

PATENT SPECIFICATION

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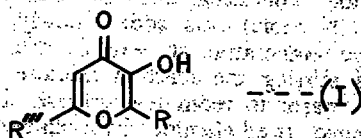


(54) PROCESS FOR THE PREPARATION OF 6-ALKOXY AND 6-ACYLOXY-4-HALO-2H-PYRONES AND THEIR USE IN THE SYNTHESIS OF GAMMA-PYRONES

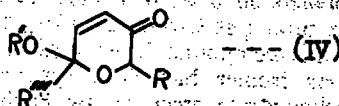
(71) We, PFIZER, INC., a Corporation organised under the laws of the State of Delaware, United States of America, of 235 East 42nd Street, New York, State of New York, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which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

According to the Complete Specification of co-pending application 4240/78 (Serial No. 1,538,372) 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 treating a compound of the general formula:

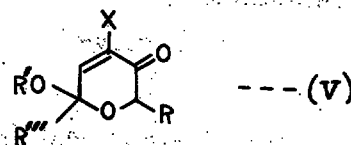


wherein R is hydrogen, alkyl of 1 to 4 carbon atoms, phenyl or benzyl and R' is hydrogen, alkyl of 1 to 4 carbon atoms or

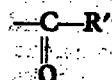


wherein R'' is methyl, ethyl or phenyl; and R''' is hydrogen or alkyl of 1 to 4 carbon atoms, with 1 equivalent of a halogen oxidant and heating at 70 to 160°C to hydrolyse the product.

The intermediate 4 - halogeno - 6 - substituted - 2H - pyran - 3(6H) - one may also be isolated and hydrolysed in a separate step, thus according to the present invention there is provided a process for preparing 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



wherein R'' is methyl, ethyl or phenyl; R''' is hydrogen or alkyl of 1 to 4 carbon atoms; and X is bromine, or chlorine which comprises contacting a compound of the formula (IV) in a reaction inert solvent at a temperature of -50 to 50°C with at least one equivalent

lent of a halogen oxidant selected from chlorine, bromine, chlorine-bromide, hypochlorous acid, hypobromous acid or mixtures thereof in the presence of an organic base until the reaction is substantially complete.

Suitable reaction-inert solvents are water, alkanols or diols of 1 to 4 carbon atoms, ethers and nitriles of 2 to 10 carbon atoms, and ketones, esters and amides of 3 to 10 carbon atoms.

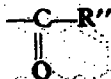
Excess halogen oxidant may be employed but for optimum results and efficiency of operation 1 equivalent is used.

The 4 - halo - dihydropyran of formula (V) may be prepared and isolated by conducting the halogenation at about -20 to 20°C ., preferably $5-10^{\circ}\text{C}$., in the presence of an organic base such as triethylamine. After about 30 minutes the reaction mixture is allowed to warm to room temperature, filtered to remove triethylamine hydrochloride and the solvent removed under vacuum to yield the 4 - halo - dihydro - pyran of formula (V).

Hydrolysis of the 6 - hydroxy - 4 - halo - dihydropyrans of formula (V) where R' is hydrogen to yield gamma-pyrone is described and claimed in our co-pending application of even date 4242/78 (Serial No. 1,538,374).

6 - Alkoxy - 2H - pyran - 3(6H) - ones of formula (IV) where R is alkyl of 1 to 4 carbon atoms are prepared by the method of U.K. Patent Specification No. 1,505,028. A 6 - acyloxy compound of formula (IV) where R' is $-\text{COR}''$ 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.

According to the present invention there is provided a process for the preparation of a gamma-pyrone of the formula (I) which comprises hydrolysis of a 4-halogeno intermediate of formula (V) wherein R' is alkyl of 1 to 4 carbon atoms or



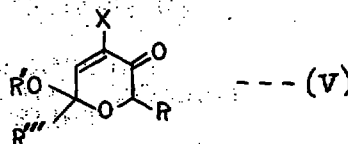
wherein R'' is methyl, ethyl or phenyl by heating in aqueous solution until hydrolysis is substantially complete.

The hydrolysis reaction is performed with the 4 - halogeno - 6 - acyl or 6 - alkoxy - 2H - pyran - 3(6H) - one 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, and the reaction mixture is heated to $70-160^{\circ}\text{C}$., generally $100-110^{\circ}\text{C}$., until the conversion to the desired gamma-pyrone is substantially complete (approximately 1-3 hours). The

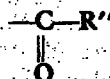
gamma-pyrone may be obtained from the cooled, neutralized reaction mixture on standing or by extracting the reaction mixture with a solvent such as chloroform which yields the gamma-pyrone on concentration.

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 gamma-pyrone.

