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METHOD FOR PREPARING PARTIAL FATTY ESTERS OF INOSITOL

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This invention relates to a process for preparing partial fatty esters of hydroxy-substituted cyclo-hexanes.

More specifically, this invention relates to the preparation of partial fatty esters of inositol.

The preparation of fatty esters of inositol utilizing a reaction between inositol and a free fatty acid or a fatty acid chloride are known. However, all such prior methods, resulted in the formation of the complete fatty ester of inositol, i.e. the hexa-substituted inositol, regardless of the ratio of inositol to acylating agent in the reaction mixture. The complete fatty esters of inositol are not suitable for all purposes in which it is desired to employ an inositol derivative. Consequently, a method has long been sought whereby a partial fatty ester of inositol could be prepared readily and economically.

Prior to the invention disclosed and claimed herein, one of the present inventors had found two methods by which partial esters of inositol could be prepared. The first of these methods involved the use of liquid hydrogen fluoride as a solvent medium for the reactants. However, even with this solvent, the acylating agent most usually had to be the free fatty acid or the acid chloride. Moreover, the use of liquid hydrogen fluoride as a solvent medium for the reaction was extremely hazardous and involved the use of special equipment because of the extreme corrosivenes of the hydrogen fluoride.

The second of these methods is fully set forth in the co-pending application of Wilson F. Huber, Serial No. 811,786, filed May 8, 1959. In the process of that invention the partial fatty esters of inositol are prepared by interesterifying inositol with fatty acid esters of an aliphatic primary monohydroxy alcohol having from 1 to 8 carbon atoms or with fatty acid esters of polyhydric alcohols having not more than three carbon atoms in the presence of dimethylsulfoxide.

It has now been found that partial esters of inositol can also be prepared by subjecting to interesterification a mixture of inositol and a fatty acid ester of an aliphatic primary monohydroxy alcohol or a completely or incompletely esterified fatty acid ester of a polyhydric alcohol having from 2 to 6 hydroxyl groups in the presence of dimethylacetamide.

It is an object of this invention to provide a method whereby partial fatty esters of inositol can be prepared.

A further object of this invention is to provide a method whereby partial esters of inositol can be prepared readily and economically and under conditions which are not hazardous.

A still further object of this invention is to provide a method whereby partial fatty esters of inositol can be prepared with the exercise of control over the degree of esterification.

Other objects and advantages will be apparent from the following detailed description.

Generally speaking, the invention contemplates reacting inositol with the fatty acid ester in the presence of an alkaline catalyst which shows activity in interesterification reactions, and in the presence of dimethylacetamide. Following completion of the interesterification of the components to the desired degree, the catalyst is inactivated by the addition of water and/or acids such as acetic, phosphoric, citric, hydrochloric and the like, and the desired

reaction products are freed from solvent and purified by any suitable means.

The fatty esters which can be employed in the reaction herein concerned are the fatty acid esters of primary aliphatic monohydroxy alcohols having from 1 to 8 carbon atoms, for example, methanol, ethanol, hexanol and octanol, specific examples being methyl palmitate, ethyl palmitate and octyl palmitate. In addition, completely or incompletely esterified fatty acid esters of polyhydric alcohols having from 2 to 6 hydroxyl groups such as ethylene glycol, glycerol, erythritol, pentaerythritol, mannitol and sorbitol can be employed. Glycol dipalmitate, glycerol mono-, di-, and tri-palmitate, mannitol partial palmitates, erythritol tetra palmitate, pentaerythritol tetrapalmitate and sorbitol hexapalmitate are examples of such fatty esters. Of this latter group of esters the fatty triglycerides have been found to be particularly advantageous reactants.

Just as mono- and diesters of glycerol can be prepared from the triglyceride, so incompletely esterified inositol can be prepared in accordance with the present invention by reaction of inositol with completely esterified inositol. Thus, the reaction of inositol with inositol hexapalmitate can be carried out advantageously with the aid of the present invention.

