

1

3,051,738

ANTIHEMORRHAGIC COMPOUNDS AND PROCESSES FOR PREPARING THE SAME

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24 Claims. (Cl. 260-461)

This invention relates to water-soluble derivatives of dihydro vitamin K₁ (2-methyl-3-phytyl-1,4-naphthohydroquinone) having anti-hemorrhagic activity and to the processes for preparing these novel derivatives. More particularly, this invention relates to 1-monocarboxylic acid esters of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate and to 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate, and to the intermediates produced in accordance with this invention.

This application is a division of U.S. application Serial No. 647,747, filed March 22, 1957, now U.S. Patent No. 2,913,477.

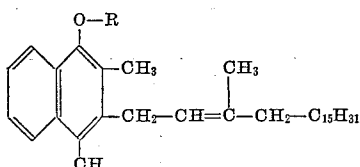
Due to an overdose of certain anticoagulants or where a proper amount of the anticoagulant is administered but the patient is hypersensitive to such drugs, such anticoagulants may cause serious hemorrhaging in the patient. The immediate concern of the clinician with a patient having a dangerously low prothrombin level due to these anticoagulants is to bring the prothrombin to a safe level as rapidly as possible. Prior to this invention certain types of hemorrhage occurring spontaneously were treated with vitamin K preparations, one of the most active of which being an emulsion of vitamin K₁ (2-methyl-3-phytyl-1,4-naphthohydroquinone). In instances of hypoprothrombinemia and bleeding due to a variety of anticoagulants, vitamin K₁, for example vitamin K₁ emulsion, has been established as the only effective preparation available. Nevertheless, in certain critical cases of drug induced hypoprothrombinemia, the action of even vitamin K₁ emulsion was not as rapid as might be desired.

Now an anti-hemorrhagic compound is available which is capable of effecting a more rapid lowering of the prothrombin time and blood clotting time than that noted with previous preparations.

Water-soluble dihydro vitamin K₁ was found to be appreciably more effective than vitamin K₁ emulsion by the intramuscular route. Data obtained in prophylactic and therapeutic studies indicate that water-soluble dihydro vitamin K₁ has a shorter duration of action than vitamin K₁ emulsion. Because of this property, water-soluble dihydro vitamin K₁ should be capable of rapidly reversing excessive hypoprothrombinemia with less likelihood of inducing refractoriness to reinstitution of anticoagulant therapy.

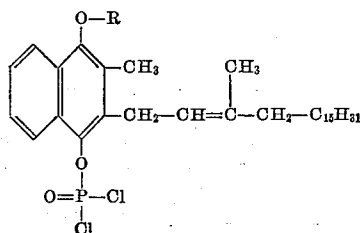
The novel compounds described in this invention, namely, 1-carboxylic acid esters of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate and 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate are water-soluble and have been found to provide a prompt lowering of prothrombin time and blood clotting time.

In accordance with this invention a 1-monocarboxylic acid ester of 2-methyl-3-phytyl-1,4-naphthohydroquinone represented by the following structure

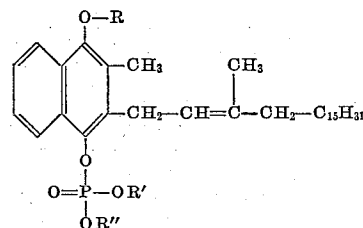


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wherein R represents a monocarboxylic acid radical, is reacted with phosphorus oxychloride to form a 1-monocarboxylic acid ester of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-(dichloro)phosphate having the structure

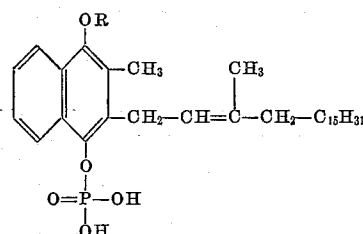


wherein R is as above. The above compound is treated with alkali to form a mono- or di-alkali metal salt of 1-monocarboxylic acid ester of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate having the structure



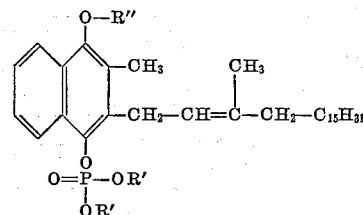
wherein R' is an alkali metal and R'' is hydrogen or an alkali metal.

The above compound is reacted with an aqueous acid solution to form a 1-monocarboxylic acid ester of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate which may be indicated graphically as follows:



wherein R is as above.

