ESTERS OF DIACYL-GLYCEROPHOSPHORIC ACIDS

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1 This application is made under the act of March 3, 1883, as amended by the act of April 30, 1928, and the invention herein described, if patented, may be manufactured and used by or for the Government of the United States of America for governmental purposes without the payment to me of any royalty thereon.

This invention relates to esters of diacyl-glycerophosphoric acids.

More particularly, the invention relates to the preparation of aminooethyl esters of diacyl-glycerophosphoric acids wherein the acyl groups are aliphatic and contain at least eight carbon atoms. These compounds may be illustrated by the following formulae:

\[
\text{(Aminooethyl ester of alpha, gamma-diacyl-glycerophosphoric acid)}
\]

\[
\begin{align*}
\text{H}_2\text{C} & - \text{O} - \text{C} - \text{R} \\
\text{H}_2\text{C} - \text{O} - \text{O} - \text{CH}_2 - \text{CH}_2 - \text{NH}_2 \\
\text{H}_2\text{C} & - \text{O} - \text{C} - \text{R}
\end{align*}
\]

2 Thus, these esters can also be named with respect to their relationship to cephalin. For instance, the following compound can be named the aminooethyl ester of alpha, gamma-dipalmitoglycerophosphoric acid or alpha, gamma-dipalmitocephalin:

\[
\begin{align*}
\text{H}_2\text{C} & - \text{O} - \text{C} - \text{C}_n\text{H}_{2n} \\
\text{H}_2\text{C} - \text{O} & - \text{O} - \text{CH}_2 - \text{CH}_2 - \text{NH}_2 \\
\text{H}_2\text{C} & - \text{O} - \text{C} - \text{C}_n\text{H}_{2n}
\end{align*}
\]

and the following compound can be named the aminooethyl ester of alpha, gamma-distearylglycerophosphoric acid or alpha, gamma-distearylcephalin.

\[
\begin{align*}
\text{H}_2\text{C} & - \text{O} - \text{C} - \text{C}_n\text{H}_{2n} \\
\text{H}_2\text{C} - \text{O} & - \text{O} - \text{CH}_2 - \text{CH}_2 - \text{NH}_2 \\
\text{H}_2\text{C} & - \text{O} - \text{C} - \text{C}_n\text{H}_{2n}
\end{align*}
\]

This invention relates with further particularity to the preparation of novel compounds, namely, phthalimidoethyl esters of diacyl-glycerophosphoric acids wherein the acyl groups are aliphatic and contain at least eight carbon atoms. These compounds may be illustrated by the formulae:

\[
\text{(Phthalimidoethyl ester of alpha, gamma-diacyl-glycerophosphoric acid)}
\]

\[
\begin{align*}
\text{H}_2\text{C} & - \text{O} - \text{C} - \text{R} \\
\text{H}_2\text{C} - \text{O} & - \text{O} - \text{CH}_2 - \text{CH}_2 - \text{N} \\
\text{H}_2\text{C} & - \text{O} - \text{C} - \text{R}
\end{align*}
\]

Cephalin is a naturally occurring mixture of aminooethyl esters of diacyl-glycerophosphoric acids.
and

![Chemical Structure](image)

(Pthalimidoethyl ester of alpha, beta-diacyl-glycerophosphoric acid)

wherein

represents an aliphatic acyl radical containing at least 8 carbon atoms.

These novel compounds can also be named

![Chemical Structure](image)

with respect to their relationship to cephalin. Thus, for instance, the phthalimidoethyl ester of alpha, gamma-dipalmitoyl-glycerophosphoric acid can be referred to as alpha, gamma-dipalmito-phemalycerophosphoric acid.

Accordingly, an object of this invention is to prepare aminoethyl esters of diacyl-glycerophosphoric acids wherein the acyl groups are aliphatic and contain at least eight carbon atoms.

Another object of this invention is to prepare phthalimidoethyl esters of diacyl-glycerophosphoric acids wherein the acyl groups are aliphatic and contain at least eight carbon atoms.

A further object of this invention is to provide novel compounds, namely, phthalimidoethyl esters of diacylglycerophosphoric acids wherein the acyl groups are aliphatic and contain at least eight carbon atoms.

