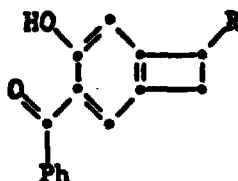


Description

The invention relates to novel substituted benzophenones of the formula



(I)

in which Ph is unsubstituted or substituted phenyl and R is free, esterified or amidated carboxyl, and their salts, to processes for their preparation, to the use of compounds of the formula I and their salts as active ingredients in or for the preparation of pharmaceutical preparations and to pharmaceutical preparations of this type.

Substituted phenyl is, for example, phenyl which is substituted, in particular mono- or disubstituted, by lower alkyl, lower alkoxy, lower alkylthio, lower alkanoyloxy, halogen, trifluoromethyl, carboxyl, lower alkoxycarbonyl, cyano and/or nitro.

Esterified carboxyl is, for example, carboxyl esterified with a lower aliphatic alcohol, such as lower alkoxycarbonyl.

Amidated carboxyl has as the amino group, for example, unsubstituted amino or amino which is mono- or disubstituted by lower aliphatic radicals, and is, for example, carbamyl, N-mono (sic) or N,N-di-lower alkyl-carbamyl or N,N-lower alkylene or N,N-(aza)-, N,N-(oxa)- or N,N-(thia)-lower alkylene-carbamyl.

In the above and the following text, lower organic radicals and compounds are preferably to be understood as meaning those which have not more than 7, in particular not more than 4 carbon atoms (C atoms).

Lower alkyl is, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, secondary butyl or tertiary butyl, but can also be a pentyl, hexyl or heptyl radical.

Lower alkoxy is, for example, methoxy, ethoxy, propyloxy, isopropyloxy, butyloxy, isobutyloxy, secondary butyloxy or tertiary butyloxy, but can also be a pentyl, hexyl or heptyloxy radical.

Lower alkylthio is, for example, methylthio, ethylthio, propylthio, butylthio, isobutylthio, secondary butylthio or tertiary butylthio, but can also be a pentylthio, hexylthio or heptylthio group.

Lower alkanoyloxy is, for example, acetoxy, propionyloxy, butyryloxy or isobutyryloxy, and furthermore valeroyloxy, pivaloyloxy or caproyloxy, and halogen is, for example, halogen of atomic number of not more than 35, such as fluorine or chlorine and furthermore bromine.

Lower alkoxycarbonyl is, for example, methoxy-, ethoxy-, propyloxy-, isopropyloxy-, butyloxy-, isobutyloxy-, secondary butyloxy- or tertiary butyloxycarbonyl, but can also be a pentyloxy-, hexyloxy- or heptyloxycarbonyl radical.

N-Mono- or N,N-di-lower alkyl-carbamyl is, for example, N-methyl-, N,N-dimethyl-, N-ethyl-, N,N-diethyl-, N-propyl-, N-isopropyl-, N-butyl- or N-isobutylcarbamyl.

N,N-lower alkylene- or N,N-(aza)-, N,N-(oxa)- or N,N-(thia)-lower alkylene-carbamyl has, for example, from 3 to not more than 8, in particular 5 or 6, ring members and is, for example, pyrrolidino-, piperidino-, piperazino- or N'-lower alkyl-, such as N'-methyl-piperazino-, morpholino- or thiomorpholinocarbonyl.

Salts of compounds of the formula I are in particular their salts with pharmaceutically acceptable bases, such as non-toxic metal salts derived from metals or (sic) groups Ia, Ib, IIa and IIb, for example alkali metal salts, in particular sodium salts or potassium salts, alkaline earth metal salts, in particular calcium salts or magnesium salts, copper salts, aluminium salts or zinc salts, and also ammonium salts with ammonia or organic amines, such as aliphatic amines, which may be

C-hydroxyl substituted, in particular mono-, di- or tri-lower alkyl- amines, for example methyl-, ethyl-, dimethyl- or diethylamine, mono-, di- or tri(hydroxy-lower alkyl)-amines, such as ethanol-, diethanol- or triethanolamine, tris(hydroxymethyl)-aminomethane or 2-hydroxy-tertiary butyl-amine, or N-(hydroxy-lower alkyl)-N,N-di-lower alkyl-amines or N-(polyhydroxy-lower alkyl)-N-lower alkyl-amines, such as 2-(dimethylamino)-ethanol or D-glucamine.

The novel compounds of the formula I show valuable pharmacological properties. In particular, they show a pronounced antinociceptive activity and an excellent inhibitory action on prostaglandin synthesis, and also a pronounced antiinflammatory action. Thus, they prove active in vivo in the phenyl-p-benzoquinone-induced writhing syndrome in mice according to J. Pharmacol. exp. Therap. 125, 237 (1959), and also in the acetic acid-induced writhing syndrome in mice at peroral doses from about 1.0 mg/kg, and equally in experimental carrageenan foot oedema and in adjuvant arthritis in rats, at peroral doses from 1 and from 0.1 mg/kg respectively. In vitro, they show a clear inhibitory action on prostaglandin synthesis from arachidonic acid in the experimental arrangement according to Prostaglandins 7, 123 (1974) in a concentration range from about 0.1 μ M/litre.

The compounds of the formula I and their pharmaceutically acceptable salts are accordingly outstandingly suitable as active ingredients of medicaments for the treatment of painful inflammatory disease, in particular rheumatic disorders, such as chronic arthritis.

The invention relates above all to compounds of the formula I in which Ph is unsubstituted phenyl or phenyl which is substituted by lower alkyl, lower alkoxy, lower alkylthio, lower alkanoyloxy, halogen, trifluoromethyl, carboxyl, lower alkoxycarbonyl, cyano and/or nitro and R is carboxyl, carboxyl esterified with a lower aliphatic alcohol, or carbamyl in which the amino group is unsubstituted amino or amino mono- or disubstituted by lower aliphatic radicals, and their salts, in particular pharmaceutically acceptable salts, with bases.

The invention relates especially to compounds of the formula I in which Ph is unsubstituted phenyl or phenyl which is mono- or disubstituted by lower alkyl, lower alkoxy, lower alkanoyloxy, halogen, trifluoromethyl, cyano and/or nitro and R is carboxyl, carboxyl esterified with a lower aliphatic alcohol, such as lower alkoxycarbonyl, or carbamyl in which the amino group is unsubstituted amino or amino mono- or disubstituted by lower aliphatic radicals, such as carbamyl, N-mono- or N,N-di-lower alkyl-carbamyl or N,N-lower alkylene- or N,N-(aza)lower alkylene-, N,N-(oxa)lower alkylene- or N,N-(thia)lower alkylene-carbamyl, and their salts, in particular pharmaceutically acceptable salts, with bases.

The invention relates in particular to compounds of the formula I in which Ph is unsubstituted phenyl or phenyl which is mono- or disubstituted by lower alkyl having not more than 4 C atoms, such as methyl, lower alkoxy having not more than 4 C atoms, such as methoxy, lower alkanoyloxy having not more than 4 C atoms, such as acetoxy, halogen of atomic number of not more than 35, such as fluorine or bromine, and/or trifluoromethyl and R is carboxyl, lower alkoxycarbonyl having not more than 5 C atoms, such as methoxy- or ethoxycarbonyl, or carbamyl or N-lower alkyl-carbamyl having not more than 5 C atoms, such as carbamyl or N-methylcarbamyl, and their salts, in particular pharmaceutically acceptable salts, with bases.

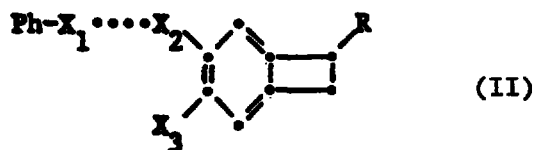
The invention likewise relates in particular to compounds of the formula I in which Ph is unsubstituted phenyl or phenyl which is mono- or disubstituted, in particular in the 2- and/or 4-position, by lower alkyl having not more than 4 C atoms, such as methyl, lower alkylthio having not more than 4 C atoms, such as methylthio, lower alkoxycarbonyl having not more than 4 C atoms in the lower alkoxy part, such as methoxycarbonyl, halogen of atomic number of not more than 35, such as fluorine, chlorine or bromine, and/or cyano and R is carboxyl or carbamyl, or also lower alkoxycarbonyl having not more than 4 C atoms in the lower alkoxy part, such as methoxycarbonyl, and their salts, in particular pharmaceutically acceptable salts, with bases.

The invention relates primarily to compounds of the formula I in which

Ph is phenyl which is monosubstituted, in particular in the 2-position, or disubstituted, in particular in the 2- and 4-position, by lower alkyl having not more than 4 C atoms, such as methyl, or preferably halogen of atomic number of not more than 35, such as fluorine, chlorine or bromine, and R is carboxyl or carbamyl, or also lower alkoxy carbonyl having not more than 4 C atoms in the lower alkoxy part, such as methoxycarbonyl, and their salts, in particular pharmaceutically acceptable salts, with bases.

The invention relates namely to the compounds of the formula I mentioned in the examples and to their pharmaceutically acceptable salts.

The compounds of the formula I can be prepared by methods which are known per se, for example by subjecting a compound or a mixture of compounds of the formula



in which X_1 and X_2 together are a group of the formula $-\text{C}(=\text{O})-\text{O}-$ bonded via the carbonyl group to the radical Ph and X_3 is hydrogen or one of the radicals X_1 and X_2 is a group of the formula $-\text{C}(=\text{O})-\text{Z}$ and the other is hydrogen and X_3 is a group $\text{R}'\text{O}-$, where R' is lower alkyl, for example methyl, or a hydroxyl protective group R'' , such as α -aryl-lower alkyl, for example benzyl, tri-lower alkyl-silyl, for example trimethylsilyl, or a group of the formula $\text{Ph}-\text{C}(=\text{O})-$, or if X_3 is hydrogen, R' can also be hydrogen and Z is reactive esterified hydroxyl, for example halogen, in particular chlorine, or if X_1 is a group $\text{C}(=\text{O})-\text{Z}$, R_1 is a group $\text{Ph}-\text{C}(=\text{O})-\text{O}-$, to acid treatment, solvolitically decomposing the primary product without isolation and, if desired, converting the compound obtainable according to the process into another compound of the formula I and/or converting a compound obtainable according to the process into a salt or converting a salt obtainable according to the process into the free compound or into another salt.

Acids suitable for the acid treatment are, for example, complex protonic acids, such as sulfuric, pyrosulfuric, phosphoric, pyrophosphoric or

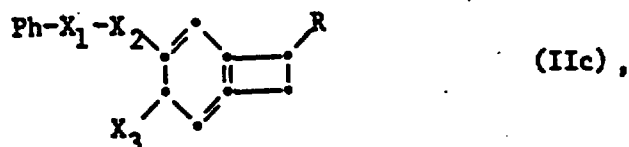
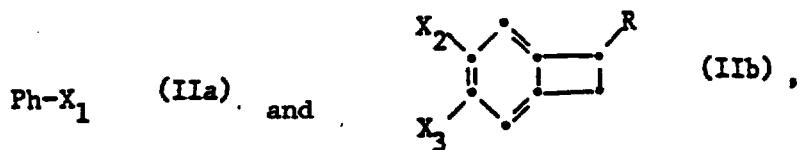
polyphosphoric acid or Lewis acids, such as complex metal halides of the formula M^nY_n (III), in which M is an n-valent, coordinatively unsaturated metal cation of group IIb, IIIa, IIb, IVb, Va or VIIb of the Periodic Table of the Elements, for example the zinc^{II}, boron^{III}, aluminium^{III}, gallium^{III}, tin^{IV}, titanium^{IV}, antimony^V or iron^{III} or iron^{VI} ion and Y is a halogen atom of atomic number of not more than 35, such as fluorine or chlorine.

The acid treatment is carried out in a customary manner, for example in a solvent which is inert towards the reactants, such as an alkane, for example in hexane, aromatics, for example in benzene, toluene or the like, a haloalkane, for example tetrachloromethane, dichloromethane or trichloroethane, or carbon disulfide, if necessary with cooling or warming, for example in the temperature range from about -5° to +30°C, and/or under an inert gas, such as nitrogen.

The solvolytic decomposition of the primary product is carried out in a customary manner, for example by hydrolysis, i.e. treatment with water, but also by treatment with hydroxyl group-containing organic compounds, such as alcohols, for example lower alkanols, or a carboxylic acid, for example lower alkanolic acids, if necessary in the presence of acidic solvolytic agents, such as mineral acids, for example hydrochloric acid or sulfuric acid, or ammonium salts of such acids, for example ammonium chloride, if appropriate with cooling, for example in the temperature range from about -15° to +20°C and/or under an inert gas such as nitrogen.

A preferred procedure comprises, for example, allowing one of the said complex protonic acids and/or their anhydrides or a metal halide of the formula M^nY_n , preferably zinc chloride, aluminium trichloride, tin tetrachloride or antimony pentachloride, where Y and n have the abovementioned meanings, to act on a mixture of compounds of the formula IIa and IIb or on a compound of the formula IIc

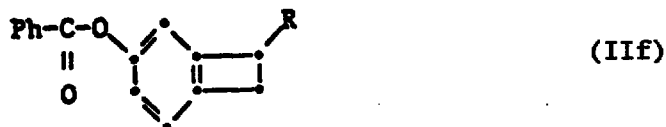
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In a particularly preferred embodiment of this process, compounds of the formulae

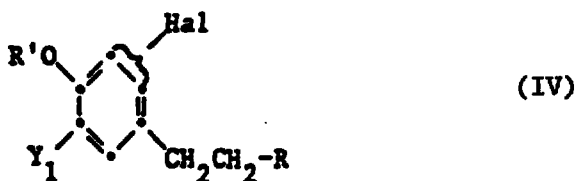


or a compound of the formula



in which Hal is a halogen, for example chlorine, and Alk is lower alkyl, are, for example, used as starting materials and aluminium trichloride is preferably used as the metal halide.

The intermediates of the formula II can be prepared, for example, by cyclizing a compound of the formula

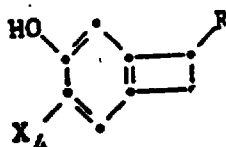


in which Y₁ is hydrogen or free or esterified carboxyl, such as carboxyl or lower alkoxycarbonyl, or a phenoxide and, if appropriate, carboxylate

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salt thereof, in a customary manner, for example by means of an alkali metal amide, such as potassium amide in ammonia or lithium N,N-diethylamide in tetrahydrofuran and, if desired, O-acylating a reaction product of the formula IIb ($X_2 = OH$, $X_3 = H$) by means of a compound of the formula IIId, or, in a reaction product IIb ($X_2 = OR''$, $X_3 = \text{free or esterified carboxyl}$), hydrolysing esterified carboxyl to carboxyl and converting carboxyl into halogenocarbonyl, for example by means of thionyl chloride.

The compounds of the formula I can be prepared by oxidizing or solvolysing X_4 in a compound of the formula



(V)

in which X_4 is a radical which can be converted oxidatively or solvolytically into a group of the formula $-C(=O)-Ph$, to the desired group of the formula $-C(=O)-Ph$ and, if desired, converting the compound obtainable according to the process into another compound of the formula I and/or converting a compound obtainable according to the process into a salt or converting a salt obtainable according to the process into the free compound or into another salt.

Radicals which can be converted oxidatively into a group of the formula $-C(=O)-Ph$ are, for example, those of the formula $-C(X_5X_6)-Ph$, in which X_5 is hydrogen and X_6 is hydrogen or free, etherified or esterified hydroxyl, such as hydroxyl, lower alkoxy, halogen, lower alkanoyloxy or substituted or unsubstituted benzoyloxy.

The oxidation is carried out in a customary manner by reaction with a suitable oxidizing agent, advantageously in a solvent or diluent, if necessary with cooling or warming, for example at about 0 to 100°C, in a closed vessel and/or under an inert gas, such as nitrogen. Suitable oxidizing agents are, for example, oxygen, preferably in the presence of a catalyst, such as a silver, manganese, iron or cobalt compound, percompounds, such as hydrogen peroxide, metal peroxides, for example

nickel peroxide, percarbonic acid and its salts or organic per-acids, for example N-chloroperbenzoic acid, monoperphthalic acid or peracetic acid, or their salts, oxidizing oxy acids or their salts or anhydrides, such as hypohalous acids and their salts, for example sodium hypochlorite, halogen acids and their salts, for example iodic acids, periodic acids, potassium iodate, sodium periodate or potassium chlorate, nitric acid or nitrous acid and their salts and anhydrides, for example potassium nitrate, sodium nitrite, nitric oxide, dinitrogen trioxide or nitrogen dioxide, or oxidizing heavy metal compounds, such as chromium(VI), chromium(IV), manganese(IV), manganese(VII), silver(II), copper(II), mercury(II), vanadium(V) or bismuth(II) compounds, for example pyridinium dichromate, potassium dichromate, chromium trioxide, manganese dioxide, potassium permanganate, silver(II) oxide, copper(II) oxide, mercuric oxide or bismuth oxide. Inert solvents are, for example, solvents which are inert towards the oxidizing agents being used in each case, such as water, ketones, for example acetone, carboxylic acids and their anhydrides, for example acetic acid or acetic anhydride, halogenated hydrocarbons, for example di- or tetra-chloromethane, or aromatics or heteroaromatics, for example benzene, or pyridine, or their mixtures.

Other suitable oxidizing agents are, for example, N-halogeno-, preferably N-chloro- or N-bromodicarboximides, for example N-chloro- or N-bromo-lower alkane-dicarboxyimides, such as N-chloro or N-bromosuccinimide, in the presence of thioethers, such as aliphatic and/or araliphatic sulfides, for example lower alkylthioalkanes, such as dimethyl sulfide, or lower alkylthio-lower alkylbenzenes, such as α -methylthiotoluene. Other selective oxidizing agents for hydroxymethylene are, for example, ketones, such as di-lower alkyl ketones, for example acetone or methyl ethyl ketone, saturated or unsaturated cycloalkanones, preferably those having 5 to 7 ring members, for example cyclopentanone, cyclohexanone, cyclohex-2-enone or quinones. The reaction with ketones is advantageously carried out in the presence of a catalytic agent and using an excess of the oxidizing ketone. Suitable catalytic agents for this purpose are, for example, alkoxides, preferably lower alkoxides or phenoxides of coordinatively unsaturated

metals, such as magnesium, boron or in particular aluminium, for example aluminium phenoxide or isopropoxide.

Radicals which can be converted solvolytically into a group of the formula $-C(=O)-Ph$ are, for example, radicals $-C(=O)-Ph$ which are functionally modified on the carbonyl group, for example of the formula $-C(X_5X_6)-Ph$, in which X_5 and X_6 independently of one another are hydroxyl which is etherified with a monohydric alcohol or esterified, such as lower alkoxy, substituted or unsubstituted phenoxy, halogen, lower alkanoyloxy or substituted or unsubstituted benzyloxy, mercapto which is free or etherified with a monohydric mercaptan, such as mercapto, lower alkylthio or substituted or unsubstituted phenylthio, or substituted or unsubstituted amino, such as amino, N-mono- or N,N-di-lower alkylamino or substituted or unsubstituted anilino or, together with a dihydric alcohol or mercaptan, are etherified hydroxyl or mercapto, such as lower alkylenedioxy, for example ethylenedioxy or 1,3-propylenedioxy, lower alkylenedithio, for example ethylenedithio or 1,3-propylenedithio, or substituted or unsubstituted 1,2-phenylenedioxy or 1,2-phenylenedithio, or thioxo or substituted or unsubstituted imino, such as lower alkylimino or substituted or unsubstituted anilo or benzylimino.

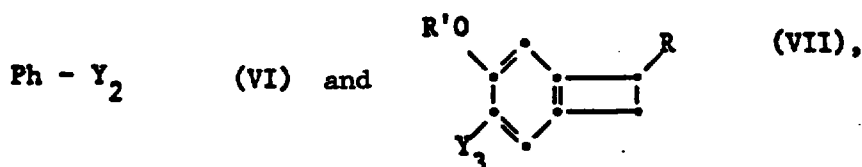
The solvolytic conversion of X_4 groups into those of the formula $-C(=O)-Ph$ is carried out, for example, by hydrolysis. The hydrolysis is carried out in a customary manner, if necessary in the presence of a solvent or diluent and/or adjunct, with cooling or warming, for example in the temperature range from about 0 to 100°C, in a closed vessel and/or under an inert gas. Suitable solvents or diluents are, for example, water-miscible solvents, such as alcohols or ketones, for example lower alkanols or di-lower alkyl ketones, and also N,N-di-lower alkylamides or N-lower alkyl lactams, for example dimethylformamide or N-methylpyrrolidone, and also di-lower alkyl sulfoxides, for example dimethyl sulfoxide, and also dioxane or acetic acid. Auxiliaries are, for example, acids or basic solvolytic agents, such as protonic acids, for example mineral acids, inter alia hydrochloric, hydrobromic or hydriodic acid, sulfuric acid or phosphoric acid, or organic carboxylic

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acid (sic), for example lower alkanolic acids, inter alia acetic acid, or bases, such as alkali metal hydroxides or alkaline earth metal hydroxides, for example sodium hydroxide, potassium hydroxide or calcium hydroxide, alkali metal carbonates, for example sodium carbonate or potassium carbonate, or nitrogen bases, such as ammonia, and in addition for the transesterification, alkoxides, such as alkali metal lower alkoxides, for example sodium methoxide. Starting from free or thioketalized thioxo compounds, for example of the formula V, in which X_5 and X_6 are etherified mercapto of the common thioxo, other possible auxiliaries are heavy metal compounds, for example mercury compounds, or customary oxidizing agents, for example N-chlorosuccinimide.

The starting substances can be prepared by methods which are known per se.

