list of the derivatives of *o*-hydroxybenzylacetone, and the peculiar behavior of these compounds has been discussed.

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

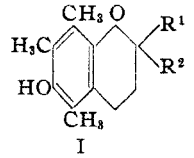
The Chemistry of Vitamin E. XXXIII. A New Synthesis of 6-Hydroxychromans, Including α-Tocopherol[1]

BY LEE IRVIN SMITH AND HENRY C. MILLER[2]

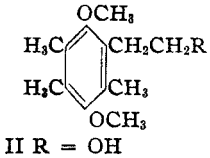
By degradative methods, several workers have shown that α-tocopherol, the most active vitamin E factor, possesses structure I, $R^1 = CH_3$; $R^2 = C_{16}H_{33}$.[3] However, the only methods so far available for synthesis of α-tocopherol—namely, condensation of phytol or its derivatives with trimethylhydroquinone—do not require, in themselves, that α-tocopherol should possess a chroman structure. Model researches have shown[4] that when condensed with hydroquinones, simple γ,γ-disubstituted allylic alcohols or halides give chromans exclusively while the γ-monosubstituted analogs give both chromans and coumarans, and the unsubstituted allyl alcohols or halides give only coumarans. From the synthetic point of view, structure I for α-tocopherol rests entirely upon the assumption that phytol and its derivatives, which are γ,γ-disubstituted allylic compounds of rather high molecular weight, will behave in the condensation reaction as the simpler analogs do.

It was the aim of this research to synthesize α-tocopherol by a method which did not involve condensation of a phytol derivative with trimethylhydroquinone, and to utilize for this purpose a series of known reactions leading via intermediates of unambiguous structure to the final product (I). Synthesis of chromans such as I in which the two alkyl groups attached to the hetero ring are different is a matter of some difficulty, and although John and his collaborators[5] have recently made considerable progress in this direction, their methods did not lead them to α-tocopherol. Moreover, their methods require 100–200% excess of a Grignard reagent derived from a long chain halide—often the most difficult of the intermediates to obtain—and the excess of the reagent is lost as a saturated hydrocarbon.

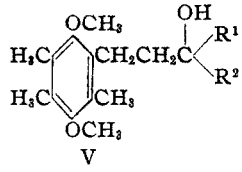
Our synthesis started with the carbinol (II)



I



II R = OH
III R = Br or Cl
IV R = MgBr or MgCl



V

which was prepared from trimethyldimethoxyphenylmagnesium bromide and ethylene oxide.[6]

This carbinol was transformed into the bromide (III) and then into the Grignard reagent (IV). The Grignard reagent was then converted into the carbinol (V) by reaction with a ketone. By proper selection of the ketone, the two groups R^1 and R^2 may be varied within wide limits. These carbinols were viscous oils of low vapor pressure, and, while the pure carbinols were not isolated, it was possible to remove most of the impurities present by steam distillation. The carbinol derived from acetone was converted into the 3,5-dinitrobenzoate which proved to be identical with a specimen of this ester prepared by another method.[7]

The carbinols (V), when subjected to the action of hydrobromic acid in acetic acid, were smoothly demethylated and cyclized to the chromans (I). By varying the nature of the ketone, five 2,5,7,8-tetramethyl-2-alkyl-6-hydroxychromans were prepared: those in which R^2 was methyl, ethyl, *n*-

(1) Paper XXXII, THIS JOURNAL, **64**, 435 (1942).

(2) Abstracted from a thesis by Henry C. Miller, presented to the Graduate Faculty of the University of Minnesota, in partial fulfillment of the requirements for the Ph.D. degree, July, 1941.

(3) (a) Fernholz, THIS JOURNAL, **60**, 700 (1938); (b) John, *Z. physiol. Chem.*, **252**, 222 (1938); (c) John, Dietzel and Emte, *ibid.*, **257**, 173 (1939); (d) Tishler and Wendler, THIS JOURNAL, **63**, 1532 (1941).

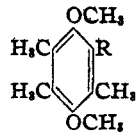
(4) (a) Smith, Ungnade, Hoehn and Wawzonek, *J. Org. Chem.*, **4**, 305 (1939); (b) Karrer, Escher and Rentschler, *Helv. Chim. Acta*, **22**, 1287 (1939).

(5) (a) John and Günther, *Ber.*, **74**, 879 (1941); (b) John and Rathmann, *ibid.*, **74**, 890 (1941).