Certain 4 - halo - dihydropyran intermediates of the formula:



wherein R is ethyl; R' is alkyl of 1 to 4 carbon atoms or



wherein R'' is methyl, ethyl or phenyl; 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 (V) and their conversion to gamma-pyrone is illustrated by the following Examples:

Example 1

4 - chloro - 6 - methoxy - 2 - methyl - 2H - pyran - 3(6H) - one

To a solution of 6 - methoxy - 2 - methyl - 2H - pyran - 3(6H) - one (0.05 mole) in 70 ml of dichloromethane at -10°C ., was added chlorine (0.05 mole) via a gas inlet tube. Following this addition, triethylamine (0.05 mole) was added slowly, maintaining the temperature at -10°C . After 30 minutes of stirring the reaction mixture was allowed to warm to room temperature, filtered to remove triethylamine hydrochloride and the solvent removed under vacuum. Redissolving the crude product in ether-benzene and filtration removed the last traces of triethylamine hydrochloride. Removal of the solvent gave 4 - chloro - 6 - methoxy - 2 - methyl - 2H - 3(6H) - one (yield, 99%). NMR analysis of the signals at 5.05 to 5.25 clearly showed two doublets in a 3 to 1 ratio corresponding to the proton at C-6 of the two possible isomers of the compound. Both optical forms of the *trans* isomer had been synthesized from a carbohydrate precursor by Paulsen, Eberstein

and Koebernick, Tetrahedron Letters 4377 (1974).

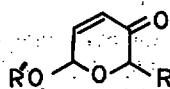
Example 2

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

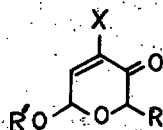
The method of Example 1 was repeated replacing chlorine with bromine to obtain 4 - bromo - 6 - methoxy - 2 - methyl - 2H-pyran - 3(6H) - one in 93% yield. The two optical forms of the *trans* isomer had been synthesized by Paulsen and co-workers, Tetrahedron Letters 4377 (1974).

Example 3

The methods of Examples 1 and 2 may be repeated starting with a compound of the formula:



wherein R is hydrogen, alkyl of 2 to 4 carbon atoms, phenyl or benzyl; R' is alkyl of 2 to 4 carbon atoms to yield a compound of the formula



wherein R and R' are as defined above; and X is chlorine or bromine.

Example 4

4 - bromo - 6 - acetoxy - 2H - pyran - 3(6H) - one

A solution in dichloromethane of 6 - acetyl-2H - pyran - 3(6H) - one, prepared by the method described in Tetrahedron 27, 1973 (1971), was brominated by the method of Example 2 to yield 4 - bromo - 6 - acetoxy-2H - pyran - 3(6H) - one, mp 78-80°C. The mass spectrum of the compound showed the expected parent peaks at 234 and 236 mass units.

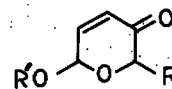
Example 5

4 - bromo - 6 - acetoxy - 2 - methyl - 2H-3(6H) - one

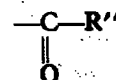
The method of Example 4 was repeated with 6 - acetyl - 2 - methyl - 2H - pyran-3(6H) - one to yield 4 - bromo - 6 - acetoxy-2 - methyl - 2H - 3(6H) - one which showed parent masses of 249.96 and 247.96 by mass spectroscopy and the following MNR spectrum: (δ , CDCl_3): 7.3(1H, d); 6.4(1H, d of d); 4.7(1H, Q); 2.2(3H, S); 1.4(3H, S).

Example 6

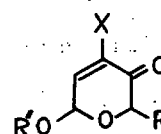
The method of Example 1 may be repeated starting with a compound of the formula



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



where R'' is methyl, ethyl or phenyl to yield a compound of the formula



wherein R and R' are as defined above and X is chlorine.

Example 7

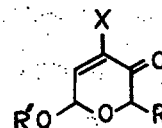
To a round bottom flask equipped with a stirring bar and a condenser was added 4-chloro - 6 - methoxy - 2 - methyl - 2H-pyran - 3(6H) - one and acetic acid and the reaction mixture heated to reflux for an hour. Maltol (65%) was obtained on cooling.

Example 8

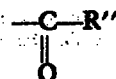
The method of Example 7 was repeated with comparable results adding formic acid in place of acetic acid.

Example 9

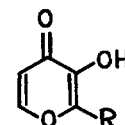
The method of Example 7 may be repeated starting with a compound of the formula



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



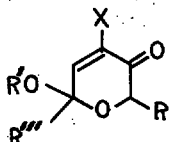
where R'' is methyl, ethyl or phenyl; X is bromine or chlorine to yield a compound of the formula



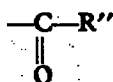
where R is hydrogen, alkyl of 1 to 4 carbon atoms, phenyl or benzyl.

