The racemic beta lactone, which is an equimolecular mixture of the optically active beta lactone IV and its optical opposite, also reacts slowly at room temperature with methanol to give a racemic methyl ether VII, identical in structure with VI. Either of these methyl ethers can be obtained more readily by boiling the methanol solution of the beta lactone for twenty-four hours. No other products were found.

The isomeric optically active beta lactone V does not exhibit mutarotation in methanol and does not react with methanol under the conditions which produce the methyl ether VI.

Experimental Part

The resolution of α-phenyl-β-benzoylpropionic acid I has been adequately described in a previous paper.[4]

The methods employed in obtaining the bromo acids II and III as well as the beta lactones IV and V were identical with those used for the racemic substances.[2,3]

The polarimetric studies were carried out in methanol, using Pyrex polarimeter tubes described previously.[4] The methanol was distilled from oxalic acid through an all Pyrex system, using a good column.

The Methyl Ether VI.—The methyl ether was prepared either by allowing a methanol solution of beta lactone IV to stand until no further change in rotation of the solution was observed, or by boiling the solution for twenty-four hours. The methyl ether was then isolated in the usual way.

The analyses and physical properties of these new substances are given in the following tables:

Substance	Theory, % C	Theory, % H	Found, % C	Found, % H	$[\alpha]^{25}D$
II	57.7	3.9	57.8	4.1	+157°
III	57.7	3.9	57.3	4.0	+ 90°
IV	76.1	4.8	76.0	5.0	+155°[a]
V	76.1	4.8	76.0	5.0	+ 92°
VI	71.8	5.7	71.8	5.7	+153°
VII	71.8	5.7	71.7	5.9	

Substance[b]	Crystal form	Solubility	M. p., °C.	Mixed m. p., °C.[c]
III	Needles	v. s. ether; s. methanol	148	180
IV	Needles	s. ether, methanol; i. pet. ether	75	96
V	Needles	s. ether, sl. s. methanol	130	148
VI	Plates	v. s. ether; s. methanol; sl. s. pet. ether	132	117
VII	Plates	Same as VI	117	

[a] From Fig. 1 by extrapolation to zero time. [b] Bromo acid II has so far failed to give a crystalline solid. The rotation and analysis were run on the oil obtained by treating the lactone IV with 2% HBr in acetic acid. The identity of the oil is certain, however, since it regenerated lactone IV by the action of 1% aqueous sodium bicarbonate solution. [c] The optical opposite of each active compound derived from the dextro acid was prepared from the levo acid by identical methods. The mixed melting point in each case was the same as the melting point of the corresponding racemic compound. Moreover, the identity of each "synthetic" racemate was proved by a mixed melting point with the known racemic compound.

Summary

The two beta lactones formed from the beta bromo acids of dextro α-phenyl-β-benzoylpropionic acid behave quite differently in methanol. The one lactone exhibits mutarotation and also gives the methyl ether of α-phenyl-β-benzoyl-β-hydroxypropionic acid; the other lactone does not.

EXETER, NEW HAMPSHIRE RECEIVED FEBRUARY 8, 1941

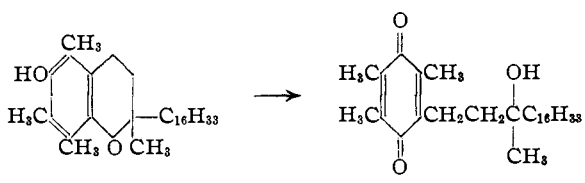
(4) Bickel, THIS JOURNAL, **60**, 928 (1938).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, MERCK & CO., INC.]

Interrelation of α-Tocopherol and α-Tocopherylquinone

BY M. TISHLER AND N. L. WENDLER

The oxidation of α-tocopherol has been the subject of much discussion ever since the sensitivity of this vitamin factor to oxidants was first demonstrated.[1] Under mild conditions ferric chloride or silver nitrate converts natural α-tocopherol into a yellow liquid which was designated by John and his collaborators as α-tocopherylquinone, II.[2]



α-Tocopherol, I II

The stability of the quinone to chromic oxide indicated that the hydroxyl group in the side chain is tertiary, confirming[2] the chroman structure, I, for α-tocopherol as proposed by Fernholz.[3] Kar-

(1) Olcott, *J. Biol. Chem.*, **107**, 471 (1934); Evans, Emerson and Emerson, *ibid.*, **113**, 319 (1936).

