

Analogously to Example 3, 0.55 g of 3-isobutyl-1-(4-nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione is dissolved in 25 ml of ethanol and the solution is hydrogenated in the presence of 0.1 g of 5% palladium-on-carbon and worked up, affording the title compound which melts at 115°-117° after recrystallisation from ether/-petroleum ether.

The starting material used is synthesised analogously to Example 3 starting from 4.6 g of 1-(4-nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione, 0.72 g of sodium hydride (pract. Fluka) and 3.5 ml of isobutyl iodide, m.p. 100°-101° (ethyl acetate/petroleum ether).

Example 9

1-(4-Aminophenyl)-3-n-pentyl-3-azabicyclo[3.1.0]hexane-2,4-dione

Analogously to Example 3, 5.3 g of 1-(4-nitrophenyl)-3-n-pentyl-3-azabicyclo[3.1.0]hexane-2,4-dione are dissolved in 150 ml of ethanol and the solution is hydrogenated in the presence of 0.25 g of 5% palladium-on-carbon and worked up, affording the title compound which melts at 113°-115° after recrystallisation from ethyl acetate/petroleum ether.

The starting material used is synthesised analogously to

Example 3 starting from 4.6 g of 1-(4-nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione, 0.72 g of sodium hydride (pract. Fluka) and 3.3 ml of pentyl iodide; yellow oil with an R_f value of 0.52 on thin-layer silica gel plates in the system hexane/ethyl acetate (4:6).

Example 10

1-(4-Aminophenyl)-3-neopentyl-3-azabicyclo[3.1.0]hexane-2,4-dione

Analogously to Example 3, 0.85 g of 3-n-pentyl-1-(4-nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione is dissolved in 30 ml of ethanol and the solution is hydrogenated in the presence of 0.1 g of 5% palladium-on-carbon and worked up, affording the title compound which melts at 140°-143° after recrystallisation from ether/-petroleum ether.

The starting material used is synthesised analogously to Example 3 starting from 4.6 g of 1-(4-nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione, 0.72 g of sodium hydride (pract. Fluka) and 3.3 ml of neopentyl iodide, m.p. 118°-119° (ether/petroleum ether).

Example 11

1-(4-Aminophenyl)-3-n-heptyl-3-azabicyclo[3.1.0]hexane-2,4-dione

Analogously to Example 3, 5.0 g of 3-n-heptyl-1-(4-nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione are dissolved in 100 ml of ethanol and the solution is hydrogenated in the presence of 0.3 g of 5% palladium-on-carbon and worked up, affording the title compound which melts at 78°-79° after recrystallisation from ether/-petroleum ether.

The starting material used is synthesised analogously to Example 3 starting from 4.6 g of 1-(4-nitrophenyl)-3-

azabicyclo[3.1.0]hexane-2,4-dione, 0.72 g of sodium hydride (pract. Fluka) and 3.9 ml of n-heptyl bromide; yellow oil with an R_f value of 0.55 on thin-layer silica gel plates in the system hexane/ethyl acetate (4:6).

Example 12

1-(4-Aminophenyl)-3-cyclohexylmethyl-3-azabicyclo[3.1.0]-hexane-2,4-dione

Analogously to Example 3, 0.5 g of 3-cyclohexylmethyl-1-(4-nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione is dissolved in 30 ml of ethanol and the solution is hydrogenated with hydrogen in the presence of 0.1 g of 5% palladium-on-carbon and worked up, affording the title compound which melts at 125°-128° after recrystallisation from ethyl acetate/petroleum ether.

The starting material used is synthesised analogously to Example 3 starting from 2.3 g of 1-(4-nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione, 0.36 g of sodium hydride (pract. Fluka) and 1.7 g of cyclohexylmethyl chloride, m.p. 125°-128° (ether/petroleum ether).

Example 13

1-(4-Aminophenyl)-3-benzyl-3-azabicyclo[3.1.0]hexane-2,4-dione

Analogously to Example 3, 2.0 g of 3-benzyl-1-(4-nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione are dissolved in 100 ml of ethanol and the solution is hydrogenated with hydrogen in the presence of 0.2 g of 5% palladium-on-carbon and worked up, affording the title compound which melts at 154°-155° after recrystallisation from ethanol.

The starting material used is synthesised analogously to Example 3 starting from 2.3 g of 1-(4-nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione, 0.3 g of sodium

hydride (pract. Fluka) and 1.2 ml of benzyl chloride, m.p. 147°-149° (ethyl acetate).

Example 14

a) 1-(4-Aminophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione

In a glass bomb tube, 2.3 g of 1-(4-aminophenyl)-1,2-cyclopropanedicarboxylic acid are stirred in 80 ml of approx. 1N methanolic ammonia solution for 7 days at 100°C. The reaction mixture is concentrated to dryness by evaporation in vacuo and the residue is then chromatographed over silica gel with hexane/ethyl acetate (4:6). Recrystallisation from ethanol affords white crystals of the title compound, which is identical with the title compound of Example 1.

Preparation of the starting material:

b) 1-(4-Aminophenyl)-1,2-cyclopropanedicarboxylic acid

20 g of 1-(4-nitrophenyl)-1,2-cyclopropanedicarboxylic acid are dissolved in 200 ml of ethanol and the solution is hydrogenated in the presence of 5% palladium-on-carbon. The suspension so obtained is diluted with methanol and the precipitated product is dissolved by addition of 1 equivalent of methanolic hydrochloric acid. The catalyst is then filtered off. A part of the solvent is evaporated off in vacuo, then 1 equivalent of 2N sodium hydroxide solution is added and the mixture is concentrated to dryness by evaporation. The residue obtained is recrystallised from water and dried in vacuo over KOH pellets at 60°. The title compound b) is obtained in the form of pale brown crystals with a melting point above 230° and an R_f of 0.55 on thin-layer silica gel plates in the system methylene chloride/-methanol/glacial acetic acid (20:10:2).

Example 15

1-(4-Aminophenyl)-3-methyl-3-azabicyclo[3.1.0]hexane-2,4-dione

A mixture of 220 mg of 1-(4-aminophenyl)-1,2-cyclopropanedicarboxylic acid, 10 ml of methanol and 0.26 ml of methylamine (40%) is stirred in a glass bomb tube for 7 days at 100°. The mixture is concentrated by evaporation in vacuo and the residue is chromatographed over a column of silica gel with a 4:6 mixture of hexane/ethyl acetate. Recrystallisation from ethyl acetate/petroleum ether affords yellow crystals of the title compound, which is identical with the title compound of Example 3a).

Example 16

a) 1-(4-Aminophenyl)-3-n-propyl-3-azabicyclo[3.1.0]-hexane-2,4-dione

A mixture of 52 mg of 1-(4-aminophenyl)-1,2-cyclopropanedicarboxylic acid 2-N-propylamide and 5 ml of xylene (mixture of isomers) is stirred for 24 hours at 150°. The mixture is concentrated by evaporation and the residue is then taken up in ethyl acetate, filtered over Hyflo-Supercel® and crystallised by addition of petroleum ether, affording the title compound, which is identical with the title compound of Example 5.

