

PATENT SPECIFICATION

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 400 40Y 624 625 672 760 TZ
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(54) 2-ETHYL-6-ALKOXY-2,3-DIHYDRO-
6H-PYRAN-3-ONES

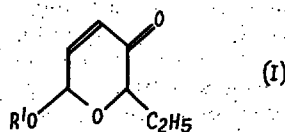
(71) We, PFIZER INC., a Corporation organized under the laws of the State of Delaware, United States of America, of 235 East 42nd Street, New York, State of New York, United States of America, do hereby declare the invention, for which we pray that a Patent may be granted to us, and the method by which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

This invention relates to intermediate pyran compounds which are useful intermediates for the preparation of gamma-pyrone according to the process described and claimed in our patent application No. 30470/76 (Serial No. 1,505,028).

Our patent application No. 30470/76 (Serial No. 1,505,028), discloses the preparation of maltol (2-methyl-3-hydroxy-gamma-pyrone) from furfural through intermediates (a) 1-(2-furyl)-1-ethanol; (b) 2-(1-hydroxyethyl)-2,5-dialkoxy-2,5-dihydrofuran; (c) alkoxy-2-methyl-2H-pyran-3(6H)-one; and (d) 2-alkoxy-4-methyl-3,7-dioxabicyclo[4.1.0]heptan-5-one.

Application No. 30470/76 (Serial No. 1,505,028), also discloses the preparation of pyromeconic acid (3-hydroxy-gamma-pyrone), ethyl maltol (3-hydroxy-2-ethyl-gamma-pyrone) and other valuable 2-substituted-3-hydroxy-gamma-pyrones in an analogous manner from furfural.

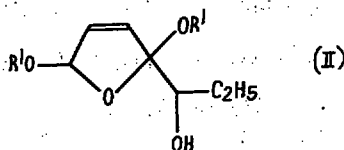
Certain of the intermediate compounds used in the process for the preparation of the aforesaid gamma-pyrones as disclosed in Application No. 30470/76 (Serial No. 1,505,028) are novel compounds and the present invention provides a compound of the formula:—



wherein R' is an alkyl group of 1 to 6 carbon atoms.

As used herein, the term "alkyl" means both straight and branched chain alkyl groups containing from one to six carbon atoms.

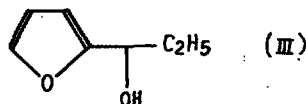
The compound of formula (I) above is preferably prepared by reacting a compound of the general formula:—



wherein R' is as defined above with a substantially anhydrous acid.

The substantially anhydrous acid used in the above reaction is preferably formic acid, trifluoroacetic acid, *p*-toluenesulphonic acid, methanesulphonic acid, citric acid, oxalic acid, chloroacetic acid, sulphuric acid, hydrochloric acid or phosphoric acid.

The compound of formula (II) above is preferably prepared by reacting a compound of the formula:—



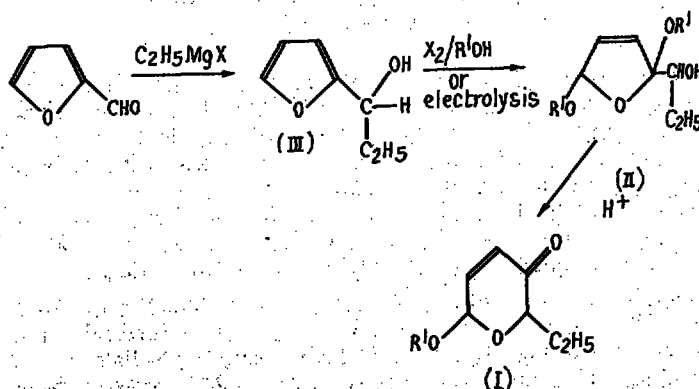
with an alcoholic ($R'OH$) solution of chlorine or bromine.

The intermediate compound (III) may be prepared by reacting furfural with a Grignard reagent of the formula C_2H_5MgX , wherein X is chlorine or bromine.

Furfural is an inexpensive raw material which is prepared industrially from pentosans which are contained in cereal straws and brans.

The said processes for the preparation of compounds (II) and (III) are more particularly described in our Application No. 30470/76 (Serial No. 1,505,028).

The reactions involved in the preparation of the compounds of the present invention are illustrated in the following reaction scheme:



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

The reaction of furfural with the appropriate Grignard reagent C_2H_5MgX is described in Chemical Abstracts 44, 1092d (1949).

It has been found that the reaction of intermediate (III) with chlorine in an alcoholic solvent at a temperature from -70° to $50^\circ C$ gives a clean conversion to the desired intermediate (II) with the HCl by-product being neutralized by a base such as ammonia, sodium carbonate or other alkali metal base.

