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Scanio

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[54] **ELECTROLYTIC PROCESS FOR THE MANUFACTURE OF ALPHA-KETOGLUTARATE ESTERS**

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[51] **Int. Cl.** **C07b 3/00,** B01k 1/00

[58] **Field of Search** ..... 204/78, 72, 59 R

[56] **References Cited**

UNITED STATES PATENTS

2,714,576	8/1955	Clauson-Kaas et al.	204/78
3,574,072	4/1971	Louvar	204/72

Primary Examiner—R. L. Andrews

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[57] **ABSTRACT**

Continuous process for the production of a mixture of δ-monoalkyl α-ketoglutarate, dialkyl α-ketoglutarate and the corresponding ketals by electrolysis of 2-furoic acid in acidic alcoholic solvent.

6 Claims, No Drawings

ELECTROLYTIC PROCESS FOR THE MANUFACTURE OF ALPHA-KETOGLUTARATE ESTERS

BACKGROUND OF THE INVENTION

The present invention relates to a process for producing esters and ketals of α-ketoglutaric acid. More particularly the present invention concerns a process of producing a mixture of α-ketoglutarate δ-monoesters, diesters and the ketals thereof by electrolysis of an acidified alcoholic solution of 2-furoic acid. 2,5-Dialkoxy-2,5-dihydrofuran-2-carboxylic acid and the corresponding alkyl ester which are obtained as by-products in the same electrolysis reaction may also be converted to α-ketoglutarate esters by subjecting the acidified alcoholic electrolysis product mixture to somewhat elevated temperatures followed by mild acid hydrolysis of ketals present, thus affording a crude product which is composed almost entirely of α-ketoglutarate esters.

While the α-ketoglutarate esters obtained by the process of this invention are themselves of use as chemical intermediates, they may be further hydrolyzed to obtain α-ketoglutaric acid of excellent quality suitable for use as a food acidulant or as a food buffering agent when used either as the acid or in the form of an alkali metal or alkaline earth salt thereof. α-Ketoglutaric acid also has utility as a raw material for organic synthesis, e.g., in the manufacture of glutamic acid.

Prior art methods for either electrolytic or chemical oxidation of 2-furoic acid or furfural have invariably resulted in decarboxylated reaction products, except in those cases involving the oxidation of furfural to 2-furoic acid e.g., Organic Synthesis, Collective Vol IV, 493 (1963). D. A. Deribas, et al., Russian Pat. No. 40,972 (1935); Chem. Abstr., 30,7127[8] (1936), obtained maleic acid upon electrolysis of furfural in sulfuric acid. N. Hellstrom, Svensk. Kem. Tidskr., 60,214–220 (1948); Chem. Abstr., 431271e (1949) obtained β-formyl acrylic acid by electrolysis of either furfural or 2-furoic acid in 1% aqueous sulfuric acid using lead electrodes. M. Taniyama, Chem. Abstr., 53,4248a (1959), reported that succinic acid was prepared in good yield by electrolyzing furfural using 5% sulfuric acid in the anodic cell and 10% sulfuric acid in the cathodic cell. The intermediate maleic acid was not isolated but immediately reduced. Oxalic, tartaric, citric and malic acid byproducts were identified by a systematic separation method.

Both chemical and electrolytic methods for the preparation of 2,5-dialkoxy-2,5-dihydrofurans were reviewed by N. Elming in Vol. II of Advances in Organic Chemistry, Methods and Results, R. A. Raphael, E. C. Taylor and H. Wynberg, Editors, New York, 1960, pp. 67–115. No mention is made of conversion of 2 -furoic acid to the corresponding 2,5-dialkoxy-2,5-dihydrofuran although the methyl and ethyl esters of 2-furoic acid as well as 4-alkyl and 5-alkyl substituted 2-carbomethoxy furans are reported to provide good yields of the corresponding 2,5-dimethoxy-2,5-dihydrofurans.

M. Murakami et al., Proc. Japan Acad., 32135 (1956), Chem. Abstr. 50, 15504i (1956), reported that diethyl α-ketoglutarate can be obtained by treatment of ethyl 2,5-diethoxy-2,5-dihydro-2-furoate with absolute ethanol containing dry hydrogen chloride. Electrochemical oxidation of furans was later reviewed by N. L. Weinberg, Chem. Revs., 68,449 (1968); no disclosure of the present invention is made therein or in a subsequent studies by S. Torii et al., Bull, Chem. soc. Japan, 44,1079 (1971); 45,2783–87 (1972).