(2) (a) John, *Z. physiol. Chem.*, **252**, 222 (1938); (b) John, Dietzel and Emte, *ibid.*, **257**, 173 (1939); (c) John and Emte, *ibid.*, **261**, 24 (1939).

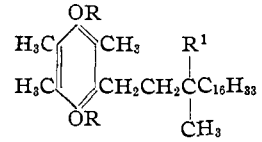
(3) Fernholz, THIS JOURNAL, **60**, 700 (1938).

rer and his collaborators[4] prepared this quinone by oxidizing α-tocopherol with gold chloride, and in a recent, more comprehensive paper[5] it is reported that the latter reagent yields a pure product, whereas ferric chloride and silver nitrate do not. The oxidation of α-tocopherol by ferric chloride was also studied by Golumbic and Mattill[6] who found that unless the oxidation is carried out at elevated temperatures the reaction is incomplete.

In connection with a study of naphthotocopherol,[7] we investigated the oxidation of α-tocopherol under mild conditions with results in agreement with the recent reports concerning this reaction.[5,6]

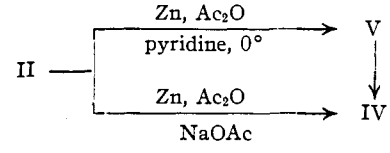
In the present work the quinone has been isolated from the reaction mixtures in much the same way as vitamin K_1 is separated in the synthesis developed by Fieser[8] and not by chromatographic adsorption which has been employed hitherto.[2,4,5] Our procedure takes advantage of the sparing solubility of the corresponding hydroquinone, III, in petroleum ether. From this solvent the hydroquinone is separated by centrifugation, washed several times with the same solvent to remove unchanged tocopherol or by-products, and then reconverted into α-tocopherylquinone by mild oxidation. The quinone isolated in this manner is very pure,[9] and its absorption characteristics are in excellent agreement with those of the best samples prepared by Karrer and Geiger.[5] Our samples show absorption in the region λ 245–280 mμ with a bicuspid peak between 263–269 mμ ($E_{mol.} = 18.7 \times 10^3$).

This rapid and quantitative method of isolating the quinone may be applied successfully to mixtures containing small amounts of this compound, and it forms the basis of a new procedure for isolating pure α-tocopherol from the reaction between phytol or phytyl bromide and 2,3,5-trimethyl-1,4-benzohydroquinone without the use of chromatographic adsorption or distillation as hitherto employed.[10] The crude reaction mixture remaining after removal of unchanged trimethylbenzohydroquinone is oxidized with ferric or gold chloride, the resulting mixture reduced and pure α-tocopherylhydroquinone, III, is isolated. The latter is heated with a dilute acid in the presence of a reducing agent to effect cyclization; pure α-tocopherol is obtained on extracting the reaction mixture with petroleum ether and concentrating the extracts. The high purity of samples isolated in this manner was established by analysis, absorption spectra, gold chloride titration[4] and bioassays.



III, R = H; R^1 = OH
IV, R = Ac; R^1 = OAc
V, R = Ac; R^1 = OH
VI, R = Ac; R^1 = Cl
VII, R = Ac; R^1 = Br

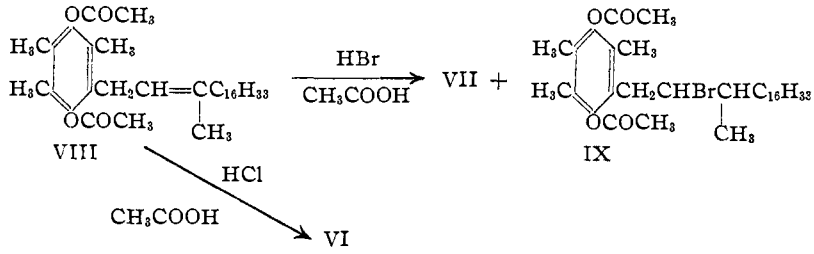
It has been found that when α-tocopherylquinone is reductively acetylated,[2] using zinc, acetic anhydride, and anhydrous sodium acetate at the boiling point, the hydroquinone triacetate, IV, is formed. Since tertiary carbinols usually are difficult to esterify, this fact is somewhat surprising. We found, however, that the tertiary hydroxyl group remains unattacked when the quinone is reductively acetylated with acetic anhydride, zinc dust, and pyridine at 0°. The crystalline diacetate, V, obtained by this milder treatment is converted into the triacetate, IV, by heating with acetic anhydride and anhydrous sodium acetate.