WHAT WE CLAIM IS:—

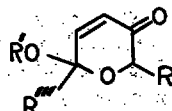
1. A process for preparing a compound of the formula



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



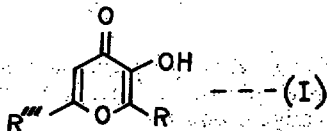
wherein R'' is methyl, ethyl or phenyl; R''' is hydrogen or alkyl of 1 to 4 carbon atoms; and X is bromine, or chlorine which comprises contacting a compound of the formula



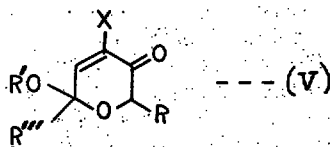
where R, R' and R''' are as previously defined in a reaction-inert solvent at a temperature of -50 to 50°C . with at least one equivalent of a halogen oxidant selected from chlorine, bromine, chlorine-bromide, hypochlorous acid, hypobromous acid or mixtures thereof in the presence of an organic base until the reaction is substantially complete.

2. The process of claim 1 wherein said reaction-inert solvent is selected from water, alkanols or diols of 1 to 4 carbon atoms, ethers and nitroles of 2 to 10 carbon atoms, and ketones, esters and amides of 3 to 10 carbon atoms.

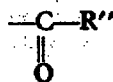
3. A process for preparing a gamma-pyrone of the formula



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

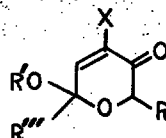


wherein R is hydrogen, alkyl of 1 to 4 carbon atoms, phenyl or benzyl; R' is alkyl of 1 to 4 carbon atoms or

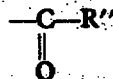


wherein R'' is methyl, ethyl or phenyl; R''' is hydrogen or alkyl of 1 to 4 carbon atoms; and X is chlorine or bromine.

4 A compound of the general formula



wherein R is ethyl; R' is alkyl of 1 to 4 carbon atoms or



wherein R'' is methyl, ethyl or phenyl; R''' is hydrogen or alkyl of 1 to 4 carbon atoms; and X is chlorine or bromine.

5. A process as claimed in claims 1 to 3 substantially as hereinbefore described with reference to the Examples.

P. C. C. GRAHAM,
Chartered Patent Agent,
Agent for the Applicants.



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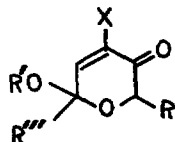
where R is hydrogen, alkyl of 1 to 4 carbon atoms, phenyl or benzyl.

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

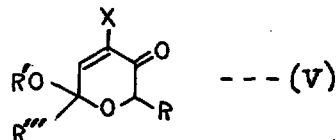
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WHAT WE CLAIM IS:—

1. A process for preparing a compound of the formula

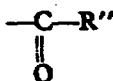


wherein R is hydrogen, alkyl of 1 to 4 carbon atoms, phenyl or benzyl; R' is hydrogen, alkyl of 1 to 4 carbon atoms or

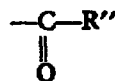


wherein R is hydrogen, alkyl of 1 to 4 carbon atoms, phenyl or benzyl; R' is alkyl of 1 to 4 carbon atoms or

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wherein R'' is methyl, ethyl or phenyl; R''' is hydrogen or alkyl of 1 to 4 carbon atoms; and X is bromine, or chlorine which comprises contacting a compound of the formula

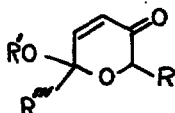


wherein R'' is methyl, ethyl or phenyl; R''' is hydrogen or alkyl of 1 to 4 carbon atoms; and X is chlorine or bromine.

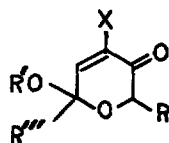
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4 A compound of the general formula

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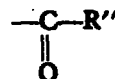
where R, R' and R''' are as previously defined in a reaction-inert solvent at a temperature of -50 to 50°C. with at least one equivalent of a halogen oxidant selected from chlorine, bromine, chlorine-bromide, hypochlorous acid, hypobromous acid or mixtures thereof in the presence of an organic base until the reaction is substantially complete.



wherein R is ethyl; R' is alkyl of 1 to 4 carbon atoms or

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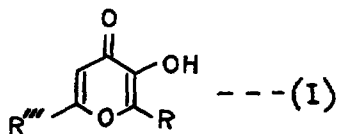
2. The process of claim 1 wherein said reaction-inert solvent is selected from water, alkanols or diols of 1 to 4 carbon atoms, ethers and nitroles of 2 to 10 carbon atoms, and ketones, esters and amides of 3 to 10 carbon atoms.

wherein R'' is methyl, ethyl or phenyl; R''' is hydrogen or alkyl of 1 to 4 carbon atoms; and X is chlorine or bromine.

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

5. A process as claimed in claims 1 to 3 substantially as hereinbefore described with reference to the Examples.



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