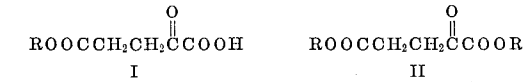
Other prior art disclosing electrolytic oxidation of 2-furoates but not known to disclose the process of the present invention include U.S. Pat. Nos. 2,714,576, 2,801,252, 2,806,852 and Japan Pat. No. 23,727(1964), 283(1951).

SUMMARY

While prior art methods of electrochemical oxidation of 2-furoic acid have invariably afforded decarboxylated products, the present invention discloses a novel process for the production of esters of α-ketoglutaric acid by electrochemical oxidation of 2-furoic acid, in which the carboxyl group remains intact in the major products. More particularly the invention discloses a continuous process for producing a mixture of δ-monoesters and diesters of α-ketoglutaric and the corresponding ketals thereof which comprises electrolyzing a solution of 2-furoic acid in alcoholic solvent containing acid catalyst at a concentration of about 0.01 to 1 mole per liter, wherein said alcoholic solvent is an alkanol of from about one to five carbon atoms, and wherein said acid catalyst is a reaction inert acid of pK_a less than about 2.5, and continuing said electrolysis until a substantial amount of said mixture of esters and ketals of α-ketoglutaric acid is formed. The electrolyzed solution also contains 2,5-dialkoxy-2,5-dihydrofuran 2-carboxylic acid and ester byproducts. The yield of α-ketoglutarate esters and ketals thereof is enhanced by heating said electrolyzed solution at about 50° to 100°C. to substantially convert said by-products to additional amounts of said esters and ketals of α-ketoglutaric acid. Ketals present may then also be converted to α-ketoglutarate esters by subjecting the reaction mixture to mild acid hydrolysis. The α-ketoglutarate esters can be isolated by standard methods or hydrolyzed under acidic or alkaline conditions to afford excellent yields of α-ketoglutaric acid.

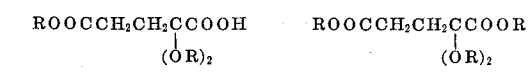
DETAILED DESCRIPTION OF THE INVENTION

The novel process of the invention can be employed to prepare excellent yields of a mixture of δ-monoalkyl α-ketoglutarates (I) and the corresponding diesters (II)

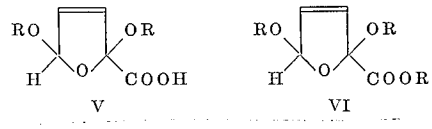


I II

These esters are obtained in the presently disclosed process by electrolysis of 2-furoic acid in a lower alkanol solvent containing a reaction inert acid of pK_a less than about 2.5 which serves as a catalyst to initially produce a mixture containng the above esters I and II and their ketals III and IV along with significant amounts of 2,5-dialkoxy-2,5-dihydrofuran-2-carboxylic acid (V) and the corresponding alkyl ester (VI).



III IV



V VI

The electrolyzed solution, of course, also contains small amounts of unreacted 2-furoic acid and alkyl 2-furoate ester in which the alkyl group is derived from the alkanol solvent.

In each of the above structures R is the alkyl group derived from the alkanol employed as electrolysis medium, said alkanol being of from about one to five carbon atoms. This initial mixture can then be treated further by heating the electrolysis products in the presence of an acid catalyst at a concentration of about 0.2–2.0 moles/liter to convert the byproduct 2,5-dialkoxy-2,5-dihydrofuran-2-carboxylates (V,VI) to additional α-ketoglutarate esters. The products in the solution thus obtained are almost entirely compounds of the structures I, II, III, and IV. Subsequent mild acid hydrolysis may then be employed to selectively convert ketals III and IV to δ-monoalkyl α-ketoglutarate (I) and dialkyl α-ketoglutarate (II). Alternatively, the mixture of compounds of the structures I, II, III and IV obtained by heating the electrolysis products in the presence of acid catalyst at a concentration of about 0.2–2.0 moles/liter, may be directly converted to α-ketoglutaric acid by standard methods such as for example, mild acid hydrolysis to decompose the ketals, followed by more vigorous hydrolysis under either acidic or alkaline conditions. The α-ketoglutaric acid may then be isolated and purified, if necessary, by methods well known to those skilled in the art.

