

PATENT SPECIFICATION

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(54) PROCESS FOR THE PREPARATION 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-pyrones and is particularly concerned with a process for the preparation of maltol (3-hydroxy-2-methyl-4H-pyran-4-one) and related compounds.

Maltol is a naturally occurring substance found in the bark of young larch trees, pine needles and chicory. Early commercial production was from the destructive distillation of wood. Synthesis of maltol from 3-hydroxy-2-(1-piperidylmethyl)- γ -pyrone was reported by Spielman and Freifelder in J. Am. Chem. Soc., 69, 2908 (1947). Schenck and Spielman, J. Am. Chem. Soc., 67, 2276 (1945), obtained maltol by alkaline hydrolysis of streptomycin salts. Chawla and McGonigal, J. Org. Chem., 39, 3281 (1974) and Lichtenthaler and Heidel, Angew. Chem., 81, 998 (1969), reported the synthesis of maltol from protected carbohydrate derivatives. Shono and Matsumura, Tetrahedron Letters No. 17, 1363 (1976), described a five step synthesis of maltol starting with methyl furfuryl alcohol.

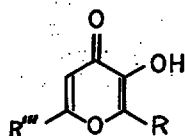
The isolation of 2-ethyl-3-hydroxy-6-methyl-4H-pyran-4-one as one of the characteristic sweet-aroma components in refinery final molasses was reported by Hiroshi Ito in Agr. Biol. Chem., 40 (5), 827—832 (1976). This compound was previously synthesized by the process described in U.S. 3,468,915.

Syntheses of gamma-pyrones such as pyromeconic acid, maltol, ethyl maltol and other 2-substituted-3-hydroxy-gamma-pyrones are described in U.S. Patents 3,130,204; 3,133,089; 3,140,239; 3,159,652; 3,365,469; 3,376,317; 3,468,915; 3,440,183 and 3,446,629.

Maltol and ethyl maltol enhance the flavour and aroma of a variety of food products.

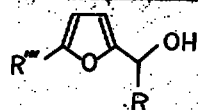
In addition, these materials are used as ingredients in perfumes and essences. The 2-alkenylpyromeconic acids reported in U.S. 3,644,635 and the 2-arylmethylpyromeconic acids described in U.S. 3,365,469 inhibit the growth of bacteria and fungi and are useful as flavour and aroma enhancers in foods and beverages and aroma enhancers in perfumes.

Thus, according to the invention there is provided a process for preparing a gamma-pyrone of the general formula:



(I)

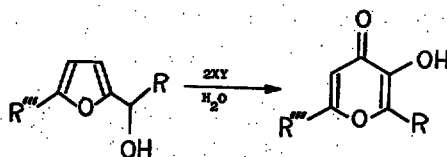
wherein R is hydrogen, alkyl of 1 to 4 carbon atoms, phenyl or benzyl; and R'' is hydrogen or alkyl of 1 to 4 carbon atoms which comprises contacting a furfuryl alcohol of the general formula:



(II)

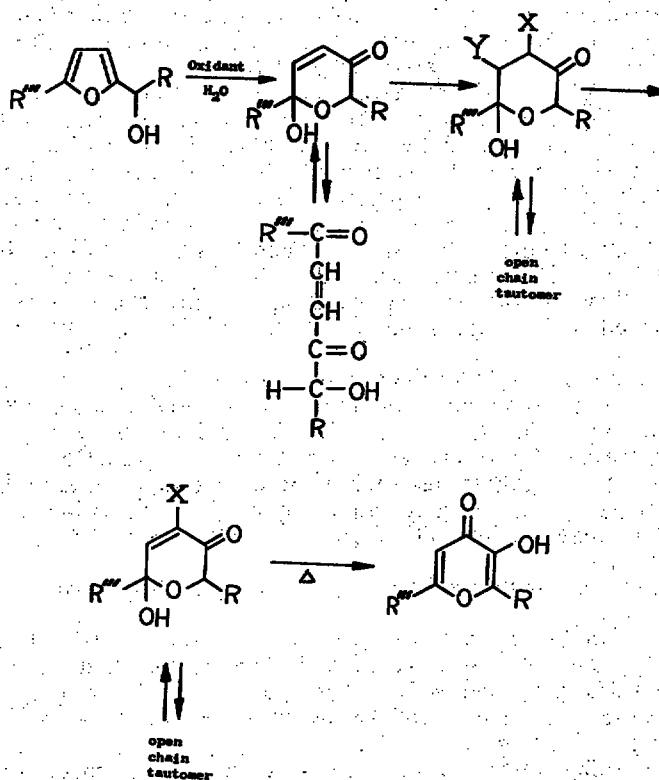
with at least two equivalents of a halogen oxidant at a temperature of -50 to $+50^{\circ}\text{C}$. and, without isolating the 4-halo-6-hydroxy-2,6-dihydropyran-3-one so formed, heating at $70-160^{\circ}\text{C}$. until hydrolysis is substantially complete.

The process is generally performed by treating the furfuryl alcohol, in aqueous medium, with two equivalents of oxidant, although excess oxidant may be used 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 hydrogen or alkyl of 1 to 4 carbon atoms; and XY is Cl_2 , Br_2 , ClBr , HOCl , HOBr or mixtures thereof.

The reaction pathway is shown in the following scheme:



Lefebvre and co-workers in *J. Med. Chem.*, 16, 1084 (1973) demonstrated that furfuryl alcohols could be directly converted to 6-hydroxy-2H-pyran-3(6H)-ones when a peracid oxidant such as peracetic acid or *m*-chloroperbenzoic acid is employed.

The first step of the Lefebvre work uses a peracid in an organic solvent and probably leads to a 6-acetoxy or 6-*m*-chlorobenzoyloxy pyran derivative which is hydrolyzed to the 6-hydroxy compound during the aqueous work-up. Water is not used in the first step of the reaction, and would in fact be deleterious. In any case,

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the process of Lefebvre and co-workers cannot lead directly to the conversion of a furfuryl alcohol to a gamma-pyrone.

Critical to the process of the present invention is the use of an aqueous solution of a halogen oxidant. A furfuryl alcohol can be cleanly oxidized to a 6-hydroxy-2H-pyran-3(6H)-one using one equivalent of a halogen oxidant in water or water/organic co-solvent. It is surprising and an unexpected finding that 6-hydroxy-2H-pyran-3(6H)-ones can be converted to gamma-pyrones. A 6-hydroxy-2H-pyran-3(6H)-one may be regarded as a hemi-acetal of an aldehyde and as such might be expected to undergo numerous undesired side reactions such as over oxidation, aldol-type condensations, etc. Employing two or more equivalents of halogen oxidant in water or water and organic co-solvent, the reaction proceeds smoothly from a furfuryl alcohol to a gamma-pyrone. This novel "one pot" process offers the advantages of employing low cost Cl_2 , Br_2 , ClBr , HOCl , HOBr or mixtures thereof as the halogen oxidant. Isolation of the desired gamma-pyrone is greatly simplified since solvent, oxidant and by-product mineral acid are all volatile and can be removed *in vacuo* to afford crude gamma-pyrone directly in high yield by simple concentration.

The one-pot process is conveniently operated by dissolving a furfuryl alcohol in water or 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 C_1 to C_4 alkanols or diols; C_2 to C_{10} ethers or nitriles C_3 — C_{10} ketones or esters. The preferred co-solvents are C_1 to C_4 alkanols and C_2 to C_{10} 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 two equivalents) 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. The reaction mixture is then heated to a temperature at which the hydrolysis proceeds at a reasonable rate (70 to 160°C .). The generally employed reaction temperature is 100 — 110°C . The heating is continued until the hydrolysis of the formed 4-halo-6-hydroxy-2,6-dihydropyran-3-one intermediates is substantially complete (1 to 2 hours). The acid necessary to catalyze this final hydrolysis is generated *in situ* by loss of acid from the intermediates formed during the course of the reaction. Additional acid can be added if desired.

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 , etc.) 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*.

The intermediates shown in the reaction scheme may also be isolated and reacted in separate steps as described in co-pending applications Nos. 4240/78 and 4242/78 (Serial Nos. 1,538,372 and 1,538,374).

The process of the invention is illustrated by the following Examples:

Example 1.

In a 3-neck round bottom flask equipped with a magnetic stirring bar, a gas inlet tube, a thermometer and an addition funnel was added 20 ml of tetrahydrofuran and 50 ml of water. The solution was cooled to a temperature of 0 to 10°C . The addition funnel was charged with a solution of 1(2-furyl)-1-ethanol (0.089 moles) in 20 ml of tetrahydrofuran and this was added dropwise to the stirred reaction flask while chlorine (0.30 mole) was added via the gas inlet tube. The rate of addition was such that all the alcohol was added in the first 1.3—1.5 equivalents of chlorine (approximately 30 minutes) while maintaining the reaction temperature below 10°C . The reaction mixture was heated to reflux and the tetrahydrofuran removed by distillation. When the reaction mixture reached a temperature of about 105°C ., a condenser was added and the refluxing continued for about 2 hours. The reaction mixture was then filtered hot, cooled, the pH adjusted to 2.2 and the reaction mixture was cooled to 5°C . Crystallization and filtration yielded 3.43

grams of crude 3-hydroxy-2-methyl- γ -pyrone (maltol). The aqueous filtrate was extracted with CHCl_3 to obtain a second crop of 2.58 g of maltol. Distillation of the combined solids and recrystallization from methanol gave 5.5 g (49%) of pure white maltol, m.p. 159.5–160.5°C.

Example 2.

The method of Example 1 was repeated under varying conditions as shown in Table I with furfuryl alcohols of the formula

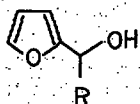


TABLE I

One Pot Process using Chlorine as the Oxidant

R	Cosolvent	Temp. (°C) of oxidation	Temp. (°C) of hydrolysis	Yield (%)
CH_3	methanol	10	100	45
CH_3	methanol	5	110	56
CH_3	methanol	-5	104	60
CH_3	methanol	-10	104	77
CH_3	methanol	-20	106	62–67
CH_3	THF	10	105	49
CH_3	acetone	-5	110	36
CH_3	CH_3CN	-5	110	29
CH_3	Et OAc	0	110	26
CH_3	none	10	110	17–30
CH_3	benzene	10	110	26
CH_3	methyl isobutyl ketone	5	110	44
CH_3	isopropyl alcohol	0	110	49
CH_2CH_3	methanol	5	110	49
CH_2CH_3	methanol	-10	110	58
CH_2CH_3	THF	10°	110	47
H	methanol	-10°	110	57
CH_3	methanol	-30°	110	50

THF = tetrahydrofuran

EtOAc = ethyl acetate

Example 3.

The method of Example 2 was repeated with comparable results employing each of the following co-solvents:

ethanol
n-propanol
iso-butanol
n-butanol
t-butanol
dioxane
ethyl ether
isopropyl ether
dimethoxy ethane
2-methoxy ethanol
2-ethoxy ethanol
ethylene glycol

Example 4.

In a 3-neck round bottom flask equipped with a stirring bar, a gas inlet tube and an addition funnel was added 20 ml of tetrahydrofuran, 50 ml of water and sodium bromide (0.20 mole). The solution was cooled to a temperature of 0 to 20°C. The addition funnel was charged with a solution of 1(2-furyl)-1-ethanol (0.18 mole) in 20 ml of tetrahydrofuran and this was added dropwise to the rapidly stirred reaction flask while gaseous chlorine (0.40 mole) is added via the gaseous inlet tube. The rate of the alcohol addition was such that a yellow orange color was maintained. The reaction temperature was kept below 20°C. with ice bath cooling. After the alcohol and chlorine had both been added to the reaction flask, the temperature was raised to reflux to distill off the tetrahydrofuran. The isolation procedure of Example 1 was used to isolate 12.47 g of pure maltol (55% yield).

Substantially the same results are obtained substituting potassium bromide for sodium bromide.

Example 5.

The method of Example 4 was repeated under varying conditions shown in Table 2 with furfuryl alcohols of the formula

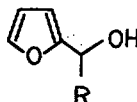


TABLE 2

One Pot Process using Cl-Br as the oxidant, generated by addition of chlorine *in situ* to NaBr

R	Cosolvent	Temp. (°C) of oxidation	Temp. (°C) of hydrolysis	Yield (%)
CH ₃	THF	20°	104	55
CH ₃	THF	27°	110	54
CH ₃	THF	15°	110	52
CH ₃	Isopropyl ether	25	110	46
CH ₃	ethyl ether	20	110	43
CH ₃	acetone	15	105	47
CH ₃	CH ₃ OH	15	110	32
CH ₂ CH ₃	THF	16	113	47
H	THF	20	109	48

THF = tetrahydrofuran

Example 6.