(6) Smith, Wawzonek and Miller, *J. Org. Chem.*, **6**, 230 (1941).

(7) Smith, Ungnade and Irwin, THIS JOURNAL, **62**, 143 (1940).

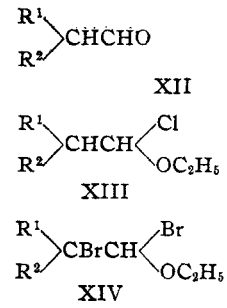
propyl, isobutyl and $C_{16}H_{33}$ (α-tocopherol). Except for α-tocopherol, these chromans were all solids of low melting point; in each case a solid derivative, the 3,5-dinitrophenylurethan, was prepared.[8]



VI R = H
VII R = CH_2Cl
VIII R = CH_2CN
IX R = $CH_2COOC_2H_5$
X R = Br

XI R = CH_2CHO
XV R = $CH_2CH(OC_2H_5)CBrR^1R^2$
XVI R = $CH_2CH=CHR^1R^2$

XVII R = CH_3



XII XIII XIV

For the synthesis of α-tocopherol, the necessary ketone was prepared from phytol by ozonolysis and also by oxidation with chromic oxide.[9] The Grignard reagent (IV) in this case was not prepared by the entrainment method in order to avoid the difficulty of separating two high molecular weight carbinols, one derived from IV and the other derived from ethyl bromide, the entrainment halide. The carbinol (V) was obtained in a yield of 77%, and from this carbinol crude α-tocopherol (I) was obtained in a yield of 72.3%. Purification of the α-tocopherol was more difficult than that of the lower homologs: the best, and only really feasible, method of purification was that of Tishler and Wendler.[3d] The identity of the α-tocopherol was established comparing six of its characteristics with those of a specimen of α-tocopherol prepared in the usual way from phytol. These were: carbon and hydrogen analysis; polarographic analysis[10]; preparation of the 3,5-dinitrophenylurethan[8]; Emmerie and Engel titration[11,12]; measurement of the ultraviolet absorption spectrum (Fig. 1)[11,13]; and biological assay.[14]

In addition to the method cited[6] for the preparation of the carbinol (II) two other approaches were investigated. Both of these started with the dimethyl ether of trimethylhydroquinone (VI), which was chloromethylated.

The chloromethyl derivative (VII) was converted via the nitrile (VIII)[15] to the ester (IX)[6] which was then reduced to II by action of sodium and methanol. Although II could be obtained this way, the yields in this series were comparatively poor. The nitrile (VIII) could not be reduced to the aldehyde (XI) by action of stannous chloride and hydrogen chloride in dry ether.

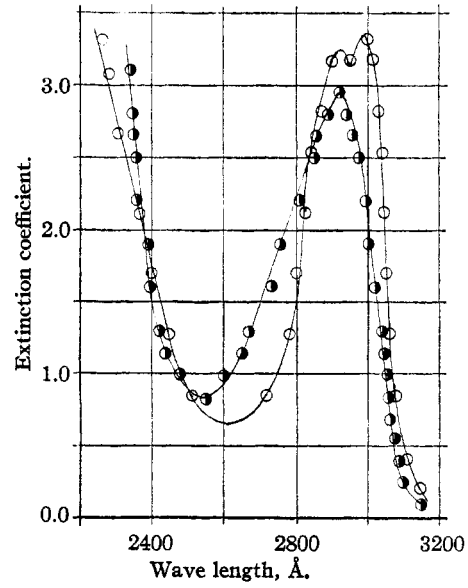


Fig. 1.—Ultraviolet absorption of α-tocopherol in ethanol, one millimole per liter: ◑, this α-tocopherol; ○, authentic α-tocopherol.

