[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

THE CHEMISTRY OF VITAMIN E. IV. THE SYNTHESIS OF TOCOPHEROLS[1, *]

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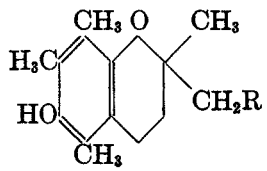
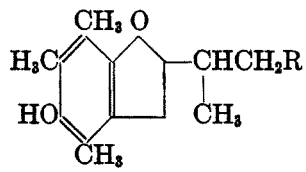
The first recorded synthesis of *dl*-α-tocopherol (I, R = 3,7,11-trimethyldodecyl-1), was that of Karrer, Fritzsche, Ringier, and Salomon.[2]



I



II

These authors, by heating trimethylhydroquinone, phytyl bromide and anhydrous zinc chloride in petroleum ether, obtained the product "in almost quantitative yields."† After chromatographing twice, the substance was a light-yellow oil which had the proper composition, and which was biologically active 100 per cent in 6 mg. doses.

A second synthesis of α-tocopherol was achieved by Bergel, Jacob, Todd, and Work[3] who first used phytol, trimethylhydroquinone, and zinc chloride, and then later modified the synthesis by adding decalin as the solvent.

In our work, we found that much better results were obtained by conducting the condensation in the absence of any catalyst or solvent. Under

[1] Papers I, II, III: *Science*, **88**, 37, 38, 40 (1938).

* Presented (in part) at the 96th meeting of the American Chemical Society, Milwaukee, Sept. 5–9, 1938.

[2] KARRER, FRITZSCHE, RINGIER, AND SALOMON, *Helv. Chim. Acta*, **21**, 520 (1938).

† The nomenclature of derivatives of phytol does not follow accepted rules. Thus the unsaturated alcohol $C_{20}H_{40}O$ from chlorophyll, is called phytol; the saturated hydrocarbon, $C_{20}H_{42}$ is phytane; the diene $C_{20}H_{38}$ is phytadiene. The name phytyl should properly belong to the alkyl group $C_{20}H_{41}$ corresponding to phytane, while the radical $C_{20}H_{39}$ should be called phytenyl and the alcohol $C_{20}H_{40}O$, phytenol. It appears to be accepted practice in this field to use phytol for $C_{20}H_{40}O$; phytyl for the corresponding radical $C_{20}H_{39}$; hydrophytyl or phytanyl for the radical $C_{20}H_{41}$ corresponding to hydrophytyl alcohol or phytanol, $C_{20}H_{42}O$, while the names phytane, phytene, and phytadiene are used for the saturated, ethylenic, and diethylenic hydrocarbons respectively.

[3] (*a*) BERGEL, JACOB, TODD, AND WORK, *Nature*, **142**, 36 (1938); (*b*) *J. Chem. Soc.*, **1938**, 1382.

these circumstances, excellent yields of a fairly pure product are obtained, and what is more important, this product can be purified by high-vacuum distillation alone. This avoids the chromatographic adsorption, which our earlier experiments had shown to give a distinctly inferior product and to entail much loss. Recently Isler[4] has also stressed this point; he found, as we have, that synthetic *dl*-α-tocopherol is very susceptible to oxidation by the air. But Isler also discovered this susceptibility to be increased markedly when the substance is spread over a large surface as it is in the chromatograph tube, or when it is mixed with powders of any sort.

TABLE I

PREPARATION OF PHYTYL BROMIDE

EXPT. NO.	PHYTOL (G.)	Na_2SO_4 (G.)	HBr ABSORBED (G.)	YIELD OF BROMIDE (G.)
1	5.35	0.5	1.94	6
2	5.36	0.5	2.16	6.5
3	10.80	1.8	4.91	13.0

TABLE II

SYNTHESIS OF TOCOPHEROLS

HYDROQUINONE,	G.	PHYTYL BROMIDE (G.)	TEMP., °C.	TIME (HRS.)	PRODUCT (G.)
Trimethyl-	2.0	5.0	125	4	2.44
Trimethyl-	4.0	12.0	105	5	6.0
Trimethyl-	5.0	13.0	105	5	3.0[a]
p-Xylo-	2.0	6.0	105	2.5	None
p-Xylo-	2.0	6.0	150	5	[b]
m-Xylo	2.0	6.5	120	3	[b]

[a] Two grams of hydroquinone was recovered.

[b] The products from these reactions could not be weighed as the material was collected in several small ampoules. Judging from the appearance, the yields were quite good.