Thus, intermediates of the formula V, in which X_5 is hydrogen and X_6 is hydroxyl are obtained, for example, by reacting compounds of the formulae



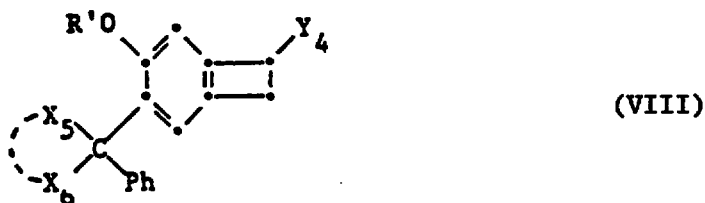
in which R'O is hydroxyl which is free or preferably present in the form of a salt, for example in the form of an alkali metal or alkaline earth metal salt, or which is protected by a hydroxyl protective group R'', such as tri-lower alkylsilyl, for example trimethylsilyl, or α -aralkyl, for example benzyl, with one another in a customary manner, in which formulae one of the radicals Y₂ and Y₃, preferably Y₂, is a metallic radical, such as an alkali metal atom or a halomagnesium group, and the other, preferably Y₃, is formyl, for example in an ethereal solvent, such as tetrahydrofuran, and, if appropriate, removing the protective group R'' in a customary manner. From compounds of the formula V, in which X_4 is a group Ph(X_5)(X_6)-, X_5 is hydrogen and X_6 is hydroxyl, which are thus obtainable, their esters with organic carboxylic acids are also accessible by customary esterification by means of an appropriate

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carboxylic acid anhydride. In an analogous manner, compounds of the formula V are also obtained, in which X_5 and X_6 are halogen, hydrogen or together are substituted or unsubstituted imino, by starting from compounds of the formulae VI and VII, in which Y_2 or Y_3 is a metallic radical and Y_3 or Y_2 is a trihalomethyl, halomethyl or unsubstituted or N-substituted α -haloiminomethyl or cyano group.

Intermediates of the formula V, in which X_4 is a group $-C(X_5)(X_6)-Ph$ and X_5 and X_6 are halogen or together are imino, can also be obtained, however, by treating a compound or a mixture of compounds of the formula II, in which one of the radicals X_1 and X_3 is trihalogenomethyl or cyano and the other is hydrogen and X_2 is etherified hydroxyl, or X_1 and X_2 is a group of the formula $-C(-NH)-O-$ bonded via the iminomethyl group to Ph, with a complex protonic acid, such as sulfuric or polyphosphoric acid, or especially with a coordinatively unsaturated metal halide, such as aluminium trichloride.

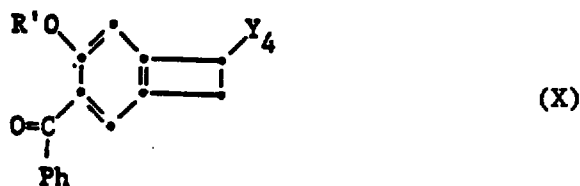
Intermediates of the formula V, in which X_5 and X_6 are in each case hydroxyl etherified with a monovalent alcohol or mercaptan or together are hydroxyl etherified with a dihydric alcohol or mercaptan, can also be prepared by reacting a compound of the formula



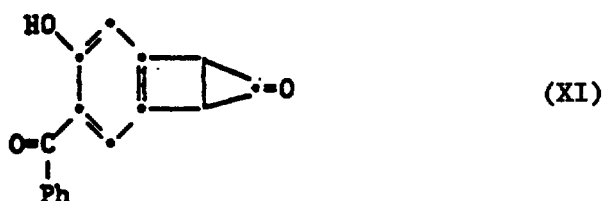
in which $R'O$ is hydroxyl which is free or preferably present in the form of a salt, for example in the form of an alkali metal or alkaline earth metal salt, or is protected by a hydroxyl protective group R'' , such as tri-lower alkylsilyl, for example trimethylsilyl, or α -aralkyl, for example benzyl, and Y_4 is halogen, in a customary manner, for example by reaction with magnesium and subsequently with carbon dioxide or a haloformic acid derivative, for example, of the formula $Hal-R$ (IX), or with a metal carbonyl, such as iron tetracarbonyl or nickel tetracarbonyl and, if appropriate, removing the protective group R'' . Compounds of the formula V, in which X_5 is etherified hydroxyl or

mercapto and X_6 is hydrogen, are also accessible by this method.

The starting substances can be obtained, for example, by customary ketalization, for example by means of a tri-lower alkyl orthoformate, of a compound of the formula



The compounds of the formula I can further be prepared by treating a compound of the formula



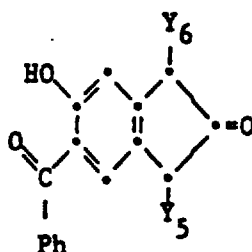
or a phenoxide salt thereof, with water or an alcohol or with ammonia or an amine having at least one hydrogen atom, if necessary isolating the isomer of the formula I from a mixture of isomers obtainable according to the process and, if desired, converting the compound obtainable according to the process into another compound of the formula I and/or converting a compound obtainable according to the process into a salt or converting a salt obtainable according to the process into the free compound or into another salt.

The reaction is carried out in a customary manner, if necessary in the presence of a base, such as an alkali metal hydroxide, alkoxide or amide or by employing an alcohol, ammonia or the amine in the form of a metal salt, for example in the form of the alkali metal salt, advantageously in a solvent or diluent which may be inert towards the reactants or which may consist of an excess of water, the alcohol or the amine, if necessary with warming, for example at about 20 to 100°C, and/or under an inert gas, such as nitrogen.

The starting substances of the formula XI are advantageously prepared in

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situ and reacted further without isolation. In this case the starting material is, for example, a compound of the formula



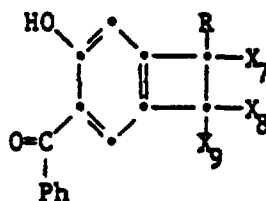
(XII)

in which one of the radicals Y_5 and Y_6 is reactive esterified hydroxyl such as halogen, for example chlorine, bromine or iodine, or sulfonyloxy, such as lower alkane-, substituted or unsubstituted benzene- or fluorosulfonyloxy, for example methane-, ethane-, benzene-, p-toluene- or fluorosulfonyloxy, and the other is hydrogen, or a phenoxide and (sic) enolate salt thereof, and this is reacted in the presence of a suitable base with water, an alcohol, ammonia or an amine. For the reaction with water, suitable bases are, for example, alkali metal hydroxides, such as sodium hydroxide or potassium hydroxide, for the reaction with an alcohol suitable bases are, for example, metal alkoxides, preferably alkali metal alkoxides, of this, such as its sodium or potassium alkoxide, and for the reaction with ammonia or an amine suitable bases are corresponding alkali metal amides, for example sodium or potassium amides.

However, the reaction can also be carried out such that the compound of the formula XII is first converted by treatment with a base, suitable bases also being, in addition to those mentioned, metal bases, i.e. organometallic compounds derived from hydrocarbons, such as lower alkyl- or phenyllithium compounds, lower alkyl- or phenylmagnesium halides and the like, into the corresponding salt, which spontaneously cyclizes to give a compound of the formula XI, and this is then reacted further without isolation, in the manner indicated.

The compounds of the formula I can furthermore be prepared by reducing a compound of the formula

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(XIII)

in which at least one of the radicals X_7 and X_8 is free, etherified or esterified hydroxyl and a radical X_7 or X_8 which differs from this and who X_9 is also hydrogen, or X_7 is hydrogen and X_8 and X_9 are free or functionally modified oxo, or a phenoxide and/or carboxylate salt thereof and, if desired, converting the compound obtainable according to the process into another compound of the formula I and/or a converting compound obtainable according to the process into a salt or converting a salt obtainable according to the process into the free compound or into another salt.

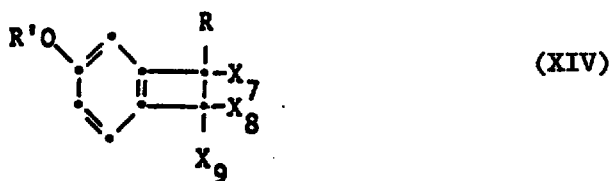
Etherified or esterified hydroxyl is, for example, lower alkoxy, substituted or unsubstituted phenoxy, halogen, such as chlorine, bromine or iodine, lower alkanoyloxy or substituted or unsubstituted benzoyloxy. Functionally modified oxo is, for example, thioxo, substituted or unsubstituted imino, such as imino or anilo, ketalized or thioketalized oxo, for example bis-lower alkoxy, such as bismethoxy or bisethoxy, lower alkylenedioxy, such as ethylenedioxy or 1,3-propylenedioxy, bis-lower alkylthio, such as bismethylthio, or lower alkylenedithio, such as ethylenedithio.

The reduction is carried out in a customary manner, for example by treatment with catalytically activated or nascent hydrogen, such as with hydrogen in the presence of a hydrogenation catalyst, for example platinum, nickel or palladium or a compound of these metals, inter alia platinum, platinum oxide, Raney nickel or palladium, or nascent hydrogen produced by acid treatment of base metals or metal alloys, for example zinc, sodium amalgam, amalgamated aluminium and the like. Compounds of the formula XIII ($X_8 + X_9 = \text{oxo}$) can further advantageously be reduced by treatment with hydrazine in the presence of a base, such as an alkali metal hydroxide or alkoxide, advantageously with heating, for example to about 130 to 250°C. Compounds of the formula XIII in which X_8 and X_9 together are functionally modified oxo (apart from ketalized or

thioketalized oxo) can also be used as starting materials for this reaction. The oxo compound must first be set free, for example by acid hydrolysis, from ketals or thioketals.

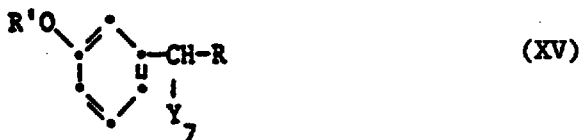
If X_7 is a free hydroxyl group and X_8 and X_9 are hydrogen, an aqueous suspension of phosphorus and iodine, hydriodic acid, tin(II) chloride or an alkali metal sulfite or dithionite, for example sodium sulfite or dithionite, can be used as the reducing agent.

The starting materials of the formula XIII can be prepared by methods which are known per se, for example by introducing the group of the formula Ph-C(=O)- into a compound of the formula



where R' is hydrogen, lower alkyl such as methyl, or a hydroxyl protective group R'' , such as α -aralkyl, for example benzyl, or tri-lower alkylsilyl, for example trimethylsilyl, or a group of the formula Ph-C(=O)- , in a customary manner, for example as indicated for the compounds of the formulae II.

Compounds of the formula XIV, in which X_7 is hydrogen and X_8 and X_9 are oxo, are for their part accessible, for example, by ring closure of a compound of the formula

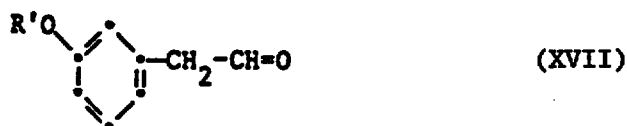


in which Y_7 is free or esterified carboxyl or carboxyl which has been converted into an anhydride with a mineral acid, such as carboxyl, lower alkoxy carbonyl or chlorocarbonyl, for example under the conditions of the condensation or rearrangements of compounds of the formula II, or starting from a compound of the formula

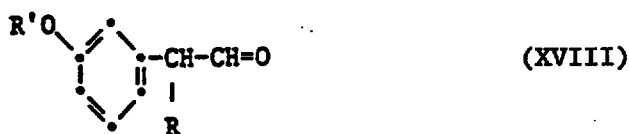


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by conversion into the enolate set (sic), for example by means of a metal base, such as sodium hydride, and subsequent reaction with a reactive carbonic acid derivative, such as carbon dioxide, a carbonic acid diester, haloformic acid esters or carbamyl chloride, or by α -halogenation, for example with bromine, N-bromosuccinimide or N-chlorosuccinimide, reaction with an alkali metal cyanide and subsequent solvolysis of the cyano group to give a group R. In an analogous manner, compounds of the formula XIV (X_7 = hydroxyl; X_8 and X_9 = H) are obtained by conversion of an aldehyde of the formula

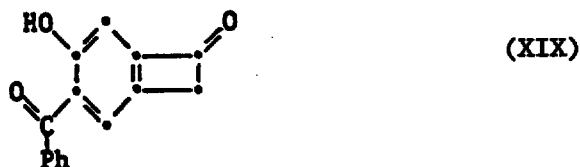


into a salt, reaction with a reactive carbonic acid derivative to give a compound of the formula

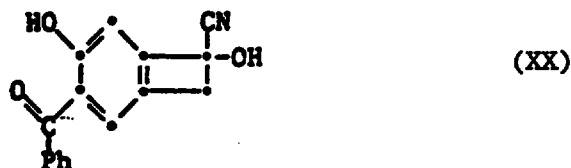


and subsequent ring closure. The group $\text{Ph}-\text{C}(=\text{O})-$ is then introduced in the manner indicated for compounds of the formula II.

Compounds of the formula XIII, in which X_7 is hydroxyl and X_8 and X_9 are hydrogen, can further be prepared by reacting a compound of the formula



with aqueous alkali metal cyanide in a customary manner and converting the cyano group in the resulting α -hydroxynitrile of the formula

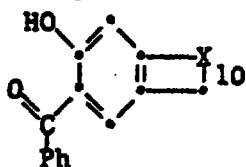


into free, esterified or amidated carboxyl R in a customary manner.

The compounds of the formula I can further be prepared by solvolitically converting the functionally modified carboxyl group in a functional carboxyl derivative thereof which is different from an ester or amide of the formula I, or in a salt thereof, into a free, esterified or amidated carboxyl group and, if desired, converting a compound obtainable according to the process into another compound of the formula I and/or converting a free compound obtainable according the process into a salt or converting a salt obtainable according to the process into the free compound or into another salt, and/or separating a mixture of isomers obtainable according to the process into the components.

Functional carboxyl derivatives of this type, are, for example, acid anhydrides, such as mixed anhydrides with carboxylic acids, such as lower alkanolic acids, for example with formic or acetic acid, or inorganic acids, such as hydrohalic acids, for example with hydrochloric acid, or hydrocyanic acid, or internal anhydrides, i.e. ketones, ortho-anhydrides, such as corresponding trihalogeno, for example trichloro- or tribromomethyl compounds, ortho-anhydride esters, such as dihalomethanol esters corresponding to esters of the formula I, for example lower alkoxydihalomethyl compounds, orthoesters, such as orthoesters corresponding to esters of the formula I, for example tri-lower alkoxymethyl compounds, imino ethers and amidines, such as imino ethers, imino esters and amidines corresponding to esters or amides of the formula I, or lower alkylene-imino ethers, such as imino ethers containing 4,4- or 5,5-dimethyl-2-oxazinyl or 4,6,6-trimethyl-dihydro-2-oxazinyl functionally modified carboxyl group, and mono- and dithiocarboxylic acids and their esters and amides, but preferably nitriles.

Functional carboxyl derivatives of compounds of the formula I are, for example, compounds of the formula



(XXI)

83

in which X_{10} is a group of the formulae >CH-X_{11}
or >O-X_{12} ,

X_{11} is functionally modified carboxyl which differs from esterified or amidated carboxyl R, such as carboxyl which has been converted into an anhydride, trihalomethyl, etherified hydroxydihalomethyl, for example lower alkoxydichloromethyl, etherified trihydroxymethyl, for example tri-lower alkoxymethyl, etherified or esterified C-hydroxyiminomethyl, for example C-lower alkoxyiminomethyl, 4,4-or 5,5-dimethyloxa-2-zinyl, 4,6,6-trimethyldihydro-2-oxazinyl or C-halogenoiminomethyl, free, etherified or amidated mono- or dithiocarboxyl or cyano, and X_{12} is free or functionally modified carbonyl, such as acetalized or thioacetalized carbonyl, for example 1,3-dithian-2-ylidene.

The solvolysis is carried out in a customary manner, for example by hydrolysis, alcoholysis, i.e. reaction with an alcohol, or ammonolysis or aminolysis, i.e. reaction with ammonia or an amine having at least one hydrogen atom.

By means of hydrolysis, for example, one of the said functional carboxyl derivatives, and also esters and amides, can be converted into the carboxylic acids of the formula I (R = carboxyl), and in addition ortho-anhydride esters, orthoesters and imino ethers can be converted into esters of the formula I (R = esterified carboxyl) and imino esters, amidines and nitriles can be converted into amides (R = amidated carboxyl).

The hydrolysis is carried out in a customary manner by treatment with water, if necessary in the presence of a hydrolysing agent, in a solvent or diluent, which cooling or warming, for example in the temperature range from about 0 to 100°C, and/or under an inert gas, such as nitrogen, hydrolysing agents being, for example, acidic or basic hydrolysing agents. Acidic hydrolysing agents are, for example, protonic acids, such as mineral acids, for example sulfuric acid, such as (sic) hydrohalic, for example hydrochloric, hydrobromic or hydriodic acid, or phosphoric acid, sulfonic acids, such as p-toluenesulfonic acid, or carboxylic acids, for example lower alkanoic acids, for example formic or acetic

acid. Basic hydrolysing agents are, for example, hydroxides or carbonates of alkali metals or alkaline earth metals, for example sodium hydroxide or potassium hydroxide, sodium carbonate or potassium carbonate or calcium hydroxide, or nitrogen bases, such as ammonia or organic amines, such as tri-lower alkylamines, pyridine or benzyl-triethylammonium hydroxide. Solvents or diluents are, for example, water-miscible organic solvents, such as alcohols, for example lower alkanols, ketones, for example di-lower alkyl ketones, N,N-di-lower alkyl-lower alkanolic acid amides or N-lower alkyl-lower alkanolic acid lactams, for example dimethylformamide or N-methylpyrrolidone, or di-lower alkyl sulfoxides, for example dimethyl sulfoxide.

By means of alcoholysis, for example, acid anhydrides, such as mixed anhydrides with carboxylic acids or inorganic acids or ketenes, can be converted into esters of the formula I (R = esterified carboxyl).

The alcoholysis is carried out in a customary manner, if necessary in the presence of a condensing agent, in a solvent, with cooling or warming, for example in the temperature range from about 0° to 150°C, in a closed vessel and/or under an inert gas, such as nitrogen. Condensing agents are, for example, acid condensing agents, such as mineral acids, for example sulfuric acid or hydrohalic acid, such as hydrochloric, hydrobromic or hydriodic acid, or in particular basic condensing agents, such as alkali metal alkoxides of corresponding alcohols, such as alkali metal lower alkanooates, for example sodium methoxide or sodium ethoxide, alkali metal hydroxides or carbonates, for example sodium hydroxide or potassium hydroxide or potassium carbonate, or tertiary nitrogen bases, such as hetero-aromatic nitrogen bases, for example pyridine, or tri-lower alkylamines, for example triethylamine. Suitable solvents are, in addition to an excess of the alcohol concerned or of the tertiary nitrogen base used, for example, ethers, such as di-lower alkyl or lower alkylene ethers, for example diethyl ether, tetrahydrofuran or dioxane, hydrocarbons, such as aromatic or aliphatic hydrocarbons, for example benzene, toluene or xylenes, N,N-di-lower alkyl-lower alkanolic acid amides or N-lower alkyl lower alkanolic acid lactams, for example dimethylformamide or N-methylpyrrolidone, or di-lower alkyl sulfoxides,

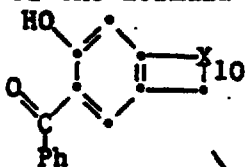
83

for example dimethyl sulfoxide.

By means of ammonolysis or aminolysis, for example, acid anhydrides, such as mixed anhydrides with carboxylic acids or mineral acids and ketenes, can be converted into amides of the formula I (R = amidated carboxyl).

The ammonolysis or aminolysis is carried out in a customary manner, if necessary in the presence of a condensing agent, in a solvent, with cooling or warming, for example in the temperature range from about 0 to 150°C, in a closed vessel and/or under an inert gas, such as nitrogen. Condensing agents are, for example, basic condensing agents, such as alkali metal hydroxides or carbonates, for example sodium hydroxide or potassium hydroxide or potassium carbonate, or tertiary organic nitrogen bases, such as heteroaromatic nitrogen bases, for example pyridine, or tri-lower alkylamines, for example triethylamine. Suitable solvents are, in addition to an excess of an organic amine which may be used, for example ethers, such as di-lower alkyl or lower alkylene ethers, for example diethyl ether, tetrahydrofuran or dioxane, hydrocarbons, such as aromatic or araliphatic hydrocarbons, for example benzene, toluene or xylenes, N,N-di-lower alkyl-lower alkanolic acid amides or N-lower alkyl-lower alkanolic acid lactams, for example dimethylformamide or N-methylpyrrolidone, or di-lower alkyl sulfoxides, for example dimethyl sulfoxide.

The compounds of the formula I can further be prepared by oxidizing the radical X_{11} in a compound of the formula



(XXI)

in which X_{10} is a group of the formula CH-X_{11}

and X_{11} is a radical which can be converted into a group R by oxidation, to a group R and, if desired, converting a compound obtainable according to the process into another compound of the formula I and/or converting a free compound obtainable according to the process into a salt or

converting a salt obtainable according to the process into the free compound or into another salt.

Radicals which can be converted into groups R by oxidation are, for example, acyl groups which are oxidizable to carboxyl R and are derived from organic carboxylic acids, which are unsubstituted or substituted, such as by lower alkenyl or lower alkynyl radicals or a phenyl radical, or methyl, aminomethyl or hydroxymethyl, and further 2-furyl which is unsubstituted or substituted in the 5-position, such as by dilower alkoxymethyl. Acyl X_{11} which is oxidizable to carboxyl and is derived from organic carboxylic acids is, for example, lower alkanoyl which is unsubstituted or substituted, for example in the 2-position, by free or functionally modified carboxyl, halogen (sic) or oxo and/or in the 2- and/or 3-position by hydroxyl and if desired additionally substituted in higher than the 2-position by free or esterified carboxyl or a phenyl group, or lower alkenoyl, such as lower alkanoyl, if desired in particular in hydrate form or enol ether form, for example in the form of the enol ether with an alcohol of the formula R_0-OH , in which R_0 is a hydrocarbon radical, such as lower alkyl, in the form of the acetal, for example the di-lower alkyl or lower alkylene acetal, or in the form of the acylate, for example in the form of formyl present in the form of the di-lower alkanoyloxy or dihalomethyl group, or also acetyl, propionyl, pivaloyl and the like, free or functionally modified, such as esterified or amidated, oxalo, for example oxalo or lower alkoxyoxyoxalyl, 2-mono-, 2,2-di- or 2,2,2-tri-halo-lower alkanoyl, for example mono-, di- or trichloroacetyl, mono-, di- or tribromoacetyl or mono-, di- or triiodoacetyl, 2-oxo-lower alkanoyl or 2-oxophenyl-lower alkanoyl, such as pyruvoyl or benzoylcarbonyl, 2-hydroxy-lower alkanoyl, for example glycoloyl, or free or functionally modified, for example esterified or amidated, 3-carboxy-2,3-dihydroxypropionyl, such as tartrono or lower alkoxy-tartronoyl, or lower alkenoyl which is unsubstituted or substituted by a phenyl group, for example acryloyl, methacryloyl, crotonyl, cinnamoyl and the like. Other X_{11} groups are etherified hydroxymethyl groups, such as lower alkoxymethyl, which can be oxidized to esterified carboxyl, such as lower alkoxycarbonyl R.