The tertiary character of the hydroxyl group in the side chain is further demonstrated by the behavior of the diacetate, V, toward acetyl chloride and acetyl bromide. With these reagents excellent yields of the corresponding halides VI and VII are obtained; with acetyl bromide the yield is quantitative, whereas with acetyl chloride the yield is slightly less.

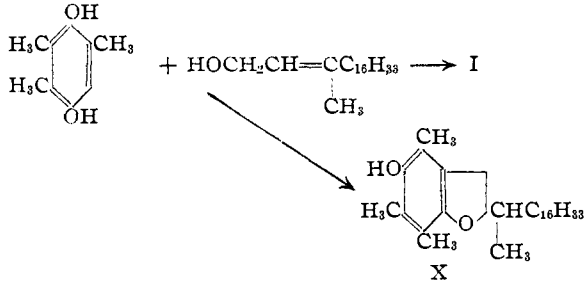
As further confirmation of the structures of the halides, VI and VII, syntheses from the diacetate of 2,5,6-trimethyl-3-phytyl-1,4-benzohydroquinone, VIII,[11] and the corresponding halogen hydrides were carried out.

(4) Karrer, Escher, Fritzsche, Killer, Ringier and Salomon, *Helv. Chim. Acta*, **21**, 951 (1938).
(5) Karrer and Geiger, *ibid.*, **23**, 455 (1940).
(6) Golumbic and Mattill, *J. Biol. Chem.*, **134**, 535 (1940).
(7) Fieser, Campbell, Fry and Gates, THIS JOURNAL, **61**, 2559 (1939); Tishler, Fieser and Wendler, *ibid.*, **62**, 1982 (1940).
(8) Fieser, *ibid.*, **61**, 2559 (1939).
(9) α-Tocopherylquinone shows no vitamin E activity, at a dose of 100 mg. A discussion of the biological assay of this substance is reported elsewhere (Tishler and Evans, *J. Biol. Chem.*, (in press) (1941).
(10) Karrer, Fritzsche, Ringier and Salomon, *Helv. Chim. Acta*, **21**, 520 (1938); Bergel, Jacob, Todd and Work, *J. Chem. Soc.*, 1382 (1938); Smith and Ungnade, *J. Org. Chem.*, **4**, 305 (1939).
(11) Fieser, Tishler, and Wendler, THIS JOURNAL, **62**, 2861 (1940).



Although the action of hydrogen chloride in acetic acid on the diacetate VIII gave exclusively a chloride identical with VI, as established by melting point and other criteria, the hydrogen bromide reaction was not as well defined. In the latter instance the solid melted about 7° lower than the bromide obtained from the diacetate of α-tocopherylhydroquinone, although its analysis was in agreement with the empirical formula. By fractional crystallization of this low melting bromide, there was obtained a compound identical with VII and an isomeric bromide, undoubtedly the secondary halide IX, which was not isolated in a pure form. That a difference exists between the reactions of the diacetate VIII and the two halogen hydrides is not surprising inasmuch as it is known that hydrogen chloride usually adds to olefins almost exclusively in accordance with Markovnikov's rule, whereas with hydrogen bromide abnormal addition also takes place.[12] It is noteworthy that the reaction between the diacetate VIII and hydrogen bromide in acetic acid is not materially influenced by the addition of benzohydroquinone to counteract the possible "peroxide effect."

In the synthesis of α-tocopherol from 2,3,5-trimethylbenzohydroquinone and phytol or phytyl halides, it has been deduced from model experiments[13] utilizing simpler allylic halides or alcohols that the chroman I is formed exclusively and that no isomeric coumaran X is present in the product.



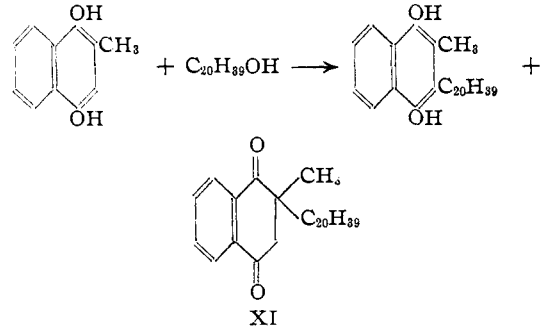
(12) Mayo and Walling, *Chem. Rev.*, **27**, 354 (1940).