Preparation of the starting material:

b) 1-(4-Nitrophenyl)-1,2-cyclopropanedicarboxylic acid 2-N-propylamide

2.1 g of N,N'-dicyclohexylcarbodiimide are added to a solution of 2.5 g of 1-(4-nitrophenyl)-1,2-cyclopropanedicarboxylic acid in 50 ml of tetrahydrofuran and the mixture is stirred for 1 hour at room temperature. A solution of 0.83 ml of propylamine and 10 ml of tetrahydrofuran is then added dropwise at room temperature to the suspension. The mixture is then stirred at room

temperature until the reaction is complete. The solvent is evaporated off, the residue is taken up in water and 1 equivalent of sodium hydroxide solution, and the precipitated urea is removed by filtration. 1 equivalent of hydrochloric acid is added to the filtrate, and the mixture is extracted twice with methylene chloride. The organic phases are washed once with water, dried over magnesium sulfate and concentrated by evaporation. Recrystallisation from ethyl acetate/ether/petroleum ether affords white crystals of the title compound b) with m.p. 154°-155° and an R_f value of 0.45 on thin-layer silica gel plates in the system methylene chloride/-methanol/glacial acetic acid (40:5:1).

c) 1-(4-Aminophenyl)-1,2-cyclopropanedicarboxylic acid 2-N-propylamide

A solution of 1.5 g of 1-(4-nitrophenyl)-1,2-cyclopropanedicarboxylic acid 2-N-propylamide in 30 ml of ethanol is hydrogenated in the presence of 5% palladium-on-carbon. For working up, the reaction mixture is diluted with methanol in the ratio 1:1, filtered to remove the catalyst, and then concentrated by evaporation. Recrystallisation from isopropanol affords pale beige crystals of the title compound c) with m.p. 170°-172° (decomposition) and an R_f value of 0.3 on thin-layer silica gel plates in the system methylene chloride/methanol/glacial acetic acid (40:5:1).

Example 17

1-(4-Acetylaminophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione

A solution of 2.4 ml of acetic anhydride in 10 ml of tetrahydrofuran is added dropwise to a solution of 4 g of 1-(4-aminophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione and 120 mg of dimethylaminopyridine in 150 ml of tetrahydrofuran, and the mixture is stirred overnight at room

temperature. Then 0.5 ml of ethanol is added to the reaction mixture, which is then stirred for 1 hour and filtered. The crystals are washed with tetrahydrofuran and ether, affording white crystals of the title compound with m.p. above 230° and an R_f of 0.3 on thin-layer silica gel plates in the system methylene chloride/-methanol (10:1).

Example 18

1-(4-Aminophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione

61 mg of 1-(4-acetylaminophenyl)-3-azabicyclo[3.1.0]-hexane-2,4-dione are stirred for 3 hours at 100° in 0.5 ml of approx. 18% hydrochloric acid. The reaction mixture is cooled to 0° and adjusted to pH 7 with saturated aqueous bicarbonate solution. The crystalline precipitate is isolated by filtration, washed with a small amount of cold water and recrystallised from ethanol. The title compound so obtained is identical with the title compound of Example 1.

Example 19

1-(4-Acetylaminophenyl)-3-methyl-3-azabicyclo[3.1.0]-hexane-2,4-dione

1.2 g of 1-(4-acetylaminophenyl)-3-azabicyclo[3.1.0]-hexane-2,4-dione, 120 mg of sodium hydride and 25 ml of N,N'-dimethylformamide are stirred, under nitrogen, for 15 minutes at 50°. The mixture is cooled to 20° and then a solution of 0.32 ml of methyl iodide in 2.5 ml of dimethylformamide is slowly added dropwise. The reaction mixture is stirred for 16 hours at room temperature. Excess sodium hydride is destroyed with methanol and the reaction mixture is freed of solvent in a high vacuum. The residue is partitioned repeatedly between ethyl acetate and a dilute solution of sodium chloride. The organic phases are dried over magnesium sulfate, filtered and concentrated by evaporation, and the residue

is crystallised from ethyl acetate/petroleum ether. The title compound is obtained in the form of white crystals with m.p. 183°-184° and Rf 0.37 on thin-layer silica gel plates in the system methylene chloride/methanol (10:1).

Example 20

1-(4-Aminophenyl)-3-methyl-3-azabicyclo[3.1.0]hexane-2,4-dione

A mixture of 130 mg of 1-(4-acetylamino-phenyl)-3-methyl-3-azabicyclo[3.1.0]hexane-2,4-dione and 1 ml of approx. 18% hydrochloric acid is stirred for about 4 hours at 100°. The reaction mixture is adjusted at 0° to pH 9-10 with saturated aqueous sodium bicarbonate solution and extracted twice with ethyl acetate. The organic phases are washed until neutral with a small amount of water and a dilute solution of sodium chloride, dried over magnesium sulfate, filtered and concentrated by evaporation. Recrystallisation from ethyl acetate/-petroleum ether affords the title compound which is identical with the title compound of Example 3a).

Example 21

1-(4-Aminophenyl)-3-methyl-3-azabicyclo[3.1.0]hexane-2,4-dione

An approx. 0.3 molar solution of diazomethane is added dropwise at 0° to a solution of 202 mg of 1-(4-amino-phenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione in 10 ml of methanol. The reaction mixture is allowed to stand for 16 hours, concentrated by evaporation, and partitioned twice between ethyl acetate and water. The organic phases are dried over magnesium sulfate, filtered and concentrated by evaporation. The residue is crystallised from ethyl acetate/petroleum ether, affording the title compound which is identical with the title compound of Example 3a).

Example 22

1-(4-Methanesulfonylaminophenyl)-3-azabicyclo[3.1.0]-
hexane-2,4-dione

A solution of 1.2 ml of methanesulfonyl chloride in 10 ml of methylene chloride is stirred dropwise at room temperature into a mixture of 3 g of 1-(4-aminophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione, 90 mg of dimethylaminopyridine and 37 ml of pyridine. After the reaction mixture has been stirred for 16 hours, it is freed of solvent in vacuo. The residue is dissolved in 100 ml of water and the solution is adjusted to pH 1 with hydrochloric acid. After further stirring, the crystals are isolated by filtration and recrystallised from methanol. The title compound is obtained in the form of white-orange crystals with m.p. 208°-209° and an R_f value of 0.32 on thin-layer silica gel plates in the system methylene chloride/methanol (10:1).

Example 23

1-(4-Acetylaminophenyl)-3-methyl-3-azabicyclo[3.1.0]-
hexane-2,4-dione

100 ml of a 0.3N solution of diazomethane in ether are stirred dropwise into a solution, cooled to 0°, of 2.3 g of 3-(4-acetylaminophenyl)-2,5-dihydro-1H-pyrrole-2,5-dione in 200 ml of tetrahydrofuran, and the mixture is stirred for 16 hours in an ice bath. The crystallised product is filtered off with suction, washed with ether, and suspended in 60 ml of ethanol. This mixture is heated for 20 minutes under reflux, filtered and cooled. The white crystals are isolated by filtration, affording the title compound, which is identical with the title compound of Example 19.

Example 24

1-(4-N-Acetyl-N-methylaminophenyl)-3-azabicyclo[3.1.0]-hexane-2,4-dione

A mixture of 3.9 g of 1-(4-methylaminophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione, 180 ml of tetrahydrofuran, 0.2 g of dimethylaminopyridine and 2 ml of acetic anhydride is stirred for 20 hours at room temperature. Then 5 ml of ethanol are added to the reaction mixture, which is stirred for another 30 minutes and subsequently concentrated by evaporation in vacuo. The residue is partitioned twice between 500 ml of ethyl acetate and 50 ml of water. The combined organic phases are dried over magnesium sulfate, filtered, concentrated by evaporation and crystallised from ethyl acetate. The title compound is obtained in the form of white crystals (m.p. 194°-195°) and an R_f value of 0.35 on thin-layer silica gel plates in the system methylene chloride/-methanol (10.1).