Further objects and advantages will be apparent from the description of the invention.

Methods of preparing the aminoethyl esters are known but are arduous, expensive and give poor yields. One method involves heating distearin with phosphoric anhydride and adding ethanalamine carbonate to this reaction product. This procedure has been found to be unsatisfactory because of reaction between the amine group of the ethanalamine and the diacylglycerophosphoric anhydride to form a diacylglycerophosphoric acid amide instead of the desired ester. Another method involves the heating together of bromethylamine picrate and the monostearin salt of dipalmitoyl-glycerophosphoric acid. This procedure gives very poor yields probably due to formation of piperazine derivatives.

I have found that the aminooethyl esters can be obtained in good yield by the reaction of a diacylglycerophosphoryl chloride with beta-hydroxyethylphthalimide. The resulting compound, phthalimidoethyl ester of diacyl-glyceromonomchlorophosphoric acid, is subjected to a limited hydrolysis to remove the chlorine atom attached to the phosphorus atom whereby the phthalimidoethyl ester of the diacylglycerophosphoric acid is produced. This material is then cleaved by reaction under reducing conditions with hydrazine, hydrazine hydrate, or the mineral acid salts of hydrazine to produce the aminoethyl ester of the diacylglycerophosphoric acid. The reactions can be demonstrated by the following equations:

![Chemical Equations]

The following example, which describes the preparation of alpha, gamma-dipalmitophthalylcephalin (A), and of alpha, gamma-dipalmitoccephalin (B), discloses particular steps and conditions within the scope of this invention, but it is to be understood that this example is given only by way of illustration and not limitation.

(A) Preparation of alpha, gamma-dipalmito-phthalycerophosphoric acid

Phosphorus oxychloride in the quantity of 9.18 grams was placed in a two-necked flask with 30 ml. of dry pyridine and 40 ml. of chloroform. The flask was provided with an agitator adapted to scrape the bottom of the flask and was surrounded by a water bath at 10°-15° C. The agitator was started and then 34.2 grams of alpha-gamma-dipalmitin in 200 ml. of alcohol-free chloroform was added during the course of 1 hour. The solution was stirred at 25° C. for 30 minutes, then at 30°-35° C. for 30 minutes, then cooled to 10°-15° C. again, and 11.45 grams beta-hydroxyethylphthalimide in 200 ml. chloroform added during the course of 1 hour. The solution was then stirred at 28° C. for 30 minutes and at 30°-35° C. for 30 minutes to complete the reaction. After cooling to 28° C. 1.15 ml. of water in 4 ml. pyridine was added. This step causes the hydrolysis of the chlorine atom. Most of the
chloroform was then removed with the aid of a water pump vacuum, and ice and water were thereafter added to the residue. The mixture was transferred to a separatory funnel with the aid of ether, and was shaken moderately. The emulsion formed was rinsed, the other layer was removed, and the ether that separated added to the main ether solution. The ether layer was washed with dilute hydrochloric acid and with water and was then filtered through a thick soft paper or through cotton and left overnight at 5° C.

Filtration removed 3.4 grams of material that melted at 50°–60° C, but did not become clear until 160° C. To obtain the principal reaction product, the filtrate was next left for 5 hours at 18° C, and filtered at this temperature. The precipitate retained much ether and was air-dried overnight, as it melted in the retained solvent when it was dried in a vacuum desiccator without preliminary air drying. The dried product weighed 39.5 grams and melted at 43°–46° C. It was found later to be largely phthalylcelphalin, but contained several other substances.

The crude material was purified by dissolving it in 600 ml. of hot hexane, filtered hot and allowed to stand 18 hours at room temperature. Filtration gave 4.8 grams of impure phthalylcelphalin that sintered at 63° C, and melted from 70°–72° C. The filtrate was dissolved in 50 ml. of methanol, filtered hot and allowed to stand at room temperature overnight. Filtration gave 3.0 grams of crystals of phthalylcelphalin that sintered at 64° C and melted at 67°–68° C. The hexane filtrate (above) contained still more phthalylcelphalin. It was concentrated to 200 ml. and seeded with some of the crystals from the methanol crystallization and therupon deposited more crystals when allowed to stand at room temperature for 3 hours with occasional stirring. Filtration gave 14.7 grams that sintered at 60° C and melted at 64°–73° C. This product was dissolved in 150 ml. of hot methanol and the hot solution was filtered through cotton and allowed to stand for 16 hours at room temperature.