In a 3-neck round bottom flask equipped with a magnetic stirring bar, a gas inlet tube, a thermometer and an addition funnel was added 50 ml of tetrahydrofuran and 50 ml of water. This solution was then cooled to 0°C. and chlorine (0.10 mole) was added slowly to the reaction flask while 1(2-furyl)-1-ethanol (0.09 mole) was added dropwise. The temperature of the reaction mixture was not allowed to exceed 10°C. Bromine (0.10 mole) was then added and the reaction mixture heated to reflux. Following the isolation procedure of Example 1, a yield of 5.7 g of maltol was obtained.

Example 7.

To a 4-neck round bottom flask equipped with a thermometer, a condenser and two addition funnels was charged 50 ml of tetrahydrofuran and 50 ml of water and the solution was cooled to 10°C. To this well stirred solution was added together in the two addition funnels bromine (0.20 mole) and 1(2-furyl)-1-ethanol (0.09 mole). The temperature of the reaction was maintained at 15°C. throughout the double addition. The reaction mixture was then heated to 75°C. for 10 hours. Maltol was isolated by the procedure of Example 1 (53% yield).

Example 8.

The method of Example 7 was repeated under varying conditions shown in Table 3 with furfuryl alcohols of the formula

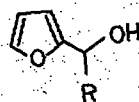


TABLE 3

R	Cosolvent	Temp. (°C) of oxidation	Temp. (°C) of hydrolysis	Yield (%)
CH ₃	THF	15°	75	53
CH ₃	CH ₃ OH	5°	105	47
CH ₃	none	15°	100	30
CH ₂ CH ₃	THF	25	105	47
H	THF	15°	100	45
CH ₃	THF	50°	100	20

Example 9.

A 2.8 M sodium hypochlorite solution was prepared by passing chlorine gas (42.6 g) into a solution of 48 g of sodium hydroxide in 150 ml of water at 0°C. A solution of 1(2-furyl)-1-ethanol (0.50 mole) in 15 ml of tetrahydrofuran and 15 ml of water was prepared in a 3-neck flask and cooled to 5°C. While maintaining a pH from 1.0 to 0.8 with 6 N HCl, 21.7 ml of the hypochlorite solution was added dropwise to the reaction flask over a period of about 33 minutes while maintaining the reaction temperature below 5°C. A 15 ml portion of concentrated HCl was then added to the reaction mixture which was then heated to remove the tetrahydrofuran by distillation. Heating was continued for an additional hour. Maltol was isolated as described in Example 1.

Substantially the same results are obtained when sodium hypobromite is used in place of sodium hypochlorite.

Example 10.

To a solution of 1(2-furyl)-1-ethanol (0.05 mole) in 15 ml of tetrahydrofuran and 15 ml of water at 5°C. is added 21.7 ml of 2.8 M sodium hypochlorite solution.

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Chlorine (0.05 mole) is added to the reaction flask via a gas inlet tube maintaining the reaction temperature below 5°C. The reaction mixture is then heated to reflux and the tetrahydrofuran removed by distillation. Heating is continued for an additional hour. The reaction mixture is cooled and maltol is isolated by the procedure described in Example 1.

Example 11.

To a 3-neck round bottom flask is charged a solution of 50 ml of water and 20 ml of tetrahydrofuran and the solution is cooled to 0°C. An addition funnel is charged with a solution of 1(2-furyl)-1-ethanol (0.89 mole) in 25 ml of tetrahydrofuran and this solution is added dropwise to the reaction flask while BrCl (0.30 mole) is added via a gas inlet tube. The rate of addition is such that all the furfuryl alcohol is added in the first 1.3—1.5 equivalents of BrCl while maintaining the temperature below 30°C. The reaction mixture is heated to reflux and the tetrahydrofuran removed by distillation. When the temperature reaches 105°C., a condenser is attached and the reaction mixture heated under reflux for about 2 hours. The reaction mixture is cooled and maltol isolated by the method of Example 1.

Example 12.

In a 3-neck round bottom flask equipped with a magnetic bar, a thermometer and two additional funnels is charged 25 ml of tetrahydrofuran and 50 ml of water. To this solution is added 1(2-furyl)-1-ethanol (0.89 mole) in 25 ml of tetrahydrofuran while bromine (0.16 mole) is added dropwise, maintaining the temperature below 15°C. After the additions are complete, chlorine (0.10 mole) is added via a gas inlet tube and the reaction is heated to reflux. Maltol is isolated from the cooled solution by the method of Example 1.

Example 13.

2-Ethyl-3-hydroxy-6-methyl-4H-pyran-4-one.

In a three necked round bottom flask were combined 28 ml of methanol and 38 ml of water. The solution was cooled to -15°C. and 0.166 mole of 5-methyl-2-(2-hydroxy-propyl)furan (J. Org. Chem. 26, 1673, 1960) and 0.416 mole of chlorine were added simultaneously. During the addition, the reaction was maintained between -16 and -8°C. When addition was completed, the solution was warmed to 80°C. and refluxed for about 3 hours. Upon cooling to room temperature, the pH was adjusted to 2.1 and extracted with chloroform (3 x 100 ml). The combined organic layers were washed with water, brine and dried over magnesium sulfate. The organic solution was filtered and evaporated to give a thick dark solid. The solid was recrystallized twice from methanol to give 8.06 grams (30% yield) of white solid. Sublimation yielded pure product, m.p. 157—159°C.

Analysis

Calc'd. for $C_8H_{10}O_3$: C, 62.33; H, 6.54

Found: C, 62.05; H, 6.44

NMR ($CDCl_3$, δ): 6- CH_3 , 2.33 (3H, s); 2- CH_3 , 1.30 (3H, t); 2- CH_2 —, 2.75 (2H, quartet); 5H, 6.23 (1H, s).

Example 14.

3-Hydroxy-2,6-dimethyl-4H-pyran-4-one.

In a three necked round bottom flask were combined 28 ml of water and 32 ml of methanol and cooled to -15°C. The solution was treated with 0.167 mole of 5-methyl-2-(α -hydroxy-ethyl)furan (J. Org. Chem., 26, 1673, 1960) and 0.416 mole of chlorine simultaneously. The temperature was maintained at -15 to -10°C. during addition. The reaction was allowed to warm to room temperature over 30 minutes and heated to reflux for 3 hours. The cooled solution was adjusted to pH 2.1 and extracted with chloroform (3 x 100 ml). The chloroform extracts were combined, washed with water and brine, dried over magnesium sulfate, filtered and evaporated. The residue, a dark oil, was chromatographed on silica gel developed with methylene chloride/ethyl acetate (95:5). The product isolated by evaporation, was recrystallized from methanol as a tan solid (yield, 25%). Sublimation yielded white crystals, m.p. 161—163°C.

Analysis

Calc'd. for $C_7H_8O_3$: C, 59.99; H, 5.75

Found: C, 59.83; H, 5.82

NMR ($CDCl_3$, δ): 6- CH_3 , 2.33 (3H, s); 2- CH_3 , 2.26 (3H, s); 5-H, 6.10 (1H, s).

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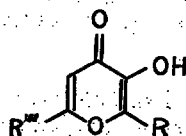


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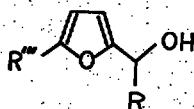
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WHAT WE CLAIM IS:—

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



which comprises contacting a furfuryl alcohol of the general formula



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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 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. and, without isolating the 4-halo-dihydropyran so formed, heating at 70—160°C. until hydrolysis is substantially complete.

2. The process of claim 1 wherein the hydrolytic reaction temperature is 100—110°C.

3. 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, and ketones or esters of 3 to 10 carbon atoms.

4. The process of claim 3 wherein said alkanol is methanol.

5. The process of claim 3 wherein said ether is tetrahydrofuran.

6. The process of claim 3 wherein said ether is isopropyl ether.

7. The process of claim 3 wherein said ketone is acetone.

8. The process of claim 1 wherein said halogen oxidant is chlorine.

9. The process of claim 1 wherein said halogen oxidant is chlorine-bromide.

10. The process of claim 1 wherein said gamma-pyrone is 3-hydroxy-2-methyl-4H-pyran-4-one.

11. The process of claim 1 wherein said gamma-pyrone is 2-ethyl-3-hydroxy-4H-pyran-4-one.

12. The process of claim 1 wherein said gamma-pyrone is 2-ethyl-3-hydroxy-6-methyl-4H-pyran-4-one.

13. A process as claimed in any one of claims 1 to 12 substantially as hereinbefore described with reference to any of the Examples.

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