Wherein any and all acids, organic and inorganic, having a pK_a less than about 2.5 may be used as catalysts in the process of the invention, it is preferred to use those acids which are also inert under the conditions of the electrolysis. Such acids having pK_a less than about 2.5 and which are also inert to the electrolysis conditions include sulfuric, phosphoric, perchloric, ρ-toluenesulfonic, naphthalenesulfonic, benzenesulfonic, dichloroacetic, trichloroacetic and pyrophosphoric acids. Sulfuric, phosphoric and perchloric acids are preferred. However, sulfuric acid because of its low cost and ease of availability is especially preferred. Any of these acids may also be used for catalysis of the above-mentioned reactions subsequent to electrolysis. While is is usually preferred to utilize the same acid as that employed for the electrolysis, a different acid selected from those mentioned above as well as hydrochloric and hydrobromic acids may also be used as catalyst for these reactions subsequent to the electrolysis.

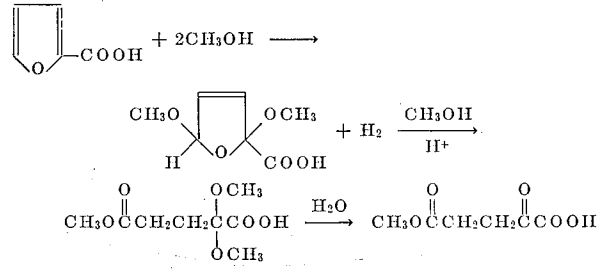
The alkanol employed in the process of this invention serves both as a solvent and as a source of alkyl groups for formation of the esters, ketals, and ethers produced in the electrolysis. The alkanol employed may be methanol, ethanol, isopropanol, tertiary butanol, 3-pentanol, or any of the alkanols of from about one to five carbon atoms. For reasons of economy the preferred alkanol is methanol.

For the electrolysis process of this invention the concentration of acid catalyst may be from about 0.01M to 1M. At the lower end of this concentration range the electrolyzed solution tends to contain relatively more of the 2,5-dialkoxy-2,5-dihydrofuran 2-carboxylates (V and VI) and relatively less of the desired α-ketoglutarate esters (I and II) and the corresponding ketals (III and IV). As the acid catalyst concentration of the initial solution is increased within this range the relative amount of α-ketoglutarate esters and ketals (I, II, III and IV) in the electrolyzed solution also tends to increase, but not in a directly proportional manner. At acid catalyst concentrations substantially greater than about 1 molar undesirable reactions take place, including one or more which generate decarboxylated products. At acid catalyst concentrations substantially below 0.01 molar current efficiency is significantly reduced and the reaction stops at the dihydrofuran (V and VI) with little or no production of the desired products I, II, III and IV.

For the conversion of byproduct 2,5-dialkoxy-2,5-dihydrofuran-2-carboxylates, V and VI to esters and ketals of α-ketoglutaric acid, acid catalyst concentrations in the range of about 0.2 to 2 molar are utilized. At acid catalyst concentrations substantially lower than 0.2 molar the conversion is exceedingly slow. At substantially higher concentrations than 2.0 molar decomposition products are observed. The optimum concentration of acid catalyst for this conversion is about 1 molar.

When acid catalyst concentrations of about 0.2 to 1 molar are employed in the electrolysis solution, the electrolyzed products may be directly treated to convert byproduct 2,5-dialkoxy-2,5-dihydrofuran-2-carboxylates to α-ketoglutarates without further addition of acid.

The formation of the ketals III and IV from 2-furoic acid via the dihydrofurans V and VI does not require water as illustrated below using methanol as solvent. However, one mole of water is required for the conversion of the



ketal group to the corresponding ketone group. Thus, when water is rigorously excluded from the electrolysis and subsequent treatment at 50°–100°C. in 0.2–2M acid catalyst, the products obtained are almost entirely ketals of the general structures III and IV. When commercial quality 2-furoic acid, alcoholic solvent and mineral acid are employed small amounts of moisture ae normally contained therein. Accordingly, the products of the process of the invention contain greater amounts of δ-monoalkyl α-ketoglutarate (I) and dialkyl α-ketoglutarate (II) and little or none of the ketals. While such a level of moisture is not detrimental to the instant process, it is preferred to limit the amount of water introduced so that it does not substantially exceed the theoretical amount of one mole per mole of 2-furoic acid employed in the electrolysis.