Filtration gave 12.5 grams that sintered at 69° C and melted at 70°–72° C. The two products that had been isolated from methylcelinel were combined and recrystallized from 200 ml. of hexane, the solution being filtered after standing 1 hour at room temperature. The yield was 13.25 grams of product (alpha, gamma-dipalmitocephalin) that melted at 71°–72° C.

Analysis: Calcd. for CuH_{10}O_{6}N_{8}: N, 1.70; P, 3.77; C, 65.74; H, 9.32; equiv. wt. 822.1. Found: N, 1.66; P, 3.85; C, 65.09; H, 9.47; equiv. wt. 825.

(B) Preparation of alpha, gamma-dipalmitocephalin

Four and eleven-hundredths grams of phthalylcelphalin prepared as described above was dissolved in 100 ml. of hot neutral monomethyl ether of glycerol and neutralized by the addition of 10 ml. of 0.5 N NaOH. Hydrazine hydrate in monomethyl ether of glycerol (7.3 ml. of 1.45 M solution) was added, and the solution heated on a steam bath under reflux for 30 minutes. The solution was cooled, 10 ml. of 6 N hydrochloric acid was added, and the solution was then allowed to stand at room temperature for 15 minutes. The reaction mixture was then poured into 1 liter of cold water and 9 liters of ether.

Removal of the alpha, gamma-dipalmitocephalin was accomplished by taking advantage of the unexpected property that it is insoluble in ether but is very readily suspended therein. The water suspension was transferred to a separatory funnel with 500 ml. of ether, shaken and the aqueous layer removed. The ether layer and the solid that collected at the ether-water interface were washed with water until the washings were neutral. The ether containing the suspended solid was then filtered, washed with ether and dried. The dry residue amounted to 2.9 grams and melted at 178°–200° C. Recrystallization from 190 ml. absolute alcohol gave 2.4 grams that sintered at 187° C and melted with decomposition at 192°–193° C, depending on the rate of heating. Further recrystallization from alcohol did not alter the melting point. The product was alpha, gamma-dipalmitocephalin or aminoethyl ester of alpha, gamma-dipalmitocephalin.

Analyses: Calcd. for alpha, gamma-dipalmitocephalin, CuH_{10}O_{6}N_{8}: N, 2.02; P, 4.48; C, 64.22; H, 10.78 percent; equiv. wt. 682.0. Found: N (Dumas), 2.07; Amino N (Nov. 10), 1.03 (as nitric acid), 1.86; P, 4.50; C, 63.75; H, 10.52 percent; equiv. wt. (titration in neutral alcohol), 689.

It was necessary to add vanadium pentoxide to the substance, as described for phosphoric acid esters by Wagner-Jauerg and Grieshaber (Berichte Deut. Chem. Gesell., vol. 70, p. 1488 (1937)) to obtain correct carbon analyses. Combustion of the substance alone, or with copper oxide gave carbon values that were 2 to 3 percent low.

As set forth above the first step in the process involves the reaction of beta-hydroxyethylphthalimide with a diacyl-glycerophosphoryl chloride. As the latter reactant, many different compounds can be used wherein the acyl radicals are aliphatic and contain at least eight carbon atoms. The acyl radicals can be attached at the alpha and gamma positions of the glycerine nucleus, in which case the phosphoryl chloride group is at the beta position; or, the acyl groups can be attached at the alpha and beta positions, in which case the phosphoryl chloride group is attached at the gamma position.