Since the beginning of the work on the tocopherols, two structural formulas have been under discussion. The difference between these formulas lies in the size of the hetero ring. In his earlier work, Karrer[2,5] although mentioning both structures, chose II (R = 3,7,11-trimethyldodecyl-1) as the most likely, basing his choice upon the fact that allyl phenol actually does cyclize to a coumaran. But as will be shown in a later paper, allyl bromide itself and γ,γ-disubstituted allyl bromides behave entirely differently in these condensations, the latter giving chromans; hence the

[4] ISLER, *Helv. Chim. Acta*, **21**, 1756 (1938).

[5] KARRER, SALOMON, AND FRITZSCHE, *ibid.*, **21**, 309 (1938).

correct substance to use as an analogue of phytyl bromide is not allyl bromide itself, but a γ,γ-disubstituted allyl bomide. That α-tocopherol is a chroman (I) was first suggested seriously by Fernholz, and that it actually has this structure has been amply shown by the beautiful oxidation experiments of Fernholz[6] and by the elegant degradative experiments of W. John and his collaborators.[7] Recently Karrer[8] reported what appeared to be convincing evidence that trimethylhydroquinone and crotyl bromide condensed to give a chroman, while allyl bromide and the hydroquinone gave a coumaran. This evidence was based upon the fact that both compounds, on gentle oxidation, gave tetrasubstituted quinones, and these quinones, in turn, both gave positive iodoform reactions, indicating that both had, in a side-chain, the group—$CHOHCH_3$. Later[9] when it was discovered that duroquinone itself gave a positive iodoform reaction, this evidence became of no value in deciding between the chroman and coumaran structures. Very recently, however, Karrer and Escher on the basis of the results of a careful oxidation of this compound, have concluded that it is definitely a chroman.[10]

The English workers likewise, while recognizing the possibility of structure II, have preferred structure I, and have considered the analogy between allyl bromide and phytyl bromide to be invalid.[3, 11]

Five different tocopherols have reported in the literature, known as α-, β-, γ-, cumo-, and neo-tocopherols. Cumo-tocopherol, reported by John[12] was later shown by him[13] to be identical with β-tocopherol. Karrer's neo-tocopherol was also found to be identical with β-tocopherol.[5] There remain, then, only three natural tocopherols definitely established as chemical entities, namely, α-, β-, and γ-tocopherols. Of these, α-tocopherol has the composition $C_{29}H_{50}O_2$, while β- and γ-tocopherols are isomers and have the composition $C_{28}H_{48}O_2$. Emerson[14] using the degradative method of Fernholz[6] has shown that the same oxidation products are obtained from all three tocopherols. This work establishes that the hetero ring and the aliphatic side-chains are the same in all three toco-

[6] FERNHOLZ, *J. Am. Chem. Soc.*, **60**, 700 (1938); see also EMERSON, *Science*, **88**, 40 (1938).

[7] JOHN, *Z. physiol. Chem.*, **252**, (*a*) 208, (*b*) 222 (1938).

[8] KARRER, ESCHER, FRITZSCHE, KELLER, RINGIER, AND SALOMON, *Helv. Chim. Acta*, **21**, 939 (1938).

[9] KARRER AND JENSEN, *ibid.*, **21**, 1622 (1938).

[10] KARRER AND ESCHER, *ibid.*, **22**, 264 (1939).

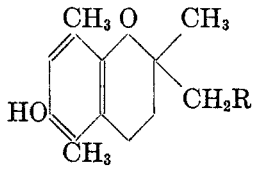
[11] (*a*) BERGEL, TODD, AND WORK, *J. Chem. Soc.*, **1938**, 253; (*b*) BERGEL, JACOB, TODD, AND WORK, *Nature*, **141**, 646 (1938).

[12] JOHN, *Z. physiol. Chem.*, **250**, 11 (1937).

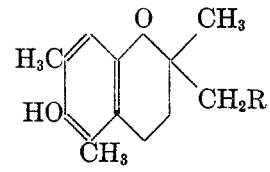
[13] JOHN, *Ibid.*, **252**, 201 (1938).

[14] EMERSON, *J. Am. Chem. Soc.*, **60**, 1741 (1938).