While the aforementioned electrolysis process of this invention may be carried out in a batch operation, it is perferably conducted in a flow cell to allow continuous production of the primary electrolysis products. The flow cell consists of a cylindrical carbon anode centered within a hollow metal cylinder which serves as cathode. The cell may be mounted in a chemically inert, non-conductive vessel, and suitable means provided for continuous flow of 2-furoic acid solution,

electrical connections to a power source and standard instruments for control and measurement of the pertinent electrical parameters. Said instruments are well known to those skilled in the art. Metals which have been found to function adequately as cathode include nickel, platinum, palladium, silver and gold, although other metals and alloys may also be used. Nickel is especially preferred as the cathode material.

The optimum flow rate of alcoholic solution through the cell is primarily governed by the concentration of 2-furoic acid in the solution being electrolyzed and the current employed. The theoretical current required is about 54 ampere hours per mole of 2-furoic acid. Thus, the flow rate may be increased as the concentration of 2-furoic acid is decreased at constant current; and, conversely, flow is decreased at higher concentrations of substrate. Since electrochemical yields are usually somewhat less than theoretical, greater quantities of electricity are ordinarily required to obtain an optimum yield of the desired product. The electrolysis is preferably carried out at constant current such that total electrical consumption is from about 50–100 ampere hours per mole of 2-furoic acid. Cell voltage should be maintained in the range of about 0.01 to 1.0 volt/cm^2 of anode surface, and preferably about 0.02 to 0.2 volts/cm^2 of anode surface.

The electrolysis of 2-furoic acid when carried out according to the process of the invention is only mildly exothermic. Ordinarily it may be carried out at ambient temperature without the necessity of cooling or heating. However, it is preferred to maintain the temperature at about 15° to 35°C. during the electrolysis.

After adjusting the acid catalyst concentration, if necessary, to within 0.2 – 2 molar, the electrolyzed solution may be heated at temperatures of about 50° to 100°C. to effect substantial conversion of 2,5-dialkoxy-2,5-dihydrofuran-2-carboxylate byproducts (V and VI) to the desired α-ketoglutarate esters and ketals, I, II, III, and IV. The time required to effect substantially complete conversion will vary, of course, with the temperature, acid catalyst concentration, and the nature of the alkyl group derived from the alkanol used as solvent in the electrolysis; however, from about 2 to 24 hours is usually sufficient. As mentioned above, water is not required for this conversion and it should be limited to a maximum of about one mole per mole of 2-furoic acid employed in the electrolysis. When perchloric acid is used, it is preferred to carry out this conversion at temperatures near the low end of the range 50°–100°C. for reasons of safety.

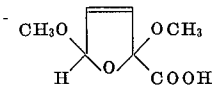
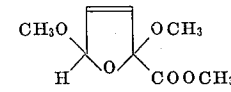
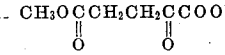
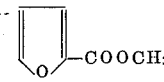
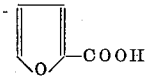
The following examples are illustrative of the invention.

EXAMPLE I

1.0 gram of 2-furoic acid was dissolved in 65 ml. of methanol containing 0.10 ml. of 98% sulfuric acid. A portion of the solution was introduced into a 15 ml. flow cell set within a glass tube. The cell consisted of a cylindrical carbon anode (6 mm. diam., 23.5 cm. long) centered within a hollow cylindrical nickel cathode (1.2 cm. diam. 23.5 cm. long). The glass tube containing the cell was fitted at either end with rubber stoppers with holes to accomodate glass inlet and outlet tubes as well as electrode leads.

The remainder of the methanolic solution was placed in a reservoir leading to the inlet of a peristaltic pump. The pump outlet was, in turn, connected to the cell inlet by means of inert flexible tubing. At ambient temperature, 200 ma. current was passed through the solution at 1.0 volt. After a few minutes pumping was started and the inlet and outlet to the cell were opened to accomodate fresh 2-furoic acid solution. Flow was regulated so that the total electrolysis time was 140 minutes during which a total of 480 milliampere hours current was passed through the cell. The comsumption of 2-furoic acid was monitored by measuring the decrease in absorbance at 243 nm.