(13) (a) Karrer, Escher and Rentschler, *Helv. Chim. Acta*, **22**, 1287 (1938); (b) Smith, Ungnade, Stevens, Christman, THIS JOURNAL, **61**, 2615 (1939); (c) Hurd and Hoffman, *J. Org. Chem.*, **5**, 212 (1940); (d) Smith, *Chem. Rev.*, **27**, 297 (1940).

In addition to the fact that interpretations from model experiments are not entirely free from objections, it should be noted that, in these experiments themselves, the yields of crystalline products are by no means quantitative and indicate at best the predominating course of reaction. The formation of a mixture of the isomeric bromides, VII and IX, from the diacetate of 2,5,6-trimethyl-3-phytyl-1,4-benzohydroquinone, VIII, even in the presence of benzohydroquinone as an antioxidant suggests that the formation of both chroman and coumaran structures in the synthesis of α-tocopherol is possible.

The fact that synthetic α-tocopherol is converted almost quantitatively into the tertiary halide, VII, by oxidation with gold chloride, followed by reductive acetylation and treatment with acetyl bromide, provides conclusive evidence that synthetic α-tocopherol is at least 95% chroman, I, and that very little, if any, of the isomeric coumaran can be present in this product.

The specific nature of the reaction between 2,5,6-trimethyl-1,4-benzohydroquinone and phytol is striking in view of the behavior of phytol and 2-methyl-1,4-naphthohydroquinone in the synthesis of vitamin K_1.[7] Although the reaction in the latter instance is carried out under milder conditions to avoid ring formation, a by-product X is formed in addition to vitamin K_1 hydroquinone.



A careful examination of the products obtained in the tocopherol syntheses, indicates that a substance analogous to XI is not present in any detectable amount.

Further confirmation of the homogeneity of α-tocopherol was obtained by applying the same reactions (tocopherol ⟶ dihydrodiacetobromide, VII) to natural α-tocopherol. The yield of the tertiary bromide from natural α-tocopherol

is about the same as with the synthetic (91%). The bromide obtained from the natural tocopherol, however, melts at 74° as compared to 75° for the synthetic bromide and its melting point could not be raised in spite of several recrystallizations. A more striking difference between the two bromides is revealed by a comparison of their optical rotations. The natural bromide has a small but definite rotation ($[\alpha]^{25}D - 2.5°$, whereas the synthetic bromide shows none. Although natural α-tocopherol shows very little or no optical activity,[1] the chemical difference between natural and synthetic α-tocopherol has been demonstrated by Karrer[14] who resolved the bromcamphor sulfonate of the synthetic *dl* mixture. It is interesting that this stereoisomerism is retained through the opening of the heterocyclic ring and the replacement of the tertiary hydroxyl group by halogen, both reactions involving operations about the asymmetric carbon atom of the chroman ring.

Experimental Part

Isolation of α-Tocopherylquinone, II.—The procedure applied to a large number of mixtures containing varying amounts of the quinone is illustrated by the following example.

One gram of pure synthetic α-tocopherol was oxidized with gold chloride by the method described by Karrer and Geiger.[5] The orange, oily product was suspended in 20 cc. methanol and to this was added 1 g. of sodium hydrosulfite dissolved in 2 cc. of water. The mixture was shaken for several hours and then added to a separatory funnel containing 30 cc. of water and 10 cc. of petroleum ether. After shaking the organic layer was separated and chilled at 0°, whereupon dihydrotocopherylquinone separated as a waxy solid. The mixture was centrifuged and the solid was washed several times with small amounts of petroleum ether by centrifugation until the solid was pure white and the supernatant liquor almost colorless. The hydroquinone was dissolved in 15 cc. of absolute ether and oxidized in the usual manner with silver oxide and anhydrous magnesium sulfate. By evaporating the ether under reduced pressure the product was obtained as a golden-yellow, viscous oil (0.96 g.).

Anal. Calcd. for $C_{29}H_{50}O_3$: C, 77.97; H, 11.26. Found: C, 77.90; H, 11.35.

Samples of α-tocopherylquinone isolated in this manner do not give the Emmerie and Engel test,[15] in contrast to α-tocopherol. The quinone, however, reacts with nitric acid in ethanol producing the red color characteristic of α-tocopherol,[16] a fact which must not be overlooked in the application of the Furter–Meyer assay procedure.