The length of the fatty acid chain of the esters which can be employed in the reaction of this invention is not critical and is dictated primarily by the type of fatty acid source material available. As a general proposition, however, it has been found that fatty acids containing from about 8 to 22 carbon atoms in the alkyl chain are most useful. Therefore, the mixtures of fatty acids obtained from animal, vegetable or marine oils and fats such as coconut oil, cottonseed oil, soybean oil, tallow, lard, herring oil, sardine oil, and the like, represent readily available sources of fatty acid radicals. In the event it is desired to produce inositol esters of single fatty acids by this invention, then the fatty acid esters of relatively volatile alcohols (e.g. methanol and ethanol), the fatty acid portions of which contain from about 12 to 22 carbon atoms, can be advantageously reacted with inositol utilizing the particular solvent herein disclosed as the reaction medium.

The choice of solvent is essential to the realization of interesterification of the inositol and the aforementioned fatty esters under the conditions set forth herein. It has been found that dimethylacetamide is eminently suitable as the solvent reaction medium in the present process. This compound promotes a relatively rapid rate of reaction with minimum catalyst requirements and is not subject to decomposition during the ineresterification reaction.

It is theorized that the methods for esterifying inositol which were heretofore in the public domain resulted in the formation of only the hexa-substituted inositol because of the insolubility of inositol in the usual solvents. Therefore, as soon as any portion of the inositol was esterified, the partially esterified product became more soluble in the solvent than the unreacted inositol dissolved therein, and thereupon, being in solution, reacted preferentially with the acylating agent to yield the hexa-acylated (complete) ester. In the present process, inositol is relatively soluble in dimethylacetamide under the conditions prescribed and, as a result, there is no preferential acylation of the inositol to the hexa-acylated form exclusively.

In general, the amount of dimethylacetamide solvent required for any given interesterification is not critical. Quantities of dimethylacetamide in amounts from about ⅙ to about 30 times the weight of the fatty ester employed for reaction with the inositol can be readily used. In any event, an amount of dimethylacetamide which is

adequate to dissolve the inositol which is to be esterified should be employed. The solvent usage is normally adjusted depending upon the particular reactants which are to be interesterified and sufficient solvent should be used so that the advantages associated with solvent usage, e.g., rapid interesterification, can be realized.

The proportion of reactants is not critical and is dictated primarily by the ultimate product which is desired. Thus, the proportion of the reactants, i.e. inositol and fatty ester, can be chosen so that any one or more of the hydrogen atoms of the hydroxyl groups of the inositol can be replaced by a fatty acyl radical. In general, the molecular proportions of the reactants will determine the degree of esterification of inositol. For example, if one mole of inositol and one mole of a fatty ester of a primary aliphatic monohydroxy alcohol is reacted, the product will be predominantly the inositol monoester. If two moles of such fatty ester are present for every one mole of inositol in the reaction medium the resultant product will be predominantly the di-fatty ester of inositol. Likewise, with a ratio of such fatty ester to inositol of 3 to 1, a product containing a predominant amount of the tri-fatty ester of inositol can be prepared.

When the fatty esters of polyhydroxy substances, as herein defined, are to be used to react with inositol in accordance with the present invention the degree of esterification of the polyhydroxy substances, i.e. whether such polyhydroxy substances are partially or fully esterified, will determine the molecular proportion of fatty ester of polyhydroxy substance which should be reacted with inositol to give the desired degree of esterification of the inositol. Thus, if it is desired to obtain a product predominating in inositol mono-ester from the reaction of inositol with inositol hexapalmitate, the reactants should be in the proportion of 5 parts inositol to 1 part of inositol hexapalmitate. In any event, the molar ratio of fatty ester to inositol should be less than that which would be necessary for complete esterification of the inositol.

If it is desired to obtain the mono-, di-, or tri-fatty acid ester of inositol in relatively pure form, the reaction products of inositol and fatty ester predominating in the particular partial fatty ester of inositol which is desired can be subjected to appropriate crystallization or solvent partition procedures to separate the desired fraction of the product.

Although the process of the invention is illustrated herein principally with the use of sodium methoxide as the catalyst, effective practice of the process is not dependent upon the use of any particular catalyst. Rather, any alkaline molecular rearrangement or interesterification catalyst which will promote the interchange of radicals among the reactants of the process is suitable. Examples of usable catalysts are sodium methoxide, sodium hydroxide, metallic sodium, sodium potassium alloy and quaternary ammonium bases such as tri-methyl benzyl ammonium hydroxide. A discussion of other catalysts which are active in interesterification reactions may be found in U.S. Letters Patent 2,442,532 to E. W. Eckey, column 24, line 18 et seq.

Sodium methoxide catalyst can be advantageously used in the present invention in amounts from about 0.1% to about 2.0% by weight of the fatty ester which is to be reacted with the inositol. The choice of catalyst and the amount which is to be used are dependent upon the particular constituents which are to be reacted.

In the practice of the invention it was observed that the reaction rate for a given solvent usage and a given catalyst increased with an increase in temperature. For example, under substantially optimum conditions, and utilizing sodium methoxide as the catalyst, equilibrium can be reached in the interesterification reaction between inositol and a triglyceride in about 5 to 10 minutes' time at a temperature of 120° C. Where lower temperatures, such as about 80° C. are to be employed, a longer time is necessary to achieve the desired ester formation. Temperatures about 120° C. and up to about 150° C. may be employed and are, in fact, preferable when reacting inositol with a fatty acid ester of a primary aliphatic monohydroxy alcohol having from 1 to 8 carbon atoms. Generally speaking, with any of the aforementioned reactants or catalysts the process of the invention can be carried out at temperatures in the range from about 80° C. to about 150° C. Preferably, the interesterification reactions of this invention are carried out at temperatures in the range from about 120° C. to about 150° C.

Since the reaction of the present invention is an interesterification in which inositol is reacted with a fatty ester, the resulting product of the reaction will constitute an equilibrium mixture of inositol, esters thereof, displaced alcoholic substance from the ester originally employed, and esters of such alcoholic substance. Thus, if triglycerides are reacted with inositol, the product of the reaction will contain mono- and diglycerides as well as inositol esters. If it is desired to obtain inositol esters which are not so contaminated with original esters and derivatives thereof, then it is preferable to react fatty esters of relatively volatile alcohols such as methyl or ethyl alcohol with the inositol. In this way, unreacted volatile esters can be readily separated from the reaction products by distillation or crystallation procedures, or the reaction can be carried out under reduced pressure so that the volatile alcohols formed as a result of the interesterification reaction are removed from the reaction zone substantially as rapidly as they are liberated. Such removal of volatile reaction products will promote a substantially complete conversion of the fatty ester of the volatile alcohol to inositol fatty ester.

Under any of the foregoing conditions it has been found that the interesterification reactions herein disclosed will be substantially complete within one hour. No adverse effects have been noted if the reactants are allowed to remain in contact under interesterification conditions for considerable lengths of time, e.g. several hours, after the esterification is substantially complete. From a practical standpoint, however, little advantage would accrue from such practice.

The inositol partial fatty esters to the preparation of which this application is directed can be utilized as emulsifiers in the preparation and formulation of edible products. For example, these esters are useful in the preparation of cakes, candy, chewing gum, licorice, peanut butter and various beverages. In addition, and inasmuch as inositol is presently utilized in pharmaceutical preparations, the partial interesterification of the inositol in accordance with the present invention may result in better assimilation by the body of the inositol with a consequent enhanced pharmacological effect.

The following examples, in which amounts of all materials are expressed in parts by weight, will illustrate the manner in which the invention can be practiced. It is to be understood that the specific conditions set forth in the examples are not to be considered limiting of the invention which is defined only by the scope of the appended claims.

Example I

7.21 parts of inositol was heated to 100° C. in 72 parts of dimethylacetamide. After the inositol had dissolved, 17.8 parts of a mixture of 80% soybean oil and 20% cottonseed oil hydrogenated to an iodine value of about 76 and 2.5 parts of a 10% suspension of sodium methoxide in xylene was added. The resulting mixture was maintained at a temperature of about 100° C. and agitated. After one hour the catalyst in the reaction mix was inactivated by the addition of about 10 parts of a 50% aqueous acetic acid solution.

The reaction mixture was then taken up in a 4:1 ethyl acetate and N-butanol mixture and washed three times with hot water. The ethyl acetate-N-butanol solvent was removed from the washed mixture by evaporation on a steam bath under a nitrogen atmosphere. The mixture,

substantially solvent-free, was then steam deodorized at a pressure of 1 mm. of mercury for one-half hour at a temperature of 130 to 140° C.

The product was found, upon analysis, to have a hydroxyl value of 173.9 and a total fatty acid content of 86.61%. The formation of partial esters of inositol is indicated by the hydroxyl value which may be compared with the hydroxyl values of partially esterified inositol set forth in the table below.

The product of the preceding example can be effectively used as an adjuvant in plastic shortenings wherein its emulsifying characteristics promote improved performance of the plastic shortening in the preparation of baked goods.

Example II

9 parts of inositol, 5.4 parts of methyl palmitate and about 300 parts of dimethylacetamide were introduced into a reaction vessel provided with mechanical stirring means. This mixture was heated to about 150° C. and then about 1% by weight of the methyl palmitate of a suspension of about 9% sodium methoxide catalyst in xylene was added to the heated mixture. The resulting mixture was reacted for one hour at 150° C. and under a pressure of about 600 mm. of mercury. A reduced pressure was utilized so that a portion of the methanol formed as a by-product of the reaction could be removed from the reaction mixture. After one hour the catalyst was inactivated by the addition of a 50% aqueous solution of acetic acid.

The reaction product was then taken up in a 1:4 mixture of butanol and ethyl acetate solution and was water-washed four times after which the butanol-ethyl acetate mixture was removed from the product by evaporation under vacuum. The resultant product was crystallized from about 20 parts of a 1:1 mixture of dioxane and ethyl ether at 10° C. and vacuum dried for 18 hours at 70–80° C.

The ester product was found, by analysis, to have a hydroxyl value of 584.3 and a total fatty acid content of 63.7%.

Methyl laurate, propyl stearate, butyl oleate, hexyl palmitate and etc. can be substituted for methyl palmitate in the preceding example to give an inositol ester of substantially the same degree of completeness of esterification.

Example III

The process of Example II was repeated except that 13.5 parts of methyl palmitate was reacted with 9 parts of inositol and that the reaction was carred out at a temperature of 120° C. and a pressure of 180 mm. of mercury.

The ester product of this process was found, by analysis, to have a hydroxyl value of 501.2 and a total fatty acid content of 68.6%.

Example IV

9 parts of inositol, 3.2 parts of inositol hexapalmitate and about 100 parts of dimethylacetamide were introduced into a reaction vessel provided with mechanical stirring means. This mixture was heated to about 150° C. and then about 1% by weight of the inositol hexapalmitate of a suspension of about 9% sodium methoxide catalyst in xylene was added to the heated mixture. The resulting mixture was reacted for one hour at 150° C. and atmospheric pressure after which time the catalyst was inactivated by the addition of a 50% aqueous solution of acetic acid.

The reaction product was treated in accordance with the procedure of Example II to isolate the inositol partial fatty ester.

The ester product was found, upon analysis, to have a hydroxyl value of 586.1 and a total fatty acid content of 65.3%.

Equivalent amounts of glycol mono- or distearate, erythritol mono-, di-, tri- or tetra-laurate or mixtures thereof, pentaerythritol mono-, di-, tri-, or tetra-oleate or mixtures thereof, and manitol or sorbitol, mono- di-, tri-, tetra-, penta-, or hexa-palmitate or mixtures thereof, can be substituted for the inositol hexapalmitate in the preceding example to give a satisfactory product of different degrees of esterification.

In the foregoing examples the hydroxyl values (H.V.) and percent total fatty acids (T.F.A.) of the ester products were determined in accordance with Official Method CD4–40 and Tentative Method G3–53 respectively of the Official and Tentative Methods of the American Oil Chemists Society.

That the ester products produced in accordance with the process of this invention are the partial esters of inositol is evident from a comparison of the hydroxyl values of the products of the foregoing examples with the following calculated values for the partial palmitic acid esters of inositol.

Compound	Molecular Weight	T.F.A.	H.V.
Inositol monopalmitate	418	61.2	671
Inositol dipalmitate	656	78.0	342
Inositol tripalmitate	894	85.9	190
Inositol tetrapalmitate	1,132	90.5	99
Inositol pentapalmitate	1,370	93.4	41

It will be observed that the hydroxyl values of the products produced in accordance with the specific examples are not precisely in agreement with the calculated values set forth in the above table. Since the foregoing calculated values represent the values characteristic of the individual pure partial esters of inositol, and since, as has been pointed out hereinbefore, the reactions set forth in the examples are interesterification reactions, which will result in a product which is an equilibrium mixture of the original reactants and various esters thereof, the calculated and analytically obtained values could not be expected to precisely agree. Rather, the analytically determined values, unless, of course, a separation of the relatively pure individual ester had been made, would represent the presence in the ester product of a predominant amount of the particular individual ester, the calculated hydroxyl value of which is most closely approximated.

Having thus described the invention, what is claimed is:

1. A process for preparing partial fatty esters of inositol which comprises reacting inositol with a fatty acid ester selected from the group consisting of the fatty acid esters of aliphatic primary mono-hydroxy alcohols having from 1 to about 8 carbon atoms and completely and incompletely esterified fatty acid esters of polyhydric alcohols having from 2 to 6 hydroxyl groups, the molar ratio of the said fatty acid esters to inositol being less than that required for complete esterification of the inositol, in the presence of an interesterification catalyst at a temperature of from about 80° C. to about 150° C. and in the presence of an amount of dimethylacetamide at least sufficient to dissolve the inositol.

2. The process for preparing partial fatty esters of inositol which comprises reacting inositol with a fatty acid ester selected from the group consisting of the fatty acid esters of aliphatic primary mono-hydroxy alcohols having from 1 to about 8 carbon atoms and completely and incompletely esterified fatty acid esters of polyhydric alcohols having from 2 to 6 hydroxyl groups, the molar ratio of the said fatty acid esters to inositol being less than that required for complete esterification of the inositol, in the presence of an interesterification catalyst at a temperature of from about 120° to about 150° C. and in the presence of an amount of dimethylacetamide at least sufficient to dissolve the inositol.

3. A process for preparing partial fatty esters of inositol which comprises reacting inositol with a fatty acid ester of glycerol in the presence of from about 0.1 to

about 2.0% of an interesterification catalyst by weight of the glycerol ester, at a temperature in the range from about 80° C. to 125° C. in a reaction medium comprising essentially dimethylacetamide, the molar ratio of the said fatty acid ester of glycerol to inositol being less than that required for complete esterification of the inositol.

4. The process of claim 3 wherein the fatty acid ester is a triglyceride.

5. The process for preparing partial fatty esters of inositol which comprises reacting inositol and a fatty triglyceride in the presence of an interesterification catalyst at a temperature of about 100° C. in a reaction medium comprising essentially dimethylacetamide, inactivating the catalyst by acidulation and thereafter freeing the reaction mixture of dimethylacetamide and unreacted inositol.

6. The process for preparing partial fatty esters of inositol which comprises reacting inositol with completely esterified fatty acid ester of inositol, the molar ratio of the said fatty acid ester to inositol being less than that required for complete esterification of the inositol, in the presence of an interesterification catalyst at a temperature of from about 120° to about 150° C. and in the presence of an amount of dimethyl acetamide at least sufficient to dissolve the inositol.

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UNITED STATES PATENT OFFICE

CERTIFICATE OF CORRECTION

Patent No. 2,997,491

August 22, 1961

Wilson F. Huber et al.

It is hereby certified that error appears in the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Column 4, line 1, for "about", first occurrence, read -- above --.

Signed and sealed this 30th day of January 1962.

(SEAL)
Attest:

ERNEST W. SWIDER
Attesting Officer

DAVID L. LADD
Commissioner of Patents