The oxidation is carried out in a customary manner by reaction with a suitable oxidizing agent, advantageously in a solvent or diluent, if necessary with cooling or warming, for example at about 0 to 100°C, in a closed vessel and/or under an inert gas, such as nitrogen. Suitable oxidizing agents are, for example, oxygen, preferably in the presence of a catalyst, such as a silver, manganese, iron or cobalt compound, per-compounds, such as hydrogen peroxide, metal peroxides, for example nickel peroxide, percarbonic acid and its salts or organic peracids, for example m-chloroperbenzoic acid, monoperphthalic acid or peracetic acid, or their salts, oxidizing oxy acids or their salts or anhydrides, such as hypohalous acids and their salts, for example sodium hypochlorite halogen acids and their salts, for example sodium hypochlorite, (sic), halogen acids and their salts, for example iodic acids, periodic acids, potassium iodate sodium periodate or potassium chlorate, nitric acid or nitrous acid and their salts and anhydrides, for example potassium nitrate, sodium nitrite, nitric oxide, dinitrogen trioxide or nitrogen dioxide, or oxidizing heavy metal compounds, such as chromium(VI), chromium(IV), manganese(IV), manganese(VII), silver(II), copper(II), mercury(II), vanadium(V) or bismuth(II) compounds, for example sodium dichromate, potassium dichromate, chromium trioxide, manganese dioxide, potassium permanganate, silver(II) oxide, copper(II) oxide, mercuric oxide or bismuth oxide. Inert solvents are, for example, solvents which are inert towards the oxidizing agents used in each case, such as water, ketones, for example acetone, carboxylic acids and their anhydrides, for example acetic acid or acetic anhydride, halogenated hydrocarbons, for example tetrachloromethane, or aromatics or hetero-aromatics, for example benzene, or pyridine, or their mixtures.

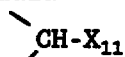
Free or esterified oxalo X_{11} of the formula $-C(=O)-R$ can also be oxidized with decarbonylation, for example in the presence of a suitable oxidizing agent, if necessary with cooling or warming, for example at about 0 to 100°C, in an inert solvent, in a closed vessel and/or under an inert gas, such as nitrogen. Suitable oxidizing agents are, for example, per-compounds, such as hydrogen peroxide or percarboxylic acids, for example percarbonic acid or organic percarboxylic acids, inter alia peracetic acid, performic acid, perbenzoic acid and the like, and also

halogenoxy acids and their salts, such as chloric acid or alkali metal chlorites, or oxidizing metal compounds, such as silver oxide, potassium permanganate or chromium trioxide. Suitable solvents are, for example, anhydrous or water-containing ketenes (sic), such as acetone, or carboxylic acids, such as acetic acids.

The compounds of the formula XXI mentioned as starting materials, in which X_{10} has the meaning indicated and is, in particular, a group



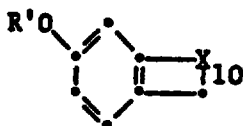
can be prepared by methods which are known per se, for example by a modification of some of the procedures described above for the preparation of the formula I (sic), in each case starting from corresponding starting materials of the formulae IIa and IIb or IIc and IIe, IIc or IIe, V, VII or XXXVII, which have a group X_{10} , preferably of the formula



in place of the group



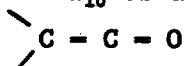
A preferred procedure consists, for example, in reacting a compound of the formula



(XXII)

where R' is hydrogen, lower alkyl, such as methyl, or a hydroxyl protective group R'' , such as α -aralkyl, for example butyl, or tri-lower alkylsilyl, for example trimethylsilyl, or a group of the formula Ph-C(=O)- , in the presence of aluminium chloride or another of the complex metal halides mentioned, with a compound Ph-C(=O)Hal (IIc), where R' is preferably a lower alkyl radical and Hal is halogen, for example chlorine.

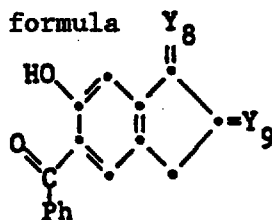
The ketenes to be used as starting materials, i.e. compounds of the formula XXI, in which X_{10} is a group of the formula



can further be prepared by rearranging a corresponding α -diazoketone,

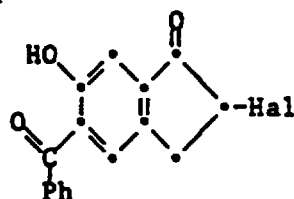
(89)

for example a compound of the formula

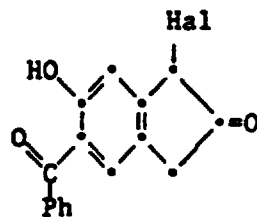


(XXIII)

in which one of the radicals Y_8 and Y_9 is oxo and the other is a group of the formula $-N_2$ in a customary manner with removal of nitrogen. If the rearrangement is carried out in the presence of water or an alcohol or of ammonia or an amine having at least one hydrogen atom, the ketene first formed reacts further according to the invention, without isolation. In this case, the reaction is advantageously carried out at elevated temperature, for example in the temperature range from about 40 to 100°C, under irradiation, for example with an ultraviolet light source, and/or in the presence of silver or silver compounds, for example silver, silver nitrate or silver oxide. Diazoketones of the formula XXIII can be obtained, for example, by reacting a compound of the formulae



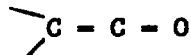
(XXIV) or



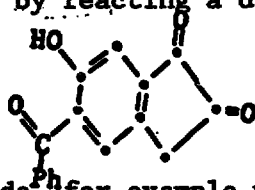
(XXV)

in which Hal is halogen, which compound is accessible from the corresponding indanone by halogenation, for example with N-bromosuccinimide, with hydrazine, for example at about 60°C in ethanol, and oxidizing the primary product, for example by treatment with manganese dioxide in chloroform.

Ketenes of the formula XXI, in which X_{10} is a group of the formula



can be further obtained by reacting a diketone of the formula

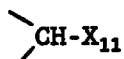


(XXVI)

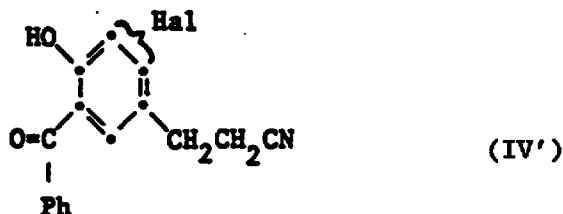
with a sulfonyl hydrazide, for example with p-toluenesulfonyl hydrazide, and treating the hydrazone XXIII formed (Y_8 or $Y_9 = N-NH_2$ instead of $-N_2$) with alkali, for example with sodium hydroxide solution, or oximating

the said hydrazone by reaction with hydroxylamine and treating the oxime (in formula XXIII Y_8 or Y_9 is $=N-OH$ instead $=N_2$) with chloramine or ammonia and sodium hypochlorite. The said oximes can also be obtained by condensing a corresponding indanone with nitrous acid. Likewise, the said hydrazone can be obtained by aminating a compound of the formulae XXIV or XXV and diazotizing the primary product in a customary manner, for example with sodium nitrite and acetic acid.

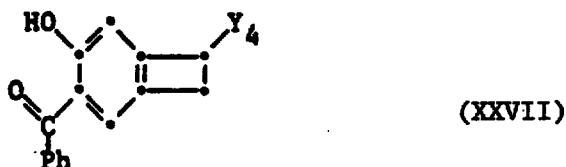
Nitriles derived from acids of the formula I, for example compounds of the formula XXI, in which X_{10} is a group



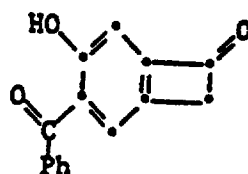
and X_{11} is cyano, can further be prepared by cyclizing a compound of the formula



or a salt thereof in a customary manner, for example by means of an alkali metal amide, such as potassium amide in ammonia or lithium N,N-diethylamide in tetrahydrofuran, or by reacting a compound of the formula



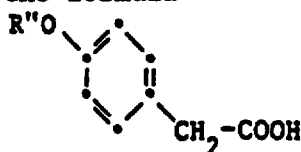
in which Y_4 is reactive esterified hydroxyl, such as halogen or sulfonyloxy, for example iodine, bromine, chlorine or p-toluenesulfonyloxy, or a phenoxide salt thereof in a customary manner with ammonium cyanide or a metal cyanide, for example with sodium cyanide or potassium cyanide. Compounds of the formula XXVII, for their part, can be obtained, for example, by halogenating a corresponding benzocyclobutene compound, for example, by treatment with a halogen or by means of N-bromo- or N-chlorosuccinimide or, in a corresponding benzocyclobutenone compound, reducing the oxo group to hydroxyl and reacting this by reaction with a halogenating agent, such as phosphorus tribromide, or a sulfonyl halide. However, hydrocyanic acid can also be added to a compound of the formula



(XXVIII)

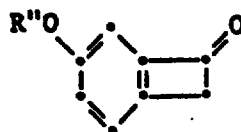
and the hydroxyl group in the α -cyanohydrin formed, reductively replaced by hydrogen, for example as indicated for corresponding compounds of the formula XIII, with previous elimination of water, if necessary.

The compounds of the formula XXVIII can be prepared, for example, by cyclizing a compound of the formula



(XXIX)

in which R'', for example, is lower alkyl, in a customary manner, for example by acid treatment, such as by heating with sulfuric acid or polyphosphoric acid, and reacting the resulting compound of the formula

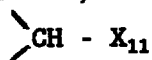


(XXX)

in the presence of aluminium trichloride with a compound of the formula Ph-C(=O)Hal (IIId).

Imino ethers and amidines to be used as starting materials are advantageously prepared in situ by treating the corresponding nitrile with an alcohol or amine, customarily in the presence of a mineral acid, or by first converting the nitrile by mineral acid treatment into an imino ester and then subjecting the latter to alcoholysis or ammonolysis or aminolysis. Hydrochloric acid or hydrobromic acid is especially suitable as the mineral acid here. In an analogous manner, orthoanhydride esters can also be prepared by partial alcoholysis of orthoanhydrides, for example trihalomethyl compounds.

Compounds of the formula XXI, in which X_{10} is a group of the formula

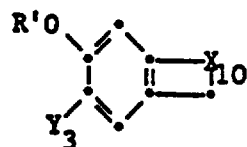


and X_{11} is a 4,4- or 5,5-dimethyl-2-oxazinyl or 4,6,6-trimethyl-dihydro-oxazinyl group, acetalized formyl or an orthoester group, can further be prepared by reacting compounds of the formulae

92



(VI) and

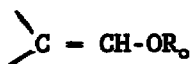


(XXXI)

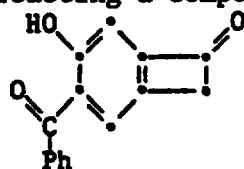
in a customary manner with one another, in which formulae one of the radicals Y_2 and Y_3 , preferably Y_2 , is a metal radical, such as an alkali metal atom or a halomagnesium group, and the other, preferably Y_3 , is carboxyl, which is free or in the form of a salt, for example in the form of an alkali metal salt, or functionally modified, such as esterified or in the form of an anhydride, for example in the form of the halide, and $\text{R}'\text{O}-$ is hydroxyl which is free or preferably in the form of a salt, for example in the form of an alkali metal or alkaline earth metal salt, or is protected by a hydroxyl protective group R'' , such as tri-lower alkylsilyl, for example trimethylsilyl, or α -aralkyl, for example benzyl, and removing the hydroxyl protective group R'' if appropriate.

In a modification of this process, it is also possible to use as starting materials compounds of the formulae VI and XXI, which contain cyano as the functionally modified carboxyl group; the imino derivative of the compound of the formula XXI is thus obtained, whose imino group is hydrolyzed to oxo in the course of the hydrolysis reaction.

Aldehydes of the formula XXI present in enol ether form, in which X_{10} is a group

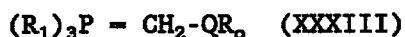


can further be prepared by reacting a compound of the formula



(XXXII)

or a phenoxide salt thereof, in a customary manner with a compound of the formula



in which the radicals R_0 and R_1 are identical or different hydrocarbon radicals, for example $(\text{R}_1)_3\text{P}$ is triphenylphosphino and R_0 is lower alkyl.

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The aldehydes of the formula XXI, in which X_{10} is a group of the formula

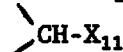


and X_{11} is free formyl or formyl present in hydrate form, can be liberated from these compounds, if desired by mild hydrolysis, advantageously with acid catalysis. Likewise, acetals and acylals, in which X_{10} is a group of the formula

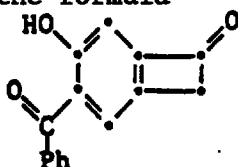


and X_{11} is acetalized or acylalized formyl, can be hydrolysed to give the corresponding aldehydes.

Compounds of the formula XXI, in which X_{10} is a group of the formula

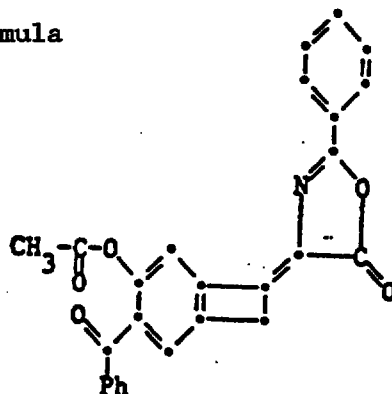


and X_{11} is a free or esterified oxalo group can further be obtained by condensing a compound of the formula



(XXVIII)

with hippuric acid in a customary manner, for example in the presence of acetic anhydride, at about 50 to 100°C, and hydrolysing the condensation product of the formula



(XXXIV)

in a customary manner, for example by treating with sodium hydroxide solution.

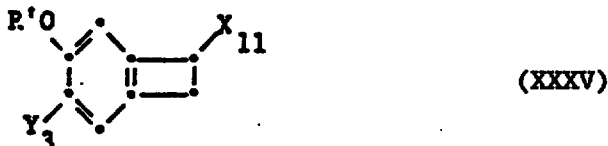
Compounds of the formula XXI, in which X_{10} is a group



and X_{11} is free formyl or formyl present in hydrate form, can further be prepared in situ under the conditions of their further oxidation, by forming the formyl group by oxidation, for example of methyl, hydroxymethyl or substituted or unsubstituted lower alkenyl, or lower alkanoyl or lower alkanoyl which is unsubstituted or substituted as

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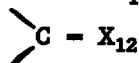
indicated, or by liberating free from one of its derivatives, which contains functionally modified formyl in place of formyl X_{11} , such as an acetal, for example from di-lower alkoxy- or lower alkylenedioxymethyl, acylal, for example from dihalomethyl, enol ethers, for example an enol lower alkyl ether, enol esters, for example enol lower alkanolic acid esters or enol esters with hydrohalic acids, an oxime or enamine, for example an enamine with pyrrolidine, piperidine, morpholine, thiomorpholine or a di-lower alkylamine, preferably hydrolytically, for example under acid conditions. The acetals mentioned can be obtained, for example, by reacting a compound of the formula



in which $\text{R}'\text{O}$ is hydroxyl which is free or preferably in the form of a salt, for example in the form of an alkali metal or alkaline earth metal salt, or is protected by a hydroxyl protective group R'' , such as tri-lower alkylsilyl, for example trimethylsilyl, or α -aralkyl, for example benzyl, with a compound of the formula

Ph-Y_2 (V)

in which X_{11} is acetalized formyl and one of the radicals Y_2 and Y_3 is a metal group for example the formula (sic) $-\text{Li}$, $-\text{Na}$, $-\text{Mg}/2$, $-\text{Mg-Hal}$, $-\text{Cd}/2$, $-\text{CdHal}$ or ZnHal (Hal = halogen, such as chlorine, bromine or iodine) and the other is a hydroxyl group in the form of a salt or an esterified hydroxyl group, and, if necessary, removing the protective group, for example by means of magnesium iodide. Analogously, compounds of the formula XXI, in which X_{10} is a group of the formula



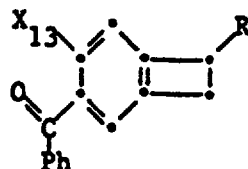
and X_{12} is 1,3-dithian-2-ylidene, can further be obtained by reacting a compound of the formula



in which R' is a hydroxyl protective group, with 2-trimethylsilyl-1,3-dithian-2-yl-lithium, reacting the reaction product with a compound of the formula V and, if necessary, removing the protective group.

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The compounds of the formula I can further be prepared by converting X_{13} in a compound of the formula



(XXXVII)

in which X_{13} is a group which can be converted to hydroxyl, or in a salt thereof, into hydroxyl and, if desired, converting the compound obtainable according to the process into another compound of the formula I and/or converting a compound obtainable according to the process into a salt or converting a salt obtainable according to the process into the free compound or into another salt.

Groups which can be converted to hydroxyl are, for example, hydroxyl groups protected in a customary manner, which contain, groups removable by neutral acidic or basic solvolysis, in particular hydrolysis, or by reduction, as the protective group, in place of the hydrogen atom. Protective groups of this type, and also selected methods for their removal, i.e. for the conversion of the protected hydroxyl group to hydroxyl, are well enough known in the literature.

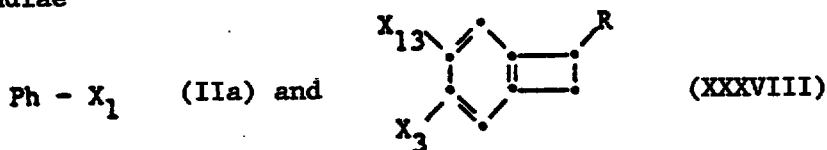
In addition to other customary hydroxyl protective groups, for example, etherified hydroxyl groups, such as lower alkoxy, tri-lower alkylsilyloxy or unsubstituted or substituted phenyl-lower alkoxy groups, for example methoxy, trimethylsilyloxy or benzyloxy, in particular protected hydroxyl groups of the formula $R''O-$, in which R'' represents lower alkyl, for example methyl, α -aralkyl, for example benzyl, or tri-lower alkylsilyl, for example trimethylsilyl, esterified hydroxyl groups, such as hydroxyl groups esterified with inorganic acids or with organic carboxylic acids, for example lower alkanoyloxy groups or groups of the formula $Ph-C(O-)-O-$, and in addition diazonium groups are suitable as groups which can be converted to hydroxyl.

The conversion of these and similar groups X_{13} is carried out in a customary manner, for example by hydrolysis, if necessary in the presence of a, preferably acidic, hydrolysing agent, a solvent or

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diluent or a solubilizer, with cooling or warming, for example in the temperature range from about 0 to 120°C, and/or under an inert gas. Hydrolysing agents are, in addition to the customary basic hydrolysing agents, such as alkali metal hydroxides, as (sic) acidic hydrolysing agents, for example Lewis acids, such as complex metal halides of the formula M^aY_n (sic) (III), in which M denotes an n-valent, coordinatively unsaturated metal cation of the group IIa, IIb, IIIa, IIIb, IVb, Va or VIIb of the Periodic Table of the Elements, for example the magnesium, zinc^{II}, boron^{III}, aluminium^{III}, gallium^{III}, tin^{IV}, titanium^{IV}, antimony^V or iron^{III} or iron (VI) ion, Y denotes a halogen atom of atomic number of up to and not more than 35, such as fluorine or chlorine, for example aluminium trichloride, or protonic acids, such as mineral acids, for example hydrochloric, hydrobromic or hydriodic acid, sulfuric acid, phosphoric acid or polyphosphoric acid, and also complex metal acids, for example hexachloroantimonic acid, tetrafluoboric acid and the like, and in the case of hydroxyl groups X_{13} esterified with organic carboxylic acids, also lower alcanoic acids, such as acetic acid. Solvents for the hydrolysis are, for example, water-miscible organic solvents.

Thus, etherified hydroxyl groups can be hydrolysed, for example by treatment with aqueous hydriodic acid, with hydrobromic acid in highly concentrated, for example 98%, acetic acid or by treatment with aluminium trichloride. In a modification of this process, for example, compounds of the formulae



in which X_1 is a group of the formula $-C(=O)-Z$ and Z is hydroxyl in anhydride form, oxide as halogen or a group of the formula $Ph-C(=O)-O$, X_{13} is, for example, etherified hydroxyl, such as lower alkoxy, and X_3 is hydrogen, can be treated with a Lewis acid, such as with a complex metal halide of the formula M^aY_n (sic) (III), for example with aluminium trichloride, and the hydroxyl group can be liberated from the compound of the formula (XXXVII), which is possibly formed as the primary product from this reaction and in which X_{13} is, for example etherified hydroxyl, by adding water. Likewise, a compound of the formula IIb, in which X_2 is

free or etherified hydroxyl and X_3 is hydrogen, can be treated with an excess of a compound of the formula IIa, in which X_1 is a group of the formula $-C(=O)-Z$, in the presence of a protonic acid or of one of the said complex metal halides of the formula M^aY_n (III), and the hydroxyl group can then be liberated from a compound of the formula XXXVII which may have formed and in which X_{13} denotes hydroxyl esterified with the acid of the formula $Ph-COOH$, by hydrolysis.

