

Process for preparing substituted 1,4-quinone methides

The invention relates to a process for preparing substituted 1,4-quinone methides of the formula (I) from 3,5-disubstituted 4-hydroxybenzaldehydes, and also to a process for preparing the 3,5-disubstituted 4-hydroxybenzaldehydes from the corresponding 2,6-disubstituted phenols.

7-Methoxy- and 7-ethoxy-substituted 1,4-quinone methides are known in the literature as important isolable intermediates for the synthesis of active pharmaceutical ingredients. In addition, some 1,4-quinone methides can be used to prevent undesired polymerization of olefinically unsaturated monomers.

The preparation of 2,6-di-tert-butyl-4-methoxymethylenecyclohexane-2,5-dienone and of 2,6-di-tert-butyl-4-ethoxymethylenecyclohexane-2,5-dienone is described by Inagaki et al. both in *J. Org. Chem.* **2002**, 67, 125-128 and in EP 0 626 377 A1. This involves reacting a mixture of 3,5-di-tert-butyl-4-hydroxybenzaldehyde with an excess of trimethyl orthoformate, absolute methanol and xylene in the presence of ammonium chloride as a catalyst to give the corresponding acetal, by heating the reaction mixture under reflux for a few hours. Subsequently, a distillation is performed, xylene is added as an additional solvent, the mixture is cooled, and then the catalyst - the ammonium chloride - is filtered off. In order to achieve the elimination of the alcohol from the acetal to give the substituted 1,4-quinone methide, in both publications, the filtrate is heated and thus methanol and xylene are distilled off. This concentrates the product, which is filtered and then recrystallized in hexane or in a mixture of petroleum ether and ligroin.

The preparation of the corresponding acetal of the 3,5-disubstituted 4-hydroxybenzaldehyde by reaction with orthoformate and/or alcohols is described by numerous publications:

Orlando describes, in *J. Org. Chem.* **1970**, 35, 3714-3717, an almost identical process for preparing the acetal to that of Inagaki et al. in their two publications. Here too, 3,5-di-tert-butyl-4-hydroxybenzaldehyde is heated under reflux with an excess of trimethyl orthoformate and absolute methanol in the presence of ammonium chloride as a catalyst, although no additional solvent is used in this process. After the filtration, the acetal is isolated by concentration and recrystallization from hexane.

Roth et al. also described, in *J. Med. Chem.* **1988**, 31, 122-129, a process for preparing the acetal from 3,5-disubstituted 4-hydroxybenzaldehydes, which also involves heating a mixture of 3,5-diisopropyl-4-hydroxybenzaldehyde, trimethyl orthoformate, ammonium chloride and methanol under reflux for a few hours. Subsequently, the reaction mixture is allowed to cool, an aqueous ammonium hydroxide solution is added, the mixture is extracted with dichloromethane and washed, and the organic phase is dried and concentrated to dryness. The desired acetal can then be crystallized from hot hexane.

The preparation of acetals of other 4-hydroxybenzaldehydes with trimethyl orthoformate and/or methanol in the presence of various catalysts is described in numerous publications. For instance, Du et al. describe, in *Synthetic Communications* **2005**, 35, 2703-2708, the use of ionic liquids as a catalyst. The use of amidosulphonic acid as a catalyst is described by Gong et al. in *Synthetic Communications* **2004**, 34, 4243-4247. Lithium tetrafluoroborate as a suitable catalyst is described by Hamada et al. in *Synlett* **2004**,

6, 1074-1076. While Ranu et al. describe the use of indium chloride as a catalyst in *Adv. Synth. Catal.* **2004**, 346(4), 446-450. Gopinath et al. describe, in *J. Org. Chem.* **2002**, 67, 5842-5845, a process for preparing the acetal in the presence of tetrabutylammonium chloride as a catalyst. The use of the highly toxic decaborane as a catalyst is described by Lee et al. in *Tetrahedron Letters* **2002**, 43, 2699-2703. A copolymer with gallium trichloride as suitable catalyst is described by Ruicheng et al. in *J. Macromol. Sci.-Chem.* **1987**, A24(6), 669-679.

The literature describes many different ways of preparing 3,5-substituted 4-hydroxybenzaldehydes. The main starting materials here are the corresponding 2,6-disubstituted phenols or 2,6-disubstituted 4-methylphenols. One means of preparing these 3,5-substituted 4-hydroxybenzaldehydes is the formylation of the 2,6-disubstituted phenols in the para position with urotropin.

For instance, Bolli et al. described, in the two PCT publications WO 2006/100633 A1 and WO 2006/010544 A2, the reaction of, respectively, 2-ethyl-6-methylphenol and 2,6-diethylphenol with an excess of urotropin in the presence of acetic acid. After distilling off a first solvent fraction, the reaction mixture is heated under reflux for three hours and diluted with water, and then the corresponding 4-hydroxybenzaldehyde is extracted with ethyl acetate. The yields are 31% and 40% respectively.

Unangst et al. described, in *J. Med. Chem.* **1994**, 37, 322-328, the reaction of 3,5-diphenylphenol with an excess of urotropin in the presence of acetic acid. This involves adding water, heating the reaction mixture under reflux and removing distillate until a temperature of 114°C is achieved. The yield is 64%.

A process with a yield of 81% is described by Roth et al. in *J. Med. Chem.* **1988**, 31, 122-129. Here, 3,5-diisopropylphenol is reacted with an excess of urotropin in the presence of glacial acetic acid and water, which also involves first removing distillate before the reaction mixture is heated under reflux.

It was an object of the present invention to provide a process for preparing substituted 1,4-quinone methides of the formula (I), which is suitable for industrial scale application and is thus economically viable and not intensive in terms of plant resources. In addition, not only the 7-methoxy- and 7-ethoxy-substituted 1,4-quinone methides described in the literature should be preparable, but also further substituted 1,4-quinone methides of the formula (I).

Surprisingly, a broadly applicable process for preparing substituted 1,4-quinone methides of the formula (I) has been found, wherein a (thio)acetal is first formed from 4-hydroxybenzaldehydes of the formula (II), which can then be converted directly to the desired substituted 1,4-quinone methides in a further step by thermally induced elimination of alcohol or thiol. With this process according to the invention, not only are the 7-methoxy and 7-ethoxy-substituted 1,4-quinone methides described in the literature preparable, but completely new compounds are also obtainable.