These diacyl-glycerophosphoryl chlorides are most conveniently prepared by reacting a diacyl ester of glycerine with phosphorus oxychloride. For example, by reacting alpha, gamma-dipalmityl ester of glycerine with phosphorus oxychloride in the presence of pyridine, alpha, gamma-dipalmitylglycerophosphoryl chloride can be prepared. Thus, one can employ as the diacyl-glycerophosphoryl chloride reactant the phosphorus oxychloride reaction product with any of the following diacyl esters of glycerine, i.e., alpha, gamma-diacaprylin; alpha, beta-diacapryrin; alpha, gamma-dipalmitoglycerol ester of glycerine; alpha, beta-dipalmitonic ester of glycerine; alpha, gamma-diacaprin; alpha, beta-diacaprin; alpha, gamma-dienecylic ester of glycerine; alpha, beta-dienecylic ester of glycerine; alpha, gamma-dilaurin; alpha, beta-dilaurin; alpha, gamma-ditridecyl ester of glycerine; alpha, beta-ditrdecylic ester of glycerine; alpha, gamma-dimyristin; alpha, beta-dimyristin; alpha, gamma-dipentadecylic ester of glycerine; alpha, beta-dipentadecylic ester of glycerine; alpha, gamma-dimarmargin; alpha, beta-dimargarin; alpha, gamma-distearin; alpha, beta-distearin; alpha, gamma-dimyristic ester of glycerine; alpha, beta-dimonocylic ester of glycerine; alpha, gamma-diarachadin; alpha, beta-
diosparachadin; alpha, gamma-diolein; alpha, beta-diolein; alpha, gamma-dielaidin; alpha, beta-dielaidin; alpha, gamma-dipalmitylolein; alpha, beta-dipalmitylolein; alpha, gamma-dilinolein; alpha, beta-dilinolein; and so forth.

Further, it is possible to use glycerine esters wherein the two acyl groups are dissimilar, for instance—alpha-stearic, beta-palmitic ester of glycerine; alpha-lauric, gamma-palmitic ester of glycerine; alpha-stearic, gamma-oledo ester of glycerine; alpha-palmitic, gamma-linoleic ester of glycerine; and so forth.

Further, if it is not desired to prepare an individual final compound but mixtures, one can employ mixtures of different diesters of glycerine. For instance, one could employ the mixtures of diglycerides formed by heating glycerine and a catalyst with a triglyceride. Thus, mixtures of diglycerides suitable for use in the process could be prepared by heating glycerine with a catalyst and with coconut oil, palm-kernel oil, olive oil, tallow, suet, cottonseed oil, peanut oil, lard, olive oil, whale oil, sardine oil, corn oil, soybean oil, and so forth. Mixtures of diglycerides can also be prepared by reacting an excess of glycerine, in the presence of an esterification catalyst, with mixtures of homologous fatty acids such as the mixture of fatty acids produced by hydrolysis of any of the fats or oils listed above.

The phthalimidohalide can be prepared by the heating of ethylene oxide with phthalimide in a sealed tube at 170° C. (Gabriel and Ohle, Ber. Deut. Chem. Gesell., vol. 50, p. 830 (1917)). However, it is preferred to use the following technique:

Twenty-five grams of ethylamine was added to 59.2 grams of phthalic anhydride, and after the initial heat of reaction had subsided, the mixture was heated at 150° C. for 30 minutes. It was then allowed to cool to about 90° C. and poured into 800 ml. of water. The crystals so obtained were filtered off and recrystallized, giving 46.7 grams of beta-hydroxyethylphthalimide, M. P. 126°-127° C.

Analysis: Caled. for C_{19}H_{24}O; C, 62.82; H, 4.74; N, 7.33. Found: C, 62.81; H, 4.63; N, 7.40.

In the reaction of the diacyl glycerine ester with phosphorus oxychloride, to prepare the diacyl-glycophosphoryl chloride, it is necessary to add a hydrogen chloride acceptor to the reaction mixture. For this purpose, pyridine, quinoline, dimethyl aniline or other tertiary amines are suitable. The temperature of the reaction should be kept low. It has been found that temperatures from about 10° to about 35° C. are suitable. Preferably, the reaction should be conducted at the lower temperature, about 10°-15° C., and then heating to about 30°-35° C. for a short time to insure complete reaction. The diacyl-glyceryl ester and phosphorus oxychloride should be employed in approximately equimolar proportions. It is preferable to employ a solvent in this reaction. Organic solvents such as chloroform, dichloromethane, benzene and so forth are suitable. The other liquid which will dissolve the diacyl-glycerine ester-phosphorus oxychloride complex and the tertiary amine hydrochloride can be used.