A second series of reactions investigated for the preparation of chromans of general type VI was patterned after the well-known Boord-Swallen synthesis of olefins.[16] In this series, the two groups R^1 and R^2 of I were present in an open chained aldehyde (XII). This aldehyde was converted to the α,β-dibromo ether (XIV) via the chloroether (XIII). It was planned to couple XIV with the Grignard reagent from VII to give XV, which could be converted into the olefin (XVI) of known structure. Demethylation and cyclization of this γ,γ-dialkyl allylic compound (XVI) would lead to the chroman (I). Unfor-

(8) Smith and Sprung, THIS JOURNAL, **64**, 433 (1942).
(9) Fischer and Löwenberg, *Ann.*, **464**, 69 (1928).
(10) The authors wish to thank Mr. L. J. Spillane, who carried out the polarographic analysis.
(11) The authors wish to thank Dr. T. J. Webb of the Research Laboratories Merck & Co., Inc., for carrying out this determination.
(12) Emmerie and Engel, *Rec. trav. chim.*, **57**, 1351 (1938); **58**, 283 (1939).
(13) Webb, Smith and others, *J. Org. Chem.*, **4**, 395 (1939).
(14) Carried out by Dr. H. M. Evans, of the Institute of Experimental Biology, University of California, to whom the authors are greatly indebted.
(15) Smith and MacMullen, THIS JOURNAL, **58**, 634 (1936).
(16) (a) Boord and Swallen, THIS JOURNAL, **52**, 654, 3400 (1930); (b) Boord and Shoemaker, *ibid.*, **53**, 1508 (1931); (c) Schmitt and Boord, *ibid.*, **54**, 759 (1932); (d) Soday and Boord, *ibid.*, **55**, 3298 (1933).

tunately this synthesis failed because it was impossible, under any of the conditions tried, to couple XIV with the Grignard reagent from VII. Although the Grignard reagent apparently was formed in good yields, reaction with XIV gave nothing but coupling and reduction products—durohydroquinonedimethyl ether (XVII) and the dibenzyl ether derived from (VII). This might have been anticipated from the work of Fuson[17] although it was felt that the α-bromo ether (XIV) might couple with the very active Grignard reagent from VI, in analogy with the many cases which have been investigated by Boord and his collaborators.

Experimental[18]

Bromotrimethylquinone.—Liquid bromine (112 g.) was slowly added (2 hours) to a solution of trimethylquinone (105 g.) in carbon tetrachloride (1000 cc.) at room temperature. When about half the bromine had been added, shiny black needles began to separate. After all the bromine was added, the mixture was washed with saturated aqueous bicarbonate and then with water, and the carbon tetrachloride was removed. The black solid mass was taken up in hot ethanol and solid sodium bicarbonate was added in small portions until carbon dioxide was no longer evolved. Nitric acid was then added, in very small portions, until the red color entirely disappeared and was replaced by bright yellow. The cooled mixture deposited the quinone, and a second crop was obtained by concentrating the mother liquor. The yield was quantitative (160 g.) and the product melted at 80–81.5°. This procedure is superior to those previously used.[6,19]

Bromotrimethyl hydroquinone was prepared in quantitative yield by reduction of the quinone using zinc and acetic acid[20] and in 81% yield by reduction of an alcoholic solution of the quinone with sodium hydrosulfite.

Bromotrimethylhydroquinone dimethyl ether (X) was prepared in 85–97% yields in 0.1–0.2 molar quantities using the procedure previously described[6,19] with as rapid addition of the alkali as possible.

Bromotrimethylhydroquinone Dibenzyl Ether.—A mixture of the bromohydroquinone (6.1 g.), dry acetone (30 cc.), anhydrous potassium carbonate (7.3 g.), potassium iodide (4.35 g.) and benzyl bromide (10.9 g.) was refluxed for twenty-seven hours. Enough water was added to dissolve the inorganic salts, and the mixture was extracted with chloroform. The extract was washed with aqueous sodium hydroxide (20%) until no further color developed in the alkali, and then with water. The solution was concentrated to 50 cc., an equal volume of methanol was added, and the mixture was cooled. The solid (7.65 g.) was removed; it melted at 144–147°. A second crop (0.6 g.) was obtained by concentration of the filtrate. The combined solids (8.25 g., 77%) were recrystallized twice from acetic acid. The substance then melted at 144.5–146°.

Anal. Calcd. for $C_{23}H_{23}O_2Br$: C, 67.15; H, 5.64. Found: C, 66.79; H, 5.87.

This dibenzyl ether of the bromohydroquinone could not be converted into a Grignard reagent in ether or in anisole, nor in ether by the entrainment method. In every case the starting material was recovered; no acid resulted from carbonation of the reaction mixture.

3,6-Dimethoxy-2,4,5-trimethylphenyl magnesium bromide was prepared from the bromo compound X as previously described.[6] The Grignard reagent was only sparingly soluble in ether although it frequently formed a supersaturated solution which did not precipitate even at −15°. Carbonation gave 3,6-dimethoxy-2,4,5-trimethylbenzoic acid, m. p., 98–101°, in 71% yield.[21]

3,6-Dimethoxy-2,4,5-trimethylbenzylcarbinol (II) was prepared from the above Grignard reagent and ethylene oxide, as previously described.[6] The yields of II were much better in the larger runs than in the smaller ones, reaching 29.4 g. (62%) when 55 g. (0.246 mole) of the bromo compound (X) was used. The crude carbinol melted at 70.5–73°; after crystallization from ether–petroleum ether, it melted at 73.5–75°.

3,6-Dimethoxy-2,4,5-trimethylbenzylcyanide (VIII) was prepared from the chloride (VII) in 78–87% yields, as previously described.[15] The above nitrile (VIII) (15 g.) in chloroform (30 cc.) was added to a mixture of ether and anhydrous stannous chloride (19.5 g.) which had been saturated with hydrogen chloride. Fine white needles separated at once, but after thirty minutes these dissolved and the mixture separated into two layers. The mixture was poured into water and heated on the steam-bath for forty-five minutes to remove the ether and complete the hydrolysis. The aqueous suspension was then cooled and the solid was removed. It weighed 10.2 g. and by fractional crystallization from ether–chloroform and ether–petroleum ether, it was separated into 7.0 g. of impure nitrile (VIII) and 3.2 g. of a substance melting at 195–202°, probably the amide.[15]

Ethyl-3,6-Dimethoxy-2,4,5-trimethylphenyl Acetate (IX).—The nitrile (VIII) (10 g.) was converted to the ester (IX) by the procedure already described.[22] Sodium (0.5 g.) was added to a solution of the ester (IX) (0.8 g.) in methanol (6 cc.). After the initial reaction was over, the mixture was refluxed until all of the metal dissolved. The solution was diluted with water and extracted with ether. From the aqueous layer there was obtained, after acidification, 0.15 g. (21%) of the phenylacetic acid. The ether layer was washed, dried (sodium sulfate) and the solvent was evaporated. The residual oil was rubbed with petroleum ether (b. p. 28–38°) and cooled. The solid (0.2 g., 30%) melted at 61–67° alone or when mixed with a specimen of the carbinol II prepared from ethylene oxide.

β-(3,6-Dimethoxy-2,4,5-trimethylphenyl)-ethyl Chloride (III).—Thionyl chloride (14.8 g.) dissolved in dry benzene (10 cc.) was added to the carbinol (II) (18 g.) in benzene (30 cc.). There was an immediate evolution of gas. The

(17) Fuson, THIS JOURNAL, **48**, 2681 (1926); Fuson and Corse, *ibid.*, **60**, 2063 (1938); Fuson, Denton and Kneisley, *ibid.*, **63**, 2652 (1941).

(18) Microanalyses by E. E. Renfrew, E. E. Hardy, H. H. Hoehn and C. H. Stratton.

(19) Smith and Johnson, THIS JOURNAL, **59**, 673 (1937).

(20) Smith, *ibid.*, **56**, 473 (1934).

(21) Smith and Denyes, *ibid.*, **56**, 475 (1934).

(22) Ref. 6, p. 233.

mixture was refluxed for three hours, then cooled and washed successively twice with water, once with saturated bicarbonate and again with water. Removal of the solvent left a red oil which was distilled. There resulted a distillate of 14.26 g. of yellow oil which boiled at 130–138° under 3–4 mm. pressure, and a residue of 5–8 g. of black, tarry material. The distillate, after crystallization twice from methanol, gave 8.0 g. of pure white material which melted at 60.5–61.5°, and 1.1 g. of less pure material, a total of 9.1 g. or 41%. The analytical sample melted at 61–62°.

Anal. Calcd. for $C_{13}H_{19}O_2Cl$: C, 64.28; H, 7.91. Found: C, 64.13; H, 7.91.

Substitution of ether for benzene as the solvent led to approximately the same yields. The following reagents, however, were quite unsuitable for use in the preparation of the chloride: dry hydrogen chloride at 85–90°, no solvent; aqueous hydrochloric acid and zinc chloride; thionyl chloride and hydrogen chloride with no added solvent; thionyl chloride and pyridine in benzene.