Reaction of the above compound with a concentrated aqueous alcoholic metal hydroxide such as Claisen's alkali, which is a solution of potassium hydroxide in aqueous methanol, results in the formation of the mono-, di- and tri-alkali metal salt of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate which can be represented by the following formula

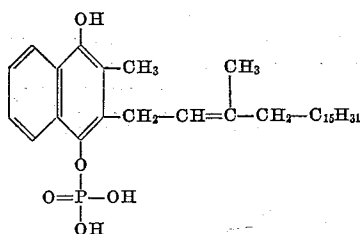


wherein R' and R'' are as above.

The above compound is reacted with an aqueous acid

3

solution and 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate having the following structure is recovered.



Instead of employing Claisen's alkali, 1-monocarboxylic acid ester of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate may be reacted with an alcoholic solution in the presence of an acid catalyst such as sulfuric, perchloric, paratoluene sulfonic or sulfosalicylic acid and 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate is recovered.

In general, any suitable 1-monocarboxylic acid ester of 2-methyl-3-phytyl-1,4-naphthohydroquinone can be employed as the starting material in this process. Thus, the acyloxy substituent present at the 1-position of the naphthohydroquinone nucleus may be an alkyl-acyloxy, or arylacyloxy or aralkylacyloxy group derived from a mono-carboxylic acid. Ordinarily, however, it is preferred to effect the reaction using a 1-monocarboxylic acid ester of 2-methyl-3-phytyl-1,4-naphthohydroquinone in which the acyloxy group contains eight carbons or less. Specific examples of such compounds which can be used in this invention that might be mentioned are

2-methyl-3-phytyl-1,4-naphthohydroquinone-1-acetate,
2-methyl-3-phytyl-1,4-naphthohydroquinone-1-propionate,
2-methyl-3-phytyl-1,4-naphthohydroquinone-1-butyrate,
2-methyl-3-phytyl-1,4-naphthohydroquinone-1-valerate,
2-methyl-3-phytyl-1,4-naphthohydroquinone-1-caproate,
2-methyl-3-phytyl-1,4-naphthohydroquinone-1-caprylate,
2-methyl-3-phytyl-1,4-naphthohydroquinone-1-phenylacetate,
2-methyl-3-phytyl-1,4-naphthohydroquinone-1-benzoate,

and the like. These and similar esters can be prepared by reacting 1-monocarboxylic acid ester of 2-methyl-1,4-naphthohydroquinone with phytol in the presence of boron trifluoride to produce the corresponding 1-monocarboxylic acid ester of 2-methyl-3-phytyl-1,4-naphthohydroquinone.

The reaction of a 1-monocarboxylic acid ester of 2-methyl-3-phytyl-1,4-naphthohydroquinone with phosphorous oxychloride is conveniently achieved by contacting the reactants in the presence of a suitable reaction medium. Solvents such as pyridine, triethylamine and other tertiary amines are examples of suitable reaction media in which the reaction may be effected.

Following completion of this reaction the desired 1-monocarboxylic acid ester of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-(dichloro)phosphate is recovered by removing the excess phosphorous oxychloride and pyridine by evaporation. The product then may be reacted with dilute aqueous alkali to form 1-monocarboxylic acid ester of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate in aqueous solution as a mixture of the alkali metal and dialkali metal salt. The solution is extracted with ether and acidified with dilute acid to about pH 1. The mixture is then extracted with ether, the ether layer separated and concentrated to dryness. The last traces of water are then removed by co-distillation with benzene. The residue thus obtained is the 1-monocarboxylic acid ester of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate.

The 1-monocarboxylic acid ester of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate can then be reacted with Claisen's alkali to form a mixture of the mono-, di- and tri-alkali metal salt of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate. This latter mixture is then

4

treated with aqueous acid solution to form 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate.

Instead of employing Claisen's alkali the 1-monocarboxylic ester of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate can be reacted with methanolic sulfuric acid to form directly the 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate.

The described reaction may be specifically illustrated by the reaction of 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-acetate with phosphorous oxychloride to form 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-acetate-4-(dichloro)phosphate. Similarly, 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-propionate is reacted with phosphorous oxychloride to produce 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-propionate-4-(dichloro)phosphate. In like manner by starting with other appropriate reactants there is obtained

2-methyl-3-phytyl-1,4-naphthohydroquinone-1-valerate-4-(dichloro)phosphate,
2-methyl-3-phytyl-1,4-naphthohydroquinone-1-butyrate-4-(dichloro)phosphate,
2-methyl-3-phytyl-1,4-naphthohydroquinone-1-caproate-4-(dichloro)phosphate,
2-methyl-3-phytyl-1,4-naphthohydroquinone-1-caprylate-4-(dichloro)phosphate,
2-methyl-3-phytyl-1,4-naphthohydroquinone-1-phenylacetate-4-(dichloro)phosphate,
2-methyl-3-phytyl-1,4-naphthohydroquinone-1-benzoate-4-(dichloro)phosphate

and other similar 1-monocarboxylic acid esters of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-(dichloro)phosphate.

Any of the 1-monocarboxylic acid esters of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-(dichloro)phosphate obtained above may be reacted with sodium hydroxide solution to form 1-monocarboxylic acid esters of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate as a mixture of the sodium and disodium salt.

The mixture of the sodium and disodium 1-monocarboxylic acid esters of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate when reacted with water or hydrochloric acid forms the 1-monocarboxylic acid ester of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate.

The 1-monocarboxylic acid ester of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate may be reacted with Claisen's alkali to form the mono-, di- and tri-sodium salt of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate. In accordance with the reaction with Claisen's alkali, the 1-monocarboxylic acid ester of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate is dissolved in a suitable solvent such as a low boiling petroleum ether and the resulting solution is extracted with Claisen's alkali. In this manner purification and unexpected solvolysis of the acyl group is achieved simultaneously to give an alkaline solution of essentially pure 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate as a mixture of the monosodium, disodium and trisodium salt. The phosphate ester linkage is not cleaved. To isolate the free acid, the alkaline aqueous layer is extracted with petroleum ether and then acidified with dilute hydrochloric acid to about pH 1. The ether is removed by evaporation and the residual water is removed by codistillation with benzene resulting in 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate.

Alternatively, a 1-monocarboxylic acid ester of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate may be reacted with methanolic sulfuric acid to form directly 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate.

The comparative efficiencies of vitamin K₁ emulsion (2-methyl-3-phytyl-1,4-naphthohydroquinone), 2-methyl-3-phytyl-1,4-naphthohydroquinone-1,4-diphosphate, 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-propionate-4-phosphate and 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate

phosphate by intravenous administration in dogs rendered hypoprothrombinemic by 3,3'-methylenebis (4-hydroxy-coumarin) has been experimentally demonstrated according to the following test:

The prothrombin time (in seconds) of ten well standardized dogs was determined and found to range between nine and ten seconds. Then these dogs were fed orally 2 mg./kg. of the anticoagulant 3,3'-methylenebis (4-hydroxycoumarin) on two successive days. Prothrombin tests were made each day and on the second day the prothrombin time had risen to between nineteen and thirty-one seconds. Three dogs were used as controls and did not receive any of the vitamin K compounds. The other seven dogs then received the vitamin K derivatives and prothrombin determinations were made 2½, 5, 24, 48 and 120 hours after the vitamin K derivative injection. The results of these tests are given in the following table:

TABLE

Comparative Efficacies of Vitamin K Compounds in Reversing 3,3'-Methylenebis (4-Hydroxycoumarin) Induced Hypoprothrombinemia

Test Cmpd.	Dose ¹ mg./kg.	Prothrombin Time—Seconds								
		Day 0	Day 1	Day 2	Day 2	Day 2	Day 3	Day 4	Day 7	
		(²) Hrs. 0	(²)	(³) Hrs. 0	Hrs. 2.5	Hrs. 5	Hrs. 24	Hrs. 48	Hrs. 120	
A.....	-----	10	12	26.5	28	27	33	37	13	30
A.....	-----	10	10	21.5	24	26	36	25.5	10	
A.....	-----	9.5	12.5	24.5	25	26	35.5	25	10	
B.....	-----	9.5	12	21.5	18.5	14	11	10	11	
B.....	2	10	11	31	31	19	11.5	12	10	
B.....	1	10	11	19	16	13.5	17	12	9.5	
C.....	2	10	15	29	13	13	17	14.5	10	
D.....	10	10	14	26	23.5	17	11	11	10	
E.....	2	9.5	26.5	30	11.5	12	20	28	9	35
E.....	5	9.5	11.5	24.5	11.5	11	14	24	12	

Legend:

- A—Control (no vitamin K compound).
 B—Emulsion of 2-methyl-3-phytyl-1,4-naphthoquinone.
 C—2-methyl-3-phytyl-1,4-naphthohydroquinone-1,4-diphosphate.
 D—2-methyl-3-phytyl-1,4-naphthohydroquinone-1-propionate-4-phosphate.
 E—2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate.
¹ Dose given in terms of vitamin K₁ molar equivalent.
² 3,3'-methylenebis(4-hydroxycoumarin), 2 mg./kg. administered orally.
³ The test compound was administered intravenously.

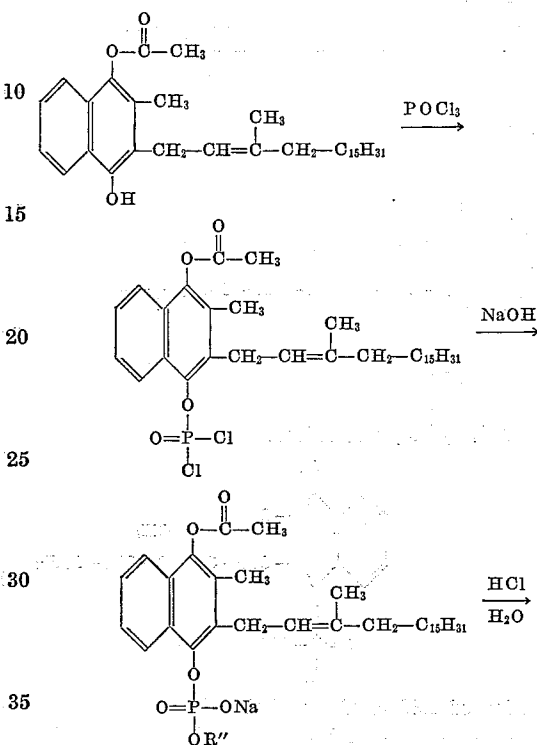
The table shows that even after four days the prothrombin time of the control dogs who received no vitamin K₁ derivatives is between 25 and 37, very much above the normal of 9 to 10 seconds. Vitamin K₁ emulsion, 2-methyl-3-phytyl-1,4-naphthohydroquinone, at 1 and 2 mg./kg. showed little or no activity within 2½ hours. At 5 hours a significant lowering of prothrombin time was observable but this effect was less than with the 2-methyl-3-phytyl-1,4-naphthohydroquinone diphosphate and 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate. However, at both dose levels, prothrombin levels were essentially normal at the 24 hour interval and remained so thereafter. 2-methyl-3-phytyl-1,4-naphthohydroquinone diphosphate, at 1 and 2 mg./kg., showed good activity in reversing hypoprothrombinemia but reversal was not complete even at 5 hours. One day after treatment, prothrombin times rose again slightly and thereafter returned to normal. 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-propionate-4-phosphate exhibited definite activity. The most rapidly acting preparation, 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate, brought about essentially complete reversal of hypothrombinemia within two and one-half hours after doses of 2 or 5 mg./kg. Prothrombin times remained low for the next two and one-half hours but then progressively increased on the following two days, after which they declined toward normal limits.

The following examples are given to illustrate specific applications of the invention but it should be recognized that the scope of the invention is not to be restricted to the

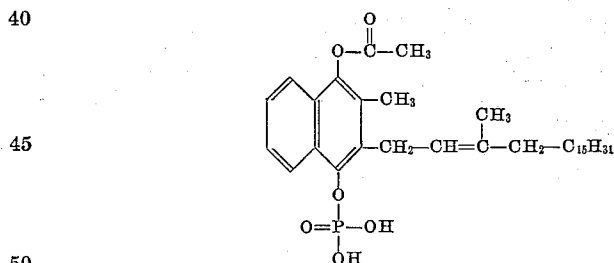
particular embodiments of the invention as disclosed in these examples.

EXAMPLE 1

2-Methyl-3-Phytyl-1,4-Naphthohydroquinone-1-Acetate-4-Phosphate



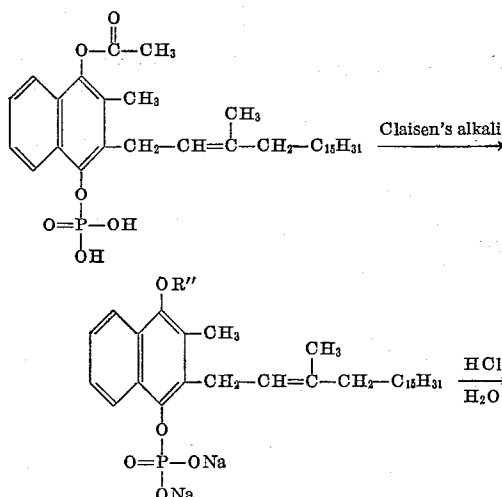
wherein R'' is hydrogen or sodium



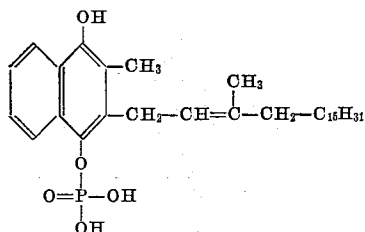
To a solution of 6.5 ml. of phosphorus oxychloride in 17 ml. of dry pyridine was added with vigorous stirring a solution of 4.6 g. of crude 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-acetate (which can be prepared as described hereinbelow) in 17 ml. dry pyridine. The reaction was allowed to continue in an ice bath for about 30 minutes during which time the temperature rose to about 20–25° C., and 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-acetate-4-(dichloro)phosphate was formed.

The excess phosphorus oxychloride and pyridine was removed at 40° C. in vacuo and the residue thus obtained was neutralized with dilute aqueous sodium hydroxide to about pH 8 to form 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-acetate-4-phosphate as a mixture of the sodium and disodium salts. The alkaline aqueous layer was extracted portionwise with 150 ml. of ether and then acidified with dilute hydrochloric acid to about pH 1. The aqueous solution was then extracted with about 100 ml. of ether, the ether layer separated and concentrated to dryness in vacuo. The last portions of water were removed by codistillation with benzene. The residue thus obtained was 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-acetate-4-phosphate.

2-Methyl-3-Phytyl-1,4-Naphthohydroquinone-4-Phosphate



wherein R'' is hydrogen or sodium



A solution of 1.88 g. of 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-acetate-4-phosphate dissolved in 60 ml. of petroleum ether was extracted with 20 ml. of Claisen's methanolic alkali (prepared by dissolving 35 g. of potassium hydroxide in 25 ml. of water and diluting to 100 ml. with methanol). This reaction mixture contains predominantly disodium 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate, however some mono and trisodium 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate may be present.

The alkaline aqueous layer was extracted with 20 ml. of petroleum ether and then acidified with dilute hydrochloric acid to about pH 1. The 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate thus formed was then extracted into 100 ml. of ether and the ether solution evaporated to dryness in vacuo. The residual water was removed by co-distillation with benzene. The crude 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate was purified by precipitation from 10 ml. of acetone solution with petroleum ether and benzene.

2-Methyl-3-Phytyl-1,4-Naphthohydroquinone-1-Acetate

The 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-acetate utilized as the starting material in this example was prepared as follows:

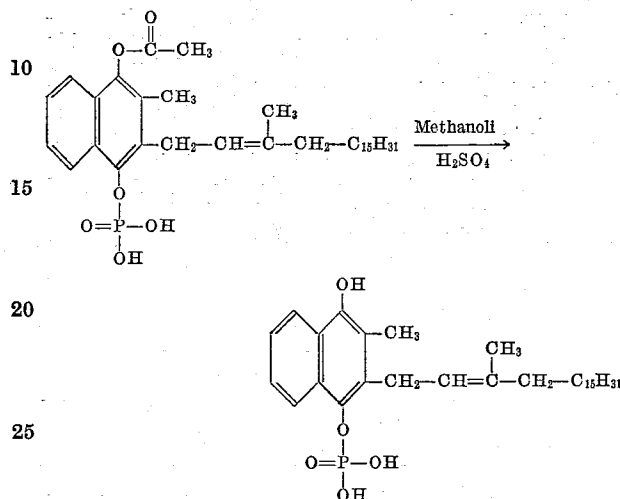
A mixture of 3.07 g. of phytol in 8 ml. of dioxane was added slowly to 23.45 g. of 2-methyl-1,4-naphthohydroquinone-1-acetate in 20 ml. of dioxane to which about 0.54 ml. of boron trifluoride etherate had been added. The addition was carried out at about 50° C. in an inert atmosphere and the reaction allowed to continue for a total of about 1 hour.

At the end of this time, the solution was cooled to about 20° C. and diluted with 100 cc. of ether. The ether solution was washed twice with 100 ml. portions of sodium bicarbonate, water and salt. It was then evaporated to dryness in vacuo and about 54 ml. of petroleum ether was added to the residue. Any solid was removed by filtration, and the filtrate treated with activated charcoal and subsequently extracted with 2% aqueous potas-

sium hydroxide. It was then washed further with sodium chloride solution and the petroleum ether finally removed by concentration in vacuo to about 80° C.

EXAMPLE 2

2-Methyl-3-Phytyl-1,4-Naphthohydroquinone-4-Phosphate



To a mixture of 2.68 g. of 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-acetate-4-phosphate, prepared as described in Example 1, in 10 ml. of methanol, was added 0.2 ml. of concentrated sulfuric acid. The solution was allowed to stand at room temperature. The solution was diluted to 40 ml. with methanol and 160 ml. of a saturated solution of sodium chloride was added. This mixture was extracted with three 80 ml. portions of ether. The remaining aqueous layer showed no ultra-violet absorption. The combined ether layers consisting of 240 ml. were washed twice with 50 ml. of saturated sodium chloride solution. The sodium chloride solution picked up some color, leaving behind a slightly brown colored ether layer. The ether layer was evaporated to dryness and further dried by azeotropic distillation with benzene.

The 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate thus obtained showed the same infra-red spectrum as described in the above example.

Treatment of the 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate thus obtained with one equivalent of base results in the formation of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-sodium phosphate, while at higher pH 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-disodium phosphate is formed.

EXAMPLE 3

2-Methyl-3-Phytyl-1,4-Naphthohydroquinone-1-Propionate-4-Phosphate

To a solution of 6.5 ml. of phosphorus oxychloride in 17 ml. of dry pyridine was added with vigorous stirring a solution of 4.6 g. of crude 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-propionate (which can be prepared as described hereinbelow) in 17 ml. dry pyridine. The reaction was allowed to continue in an ice bath for about 30 minutes during which time the temperature rose to about 20-25° C., and 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-propionate-4-(dichloro)phosphate was formed.

The excess phosphorus oxychloride and pyridine was removed at 40° C. in vacuo and the residue thus obtained was neutralized with dilute aqueous sodium hydroxide to about pH 8 to form 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-propionate-4-phosphate as a mixture of the sodium and disodium salts. The alkaline aqueous layer was extracted portionwise with 150 ml. of ether and then acidified with dilute hydrochloric acid

to about pH 1. The aqueous solution was then extracted with about 100 ml. of ether, the ether layer separated and concentrated to dryness in vacuo. The last portions of water were removed by co-distillation with benzene. The residue thus obtained was 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-propionate-4-phosphate.

A sample of 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-propionate-4-phosphate was dried at 100° C. for 90 minutes and showed the following ultra-violet properties in 1% sodium bicarbonate solution: λ max. 235 m μ , E_m =52,500; 291 m μ E_m =5,150.

2-Methyl-3-Phytyl-1,4-Naphthohydroquinone-4-Phosphate

A solution of 1.88 g. of 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-propionate-4-phosphate dissolved in 60 ml. of petroleum ether was extracted with 20 ml. of Claisen's methanolic alkali (prepared by dissolving 35 g. of potassium hydroxide in 25 ml. of water and diluting to 100 ml. with methanol). This reaction mixture contains predominantly disodium 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate, however some mono and trisodium 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate may be present.

The alkaline aqueous layer was extracted with 20 ml. of petroleum ether and then acidified with dilute hydrochloric acid to about pH 1. The 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate thus formed was then extracted into 100 ml. of ether and the ether solution evaporated to dryness in vacuo. The residual water was removed by co-distillation with benzene. The crude 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate was purified by precipitation from 10 ml. of acetone solution with petroleum ether and benzene.

2-Methyl-3-Phytyl-1,4-Naphthohydroquinone-1-Propionate

The 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-propionate, utilized as the starting material in this example was prepared as follows:

A mixture of 3.07 g. of phytol in 8 ml. of dioxane was added slowly to 23.45 g. of 2-methyl-1,4-naphthohydroquinone-1-propionate in 20 ml. of dioxane to which about 0.54 ml. of boron trifluoride etherate had been added. The addition was carried out at about 50° C. in an inert atmosphere and the reaction allowed to continue for a total of about 1 hour.

