

PATENT SPECIFICATION

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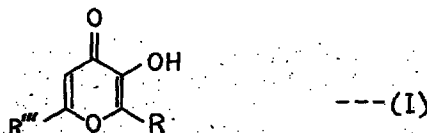


(54) PROCESS FOR THE PREPARATION OF 6-HYDROXY-2H-PYRAN-3(6H)-ONES USEFUL IN THE SYNTHESIS OF GAMMA-PYRONES

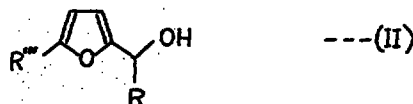
(71) We, PFIZER INC., a Corporation organised under the laws of the State of Delaware, United States of America, of 235 East 42nd Street, New York, State of New York, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a process for the preparation of gamma-pyrone and is particularly concerned with a process for the preparation of maltol (3-hydroxy-2-methyl-4H-pyran-4-one) and related compounds and with 6-hydroxy-2H-pyran-3(6H)-one intermediates for use in the process.

According to the complete specification of copending application No. 30759/77 (Serial No. 1,538,371) there is provided a process for preparing a gamma-pyrone of the general formula:

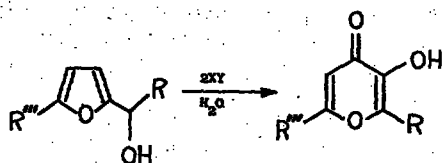


wherein R is hydrogen, alkyl of 1 to 4 carbon atoms, phenyl or benzyl; and R''' is hydrogen or alkyl of 1 to 4 carbon atoms which comprises contacting a furfuryl alcohol of the general formula:



with at least two equivalents of a halogen oxidant and heating at 70—160°C until the hydrolysis of the formed 4-halo-6-hydroxy-2,6-dihdropyran-3-one is substantially complete.

The process is generally performed by treating the furfuryl alcohol, in aqueous medium, with two equivalents of oxidant and the reaction mixture is then heated to hydrolyse the intermediate formed. The overall reaction is represented as follows:



wherein R is hydrogen, alkyl of 1 to 4 carbon atoms, phenyl or benzyl; R''' is

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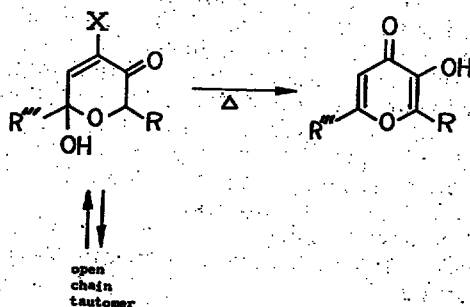
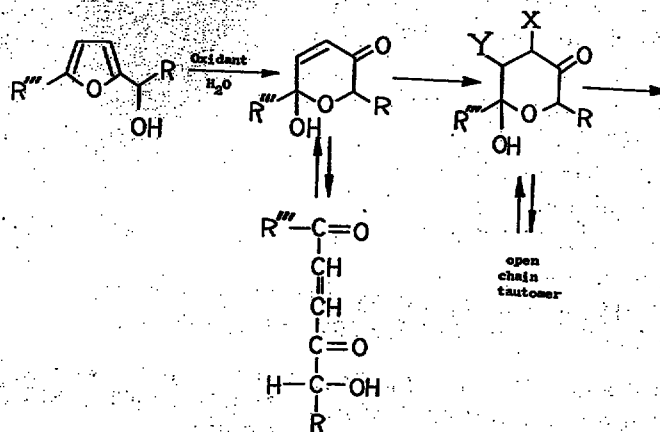
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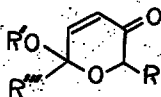
hydrogen or alkyl of 1 to 4 carbon atoms, and XY is Cl₂, Br₂, ClBr, HOCl, HOBr or mixtures thereof.

The reaction pathway is shown in the following scheme:



However, if desired, the intermediate 6-hydroxy-2H-pyran-3(6H)-one can be prepared by contacting the appropriate furfuryl alcohol with one equivalent of a halogen oxidant. The isolated product is readily converted to the desired gamma-pyrone by contacting it with an additional equivalent of a halogen oxidant and hydrolysing the formed 4-halogeno-6-hydroxy-2H-pyran-3(6H)-one as described in said application No. 30759/77 (Serial No. 1,538,371).