β-(3,6-Dimethoxy-2,4,5-trimethylphenyl)-ethyl Bromide (III).—The carbinol (II) (8.0 g.) was dissolved in petroleum ether (100 cc., b. p. 30–60°) and cooled (0°). Phosphorus tribromide (11.4 g.) in petroleum ether (100 cc.) was added (20 minutes) with stirring. The cooling bath was removed and the mixture was allowed to stand for ten hours at room temperature. After refluxing the mixture for thirty minutes, water (40 cc.) was cautiously added in small portions. Ether (100 cc.) was added and the organic layer was washed with water, aqueous bicarbonate and again with water and then dried (sodium sulfate). Removal of the solvents left a yellow oil (5.5 g.) which was crystallized from methanol. There resulted 2.8 g. (28%) of white platelets which, after several crystallizations, melted at 66–67°.

Anal. Calcd. for $C_{13}H_{19}O_2Br$: C, 54.34; H, 6.69. Found: C, 54.64; H, 6.76.

2,2,5,7,8-Pentamethyl-6-hydroxychroman I ($R^1 = R^2 = CH_3$).—The chloride (III) (1.21 g.) in ether (2.0 cc.) was added to magnesium turnings (0.3 g.) which had been activated by reaction with ethyl bromide (0.07 g.) in ether (1.0 cc.). The mixture was refluxed for five hours after all the chloride was added, and it was quite thick with a suspended white solid. After standing for five hours at room temperature, acetone (2.0 cc.) was slowly added and the solid dissolved. After refluxing for fifteen minutes, the mixture was decomposed by addition of dilute sulfuric acid, the layers were separated and the aqueous layer was extracted with ether. The combined ether layers were dried (magnesium sulfate) and the solvent was removed. The residual oil (carbinol V, $R^1 = R^2 = CH_3$) was refluxed for two hours with acetic acid (10 cc.) and hydrobromic acid (4 cc., 40%). The cooled mixture was diluted with water and the solid was removed and crystallized from methanol (Norit). The white needles (0.21 g.) melted at 86.5–94° alone or when mixed with an authentic specimen.[23] This chroman, when treated with 3,5-dinitrobenzazide[8] gave a 3,5-dinitrophenylurethan which melted at 203–206° alone or when mixed with an authentic specimen.

(23) Smith, Unguade and Prichard, *J. Org. Chem.*, **4**, 358 (1939).

In one experiment, the carbinol V, $R^1 = R^2 = CH_3$, (0.84 g.) was dissolved in pyridine (8.0 cc.), 3,5-dinitrobenzoyl chloride (0.75 g.) was added, and the mixture was allowed to stand overnight. From this mixture was isolated the 3,5-dinitrobenzoate of V, $R^1 = R^2 = CH_3$, which melted at 140–145° alone or when mixed with an authentic specimen.[7]

2-Ethyl-2,5,7,8-tetramethyl-6-hydroxychroman I ($R^1 = CH_3$; $R^2 = C_2H_5$).—The reagents were: chloride III (2.42 g.), ethyl bromide (1.09 g.), ether (8.0 cc.), magnesium (0.60 g.), methyl ethyl ketone (3.0 cc.). Processed as above except that, after decomposition of the Grignard product, all material volatile with steam was removed. The non-volatile portion (carbinol) was cyclized and processed as above. There resulted 0.74 g. of the crude chroman which when distilled in a Hickman type of still (bath temperature, 160–170°, pressure 9–10 mm.) gave a distillate of 0.63 g. of yellow oil. When rubbed with petroleum ether (b. p. 28–38°), this crystallized. After recrystallization from the same solvent, the substance was white and melted at 60.5–62.5°.

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.92; H, 9.40. Found: C, 76.81, 76.83; H, 9.14, 9.06.

The 3,5-dinitrophenylurethan melted at 200–201.5°.

Anal. Calcd. for $C_{22}H_{25}O_7N_3$: C, 59.57; H, 5.69. Found: C, 59.23; H, 5.81.

2-*n*-Propyl-2,5,7,8-tetramethyl-6-hydroxychroman I ($R^1 = CH_3$; $R^2 = n\text{-}C_3H_7$).—The reagents were: chloride III (1.21 g.), ethyl bromide (0.55 g.), ether (2.0 cc.), magnesium (0.30 g.), methyl *n*-propyl ketone (1.22 g.). Processed as above, including the steam distillation. The crude chroman, distilled in the Hickman still (bath temperature 160–170°, pressure 8–10 mm.) gave a distillate of 0.32 g. yellow oil. After crystallization from petroleum ether, the substance melted at 57–59°.