(14) Karrer, Fritzsche, Ringier and Salomon, *Helv. Chim. Acta*, **21**, 820 (1938); Karrer, Koenig, Ringier and Salomon, *ibid.*, **22**, 1139 (1939).

(15) Emmerie and Engel, *Rec. trav. chim.*, **57**, 1351 (1938).

(16) Furter and Meyer, *Helv. Chim. Acta*, **22**, 240 (1939).

Variations in the Oxidation of α-Tocopherol.—Employing the above procedure for isolating α-tocopherylquinone, the gold chloride and ferric chloride methods for oxidizing α-tocopherol were compared. The results are tabulated below:

α-Tocopherol	Oxidant	Method reference	Temp., °C.	Yield, %
Synthetic	$AuCl_3$	4, 5	25	95–97
	$FeCl_3$	2b, 6	75	90
	$FeCl_3$	6	25 (3 hr.)	75
Natural	$AuCl_3$	4, 5	25	95

Cyclization of α-Tocopherylhydroquinone to α-Tocopherol.—The cyclization of the hydroquinone has been reported previously.[2b] We found that the following procedure gives the best product. A mixture of 3 g. of pure α-tocopherylquinone, 30 cc. of dioxane, 5 cc. of concd. hydrochloric acid, and 7 g. of stannous chloride was boiled for four hours. The mixture became colorless within a few minutes and remained so during the heating. The solution was diluted with water, extracted with petroleum ether, washed well with water, dried over anhydrous magnesium sulfate, and concentrated under a stream of nitrogen to a pale straw-colored product weighing 2.8 g.

Anal. Calcd. for $C_{29}H_{50}O_2$: C, 80.86; H, 11.70. Found: C, 80.64; H, 11.88; gold chloride titration, 102 ± 3%.

Isolation of α-Tocopherol from Synthesis.—Phytol and 2,5,6-trimethyl-1,4-benzohydroquinone were condensed[13b] and after the removal of unchanged trimethylbenzohydroquinone,[13b] the product was oxidized with gold chloride, and the tocopherylhydroquinone was isolated in a pure form. The hydroquinone was then cyclized in dioxane in the presence of stannous chloride and hydrochloric acid, and the product was isolated by the above procedure. The yield of α-tocopherol isolated by this method was the same as that obtained by distillation under high vacuum.[13b]

2,5,6-Trimethyl-3-(γ-hydroxy-β,γ-dihydrophytyl)-1,4-benzohydroquinone Diacetate, V.—A mixture of 1 g. of α-tocopherylquinone, 1 g. of zinc dust, 10 cc. of acetic anhydride, and 6 drops of pyridine was stirred by hand at 0° for one hour. After separating the zinc, the mixture was diluted with ice water and extracted with ether. The ether extract was washed with water, sodium bicarbonate solution and dilute hydrochloric acid. After drying over anhydrous magnesium sulfate, the ether solution was concentrated to an oil which slowly crystallized. The diacetate was recrystallized from a small amount of ethanol, in which it is quite soluble. The diacetate separates as needles melting at 65°.

Anal. Calcd. for $C_{33}H_{56}O_5$: C, 74.39; H, 10.58. Found: C, 74.30; H, 10.71.

The diacetate on boiling with acetic anhydride, sodium acetate and acetic acid yields the corresponding triacetate, IV (m. p. 74–75°; found: C, 73.18; H, 10.24), first prepared by John[2a] from α-tocopherylquinone by reductive acetylation.

Conversion of Synthetic α-Tocopherol to 2,5,6-Trimethyl-3-(γ-bromo-β,γ-dihydrophytyl)-1,4-benzohydroquinone Diacetate, VII.—One gram of synthetic α-tocopherol was oxidized with gold chloride and subjected to reductive acetylation by the method outlined above. Without attempting to crystallize the product,

the oily diacetate V was dissolved in 5 cc. of acetyl bromide and allowed to stand at room temperature for fourteen hours. The mixture was then added cautiously to ice water and the product was extracted with ether. After washing the ether extracts with water, and aqueous sodium bicarbonate, the solution was concentrated to an oil. On the addition of 1 cc. of ether and 4 cc. of methanol crystallization set in. The bromide (1.30 g.) separates as microscopic platelets which melt at 75–76°.