Intermediate compound (II) is a new compound which may be made by methods already described.

The reaction of intermediate (II) with a strong organic acid is novel and it produces the desired 6-alkoxy derivative (I) directly in high yield and avoids the formation of the corresponding hydroxy derivative which is very unstable to further reactions. Intermediate (II) is contacted with a substantially anhydrous acid. The presence of a protic solvent such as an alcohol or a small amount of water is actually beneficial. Following this reaction, the product, in a state of purity suitable for conversion to compound (I), is separated from the acid medium by conventional extraction techniques. Although formic and trifluoroacetic acids are preferred, any acid with a pK_a of 4 or below will convert intermediate (II) to the desired compound (I). Other suitable organic acids include *p*-toluenesulphonic acid; methane-sulphonic acid, citric acid, oxalic acid and chloroacetic acid; suitable mineral acids include sulphuric acid, hydrochloric acid and phosphoric acid. Acidic resins such as "Amberlite" GC-120 and "Dowex" 50W also may be employed. The words "Amberlite" and "Dowex" are registered Trade Marks.

The following Examples illustrate the preparation of compounds according to the invention.

EXAMPLE 1

To a 3 neck-roundbottom flask equipped with a magnetic stirring bar, a jacketed addition funnel, a thermometer and a dry ice condensor were added 0.2 mol of intermediate (III), 100 ml of methanol and 21.1 g (0.2 mol) of sodium carbonate, and this mixture was cooled to $0^\circ C$ using an ice-acetone bath. To this rapidly stirred solution was then added dropwise a cold (-30°) solution of chlorine (11.0 ml. 0.24 mol) in methanol. The addition of chlorine was controlled to keep the reaction temperature

under 40°C. The addition required about 2 hours. After the addition, the reaction mixture was stirred at ice bath temperature for 30 minutes, and then allowed to warm to room temperature. The resulting slurry was filtered, the methanol removed *in vacuo*, the residue taken up in benzene and passed through an alumina plug as a final filter. Removal of the benzene provided the desired compound (II) ($R' = CH_3$) b.p. 102°/10 mm.

Analysis:

		C	H
Calc'd for $C_9H_{16}O_4$:		57.50	8.58
Found:		57.39	8.59

EXAMPLE 2

The method of Example 1 may be repeated using bromine instead of chlorine using intermediate (III) to yield intermediate (II).

EXAMPLE 3

In a small glass electrolysis vessel having a carbon anode and nickel cathode were placed 50 ml of methanol, 0.5 ml of concentrated sulfuric acid, and 0.01 mol of the intermediate (III) ($R' = CH_3$) and the solution was cooled to -20°C. An electrolysis was then carried out using a potentiostat/galvanostat Princeton Applied Research Corporation Model 373 instrument set to deliver a constant current of 0.6 amperes. After a reaction time of 30 minutes, the reaction was poured into water and the product (II) ($R' = CH_3$), isolated by a chloroform extraction procedure. This procedure is similar to that described in United Kingdom Patent Specification No. 682,736 with sulphuric acid replacing ammonium bromide as the electrolyte.

EXAMPLE 4

To a 2-litre, 3-neck roundbottom flask equipped with a magnetic stirrer, dropping funnel and a thermometer were added 400 ml of formic acid and 20 ml of methanol. To this solution was added a solution of intermediate (II) ($R' = CH_3$) 0.6 mol in 40 ml of methanol. The dropwise addition required 15 minutes. The reaction mixture was poured in a litre of water and extracted 3 times with 500 ml portions of chloroform. The combined chloroform washings were washed with a sodium bicarbonate aqueous solution and with brine. The chloroform solutions was evaporated to yield compound (I) ($R' = CH_3$), b.p. 79° to 80°/14 mm.

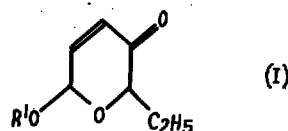
EXAMPLE 5

The method of Example 4 may be repeated, with comparable results, replacing formic acid by citric acid, oxalic acid, chloroacetic acid, *p*-toluenesulphonic acid, methanesulphonic acid or trifluoroacetic acid.

Similar results may be obtained using sulphuric acid, hydrochloric acid or phosphoric acid.

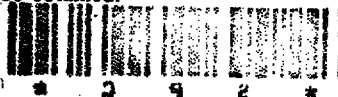
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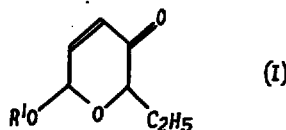
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