Anal. Calcd. for $C_{17}H_{24}O_2$: C, 77.42; H, 9.86. Found: C, 77.19; H, 9.55.

Because of insufficient material, a derivative of this chroman could not be prepared.

2-*iso*-Butyl-2,5,7,8-tetramethyl-6-hydroxychroman I ($R^1 = CH_3$; $R^2 = iso\text{-}C_4H_9$).—Reagents: chloride III (2.42 g.), ethyl bromide (1.09 g.), ether (8.0 cc.), magnesium (0.6 g.), methyl *iso*-butyl ketone (3.2 g.). Product after distillation: 1.19 g. of yellow oil which, after crystallization from petroleum ether gave the white chroman melting at 42.5–44.5°.

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 77.80; H, 9.99. Found: C, 77.83; H, 9.78.

The 3,5-dinitrophenylurethan melted at 188–190°.

Anal. Calcd. for $C_{24}H_{29}O_7N_3$: C, 61.12; H, 6.20. Found: C, 60.76; H, 6.04.

Methyl-4,8,12-trimethyl tridecyl ketone ("Phytol Ketone") was prepared from phytol by chromic acid oxidation.[9] From 14.8 g. of phytol there was obtained 7.5 g. (28%) of the ketone boiling at 130–133° under 10 mm. pressure. Ozonolysis (ozone 7% by volume in oxygen, rate 10 l. per hour) of phytol (12.0 g.) in ethyl bromide (200 cc.) at 0° (until the exit gases gave a color with potassium iodide solution), followed by reductive cleavage (zinc dust, 10.9 g., acetic acid, 13 cc.) of the ozonide gave the

ketone (6.72 g.) boiling at 138–140° under 2–3 mm. This yield (62%) is not only better than that obtained using chromic oxide, but the ketone is much purer, as shown by the higher boiling point. The semicarbazone melted at 64.5–66°.[9]

α-Tocopherol.—Magnesium (0.90 g., 0.038 mole) was placed in a three-necked flask equipped with a stirrer, dropping funnel and reflux condenser. A drop of ethyl bromide and a little ether (0.5 cc.) were added. As soon as the reaction began, the stirrer was started and the chloride III (4.7 g., 0.0195 mole) in ether (10 cc.) was slowly (two hours) added while the mixture was gently refluxed. Refluxing was continued for four hours after all the halide was added. The thick suspension of the Grignard reagent was cooled (0°) and to it was added "phytol ketone" (4.0 g., 0.015 mole). The precipitate dissolved. After refluxing for one hour, the mixture was cooled and dilute hydrochloric acid was carefully added. Sometimes, but not always, a small amount (about 0.25 g.) of a solid appeared at this point. It melted at 160–161° and was the 1,4-diphenylbutane corresponding to III, resulting from coupling.

Anal. Calcd. for $C_{26}H_{38}O_4$: C, 75.36; H, 9.18. Found: C, 75.40; H, 9.18.

After removal of this solid (if any) the mixture was steam distilled and the distillate (750 cc.) was discarded. The residue was extracted thoroughly with ether, the ether solution was washed with water and dried (magnesium sulfate). Removal of the ether left the carbinol as a pale yellow oil (5.83 g., 77%) which was demethylated and cyclized by refluxing it for nine hours under nitrogen in acetic acid (70 cc.) containing dry hydrogen bromide (6.0 g.). Water (2 volumes) was added and the mixture was extracted three times with ether. The combined ether extracts were washed successively four times with water, twice with saturated bicarbonate, and once again with water. After drying (magnesium sulfate) the solvent was evaporated. The residual red oil (5.45 g.) was refluxed for one hour in a nitrogen atmosphere with ethanol (50 cc.) in which sodium (0.5 g.) had been dissolved. The solution was diluted with water (2 volumes) and extracted three times with ether. After washing twice with water, the ether solution was dried (magnesium sulfate) and the solvent was evaporated. The residual red oil weighed 4.69 g. (72%) and was impure α-tocopherol. It could not be purified by shaking with activated alumina (Brockmann) followed by high vacuum distillation. Although a specimen treated in this manner gave good carbon and hydrogen values, it was still rather red in color. This red color could be removed by boiling the substance in dioxane (10 cc.) with stannous chloride (1.0 g.) and hydrochloric acid (3 cc.), but the product, though yellow and giving good analytical values, was shown by polarographic analysis to be quite impure (52.7%). The only feasible method of purification involved conversion of the crude tocopherol to tocopherylquinone, reduction of this to the hydroquinone, and cyclization of the pure tocopheryl hydroquinone to α-tocopherol, according to the method of Tishler and Wendler.[3d] By this method, the 4.69 g. of crude tocopherol above was converted into 1.06 g. (20%) of pure α-tocopherol and 2.63 g. of a red oil, probably the partially demethylated carbinol (V) or its dehydration product. This red oil was not investigated further. The 1.06 g. of pure tocopherol was used for the following identity tests.