Thus according to the present invention there is provided a process for preparing a compound of the formula:



--- (III)

wherein R is hydrogen, alkyl of 1 to 4 carbon atoms, phenyl or benzyl, R' is hydrogen and R'' is hydrogen or alkyl of 1 to 4 carbon atoms, which comprises contacting a furfuryl alcohol of the formula (II) in aqueous solution with at least one but less than two equivalents of a halogen oxidant selected from chlorine, bromine, chlorine-bromide, hypochlorous acid, hypobromous acid or mixtures thereof at a temperature of -50 to 50°C until the reaction is substantially complete and isolating the desired product of formula (III).

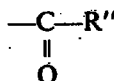
The process is conveniently performed by dissolving the furfuryl alcohol in water or in water and a co-solvent. The co-solvent can be water-miscible or water-immiscible and can be selected from a wide range of solvents such as C₁ to C₄ alkanols or diols; C₂ to C₁₀ ethers or nitriles; and C₃ to C₁₀ ketones or esters. The preferred co-solvents are C₁ to C₄ alkanols and C₂ to C₁₀ ethers, with methanol the preferred solvent because of cost. The solution is kept at a temperature of -50 to 50°C, preferably -10 to 10°C. To this solution is charged a desired furfuryl alcohol while simultaneously adding a halogen oxidant (preferably one

equivalent) to the reaction mixture. The temperature of the reaction mixture is maintained at -10 to 10°C . during halogen addition. If a low-boiling co-solvent is employed, it is preferably removed by distillation after all additions are complete and the compound of formula (III) is isolated.

The halogen oxidant can be chlorine, bromine, chlorine-bromide, hypochlorous or hypobromous acid or mixtures thereof. Chlorine-bromide is a commercially available gas. It can be prepared *in situ* by addition of chlorine to a solution of sodium or potassium bromide or by the addition of bromine to a solution of sodium or potassium chloride.

Hypochlorous and hypobromous acid can be conveniently generated *in situ* by the addition of aqueous acid (HCl , H_2SO_4 , HBr), to a solution of the alkali or alkali earth metal hypohalite, e.g. NaOCl , KOCl or $\text{Ca}(\text{OCl})_2$. The preferred halogen oxidants, based on cost factors, are chlorine and chlorine-bromide prepared *in situ*. A small excess of halogen oxidant (up to two equivalents) may be used but for optimum results one equivalent is employed.

Also according to the invention the gamma-pyrones of formula (I) can be prepared by treating a compound of the formula III wherein R is hydrogen, alkyl of 1 to 4 carbon atoms, phenyl or benzyl and R' is hydrogen, alkyl of 1 to 4 carbon atoms or



wherein R'' is methyl, ethyl or phenyl; and R''', is hydrogen or alkyl of 1 to 4 carbon atoms, with one equivalent of a halogen oxidant and heating at 70 — 160°C to hydrolyse the product.

A 6-alkoxy-2H-pyran-3(6H)-one of formula (III) wherein R' is alkyl of 1 to 4 carbon atoms is prepared by the method of U.K. Patent Specification No. 1,505,028. A furfuryl alcohol is anodically alkoxyated to the 2-(1-hydroxyalkyl)2,5-dialkoxy-dihydrofuran. Treatment with a strong organic acid produces the desired 6-alkoxy compound. A 6-acyloxy compound of formula (III) wherein R' is —COR'' and R'' is methyl, ethyl or phenyl may be prepared by conventional treatment of the 6-hydroxy compound with the appropriate anhydride in the presence of pyridine.

In the process for preparing gamma-pyrones of formula (I) from a compound of formula (III), wherein R' is a hydroxy group, the reaction with a halogen oxidant is performed as described above. The reaction mixture is then heated as described in the Complete Specification of copending Application No. 30759/77 (Serial No. 1,538,371) to effect hydrolysis of the formed 4-halo-6-hydroxy-2,6-dihydropyran-3-one intermediate.