The combined effluent from the cell was neutralized with methanolic sodium methoxide and the solvent was evaporated at reduced pressure to afford a solid residue. The residue was taken up in ether, filtered to remove sodium sulfate and the filtrate evaporated to dryness. The residue was chromatographed on a silica gel column, eluting with ethyl acetate. Four fractions, tabulated below, were obtained. They were identified by nuclear magnetic resonance spectroscopy and by comparison with independently prepared samples.

Fraction No.	Structure	Comments
1		A major component, both *cis* and *trans* isomers present.
	plus	
		Do.
2		A major component.
3		Trace.
4		Do.

Gas-liquid chromatography of Fraction 2 revealed the presence of about 5% dimethyl α-ketoglutarate and lesser amounts of δ-monomethyl α,α-dimethoxy glutarate and dimethyl α,α-dimethoxy glutarate in this fraction. The GLC was carried out using a 5 ft. × ¼ in. SE–30 column at 175°C.; thermal conductivity detector temperature, 225°C; Helium flow rate, 35 ml/min.

EXAMPLE II

The experiment was conducted under rigorously anhydrous conditions throughout.

A solution of 1.26g. of 2-furoic acid and 0.83g. of H_2SO_4in 45 ml. of methanol was prepared and electrolyzed as described in Example I. The methanol was removed in vacuo and the residue was dissolved in 10 ml. of methanol containing 0.5g. of H_2SO_4 to give a solution 1.4 molar in H_2SO_4. The resulting solution was heated at reflux temperature for 24 hours, cooled and the methanol removed at reduced pressure.

The residual oil was chromatographed on a silica gel column, eluting with benzene/ethyl acetate mixtures. Reduced amounts of the products found in Example I were obtained as well as a fraction containing the large amount (1.02g) of a new material. This material was found to be at least 95% pure by gas-liquid chromato-

graphic analysis on an SE–30 column at 175°C. It was identified by means of NMR and infrared spectra as dimethyl 2,2-dimethoxyglutarate.

EXAMPLE III

To 90 ml. of 0.015 M methanolic sulfuric acid, 2.5g of 2-furoic acid was added. The solution was electrolyzed under the conditions described in Example I. The electrolyzed solution was treated with 7.2g. of conc. H_2SO_4 and then heated to reflux for 2 hours, cooled to about 20°C. and aqueous 5M NaOH was added in portions to effect cleavage of ketals and neutralization of the excess H_2SO_4. After filtering, solvent was removed by distillation to afford 3.1g (ca. 90% of theory) of a mixture of δ-monomethyl α-ketoglutarate and dimethyl α-ketoglutarate.

EXAMPLE IV

Seven grams of 2-furoic acid was dissolved in 250 ml. of methanol containing 0.37g. of H_2SO_4. The solution was electrolyzed over a 6 hour period using the procedure and equipment described in Example I. The total current consumption was 3.4 ampere hours at 2.2 volts. The accumulated cell effluent was treated with an increment of H_2SO_4 to adjust the concentration of H_2SO_4 to 1.0 molar. The resulting solution was heated to reflux for 2.5 hours, then cooled to room temperature. Sufficient water was added to hydrolyze the ketal, then an excess of an aqueous suspension of $Ca(OH)_2$ was added, the mixture heated to reflux for an additional 2 hours then filtered. The solid was suspended in water (200 ml.), an excess of H_2SO_4 was added and the resulting $CaSO_4$ removed by filtration. Concentration of the aqueous filtrate afforded 8.1g (88% of theory) of α-ketoglutaric acid.

EXAMPLE V

One gram of 2-furoic acid and 0.28g of 70% perchloric acid are dissolved in 25 ml. of absolute ethanol. The solution is electrolyzed as described in Example I except that the cathode employed is a platinum foil cylinder (1.2 cm. diam. 23.5 cm. long). The total current consumed amounts to 525 milliampere hours over 2.5 hours. The electrolyzed solution is then treated with 0.44g. of perchloric acid and warmed with stirring at 50°C. for 5 hours. The solution is cooled to 10°–15°C. and aqueous 5M KOH added in portions to hydrolyze ketals and neutralize the excess mineral acid. The solvent is then removed in vacuo on a rotary evaporator and the residue filtered to afford a mixture of δ-monoethyl-and diethyl α-ketoglutarate.

