periodic and pointwise almost periodic transformations.

Lloyd Girton Humphreys (Ph.D. in psychology, Stanford University, 1938). To work at Yale University. Subject: The relationship of simple reinforcement and success as factors in the acquisition and extinction of conditioned responses.

Willis Eugene Lamb, Jr. (Ph.D. in physics, University of California, 1938). To work at the University of Wisconsin. Subject: Problems in nuclear physics.

Raymond Braislin Montgomery (D.Sc. in meteorology, Massachusetts Institute of Technology, 1938). To work at the Institut für Meereskunde, Berlin, Germany. Subject: Isentropic analysis of the major circulation phenomena of the upper layers of the southern North Atlantic Ocean.

Keith Roberts Porter (Ph.D. in biology, Harvard University, 1938). To work at Princeton University. Subject: The development of androgenetic frog embryos.

Van Rensselaer Potter (Ph.D. in agricultural chemistry, University of Wisconsin, 1938). To work at the Biokemiska Institutet, Stockholm, Sweden. Subject: A study of the physiological action of the antipellagra vitamin (nicotinic acid).

Hermann Rahn (Ph.D. in embryology genetics, University of Rochester, 1938). To work at Harvard University. Subject: Cytology and physiology of the bird pituitary.

Birdsey Renshaw (Ph.D. in zoology, Harvard University, 1938). To work at the Rockefeller Institute for Medical Research. Subject: The activity of the nervous system investigated with microelectrodes.

Lewis Joseph Sargent (Ph.D. in organic chemistry, University of Edinburgh, 1938). To work at the University of Virginia. Subject: To attempt the synthesis of oestrogenic substances.

Hurst Hugh Shoemaker (Ph.D. in zoology, University of Chicago, 1938). To work at Stanford University. Subject: A study of hormonal influences on position in the social hierarchy among canaries.

Lyman Spitzer, Jr. (Ph.D. in physics, Princeton University, 1938). To work at Harvard College Observatory. Subject: The structure of stellar atmospheres.

David P. Stevenson (Ph.D. in chemistry, Princeton University, 1938). To work at California Institute of Technology. Subject: The electric diffraction investigation of the structure of oximes and related molecules.

Gustav McKee Watkins (Ph.D. in plant cytology, Columbia University, 1935). To work at the Bureau of Plant Industry, Washington, D. C. Subject: A study of host-parasite relations in the *Phymatotrichum* root rot disease.

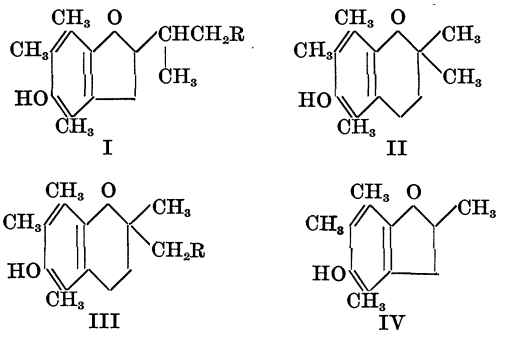
Frederick Taylor Wolf (Ph.D. in botany, University of Wisconsin, 1938). To work at Harvard University. Subject: The biology and cytology of the aquatic Phycomycetes.

ROSS G. HARRISON,
Chairman, National Research Council

SPECIAL ARTICLES

THE CHEMISTRY OF VITAMIN E. I. THE STRUCTURE AND SYNTHESIS OF α-TOCOPHEROL

IN a recent publication Karrer[1] has reported the synthesis of α-tocopherol from trimethylhydroquinone, phytylbromide and zinc chloride. On the basis of a supposed analogy in this reaction between phytylbromide and allylbromide, Karrer has assigned to the vitamin the structure I (R = perhydrofarnesyl), with a 5-membered hetero ring. It is true that the reaction between trimethylhydroquinone and allylbromide leads to IV, mp. 123–123.5 (uncorr.) with a 5-membered hetero ring. We prepared IV in this manner, and also by reduction of the corresponding coumarone which was obtained from trimethylquinone and acetoacetic ester;[2] the two syntheses led to the same substance, which is certainly, therefore, a coumarane. Bergel, Jacob, Todd and Work[3] have also synthesized IV, mp. 124–125°. Several years ago, Claisen[4] showed that, while phenols and allyl bromide condensed to give coumaranes, the use of γ,γ-disubstituted allyl bromides led to chromanes. We have prepared II in three different ways: (a) from trimethylhydroquinone and γ,γ-dimethylallylbromide; (b) from trimethylhydroquinone and isoprene, and (c) from 5,7,8-trimethyl-6-hydroxy-3,4-dihydrocoumarin[5] and methyl magnesium iodide. All three syntheses led to the same crystalline product, mp., and mixed mp., 94–94.5°. The third synthesis could lead only to a chromane; therefore the product of all these syntheses is II. If, therefore, the analogy is correct and phytyl bromide is regarded as a γ,γ-disubstituted allylic bromide, it should react with



[1] *Helv. Chim. Acta.*, 21: 520, 1938.

[2] Smith and MacMullen, *Jour. Am. Chem. Soc.*, 58: 629, 1936.

[3] *Nature*, 141: 646, 1938.

[4] *Ann.*, 442: 228, 1925.