In compounds of the formula XXXVII containing as the group X_{13} , an unsubstituted or substituted α -phenyl-lower alkoxy group or another customary protected hydroxyl group removable by reduction, the hydroxyl group can advantageously be liberated by reduction. Thus, for example, the protected hydroxyl group can be hydrogenated, i.e. reduced with hydrogen in the presence of a hydrogenation catalyst, for example a palladium, platinum, nickel or rhodium catalyst, for example palladium-on-charcoal or Raney nickel.

In addition, using compounds of the formula XXXVII, in which X_{13} is hydroxyl esterified with an organic carboxylic acid, as the starting materials, the hydroxyl group can be liberated by transesterification, i.e. treatment with an alcohol, for example a lower alkanol, in the presence of an acidic or basic agent, such as a mineral acid, for example sulfuric acid, or alkali metal hydroxide or alkoxide, for example sodium hydroxide or a sodium lower alkoxide.

The conversion of diazonium X_{13} into hydroxyl is carried out, for example, with in situ formation of the diazonium group, for example by diazotizing a corresponding amino compound, in which X_{13} is amino, in a customary manner and replacing the diazonium salt formed by hydroxyl, without isolation, by treatment with water, preferably at elevated temperature, for example at about 40 to 120°C.

The starting materials of the formula XXXVII can be prepared by methods which are known per se, for example starting from compounds of the formulae IIe, IIf or XXXIV, from compounds of the formulae V, XI, XII, XIII, XIX, XX, XXI, XXIII, XXIV, XXV, XXVI, XXVII, XXVIII or XXXII,

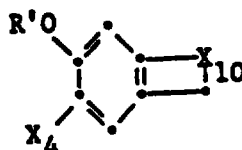
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which contain a group X_{13} (apart from diazonium including amino) in place of the phenolic hydroxyl group, from compounds of the formulae II, IIb, IV, VII, VIII, X, XIV, XV, XVI, XVII, XVIII, XXII, XXXI, XXXV, XXXVI or XXXIX, which contain a group X_{13} in place of the group $R'O$, or from compounds of the formulae XXIX or XXX, which contain another group X_{13} in place of the group $R''O$, in which case, for example, the procedure indicated is used.

When carrying out the modes of formation described above in practice, it may be advantageous to combine a number of reactions of the same type in the style of a "one-pot reaction", for example to combine the oxidative conversion of a radical X_4 to a group $Ph-C(=O)-$ in a compound of the formula V with the oxidative conversion of a radical X_{10} to a group



in compounds of the formula XXI by using an appropriate compound of the formula

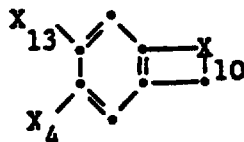


(XXXIX)

as the starting material. Likewise, the solvolytic conversion of a radical X_4 to a group $Ph-C(=O)-$ in compounds of the formula V can be combined with the solvolytic conversion of a radical X_{10} to a group



in compounds of the formula XXI and/or the solvolytic conversion of X_{13} to hydroxyl in compounds of the formula XXXVII by using a corresponding compound of the formula XXXIX or a compound of the formula



(XL)

as the starting material. In addition, for example, the phenolic hydroxyl group in compounds of the formulae V, XI, XII, XIII, XIX, XXI, XXIII, XXIV, XXV, XXVI, XXVII, XXVIII and XXXII can be temporarily protected by silylation and that in compounds of the formulae XI, XII, XIII, XIX, XXI, XXIII, XXIV, XXV, XXVI, XXVII, XXVIII and XXXII can be protected by benzylation, acylation, alkylation or silylation, and the protective group removed again after carrying out the reaction.

Compounds obtainable according to the process can further be converted into other compounds of the formula I.

Thus, for example, a free carboxyl group R can be esterified to an esterified carboxyl group R in a customary manner, for example by treating with a diazo-lower alkane or tri-lower alkyloxonium/tri-lower alkylcarboxonium or di-lower alkylcarbonium salt, such as hexachloroantimonate or hexafluorophosphate, or especially by reaction with the corresponding alcohol or a reactive derivative, such as a carboxylic, phosphorous, sulfurous or carbonic acid ester, for example a lower alkanecarboxylic acid ester, tri-lower alkyl phosphite, di-lower alkyl sulfite or the pyrocarbonate, or a mineral acid ester or sulfonic acid ester, for example the hydrochloric or hydrobromic acid or sulfuric acid, benzenesulfonic acid, toluenesulfonic acid or methanesulfonic acid ester, ... (sic) the corresponding alcohol or an olefin derived therefrom.

The reaction with the corresponding alcohol itself can advantageously be carried out in the presence of an acid catalyst, such as a protonic acid, for example hydrochloric or hydrobromic, sulfuric, phosphoric, boric, benzenesulfonic and/or toluenesulfonic acid, or a Lewis acid, for example boron trifluoride etherate, in an inert solvent, in particular an excess of the alcohol employed and, if necessary, in the presence of a water-binding agent and/or with distillative, for example azeotropic, removal of the water of reaction and/or at elevated temperature.

The reaction with a reactive derivative of the corresponding alcohol can be carried out in a customary, starting from a carboxylic acid, phosphorous, sulfurous or carbonic acid ester, for example in the presence of an acid catalyst, such as one of those mentioned above, in an inert solvent, such as aromatic hydrocarbon, for example in benzene or toluene, or an excess of the alcohol derivative employed or of the corresponding alcohol. Starting from a mineral acid ester or sulfonic acid ester, the acid to be esterified is advantageously employed in the form of a salt, for example the sodium or potassium salt, and the

reaction is carried out, if necessary, in the presence of a basic condensing agent, such as an inorganic base, for example sodium hydroxide, sodium carbonate, potassium hydroxide, potassium carbonate, calcium hydroxide or calcium carbonate, or a tertiary organic nitrogen base, for example triethylamine or pyridine, and/or in an inert solvent, such as one of the above tertiary nitrogen bases, or of (sic) a polar solvent, for example in dimethylformamide, and/or at elevated temperature.

The reaction with an olefin can be carried out, for example, in the presence of an acid catalyst, for example a Lewis acid, for example boron trifluoride, a sulfonic acid, for example p-toluenesulfonic acid, or in particular of a basic catalyst, for example sodium or potassium hydroxide, advantageously in an inert solvent, such as an ether, for example in diethyl ether or tetrahydrofuran.

A free carboxyl group R can further be converted to an amidated carboxyl group R by reaction with ammonia or an amine containing at least one hydrogen atom in a customary manner, with dehydration of the ammonium salt formed as an intermediate, for example by azeotropic distillation with benzene or toluene or by heating dry.

The conversions of free carboxyl groups R into esterified or amidated carboxyl groups R described above can, however, also be carried out, in such a way that a compound of the formula I, in which R is carboxyl, is first converted in a customary manner into a reactive derivative, for example into an acid halide by means of a halide of phosphorus or sulfur, for example by means of phosphorus trichloride (sic) or bromide, phosphorus pentachloride or thionyl chloride, or into a reactive ester, i.e. esters with electron-withdrawing structures, such as the ester with phenol, thiophenol, p-nitrophenol or cyanomethyl alcohol, or a reactive amide, for example the amide derived from imidazole or 3,5-dimethylpyrazole, by reaction with a corresponding alcohol or amine, and the reactive derivative obtained is then reacted with a corresponding alcohol or ammonia or the corresponding amine containing at least one hydrogen atom in a customary manner, for example as described below for

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the transesterification or mutual conversion of esterified and amidated carboxyl groups R, to give the desired group R.

An esterified carboxyl group R can be converted in a customary manner to the free carboxyl group R, for example by hydrolysis in the presence of a catalyst, for example a basic or acid agent, such as a strong base, for example sodium hydroxide or potassium hydroxide, or a mineral acid, for example hydrochloric acid, sulfuric acid or phosphoric acid, or to an amidated carboxyl group R, for example by reaction with ammonia or the corresponding amine containing at least one hydrogen atom.

An esterified carboxyl group R can further be transesterified to another esterified carboxyl group R in a customary manner, for example by reaction with a metal salt, such as the sodium or potassium salt, of a corresponding alcohol or with this itself in the presence of a catalyst, for example a strong base, for example sodium hydroxide or potassium hydroxide, or a strong acid, such as a mineral acid, for example hydrochloric acid, sulfuric acid or phosphoric acid, or an organic sulfonic acid, for example p-toluenepulfonic acid (sic), or a Lewis acid, for example boron trifluoride etherate.

An amidated carboxyl group R can be converted into the free carboxyl group R in a customary manner, for example by hydrolysis in the presence of a catalyst, for example a strong base, such as an alkali metal hydroxide or carbonate or an alkaline earth metal hydroxide or carbonate, for example sodium hydroxide, sodium carbonate, potassium hydroxide or potassium carbonate, or a strong acid, such as a mineral acid, for example hydrochloric acid, sulfuric acid or phosphoric acid.

Depending on the choice of starting materials and procedures, the novel compounds may be in the form of one of the possible isomers or of a mixture thereof, for example, depending on the number of asymmetric carbon atoms, in the form of the pure optical isomer, of antipodes or of mixtures of isomers, such as racemates, diastereomer mixtures or racemate mixtures.

Resulting diastereomer mixtures and racemate mixtures can be separated into the pure isomers, diastereomers or racemates, on the basis of the physicochemical differences between the constituents in a known manner, for example by chromatography and/or fractional crystallization.

Resulting racemates can further be resolved into the optical antipodes by known methods, for example by recrystallization from an optically active solvent, with the aid of microorganisms, or by reaction of an acidic end product with an optically active base forming salts with the racemic acid and separation of the salts thus obtained, for example on the basis of their different solubilities, into the diastereomers, from which the antipodes can be liberated by the action of suitable agents. Advantageously, the more active of the two antipodes is isolated.

Resulting free compounds of the formula I can be converted into salts in a manner known per se. Acidic compounds, for example those in which R_4 is carboxyl and/or R_2 and/or R_3 is hydroxyl, are converted into salts, for example, with the corresponding base, others, for example, by treatment with an acid, for example an acid forming salts which was mentioned at the beginning, customarily in the presence of a solvent or diluent.

Resulting salts can be converted into the free compounds in a manner known per se, for example by treatment with an acidic reagent, such as a mineral acid, or a base, for example alkali metal hydroxide solution.

The compounds, including their salts, can also be obtained in the form of their hydrates or can include since (sic) solvents used for crystallization.

Because of the close relationship between the novel compounds in the free form and in the form of their salts, in the preceding and following text the free compounds or their salts are analogously and where appropriate also to be understood as meaning the corresponding salts or free compounds.

The invention also relates to those embodiments of the process according

to which the starting materials used are compounds obtainable as an intermediate at any step of the process and the missing steps are carried out or a starting material is used in the form of a salt and/or racemate or antipode or, in particular, is formed under the reaction conditions.

In the process of the present invention, the starting materials preferably used are those which lead to the compounds described initially as being particularly valuable. The invention also relates to novel starting materials and to processes for their preparation.

The pharmaceutical preparations according to the invention, which contain compounds of the formula I or pharmaceutically utilizable salts thereof, are those for enteral, such as oral or rectal, and parenteral administration and also for topical application to (a) warm-blooded animal(s), which contain the pharmacological active ingredient on its own or together with a pharmaceutically utilizable carrier. The dosage of the active ingredient depends on the species of warm-blooded animal, on the age and the individual condition, and on the mode of administration. Normally, an approximate daily dose of 30-300 mg, advantageously divided into several equal partial doses, is to be estimated for oral administration for a warm-blooded animal weighing approximately 75 kg.

The novel pharmaceutical preparations contain, for example, from about 10% to about 80%, preferably from about 20% to about 60% of the active ingredient. Pharmaceutical preparations according to the invention for enteral or parenteral administration are, for example, those in unit dose forms such as coated tablets, tablets, capsules or suppositories, and also ampoules. These are prepared in a manner known per se, for example by means of conventional mixing, granulating, tablet coating, dissolving or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active ingredient with solid carriers, granulating a resulting mixture if necessary, and processing the mixture or granules, if desired or necessary, after addition of suitable auxiliaries, to give tablets or coated tablet

cores.

Suitable carriers are, in particular, fillers, such as sugars, for example lactose, sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starch pastes, using, for example, maize, wheat, rice or potato starch, gelatin, tragacanth, methylcellulose and/or polyvinylpyrrolidone, and/or if desired, disintegrants, such as the abovementioned starches, and also carboxymethyl starch, cross-linked polyvinylpyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate. Auxiliaries are primarily glidants and lubricants, for example silica, talc, stearic acid or salts thereof, such as magnesium stearate or calcium stearate, and/or polyethylene glycol. Coated tablet cores are provided with suitable coatings, which if appropriate are resistant to gastric juices, using, inter alia, concentrated sugar solutions which may contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions in suitable organic solvents or solvent mixtures or, for the preparation of coatings resistant to gastric juices, solutions of suitable cellulose preparations, such as acetylcellulose phthlate or hydroxypropylmethylcellulose phthlate. Dyes or pigments can be added to the tablets or coated tablets, for example to identify or indicate different doses of active ingredient.

Other pharmaceutical preparations suitable for oral use are hard gelatin capsules and also soft sealed capsules made from gelatin and a plasticizer such as glycerol or sorbitol. The hard capsules can contain the active ingredient in the form of granules, for example in a mixture with fillers, such as lactose, binders, such as starches, and/or lubricants, such as talc or magnesium stearate, and, if desired, stabilizers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, it also being possible to add stabilizers.

Pharmaceutical preparations suitable for rectal use are, for example, suppositories, which consist of a combination of the active ingredient with a suppository base. Suitable suppository bases are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alcohols. In addition, gelatin rectal capsules can also be used, which contain a combination of the active ingredient with a base; suitable base substances are, for example, liquid triglycerides, polyethylene glycols or paraffin hydrocarbons.

Suitable preparation for parenteral administration are primarily aqueous solutions of an active ingredient in water-soluble form for example of a water-soluble salt, and also suspensions of the active ingredient, such as appropriate oily injection suspensions, using 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 viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, if necessary, also stabilizers.

Suitable pharmaceutical preparations for topical application are primarily creams, ointments, pastes, foams, tinctures and solutions, which contain from about 0.5 to about 20% of the active ingredient.

Creams are oil-in-water emulsions which contain more than 50% water. Oily bases used are primarily fatty alcohols, for example lauryl, cetyl or stearyl alcohol, fatty acids, for example palmitic or stearic acid, liquid to solid waxes, for example isopropyl myristate, wool wax or bees wax, and/or hydrocarbons, for example petroleum jelly (petrolatum) or paraffin oil. Suitable emulsifiers are surface-active substances having predominantly hydrophilic properties, such as appropriate non-ionic emulsifiers, for example fatty acid esters of polyalcohols or ethylene oxide adducts thereof, such as polyglycerol fatty acid esters or polyoxyethylene sorbitan fatty acid esters (Tweens), and also polyoxyethylene fatty alcohol ethers or fatty acid esters, or appropriate ionic emulsifiers, such as alkali metal salts of fatty alcohol sulfates, for example sodium lauryl sulfate, sodium cetyl

sulfate or sodium stearyl sulfate, which are customarily used in the presence of fatty alcohols, for example cetyl alcohol or stearyl alcohol. Substances added to the aqueous phase are, for example, agents which reduce the drying out of the cream, for example polyalcohols such as glycerol, sorbitol, propylene glycol and/or polyethylene glycols, and also preservatives, fragrances, etc.

Ointments are water-in-oil emulsions which contain up to 70%, but preferably from about 20% to about 50%, of water or aqueous phases. Suitable fatty phases are primarily hydrocarbons, for example petroleum jelly, paraffin oil and/or hard paraffins, which preferably contain suitable hydroxy compounds, such as fatty alcohols or esters thereof, for example cetyl alcohol or wool wax alcohols, or wool wax to improve the water-binding capacity. Emulsifiers are appropriate lipophilic substances, such as sorbitan fatty acid esters (Spans), for example sorbitan oleate and/or sorbitan isostearate. Substances added to the aqueous phase are, for example, humectants, such as polyalcohols, for example glycerol, propylene glycol, sorbitol and/or polyethylene glycol, and also preservatives, fragrances, etc.

Fatty ointments are anhydrous and contain as the base in particular a hydrocarbon, for example paraffin, petroleum jelly and/or liquid paraffins, and also natural or partially synthetic fat, for example coconut fatty acid triglyceride, or preferably hardened oils, for example hydrogenated groundnut or castor oil, as well as fatty acid partial esters of glycerol, for example glycerol mono- and distearate, and, for example the fatty alcohols which improve the water-absorbing capacity and have been mentioned in connection with the ointments, emulsifiers and/or additives .

Pastes are creams and ointments having secretion-absorbing powder constituents, such as metal oxides, for example titanium dioxide or zinc oxide, and in addition talc and/or aluminium silicates, which have the task of binding moisture or secretions which are present.

Foams are administered from pressurised containers and are liquid oil-

in-water emulsions in aerosol form, halogenated hydrocarbons, such as chlorofluoro-lower alkanes, for example dichlorodifluoromethane and dichlorotetrafluoroethane being used as propellants. Oil phases used are, inter alia, hydrocarbons, for example paraffin oil, fatty alcohols, for example cetyl alcoho (sic), fatty acid esters, for example isopropyl myristate, and/or other waxes. Emulsifiers used are, inter alia, mixtures of those with predominantly hydrophilic properties, such as polyoxyethylene sorbitan fatty acid esters (Tweens), and those with predominantly lipophilic properties, such as sorbitan fatty acid esters (Spans). In addition, the customary additives, such as preservatives, etc. are used.

Tinctures and solutions usually contain an aqueous-ethanolic base, to which, inter alia, polyalcohols, for example glycerol, glycols and/or polyethylene glycol are added as humectants to reduce evaporation, and fat-restoring substances, such as fatty acid esters with low polyethylene glycols, i.e. lipophilic substances soluble in the aqueous mixture as a replacement for the fatty substances removed from the skin by the ethanol, and, if necessary, other auxiliaries and additives.

The preparation of the pharmaceutical preparations suitable for topical application is carried out in a manner known per se, for example by dissolving or suspending the active ingredient in the base or in a portion thereof, if necessary. When processing the active ingredient as a solution, it is, as a rule, dissolved in one of the two phases of (sic) the emulsification; when processing as a suspension, it is mixed with a portion of the base after the emulsification and then added to the rest of the formulation.

The present invention also relates to the use of the compounds of the formulae I and the salts of such compounds having salt-forming properties, preferably for the treatment of inflammations, primarily inflammatory rheumatic disorders, particularly chronic arthritis.

The following examples illustrate the invention described above; however, these are in no way intended to be limiting in their scope.

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Temperatures are indicated in degrees Celsius.

Example 1:

95.7 g of finely powdered aluminum chloride are suspended in 180 ml of absolute methylene chloride. With stirring and cooling, 35 g of methyl 5-methoxybenzocyclobutene-1-carboxylate, dissolved in a little methylene chloride, are added dropwise at such a rate that the temperature remains below 30°. 50.5 g of benzoyl chloride are added dropwise at the same temperature and the mixture is then refluxed for 4 hours. After cooling, the reaction mixture is poured onto 600 g of ice. The organic phase is separated off and the aqueous phase is extracted 3 times with 150 ml of methylene chloride each time. The combined organic phases are washed once with 250 ml of water, dried over magnesium sulfate and evaporated. The excess benzoyl chloride is distilled off under a high vacuum and the residue is crystallized from ether/petroleum ether. Methyl 4-benzoyl-5-hydroxy-benzocyclobutene-1-carboxylate is obtained in the form of yellow crystals of m.p. 75-76°.

Example 2:

14 g of methyl 4-benzoyl-5-hydroxy-benzocyclobutene-1-carboxylate are dissolved in 150 ml of ether and the solution is added to 62 ml of 2N aqueous sodium hydroxide solution and 25 ml of water. This mixture is stirred vigorously for 1 hour at room temperature. The ether phase is separated off and extracted once with 75 ml of water. The aqueous phase is washed once with 75 ml of ether. The combined aqueous phases are rendered acidic with 2N aqueous hydrochloric acid and extracted 3 times with 100 ml of methylene chloride each time. The combined methylene chloride extracts are dried over magnesium sulfate and evaporated. Crystallization of the residue from ether/petroleum ether yields 4-benzoyl-5-hydroxy-benzocyclobutene-1-carboxylic acid as yellow crystals of m.p. 167-169°.

Example 3:

26.6 g of finely powdered aluminum chloride are suspended in 60 ml of methylene chloride. While stirring and cooling slightly, 9.61 g of methyl 5-methoxybenzocyclobutene-1-carboxylate dissolved in a little

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methylene chloride are added dropwise at room temperature. After stirring for 30 minutes at room temperature, 15.85 g of o-fluorobenzoyl chloride are added dropwise and the resultant reaction mixture is refluxed for 4 hours. After cooling, the reaction mixture is poured onto ice and the mixture is extracted well with methylene chloride. The combined organic phases are washed with water, dried over magnesium sulfate and evaporated. The yellow oily residue (20 g) is chromatographed on 400 g of silica gel using methylene chloride. Fractions 7-16 (50 ml fractions) are combined and concentrated. The residue is crystallized from ether/petroleum. Methyl 4-(o-fluorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate is obtained in the form of yellow crystals of m.p. 59-61°.

Example 4:

12.1 g of methyl 4-(m-chlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate are dissolved in 120 ml of ether, 100 ml of 2N aqueous sodium hydroxide solution are added and the mixture is stirred well at room temperature for 15 minutes. The ether phase is separated off and washed with water. The strongly yellow-coloured aqueous phase is washed with ether. The combined aqueous phases are rendered acidic with concentrated hydrochloric acid and extracted well with methylene chloride. The combined methylene chloride extracts are dried over magnesium sulfate and evaporated. Crystallization of the residue from ether/petroleum ether gives 4-(m-chlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid as yellow crystals of m.p. 138-139°.

Example 5:

28.26 g of aluminium trichloride are suspended in 70 ml of dichloromethane and 10.19 g of methyl 5-methoxybenzocyclobutene-1-carboxylate are added dropwise at 20 to 30° in the course of 15 minutes. The mixture is stirred for 30 minutes, 20.8 g of m-methylthiobenzoyl chloride are added dropwise in the course of 20 minutes, the mixture is stirred for 4 hours at room temperature and poured onto a mixture of 200 g of ice, 20 ml of concentrated hydrochloric acid and 200 ml of water, and the resultant mixture is stirred for 30 minutes and extracted by shaking, twice with 50 ml of dichloromethane each time and once with

50 ml of a mixture of trichloromethane and methanol (3:1). The organic phases are combined, washed twice with water, dried over magnesium sulfate, treated with kieselguhr and evaporated. Chromatography on silica gel using hexane/ethyl acetate (4:1) as the eluant gives methyl 4-(m-methylthiobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate as a yellow oil.

Example 6:

In an analogous manner to that described in Example 5, methyl 4-(o-methylthiobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate is obtained as a viscous yellow oil using 37.12 g of aluminium trichloride, 13.42 g of methyl 5-methoxybenzocyclobutene-1-carboxylate and 26.05 g of o-methylthiobenzoyl chloride as the starting materials.

Example 7:

In an analogous manner to that described in Example 5, methyl 4-(p-cyanobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate of m.p. 113-114° is obtained using 26.6 g of aluminium trichloride, 9.61 g of methyl 5-methoxybenzo-cyclobutene-1-carboxylate and 17.56 g of p-cyanobenzoyl chloride as the starting materials.

Example 8:

In an analogous manner to that described in Example 5, methyl 4-(2,4-dichlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate of m.p. 99-100° is obtained using 26.6 g of aluminium trichloride, 9.61 g of methyl 5-methoxybenzocyclobutene-1-carboxylate and 20.95 g of 2,4-dichlorobenzoyl chloride as the starting materials.

Example 9:

In an analogous manner to that described in Example 5, methyl 4-(3,4-dichlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate of m.p. 95-96° is obtained using 26.6 g of aluminium trichloride, 9.61 g of methyl 5-methoxybenzocyclobutene-1-carboxylate and 20.95 g of 3,4-dichlorobenzoyl chloride as the starting materials.

Example 10:

5.71 g of methyl 4-(o-methylthiobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate are dissolved in 70 ml of ether, 45 ml of 2N sodium hydroxide solution are added and the mixture is stirred at room temperature for 1 hour. The aqueous phase is separated off and the ether phase is twice extracted by shaking, with 25 ml of water each time. The aqueous phases are combined, acidified with 2N hydrochloric acid and extracted three times with 50 ml of dichloromethane each time. The extracts are combined, washed with water, dried over magnesium sulfate and evaporated. After recrystallizing the residue from dichloromethane/hexane, 4-(o-methylthiobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid of m.p. 177-178° is obtained.

Example 11:

In an analogous manner to that described in Example 10, 4-(m-methylthiobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid of m.p. 122-124° is obtained using 4.9 g of methyl 4-(m-methylthiobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate as the starting material.

Example 12:

3.0 g of 4-(α -hydroxybenzyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid are dissolved in 30 ml of dichloromethane and 30 g of pyridinium dichromate in 100 ml of dichloromethane are added dropwise with stirring in the course of 10 minutes. The mixture is stirred at room temperature for a further 7 hours, decanted from the black residue, filtered through silica gel and evaporated to dryness, and the residue is recrystallized from ether/hexane. 4-Benzoyl-5-hydroxy-benzocyclobutene-1-carboxylic acid of m.p. 167-169° is obtained.

The starting material can be prepared, for example, as follows:

3.84 g of methyl 5-methoxybenzocyclobutene-1-carboxylate are dissolved in 20 ml of dichloromethane and the solution is cooled to 0°, and, at 0 to 5°, first 3.16 g of titanium tetrachloride are added dropwise in the course of 3 minutes and then 3.83 g of dichlorodimethyl ether ($\text{Cl}_2\text{CHOCH}_3$) in the course of 20 minutes. The mixture is stirred at 0 to 5° for a

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further 5 minutes, gradually warmed to room temperature and stirred at 35° for a further 15 minutes. The mixture is then allowed to cool to room temperature and is poured onto 25 g of ice, the organic phase is separated off, the aqueous phase is three times further extracted by shaking with 10 ml of dichloromethane each time, the organic phases are combined, washed three times with 15 ml of ice-water each time, dried over magnesium sulfate and evaporated to dryness, and the residue is chromatographed on silica gel using dichloromethane as the eluant. Methyl 4-formyl-5-methoxybenzocyclobutene-1-carboxylate is obtained as a colourless oil.

1.6 g of the latter are dissolved in 25 ml of ether, 19 ml of 2N sodium hydroxide solution is added and the mixture is stirred vigorously at room temperature for 20 minutes. The ether phase is separated off, the aqueous phase is slightly acidified with 2N hydrochloric acid, twice extracted by shaking with 50 ml of a mixture of dichloromethane and ethyl acetate (4:1) each time, and the organic phases are washed with a little ice-water, dried over magnesium sulfate and evaporated to dryness. 4-Formyl-5-methoxy-benzocyclobutene-1-carboxylic acid is obtained as a yellowish oil.

0.91 g of the latter are dissolved in 5 ml of tetrahydrofuran and the solution is added dropwise to a boiling, freshly prepared solution of phenylmagnesium bromide (from 0.39 g of magnesium and 2.51 g of bromobenzene in 10 ml of tetrahydrofuran). The mixture is refluxed with stirring for 90 minutes and allowed to cool to room temperature, and 20 g of ice, followed by saturated ammonium chloride solution until the turbidity has disappeared, are added. The organic phase is separated off and the aqueous phase is twice extracted by shaking with ethyl acetate. The organic phases are combined, washed successively with 40% sodium bisulfite solution, saturated sodium bicarbonate solution and water, dried over magnesium sulfate and evaporated. 4-(α -Hydroxybenzyl)-5-methoxy-benzocyclobutene-1-carboxylic acid of m.p. 143-146° is obtained, which can be converted to 4-(α -hydroxybenzyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid in an analogous manner to that described in Example 20.

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Example 13:

10.65 g of 4-(2,6-dichlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carbonitrile are suspended in a mixture of 100 ml of concentrated hydrochloric acid and 100 ml of acetic acid and the suspension is stirred at 100° for 4 hours. The mixture is allowed to cool to room temperature, and the precipitate is filtered off with suction, washed thoroughly with water, allowed to dry in the air and recrystallized from trichloromethane/hexane with the addition of a little methanol. 4-(2,6-Dichlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid of m.p. 202-203° are obtained.

The starting material can be prepared, for example, as follows:

7.96 g of 5-methoxybenzo-cyclobutene-1-carbonitrile in 40 ml of dichloromethane are added dropwise to a suspension of 26.6 g of aluminium trichloride in 60 ml of dichloromethane with stirring at 20 to 30°. The mixture is stirred at 20 to 30° for 30 minutes and 20.95 g of 2,6-dichlorobenzoyl chloride are then added dropwise in the course of 15 minutes, and the mixture is stirred at room temperature for 4 hours and then poured into a mixture of 500 g of ice-water and 10 ml of concentrated hydrochloric acid. The mixture is stirred for a further 30 minutes, 200 ml of trichloromethane are added, the mixture is shaken vigorously, the organic phase is separated off, washed several times with half-concentrated hydrochloric acid, dried over magnesium sulfate and evaporated to dryness, and the residue is recrystallized from dichloromethane/hexane. 4-(2,6-Dichlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carbonitrile of m.p. 174-175° is obtained.

Example 14:

20 ml of concentrated hydrochloric acid and 10 ml of Cellusolve are added to 2 g 4-(2,6-dichlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carbonitrile and the reaction mixture is stirred at room temperature for 2 days. The mixture is stirred with 100 ml of water, and the precipitate is filtered off with suction and recrystallized from ether/hexane. 4-(2,6-Dichlorobenzoyl)-4-hydroxy-benzocyclobutene-1-carboxamide of m.p. 174° is obtained.

Example 15:

2 g of 4-(2,6-dichlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxamide are stirred in 20 ml of acetic acid and 20 ml of concentrated hydrochloric acid at 95-100° for 4 hours. The mixture is allowed to cool, and the precipitate is filtered off with suction, washed with water and recrystallized from trichloromethane/hexane. 4-(2,6-Dichlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid of m.p. 202-203° is obtained.

Example 16:

28 g of 4-(2,6-dichlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carbonitrile are dissolved in 50 ml of ethanol and the solution is cooled to 0°, and 10 g of 30% hydrogen peroxide are added dropwise with stirring at 0°. 1.0 ml of 30% sodium hydroxide solution is then slowly added dropwise and the mixture is stirred at room temperature for a further 6 hours. The mixture is neutralized with 6N hydrochloric acid and extracted by shaking thoroughly with 250 ml of dichloromethane. The organic phase is dried over magnesium sulfate and evaporated to dryness. After recrystallizing from ether/hexane, 4-(2,6-dichlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxamide of m.p. 174-175° is obtained.

Example 17:

4.86 g of 4-(2,6-dichlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carbonyl chloride are added dropwise with stirring in the course of 15 minutes to 15 ml of a 2.5% solution of ammonia in dichloromethane. The mixture is stirred at room temperature for 7 hours, small amounts of a finely crystalline precipitate are filtered off, the filtrate is evaporated to dryness, and the residue is chromatographed on silica gel using dichloromethane/methanol (15:1) as the eluant and recrystallized from ether/hexane. 4-(2,6-Dichlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxamide of m.p. 174° is obtained.

The starting material can be prepared, for example, as follows:

3.37 g of 4-(2,6-dichlorobenzoyl)-5-hydroxy-benzocyclobutene-1-

carboxylic acid are suspended in 100 ml of toluene, 0.1 ml of dimethylformamide (sic) and 1.64 g of thionyl chloride are added, and the mixture is heated to 80°, stirred at 80-90° for 2 hours and evaporated to dryness under reduced pressure. 4-(2,6-Dichlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carbonyl chloride is obtained, which can be used without further treatment.

Example 18:

5.0 g of methyl 4-(o-fluorobenzoyl)-5-methoxy-benzocyclobutene-1-carboxylate are dissolved in 100 ml of dichloromethane, 6.4 g of aluminium trichloride are added and the mixture is heated at the boil with stirring for 4 hours. It is poured onto ice, 20 ml of concentrated hydrochloric acid are added and the mixture is twice extracted by shaking, using 100 ml of dichloromethane each time. The organic phases are combined, washed with water, dried over magnesium sulfate and evaporated to dryness. The residue is chromatographed on silica gel and recrystallized from ether/hexane. Methyl 4-(o-fluorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate of m.p. 72-73° is obtained.

The starting material can be prepared, for example, as follows:

9.61 g of methyl 5-methoxybenzocyclobutene-1-carboxylate are added dropwise at 0 to 3° with stirring to a suspension of 26.6 g of aluminium trichloride in 60 ml of dichloromethane which has been cooled to 0°. The mixture is stirred at 0° for 30 minutes, 15.9 g of o-fluorobenzoyl chloride are added and the mixture is stirred at 0 to 3° for 82 hours. It is then poured into a mixture of 100 g of ice-water and 5 ml of concentrated hydrochloric acid, the mixture is twice extracted by shaking with 100 ml of dichloromethane each time, and the extracts are washed with water, dried over magnesium sulfate and evaporated to dryness. The residue is taken up in a little dichloromethane, petroleum ether is added until a precipitate starts to form and the mixture is placed in the cold. The precipitate formed is filtered off with suction, the filtrate is evaporated, and the residue is chromatographed on silica gel using dichloromethane as the eluant. After small first running, methyl 4-(o-fluorobenzoyl)-5-methoxy-benzocyclobutene-1-carboxylate of

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m.p. 73-74° is obtained.

Example 19:

1.0 g of 4-benzoyl-5-hydroxy-benzocyclobutene-1-methanol is dissolved in 50 ml of acetic acid and 4.0 g of chromium trioxide is added in portions. The mixture is stirred at 40° for 16 hours and evaporated to dryness under reduced pressure, and the residue is taken up in 20 ml of water and extracted by shaking with 80 ml of dichloromethane (sic). The organic phase is dried over magnesium sulfate and evaporated. After recrystallizing the residue from ether/hexane, 4-benzoyl-5-hydroxy-benzocyclobutene-1-carboxylic acid of m.p. 167-169° is obtained.

The starting material can be prepared, for example, as follows:

A solution of 1.92 g of methyl 5-methoxybenzocyclobutene-1-carboxylate in 30 ml of ether is added dropwise in the course of 30 minutes, with stirring, to a suspension of 0.21 g of lithium aluminium hydride in 30 ml of ether. The mixture is stirred for 1 hour, a further 1.0 g of lithium aluminium hydride is added and the mixture is stirred for a further 2 hours. 5 ml of water and, after some time, 12.5 ml of 2N sulfuric acid are then added dropwise, the mixture is stirred for 30 minutes, the ether phase is separated off, the aqueous phase is extracted twice more by shaking with ether, and the ether phase is dried over magnesium sulfate and evaporated to dryness. 5-Methoxybenzocyclobutene-1-methanol is obtained in the form of a colourless oil.

1.64 g of the latter are dissolved in 30 ml of dichloromethane and 1.21 g of triethylamine are added. 0.94 g of acetyl chloride in 10 ml of dichloromethane are then added dropwise at 10 to 20° in the course of 5 minutes. The mixture is stirred at room temperature for a further 5 hours, water is added and the organic phase is separated off. This is washed with water, dried over magnesium sulfate and evaporated. 1-Acetoxymethyl-5-methoxy-benzocyclobutene is obtained as a colourless oil.

1.78 g of the latter are dissolved in 20 ml of dichloromethane and the

solution is added dropwise to a suspension of 4.6 g of aluminium trichloride in 40 ml of dichloromethane, with stirring. The mixture is stirred for 30 minutes and 2.4 g of benzoyl chloride, dissolved in 10 ml of dichloromethane, are then added dropwise at 20 to 30°. The mixture is stirred at room temperature for 4 hours and poured onto ice, 5 ml of concentrated hydrochloric acid are added, the mixture is stirred for 30 minutes, and the organic phase is separated off, washed three times with water, dried over magnesium sulfate and evaporated to dryness. 1-Acetoxymethyl-4-benzoyl-5-hydroxy-benzocyclobutene is obtained as a yellowish oil.

2.2 g of the latter are dissolved in 80 ml of methanol, a solution of 1.5 g of potassium carbonate in 50 ml of water is added and the mixture is stirred at room temperature for 6 hours. It is then evaporated to dryness under reduced pressure, the residue is taken up in 50 ml of water, the solution is twice extracted by shaking, using 100 ml of dichloromethane each time, the combined extracts are dried over magnesium sulfate and evaporated to dryness, and the residue is purified by chromatography on a silica gel column using dichloromethane/ethyl acetate (9:1) as the eluant. 4-Benzoyl-5-hydroxy-benzocyclobutene-1-methanol is obtained as a yellow viscous oil.

Example 20:

5 g of methyl 5-benzoyloxybenzocyclobutene-1-carboxylate are dissolved in 50 ml of 1,2-dichloroethane, 11.8 g of aluminium trichloride are added and the mixture is heated at the boil for 35 hours. The reaction mixture is poured onto ice and 20 ml of concentrated hydrochloric acid are added. The organic phase is separated off and the aqueous phase is extracted twice by shaking with dichloromethane. The organic phases are combined, dried over magnesium sulfate and evaporated. The evaporation residue is recrystallized from ether/hexane. Methyl 4-benzoyl-5-hydroxy-benzocyclobutene-1-carboxylate is obtained; yellowish crystals of m.p. 75-76°.

The starting material can be prepared, for example, as follows:

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1000 ml of a 1 molar solution of boron tribromide in dichloromethane are poured over 19.5 g of methyl 5-methoxybenzocyclobutene-1-carboxylate and the mixture is refluxed for 6 hours. The mixture is evaporated to dryness, the residue is extracted by shaking with a mixture of 2000 ml of dichloromethane and 1000 ml of water, and the organic phase is separated off, washed with water, dried over magnesium sulfate and evaporated to dryness. Methyl 5-hydroxybenzocyclobutene-1-carboxylate is obtained in the form of white crystals of m.p. 108-109° (from ether/hexane).

27 g of methyl 5-hydroxybenzocyclobutene-1-carboxylate are dissolved in 2000 ml of dichloromethane and 18 g of triethylamine are added. 25 g of benzoyl chloride are then added in portions in the course of 5 minutes at 10-20° with stirring, the mixture is stirred for 5 hours at room temperature, 200 ml of water are added, and the organic phase is separated off, dried over magnesium sulfate and evaporated to dryness. Methyl 5-benzoyloxybenzocyclobutene-1-carboxylate is obtained as a colourless viscous oil.

Example 21:

The following compounds can also be prepared in an analogous manner to that described in Examples 1, 3, 5, 12, 18 and 20:

Methyl 4-(o-chlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate as a yellow oil,

Methyl 4-(m-chlorobenzene (sic))-5-hydroxy-benzocyclobutene-1-carboxylate as a yellow oil,

Methyl 4-(m-methoxycarbonylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, m.p. 109-110°,

4-(o-Fluorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxamide,

Methyl 4-(m-methylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate as a yellow oil,

Methyl 4-(p-chlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate as yellow crystals of m.p. 82-84°,

Methyl 4-(p-methylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate as yellow crystals of m.p. 100-102°,

Methyl 4-(2,6-dichlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate

Methyl 4-(o-bromobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, oil,
Methyl 4-(o-acetoxybenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate,
Methyl 4-(m-trifluoromethylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate,
Methyl 4-(m-trifluoromethylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate,
Methyl 4-(p-methoxybenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate,
Methyl 4-(o-methoxybenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate,
Methyl 4-(2,6-dimethylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate,
Methyl 4-(2,6-dimethoxybenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate,
Methyl 4-(o-methylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate.

Example 22:

The following compounds also can be prepared in an analogous manner to that describes in Examples 2, 4, 10, 12, 13, 15 and 19:

4-(o-Chlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid in the form of pale yellow crystals of m.p. 151-152°,
4-(m-Methylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid in the form of yellow crystals of m.p. 142-144°,
4-(p-Chlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid in the form of yellow crystals of m.p. 181-183°,
4-(p-Methylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid in the form of yellow crystals of m.p. 199-201°,
4-(o-Methylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid of m.p. 120.5-121°,
4-(o-Fluorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid of m.p. 138-139°,
4-(2,4-Dichlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid of m.p. 180-181°,
4-(3,4-Dichlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid of m.p. 189-190°,
4-(o-Bromobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid of m.p. 157-158°,
4-(o-Acetoxybenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid,
4-(o-Trifluoromethylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic

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acid,

4-(m-Trifluoromethylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid,

4-(o-Methoxybenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid,

4-(p-Methoxybenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid,

4-(p-Cyanobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid,

m.p. 164-165°,

4-(2,6-Dimethylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid and

4-(2,6-Dimethoxybenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid.

Example 23:

Tablets containing 25 mg of active ingredient, for example 4-benzoyl-5-hydroxy-benzocyclobutene-1-carboxylic acid or a salt, for example the sodium salt, thereof, can be prepared as follows:

Constituents (for 1000 tablets):

Active ingredient	25.0 g
Lactose	100.7 g
Wheat starch	7.5 g
Polyethylene glycol 6000	5.0 g
Talc	5.0 g
Magnesium stearate	1.8 g
Demineralized water	q.s.

Preparation:

All solid ingredients are first forced through a sieve of 0.6 mm mesh width. The active ingredient, the lactose, the talc, the magnesium stearate and half of the starch are then mixed in. The other half of the starch is suspended in 40 ml of water and this suspension is added to a boiling solution of the polyethylene glycol in 100 ml of water and the mixture is granulated, adding water if necessary. The granules are dried overnight at 35°, forced through a sieve of 1.2 mm mesh width and compressed to give biconcave tablets about 6 mm in diameter.

In an analogous manner, tablets in each case containing 25 mg of another of the compounds of the formula I named in Examples 1 to 22 can be

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prepared, it also being possible for compounds in which R is carboxyl also to be present in the form of salts with bases, for example as the sodium salt.

Example 24:

Chewable tablets containing 30 mg of active ingredient, for example 4-benzoyl-5-hydroxy-benzocyclobutene-1-carboxylic acid or a salt, for example the sodium salt, thereof, can be prepared, for example, as follows:

Composition (for 1000 tablets):

Active ingredient	30.0 g
Mannitol	267.0 g
Lactose	179.5 g
Talc	20.0 g
Glycine	12.5 g
Stearic acid	10.0 g
Saccharin	1.0 g
5% gelatin solution	q.s.

Preparation:

All solid ingredients are first forced through a sieve of 0.25 mm mesh width. The mannitol and the lactose are mixed, granulated while adding gelatin solution, and the granules are forced through a sieve of 2 mm mesh width, dried at 50° and again forced through a sieve of 1.7 mm mesh width. The active ingredient, the glycine and the saccharin are carefully mixed in, the mannitol, the lactose granules, the stearic acid and the talc are added and the whole is thoroughly mixed and compressed to give biconcave tablets about 10 mm in diameter having a breaking groove on the top.

In an analogous manner, tablets in each case containing 30 mg of another of the compounds of the formula I named in Examples 1 to 22 can be prepared, it being possible for compounds in which R is carboxyl also to be present in the form of salts with bases, for example as the sodium salt.

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Example 25:

Tablets containing 100 mg of active ingredient, for example 4-benzoyl-5-hydroxy-benzocyclobutene-1-carboxylic acid or a salt, for example the sodium salt, thereof, can be prepared as follows:

Composition (for 1000 tablets):

Active ingredient	100.0 g
Lactose	248.5 g
Maize starch	17.5 g
Polyethylene glycol 6000	5.0 g
Talc	15.0 g
Magnesium stearate	4.0 g
Demineralized water	q.s.

Preparation:

The solid ingredients are first forced through a sieve of 0.6 mm mesh width. Active ingredient, lactose, talc, magnesium stearate and half of the starch are then intimately mixed. The other half of the starch is suspended in 65 ml of water and this suspension is added to a boiling solution of the polyethylene glycol in 260 ml of water. The paste obtained is added to the powdered substances and the whole is mixed and granulated, if necessary with addition of water. The granules are dried overnight at 35°, forced through a sieve of 1.2 mm mesh width and compressed to give biconcave tablets about 10 mm in diameter having a breaking groove on the top.

In an analogous manner, tablets containing 100 mg of another compound of the formula I according to Examples 1 to 22 can be prepared, it being possible for compounds in which R is carboxyl also to be present in the form of salts with bases, for example as the sodium salt.

Patent claims

for the contracting states: BE, CH, LI, DE, FR, IT, LU, NL, SE, GB.

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Example 25:

Tablets containing 100 mg of active ingredient, for example 4-benzoyl-5-hydroxy-benzocyclobutene-1-carboxylic acid or a salt, for example the sodium salt, thereof, can be prepared as follows:

Composition (for 1000 tablets):

Active ingredient	100.0 g
Lactose	248.5 g
Maize starch	17.5 g
Polyethylene glycol 6000	5.0 g
Talc	15.0 g
Magnesium stearate	4.0 g
Demineralized water	q.s.

Preparation:

The solid ingredients are first forced through a sieve of 0.6 mm mesh width. Active ingredient, lactose, talc, magnesium stearate and half of the starch are then intimately mixed. The other half of the starch is suspended in 65 ml of water and this suspension is added to a boiling solution of the polyethylene glycol in 260 ml of water. The paste obtained is added to the powdered substances and the whole is mixed and granulated, if necessary with addition of water. The granules are dried overnight at 35°, forced through a sieve of 1.2 mm mesh width and compressed to give biconcave tablets about 10 mm in diameter having a breaking groove on the top.

In an analogous manner, tablets containing 100 mg of another compound of the formula I according to Examples 1 to 22 can be prepared, it being possible for compounds in which R is carboxyl also to be present in the form of salts with bases, for example as the sodium salt.

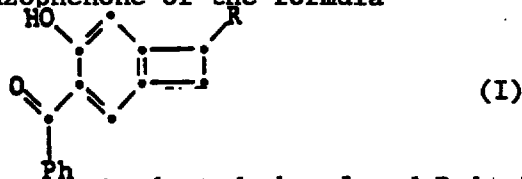
Patent claims

for the contracting states: BE, CH, LI, DE, FR, IT, LU, NL, SE, GB.



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1. A novel substituted benzophenone of the formula



in which Ph is unsubstituted or substituted phenyl and R is free, esterified or amidated carboxyl, or a salt thereof.

2. A compound according to patent claim 1, in which Ph is unsubstituted phenyl or phenyl which is substituted by lower alkyl, lower alkoxy, lower alkylthio, lower alkanoyloxy, halogen, trifluoromethyl, carboxyl, lower alkoxy carbonyl, cyano and/or nitro and R is carboxyl, carboxyl esterified with a lower aliphatic alcohol or carbamyl in which the amino group is unsubstituted amino or amino mono- or disubstituted by lower aliphatic radicals, or a salt thereof with a base.

3. A compound according to patent claim 1, in which Ph is unsubstituted phenyl or phenyl which is mono- or disubstituted by lower alkyl, lower alkoxy, lower alkanoyloxy, halogen, trifluoromethyl, cyano and/or nitro and R is carboxyl, carboxyl esterified with a lower aliphatic alcohol or carbamyl in which the amino group is unsubstituted amino or amino mono- or disubstituted by lower aliphatic radicals, or a salt thereof with a base.

4. A compound according to patent claim 1, in which Ph is unsubstituted phenyl or phenyl which is mono- or disubstituted by lower alkyl having not more than 4 C atoms, lower alkoxy having not more than 4 C atoms, lower alkanoyloxy having not more than 4 C atoms, halogen of atomic number of not more than 35 and/or trifluoromethyl and R is carboxyl, lower alkoxy carbonyl having not more than 5 C atoms or carbamyl or N-lower alkyl-carbamyl having not more than 5 C atoms, or a salt thereof with a base.

5. A compound according to patent claim 1, in which Ph is unsubstituted phenyl or phenyl which is mono- or disubstituted by lower alkyl having not more than 4 C atoms, lower alkylthio having not more than 4 C atoms, lower alkoxy carbonyl having not more than 4 C atoms in the lower alkoxy



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part, halogen of atomic number of not more than 35 and/or cyano, and R is carboxyl or carbamyl, or also lower alkoxy carbonyl having not more than 4 C atoms in the lower alkoxy part, or a salt thereof with a base.

6. A compound according to patent claim 1, in which Ph is phenyl which is monosubstituted or disubstituted by lower alkyl having not more than 4 C atoms or halogen of atomic number of not more than 35, and R is carboxy or carbamyl, or also lower alkoxy carbonyl having not more than 4 C atoms in the lower alkoxy part, or a salt thereof with a base.

7. A compound according to patent claim 1, in which Ph is phenyl which is monosubstituted in the 2-position by halogen of atomic number of not more than 35 and R is carboxyl or carbamyl, or a salt thereof with a base.

8. Methyl 4-(benzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, ethyl (sic) 4-(o-chlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-(m-chlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-(m-methylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-(p-chlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-(p-methylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-(2,6-dichlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-(2,4-dichlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-(3,4-dichlorobenzoyl)-5-hydroxy-benzoylcyclobutene-1-carboxylate, methyl 4-(o-bromobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-(o-acetoxybenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-(o-methylthiobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-(o-trifluoromethylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 44 (sic)-(m-trifluoromethylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-(p-methoxybenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-(o-methoxybenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-x (sic)(p-cyanobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-(2,6-dimethylbenzoyl)-5-hydroxy-benzoyl(sic)cyclobutene-1-carboxylate, methyl 4-(2,6-dimethoxybenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-(o-methylbenzoyl)-5-hydroxy-benzocyclobutene-1-



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carboxylate or methyl 4-(o-fluorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate according to claim 1.

9. 4-(Benzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(m-chlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(m-methylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(p-chlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(2,6-dichlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(3,4-dichlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(o-acetoxybenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, methyl 4-(m-methylthiobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate (sic), 4-(o-methylthiobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(o-trifluoromethylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(m-trifluoromethylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(o-methoxybenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(p-methoxybenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(p-cyanobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(2,6-dimethylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(m-methylthiobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(2,6-dimethoxybenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(p-methylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(o-chlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(o-methylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid or 4-(2,4-dichlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid or in each case a salt thereof with a base according to claim 1.

10. 4-(o-Fluorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid or a salt thereof with a base according to claim 1.

11. 4-(o-Bromobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid or a salt thereof with a base according to claim 1.

12. 4-(o-Fluorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxamide, methyl 4-(m-methoxycarbonylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate or 4-(2,6-dichlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxamide according to claim 1.



* C L H S *

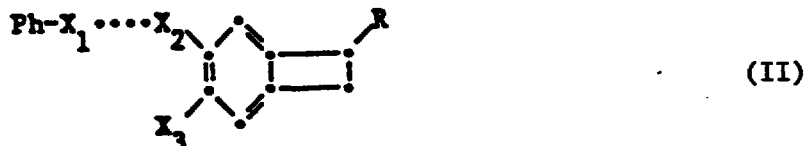
13. A compound according to one of patent claims 1, 3, 4 and 8 to 11 for use in a process for the therapeutic treatment of the human or animal body.

14. A compound according to one of patent claims 2, 5, 6, 7 and 12 for use in a process for the therapeutic treatment of the human or animal body.

15. A compound according to one of patent claims 1, 3, 4 and 8 to 11 for use according to patent claim 13 as an antiinflammatory agent and/or antinociceptive agent.

16. A compound according to one of patent claims 2, 5, 6, 7 and 12 for use according to patent claim 14 as an antiinflammatory agent and/or antinociceptive agent.

17. Process for the preparation of novel substituted benzophenones of the formula I according to claim 1, and their salts, which comprises subjecting a compound or a mixture of compounds of the formula



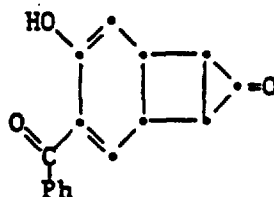
in which X_1 and X_2 together are a group of the formula $-C(=O)-O$ bonded via the carbonyl group to the radical Ph and X_3 is hydrogen or one of the radicals X_1 and X_2 is a group of the formula $-C(=O)-Z$ the other is hydrogen and X_2 is a group $R'O-$, in which R' is lower alkyl or a hydroxyl protective group R'' or, if X_3 is hydrogen, R' can also be hydrogen, to acid treatment and solvolytically decomposing the primary product, or oxidizing or solvolysing X_4 in a compound of the formula



in which X_4 is a radical which can be converted oxidatively or solvolytically into a group of the formula $-C(=O)-Ph$ to the desired group of the formula $-C(=O)-Ph$, or treating compound (sic) of the formula

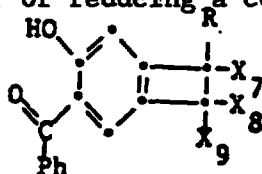


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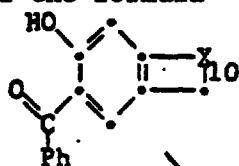
(XI)

or a phenoxide salt thereof, with water or an alcohol or with ammonia or an amine having at least one hydrogen atom and, if necessary, isolating the isomer of the formula I from a mixture of isomers obtainable according to the process, or reducing a compound of the formula



(XIII)

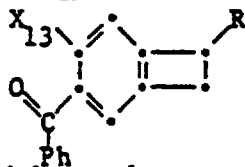
in which at least one of the radicals X_7 and X_8 is free, etherified or esterified hydroxyl and a radical X_7 or X_8 which differs from this, and also X_9 is hydrogen, or X_7 is hydrogen and X_8 and X_9 are free or functionally modified oxo, or a phenoxide and/or carboxylate salt thereof, or, solvolytically converting the functionally modified carboxyl group in a functional carboxyl derivative thereof which is different from an ester or amide of the formula I, or in a salt thereof, into a free, esterified or amidated carboxyl group, or oxidizing the radical X_{11} in a compound of the formula



(XXI)

in which X_{10} is a group of the formula $\text{CH}-X_{11}$

and X_{11} is a radical which can be converted oxidatively into a group R, to a group R, or converting X_{13} in a compound of the formula



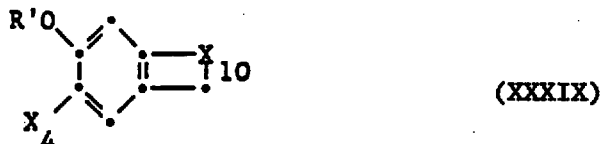
(XXXVII)

in which X_{13} is a group which can be converted into hydroxyl, or in a salt thereof, to hydroxyl, it being possible to combine the oxidative conversion of a radical X_4 to a group $\text{Ph}-\text{C}(=\text{O})-$ in compound (sic) of the formula V with the oxidative conversion of a radical X_{10} to a group

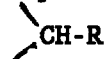


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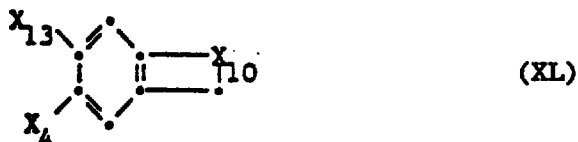
in compounds of the formula XXI by using a corresponding compound of the formula



as the starting material, or to combine the solvolytic conversion of a radical X_4 to a group Ph-C(=O)- in compounds of the formula V with the solvolytic conversion of a radical X_{10} to a group



in compound (sic) of the formula XXI and/or the solvolytic conversion of X_{13} to hydroxyl in compounds of the formula XXXVII by using a corresponding compound of the formula XXXIX or a compound of the formula



as the starting material, and, if appropriate, removing the hydroxyl protective group after carrying out the reaction, and, if desired, converting the compound obtainable according to the process into another compound of the formula I and/or converting a compound obtainable according to the process into a salt or converting a salt obtainable according to the process into the free compound or into another salt.

18. A pharmaceutical preparation containing a compound according to one of patent claims 1, 3, 4 and 8 to 11 in addition to customary pharmaceutical adjuncts and/or carriers.

19. A pharmaceutical preparation containing a compound according to one of patent claims 2, 5, 6, 7 and 12 in addition to customary pharmaceutical adjuncts and/or carriers.

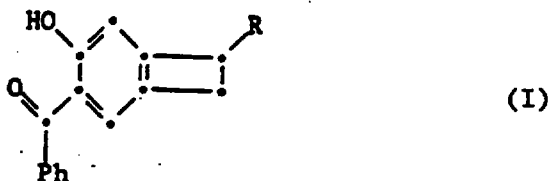
Patent claims

for the contracting state AT

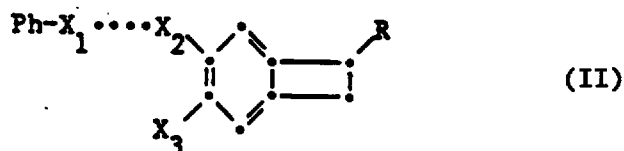
1. A process for the preparation of novel substituted benzophenones of the formula



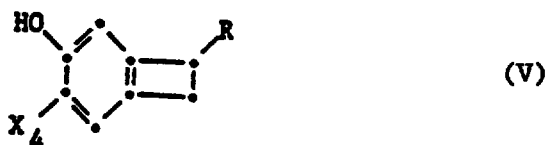
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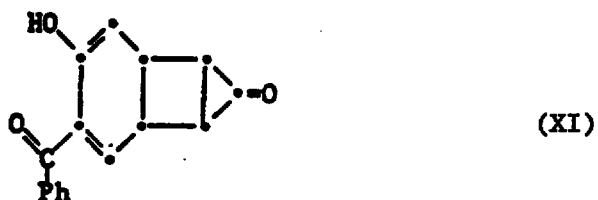
in which Ph is unsubstituted or substituted phenyl and R is free, esterified or amidated carboxyl, and their salts, which comprises subjecting a compound or a mixture of compounds of the formula



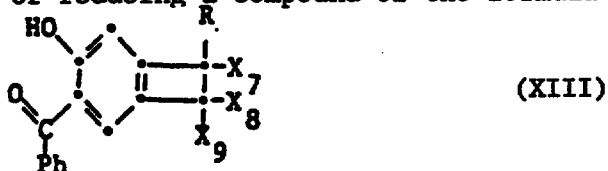
in which X_1 and X_2 together are a group of the formula $-C(=O)-O$ bonded via the carbonyl group to the radical Ph and X_3 is hydrogen or one of the radicals X_1 and X_3 is a group of the formula $-C(=O)-Z$ and the other is hydrogen and X_2 is a group $R'O-$, in which R' is lower alkyl or a hydroxyl protective group R'' or, if X_3 is hydrogen, R' can also be hydrogen, to acid treatment and solvolytically decomposing the primary product, or oxidizing or solvolysing X_4 in a compound of the formula



in which X_4 is a radical which can be converted oxidatively or solvolytically into a group of the formula $-C(=O)-Ph$ to the desired group of the formula $-C(=O)-Ph$, or treating compound (sic) of the formula



or a phenoxide salt thereof, with water or an alcohol or with ammonia or an amine having at least one hydrogen atom and, if necessary, isolating the isomer of the formula I from a mixture of isomers obtainable according to the process, or reducing a compound of the formula

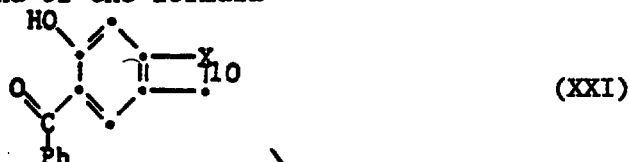


in which at least one of the radicals X_7 and X_8 is free, etherified or esterified hydroxyl and a radical X_7 or X_8 which differs from this, and also X_9 , is hydrogen, or X_7 is hydrogen and X_8 and X_9 are free or functionally modified oxo, or a phenoxide and/or carboxylate salt



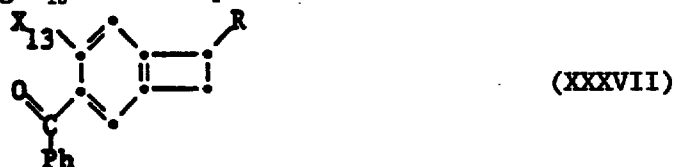
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thereof, or, solvolytically converting the functionally modified carboxyl group in a functional carboxyl derivative thereof which is different from an ester or amide of the formula I, or in a salt thereof, into a free, esterified or amidated carboxyl group, or oxidizing the radical X_{11} in a compound of the formula



in which X_{10} is a group of the formula CH-X_{11}

and X_{11} is a radical which can be converted oxidatively into a group R to a group R, or converting X_{13} in a compound of the formula



in which X_{13} is a group which can be converted into hydroxyl, or in a salt thereof, to hydroxyl, it being possible to combine the oxidative conversion of a radical X_4 to a group Ph-C(=O)- in compound (sic) of the formula V with the oxidative conversion of a radical X_{10} to a group



in compounds of the formula XXI by using a corresponding compound of the formula



as the starting material, or to combine the solvolytic conversion of a radical X_4 to a group Ph-C(=O)- in compounds of the formula V with the solvolytic conversion of a radical X_{10} to a group



in compound (sic) of the formula XXI and/or the solvolytic conversion of X_{13} to hydroxyl in compounds of the formula XXXVII by (sic) a corresponding compound of the formula XXXIX or a compound of the formula



.... (sic) removing (sic) reaction, and if desired converting the



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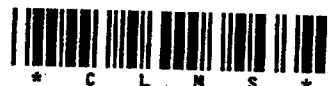
compound obtainable according to the process into another compound of the formula I and/or converting a compound obtainable according to the process into a salt or converting a salt obtainable according to the process into the free compound or into another salt.

2. A process according to patent claim 1, wherein compounds of the formula I, in which Ph is unsubstituted phenyl or phenyl which is substituted by lower alkyl, lower alkoxy, lower alkylthio, lower alkanoyloxy, halogen, trifluoromethyl, carboxyl, lower alkoxycarbonyl, cyano and/or nitro and R is carboxyl, carboxyl esterified with a lower aliphatic alcohol or carbamyl in which the amino group is unsubstituted amino or amino mono- or disubstituted by lower aliphatic radicals, or a salt thereof with a base, are prepared.

3. A process according to patent claim 1, wherein compounds of the formula I, in which Ph is unsubstituted phenyl or phenyl which is mono- or disubstituted by lower alkyl having not more than 4 C atoms, lower alkoxy having not more than 4 C atoms, lower alkanoyloxy having not more than 4 C atoms, halogen of atomic number of not more than 35 and/or trifluoromethyl and R is carboxyl, lower alkoxycarbonyl having not more than 5 C atoms or carbamyl or N-lower alkyl-carbamyl having not more than 5 C atoms, or a salt thereof with a base, are prepared.

4. A process according to patent claim 1, wherein compounds of the formula I, in which Ph is unsubstituted phenyl or phenyl which is mono- or disubstituted by lower alkyl having not more than 4 C atoms, lower alkylthio having not more than 4 C atoms, lower alkoxycarbonyl having not more than 4 C atoms in the lower alkoxy part, halogen of atomic number of not more than 35 and/or cyano, and R is carboxyl or carbamyl, or also lower alkoxycarbonyl having not more than 4 C atoms in the lower alkoxy part, or a salt thereof with a base, are prepared.

5. A process according to patent claim 1, wherein compounds of the formula I, in which Ph is phenyl which is monosubstituted or disubstituted by lower alkyl having not more than 4 C atoms or halogen of atomic number of not more than 35, and R is carboxyl or carbamyl, or



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also lower alkoxycarbonyl having not more than 4 C atoms in the lower alkoxy part, or a salt thereof with a base, are prepared.

6. A process according to patent claim 1, wherein compounds of the formula I, in which Ph is phenyl which is monosubstituted in the 2-position by halogen of atomic number of not more than 35 and R is carboxyl or carbamoyl, or a salt thereof with a base, are prepared.

7. A process according to patent claim 1, methyl 4-(benzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-(o-chlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-(m-chlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-(m-methylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-(p-chlorobenzoyl (sic))-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-(p-methylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-(2,6-dichlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-(2,4-dichlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-(3,4-dichlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-(o-bromobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-(o-acetoxybenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-(o-methylthiobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-(o-trifluoromethylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-(m-trifluoromethylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, 4-(p-methoxybenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-(o-methoxybenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-(p-cyanobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-(m-methylthiobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-(m-methoxycarbonylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, 4-(2,6-dichlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxamide, methyl 4-(2,6-dimethylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate, methyl 4-(2,6-dimethoxybenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate or methyl 4-(o-methylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylate is prepared.

8. A process according to patent claim 1, wherein 4-(benzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(m-chlorobenzoyl)-5-



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hydroxy-benzocyclobutene-1-carboxylic acid, 4-(m-methylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(p-chlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(2,6-dichlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(3,4-dichlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(o-acetoxybenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(o-methylthiobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(o-trifluoromethylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(m-trifluoromethylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(o-methoxybenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(p-methoxybenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(p-cyanobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(2,6-dimethylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(m-methylthiobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(2,6-dimethoxybenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(p-methylbenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid, 4-(o-chlorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid or in each case a salt thereof with a base is prepared.

9. A process according to patent claim 1, wherein 4-(o-fluorobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid or a salt thereof with a base is prepared.

10. A process according to patent claim 1, wherein 4-(o-bromobenzoyl)-5-hydroxy-benzocyclobutene-1-carboxylic acid or a salt thereof with a base is prepared.

11. A process for the preparation of pharmaceutical preparations, which comprises mixing a compound obtainable according to one of patent claims 1-10 with customary pharmaceutical adjuncts and/or carriers.



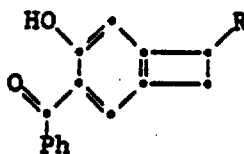
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As printed

Claims

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

1. A novel substituted benzophenone of the formula



in which Ph represents unsubstituted or substituted phenyl and R represents free, esterified or amidated carboxy, or a salt thereof.

2. A compound according to claim 1, in which Ph represents phenyl that is unsubstituted or substituted by lower alkyl, lower alkoxy, lower alkylthio, lower alkanoyloxy, halogen, trifluoromethyl, carboxy, lower alkoxy carbonyl, cyano and/or nitro, and R represents carboxy, carboxy esterified by a lower aliphatic alcohol, or carbamoyl having as amino group amino that is unsubstituted or mono- or di-substituted by lower aliphatic radicals, or a salt thereof with a base.

3. A compound according to claim 1, in which Ph represents phenyl that is unsubstituted or mono- or di-substituted by lower alkyl, lower alkoxy, lower alkanoyloxy, halogen, trifluoromethyl, cyano and/or nitro, and R represents carboxy, carboxy esterified by a lower aliphatic alcohol, or carbamoyl having as amino group amino that is unsubstituted or mono- or di-substituted by lower aliphatic radicals, or a salt thereof with a base.

4. A compound according to claim 1, in which Ph represents phenyl that is unsubstituted or mono- or di-substituted by lower alkyl having up to and including 4 C-atoms, lower alkoxy having up to and including 4 C-atoms, lower alkanoyloxy having up to and including 4 C-atoms, halogen having an atomic number of up to and including 35, and/or trifluoromethyl and R represents carboxy, lower alkoxy carbonyl having up to and including 5 C-atoms, or carbamoyl or N-lower alkylcarbamoyl having up to and including 5 C-atoms, or a salt thereof with a base.

5. A compound according to claim 1, in which Ph represents phenyl that is unsubstituted or mono- or di-substituted by lower alkyl having up to and including 4 C-atoms, lower alkylthio having up to and including 4 C-atoms, lower alkoxy carbonyl having up to and including 4 C-atoms in the lower alkoxy moiety, halogen having an atomic number of up to and including 35, and/or cyano, and R represents carboxy or carbamoyl, and also lower alkoxy carbonyl having up to and including 4 C-atoms in the lower alkoxy moiety, or a salt thereof with a base.

6. A compound according to claim 1, in which Ph represents phenyl that is mono- or di-substituted by lower alkyl having up to and including 4 C-atoms or by halogen having an atomic number of up to and including 35, and R represents carboxy or carbamoyl, and also lower alkoxy carbonyl having up to and including 4 C-atoms in the lower alkoxy moiety, or a salt thereof with a base.

7. A compound according to claim 1, in which Ph represents phenyl that is monosubstituted in the 2-position by halogen having an atomic number of up to and including 35, and R represents carboxy or carbamoyl, or a salt thereof with a base.

8. 4-(Benzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(*o*-chlorobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(*m*-chlorobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(*m*-methylbenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(*p*-chlorobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(*p*-methylbenzoyl)-5-



hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(2,6-dichlorobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(2,4-dichlorobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(3,4-dichlorobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(o-bromobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(o-acetoxybenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(o-methylthiobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(o-trifluoromethylbenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(m-trifluoromethylbenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(p-methoxybenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(o-methoxybenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(p-cyanobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(2,6-dimethylbenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(2,6-dimethoxybenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(o-methylbenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester or 4-(o-fluorobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester according to claim 1.

9. 4-(Benzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid, 4-(m-chlorobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid, 4-(m-methylbenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid, 4-(p-chlorobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid, 4-(2,6-dichlorobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid, 4-(3,4-dichlorobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid, 4-(o-acetoxybenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid, 4-(m-methylthiobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(o-methylthiobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid, 4-(o-trifluoromethylbenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid, 4-(m-trifluoromethylbenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid, 4-(o-methoxybenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid, 4-(p-methoxybenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid, 4-(p-cyanobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid, 4-(2,6-dimethylbenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid, 4-(m-methylthiobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid, 4-(2,6-dimethoxybenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid, 4-(o-methylbenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid or 4-(2,4-dichlorobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid or a salt of one said compounds with a base according to claim 1.

10. 4-(o-Fluorobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid or a salt thereof with a base according to claim 1.

11. 4-(o-Bromobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid or a salt thereof with a base according to claim 1.

12. 4-(o-Fluorobenzoyl)-5-hydroxybenzocyclobutene-1-carboxamide, 4-(m-methoxycarbonylbenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester or 4-(2,6-dichlorobenzoyl)-5-hydroxybenzocyclobutene-1-carboxamide according to claim 1.

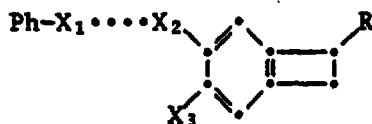
13. A compound according to any one of claims 1, 3, 4 and 8 to 11 for use in a therapeutic method of treating the human or animal body.

14. A compound according to any one of claims 2, 5, 6, 7 and 12 for use in a therapeutic method of treating the human or animal body.

15. A compound according to any one of claims 1, 3, 4 and 8 to 11 for use according to claim 13 as anti-inflammatory agent and/or antinociceptive agent.

16. A compound according to any one of claims 2, 5, 6, 7 and 12 for use according to claim 14 as anti-inflammatory agent and/or antinociceptive agent.

17. A process for the preparation of a novel substituted benzophenone of formula I according to claim 1, or of a salt thereof, characterised in that a compound or a mixture of compounds of the formula



(II)

in which X_1 and X_2 together represent a group of the formula $-C(=O)-O-$ that is bonded via the carbonyl group to the radical Ph and X_3 represents hydrogen, or one of the radicals X_1 and X_3 represents a group of the formula $-C(=O)-Z$, the other represents hydrogen and X_2 represents a group $R'O-$ in which R' represents lower alkyl or a hydroxy-protecting group R'' , or, if X_3 represents hydrogen, R' may also represent hydrogen, is subjected to acid treatment and the primary product is decomposed solvolitically, or, in a compound of the formula

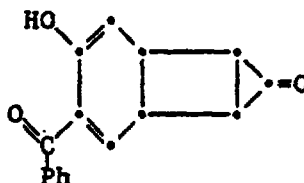


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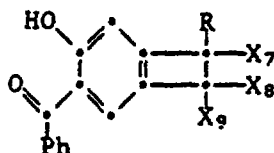
(v)

in which X_4 represents a radical that can be converted by oxidation or solvolysis into a group of the formula $-C(=O)-Ph$, X_4 is oxidised or solvolysed to the desired group of the formula $-C(=O)-Ph$, or a compound of the formula



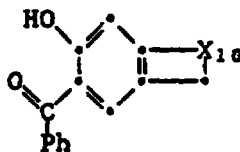
(XI)

or a phenolate salt thereof, is treated with water, an alcohol or ammonia or an amine having at least one hydrogen atom and, if necessary, the isomer of the formula I is isolated from a mixture of isomers obtainable according to the process, or a compound of the formula



(XIII)

or a phenolate and/or carboxylate salt thereof, in which formula at least one of the radicals X_7 and X_8 represents free, etherified or esterified hydroxy and a radical X_7 or X_8 that does not represent free, etherified or esterified hydroxy represents hydrogen, as does X_9 , or X_7 represents hydrogen and X_8 and X_9 represent free or functionally modified oxo, is reduced, or, in a functional carboxy derivative of the same that is other than an ester or amide of the formula I, or in a salt thereof, the functionally modified carboxy group is converted by solvolysis into a free, esterified or amidated carboxy group, or, in a compound of the formula



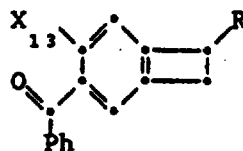
(XXI)

in which X_{10} represents a group of the formula $\text{CH}-X_{11}$

and X_{11} represents a radical that can be converted by oxidation into a group R, the radical X_{11} is oxidised to a group R, or, in a compound of the formula



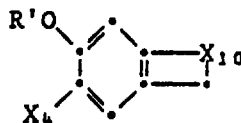
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(XXXVII)

in which X_{13} represents a group that can be converted into hydroxy, or in a salt thereof, X_{13} is converted into hydroxy, it being possible to combine the oxidative conversion of a radical X_4 into a group Ph-C(=O)- in compounds of the formula V with the oxidative conversion of a radical X_{10} into a group CH-R

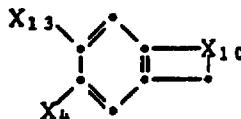
in compounds of the formula XXI by starting from a corresponding compound of the formula



(XXXIX)

or to combine the solvolytic conversion of a radical X_4 into a group Ph-C(=O)- in compounds of the formula V with the solvolytic conversion of a radical X_{10} into a group CH-R

in compounds of the formula XXI and/or with the solvolytic conversion of X_{13} into hydroxy in compounds of the formula XXXVII by starting from a corresponding compound of the formula XXXIX or a compound of the formula



(XL)

the hydroxy-protecting group is, if appropriate, removed after carrying out the reaction and, if desired, the compound obtainable according to the process is converted into a different compound of the formula I and/or a compound obtainable according to the process is converted into a salt, or a salt obtainable according to the process is converted into the free compound or into a different salt.

18. A pharmaceutical composition containing a compound according to any one of claims 1, 3, 4 and 8 to 11, together with customary pharmaceutical adjuvants and/or carriers.

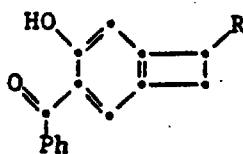
19. A pharmaceutical composition containing a compound according to any one of claims 2, 5, 6, 7 and 12, together with customary pharmaceutical adjuvants and/or carriers.

Claims

for the Contracting State: AT

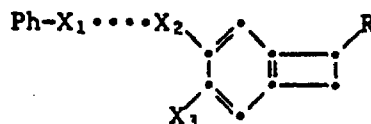
1. A process for the preparation of a novel substituted benzophenone of the formula





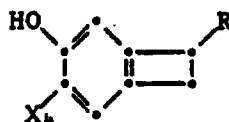
(I)

in which Ph represents unsubstituted or substituted phenyl and R represents free, esterified or amidated carboxy, or of a salt thereof, characterised in that a compound or a mixture of compounds of the formula



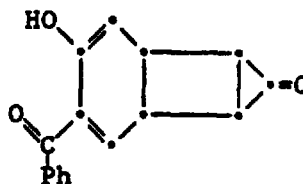
(II)

in which X_1 and X_2 together represent a group of the formula $-C(=O)-O-$ that is bonded via the carbonyl group to the radical Ph and X_3 represents hydrogen, or one of the radicals X_1 and X_3 represents a group of the formula $-C(=O)-Z$, the other represents hydrogen and X_2 represents a group $R'O-$ in which R' represents lower alkyl or a hydroxy-protecting group R'' , or, if X_3 represents hydrogen, R' may also represent hydrogen, is subjected to acid treatment and the primary product is decomposed solvolytically, or, in a compound of the formula



(V)

in which X_4 represents a radical that can be converted by oxidation or solvolysis into a group of the formula $-C(=O)-Ph$, X_4 is oxidised or solvolysed to the desired group of the formula $-C(=O)-Ph$, or a compound of the formula

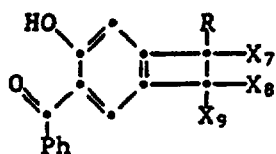


(XI)

or a phenolate salt thereof, is treated with water, an alcohol or ammonia or an amine having at least one hydrogen atom and, if necessary, the isomer of the formula I is isolated from a mixture of isomers obtainable according to the process, or a compound of the formula

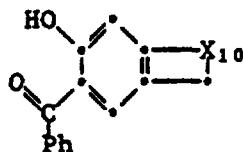


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(XIII)

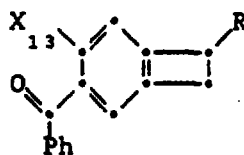
or a phenolate and/or carboxylate salt thereof, in which formula at least one of the radicals X_7 and X_8 represents free, etherified or esterified hydroxy and a radical X_7 or X_8 that does not represent free, etherified or esterified hydroxy represents hydrogen, as does X_9 , or X_7 represents hydrogen and X_8 and X_9 represent free or functionally modified oxo, is reduced, or, in a functional carboxy derivative of the same that is other than an ester or amide of the formula I, or in a salt thereof, the functionally modified carboxy group is converted by solvolysis into a free, esterified or amidated carboxy group, or, in a compound of the formula



(XXI)

in which X_{10} represents a group of the formula $\text{CH}-X_{11}$

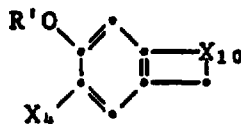
and X_{11} represents a radical that can be converted by oxidation into a group R, the radical X_{11} is oxidised to a group R, or, in a compound of the formula



(XXXVII)

in which X_{13} represents a group that can be converted into hydroxy, or in a salt thereof, X_{13} is converted into hydroxy, it being possible to combine the oxidative conversion of a radical X_4 into a group Ph-C(=O)- in compounds of the formula V with the oxidative conversion of a radical X_{10} into a group CH-R

in compounds of the formula XXI by starting from a corresponding compound of the formula



(XXXIX)

or to combine the solvolytic conversion of a radical X_4 into a group Ph-C(=O)- in compounds of the formula V with the solvolytic conversion of a radical X_{10} into a group CH-R

in compounds of the formula XXI and/or with the solvolytic conversion of X_{13} into hydroxy in compounds of the formula XXXVII by starting from a corresponding compound of the formula XXXIX or a compound of the formula





(XL)

the hydroxy-protecting group is, if appropriate, removed after carrying out the reaction and, if desired, the compound obtainable according to the process is converted into a different compound of the formula I and/or a compound obtainable according to the process is converted into a salt, or a salt obtainable according to the process is converted into the free compound or into a different salt.

2. A process according to claim 1, characterised by preparing a compound of the formula I, in which Ph represents phenyl that is unsubstituted or substituted by lower alkyl, lower alkoxy, lower alkylthio, lower alkanoyloxy, halogen, trifluoromethyl, carboxy, lower alkoxy carbonyl, cyano and/or nitro, and R represents carboxy, carboxy esterified by a lower aliphatic alcohol, or carbamoyl having an amino group amino that is unsubstituted or mono- or di-substituted by lower aliphatic radicals, or a salt thereof with a base.

3. A process according to claim 1, characterised by preparing a compound of the formula I, in which Ph represents phenyl that is unsubstituted or mono- or di-substituted by lower alkyl having up to and including 4 C-atoms, lower alkoxy having up to and including 4 C-atoms, lower alkanoyloxy having up to and including 4 C-atoms, halogen having an atomic number of up to and including 35, and/or trifluoromethyl, and R represents carboxy, lower alkoxy carbonyl having up to and including 5 C-atoms, or carbamoyl or N-lower alkylcarbamoyl having up to and including 5 C-atoms, or a salt thereof with a base.

4. A process according to claim 1, characterised by preparing a compound of the formula I, in which Ph represents phenyl that is unsubstituted or mono- or di-substituted by lower alkyl having up to and including 4 C-atoms, lower alkylthio having up to and including 4 C-atoms, lower alkoxy carbonyl having up to and including 4 C-atoms in the lower alkoxy moiety, halogen having an atomic number of up to and including 35, and/or cyano, and R represents carboxy or carbamoyl, and also lower alkoxy carbonyl having up to and including 4 C-atoms in the lower alkoxy moiety, or a salt thereof with a base.

5. A process according to claim 1, characterised by preparing a compound of the formula I, in which Ph represents phenyl that is mono- or di-substituted by lower alkyl having up to and including 4 C-atoms or by halogen having an atomic number of up to and including 35, and R represents carboxy or carbamoyl, and also lower alkoxy carbonyl having up to and including 4 C-atoms in the lower alkoxy moiety, or a salt thereof with a base.

6. A process according to claim 1, characterised by preparing a compound of the formula I, in which Ph represents phenyl that is monosubstituted in the 2-position by halogen having an atomic number of up to and including 35, and R represents carboxy or carbamoyl, or a salt thereof with a base.

7. A process according to claim 1, characterised by preparing 4-(benzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(*o*-chlorobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(*m*-chlorobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(*m*-methylbenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(*p*-chlorobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(*p*-methylbenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(2,6-dichlorobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(2,4-dichlorobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(3,4-dichlorobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(*o*-bromobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(*o*-acetoxybenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(*o*-methoxybenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(*o*-methylthiobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(*o*-trifluoromethylbenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(*m*-trifluoromethylbenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(*p*-methoxybenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(*p*-cyanobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(*m*-methylthiobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(*m*-methoxycarbonylbenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(2,6-dichlorobenzoyl)-5-hydroxybenzocyclobutene-1-carboxamide, 4-(2,6-dimethylbenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester, 4-(2,6-dimethoxybenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester or 4-(*o*-methylbenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid methyl ester.

8. A process according to claim 1, characterised by preparing 4-(benzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid, 4-(*m*-chlorobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid, 4-(*m*-methylbenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid, 4-(*p*-chlorobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid, 4-(2,6-dichlorobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid, 4-(3,4-dichlorobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid, 4-(*o*-acetoxybenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid, 4-(*o*-methylthiobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid, 4-(*o*-trifluoromethylbenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid, 4-(*m*-trifluoromethylbenzoyl)-5-hydroxybenzocyclobutene-1-



carboxylic acid, 4-(*o*-methoxybenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid, 4-(*p*-methoxybenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid, 4-(*p*-cyanobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid, 4-(2,6-dimethylbenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid, 4-(*m*-methylthiobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid, 4-(2,6-dimethoxybenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid, 4-(*p*-methylbenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid, 4-(*o*-chlorobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid or a salt of one of said compounds with a base.

9. A process according to claim 1, characterised by preparing 4-(*o*-fluorobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid or a salt thereof with a base.

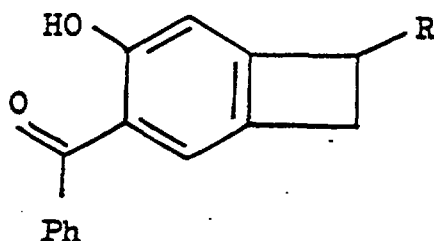
10. A process according to claim 1, characterised by preparing 4-(*o*-bromobenzoyl)-5-hydroxybenzocyclobutene-1-carboxylic acid or a salt thereof with a base.

11. A process for the preparation of a pharmaceutical composition, characterised in that a compound obtainable by a process according to any one of claims 1 to 10 is combined with customary pharmaceutical adjuvants and/or carriers.

Revendications

pour les Etats contractants: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE.

1. Une nouvelle benzophénone substituée de formule



dans laquelle Ph représente un groupe phényle non substitué ou substitué et R représente un groupe carboxy libre, estérifié ou amidé, ou un sel de ce composé.

2. Un composé selon la revendication 1, dans lequel Ph représente un groupe phényle non substitué ou substitué par des groupes alkyle inférieurs, alcoxy inférieurs, alkylthio inférieurs, alcanoyloxy inférieurs, des halogènes, des groupes trifluorométhyle, carboxy, (alcoxy inférieur)-carbonyle, cyano et/ou nitro, et R représente un groupe carboxy, un groupe carboxy estérifié par un alcool aliphatique inférieur ou un groupe carbamyle portant en tant que groupe amino un groupe amino non substitué ou mono- ou di-substitué par des groupes aliphatiques inférieurs, ou un sel d'un tel composé et d'une base.

3. Un composé selon la revendication 1, dans lequel Ph représente un groupe phényle non substitué ou mono- ou di-substitué par des groupes alkyle inférieurs, alcoxy inférieurs, alcanoyloxy inférieurs, des halogènes, des groupes trifluorométhyle, cyano et/ou nitro, et R représente un groupe carboxy, un groupe carboxy estérifié par un alcool aliphatique inférieur ou un groupe carbamyle portant en tant que groupe amino un groupe amino non substitué ou mono- ou di-substitué par des groupes aliphatiques inférieurs, ou un sel d'un tel composé et d'une base.

4. Un composé selon la revendication 1, dans lequel Ph représente un groupe phényle non substitué ou mono- ou di-substitué par des groupes alkyle inférieurs contenant jusqu'à 4 atomes de carbone inclus, alcoxy inférieurs contenant jusqu'à 4 atomes de carbone inclus, alcanoyloxy inférieurs contenant jusqu'à 4 atomes de carbone inclus, des halogènes de numéro atomique allant jusqu'à 35 inclus et/ou des groupes trifluorométhyle, et R représente un groupe carboxy, (alcoxy inférieur)-carbonyle contenant jusqu'à 5 atomes de carbone inclus, ou carbamyle ou N-(alkyle inférieur)carbamyle contenant jusqu'à 5 atomes de carbone inclus, ou un sel d'un tel composé et d'une base.

5. Un composé selon la revendication 1, dans lequel Ph représente un groupe phényle non substitué ou mono- ou di-substitué par des groupes alkyle inférieurs contenant jusqu'à 4 atomes de carbone inclus, alkylthio inférieurs contenant jusqu'à 4 atomes de carbone inclus, (alcoxy inférieur)-carbonyle contenant jusqu'à 4 atomes de carbone inclus dans la partie alcoxy inférieur, des halogènes de numéro atomique allant jusqu'à 35 inclus et/ou des groupes cyano, et R représente un groupe carboxy ou carbamyle, ou encore (alcoxy inférieur)-carbonyle contenant jusqu'à 4 atomes de carbone inclus dans la partie alcoxy inférieur, ou un sel d'un tel composé et d'une base.

6. Un composé selon la revendication 1, dans lequel Ph représente un groupe phényle mono- ou di-substitué par des groupes alkyle inférieurs contenant jusqu'à 4 atomes de carbone inclus ou des halogènes de numéro



atomique allant jusqu'à 35 inclus et R représente un groupe carboxy ou carbamyle, ou encore (alcoxy inférieur)-carbonyle contenant jusqu'à 4 atomes de carbone inclus dans la partie alcoxy inférieur, ou un sel d'un tel composé et d'une base.

7. Un composé selon la revendication 1, dans lequel Ph représente un groupe phényle monosubstitué par un halogène de numéro atomique allant jusqu'à 35 inclus en position 2 et R représente un groupe carboxy ou carbamyle, ou un sel d'un tel composé et d'une base.

8. Le 4-(benzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle, le 4-(o-chlorobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle, le 4-(m-chlorobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle, le 4-(p-chlorobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle, le 4-(p-méthylbenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle, le 4-(2,6-dichlorobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle, le 4-(2,4-dichlorobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle, le 4-(3,4-dichlorobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle, le 4-(o-bromobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle, le 4-(o-acétoxybenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle, le 4-(o-méthylthiobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle, le 4-(o-trifluorométhylbenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle, le 4-(m-trifluorométhylbenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle, le 4-(p-méthoxybenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle, le 4-(o-méthoxybenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle, le 4-(p-cyanobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle, le 4-(2,6-diméthylbenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle, le 4-(2,6-diméthoxybenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle, le 4-(o-méthylbenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle, ou le 4-(o-fluorobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle, selon la revendication 1.

9. L'acide 4-(benzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,

l'acide 4-(m-chlorobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,

l'acide 4-(m-méthylbenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,

l'acide 4-(p-chlorobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,

l'acide 4-(2,6-dichlorobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,

l'acide 4-(3,4-dichlorobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,

l'acide 4-(o-acétoxybenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,

le 4-(m-méthylthiobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle,

l'acide 4-(o-méthylthiobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,

l'acide 4-(o-trifluorométhylbenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,

l'acide 4-(m-trifluorométhylbenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,

l'acide 4-(o-méthoxybenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,

l'acide 4-(p-méthoxybenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,

l'acide 4-(p-cyanobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,

l'acide 4-(2,6-diméthylbenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,

l'acide 4-(m-méthylthiobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,

l'acide 4-(2,6-diméthoxybenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,

l'acide 4-(p-méthylbenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,

l'acide 4-(o-chlorobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,

l'acide 4-(o-méthylbenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique, ou

l'acide 4-(2,4-dichlorobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,

ou un sel de l'un de ces composés et d'une base selon la revendication 1.

10. L'acide 4-(o-fluorobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique ou un sel de cet acide et d'une base selon la revendication 1.

11. L'acide 4-(o-bromobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique ou un sel de ce composé et d'une base selon la revendication 1.

12. Le 4-(o-fluorobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxamide, le 4-(m-méthoxycarbonylbenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle ou le 4-(2,6-dichlorobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxamide selon la revendication 1.

13. Un composé selon l'une des revendications 1, 3, 4 et 8 à 11, pour l'utilisation dans un procédé pour le traitement thérapeutique de l'organisme humain ou animal.

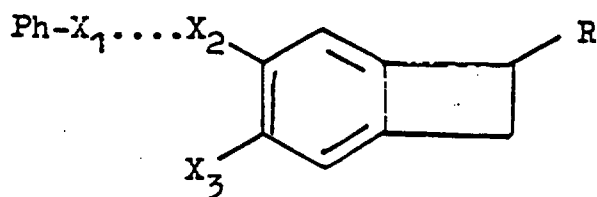
14. Un composé selon l'une des revendications 2, 5, 6, 7 et 12, pour l'utilisation dans un procédé pour le traitement thérapeutique de l'organisme humain ou animal.

15. Un composé selon l'une des revendications 1, 3, 4 et 8 à 11, pour l'utilisation selon la revendication 13 en tant qu'agent anti-inflammatoire et/ou antinociceptif.

16. Un composé selon l'une des revendications 2, 5, 6, 7 et 12, pour l'utilisation selon la revendication 14 en tant qu'agent anti-inflammatoire et/ou antinociceptif.

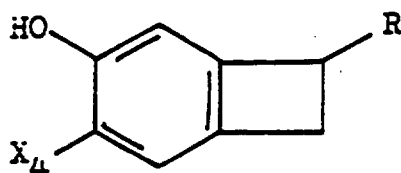
17. Procédé de préparation des nouvelles benzophénones substituées de formule I selon la revendication 1, et de leurs sels, caractérisé en ce que l'on soumet à traitement par un acide un composé ou mélange de composés de formule





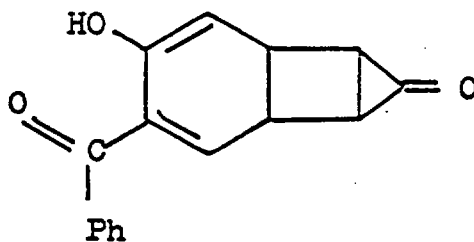
(II),

dans laquelle X_1 et X_2 représentent ensemble un groupe de formule $-C(=O)-O$ relié au cycle Ph par l'intermédiaire du groupe carbonyle et X_3 représente l'hydrogène ou bien l'un des symboles X_1 et X_3 représente un groupe de formule $-C(=O)-Z$, l'autre l'hydrogène et X_2 un groupe $R'O-$ dans lequel R' représente un groupe alkyle inférieur ou un groupe R'' protecteur du groupe hydroxy ou bien encore, lorsque X_3 représente l'hydrogène, également l'hydrogène, et on soumet le produit obtenu en premier à décomposition par solvolysé, ou bien, dans un composé de formule



(V)

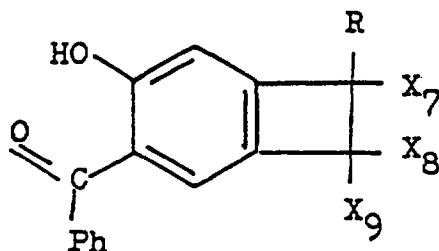
dans laquelle X_4 représente un groupe convertible par oxydation ou solvolysé en un groupe de formule $-C(=O)-Ph$, on oxyde ou on solvolysé X_4 en le groupe recherché de formule $-C(=O)-Ph$, ou bien on traite un composé de formule



(XI)

ou un phénate de ce composé par l'eau, un alcool ou l'ammoniac ou une amine portant au moins un atome d'hydrogène et, à partir d'un mélange d'isomères éventuellement obtenu par ce procédé, on isole si c'est nécessaire l'isomère de formule I, ou bien on réduit un composé de formule

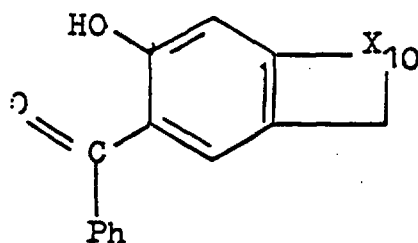




(XIII),

dans laquelle l'un au moins des symboles X_7 et X_8 représente un groupe hydroxy éventuellement étherifié ou estérifié et l'autre, ainsi que X_9 , représentent l'hydrogène, ou bien X_7 représente l'hydrogène et X_8 et X_9 un groupe oxo qui a éventuellement subi une modification fonctionnelle, ou un phénate et/ou carboxylate d'un tel composé, ou bien,

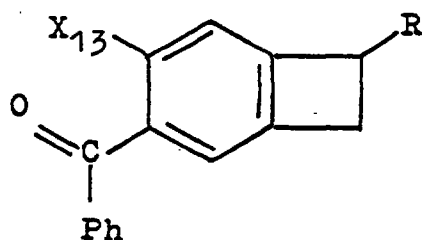
dans un dérivé carboxylé fonctionnel de formule I autre qu'un ester ou un amide de formule I, ou dans un sel d'un tel composé, on convertit le groupe carboxy à fonction modifiée par solvolysé en un groupe carboxy éventuellement estérifié ou amidé, ou bien
dans un composé de formule



(XXI)

dans laquelle X_{10} représente un groupe de formule $\text{CH}-X_{11}$

et X_{11} représente un groupe convertible par oxydation en un groupe R, on oxyde le groupe X_{11} en un groupe R, ou bien,
dans un composé de formule

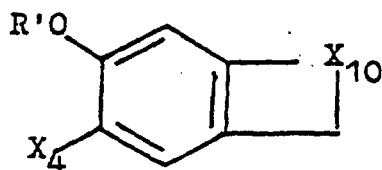


(XXXVII)

dans laquelle X_{13} représente un groupe convertible en un groupe hydroxy, ou dans un sel d'un tel composé, on convertit X_{13} en un groupe hydroxy, étant précisé que la conversion par oxydation d'un groupe X_4 en un groupe $\text{Ph}-\text{C}(=\text{O})$ - dans un composé de formule V peut être combinée avec la conversion par oxydation d'un groupe X_{10} en un groupe $\text{CH}-\text{R}$

dans les composés de formule XXI en partant d'un composé correspondant de formule

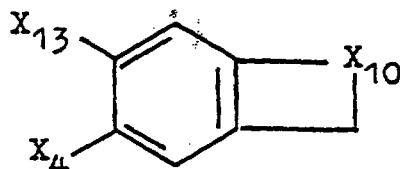




(XXXIX)

et que la conversion par solvolysé d'un groupe X_4 et un groupe Ph-C(=O)- dans les composés de formule V peut être associée à la conversion par solvolysé d'un groupe X_{10} en un groupe $>\text{CH-R}$

dans le composé de formule XXI et/ou avec la conversion par solvolysé de X_{13} en un groupe hydroxy dans les composés de formule XXXVII, en partant d'un composé correspondant de formule XXXIX ou d'un composé de formule



(XL)

le cas échéant, après la conversion, on élimine le groupe protecteur du groupe hydroxy et, si on le désire, on convertit le composé obtenu par le procédé en un autre composé de formule I et/ou un composé obtenu par le procédé en un sel ou un sel obtenu par le procédé en le composé libre ou en un autre sel.

18. Une composition pharmaceutique contenant un composé selon l'une des revendications 1, 3, 4 et 8 à 11, avec des produits auxiliaires et/ou véhicules pharmaceutiques usuels.

19. Une composition pharmaceutique contenant un composé selon l'une des revendications 2, 5, 6, 7 et 12, avec des produits auxiliaires et/ou véhicules pharmaceutiques usuels.

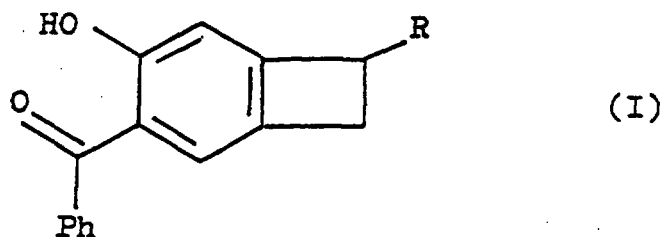
Revendications

pour l'Etat contractant: AT

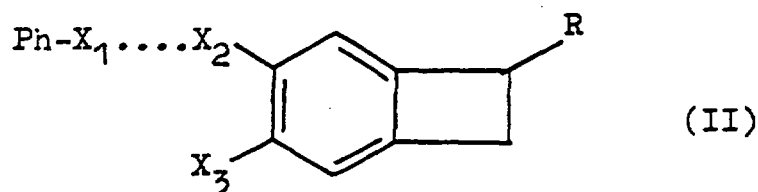
1. Procédé de préparation de nouvelles benzophénones substituées de formule



NDS

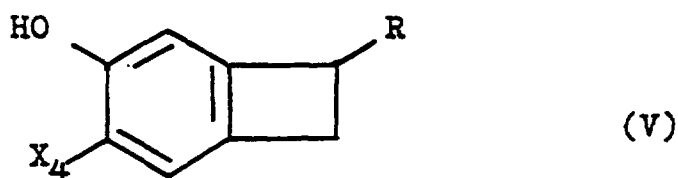


dans laquelle Ph représente un groupe phényle non substitué ou substitué et R représente un groupe carboxy libre, estérifié ou amidé, et de leurs sels, caractérisé en ce que l'on soumet à un traitement par un acide un composé ou mélange de composés de formule



dans laquelle X_1 et X_2 représentent ensemble un groupe de formule $-C(=O)-O$ relié au cycle Ph par l'intermédiaire du groupe carbonyle et X_3 représente l'hydrogène, ou bien l'un des symboles X_1 et X_3 représente un groupe de formule $-C(=O)-Z$, l'autre l'hydrogène et X_2 un groupe $R'O-$ dans lequel R' représente un groupe alkyle inférieur ou un groupe protecteur du groupe hydroxy R'' ou bien encore, lorsque X_3 représente l'hydrogène, également l'hydrogène, et on décompose le produit obtenu en premier par solvolysé, ou bien

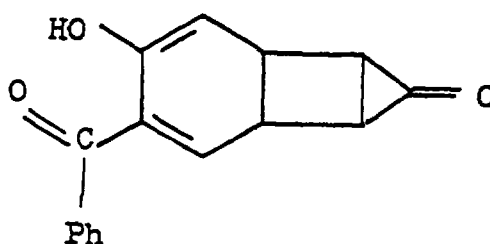
dans un composé de formule



dans laquelle X_4 représente un groupe convertible par oxydation ou par solvolysé en un groupe de formule $-C(=O)-Ph$, on convertit X_4 en le groupe recherché de formule $-C(=O)-Ph$ par oxydation ou solvolysé, ou bien on traite un composé de formule

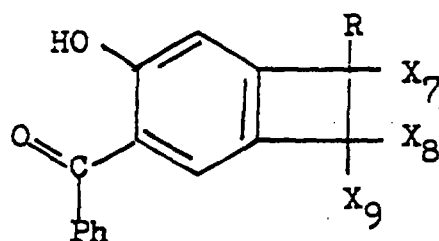


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(XI)

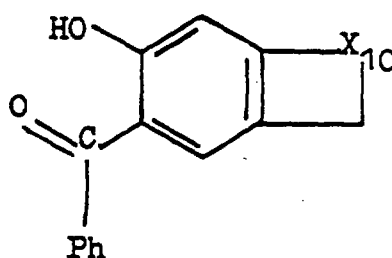
ou un phénate de ce composé par l'eau, un alcool ou l'ammoniac ou une amine portant au moins un atome d'hydrogène et à partir d'un mélange d'isomères obtenu par ce procédé, on isole, lorsque c'est nécessaire, l'isomère de formule I, ou bien on réduit un composé de formule



(XIII),

dans laquelle l'un au moins des symboles X_7 et X_8 représente un groupe hydroxy éventuellement étherifié ou estérifié et l'autre, ainsi que X_9 , représentent l'hydrogène, ou bien X_7 représente l'hydrogène et X_8 et X_9 un groupe oxo qui a éventuellement subi une modification fonctionnelle, ou un phénate et/ou un carboxylate d'un tel composé, ou bien

dans un dérivé carboxylé fonctionnel de formule I autre qu'un ester ou un amide de formule I, ou dans un sel d'un tel composé, on convertit le groupe carboxy qui a subi une modification fonctionnelle par solvolysé en un groupe carboxy éventuellement estérifié ou amidé, ou bien dans un composé de formule

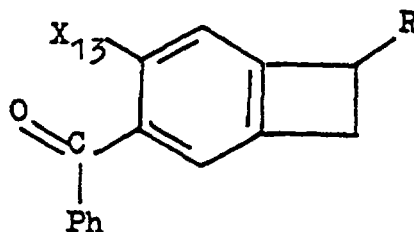


(XXI)

dans laquelle X_{10} représente un groupe de formule $\text{CH}-X_{11}$

et X_{11} un groupe convertible par oxydation en un groupe R, on convertit le groupe X_{11} en un groupe R par oxydation, ou bien, dans un composé de formule

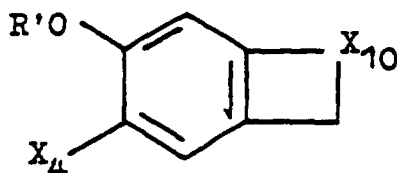




(XXXVII)

dans laquelle X_{13} représente un groupe convertible en un groupe hydroxy, ou dans un sel d'un tel composé, on convertit X_{13} en un groupe hydroxy, la conversion par oxydation d'un groupe X_4 dans un groupe $\text{Ph-C}(=\text{O})$ - d'un composé de formule V pouvant être combinée avec la conversion par oxydation d'un groupe X_{10} d'un groupe CH-R

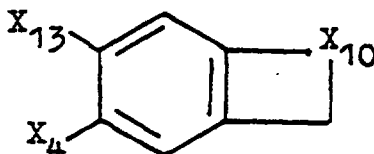
de composés de formule XXI, en partant d'un composé correspondant de formule



(XXXIX)

et la conversion par solvolysé d'un groupe X_4 dans un groupe $\text{Ph-C}(=\text{O})$ - de composés de formule V pouvant être associée avec la conversion par solvolysé d'un groupe X_{10} dans un groupe CH-R

d'un composé de formule XXI et/ou la conversion par solvolysé de X_{13} en un groupe hydroxy dans les composés de formule XXXVII, en partant d'un composé correspondant de formule XXXIX ou d'un composé de formule



(XL)

le cas échéant, après avoir réalisé la réaction, on élimine le groupe protecteur du groupe hydroxy et, si on le désire, on convertit le composé obtenu par le procédé en un autre composé de formule I et/ou un composé obtenu par le procédé en un sel ou un sel obtenu par le procédé en le composé libre ou en un autre sel.

2. Procédé selon la revendication 1, caractérisé en ce que l'on prépare des composés de formule I dans laquelle Ph représente un groupe phényle non substitué ou substitué par des groupes alkyle inférieurs, alcoxy inférieurs, alkylthio inférieurs, alcanoyloxy inférieurs, des halogènes, des groupes trifluorométhyle, carboxy, (alcoxy inférieur)-carbonyle, cyano et/ou nitro et R représente un groupe carboxy, un groupe carboxy estérifié par un alcool aliphatique inférieur ou un groupe carbamyle portant en tant que groupe amino un groupe amino non substitué ou mono- ou di-substitué par des groupes alkyle inférieurs, ou un sel d'un tel composé et d'une



base.

3. Procédé selon la revendication 1, caractérisé en ce que l'on prépare des composés de formule I dans laquelle Ph représente un groupe phényle non substitué ou mono- ou di-substitué par des groupes alkyle inférieurs contenant jusqu'à 4 atomes de carbone inclus, alcoxy inférieurs contenant jusqu'à 4 atomes de carbone inclus, alcanoyloxy inférieurs contenant jusqu'à 4 atomes de carbone inclus, des halogènes de numéro atomique allant jusqu'à 35 inclus et/ou des groupes trifluorométhyle, et R représente un groupe carboxy, (alcoxy inférieur)-carbonyle contenant jusqu'à 5 atomes de carbone inclus ou carbamyle ou N(alkyle inférieur)-carbamyle contenant jusqu'à 5 atomes de carbone inclus, ou un sel d'un tel composé et d'une base.

4. Procédé selon la revendication 1, caractérisé en ce que l'on prépare des composés de formule I dans laquelle Ph représente un groupe phényle non substitué ou mono- ou di-substitué par des groupes alkyle inférieurs contenant jusqu'à 4 atomes de carbone inclus, alkylthio inférieurs contenant jusqu'à 4 atomes de carbone inclus, (alcoxy inférieur)-carbonyle contenant jusqu'à 4 atomes de carbone inclus dans la partie alcoxy inférieur, des halogènes de numéro atomique allant jusqu'à 35 inclus et/ou des groupes cyano, et R représente un groupe carboxy ou carbamyle, ou encore (alcoxy inférieur)-carbonyle contenant jusqu'à 4 atomes de carbone inclus dans la partie alcoxy inférieur, ou un sel d'un tel composé et d'une base.

5. Procédé selon la revendication 1, caractérisé en ce que l'on prépare des composés de formule I dans laquelle Ph représente un groupe phényle mono- ou di-substitué par des groupes alkyle inférieurs contenant jusqu'à 4 atomes de carbone inclus ou des halogènes de numéro atomique allant jusqu'à 35 inclus et R représente un groupe carboxy ou carbamyle, ou encore (alcoxy inférieur)-carbonyle contenant jusqu'à 4 atomes de carbone inclus dans la partie alcoxy inférieur, ou un sel d'un tel composé et d'une base.

6. Procédé selon la revendication 1, caractérisé en ce que l'on prépare des composés de formule I dans laquelle Ph représente un groupe phényle monosubstitué en position 2 par un halogène de numéro atomique allant jusqu'à 35 inclus et R représente un groupe carboxy ou carbamyle, ou un sel d'un tel composé et d'une base.

7. Procédé selon la revendication 1, caractérisé en ce que l'on prépare le 4-(benzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle,

- le 4-(o-chlorobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle,
- le 4-(m-chlorobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle,
- le 4-(m-méthylbenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle,
- le 4-(p-chlorobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle,
- le 4-(p-méthylbenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle,
- le 4-(2,6-dichlorobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle,
- le 4-(2,4-dichlorobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle,
- le 4-(3,4-dichlorobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle,
- le 4-(o-bromobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle,
- le 4-(o-acétoxybenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle,
- le 4-(o-méthylthiobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle,
- le 4-(o-trifluorométhylbenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle,
- le 4-(m-trifluorométhylbenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle,
- le 4-(p-méthoxybenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle,
- le 4-(o-méthoxybenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle,
- le 4-(p-cyanobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle,
- le 4-(m-méthylthiobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle,
- le 4-(m-méthoxycarbonylbenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle,
- le 4-(2,6-dichlorobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxamide,
- le 4-(2,6-diméthylbenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle,
- le 4-(2,6-diméthoxybenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle, ou
- le 4-(o-méthylbenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylate de méthyle.

8. Procédé selon la revendication 1, caractérisé en ce que l'on prépare l'acide 4-(benzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,

- l'acide 4-(m-chlorobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,
- l'acide 4-(m-méthylbenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,
- l'acide 4-(p-chlorobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,
- l'acide 4-(2,6-dichlorobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,
- l'acide 4-(3,4-dichlorobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,
- l'acide 4-(o-acétoxybenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,
- l'acide 4-(o-méthylthiobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,
- l'acide 4-(o-trifluorométhylbenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,
- l'acide 4-(m-trifluorométhylbenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,
- l'acide 4-(o-méthoxybenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,
- l'acide 4-(p-méthoxybenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,
- l'acide 4-(p-cyanobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,
- l'acide 4-(2,6-diméthylbenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,
- l'acide 4-(m-méthylthiobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,
- l'acide 4-(2,6-diméthoxybenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,



l'acide 4-(p-méthylbenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,
l'acide 4-(o-chlorobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique,
ou un sel de l'un de ces acides et d'une base.

9. Procédé selon la revendication 1, caractérisé en ce que l'on prépare l'acide 4-(o-fluorobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique ou un sel de cet acide et d'une base.

10. Procédé selon la revendication 1, caractérisé en ce que l'on prépare l'acide 4-(o-bromobenzoyl)-5-hydroxy-benzocyclobutène-1-carboxylique ou un sel de cet acide et d'une base.

11. Procédé de préparation de compositions pharmaceutiques, caractérisé en ce que l'on mélange un composé obtenu selon l'une des revendications 1 à 10 des produits auxiliaires et/ou véhicules pharmaceutiques usuels.

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