It has been found that the diacyl-glycerophosphoryl chloride need not be isolated from the reaction mixture, but the beta-hydroxyethylphthalimide can be reacted with it in situ. In the reaction of the diacyl-glycerophosphoryl chloride with the beta-hydroxyethylphthalimide, it is necessary to employ a hydrogen chloride acceptor (quinoline, pyridine, dimethylamine, or other tertiary amine). It has been found to be convenient to add an excess of the hydrogen chloride acceptor in the first reaction (diacyl-glycerine ester and phosphorus oxychloride) whereby sufficient acceptor will remain in the reaction mixture for the second reaction (diacyl-glycophosphoryl chloride and beta-hydroxyethylphthalimide). In regard to the latter reaction, the same temperature, proportions, and solvents are applicable as to the former reaction.

In the hydrolysis step involving the removal of the chlorine atom from the complex phthalimidoethyl ester of diacyl-glycophosphoric acid, the amount of water is not critical. At least an equimolar proportion of water should be added but an excess will not be disadvantageous. The temperature during this step should be kept, at about 25° C. or less, to prevent hydrolysis of the ester linkages. No solvent is necessary in the hydrolysis, but a solvent such as pyridine can be used if desired to assist in the separation of the products of the mixture.

The expression "limited hydrolysis," as used herein, refers to a controlled hydrolysis whereby only the chlorine atom on the phthalidohalide is hydrolyzed and the ester linkages are not affected.

In the cleavage step, hydrazine is heated with the phthalidophenyl. One mol of the phthalidophenyl requires 1 to 2 mols of hydrazine. In this cleavage step, the hydrazine can be replaced by hydrazine hydrate, hydrazine hydrochloride, hydrazine sulphate, or other hydrazine mineral acid salts. It is preferable to use a solvent; monomethyl glycol ether, monoethyl glycol ether, ethanol and methanol are suitable. The products are preferably refluxed to bring about the reaction and to prevent loss of solvent and/or hydrazine.

The aminooxy esters produced according to the present process can be used to replace jecithin in a variety of pharmaceutical preparations and cosmetics where they are used as emulsifying and skin-softening agents. The products are also useful as anticholining agents (e.g., in chocolates and as water-binding and dispersing agents). Because of their surface-active properties, the aminooxy esters are also useful in preparing oil-in-water emulsions of insecticides and fungicides and in promoting the reaction of hydrophilic materials with hydrophobic materials.

The phthalimidoethyl esters of this invention are useful as a convenient source for the preparation of the corresponding aminooxy esters. The phthalimidoethyl esters are quite stable and can be kept for long periods without change. The phthalimidoethyl esters are required. The phthalimidoethyl esters are generally useful as intermediates from which to prepare many different glycophosphoric acid derivatives.

The foregoing example indicates methods of purifying the product and intermediates. These steps can, of course, be omitted if it is not desired to obtain a chemically pure grade of material.

In a copending application, Serial No. 754,256, filed June 12, 1947, now U. S. Patent 2,436,699, I have disclosed a method for preparing aminooxy esters of diacyl-glycophosphoric acids involving reaction of carboxenozoxime with a diacyl-glycerophosphoryl chloride, followed by
limited hydrolysis, and cleavage with phosphonium iodide.

Having thus described the invention, what is claimed is:

1. A process comprising reacting a diacyl-glycerophosphoryl chloride, wherein the acyl radicals are aliphatic and contain at least 8 carbon atoms, with a beta-hydroxyethylphthalimide in the presence of a tertiary amine at a temperature of about from 10°C to 35°C, subjecting the resulting phthallimidoethyl ester of diacyl-glyceromonochlorophosphoric acid to limited hydrolysis by reaction with water at a temperature not exceeding about 25°C to form the phthalimidioethyl ester of diacyl-glycerophosphoric acid and refluxing this last-formed ester with a member selected from the group consisting of hydrazine, hydrazine hydrate, and the mineral acid salts of hydrazine to produce an aminoethyl ester of a diacyl-glycerophosphoric acid.