Example 25

1-(4-N-Acetyl-N-methylaminophenyl)-3-methyl-3-azabicyclo-[3.1.0]hexane-2,4-dione

1.7 g of 1-(4-acetylmethylaminophenyl)-3-azabicyclo-[3.1.0]hexane-2,4-dione are dissolved in 40 ml of dimethylformamide and to this solution are added 216 mg of sodium hydride under nitrogen. After the mixture has been stirred for 30 minutes at room temperature, it is cooled to 0° and 0.9 ml of methyl iodide are added. The reaction mixture is stirred for 1 hour at 0° and then for 20 hours at room temperature. Excess sodium hydride is destroyed by the addition of methanol and the mixture is subsequently freed of solvent in vacuo. The residue is partitioned between ethyl acetate/water and a dilute aqueous solution of sodium chloride. The aqueous phases are washed once with ethyl acetate. The combined organic phases are dried over magnesium sulfate, filtered and

then concentrated by evaporation. The resulting oil is degassed for several hours in a high vacuum at about 40°, affording the title compound in the form of a yellow, viscous resin with an R_f value of 0.36 on thin-layer silica gel plates in the system methylene chloride/methanol (15:1).

Example 26

1-(4-Dimethylaminophenyl)-3-methyl-3-azabicyclo[3.1.0]-hexane-2,4-dione and 1-(4-methylaminophenyl)-3-methyl-3-azabicyclo[3.1.0]hexane-2,4-dione

2.16 g of 1-(4-methylaminophenyl)-3-azabicyclo[3.1.0]-hexane-2,4-dione are dissolved in 50 ml of dimethylformamide, and 300 mg of sodium hydride are added, under nitrogen, to the solution. The mixture is stirred for 30 minutes at room temperature and then a solution of 0.95 ml of methyl iodide in 10 ml of dimethylformamide is added dropwise at 0°. The reaction mixture is stirred overnight at room temperature. Excess sodium hydride is destroyed with a small amount of methanol and the solvent is stripped off. The residue is partitioned twice between ethyl acetate and an aqueous solution of sodium chloride, and then the organic phases are dried over magnesium sulfate, filtered and concentrated by evaporation. The residue is chromatographed on silica gel with a 1:1 mixture of hexane/ethyl acetate, affording fraction I with an R_f value of 0.35 and fraction II with an R_f value of 0.25 on thin-layer silica gel plates in the system ethyl acetate/hexane (1:1). Recrystallisation of fraction I from ether yields 1-(4-dimethylamino-phenyl)-3-methyl-3-azabicyclo[3.1.0]hexane-2,4-dione in the form of white crystals with m.p. 140°-141°. Recrystallisation of fraction II from ethyl acetate/-petroleum ether yields 1-(4-methylaminophenyl)-3-methyl-3-azabicyclo[3.1.0]hexane-2,4-dione in the form of white crystals with m.p. 128°-129°.

Example 27

1-(4-Acetylamino-phenyl)-3-allyl-3-azabicyclo[3.1.0]-
hexane-2,4-dione

1.2 g of 1-(4-acetylamino-phenyl)-3-azabicyclo[3.1.0]-hexane-2,4-dione are dissolved in 25 ml of dimethyl-formamide and to this solution are added 180 mg of sodium hydride under nitrogen. The mixture is stirred for 1 hour at room temperature. The clear, pale yellow solution is cooled in an ice-water bath and then a solution of 0.65 ml of allyl bromide in 5 ml of dimethyl-formamide is added dropwise. The reaction mixture is stirred overnight and then the solvent is stripped off. The residue is partitioned twice between ethyl acetate and water. The organic phases are dried over magnesium sulfate, filtered and concentrated by evaporation, and the residue is crystallised from ethyl acetate/ether/-petroleum ether. The title compound is obtained in the form of white crystals with m.p. 113°-116° and an R_f value of 0.33 on thin-layer silica gel plates in the system methylene chloride/methanol (10:1).

Example 28

1-(4-Amino-phenyl)-3-allyl-3-azabicyclo[3.1.0]hexane-2,4-dione

A mixture of 2.2 g of 1-(4-acetylamino-phenyl)-3-allyl-3-azabicyclo[3.1.0]hexane-2,4-dione, 8 ml of water and 8 ml of concentrated hydrochloric acid is stirred for 3 hours at 100°. The mixture is diluted with a small amount of water, cooled in an ice-water bath, rendered alkaline with 30% sodium hydroxide solution, and extracted twice with ethyl acetate. The organic phases are washed repeatedly with water and once with a concentrated aqueous solution of sodium chloride, dried over magnesium sulfate and filtered. The filtrate is concentrated by evaporation and the residue is crystallised

from ethyl acetate/petroleum ether. The title compound is obtained in the form of pale beige crystals with m.p. 104°-106° and an R_f value of 0.57 on thin-layer silica gel plates in the system methylene chloride/-methanol (10:1).

Example 29

1-(4-Aminophenyl)-3-propargyl-3-azabicyclo[3.1.0]hexane-2,4-dione

A mixture of 0.54 g of 1-(4-nitrophenyl)-3-propargyl-3-azabicyclo[3.1.0]hexane-2,4-dione and 1.5 g of tin powder in 4 ml of water and 4 ml of concentrated hydrochloric acid is stirred for 1 hour at 100°. The reaction mixture is cooled to room temperature and then diluted with 20 ml of water, filtered, and rendered alkaline by the addition of sodium hydroxide solution. The reaction mixture is extracted with ethyl acetate and the organic phase is washed with a dilute aqueous solution of sodium chloride until neutral, dried over magnesium sulfate and concentrated by evaporation. The residue is recrystallised from ethyl acetate/petroleum ether, affording the title compound with m.p. 106°-109° and an R_f value of 0.12 on thin-layer silica gel plates in the system hexane/ethyl acetate (1:1).

The starting material used is synthesised analogously to Example 3 starting from 4.6 g of 1-(4-nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione, 0.72 g of sodium hydride (pract. Fluka) and 1.9 ml of propargyl bromide in 50 ml of N,N-dimethylformamide. It has a melting point of 163°-165° after recrystallisation from ethyl acetate/petroleum ether and has an R_f value of 0.33 on thin-layer silica gel plates in the system hexane/ethyl acetate (1:1).

Example 30

1-(4-Aminophenyl)-3-n-decyl-3-azabicyclo[3.1.0]hexane-2,4-dione

Analogously to Example 3, 6.0 g of 3-n-decyl-1-(4-nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione are dissolved in 120 ml of ethanol and the solution is hydrogenated in the presence of 0.3 g of 5% palladium-on-carbon and worked up, affording the title compound which melts at 92°-94° after recrystallisation from ethyl acetate.

The starting material used is synthesised analogously to Example 3, starting from 4.6 g of 1-(4-nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione, 0.72 g of sodium hydride (pract. Fluka) and 5.3 ml of 1-decyl bromide; yellow oil with Rf value 0.50 on thin-layer silica gel plates in the system hexane/ethyl acetate (1:1).