At the end of this time, the solution was cooled to about 20° C. and diluted with 100 cc. of ether. The ether solution was washed twice with 100 ml. portions of sodium bicarbonate, water and salt. It was then evaporated to dryness in vacuo and about 54 ml. of petroleum ether was added to the residue. Any solid was removed by filtration, and the filtrate treated with activated charcoal and subsequently extracted with 2% aqueous potassium hydroxide. It was then washed further with sodium chloride solution and the petroleum ether finally removed by concentration in vacuo to about 80° C.

EXAMPLE 4

2-Methyl-3-Phytyl-1,4-Naphthohydroquinone-4-Phosphate

To a mixture of 2.68 g. of 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-propionate-4-phosphate, prepared as described in Example 3, in 10 ml. of methanol, was added 0.2 ml. of concentrated sulfuric acid. The solution was allowed to stand at room temperature. The solution was diluted to 40 ml. with methanol and 160 ml. of a saturated solution of sodium chloride was added. This mixture was extracted with three 80 ml. portions of ether. The remaining aqueous layer showed no ultra-violet absorption. The combined ether layers consisting of 240 ml. were washed twice with 50 ml. of saturated sodium chloride solution. The sodium chloride solution picked

up some color, leaving behind a slightly brown colored ether layer. The ether layer was evaporated to dryness and further dried by azeotropic distillation with benzene.

The 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate thus obtained showed the same infra-red spectrum as described in the above example.

Treatment of the 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate thus obtained with one equivalent of base results in the formation of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-sodium phosphate, while at higher pH 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-disodium phosphate is formed.

Various changes and modifications of the invention can be made and, to the extent that such variations incorporate the spirit of this invention, they are intended to be included within the scope of the appended claims.

What is claimed is:

- 1-lower fatty acid ester of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-(dichloro)phosphate.
- 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-acetate-4-(dichloro)phosphate.
- 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-propionate-4-(dichloro)phosphate.
- Sodium 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-propionate-4-phosphate.
- Disodium 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-acetate-4-phosphate.
- 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-propionate-4-phosphate.
- Dialkali metal salt of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate.
- The process which comprises reacting 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-acetate with phosphorus oxychloride to form 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-acetate-4-(dichloro)phosphate, reacting the latter compound with sodium hydroxide to form a mixture of sodium and disodium 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-acetate-4-phosphate, reacting the latter compound with hydrochloric acid to form 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-acetate-4-phosphate, reacting the latter compound with a concentrated aqueous alcoholic metal hydroxide to form a mixture of the mono-, di- and tri-sodium salt of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate and reacting the latter compound with hydrochloric acid to form 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate.
- The process which comprises reacting 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-propionate with phosphorus oxychloride to form 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-propionate-4-(dichloro)phosphate, reacting the latter compound with sodium hydroxide to form a mixture of sodium and disodium 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-propionate-4-phosphate, reacting the latter compound with hydrochloric acid to form 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-propionate-4-phosphate, reacting the latter compound with a concentrated aqueous alcoholic metal hydroxide to form a mixture of the mono-, di- and tri-sodium salt of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate and reacting the latter compound with hydrochloric acid to form 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate.
- The process which comprises reacting 1-lower fatty acid ester of 2-methyl-3-phytyl-1,4-naphthohydroquinone with phosphorus oxychloride to form the 1-lower fatty acid ester of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-(dichloro)phosphate, reacting the latter compound with alkali to form a mixture of the mono- and di-alkali metal salt of 1-lower fatty acid ester of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate, reacting the latter compound with an inorganic acid to form 1-lower fatty acid ester of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate, and reacting the latter compound with an lower alkanolic solution in the presence of an acid catalyst to form 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate.

11. The process which comprises reacting 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-acetate with phosphorous oxychloride to form 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-acetate-4-(dichloro)phosphate, reacting the latter compound with sodium hydroxide to form a mixture of sodium and disodium 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-acetate-4-phosphate, reacting the latter compound with hydrochloric acid to form 2-methyl-3-phytyl-1,4-naphthohydroquinone - 1 - acetate-4-phosphate, and reacting the latter compound with methanolic sulfuric acid to form 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate.

12. The process which comprises reacting 1-lower fatty acid ester of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate with a concentrated aqueous lower alkanolic alkali metal hydroxide to form a mixture of the di- and tri-metal salt of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate.