[5] Smith and Denyes, *Jour. Am. Chem. Soc.*, 58: 304, 1936.

trimethylhydroquinone to give the chromane III (R is perhydrofarnesyl) and not the coumarane I.

We have synthesized α-tocopherol from trimethylhydroquinone and phytylbromide without a catalyst, and also from the hydroquinone and phytadiene. The products were distilled under high vacuum (10^{-6} mm) and they are thick, viscous, nearly colorless oils. The analyses of the samples of α-tocopherol prepared and purified as outlined (the products were not chromatographed), agree fairly well with the theoretical values. The sample of α-tocopherol prepared from phytylbromide gave an allophanate which melted at 168–170°; when mixed with the allophanate (mp. 157–160°) derived from natural α-tocopherol, shows a melting point between the two.[6]

Compounds II and IV have been tested biologically and found to be completely inactive in doses of 50 mg.[7] Several of our synthetic compounds, both coumaranes and chromanes, which have been examined in the laboratories of Merck and Company, Inc., show absorption curves strikingly similar to that of α-tocopherol. John[8] has also shown that α-tocopherol is either a coumarane or a chromane, and he has succeeded in opening the hetero ring without the loss of any carbon atoms. He states, however, that his work does not enable a decision to be made between the 5- and 6-membered hetero ring, nor as to the exact location of the aliphatic side chain attached to the ring.

Our syntheses of the pentamethyl-6-hydroxy chromane (II) and the proof of the structure of this compound, together with the two analogous syntheses of α-tocopherol, indicate to us that the structure proposed by Fernholz[9] for α-tocopherol is the correct one; that is, the vitamin is a chromane with two substituents in the α-position.[10]

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THE CHEMISTRY OF VITAMIN E. II. BIOLOGICAL ASSAYS OF VARIOUS SYNTHETIC COMPOUNDS[1]

THE fact that more than a single chemical substance can function as Vitamin E was demonstrated with the isolation of alpha, beta and gamma tocopherol. This need not occasion surprise, since it is already well established that several chemical entities function as Vitamins A and D, respectively, and the same phenomena have been discovered as regards the hormones—the so-called endocrine principles, for example, estrogenic activity.

Since the detection by Fernholz[2] of durohydroquinone amongst the products of the pyrolysis of alpha tocopherol, biological study of this substance and its related compounds for the detection of Vitamin E activity was urgently indicated.

PARENT SUBSTANCES

Hydroquinone itself was fed at the 100 mg level and though sufficiently toxic to be lethal at this level for three of the animals, did not confer fertility upon four animals in which the phenomena of insemination, implantation and resorption were all typically established. As regards durohydroquinone, one is at some disadvantage because of the difficulty of its solution. After various preliminary expedients, we at last hit on the plan of giving 4 cc of water by stomach tube, followed by a solution of durohydroquinone in 95 per cent. ethyl alcohol. Durohydroquinone was thus fed at 50, 100 and 500 mg levels. While no litters were secured at the 50 mg level, a single excellent litter resulted at the 100 mg level, though there were four clear resorptions at the same level. Both the animals to whom we succeeded in feeding a total of 0.5 g of durohydroquinone as ten 50 mg doses cast litters.

ETHERS OF DUROHYDROQUINONE[3]

The following ethers of durohydroquinone were fed: mono-cetyl, mono-octadecyl, mono-do-decyl and mono-(n-nonadecyl). At the lowest level fed (50 mg) two of four of the animals fed the mono-cetyl ether of durohydroquinone cast small, somewhat undersized, but living, litters. Our experience with the same substance at the 100 mg level demonstrated that this partial result at 50 mg was exceptional, since only two of eight littered at 100 mg. Two other ethers, namely, the mono-do-decyl ether and the mono-nona-decyl ether, showed some potency at the 100 mg level. Four

[6] We are greatly indebted to Dr. O. H. Emerson and to the Research Laboratory of Merck and Company, Inc., for the preparation and comparison of these allophanates.

[7] This work as well as the bioassay of our synthetic tocopherol has been done by Dr. H. M. Evans, of the University of California. See Dr. Evans' paper in this issue of SCIENCE.

[8] *Zeits. für Physiol. Chem.*, 252: 222, 1938.

[9] *Jour. Am. Chem. Soc.*, 60: 700, 1938.

[10] Note added to proof: Since this paper was written, Dr. John has very kindly sent us a reprint of his note in *Naturwiss.* 26: 366, 1938, to which we had not previously had access. Based upon his very elegant degradative work on α-tocopherol, John has reached the same conclusion with regard to the structure of the vitamin as we have, namely, the substance is a chromane with two substituents in the α-position (III).

[1] Aided by grants from the Board of Research and from the Department of Agriculture of the University of California, from Merck and Company, Inc., Rahway, N. J., and the Rockefeller Foundation, New York. Assistance was rendered by the Works Progress Administration, Project No. 8823 A-5. The following materials were generously contributed: cod liver oil by E. R. Squibb and Sons, and brewers' yeast by The Vitamin Food Company of New York.

[2] E. Fernholz, *Jour. Am. Chem. Soc.*, 59: 1154, 1937.

[3] We wish to thank Dr. E. Fernholz and Mr. J. Finkelstein for these preparations.