Example 31

a) 1S-5R-1-(4-Aminophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione

Analogously to Example 1, a solution of 1.3 g of 1S-5R-1-(4-nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione in 70 ml of ethanol is hydrogenated in the presence of 0.1 g of 5% palladium-on-carbon and worked up. Recrystallisation from ethanol affords the title compound with a melting point of 203° and $[\alpha]_D^{20} = -66^\circ \pm 1^\circ$ (methanol, c = 0.634).

Preparation of the starting material:

b) 1S-5R-1-(4-Nitrophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione

1S-2R-1-(4-nitrophenyl)-1,2-cyclopropanedicarboxylic acid ($[\alpha]_D^{20} = -216^\circ \pm 1^\circ$ (methanol, c = 0.966)) is prepared by nitrating 2.75 g of 1S-2R-1-phenyl-1,2-cyclopropane-

dicarboxylic acid ($[\alpha]_D^{20} = -193^\circ \pm 1^\circ$ (methanol, $c = 1.09$)) with 3.45 ml of concentrated sulfuric acid and 2 ml of nitric acid. This product is reacted in boiling xylene, in the presence of 1.45 g of urea, to give the title compound ($[\alpha]_D^{20} = -82^\circ \pm 1^\circ$ (methanol, $c = 0.967$)).

Example 32

(-)-1S-5R-1-(4-Aminophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione and (+)-1R-5S-1-(4-aminophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione

A glass column is charged with 380 g of triacetyl cellulose [prepared e.g. by the method described in Chromatographie 6, 277 (1973)] in a 95:5 mixture of ethanol/water. 400 mg of 1-(4-aminophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione are added to this column. Chromatography is carried out with a 95:5 mixture of ethanol/water under a pressure of 5-6 bar and with a flow rate of 350 ml/h. First the (-) enantiomer, which is identical with the title compound of Example 31a), is eluted, followed by the (+) enantiomer. The products are isolated separately, filtered over silica gel to remove dissolved triacetyl cellulose, and recrystallised from ethanol. The (-) enantiomer with m.p. 202° - 204° and $[\alpha]_D^{20} = -65^\circ \pm 1^\circ$ (methanol, $c = 0.5$) and the (+) enantiomer with m.p. 198° - 201° and $[\alpha]_D^{20} = -65^\circ \pm 1^\circ$ (methanol, $c = 0.4$) are obtained.

Example 33: Shellac-coated tablets containing 300 mg of 1-(4-aminophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione can be prepared as follows:

Composition for 10,000 tablets

1-(4-aminophenyl)-3-azabicyclo[3.1.0]hexane- 2,4-dione	3000.0 g
corn starch	680.0 g
colloidal silica gel	200.0 g
magnesium stearate	20.0 g
stearic acid	50.0 g
sodium carboxymethyl starch	250.0 g
water	q.s.

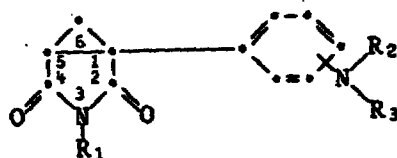
A mixture of the 1-(4-aminophenyl)-3-azabicyclo[3.1.0]-hexane-2,4-dione, 50 g of corn starch and the colloidal silica is worked to a moist composition with a starch paste consisting of 250 g of corn starch and 2.2 kg of demineralised water. This composition is forced through a sieve having a mesh width of 3 mm and dried for 30 minutes at 45° in a fluidised bed drier. The dry granulate is pressed through a sieve having a mesh width of 1 mm, mixed with a previously sieved mixture (1 mm sieve) of 330 g of corn starch, the magnesium stearate, the stearic acid and the sodium carboxymethyl starch, and compressed to form slightly curved tablets.

The tablets are put into a coating pan with a diameter of 45 cm and coated by being sprayed uniformly for 30 minutes with a solution of 20 g of shellac and 40 g of hydroxypropylmethyl cellulose (low viscosity) in 110 g of methanol and 1350 g of methylene chloride. The tablets are dried by simultaneously blowing in warm air at 60°.

Instead of using the active ingredient indicated in this Example, it is also possible to use the same amount of a different active ingredient from the preceding Examples.

Patent Claims (for the Contracting States FR, IT, LU, NL, SE, GB and CH/LI)

1. Compounds of the formula



(I),

wherein R₁ is hydrogen, R₂ is hydrogen, sulfo, C₁-C₇-alkanoyl or C₁-C₇-alkanesulfonyl and R₃ is hydrogen, or R₁ is C₁-C₁₂-alkyl, C₂-C₁₂-alkenyl, C₂-C₇-alkynyl, C₃-C₁₀-cycloalkyl, C₃-C₁₀-cycloalkenyl, C₃-C₆-cycloalkyl-C₁-C₄-alkyl, C₃-C₆-cycloalkyl-C₂-C₄-alkenyl or C₃-C₆-cycloalkenyl-C₁-C₄-alkyl, R₂ is hydrogen, C₁-C₇-alkyl, sulfo, C₁-C₇-alkanoyl or C₁-C₇-alkanesulfonyl and R₃ is hydrogen or C₁-C₇-alkyl, and salts thereof.

2. Compounds according to claim 1 of the formula I, wherein R₁ is hydrogen or C₁-C₇-alkyl, R₂ is hydrogen, C₁-C₇-alkyl, sulfo, C₁-C₇-alkanoyl or C₁-C₇-alkanesulfonyl, and R₃ is hydrogen or C₁-C₇-alkyl, and salts thereof.

3. Compounds according to claim 1 of the formula I, wherein R₁, R₂ and R₃ are hydrogen or wherein R₁ is C₁-C₁₂-alkyl, C₂-C₇-alkenyl, C₂-C₇-alkynyl, C₃-C₁₀-cycloalkyl or C₃-C₆-cycloalkyl-C₁-C₄-alkyl, R₂ is hydrogen or C₁-C₇-alkyl, and R₃ is hydrogen or C₁-C₇-alkyl, and salts thereof.

4. Compounds according to claim 2 of the formula I, wherein R₁ is hydrogen or C₁-C₇-alkyl and R₂ and R₃ are hydrogen, and salts thereof.

5. Compounds according to claim 1 of the formula I,



wherein R_1 is hydrogen, C_1 - C_7 -alkyl, C_2 - C_4 -alkenyl, C_2 - C_4 -alkynyl or C_3 - C_6 -cycloalkyl- C_1 - C_4 -alkyl, the group $-N(R_2)(R_3)$ is in the 4-position of the phenyl radical and R_2 and R_3 are hydrogen, and pharmaceutically acceptable salts thereof.

6. Compounds according to claim 2 of the formula I, wherein R_1 is hydrogen or C_1 - C_7 -alkyl, the group $-N(R_2)(R_3)$ is in the 4-position of the phenyl radical and R_2 and R_3 are hydrogen, and pharmaceutically acceptable salts thereof.

7. 1-(4-Aminophenyl)-3-methyl-3-azabicyclo[3.1.0]-hexane-2,4-dione, according to claim 1.

8. 1-(4-Aminophenyl)-3-n-propyl-3-azabicyclo[3.1.0]-hexane-2,4-dione, according to claim 1.

9. 1-(4-Aminophenyl)-3-isobutyl-3-azabicyclo[3.1.0]-hexane-2,4-dione, according to claim 1.

10. 1-(4-Aminophenyl)-3-n-butyl-3-azabicyclo[3.1.0]-hexane-2,4-dione, according to claim 1.

11. 1-(4-Aminophenyl)-3-n-pentyl-3-azabicyclo[3.1.0]-hexane-2,4-dione, according to claim 1.

12. 1-(4-Aminophenyl)-3-neopentyl-3-azabicyclo[3.1.0]-hexane-2,4-dione, according to claim 1.

13. 1-(4-Aminophenyl)-3-n-heptyl-3-azabicyclo[3.1.0]-hexane-2,4-dione, according to claim 1.

14. 1-(4-Aminophenyl)-3-cyclohexylmethyl-3-azabicyclo[3.1.0]hexane-2,4-dione, according to claim 1.



15. Pharmaceutical compositions which contain compounds of the formula I, wherein R_1 is hydrogen, C_1 - C_{12} -alkyl, C_2 - C_{12} -alkenyl, C_2 - C_7 -alkynyl, C_3 - C_{10} -cycloalkyl, C_3 - C_{10} -cycloalkenyl, C_3 - C_6 -cycloalkyl- C_1 - C_4 -alkyl, C_3 - C_6 -cycloalkyl- C_2 - C_4 -alkenyl or C_3 - C_6 -cycloalkenyl- C_1 - C_4 -alkyl, R_2 is hydrogen, C_1 - C_7 -alkyl, sulfo, C_1 - C_7 -alkanoyl or C_1 - C_7 -alkanesulfonyl, and R_3 is hydrogen or C_1 - C_7 -alkyl, or salts thereof, together with a pharmaceutically acceptable carrier.

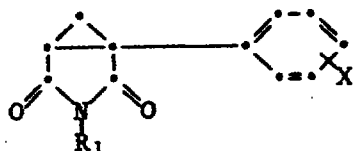
16. Pharmaceutical compositions according to claim 15 which contain 1-(4-aminophenyl)-3-azabicyclo[3.1.0]-hexane-2,4-dione.

17. Compounds of the formula I, wherein R_1 , R_2 and R_3 are as defined in claim 15, or salts thereof, for use in a therapeutic method of treating the human or animal body.

18. The use of compounds of the formula I, wherein R_1 , R_2 and R_3 are as defined in claim 15, or salts thereof, for the preparation of a carcinostatic medicament.

19. A process for the preparation of compounds of the formula I according to claim 1, and of salts thereof, which process comprises

a) converting X into the $-N(R_2)(R_3)$ group in a compound of the formula



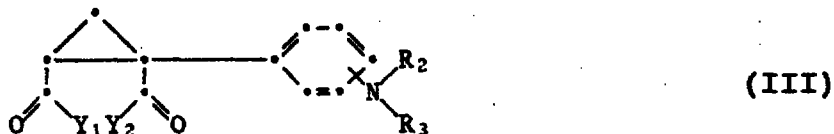
(II)

wherein R_1 is as defined for formula I and X is a group which can be converted into the $-N(R_2)(R_3)$ group, or a



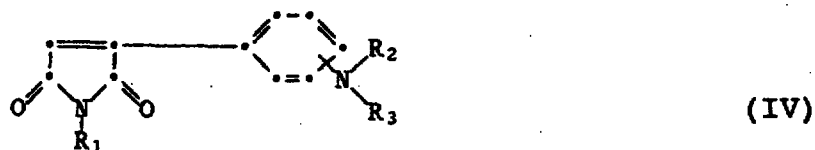
salt thereof, or

b) cyclising a compound of the formula



wherein R_2 and R_3 are as defined for formula I and Y_1 and Y_2 are leaving groups, or a salt thereof, by reaction with a compound which introduces the group $>N-R_1$, or

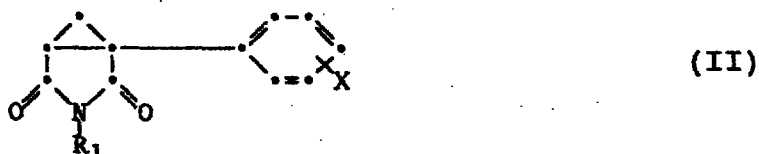
c) by addition of $-CH_2-$ (methylene) to the double bond of the maleimide in a compound of the formula



wherein R_1 , R_2 and R_3 are as defined for formula I, or a salt thereof,

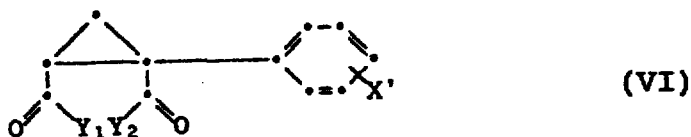
and, if desired, converting a compound of the formula I obtained in accordance with the invention into another compound of the formula I according to the definition, and/or converting a resultant salt into the free compound or into another salt, and/or converting a resultant free compound into a salt, and/or separating a resultant mixture of isomers into the individual isomers.

20. Compounds of the formula



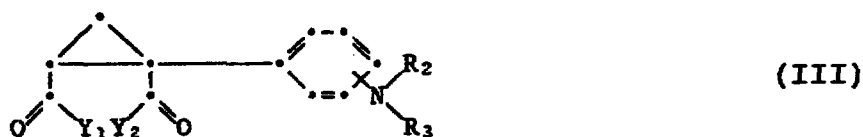
wherein R_1 is hydrogen, C_1 - C_{12} -alkyl, C_2 - C_{12} -alkenyl, C_2 - C_7 -alkynyl, C_3 - C_{10} -cycloalkyl, C_3 - C_{10} -cycloalkenyl, C_3 - C_6 -cycloalkyl- C_1 - C_4 -alkyl, C_3 - C_6 -cycloalkyl- C_2 - C_4 -alkenyl or C_3 - C_6 -cycloalkenyl- C_1 - C_4 -alkyl and X is nitroso, hydroxylamino, carbamoyl, azidocarbonyl or protected amino, and salts thereof.

21. A process for the preparation of compounds of the formula II according to claim 20, and of salts thereof, which process comprises cyclising a compound of the formula



wherein Y_1 and Y_2 are leaving groups and X' is nitroso, hydroxylamino, carboxyl or protected amino, or a salt thereof, by reaction with a compound which introduces the group $-NH-R_1$ and, in a resultant compound, converting the carboxyl group X' into carbamoyl or azidocarbonyl, and/or, if desired, converting a compound of the formula II obtained in accordance with the invention into another compound of the formula II according to the definition, and/or converting a resultant salt into the free compound or into another salt, and/or converting a resultant free compound into a salt, and/or separating a resultant mixture of isomers into the individual isomers.

22. Compounds of the formula

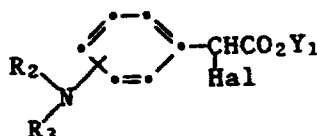


wherein R_2 is hydrogen, C_1 - C_7 -alkyl, sulfo, C_1 - C_7 -



alkanoyl or C₁-C₇-alkanesulfonyl, R₃ is hydrogen or C₁-C₇-alkyl, and Y₁ and Y₂ are leaving groups, and salts of such compounds containing salt-forming groups.

23. A process for the preparation of compounds of the formula III according to claim 22, and of salts thereof, which process comprises reacting a compound of the formula



(VII),

wherein R₂, R₃ and Y₁ are as defined in claim 22 and Hal is chlorine or bromine, with an acrylic acid derivative of the formula



(VIII)

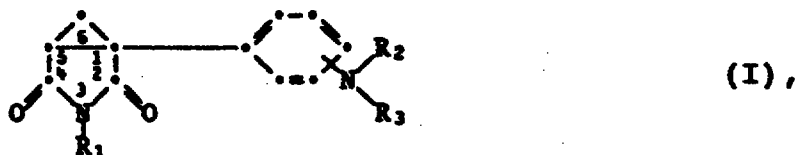
wherein Y₂ is as defined in claim 22, and, if desired, converting a resultant salt into the free compound or into another salt, and/or converting a resultant free compound into a salt, and/or separating a resultant mixture of isomers into the individual isomers.

24. A process for the preparation of pharmaceutical compositions which contain compounds of the formula I, wherein R₁, R₂ and R₃ are as defined in claim 15, or salts thereof, which process comprises preparing compounds of the formula I and salts thereof by the process as claimed in claim 19, and mixing them with a pharmaceutical carrier.



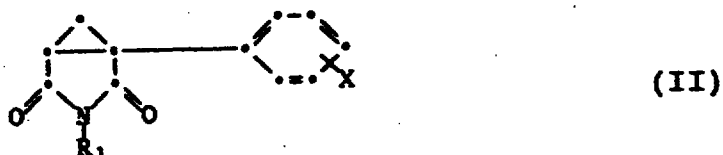
Patent Claims (for the Contracting State AT)

1. A process for the preparation of compounds of the formula



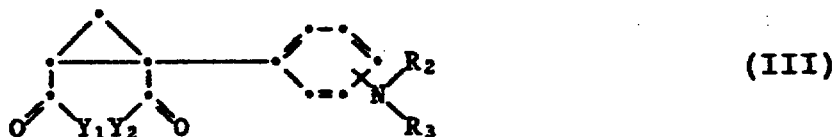
wherein R_1 is C_1 - C_{12} -alkyl, C_2 - C_{12} -alkenyl, C_2 - C_7 -alkynyl, C_3 - C_{10} -cycloalkyl, C_3 - C_{10} -cycloalkenyl, C_3 - C_6 -cycloalkyl- C_1 - C_4 -alkyl, C_3 - C_6 -cycloalkyl- C_2 - C_4 -alkenyl or C_3 - C_6 -cycloalkenyl- C_1 - C_4 -alkyl, R_2 is hydrogen, C_1 - C_7 -alkyl, sulfo, C_1 - C_7 -alkanoyl or C_1 - C_7 -alkanesulfonyl and R_3 is hydrogen or C_1 - C_7 -alkyl, and salts thereof, which process comprises

- a) converting X into the $-N(R_2)(R_3)$ group in a compound of the formula



wherein R_1 is as defined for formula I and X is a group which can be converted into the $-N(R_2)(R_3)$ group, or in a salt thereof, or

- b) cyclising a compound of the formula



wherein R_2 and R_3 are as defined for formula I and Y_1 and Y_2 are leaving groups, or a salt thereof, by reaction



with a compound which introduces the group $>N-R_1$, or

c) by addition of $-CH_2-$ (methylene) to the double bond of the maleimide in a compound of the formula



wherein R_1 , R_2 and R_3 are as defined for formula I, or a salt thereof,

and, if desired, converting a compound of the formula I obtained in accordance with the invention into another compound of the formula I according to the definition, and/or converting a resultant salt into the free compound or into another salt, and/or converting a resultant free compound into a salt, and/or separating a resultant mixture of isomers into the individual isomers.

2. A process according to claim 1 for the preparation of compounds of the formula I, wherein R_1 is C_1 - C_7 -alkyl, R_2 is hydrogen, sulfo, C_1 - C_7 -alkanoyl or C_1 - C_7 -alkane-sulfonyl, and R_3 is hydrogen or C_1 - C_7 -alkyl, and salts thereof.

3. A process according to claim 1 for the preparation of compounds of the formula I, wherein R_1 is C_1 - C_{12} -alkyl, C_2 - C_7 -alkenyl, C_2 - C_7 -alkynyl, C_3 - C_{10} -cycloalkyl or C_3 - C_6 -cycloalkyl- C_1 - C_4 -alkyl, R_2 is hydrogen or C_1 - C_7 -alkyl, and R_3 is hydrogen or C_1 - C_7 -alkyl, and salts thereof.

4. A process according to claim 1 for the preparation of compounds of the formula I, wherein R_1 is C_1 - C_7 -alkyl



and R_2 and R_3 are hydrogen, and salts thereof.

5. A process according to claim 1 for the preparation of compounds of the formula I, wherein R_1 is C_1 - C_7 -alkyl, C_2 - C_4 -alkenyl, C_2 - C_4 -alkynyl or C_3 - C_6 -cycloalkyl- C_1 - C_4 -alkyl, the group $-N(R_2)(R_3)$ is in the 4-position of the phenyl radical and R_2 and R_3 are hydrogen, and pharmaceutically acceptable salts thereof.

6. A process according to claim 1 for the preparation of compounds of the formula I, wherein R_1 is C_1 - C_7 -alkyl, the group $-N(R_2)(R_3)$ is in the 4-position of the phenyl radical and R_2 and R_3 are hydrogen, and pharmaceutically acceptable salts thereof.

7. A process according to claim 1 for the preparation of 1-(4-aminophenyl)-3-methyl-3-azabicyclo[3.1.0]hexane-2,4-dione.

8. A process according to claim 1 for the preparation of 1-(4-aminophenyl)-3-n-propyl-3-azabicyclo[3.1.0]hexane-2,4-dione.

9. A process according to claim 1 for the preparation of 1-(4-aminophenyl)-3-isobutyl-3-azabicyclo[3.1.0]hexane-2,4-dione.

10. A process according to claim 1 for the preparation of 1-(4-aminophenyl)-3-n-butyl-3-azabicyclo[3.1.0]hexane-2,4-dione.

11. A process according to claim 1 for the preparation of 1-(4-aminophenyl)-3-n-pentyl-3-azabicyclo[3.1.0]hexane-2,4-dione.

12. A process according to claim 1 for the preparation

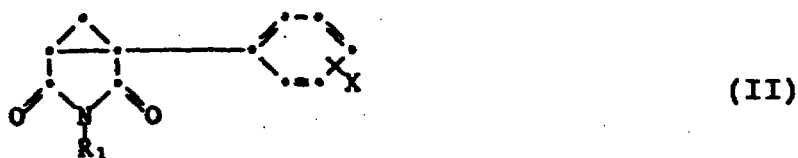


of 1-(4-aminophenyl)-3-neopentyl-3-azabicyclo[3.1.0]-hexane-2,4-dione.

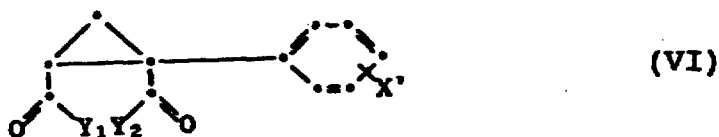
13. A process according to claim 1 for the preparation of 1-(4-aminophenyl)-3-n-heptyl-3-azabicyclo[3.1.0]-hexane-2,4-dione.

14. A process according to claim 1 for the preparation of 1-(4-aminophenyl)-3-cyclohexylmethyl-3-azabicyclo[3.1.0]hexane-2,4-dione.

15. A process for the preparation of compounds of the formula



wherein R_1 is C_1 - C_{12} -alkyl, C_2 - C_{12} -alkenyl, C_2 - C_7 -alkynyl, C_3 - C_{10} -cycloalkyl, C_3 - C_{10} -cycloalkenyl, C_3 - C_6 -cycloalkyl- C_1 - C_4 -alkyl, C_3 - C_6 -cycloalkyl- C_2 - C_4 -alkenyl or C_3 - C_6 -cycloalkenyl- C_1 - C_4 -alkyl and X is nitroso, hydroxylamino, carbamoyl, azidocarbonyl or protected amino, and salts thereof, which process comprises cyclising a compound of the formula

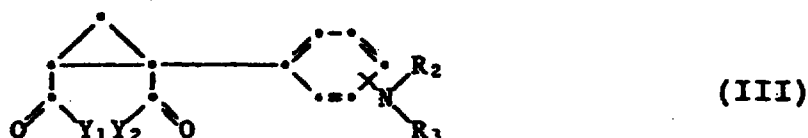


wherein Y_1 and Y_2 are leaving groups and X' is nitroso, hydroxylamino, carboxyl or protected amino, or a salt thereof, by reaction with a compound which introduces the group $-NH-R_1$ and, in a resultant compound, converting the carboxyl group X' into carbamoyl or azidocarbonyl, and/or, if desired, converting a compound of the formula

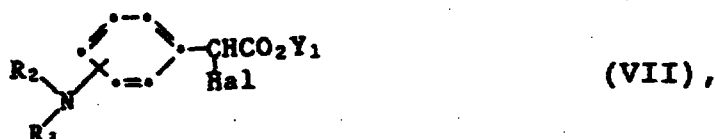


II obtained in accordance with the invention into another compound of the formula II according to the definition, and/or converting a resultant salt into the free compound or into another salt, and/or converting a resultant free compound into a salt, and/or separating a resultant mixture of isomers into the individual isomers.

16. A process for the preparation of compounds of the formula



wherein R_2 is hydrogen, C_1 - C_7 -alkyl, sulfo, C_1 - C_7 -alkanoyl or C_1 - C_7 -alkanesulfonyl, R_3 is hydrogen or C_1 - C_7 -alkyl, and Y_1 and Y_2 are leaving groups, and salts of such compounds containing salt-forming groups, which process comprises reacting a compound of the formula



wherein R_2 , R_3 and Y_1 are as defined for formula III and Hal is chlorine or bromine, with an acrylic acid derivative of the formula



wherein Y_2 is as defined for formula III, and, if desired, converting a resultant salt into the free compound or into another salt, and/or converting a resultant free compound into a salt, and/or separating a resultant mixture of isomers into the individual isomers.



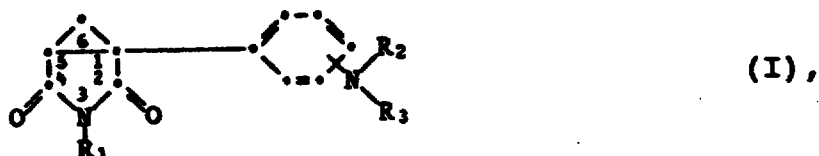
17. A process for the preparation of pharmaceutical compositions which contain compounds of the formula I, wherein R_1 is hydrogen, C_1 - C_{12} -alkyl, C_2 - C_{12} -alkenyl, C_2 - C_7 -alkynyl, C_3 - C_{10} -cycloalkyl, C_3 - C_{10} -cycloalkenyl, C_3 - C_6 -cycloalkyl- C_1 - C_4 -alkyl, C_3 - C_6 -cycloalkyl- C_2 - C_4 -alkenyl or C_3 - C_6 -cycloalkenyl- C_1 - C_4 -alkyl, R_2 is hydrogen, C_1 - C_7 -alkyl, sulfo, C_1 - C_7 -alkanoyl or C_1 - C_7 -alkanesulfonyl and R_3 is hydrogen or C_1 - C_7 -alkyl, or salts thereof, which process comprises preparing compounds of the formula I and salts thereof by the process as claimed in claim 1, and mixing them with a pharmaceutical carrier.

18. A process according to claim 17 for the preparation of pharmaceutical compositions which contain 1-(4-aminophenyl)-3-azabicyclo[3.1.0]hexane-2,4-dione.



Patent Claims (for the Contracting States BE and DE)

1. Compounds of the formula



wherein R_1 is C_1 - C_{12} -alkyl, C_2 - C_{12} -alkenyl, C_2 - C_7 -alkynyl, C_3 - C_{10} -cycloalkyl, C_3 - C_{10} -cycloalkenyl, C_3 - C_6 -cycloalkyl- C_1 - C_4 -alkyl, C_3 - C_6 -cycloalkyl- C_2 - C_4 -alkenyl or C_3 - C_6 -cycloalkenyl- C_1 - C_4 -alkyl, R_2 is hydrogen, C_1 - C_7 -alkyl, sulfo, C_1 - C_7 -alkanoyl or C_1 - C_7 -alkanesulfonyl and R_3 is hydrogen or C_1 - C_7 -alkyl, and salts thereof.

2. Compounds according to claim 1 of the formula I, wherein R_1 is C_1 - C_7 -alkyl, R_2 is hydrogen, C_1 - C_7 -alkyl, sulfo, C_1 - C_7 -alkanoyl or C_1 - C_7 -alkanesulfonyl, and R_3 is hydrogen or C_1 - C_7 -alkyl, and salts thereof.

3. Compounds according to claim 1 of the formula I, wherein R_1 is C_1 - C_{12} -alkyl, C_2 - C_7 -alkenyl, C_2 - C_7 -alkynyl, C_3 - C_{10} -cycloalkyl or C_3 - C_6 -cycloalkyl- C_1 - C_4 -alkyl, R_2 is hydrogen or C_1 - C_7 -alkyl, and R_3 is hydrogen or C_1 - C_7 -alkyl, and salts thereof.

4. Compounds according to claim 2 of the formula I, wherein R_1 is C_1 - C_7 -alkyl and R_2 and R_3 are hydrogen, and salts thereof.

5. Compounds according to claim 1 of the formula I, wherein R_1 is C_1 - C_7 -alkyl, C_2 - C_4 -alkenyl, C_2 - C_4 -alkynyl or C_3 - C_6 -cycloalkyl- C_1 - C_4 -alkyl, the group $-N(R_2)(R_3)$ is in the 4-position of the phenyl radical and R_2 and R_3 are hydrogen, and pharmaceutically acceptable salts thereof.



6. Compounds according to claim 2 of the formula I, wherein R_1 is C_1 - C_7 -alkyl, the group $-N(R_2)(R_3)$ is in the 4-position of the phenyl radical and R_2 and R_3 are hydrogen, and pharmaceutically acceptable salts thereof.
7. 1-(4-Aminophenyl)-3-methyl-3-azabicyclo[3.1.0]-hexane-2,4-dione, according to claim 1.
8. 1-(4-Aminophenyl)-3-n-propyl-3-azabicyclo[3.1.0]-hexane-2,4-dione, according to claim 1.
9. 1-(4-Aminophenyl)-3-isobutyl-3-azabicyclo[3.1.0]-hexane-2,4-dione, according to claim 1.
10. 1-(4-Aminophenyl)-3-n-butyl-3-azabicyclo[3.1.0]-hexane-2,4-dione, according to claim 1.
11. 1-(4-Aminophenyl)-3-n-pentyl-3-azabicyclo[3.1.0]-hexane-2,4-dione, according to claim 1.
12. 1-(4-Aminophenyl)-3-neopentyl-3-azabicyclo[3.1.0]-hexane-2,4-dione, according to claim 1.
13. 1-(4-Aminophenyl)-3-n-heptyl-3-azabicyclo[3.1.0]-hexane-2,4-dione, according to claim 1.
14. 1-(4-Aminophenyl)-3-cyclohexylmethyl-3-azabicyclo[3.1.0]hexane-2,4-dione, according to claim 1.
15. Pharmaceutical compositions which contain compounds of the formula I, wherein R_1 is hydrogen, C_1 - C_{12} -alkyl, C_2 - C_{12} -alkenyl, C_2 - C_7 -alkynyl, C_3 - C_{10} -cycloalkyl, C_3 - C_{10} -cycloalkenyl, C_3 - C_6 -cycloalkyl- C_1 - C_4 -alkyl, C_3 - C_6 -cycloalkyl- C_2 - C_4 -alkenyl or C_3 - C_6 -cycloalkenyl- C_1 - C_4 -alkyl, R_2 is hydrogen, C_1 - C_7 -alkyl, sulfo, C_1 - C_7 -alkanoyl or C_1 - C_7 -alkanesulfonyl, and R_3 is hydrogen or C_1 - C_7 -



alkyl, or salts thereof, together with a pharmaceutically acceptable carrier.

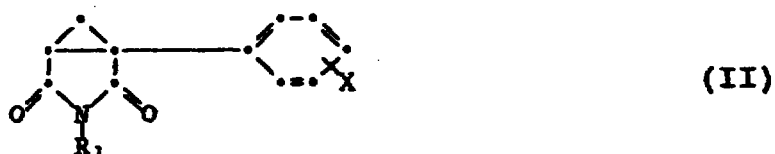
16. Pharmaceutical compositions according to claim 15 which contain 1-(4-aminophenyl)-3-azabicyclo[3.1.0]-hexane-2,4-dione.

17. Compounds of the formula I, wherein R_1 , R_2 and R_3 are as defined in claim 15, or salts thereof, for use in a therapeutic method of treating the human or animal body.

18. The use of compounds of the formula I, wherein R_1 , R_2 and R_3 are as defined in claim 15, or salts thereof, for the preparation of a carcinostatic medicament.

19. A process for the preparation of compounds of the formula I according to claim 1, and of salts thereof, which process comprises

a) converting X into the $-N(R_2)(R_3)$ group in a compound of the formula



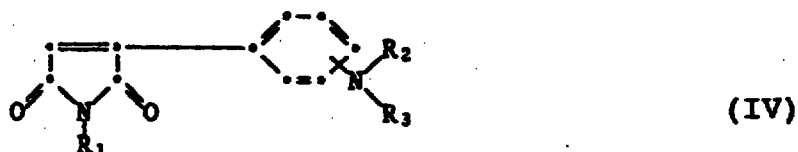
wherein R_1 is as defined for formula I and X is a group which can be converted into the $-N(R_2)(R_3)$ group, or a salt thereof, or

b) cyclising a compound of the formula



wherein R_2 and R_3 are as defined for formula I and Y_1 and Y_2 are leaving groups, or a salt thereof, by reaction with a compound which introduces the group $>N-R_1$, or

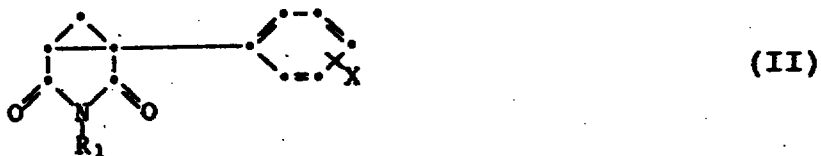
c) by addition of $-CH_2-$ (methylene) to the double bond of the maleimide in a compound of the formula



wherein R_1 , R_2 and R_3 are as defined for formula I, or a salt thereof,

and, if desired, converting a compound of the formula I obtained in accordance with the invention into another compound of the formula I according to the definition, and/or converting a resultant salt into the free compound or into another salt, and/or converting a resultant free compound into a salt, and/or separating a resultant mixture of isomers into the individual isomers.

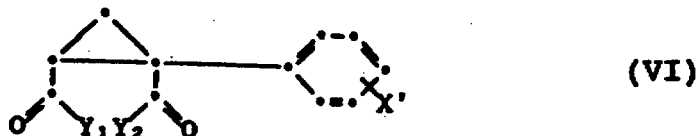
20. Compounds of the formula



wherein R_1 is C_1 - C_{12} -alkyl, C_2 - C_{12} -alkenyl, C_2 - C_7 -alkynyl, C_3 - C_{10} -cycloalkyl, C_3 - C_{10} -cycloalkenyl, C_3 - C_6 -cycloalkyl- C_1 - C_4 -alkyl, C_3 - C_6 -cycloalkyl- C_2 - C_4 -alkenyl or C_3 - C_6 -cycloalkenyl- C_1 - C_4 -alkyl and X is nitroso, hydroxylamino, carbamoyl, azidocarbonyl or protected amino, and salts thereof.

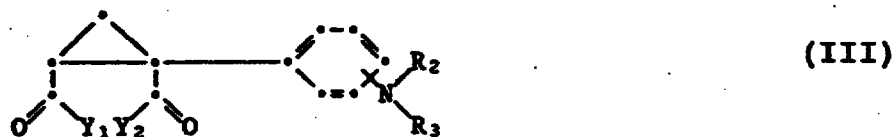


21. A process for the preparation of compounds of the formula II according to claim 20, and of salts thereof, which process comprises cyclising a compound of the formula



wherein Y_1 and Y_2 are leaving groups and X' is nitroso, hydroxylamino, carboxyl or protected amino, or a salt thereof, by reaction with a compound which introduces the group $-NH-R_1$ and, in a resultant compound, converting the carboxyl group X' into carbamoyl or azidocarbonyl, and/or, if desired, converting a compound of the formula II obtained in accordance with the invention into another compound of the formula II according to the definition, and/or converting a resultant salt into the free compound or into another salt, and/or converting a resultant free compound into a salt, and/or separating a resultant mixture of isomers into the individual isomers.

22. Compounds of the formula

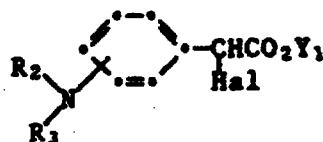


wherein R_2 is hydrogen, C_1 - C_7 -alkyl, sulfo, C_1 - C_7 -alkanoyl or C_1 - C_7 -alkanesulfonyl, R_3 is hydrogen or C_1 - C_7 -alkyl, and Y_1 and Y_2 are leaving groups, and salts of such compounds containing salt-forming groups.

23. A process for the preparation of compounds of the formula III according to claim 22, and of salts thereof, which process comprises reacting a compound of the



formula



(VII),

wherein R_2 , R_3 and Y_1 are as defined in claim 22 and Hal is chlorine or bromine, with an acrylic acid derivative of the formula



(VIII)

wherein Y_2 is as defined in claim 22, and, if desired, converting a resultant salt into the free compound or into another salt, and/or converting a resultant free compound into a salt, and/or separating a resultant mixture of isomers into the individual isomers.

24. A process for the preparation of pharmaceutical compositions which contain compounds of the formula I, wherein R_1 , R_2 and R_3 are as defined in claim 15, or salts thereof, which process comprises preparing compounds of the formula I and salts thereof by the process as claimed in claim 19, and mixing them with a pharmaceutical carrier.

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