Anal. Calcd. for $C_{33}H_{55}O_4Br$: C, 66.56; H, 9.30. Found: C, 66.68; H, 9.41.

The bromide was recrystallized by dissolving in a small amount of warm ether and adding two volumes of methanol. Recrystallization did not give a product with a different melting point. A solution of 100 mg. of the bromide in 1 cc. of carbon tetrachloride showed no optical rotation.

Natural α-tocopherol (0.5 g.) treated in the same way gave 0.63 g. of the bromide melting at 74–75°. Recrystallizations from ether–methanol did not give a product with a higher melting point.

Anal. Calcd. for $C_{33}H_{55}O_4Br$: C, 66.56; H, 9.30. Found: C, 66.51; H, 9.28.

A solution of 100 mg. of this bromide in 1 cc. of carbon tetrachloride gave $[\alpha]^{25}D$ −2.5°.

2,5,6-Trimethyl-3-(γ-chloro-β,γ-dihydrophytyl)-1,4-benzohydroquinone Diacetate, VI.—One gram of synthetic α-tocopherol was converted into the oily diacetate, V, and then allowed to stand with acetyl chloride at room temperature for fourteen hours. The product was worked up as with the corresponding bromide. The chloride (1.20 g.) was recrystallized from ether–methanol and melted at 76–77°. When warmed with alcoholic silver nitrate, silver chloride precipitates.

Anal. Calcd. for $C_{33}H_{55}O_4Cl$: C, 71.88; H, 10.06. Found: C, 71.99; H, 10.02.

Addition of Hydrogen Chloride and of Hydrogen Bromide to 2,5,6-Trimethyl-3-phytyl-1,4-benzohydroquinone Diacetate.—One gram of the diacetate[11] was added to 25 cc. of a saturated solution of hydrogen chloride in acetic acid. After standing in the refrigerator for fourteen hours, the solution was added to ice-water and worked up as in the case of the acetyl chloride reaction. The yield of chloride was 1.03 g. and it melted at 75–76°. A sample recrystallized from ether–methanol melted at 76–77° and showed the same crystal structure as the chloride previously described (fine microscopic needles). A mixed melting point of the two chlorides showed no depression. Found: C, 71.78; H, 9.99.

The addition of hydrogen bromide to the phytyl diacetate was carried out in a solution of 40% dry hydrogen bromide in acetic acid. As a two phase system was formed, the mixture was shaken for eighteen hours, during which time solid separated. The product, obtained in almost quantitative yield, appeared poorly defined when examined under the microscope and it melted at 67–68°. *Anal.* Found: C, 66.62; H, 9.43. A careful fractionation from ether–methanol and from ether separated the mixture into a less soluble bromide (m. p. 75–76°) which showed no melting point lowering when mixed with the previously described bromide (found: C, 66.57; H, 9.34), and a more soluble fraction melting at 65–66°.

When benzohydroquinone (0.05 g.) was added to the reaction mixture made up of 1 g. of the diacetate in 20 cc. of 40% hydrogen bromide in acetic acid, the product showed the same melting point (67–68°).

Acknowledgment.—The authors wish to express their thanks to Messrs. Douglass F. Hayman, Wilhelm R. Reiss and R. N. Boos for the microanalyses and to Mr. W. A. Bastedo, Jr., for carrying out the physical measurements.

Summary

1. A procedure for isolating α-tocopherylquinone from reaction mixtures has been developed which provides a new method of preparing pure synthetic α-tocopherol.

2. α-Tocopherylquinone on reductive acetylation at low temperatures forms the diacetate of 2,5,6-trimethyl-3-(γ-hydroxy-β,γ-dihydrophytyl)-1,4-benzohydroquinone, which on treatment with acetyl chloride and acetyl bromide yields the corresponding tertiary halides. The two halides were also synthesized by the addition of the corresponding halogen hydrides to the diacetate of 2,5,6-trimethyl-3-phytyl-1,4-benzohydroquinone. The almost quantitative conversion of synthetic α-tocopherol into the diacetate of 2,5,6-trimethyl-3-(γ-bromo-β,γ-dihydrophytyl)-1,4-benzohydroquinone establishes the fact that synthetic α-tocopherol contains over 95% of the chroman form. Natural α-tocopherol gives a 91% yield of the tertiary bromide which in contrast to the bromide obtained from synthetic tocopherol shows optical activity.

RAHWAY, NEW JERSEY RECEIVED FEBRUARY 6, 1941