2. A process comprising reacting a diacyl-glycerophosphoryl chloride, wherein the acyl radicals are aliphatic and contain at least 8 carbon atoms, with beta-hydroxyethylphthalimide in the presence of a tertiary amine at a temperature of about from 10°C to 35°C, subjecting the resulting phthallimidoethyl ester of diacyl-glyceromonochlorophosphoric acid to limited hydrolysis by reaction with water at a temperature not exceeding about 25°C to form the phthalimidioethyl ester of diacyl-glycerophosphoric acid, and refluxing this last-formed ester with hydrazine hydrate to produce an aminoethyl ester of a diacyl-glycerophosphoric acid.

3. A process comprising reacting an alpha, gamma-diacetylglycerophosphoryl chloride, wherein the acyl radicals are aliphatic and contain at least 8 carbon atoms, with beta-hydroxyethylphthalimide in the presence of a tertiary amine at a temperature of about from 10°C to 35°C, subjecting the resulting phthallimidoethyl ester of alpha, gamma-diacetylglyceromonochlorophosphoric acid to limited hydrolysis by reaction with water at a temperature not exceeding about 25°C to form the phthalimidioethyl ester of alpha, gamma-diacetyl-glycerophosphoric acid, and refluxing this last-formed ester with a member selected from the group consisting of hydrazine, hydrazine hydrate, and hydrazine to produce the aminoethyl ester of an alpha, gamma-diacetyl-glycerophosphoric acid.

4. A process comprising reacting alpha, gamma-diacetyl-glycerophosphoryl chloride with beta-hydroxyethylphthalimide in the presence of a tertiary amine at a temperature of about from 10°C to 35°C, subjecting the resulting phthalimidioethyl ester of alpha, gamma-diacetyl-glyceromonochlorophosphoric acid to limited hydrolysis by reaction with water at a temperature not exceeding about 25°C to form the phthalimidioethyl ester of alpha, gamma-diacetyl-glycerophosphoric acid, and refluxing this last-formed ester with a member selected from the group consisting of hydrazine, hydrazine hydrate, and the mineral acid salts of hydrazine to produce the aminoethyl ester of an alpha, gamma-diacetyl-glycerophosphoric acid.

5. The process of claim 1 wherein the tertiary amine is pyridine.

6. A process comprising reacting a diacyl-glycerophosphoryl chloride, wherein the acyl radicals are aliphatic and contain at least 8 carbon atoms, with beta-hydroxyethylphthalimide in the presence of a tertiary amine at a temperature of about from 10°C to 35°C, and subjecting the resulting phthalimidioethyl ester of diacyl-glyceromonochlorophosphoric acid to limited hydrolysis by reaction with water at a temperature not exceeding about 25°C to form the phthalimidioethyl ester of diacyl-glycerophosphoric acid.

7. A process comprising reacting an alpha, gamma-diacetyl-glycerophosphoryl chloride with beta-hydroxyethylphthalimide in the presence of a tertiary amine at a temperature of about from 10°C to 35°C, and subjecting the resulting phthalimidioethyl ester of alpha, gamma-diacetyl-glyceromonochlorophosphoric acid to limited hydrolysis by reaction with water at a temperature not exceeding about 25°C to form the phthalimidioethyl ester of alpha, gamma-diacetyl-glycerophosphoric acid.

8. A process comprising reacting an alpha, gamma-dipalmitoylglycerophosphoryl chloride with beta-hydroxyethylphthalimide in the presence of a tertiary amine at a temperature of about from 10°C to 35°C, and subjecting the resulting phthalimidioethyl ester of alpha, gamma-dipalmitoylglyceromonochlorophosphoric acid to limited hydrolysis by reaction with water at a temperature not exceeding about 25°C to form the phthalimidioethyl ester of alpha, gamma-dipalmitoylglycerophosphoric acid.

9. The process of claim 8 wherein the tertiary amine is pyridine.

10. A phthalimidioethyl ester of a diacyl-glycerophosphoric acid wherein the acyl radicals are aliphatic and contain at least 8 carbon atoms.

11. A phthalimidioethyl ester of an alpha, gamma-diacetyl-glycerophosphoric acid wherein the acyl radicals are aliphatic and contain at least 8 carbon atoms.

12. Phthalimidioethyl ester of dipalmitoylglycerophosphoric acid.

13. Phthalimidioethyl ester of alpha, gamma-dipalmitoylglycerophosphoric acid.

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REFERENCES CITED

The following references are of record in the file of this patent: