

PATENT SPECIFICATION

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- (21) Application No. 4242/78 (22) Filed 21 July 1977
 (61) Divided out of No. 1538371
 (31) Convention Application No. 710901
 (32) Filed 2 Aug. 1976
 (31) Convention Application No. 721885
 (32) Filed 9 Sept. 1976 in
 (33) United States of America (US)
 (44) Complete Specification published 17 Jan. 1979
 (51) INT CL² C07D 309/32 309/40
 (52) Index at acceptance

C2C 1671 215 220 226 22Y 247 253 25Y 305 314 31Y 337 351
 352 360 362 36Y 388 409 40Y 440 502 509 50Y 623 625
 672 760 TZ

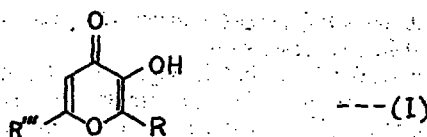


(54) PROCESS FOR THE PREPARATION OF 4-HALO-6-HYDROXY-2H-PYRAN-3(6H)-ONES AND THEIR USE IN THE SYNTHESIS OF GAMMA-PYRONES

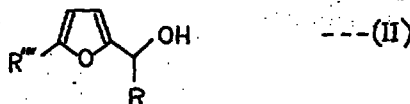
(71) We, PFIZER INC., a Corporation organised under the laws of the State of Delaware, United State of America, of 235 East 42nd Street, New York, State of New York, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which 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 and with 4-halo-6-hydroxy-2H-pyran-3(6H)one intermediates for use in the process.

According to the Complete Specification of our co-pending application No. 30759/77 (Serial No. 1,538,371) there is provided a process for preparing a gamma-pyrone of the formula:

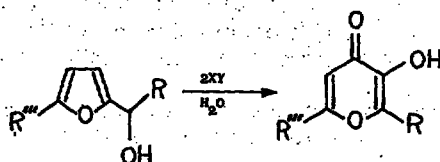


wherein R is hydrogen, alkyl of 1 to 4 carbon atoms, phenyl or benzyl; and R''' is hydrogen or alkyl of 1 to 4 carbon atoms which comprises contacting a furfuryl alcohol of the formula:



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-dihydropyran-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:



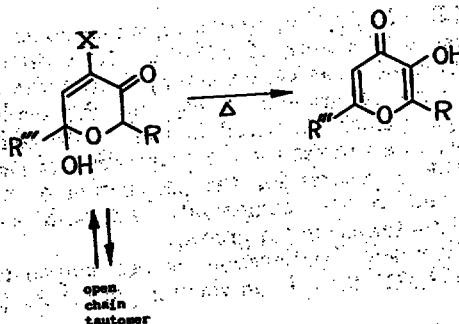
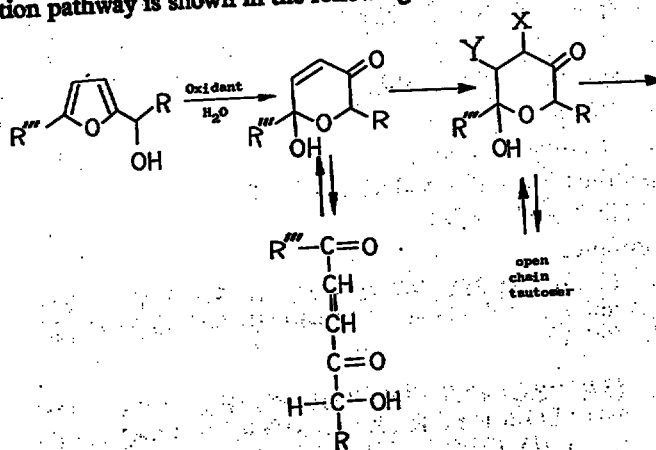
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wherein R is hydrogen, alkyl of 1 to 4 carbon atoms, phenyl or benzyl; R''' is hydrogen or alkyl of 1 to 4 carbon atoms; and XY is Cl₂, Br₂, ClBr, HOCl, HOBr or mixtures thereof.

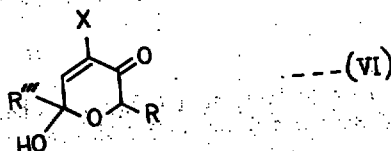
The reaction pathway is shown in the following scheme:



The intermediate 4-halogeno-6-hydroxy-2H-pyran-3(6H)-ones may also be isolated and hydrolysed in a separate step.

Thus the furfuryl alcohol in aqueous solution with an optional co-solvent may be contacted at -50 to 50°C, preferably at -10 to 10°C with two equivalents of a halogen oxidant. After stirring at room temperature for about 30 minutes, the pH of the reaction mixture is adjusted to about 2 with a strong base and the reaction mixture is extracted with a solvent such as ethyl acetate. Removal of the solvent yields the 4-halogeno-6-hydroxy-2H-pyran-3(6H)-one which may be hydrolysed to the desired gamma-pyrone as before.

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



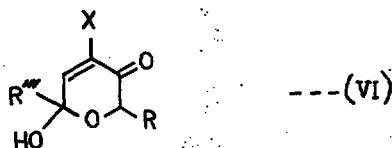
wherein R is hydrogen, alkyl of 1 to 4 carbon atoms, phenyl or benzyl; R''' is hydrogen or alkyl of 1 to 4 carbon atoms; and X is chlorine or bromine which comprises contacting a compound of the formula (II) in a reaction-inert solvent at a temperature of -50 to 50°C with at least two equivalents of a halogen oxidant selected from chlorine, bromine, chlorine-bromide, hypochlorous acid, hypobromous acid or mixtures thereof until the reaction is substantially complete and isolating the desired product of formula (VI).

Excess halogen oxidant may be used but for optimum results and efficiency of operation two equivalents are used to ensure substantial conversion to the compound of formula VI.

Also according to the invention there is provided a process for the preparation of a gamma-pyrone of the formula (I) which comprises hydrolysis of the 4-halogeno intermediates of formula (VI) by heating at 70—160°C in aqueous solution until hydrolysis is substantially complete.

The generally employed reaction temperature for the hydrolysis 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 catalyse 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 4-halo-dihydropyran intermediates of the formula:



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 X is chlorine or bromine; are novel compounds according to the invention.

The process for the preparation of the compounds of the formula (VI) and their conversion to gamma-pyrones is illustrated by the following Examples:

Example 1

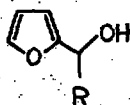
4-bromo-6-hydroxy-2-methyl-2H-pyran-3(6H)-one

To a solution of 25 g of 1(2-furfuryl)-1-ethanol in 125 ml of tetrahydrofuran and 125 ml of water at 0—5°C. was added dropwise 2.2 equivalents of bromine. Throughout the addition the temperature was maintained at 5—10°C. After the bromine addition the solution was stirred at room temperature for 30 minutes and the pH adjusted to 2.1 with 2N NaOH solution. The reaction mixture was extracted with ethyl acetate (3×100 ml). The ethyl acetate extracts were combined, dried over MgSO₄, filtered and taken to dryness. The residue was chromatographed on silica gel and eluted with chloroform-ethyl acetate (95:5). The product was an orange oil which was rechromatographed on silica gel and eluted with chloroform-ethyl acetate (95:5).

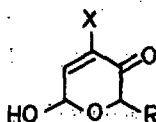
NMR (CDCl₃, δ) 7.3 (1H, d); 5.6 (1H, d); 4.7—5.0 (1H, q); 1.1—1.5 (3H, m).

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 4-bromo-6-hydroxy-2 ethyl 2H-pyran-3(6H)-one

NMR (CDCl₃, δ) 7.4 (1H, d); 5.8 (1H, d); 4.6—4.9 (1H, m); 1.8—2.2 (2H, m); 1.0—1.3 (3H, t).

Hydrogen compound 4-bromo-6-hydroxy-2H-pyran-3(6H)-one

NMR (CDCl₃, δ) 7.4 (1H, d); 5.5 (1H, d); 4.6 (2H, d of d).

Example 3

A solution of 4-bromo-6-hydroxy-2-methyl-2H-pyran-3(6H)-one was prepared

by dissolving the compound in either aqueous inorganic or organic acids. The solution was then heated to reflux, cooled to room temperature, the pH adjusted to 2.1 with 6N NaOH and the reaction mixture extracted with chloroform. Concentration yielded maltol. The acids, time of reaction and yields of maltol were as follows:

Acid	Concentration (%)	Reaction Time (Hrs.)	Yield (%)
HCl	32	2	68
HCl	32	5	52
HCl	18	5	35
HCl	25	3	49
HBr	18	5	24
H ₂ SO ₄	35	2	26
H ₃ PO ₄	35	2	29
CH ₃ COOH	35	2	69
CF ₃ COOH	neat	3	36
HNO ₃	35	3	0.4
CF ₃ COOH	neat	3	70
CH ₃ COOH	neat	3	77
HCOOH	neat	3	24
H ₂ SO ₄	35	5	48

In addition, organic solvents such as benzene and toluene, together with acidic materials such as *p*-toluenesulfonic acid and Amberlite (registered trade-mark) IR-120, may also be used.

Example 4

The method of Example 1 was repeated employing chlorine in place of bromine and the appropriate furfuryl alcohols to produce the following compounds:

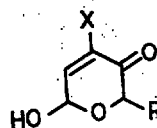
Methyl: 4-chloro-6-hydroxy-2-methyl-2H-pyran-3(6H)-one
NMR (CDCl₃, δ): 7.1 (1H, d); 5.8 (1H, d); 4.6—5.0 (1H, m); 4.4 (1H, br. s); 1.2—1.5 (3H, m).

Ethyl: 4-chloro-6-hydroxy-2-ethyl-2H-pyran-3(6H)-one
NMR (CDCl₃, δ): 7.0—7.1 (1H, d); 5.6—6.0 (2H, m); 4.4—5.0 (1H, m); 1.6—2.1 (2H, m); 0.9—1.1 (3H, t).

Hydrogen: 4-chloro-6-hydroxy-2H-pyran-3(6H)-one
NMR (CDCl₃, δ): 7.1—7.2 (1H, d); 5.6 (1H, d); 4.4—4.9 (2H, d of d) (D₂O added).

Example 5

The method of Example 1 may be repeated to yield a compound of the formula



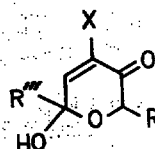
wherein R is propyl, butyl, phenyl or benzyl; X is bromine or chlorine.

Example 6

A solution of 4-bromo-6-hydroxy-2-methyl-2H-pyran-3(6H)-one (0.0025 mole) in 20 ml of 35% phosphoric acid was refluxed for about 5 hours. Maltol (34%) was isolated by the method of Example 3.

WHAT WE CLAIM IS:—

1. A process for preparing a compound of the formula



---(VI)



* C L M S *

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by dissolving the compound in either aqueous inorganic or organic acids. The solution was then heated to reflux, cooled to room temperature, the pH adjusted to 2.1 with 6N NaOH and the reaction mixture extracted with chloroform. Concentration yielded maltol. The acids, time of reaction and yields of maltol were as follows:

5	Acid	Concentration (%)	Reaction Time (Hrs.)	Yield (%)	5
	HCl	32	2	68	
	HCl	32	5	52	
	HCl	18	5	35	
	HCl	25	3	49	
10	HBr	18	5	24	10
	H ₂ SO ₄	35	2	26	
	H ₃ PO ₄	35	2	29	
	CH ₃ COOH	35	2	69	
	CF ₃ COOH	neat	3	36	
15	HNO ₃	35	3	0.4	15
	CF ₃ COOH	neat	3	70	
	CH ₃ COOH	neat	3	77	
	HCOOH	neat	3	24	
	H ₂ SO ₄	35	5	48	

20 In addition, organic solvents such as benzene and toluene, together with acidic materials such as *p*-toluenesulfonic acid and Amberlite (registered trade-mark) IR-120, may also be used. 20

Example 4

25 The method of Example 1 was repeated employing chlorine in place of bromine and the appropriate furfuryl alcohols to produce the following compounds: 25

Methyl: 4-chloro-6-hydroxy-2-methyl-2H-pyran-3(6H)-one

NMR (CDCl₃, δ): 7.1 (1H, d); 5.8 (1H, d); 4.6—5.0 (1H, m); 4.4 (1H, br. s); 1.2—1.5 (3H, m).

Ethyl: 4-chloro-6-hydroxy-2-ethyl-2H-pyran-3(6H)-one

30 NMR (CDCl₃, δ): 7.0—7.1 (1H, d); 5.6—6.0 (2H, m), 4.4—5.0 (1H, m); 1.6—2.1 (2H, m); 0.9—1.1 (3H, t). 30

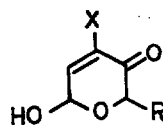
Hydrogen: 4-chloro-6-hydroxy-2H-pyran-3(6H)-one

NMR (CDCl₃, δ): 7.1—7.2 (1H, d); 5.6 (1H, d); 4.4—4.9 (2H, d of d) (D₂O added).

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Example 5

The method of Example 1 may be repeated to yield a compound of the formula



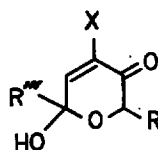
wherein R is propyl, butyl, phenyl or benzyl; X is bromine or chlorine.

Example 6

40 A solution of 4-bromo-6-hydroxy-2-methyl-2H-pyran-3(6H)-one (0.0025 mole) in 20 ml of 35% phosphoric acid was refluxed for about 5 hours. Maltol (34%) was isolated by the method of Example 3. 40

WHAT WE CLAIM IS:—

1. A process for preparing a compound of the formula



---(VI)

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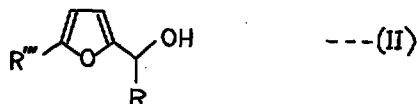


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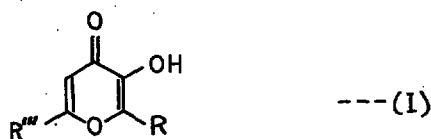
(11)

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 X is chlorine or bromine which comprises contacting a compound of the formula

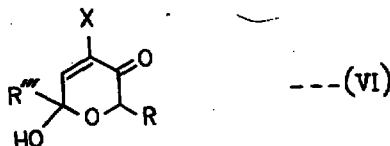


in a reaction-inert solvent at a temperature of -50 to 50°C . with at least two equivalents of a halogen oxidant selected from chlorine, bromine, chlorine-bromide, hypochlorous acid, hypobromous acid or mixtures thereof until the reaction is substantially complete and isolating the desired compound.

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

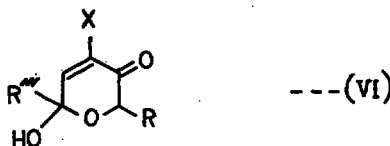


which comprises heating at 70 — 160°C in aqueous solution until hydrolysis is substantially complete a compound of the formula



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 X is chlorine or bromine.

3. A compound of the formula



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 X is chlorine or bromine.

4. A process as claimed in claims 1 or 2 substantially as hereinbefore described with reference to the Examples.

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Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1979
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from
which copies may be obtained.