EXAMPLE VI

Two grams of 2-furoic acid is dissolved in 125 ml. of n-propanol containing 12.3g of H_2SO_4. The solution is electrolyzed as described in Example V over 5.5 hours during which a total of 1.15 ampere hours passes through the cell at a potential of 1.5 volts. The solution is then heated at 55°C. for 4.5 hours, cooled to room temperature at treated with 10 ml. 10% aqueous NaOH and stirred for 30 minutes to hydrolyze the ketals. Then additional base is added to neutralize the excess mineral acid. Following filtration to remove the precipitated salt, propanol and moisture are removed by evaporation at reduced pressure to afford a mixture of δ-monopropyl-and dipropyl α-ketoglutarate in good yield.

EXAMPLE VII

2-Furoic acid, 7.0g. is dissolved in 175 ml. of methanol containing 0.4g. 85% H_3PO_4. The solution is electrolyzed as described in Example I, but maintaining the temperature at 35°C. over a 4.5 hour period during which 3.7 ampere hours of current flows through the cell at 1.8 volts. The electrolyzed solution is treated with a mixture of 8.65g. 85% H_3PO_4, 1.4g. H_2O and 7.1g. P_2O_5 to afford a methanolic solution that is 1 molar in phosphoric acid. After refluxing 4 hours the solution is cooled to room temperature, 10 ml. of water added and the solution allowed to stand overnight. An excess of aqueous $Ca(OH)_2$ slurry is then added and the resulting mixture refluxed for 2 hours, cooled and filtered. The filter cake is suspended in water and made strongly acid with 85% H_3PO_4. The insoluble calcium phosphate is removed by filtration and the filtrate concentrated in vacuo to afford an excellent yield of α-ketoglutaric acid.

EXAMPLE VIII

In 125 ml. of methanol, 0.2g H_2SO_4 and 3.5g. 2-furoic acid is dissolved and the solution electrolyzed by the procedure described in Example 1 except that the temperature is maintained at about 15°C. Ten grams of sulfuric acid is added and the resulting solution heated at reflux for 2 hours. To the warm solution 50 ml. of water is added and reflux continued for an additional 4 hours. The excess acid is then neutralized with aqueous base and evaporated to dryness at reduced pressure. The residue is triturated with acetone, filtered to remove insoluble salts and the filtrate diluted with benzene and set aside to crystallize. A good yield of α-ketoglutaric acid of high quality is obtained.

EXAMPLE IX

Example III is repeated using 3-pentanol in place of methanol as solvent. After electrolysis at 20°–30°C, 7.2 grams of conc. H_2SO_4 is added and the solution is heated at 75°C. for 4 hours then cooled to room temperature. Aqueous 5M NaOH is added in portions to effect cleavage of ketals and then neutralization of the excess H_2SO_4. After filtration, the solvent is removed at reduced pressure to afford a good yield of a mixture of δ-mono-3-pentyl α-ketoglutarate and the 3-pentyl α-ketoglutarate diester.

What is claimed is:

1. A continuous process for producing a mixture of δ-monoesters and diesters of α-ketoglutaric acid and the corresponding ketals thereof which comprises electrolysis of a solution of 2-furoic acid in alcoholic solvent containing acid catalyst at a concentration of from about 0.01 to 1 mole per liter, wherein said alcoholic solvent is an alkanol of from about one to five carbon atoms, and wherein said acid catalyst is a reaction inert acid of pK_a less than about 2.5, and continuing said electrolysis until a substantial amount of said mixture of esters and ketals of α-ketoglutaric acid is formed.

2. The process of claim **1** in which said acid catalyst is selected from the group consisting of sulfuric, phosphoric and perchloric acids.

3. The process of claim **1** in which said alcoholic solvent is methanol and said acid catalyst is sulfuric acid.

4. The process of claim **1** in which the electrolysis is carried out at about 15°–35°C.

5. -dialkoxy-process of claim 1 wherein following said electrolysis said solution is heated at from about 50° to 100°C. to substantially convert 2,5-dialkoxy-0b 2,5-dihydrofuran-2-carboxylate byproducts of said electrolysis to an additional amount of said mixture of δ-monoesters and diesters of α-ketoglutaric acid and the corresponding ketals thereof.

6. The process of claim 5 wherein additional acid having a pK_a less than about 2.5 is introduced to said solution prior to said heating to bring the total acid catalyst concentration within the range of from about 0.2 to 2.0 moles per liter.

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