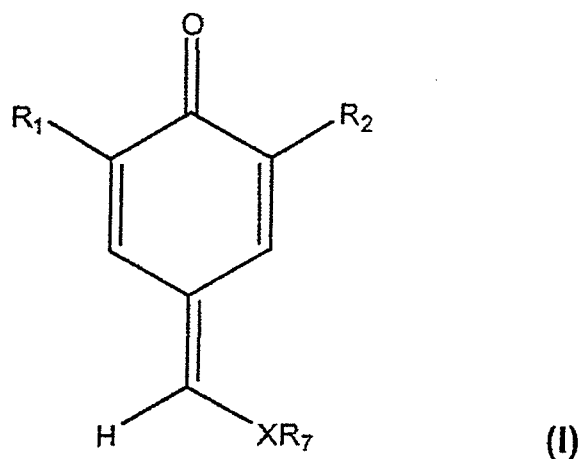
In the process according to the invention, the (thio)acetals can be formed, in contrast to the prior art, using inexpensive, nontoxic and halogen-free catalysts, for example organic sulphonic acids, sulphuric acid and/or hydrogensulphates thereof, as the catalyst. Halogen-free preparation is thus possible. Specifically in industrial scale processes, this is an important advantage owing to the risk of stress-cracking corrosion in the case of use of halides in the

reactor. It was completely surprising that inexpensive nontoxic substances which catalyse acetal formation can also be used, whereas the prior art, apart from halogenated compounds, proposes only expensive, toxic and/or CMR-active compounds, such as decaborane, as catalysts.

In addition, the proportion of the catalyst can be lowered compared to prior art processes, the conversion surprisingly rising slightly and not falling as possibly expected. In addition, in contrast to many prior art processes, the proportion of the expensive orthoformate reactant can be lowered significantly, while achieving equal conversions of more than 90%. Since the process according to the invention in the first process stage does not need an additional solvent, it is additionally possible to significantly improve the space-time yield.

In the process according to the invention, 3,5-disubstituted 4-hydroxybenzaldehydes of the formula (II) are used as the reactant; in the context of this invention, it was also possible to improve the upstream process step the preparation of the 3,5-disubstituted 4-hydroxybenzaldehyde from the 2,6-disubstituted phenol. Thus, it was found that, completely surprisingly, both through the amendment of the sequence of metered addition and through the use of a reaction temperature below the reflux temperature, yields of more than 80% can be achieved. In addition, it was surprising that the molar amount of urotropin based on the 2,6-disubstituted phenol used can be lowered to below 1:1 without having to accept yield losses.

The invention thus provides a process for preparing substituted 1,4-quinone methides of the formula (I)

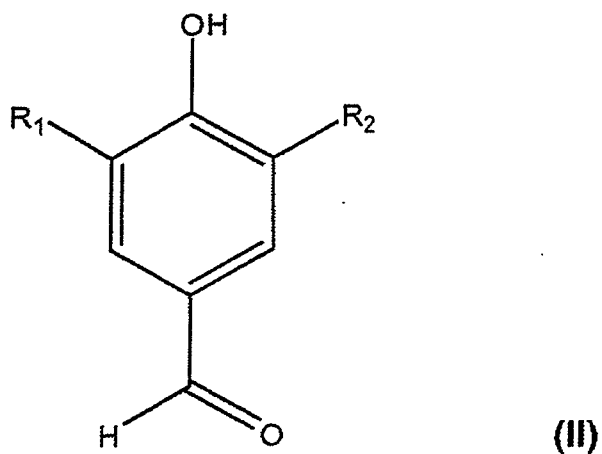


where R_1 , R_2 = each independently hydrogen, (C_1-C_{15}) -alkyl, (C_3-C_{15}) -cycloalkyl or (C_6-C_{14}) -aryl, which are unsubstituted or substituted,

R_7 = (C_1-C_{15}) -alkyl, (C_3-C_{15}) -cycloalkyl or (C_6-C_{14}) -aryl, which are substituted or unsubstituted, and

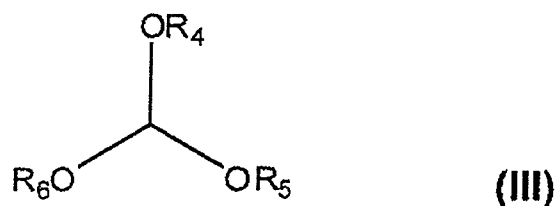
X = O, S,

which is characterized in that 3,5-disubstituted 4-hydroxybenzaldehydes of the formula (II)



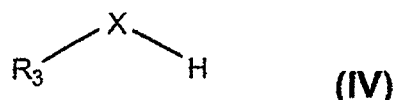
where R_1 and R_2 are each as defined in formula (I)

are reacted with orthoformates of the formula (III)



where R_4 , R_5 , R_6 = each independently $(\text{C}_1\text{-C}_{15})$ -alkyl, $(\text{C}_3\text{-C}_{15})$ -cycloalkyl or $(\text{C}_6\text{-C}_{14})$ -aryl, which are substituted or unsubstituted,

and alcohols and/or thioalcohols of the formula (IV)

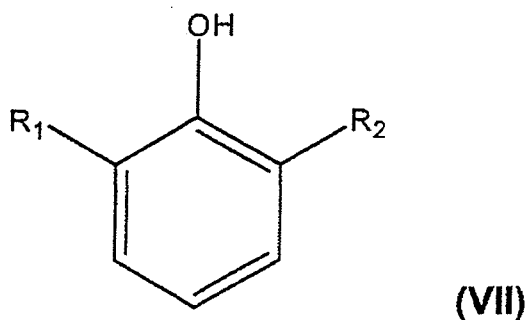


where R_3 = $(\text{C}_1\text{-C}_{15})$ -alkyl, $(\text{C}_3\text{-C}_{15})$ -cycloalkyl or $(\text{C}_6\text{-C}_{14})$ -aryl, which are substituted or unsubstituted, and

X = O, S,

in the presence of a catalyst selected from free or solid-phase-bound organic sulphonic acids, sulphuric acid, hydrogensulphates, organic or inorganic phosphorus acids, the dihydrogen and hydrogen salts thereof, and fuming nitric acid and/or boric acid, to give the corresponding acetal and then the alcohol or thiol is eliminated from the corresponding acetal to give the substituted 1,4-quinone methide of the formula (I).

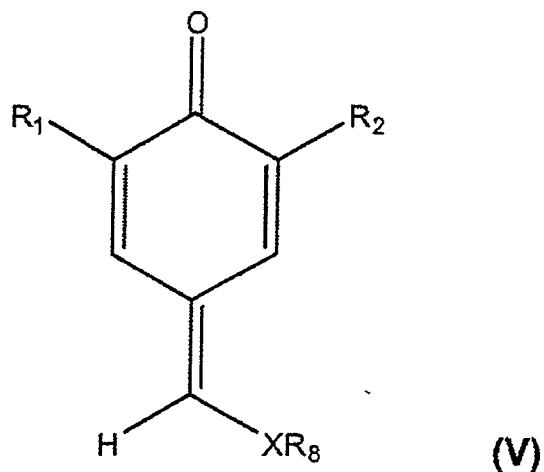
This invention further provides a process for preparing the 3,5-disubstituted 4-hydroxybenzaldehyde of the formula (II), wherein 2,6-disubstituted phenols of the formula (VII)



where R_1 and R_2 are each as defined in formula (I)

is reacted with urotropin in a solvent mixture consisting of glacial acetic acid and water at temperatures which are at least 2°C below the reflux temperature over the entire reaction time.