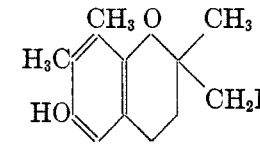
pherols; the difference then must lie in the number and position of the methyl groups in the benzene ring. Theoretically there could exist three "xylo-tocopherols", III, IV, and V. (R as in I and II) β-Tocopherol gave



III



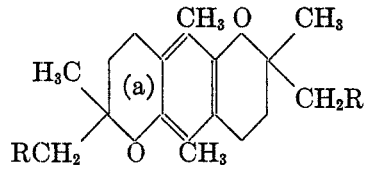
IV



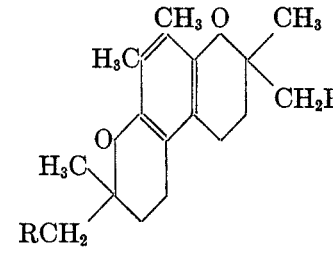
V

trimethylhydroquinone on pyrolysis, and 2,5-dimethylphenol on treatment with hydriodic acid.[7a] This establishes the structure of β-tocopherol as III; that there is one free position in the benzene ring in β-tocopherol is shown also by the fact that it can be allylated.[15] γ-Tocopherol must then have the structure IV or V; at the present time it is not possible to decide this point.

The reaction between phytyl bromide and *p*- and *m*-xylohydroquinones leads to mixtures. This was rather to be expected, because of the high reactivities of the allylic halide, phytyl bromide, and of the ring in the polymethyl hydroquinones. In Karrer's experiments[15, 16] the condensation of phytyl bromide with *p*- and *o*-xylohydroquinones gave rise to difficultly separable mixtures which consisted for the most part of the double chromans VI and VII (R as in I and II), respectively, although the tocopherols III and IV were present.



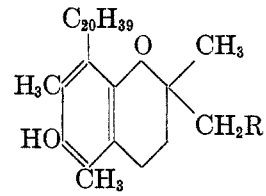
VI



VII

Although *m*-xylohydroquinone cannot give a double chroman, the vacant position in the ring can readily be attacked by such an active halide as phytyl bromide. The two products from this hydroquinone then, are the tocopherol IV and its phytyl derivative VIII.

[15] KARRER, FRITZSCHE, RINGIER, AND SALOMON, *Helv. Chim. Acta*, **21**, 820 (1938).
[16] KARRER AND FRITZSCHE, *ibid.*, **21**, 1234 (1938).



VIII

Moreover, there is the possibility also of the formation of substances analogous to VIII in the case of *p*- and *o*-xylohydroquinones. This would probably be the case when *p*-xylohydroquinone is used, for in the double chroman VI it is not possible to distribute the double bonds so that the two chroman rings are alike, and some of the evidence from a study of the Mills-Nixon effect indicates that a 6-membered ring, such as (a) in VI, is subject to considerable strain whereas a similarly constructed 5-membered ring is nearly strainless. It may well be that this effect is sufficient to overcome the tendency of the γ,γ-disubstituted allyl group to give a chroman, and that ring (a) in VI is actually part of a coumaran system, or that there is a resistance to the closing of the second ring, whatever its size, so that analogs of VIII result.‡

In our work, two xylohydroquinones, para and meta, were used. Condensation of phytyl bromide with *p*-xylohydroquinone gave a product which boiled at 145–150° in a molecular still (10^{-6} mm.) and which was noticeably more viscous than α-tocopherol. The product is almost insoluble in cold concentrated sulfuric acid although a red color develops in the oil and at the interphase, while α-tocopherol is soluble in sulfuric acid, giving a characteristic yellowish-green solution. The product gave a positive phenol reaction (Folin test). The substance was not obtained completely pure, but the analysis agreed better with the composition $C_{28}H_{48}O_2$ (III) than with $C_{48}H_{86}O_2$ (VI). When pyrolyzed, according to the procedure of Fernholz[6] a sublimate was obtained which consisted of a mixture of hydroquinones and which began to melt at about 130°. We conclude from these results that the product consisted of a mixture of III and VI.

When condensed with phytyl bromide, *m*-xylohydroquinone gave a product which boiled slightly lower than α-tocopherol. The low boiling point does not indicate that two phytyl groups have reacted, but rather only one, and that the product is essentially IV. Work on this product is still in progress and will be reported in a later paper. The product is biologically active, however, in 20- and 100-mg. doses.

‡ Dr. R. T. Arnold, of this laboratory, has had under way for some time a comprehensive investigation of the Mills-Nixon effect as it applies to heterocyclic compounds, and publications in this field will appear soon.

EXPERIMENTAL

Preparation of phytyl bromide.—Phytol was mixed with one-tenth of its weight of anhydrous sodium sulfate, and the mixture was cooled and saturated at 0° with dry hydrogen bromide. After standing overnight at 0°, the mixture was shaken with water and ether. The ether layer was separated, washed with water until the washings were neutral to litmus, then dried over sodium sulfate. The drying agent was removed, and the solvent was evaporated under reduced pressure. The product was used at once since it decomposes on standing, even at room temperature.

Anal. Calc'd for $C_{20}H_{39}Br$: C, 66.79; H, 10.96.

Found: (expt. 1) C, 65.32; H, 10.81; (expt. 2) C, 66.38; H, 9.10.

It is not possible to distil phytyl bromide, even under high vacuum, because it decomposes largely even at 75° to give phytadiene. A sample of such a distillate was analyzed: found C, 80.0; H, 12.88: calc'd for $C_{20}H_{38}$: C, 86.33; H, 13.66.

Synthesis of tocopherols.—The preparation of α-tocopherol will be described, and the results of other experiments will be given in tabular form. For small amounts of materials, trimethylhydroquinone and a slight excess of phytyl bromide are placed in the bottom of a Pyrex tube and intimately mixed. The tube is sealed and carefully heated in an upright position. After cooling, the tube is opened carefully with a torch, as there is considerable pressure of hydrogen bromide. The product is washed out with ether (peroxide-free) and dried over sodium sulfate. After removal of the drying agent, the solvent is evaporated and the residue is distilled under high vacuum (10^{-6} mm.) in a molecular pot still. In the distillation, after degassing, unchanged hydroquinone sublimes at first; thereafter it is necessary to lower the temperature somewhat in order to prevent superheating. Between 115 and 125° most of the phytadiene distills; at 135 to 140° small amounts of impure material distil, and then the pure α-tocopherol comes over at 140° (10^{-6} mm.).

For large amounts of material, the reaction was carried out in a bomb with a glass liner, under a pressure of 1100 lbs. of hydrogen, at 105° for 5 hours.

Racemic α-tocopherol.—The substance is a pale, straw-colored liquid, fairly viscous. It oxidizes quite readily when exposed to air; the oxidation becomes quite apparent if hydroquinone is present, for the material turns red and darkens quickly wherever it touches a crystal of hydroquinone in the distilling apparatus.

Anal. Calc'd for $C_{29}H_{50}O_2$: C, 80.85; H, 11.71.

Found: C, 80.75, 80.91; H, 11.69, 11.82.

The substance formed an allophanate which melted at 168–170° and which, when mixed with natural α-tocopherol allophanate (m.p. 157–160) melted between the two. The yield of allophanate was not good.

Anal. Calc'd for $C_{31}H_{52}N_2O_4$: C, 72.03; H, 10.15.

Found: C, 72.09, 72.28; H, 10.00, 10.00.§

The substance gives a positive phenol test (Folin); rapidly reduces silver nitrate in methanol; gives a bright greenish-yellow color when it dissolves in cold sulfuric acid. Biologically, the substance was active in single doses of 3 and 7 mg.**

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§ The analysis of α-tocopherol, and the preparation and analysis of the allophanate were carried out by Messrs. Emerson and Hayman in the Laboratories of Merck & Co., Inc., Rahway, N. J.

** All of the bio assays connected with this work were carried out by Dr. H. M. Evans of the University of California.

The absorption spectrum of this product was practically indistinguishable from that of natural α-tocopherol.††

p-*Xylotocopherol.*—The product boiled at 145–150° in the molecular still, was light yellow and very viscous. It was insoluble in cold, concentrated sulfuric acid, and a red color developed at the interphase. The substance gave a positive phenol test (Folin) and reduced silver nitrate in methanol. It was not completely soluble in Claisen's alkali.

Anal. Calc'd for $C_{28}H_{48}O_2$: C, 80.69; H, 11.62.
Found: C, 79.49; H, 11.84.

A small amount of the material was pyrolyzed by heating it to 355–360° under carbon dioxide for several hours. A crystalline sublimate and a red liquid were obtained. The white sublimate after washing with petroleum ether, melted over a wide range, beginning at 130°. It was undoubtedly a mixture of hydroquinones.

m-*Xylotocopherol.*—The crude product was extracted with ether, and unchanged hydroquinone was washed out with 1% potassium hydroxide. The ether layer was then washed with water and dried over sodium sulfate. The solvent was removed, and the residue distilled in the molecular still. It boiled at 120–130° (10^{-6} mm.). The pale-yellow oil gave a positive phenol test (Folin), reduced silver nitrate in methanol, and gave a yellow to red color with sulfuric acid. Although this product was biologically active in 100-mg. doses, it was not analytically pure and contained phytadiene.

SUMMARY

1. This paper contains a description of a synthesis of certain tocopherols having vitamin E activity.

2. The nature of the byproducts formed in these syntheses is discussed.

†† These curves were determined by Dr. T. J. Webb, in the Laboratories of Merck & Co., Inc. and will form the subject of a later communication.