13. The process which comprises reacting 2-methyl-3-phytyl-1,4-naphthohydroquinone - 1 - propionate-4-phosphate with a concentrated aqueous lower alkanolic sodium hydroxide to form a mixture of the di- and tri-sodium salt of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate.

14. Disodium 2-methyl - 3 - phytyl-1,4-naphthohydroquinone-4-phosphate.

15. The process which comprises reacting 2-methyl-3-phytyl-1,4-naphthohydroquinone - 1 - acetate - 4 - phosphate with methanolic sulfuric acid to form 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate.

16. The process which comprises reacting 1-lower fatty acid ester of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-(dichloro)phosphate with alkali to form a mixture of the mono- and di-alkali metal salt of 1-lower fatty acid ester of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate, reacting the latter compound with an inorganic acid to form 1-lower fatty acid ester of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate and reacting the latter compound with a concentrated aqueous lower alkanolic alkali metal hydroxide to form a mixture of the mono-, di- and tri-alkali metal salt of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate.

17. The process which comprises reacting 2-methyl-3-phytyl-1,4-naphthohydroquinone - 1 - acetate-4-(dichloro)phosphate with sodium hydroxide to form a mixture of sodium and di-sodium 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-acetate-4-phosphate, reacting the latter compound with hydrochloric acid to form 2-methyl-3-phytyl-1,4-naphthohydroquinone - 1 - acetate-4-phosphate, and reacting the latter compound with a concentrated aqueous lower alkanolic alkali metal hydroxide to form a mixture of the mono-, di- and tri-sodium salt of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate.

18. The process which comprises reacting 2-methyl-3-phytyl-1,4-naphthohydroquinone - 1 - propionate-4-(dichloro)phosphate with sodium hydroxide to form a mixture of sodium and di-sodium 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-propionate-4-phosphate, reacting the latter compound with hydrochloric acid to form 2-methyl-3-phytyl - 1,4 - naphthohydroquinone - 1 - propionate-4-phosphate, and reacting the latter compound with a concentrated aqueous lower alkanolic alkali metal hydroxide

to form a mixture of the mono-, di- and tri-sodium salt of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate.

19. The process which comprises reacting a mixture of the mono- and di-alkali metal salt of 1-lower fatty acid ester of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate with an inorganic acid to form 1-lower fatty acid ester of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate, and reacting the latter compound with a concentrated aqueous lower alkanolic alkali metal hydroxide to form a mixture of the mono-, di- and tri-alkali metal salt of 2-methyl-3-phytyl - 1,4 - naphthohydroquinone-4-phosphate.

20. The process which comprises reacting a mixture of sodium and di-sodium 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-acetate-4-phosphate with hydrochloric acid to form 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-acetate-4-phosphate and reacting the latter compound with a concentrated aqueous lower alkanolic alkali metal hydroxide to form a mixture of the mono-, di- and tri-sodium salt of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate.

21. The process which comprises reacting a mixture of sodium and di-sodium 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-propionate-4-phosphate with hydrochloric acid to form 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-propionate-4-phosphate and reacting the latter compound with a concentrated aqueous lower alkanolic alkali metal hydroxide to form a mixture of the mono-, di- and tri-sodium salt of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate.

22. The process which comprises reacting 1-lower fatty acid ester of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate with a concentrated aqueous lower alkanolic alkali metal hydroxide to form a mixture of the mono-, di- and tri-alkali metal salt of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate, and reacting the latter compound with acid to form 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate.

23. The process which comprises reacting 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-acetate-4-phosphate with a concentrated aqueous lower alkanolic alkali metal hydroxide to form a mixture of the mono-, di- and tri-sodium salt of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate, and reacting the latter compound with acid to form 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate.

24. The process which comprises reacting 2-methyl-3-phytyl-1,4-naphthohydroquinone-1-propionate-4-phosphate with a concentrated aqueous lower alkanolic alkali metal hydroxide to form a mixture of the mono-, di- and tri-sodium salt of 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate, and reacting the latter compound with acid to form 2-methyl-3-phytyl-1,4-naphthohydroquinone-4-phosphate.

References Cited in the file of this patent

UNITED STATES PATENTS

2,345,690	Solmsen	Apr. 4, 1944
2,380,716	Baker	July 31, 1945
2,407,823	Fieser	Sept. 17, 1946
2,465,320	Bergel et al.	Mar. 22, 1949
2,913,477	Hirschmann	Nov. 17, 1959