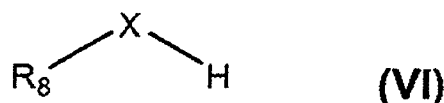
This invention likewise provides a process for preparing substituted 1,4-quinone methides of the formula (V)



where R_1 , R_2 = each independently hydrogen, (C_1-C_{15}) -alkyl, (C_3-C_{15}) -cycloalkyl or (C_6-C_{14}) -aryl, which are unsubstituted or substituted,

$R_8 =$ (C₃-C₁₅)-alkyl, (C₃-C₁₅)-cycloalkyl or (C₆-C₁₄)-aryl, which are substituted or unsubstituted, and
 $X =$ O, S,

which is characterized in that a substituted 1,4-quinone methide of the formula (I) where $R_7 =$ unsubstituted (C₁-C₂)-alkyl group and $X = O$, where R_1 and R_2 are each as defined in formula (V), is reacted in the presence of an alcohol or thioalcohol of the formula (VI)



where $R_8 =$ (C₃-C₁₅)-alkyl, (C₃-C₁₅)-cycloalkyl or (C₆-C₁₄)-aryl, which are substituted or unsubstituted, and
 $X =$ O, S.

For the acetal formation in the process according to the invention for preparing substituted 1,4-quinone methides of the formula (I), preference is given to using, as the reactant, 3,5-disubstituted 4-hydroxybenzaldehydes of the formula (II) which have (C₁-C₁₅)-alkyl, (C₃-C₁₅)-cycloalkyl and/or (C₆-C₁₄)-aryl groups as substituents R_1 and R_2 ; the 3,5-disubstituted 4-hydroxybenzaldehydes used preferably have (C₁-C₄)-alkyl and/or (C₃-C₁₅)-cycloalkyl groups as substituents R_1 and R_2 . Particular preference is given to using 3,5-disubstituted 4-hydroxybenzaldehydes with (C₁-C₄)-alkyl groups, most preferably with branched (C₃-C₄)-alkyl groups, such as tert-butyl or isopropyl groups, as substituents R_1 and R_2 .

In particular, the 3,5-disubstituted 4-hydroxybenzaldehydes used have unsubstituted groups as substituents R_1 and R_2 .

In the context of the invention, substituents are understood to mean groups selected from -COOR, -OH, -OR, -halogen, -NR₂, =O and -CO-NR₂, where R = hydrogen, (C₁-C₁₅)-alkyl, (C₃-C₁₅)-cycloalkyl and/or (C₆-C₁₄)-aryl groups, which may in turn be substituted by at least one of these substituents.

Further reactants used for the acetal formation in the process according to the invention are orthoformates of the formula **(III)**, where the substituents R₄, R₅ and R₆ are preferably (C₁-C₁₅)-alkyl or (C₃-C₁₅)-cycloalkyl groups and preferably (C₁-C₄)-alkyl groups. These substituents R₄, R₅ and R₆ are more preferably unsubstituted. In a particularly preferred embodiment of the process according to the invention, orthoformates which have (C₁-C₂)-alkyl groups as substituents R₄, R₅ and R₆ are used. Very particular preference is given to using orthoformates whose substituents R₄, R₅ and R₆ are all identical. In particular, trimethyl orthoformate is used in the process according to the invention.

In addition to the 3,5-disubstituted 4-hydroxy-benzaldehydes and the orthoformates, alcohols and/or thioalcohols of the formula **(IV)**, where the substituent R₃ is preferably unsubstituted, are also used for the acetal formation of the process according to the invention. The substituent R₃ is preferably a (C₁-C₁₅)-alkyl or (C₃-C₁₅)-cycloalkyl group and more preferably a (C₁-C₄)-alkyl group.

In a particularly preferred embodiment of the process according to the invention, alcohols are used, more preferably alcohols with a phenyl or (C₁-C₁₅)-alkyl group and most preferably with a (C₁-C₄)-alkyl group as the substituent R₃. In particular, methanol or ethanol is used in the process according to the invention.

In the process according to the invention, preference is given to using orthoformates and alcohols and/or thioalcohols, where the substituents R_4 , R_5 and R_6 of the orthoformate are identical to the substituent R_3 of the alcohol and/or thioalcohol.

When the substituents R_3 and R_4 , R_5 and R_6 are different, mixtures of different substituted 1,4-quinone methides can form. In the case of use of a thioalcohol, predominantly the quinone methide where $X = S$ and $R_7 = R_3$ of the thioalcohol forms. In contrast, in the case of use of orthoformates and (thio)alcohols with different substituents R_3 and R_4 , R_5 and R_6 , preferably the correspondingly substituted 1,4-quinone methide of the formula (I) of the least volatile (thio)alcohol forms.

The catalysts used in the process according to the invention are preferably free or solid-phase-bound organic sulphonic acids, sulphuric acid, hydrogensulphates, organic or inorganic phosphorus acids, the dihydrogen and hydrogen salts thereof, and fuming nitric acid and/or boric acid, preference being given to using free or solid-phase-bound organic sulphonic acids, sulphuric acid and/or hydrogensulphates, and particular preference to using alkylbenzenesulphonic acids, polymers which have sulphonic acid groups or hydrogensulphates of the alkali metals and alkaline earth metals. The catalysts used are most preferably hydrogensulphates of the alkali metals and alkaline earth metals, especially potassium hydrogensulphate or sodium hydrogensulphate.

The organic sulphonic acids used may be alkylbenzenesulphonic acids, for example p-toluene sulphonic acid or dodecylbenzenesulphonic acid, or polymers which have sulphonic acid groups.

The use of solids as catalysts has the advantage that this catalyst can be removed from the reaction mixture in a simple manner, for example by means of filtration. Compared to the processes with ammonium chloride - according to the prior art - the process according to the invention enables an industrial scale product without halides, and there is thus no need for any complicated corrosion protection of the plant parts. Moreover, the catalysts used in the process according to the invention are inexpensive, halogen-free and non-toxic acids.

The molar ratio of the 3,5-disubstituted 4-hydroxybenzaldehyde of the formula (II) to the catalyst in the process according to the invention is preferably from 1:0.0002 to 1:0.5, preferentially from 1:0.0005 to 1:0.2, more preferably from 1:0.001 to 1:0.1 and most preferably from 1:0.005 to 1:0.05.

The process according to the invention is characterized in that the molar ratio of the 3,5-disubstituted 4-hydroxybenzaldehyde to the orthoformate is preferably from 1:0.5 to 1:10, the ratio preferably being 1:0.9 to 1:5 and more preferably from 1:1 to 1:2. The lowering of the amount of the relatively expensive orthoformate allows the operating costs of an industrial scale plant to be lowered, without the conversions being reduced as a result.