In the process for preparing gamma-pyrones of formula (I) from a compound of formula (III) wherein R' is an alkyl group or an acyloxy group the 6-acyl or 6-alkoxy-2H-pyran-3(6H)-one is dissolved in a reaction-inert solvent selected from acetic acid, formic acid, trifluoroacetic acid, halogenated solvents, C_2 to C_{10} nitriles and ethers, C_1 to C_4 alkanols or diols, and C_2 to C_{10} ketones, esters and amides. The preferred solvents are acetic acid, formic acid or methanol. An equivalent of a halogen oxidant such as chlorine, bromine, chlorine-bromide, hypochlorous acid or hypobromous acid is added at room temperature and the reaction mixture is heated to 70 — 160°C ., generally 100 — 110°C ., until the conversion to the desired gamma-pyrone is substantially complete (approximately 1—3 hours). The gamma-pyrone may be obtained from the cooled, neutralized reaction mixture on standing or by extracting the reaction mixture with a solvent such as chloroform which yields the gamma-pyrone on concentration.

With organic acids and other protic solvents such as formic acid, acetic acid, other organic acids and alkanols that have not been vigorously dried, no additional water is added in the above described reaction. However, with non-protic solvents, water is necessary and is added for the conversion of the formed 4-halogeno-6-substituted-2H-pyran-3(6H)-one to the γ -pyrone. When a low-boiling solvent is employed in the reaction, it is preferably removed by distillation just before the reaction mixture is heated to 100 — 110°C . for the hydrolytic conversion of the formed 4-halo-dihydropyran to the gamma-pyrone.

The process for the preparation of compounds of the formula III and their conversion to gamma-pyrones is illustrated by the following Examples.

Example 1

6-hydroxy-2-methyl-2H-pyran-3(6H)-one

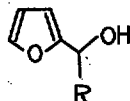
To a solution of 25 g of 1(2-furyl)-1-ethanol in 125 ml of tetrahydrofuran and 125 ml of water at 5°C. was added 1 equivalent of bromine. The temperature was maintained at 5–10°C. throughout the addition. The solution was adjusted to pH 2.1 and extracted with ethyl acetate (3×50 ml). The ethyl acetate extract was dried and evaporated to give a yellow oil. The oil was chromatographed on silica gel and eluted with chloroform-ethyl acetate (3:1) to give 4.8 g of clear oil which was shown by spectral data to be identical with 6-hydroxy-2-methyl-2H-pyran-3(6H)-one prepared from 6-methoxy-2-methyl-2H-pyran-3(6H)-one by acid hydrolysis [Tetrahedron 27, 1973 (1971)].

IR (CHCl₃, 3700, 3300, 1700 cm⁻¹).

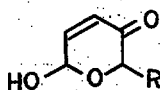
NMR (CDCl₃, δ): 6.8–7.1 (1H, d of d); 6.0–6.2 (1H, d), 5.6 (1H, br. s. exchanges with D₂O); 5.4–5.5 (1H, d); 4.8–5.0 (1H, q); 1.3–1.6 (3H, t).

Example 2

The method of Example 1 was repeated with a furfuryl alcohol of the formula



to yield a compound of the formula



wherein R is hydrogen or ethyl.

Ethyl compound: IR (CHCl₃) 3600, 3340, 1706 cm⁻¹

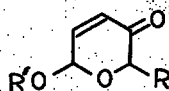
Hydrogen compound: IR (CHCl₃) 3565, 3300, 1703 cm⁻¹

Example 3

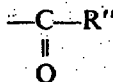
A solution of 6-methoxy-2-methyl-2H-pyran-3(6H)-one (0.01 mole) in 20 ml of acetic acid was treated with gaseous chlorine (0.01 mole) at room temperature. The reaction mixture was then heated to reflux for about one hour, cooled to room temperature, diluted with 20 ml of water, the pH adjusted with 50% NaOH solution to 7.0 and the reaction mixture extracted with chloroform. The chloroform extract was concentrated to yield maltol which was recrystallized from methanol to give the pure product (56%), mp 159.5–160.5°C.

Example 4

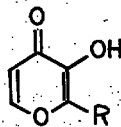
The method of Example 3 may be repeated starting with a compound of the formula



wherein R is hydrogen, alkyl of 2 to 4 carbon atoms, phenyl and benzyl; R' is alkyl of 2 to 4 carbon atoms and



where R'' is methyl, ethyl or phenyl to yield a gamma-pyrone of the formula



wherein R is hydrogen, alkyl of 2 to 4 carbon atoms, phenyl or benzyl.