The acetal formation in the process according to the invention can be performed either with an additional solvent (A) or without an additional solvent. Suitable additional solvents (A) include solvents which are inert toward the 4-hydroxybenzaldehyde, alcohol, thiol and orthoformate reactants used and to the (thio)acetal, preference being given to aromatic solvents such as toluene, ethylbenzene and/or xylenes.

In a particular preferred embodiment of the process according to the invention, the 4-hydroxybenzaldehyde is converted to the (thio)acetal in the absence of an additional solvent (A). In this way, the space-time yield of the process according to the invention can be improved.

The 4-hydroxybenzaldehyde is converted to the (thio)acetal in the process according to the invention preferably by heating under reflux for a few minutes to hours, preferably for 0.5 to 10 hours and more preferably for 1 to 5 hours.

The conversion of the 3,5-disubstituted 4-hydroxybenzaldehyde to the corresponding (thio)acetal can be performed at different pressures; this process stage is preferably effected at atmospheric pressure. In the case of use of some thioalcohols, owing to the low boiling points thereof, working under pressure is advisable.

The (thio)acetal which forms in the process according to the invention can be isolated by the customary isolation steps, such as concentration of the solution, extraction, filtration, crystallization, etc. The (thio)acetal is preferably not isolated before the elimination of the alcohol, but converted directly from the solution to the desired product - the substituted 1,4-quinone methide of the formula (I).

In the process according to the invention, before the elimination of the (thio)alcohol from the (thio)acetal, the excess orthoformate and the excess alcohol or thioalcohol should be removed - preferably by distillation. If the (thio)acetal is not to be isolated, it is advisable to add an additional solvent (B) before this distillative removal of the orthoformate and of the alcohol or thioalcohol. This can achieve the effect that the (thio)acetal remains in

solution even after the distillative removal of the orthoformate and of the alcohol or thioalcohol.

Suitable additional solvents (B) are solvents which have a higher boiling point than the alcohol and/or thioalcohol used and are inert toward the (thio)acetal and the substituted 1,4-quinone methide to be formed. The boiling point of the solvent (B) used should be at least 100°C, preferably from 110°C to 250°C. In addition, this solvent (B) should be capable of keeping the acetal formed in solution. In particular, in the process according to the invention, aromatic solvents are used, for example toluene, ethylbenzene, o-, m- or p-xylene, and mixtures of these and other aromatic solvents. It is also possible to use mixtures of aromatic hydrocarbons with a correspondingly defined boiling point range as the additional solvent (B).

This removal by means of distillation of the excess orthoformate and of the excess alcohol or thioalcohol is preferably carried out until the reaction mixture has attained the boiling point of the additional solvent (B). This removal can be effected either under atmospheric pressure or under reduced pressure.

In the process according to the invention, the catalyst should likewise be removed from the (thio)acetal before the thermal elimination of the (thio)alcohol, for example by means of mechanical separation processes. This process is suitable in particular in the case of catalysts present in solid form. Suitable mechanical separation processes for this purpose are filtration, sedimentation or centrifugation with subsequent decantation. Especially in the case of catalysts present in solid form, it is advisable to remove them before the thermal elimination of the (thio)alcohol from the (thio)acetal, in order that the column is not contaminated by introduced solids.

In the case of use of a liquid catalyst, or for unremoved traces of solid catalysts, these are preferably neutralized with a base. Particular preference is given to using, for this purpose, non-nucleophilic or sterically hindered amines and inorganic salts, for example carbonates. A removal of the neutralization product is not absolutely necessary.

The sequence of removal or neutralization of the catalyst, of addition of a solvent (B) and of the removal of the excess (thio)alcohol and of the excess orthoformate can be varied arbitrarily as required depending on the catalyst used, (thio)alcohol and orthoformate, without yield losses.

In order to carry out the elimination of the (thio)alcohol from the (thio)acetal, the acetal-containing reaction mixture of the process according to the invention is preferably heated to the boiling temperature of the solvent (B), preferably to at least 100°C, more preferably to 110 to 250°C, and the (thio)alcohol released is removed from the reaction mixture, preferably immediately after formation thereof, by means of chemical and/or physical methods. The (thio)alcohol eliminated by thermal induction can be removed from the reaction mixture by customary methods. For instance, the alcohol released can be chemically bound by adding suitable reagents, for example anhydrides. However, physical methods, for example the use of a molecular sieve in the case of short-chain (thio)alcohols, are also conceivable.

In the process according to the invention, the (thio)alcohol released is removed, preferably by means of distillation. This involves heating the acetal-containing reaction mixture to at least 100°C, preferably to 110 to 250°C, in the course of which an additional solvent (C) is continuously metered in, while the alcohol and/or thioalcohol released is

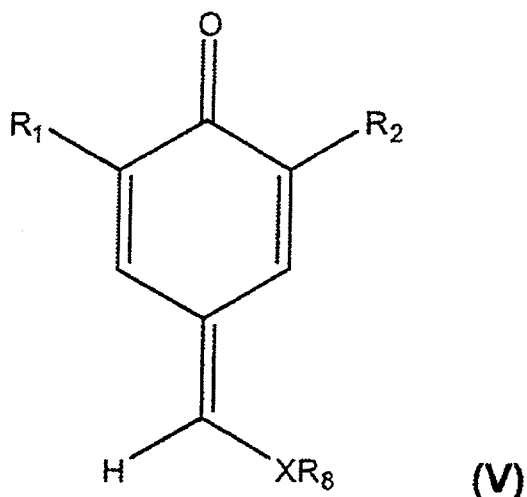
simultaneously removed from the reaction mixture together with the additional solvent (C). Particular preference is given here to metering as much additional solvent (C) into the reaction mixture as the amount of distillate, substantially consisting of (thio)alcohol and solvent (A, B and C), which is distilled off. The additional solvent (C) serves here to be able to more easily remove the excess alcohol and/or thioalcohol from the reaction mixture, and hence to achieve the elimination of the (thio)alcohol from the (thio)acetal. It is also conceivable to perform the elimination of the alcohol at lower temperatures with simultaneous pressure reduction. In addition to the shift in equilibrium in favour of the substituted 1,4-quinone methide of the formula (I), this process step also has the advantage that traces of water are likewise removed from the reaction mixture, and hence the back-reaction of the substituted 1,4-quinone methide to the 4-hydroxybenzaldehyde can be substantially suppressed.

Suitable additional solvents (C) here too are solvents which have a boiling point of at least 100°C, preferably of 110 to 250°C, and are inert toward the (thio)acetal and the substituted 1,4-quinone methide of the formula (I). In particular, in the process according to the invention, aromatic solvents are used, for example toluene, ethylbenzene, o-, m- or p-xylene, and mixtures of these aromatic solvents. It is also possible to use mixtures of aromatic hydrocarbons with a corresponding defined boiling point range as the additional solvent (C). In a very particularly preferred embodiment of the process according to the invention, the solvents (A), (B) and (C) are identical.

In a further embodiment of the process according to the invention, two different solvents are used, in which case the solvent (C) preferably has a higher boiling point than the solvent (B). This is advantageous when the substituted 1,4-quinone methide, for the further

use thereof, is to be present in a solvent which is not very suitable for the distillation of the excess orthoformate and of the excess alcohol or thioalcohol.

For the preparation of substituted 1,4-quinone methides of the formula (V)

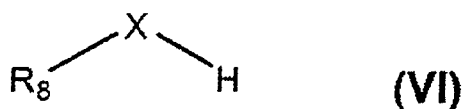


where $R_1, R_2 =$ each independently hydrogen, (C_1-C_{15}) -alkyl, (C_3-C_{15}) -cycloalkyl or (C_6-C_{14}) -aryl, which are unsubstituted or substituted,

$R_8 =$ (C_3-C_{15}) -alkyl, (C_3-C_{15}) -cycloalkyl or (C_6-C_{14}) -aryl, which are substituted or unsubstituted, and

$X =$ O, S,

the substituted 1,4-quinone methide of the formula (I) where $R_7 =$ unsubstituted (C_1-C_2) -alkyl group and $X = O$, where R_1 and R_2 are each as defined in formula (V) - preferably formed by the process according to the invention - can be reacted in the presence of an alcohol or thioalcohol of the formula (VI)



where $R_8 =$ (C₃-C₁₅)-alkyl, (C₃-C₁₅)-cycloalkyl or
(C₆-C₁₄)-aryl, which are substituted or
unsubstituted, and
 $X =$ O, S.

In this case, the reaction mixture consisting of the substituted 1,4-quinone methide of the formula (I) where $R_7 =$ unsubstituted (C₁-C₂)-alkyl group and $X =$ O, where R_1 and R_2 are each as defined in formula (V), and the (thio)alcohol of the formula (VI) of the process according to the invention is preferably heated to boiling temperature of the corresponding solvent, preferably to at least 100°C, more preferably to 110 to 250°C, and the methanol and/or ethanol is removed directly from the reaction mixture by means of chemical and/or physical methods. The methanol and/or ethanol eliminated by thermal induction can be removed from the reaction mixture by customary methods. For instance, the methanol and/or ethanol released can be chemically bound by adding suitable reagents, for example anhydrides. However, physical methods are also conceivable, for example the use of a molecular sieve.

In the process according to the invention, this removal of the methanol and/or ethanol released is preferably effected by means of distillation. This involves heating the reaction mixture to at least 100°C, preferably to 110 to 250°C, in the course of which an additional solvent (D) is metered in continuously, while the methanol and/or ethanol released is simultaneously removed from the reaction mixture together with the additional solvent (D). Particular preference is given here to metering in as much additional solvent (D) into the reaction mixture as the amount of methanol and/or ethanol and solvents which is distilled off.

Suitable additional solvents (D) here too are solvents which have a boiling point of at least 100°C,

preferably of 110°C to 250°C, and are inert toward reaction participants and also the desired product. In particular, in the process according to the invention, aromatic solvents are used, for example toluene, ethylbenzene, o-, m- or p-xylene, and mixtures of these aromatic solvents. It is also possible to use mixtures of aromatic hydrocarbons with a corresponding defined boiling point range as the additional solvent (D). In a very particularly preferred embodiment of the process according to the invention, the solvents (A), (B), (C) and (D) are identical.

In this way, substituted 1,4-quinone methides of the formula (V) with a substituent R_8 which has more than two carbon atoms are readily obtainable. This variant of the process according to the invention has the advantage that a multitude of derivatives can be prepared from a single intermediate, the substituted 1,4-quinone methide of the formula (I) where R_7 = unsubstituted (C_1-C_2) -alkyl group and $X = O$, the individual preparation processes differing only in the last process step. This is of particular interest especially in active pharmaceutical ingredient research.

According to the further use, the quinone methide solution obtained by means of the process according to the invention can be used further directly. In the case that the quinone methide solution cannot be used directly, the substituted 1,4-quinone methide can be isolated by cooling the product mixture, and crystallizing and removing the product, and optionally purified, for example by recrystallization. It may also be helpful to completely remove the solvent for the crystallization process, and exchange it for a solvent in which the substituted 1,4-quinone methide has a lower solubility. In this way, the crystallization process can be simplified or accelerated. The

substituted 1,4-quinone methide can also be obtained by a complete or partial removal of the solvent.

The 3,5-disubstituted 4-hydroxybenzaldehyde of the formula (II) used in the process according to the invention can be prepared either proceeding from 2,6-disubstituted phenol or proceeding from 2,6-disubstituted 4-methylphenol by numerous prior art processes. A particularly suitable process has been found to be one which is characterized in that 2,6-disubstituted phenol of the formula (VII) is reacted with urotropin in a solvent mixture consisting of glacial acetic acid and water at temperatures which are at least 2°C below the reflux temperature over the entire reaction time.

The reactants used for the process according to the invention for preparing the 3,5-disubstituted 4-hydroxybenzaldehyde are preferably 2,6-disubstituted phenol or mixtures of such compounds, where the substituents in the 2 and 6 positions correspond to the substituents R₁ and R₂ in the formula (II).

Preference is given to using 2,6-disubstituted phenols which have (C₁-C₁₅)-alkyl, (C₃-C₁₅)-cycloalkyl and/or (C₆-C₁₄)-aryl groups, more preferably (C₁-C₄)-alkyl and/or (C₃-C₁₅)-cycloalkyl groups as substituents R₁ and R₂. Very particular preference is given to using 2,6-disubstituted phenols with (C₁-C₄)-alkyl groups as substituents R₁ and R₂. In a particularly preferred embodiment of the process according to the invention, 2,6-disubstituted phenols which have branched (C₃-C₄)-alkyl groups, such as tert-butyl or isopropyl groups, are used.

In particular, the 2,6-disubstituted phenols used have unsubstituted groups as substituents R₁ and R₂.

This process according to the invention is likewise characterized by its freedom from halogen, since preference is given to not using any halogenated compounds.

The process according to the invention is characterized in that the molar ratio of the 2,6-disubstituted phenol to urotropin is preferably less than or equal to 1:1, preference being given to a process in which this molar ratio is from 1:1 to 1:0.8.

The ratio of glacial acetic acid to water in this process according to the invention is preferably selected such that a reaction temperature of $115^{\circ}\text{C} \pm 10^{\circ}\text{C}$ can be established without any need to distil off water.

As a result, a process step frequently mentioned in the prior art can be dispensed with, as a result of which the process according to the invention can be made more effective. In the process according to the invention, preference is given to establishing a molar ratio of acetic acid to water of 1:1 to 20:1, more preferably of 1.1:1 to 10:1 and most preferably of 1.2:1 to 5:1.

The 2,6-disubstituted phenol, the glacial acetic acid, the water and the urotropin can be combined in any desired sequence. Preference is given to dissolving the 2,6-disubstituted phenol in glacial acetic acid, and adding urotropin and finally the water. The mixing of the components can also be effected either at room temperature or at elevated temperatures.

The conversion of the 2,6-disubstituted phenol to give the 3,5-disubstituted 4-hydroxybenzaldehyde is effected in this process according to the invention, over the entire reaction time, preferably at a temperature a few degrees below the reflux temperature, the reaction temperature preferably being at least 2°C ,

preferentially at least 3°C and more preferably 5°C below the reflux temperature. This has the advantage that, firstly, the reaction temperature is sufficient for a virtually complete conversion of the 2,6-disubstituted phenol to the 3,5-disubstituted 4-hydroxybenzaldehyde; on the other hand, the temperature is insufficient to reflux the reaction mixture and thus to soil or even to block the column with the product which collects preferably at the liquid surface, which is often in solid form. Especially in industrial scale processes, this is an undesired effect. Moreover, it has been found that a process which works with a reaction temperature below the reflux temperature also allows the purity of the substituted 1,4-quinone methide to be improved. In a particular preferred embodiment of this process according to the invention, the reaction mixture is heated to a temperature of $115^{\circ}\text{C} \pm 10^{\circ}\text{C}$ over the entire reaction time. The reaction temperature over the entire reaction time is preferably not less than 10°C below the reflux temperature.

In the context of this invention, the entire reaction time is understood to mean the time span in which the desired reaction temperature for the reaction of the 2,6-disubstituted phenol with the urotropin is attained and maintained. In the context of this invention, the heating and cooling phases are not included in the entire reaction time, even though reactions of the 2,6-disubstituted phenol can already or still be observed in these phases.

The reaction mixture in the reaction of the 2,6-disubstituted phenol and of the urotropin is preferably heated to the desired reaction temperature in this process according to the invention for 1 to 10 hours, preferably for 2 to 7 hours and more preferably for 3 to 6 hours.

Owing to the different substituents in the R_1 and R_2 positions, the solubility and the melting point of the 3,5-disubstituted 4-hydroxybenzaldehydes may be very different. Depending on the substitution pattern of the 4-hydroxybenzaldehyde, different methods can be used to isolate the 3,5-disubstituted 4-hydroxybenzaldehyde in this process according to the invention.

- (A) Filtering off the precipitated solid, in which case the filtrate obtained after the filtration can be sent to a further conversion of 2,6-disubstituted phenols to the 3,5-disubstituted 4-hydroxybenzaldehyde.
- (B) Adding water, in order in this way to precipitate the 3,5-disubstituted 4-hydroxybenzaldehyde, the further workup being effected according to (A).
- (C) Extracting with a suitable solvent, then washing the extract with water and distillatively removing the solvent. The solvents used here may be solvents which are water-immiscible or do not have good water miscibility, preference being given to using aromatic solvents for this purpose, such as toluene, ethylbenzene, xylenes, or mixtures of these solvents mentioned.
- (D) Distilling off acetic acid and water, in which case the residue consisting predominantly of the 3,5-disubstituted 4-hydroxybenzaldehyde can subsequently be washed with water, in order to likewise remove the salts which form in the reaction.

The examples which follow are intended to illustrate the process according to the invention in detail, without any intention that the invention be restricted to this embodiment.

Examples 1-4:

7 g (30 mmol) of 3,5-di-tert-butyl-4-hydroxybenzaldehyde are initially charged in a reaction flask and admixed with a mixture consisting of 14.5 ml of

methanol and 14.2 g of trimethyl orthoformate. Subsequently, 5 mmol of the catalyst according to Table 1 are added. The reaction mixture is heated to reflux while stirring. After three hours, the reaction mixture is cooled to room temperature and the conversion of the aldehyde is determined by gas chromatography. The conversions of the aldehydes as a function of the catalyst used are shown in Table 1.

Table 1:

Example	Catalyst	Conversion of the aldehyde (in GC%)
CE 1	Ammonium chloride	98.6
1	p-toluenesulphonic acid	95.0
2	Sulphuric acid	91.1
3	Potassium hydrogensulphate	99.4
4	Sulphonated polystyrene (Lewatit® K2649)	98.6

CE: Comparative example

Examples 1 to 4 show that particularly organic sulphonic acids, and also sulphuric acid and the hydrogen salts thereof, are suitable catalysts for the process according to the invention. The conversions of the aldehyde are more than 90% in all examples. In example 4, the conversion is in the same order of magnitude as for a prior art catalyst (CE1); in example 3, the conversion is even higher.

Examples 3-6:

The experimental procedure is the same as already described in examples 1-4, except that the catalyst and

also the amount of the catalyst are now varied according to Table 2.

Table 2:

Example	Catalyst	Amount of catalyst (in mmol)	Molar ratio of aldehyde to catalyst	Conversion of the aldehyde (in GC%)
CE 1	NH ₄ Cl	5 mmol	1:0.17	98.6
CE 2	NH ₄ Cl	2.5 mmol	1:0.08	97.4
3	KHSO ₄	5 mmol	1:0.17	99.4
5	KHSO ₄	1.1 mmol	1:0.04	99.6
6	KHSO ₄	0.4 mmol	1:0.01	99.9

CE: Comparative example

Examples 3, 5 and 6 show clearly that a reduction in the molar amount of catalyst in the process according to the invention allows the conversions to be enhanced further. In contrast, comparative examples 1 and 2 show that, in the case of use of ammonium chloride - the prior art catalyst - a reduction in the molar amount of catalyst leads to lower conversions.

Examples 7-11:

The experimental procedure is the same as in example 5, except that the amount of methanol and trimethyl orthoformate is now varied according to Table 3.

Table 3:

Example	Methanol		Trimethyl orthoformate		Conversion of the aldehyde
	(in ml)	Molar ratio to the aldehyde	(in g)	Molar ratio to the aldehyde	(in GC%)
7	13.3	10.96	14.1	4.42	99.6%
8	17.8	14.62	10.5	3.31	99.6%
9	22.2	18.27	7.0	2.21	99.6%
10	26.7	21.93	3.5	1.10	99.5%
11	28.9	23.75	1.8	0.55	Incomplete conversion Aldehyde dissolves incompletely

CE: Comparative example

Examples 7 to 11 show that the orthoformate content can be lowered down to a molar ratio of aldehyde to orthoformate of 1:1.1 without the conversion of the aldehyde being impaired.

Example 12 - Preparation of the methoxy-substituted quinone methide:

A 35 l glass vessel with stirrer and condensor is charged with 4.0 kg of 3,5-di-tert-butyl-4-hydroxy-benzaldehyde, 2 g of trimethyl orthoformate and 6 kg of methanol are added and the contents are mixed. Subsequently, 45 g of sodium hydrogensulphate are added. Then the reaction mixture is heated under reflux for approx. 1 to 2 hours. After one hour, the conversion of the aldehyde is checked by means of gas chromatography. The aldehyde used has already been converted completely after one hour. The reaction mixture is cooled and filtered through a Schenk filter.

The filter residue is washed with 8 kg of ethylbenzene. The filtrate is returned back to the glass stirred tank, and the mixture of methanol, trimethyl orthoformate and ethylbenzene is distilled off as rapidly as possible. Subsequently, the azeotropic distillation is commenced, in the course of which 300 to 500 ml of ethylbenzene are added continuously per hour and just as much distillate is removed. After 5 hours, a conversion of 70% is attained; after 9 hours, the conversion to the desired quinone methide rises to more than 90%.

The reaction mixture is cooled. The desired quinone methide precipitates out in the course of cooling and can be isolated with a purity of > 98%.

Example 13 - Preparation of the butoxy-substituted quinone methide from 3,5-di-tert-butyl-4-hydroxybenzaldehyde:

7 g of the 3,5-di-tert-butyl-4-hydroxybenzaldehyde are admixed with 3.5 g of trimethyl orthoformate and 21 g of n-butanol. Subsequently, 0.1 g of potassium hydrogensulphate is added and the reaction mixture is heated under reflux for 2 hours. The aldehyde used has been converted quantitatively.

Then the potassium hydrogensulphate is filtered off and the filter residue is washed with 50 g of ethylbenzene. Subsequently, the mixture of methanol, trimethyl orthoformate and ethylbenzene is distilled off until a boiling temperature of 130°C is attained. Then 100 ml of ethylbenzene per hour are added constantly, and the same amount of distillate is removed simultaneously.

After 6 hours, 82% of the butoxy-substituted quinone methide has formed. As a by-product, 7% of the 3,5-di-tert-butyl-4-hydroxybenzaldehyde has formed.

Example 14 - Preparation of the butoxy-substituted quinone methide from the methoxy-substituted quinone methide:

1 g of the methoxy-substituted quinone methide (from example 12) is dissolved in 20 g of ethylbenzene. Then 1 g of n-butanol is added. The reaction mixture is heated under reflux for two hours. According to analysis by means of gas chromatography, 73% of the methoxy-substituted quinone methide has been converted to the butoxy-substituted quinone methide.

Example 15 - Preparation of an aroxy-substituted quinone methide from the methoxy-substituted quinone methide:

1 g of the methoxy-substituted quinone methide is dissolved in 35 g of ethylbenzene. Subsequently, 0.65 g of 4-tert-butylcatechol is added. The reaction mixture is heated under reflux for two hours. According to analysis by means of gas chromatography, 77% of the methoxy-substituted quinone methide has been converted to the 4-tert-butylcatechol-substituted quinone methide (aryloxy-substituted).

Examples 16-20 - Preparation of 3,5-di-tert-butyl-4-hydroxybenzaldehyde:

2,6-di-tert-butylphenol is dissolved in glacial acetic acid. Subsequently, urotropin and water are added, and the reaction mixture is heated at not more than 2°C below the reflux temperature for 4 to 5 hours. The precipitated product is filtered off and washed with water and methanol, and dried on a rotary evaporator. The molar ratios of the reactants used and also the determined yields of 3,5-di-tert-butyl-4-hydroxybenzaldehyde, based on 2,6-di-tert-butylphenol, are shown in Table 4.

Table 4:

Example	Molar ratio of ... to 2,6-di-tert- butylphenol		Molar ratio of acetic acid to water	Yield (in % based on 2,6-di- tert- butylphenol)
	Urotropin	Acetic acid		
16	0.50	14.52	1.54	60.50
17	0.67	14.52	1.54	82.57
18	0.80	14.52	1.54	89.22
19	0.80	12.66	1.34	89.47
20	1	14.52	1.54	87.46

Examples 16 to 19 show unexpectedly high yields which were not to be expected on the basis of the small amounts of urotropin. These examples show that a process with a molar ratio of urotropin to the phenol of less than 1 also leads to astonishingly high yields and conversions.

Examples 21-25 - Preparation of 3,5-di-tert-butyl-4-hydroxybenzaldehyde (variation of the reaction temperature):

2,6-di-tert-butylphenol is dissolved in glacial acetic acid. Subsequently, urotropin and water are added, and the reaction mixture is heated at different temperatures for 5.5 hours. The precipitated product is filtered off and washed with water and methanol, and dried on a rotary evaporator. The particular reaction temperatures, yields and purities are shown in Table 5.

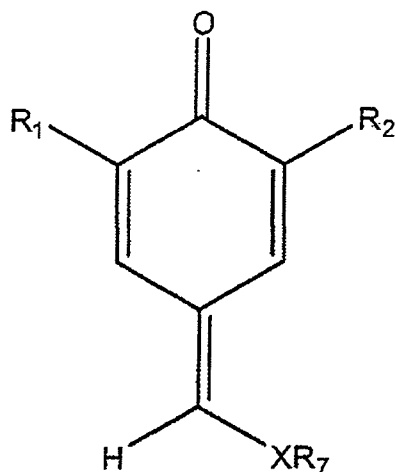
Table 5:

Example	Molar ratio of ... to 2,6-di- tert-butylphenol		Molar ratio of acetic acid to water	Reaction temperature (in °C)	Yield (in % based on 2,6-di- tert- butylphenol)	Purity (in %)
	Urotropin	Acetic acid				
21	1.00	7.26	1.54	118-140	91.4	72.0
22	1.00	7.26	1.54	118-126	92.6	96.5
23	1.00	7.26	1.54	117-120	90.1	99.9
24	1.00	14.52	1.54	118-124	88.7	98.6
25	1.00	14.52	1.54	109-118	83.1	45.1

Examples 21-25 show that excessively low reaction temperatures lead to conversion losses, but excessively high reaction temperatures lead to purity problems. In addition, at excessively high reaction temperatures from the reflux temperature, there is the risk that solids will block the column.

Claims:

1. A process for preparing substituted 1,4-quinone methides of the formula

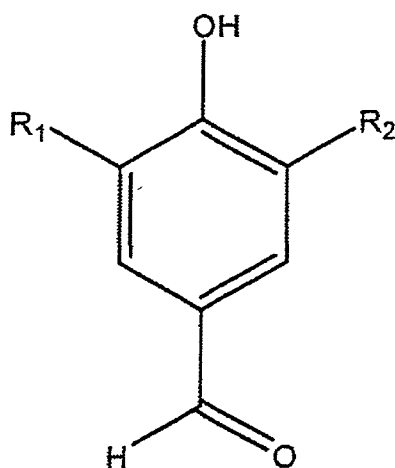


where R₁, R₂ = each independently hydrogen, (C₁-C₁₅)-alkyl, (C₃-C₁₅)-cycloalkyl or (C₆-C₁₄)-aryl, which are unsubstituted or substituted,

R₇ = (C₁-C₁₅)-alkyl, (C₃-C₁₅)-cycloalkyl or (C₆-C₁₄)-aryl, which are substituted or unsubstituted, and