Example 5

The method of Example 3 may be repeated with comparable results replacing acetic acid with each of the following solvents:

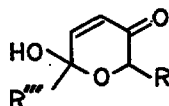
formic acid
methanol
ethanol
tetrahydrofuran
benzene
ethylene glycol
trifluoroacetic acid
acetone
acetonitrile

Example 6

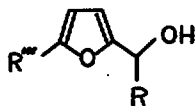
The method of Example 3 may be repeated with comparable results replacing chlorine with bromine, sodium or potassium hypochlorite or hypobromite, gaseous chlorine-bromide or chlorine-bromide prepared *in situ* by the addition of chlorine to a solution containing sodium bromide or bromine to a solution of sodium chloride.

WHAT WE CLAIM IS:—

1. A process for preparing a compound of the general formula



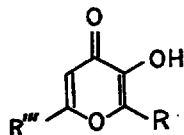
which comprises contacting a furfuryl alcohol of the general formula



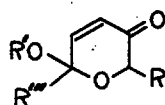
wherein R is hydrogen, alkyl of 1 to 4 carbon atoms, phenyl or benzyl and R''' is hydrogen or alkyl of 1 to 4 carbon atoms in aqueous solution with at least one but less than two equivalents of a halogen oxidant selected from chlorine, bromine, chlorine-bromide, hypochlorous acid, hypobromous acid or mixtures thereof at a temperature of -50 to 50°C. until the reaction is substantially complete and isolating the desired compound.

2. The process of Claim 1, wherein a co-solvent is present and said co-solvent is selected from alkanols or diols of 1 to 4 carbon atoms, ethers or nitriles of 2 to 10 carbon atoms, or ketones, amides and esters of 3 to 10 carbon atoms.

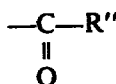
3. A process for preparing a gamma-pyrone of the general formula:



which comprises treating a compound of the general formula:



wherein R is hydrogen, alkyl of 1 to 4 carbon atoms, phenyl or benzyl, R' is hydrogen, alkyl of 1 to 4 carbon atoms or





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Example 5

The method of Example 3 may be repeated with comparable results replacing acetic acid with each of the following solvents:

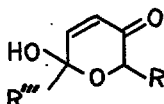
formic acid
methanol
ethanol
tetrahydrofuran
benzene
ethylene glycol
trifluoroacetic acid
acetone
acetonitrile

Example 6

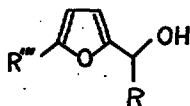
The method of Example 3 may be repeated with comparable results replacing chlorine with bromine, sodium or potassium hypochlorite or hypobromite, gaseous chlorine-bromide or chlorine-bromide prepared *in situ* by the addition of chlorine to a solution containing sodium bromide or bromine to a solution of sodium chloride.

WHAT WE CLAIM IS:—

1. A process for preparing a compound of the general formula



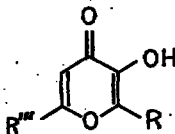
which comprises contacting a furfuryl alcohol of the general formula



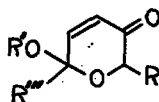
wherein R is hydrogen, alkyl of 1 to 4 carbon atoms, phenyl or benzyl and R''' is hydrogen or alkyl of 1 to 4 carbon atoms in aqueous solution with at least one but less than two equivalents of a halogen oxidant selected from chlorine, bromine, chlorine-bromide, hypochlorous acid, hypobromous acid or mixtures thereof at a temperature of -50 to 50°C . until the reaction is substantially complete and isolating the desired compound.

2. The process of Claim 1, wherein a co-solvent is present and said co-solvent is selected from alkanols or diols of 1 to 4 carbon atoms, ethers or nitriles of 2 to 10 carbon atoms, or ketones, amides and esters of 3 to 10 carbon atoms.

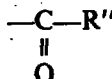
3. A process for preparing a gamma-pyrone of the general formula:



which comprises treating a compound of the general formula:



wherein R is hydrogen, alkyl of 1 to 4 carbon atoms, phenyl or benzyl, R' is hydrogen, alkyl of 1 to 4 carbon atoms or





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wherein R is a monovalent group of phenyl, and R₁ is hydrogen or alkyl of 1 to 4 carbon atoms, with the equivalent of a halogen oxidant and heating at 70—160°C to produce the product.

5 A process as claimed in any one of Claims 1 to 3 substantially as hereinbefore described with reference to any of the Examples.

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Chartered Patent Agent,
Agent for the Applicants.

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