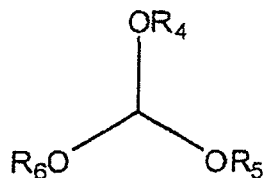
X = O, S,

characterized in that
3,5-disubstituted 4-hydroxybenzaldehydes



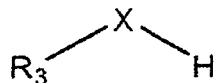
where R_1 and R_2 are each as defined above

are reacted with orthoformates of the formula



where $R_4, R_5, R_6 =$ each independently (C_1-C_{15}) -alkyl, (C_3-C_{15}) -cycloalkyl or (C_6-C_{14}) -aryl, which are substituted or unsubstituted,

and alcohols and/or thioalcohols of the formula



where $R_3 =$ (C_1-C_{15}) -alkyl, (C_3-C_{15}) -cycloalkyl or (C_6-C_{14}) -aryl, which are substituted or unsubstituted, and

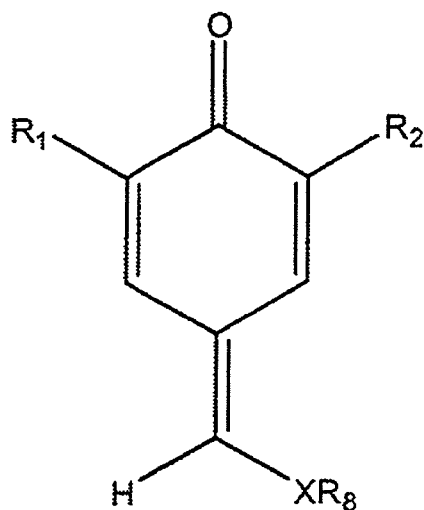
$X =$ O, S,

in the presence of a catalyst selected from free or solid-phase-bound organic sulphonic acids, sulphuric acid, hydrogensulphates, organic or inorganic phosphorus acids, the dihydrogen and hydrogen salts thereof, and fuming nitric acid and/or boric acid, to give the corresponding acetal and then the alcohol or thiol is eliminated from the corresponding acetal to give the substituted 1,4-quinone methide of the formula (I).

2. A process according to claim 1,

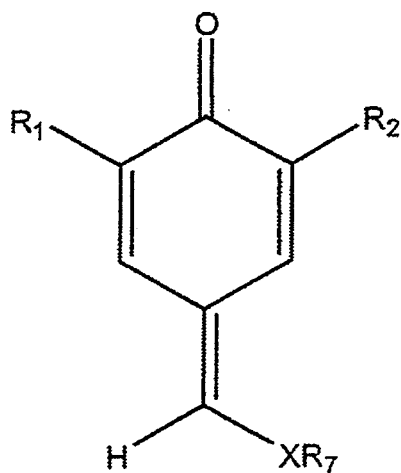
characterized in that the catalysts used are free or solid-phase-bound organic sulphonic acids, sulphuric acid and/or hydrogensulphates.

3. A process according to claim 1 or 2, characterized in that the molar ratio of the 3,5-disubstituted 4-hydroxybenzaldehyde to the catalyst is from 1:0.001 to 1:0.1.
4. A process according to at least one of claims 1 to 3, characterized in that the molar ratio of the 3,5-disubstituted 4-hydroxybenzaldehyde to the orthoformate is from 1:1 to 1:2.
5. A process according to at least one of claims 1 to 4, characterized in that the acetal-containing reaction mixture is heated to at least 100°C, the (thio)alcohol released being removed from the reaction mixture by means of chemical and/or physical methods immediately after formation thereof.
6. A process according to claim 5, characterized in that the acetal-containing reaction mixture is heated to at least 100°C, additional solvent (C) being metered in continuously while the alcohol and/or thioalcohol released is simultaneously removed from the reaction mixture together with the additional solvent (C).
7. A process for preparing substituted 1,4-quinone methides of the formula



where $R_1, R_2 =$ each independently hydrogen, (C_1-C_{15}) -alkyl, (C_3-C_{15}) -cycloalkyl or (C_6-C_{14}) -aryl, which are unsubstituted or substituted,
 $R_8 =$ (C_3-C_{15}) -alkyl, (C_3-C_{15}) -cycloalkyl or (C_6-C_{14}) -aryl, which are substituted or unsubstituted, and
 $X =$ O, S,

characterized in that
a substituted 1,4-quinone methide of the formula

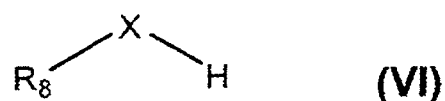


where $R_7 =$ unsubstituted (C_1-C_2) -alkyl group
and

X = O,

where R₁ and R₂ are each as defined above,

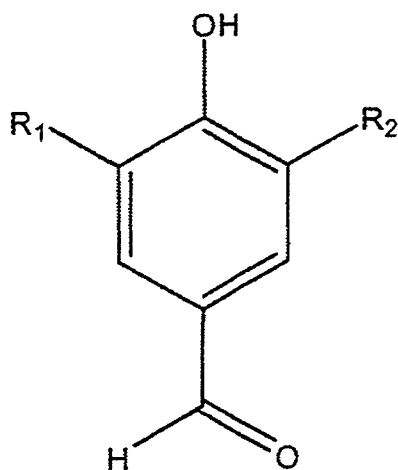
is reacted in the presence of an alcohol or thioalcohol of the formula



where X = O, S,

where R₈ is as defined above.

8. A process according to claim 7, characterized in that the substituted 1,4-quinone methides where R₇ = unsubstituted (C₁-C₂)-alkyl group and X = O used are prepared by means of a process according to at least one of claims 1 to 6.
9. A process for preparing 3,5-disubstituted 4-hydroxybenzaldehyde of the formula

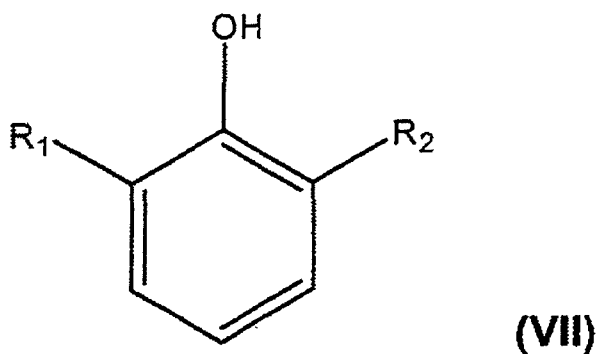


where R₁, R₂ = each independently hydrogen, (C₁-C₁₅)-alkyl, (C₃-C₁₅)-cycloalkyl or

(C₆-C₁₄)-aryl, which are substituted or unsubstituted,

characterized in that

2,6-disubstituted phenol of the formula



where R₁ and R₂ are each as defined above

is reacted with urotropin in a solvent mixture consisting of glacial acetic acid and water at temperatures which are at least 2°C below the reflux temperature over the entire reaction time.

10. A process according to claim 9, characterized in that the molar ratio of the 2,6-disubstituted phenol to the urotropin is from 1:1 to 1:0.8.