Anal. Calcd. for $C_{29}H_{50}O_2$: C, 80.86; H, 11.71. Found: C, 80.70; H, 11.75.

3,5-Dinitrophenylurethan: prepared in 69% yield, the crude derivative melted at 141.5–144°. After one recrystallization from ethanol, it melted at 142.5–144.5°, alone or when mixed with an authentic specimen (m. p., 143–145°).

Polarographic Analysis.—The buffer had a *p*H of 4.03 and was 0.1 *N* aniline, 0.1 *N* anilinium perchlorate in ethanol, 75% by volume. Found: $\pi^1/_2$ (cor.), +0.281; i_d/c, −2.14. Tocopherol prepared from phytol, $\pi^1/_2$ (cor.), +0.288; i_d/c, −2.20. Purity of the sample = 214/2.20 × 100 = 97.2%; limit of experimental error, 3%.

Emmerie and Engel titration: duplicate determinations indicated that the sample was 100% α-tocopherol within the experimental error of the method.

Ultraviolet absorption spectrum: the graph corresponded quite closely to the standard graph for α-tocopherol. The only difference was a slight disparity in the height of the minimum, a matter of little significance. (Fig. 1.)

Biological assay: when fed at a level of 6 mg. to each of eight properly conditioned female rats, there were no resorptions and 100% of good litters averaging 8.4 young each, of average weight 5.8 g. When fed to each of eight rats at a level of 3 mg., one failed implantation, two resorbed, and 5 littered (71% of 7). The litters averaged 7 young each, of average weight 5.3 g. Since the usual specimen of α-tocopherol shows 50% activity at the 3 mg. level, these results show that this sample is in every way equal in biological activity to natural α-tocopherol and to α-tocopherol synthesized from phytol.

3,6-Dimethoxy-2,4,5-trimethylbenzylmagnesium Chloride.—Magnesium (0.525 g., 0.022 mole) was placed in a three-necked flask equipped with stirrer, dropping funnel and reflux condenser. The magnesium was activated by addition of a drop of ethyl bromide in a little ether, and then the chloride VII (0.5 g., 0.0022 mole) in ether (20 cc.) was slowly (three and one-half hours) added while the solution was stirred and refluxed. A white solid formed. The Grignard mixture was poured onto iced hydrochloric acid and the mixture was steam distilled. From the distillate there was isolated durohydroquinone dimethyl ether (240 mg.), which melted at 112–115°, alone or when mixed with a specimen prepared from the hydroquinone. The residue in the distilling flask contained a white solid which was removed and crystallized from chloroform–ethanol. It weighed 75 mg., melted at 170–171°, and was the diarylethane corresponding to VII.

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.55; H, 8.90. Found: C, 74.50; H, 8.66.

The above amounts of materials indicate that the Grignard reagent was formed in 57% yield and was accompanied by 19.5% of the coupling reaction.

Durohydroquinone Dimethyl Ether.—The hydroquinone (1.91 g.) was dissolved in a mixture of methanol (22 cc.) and methyl sulfate (12 cc.). A solution of potassium hydroxide (16 g.) in methanol (80 cc.) was added as rapidly as possible and, after refluxing for thirty minutes, the mix-

ture was steam distilled. The distillate was cooled (0°) and the white platelets (1.0 g.) were removed and crystallized twice from methanol. The white product melted at 112–115°.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.32. Found: C, 74.13; H, 9.52.

Ethyl α-chloro-*i*-butyl ether (XIII) $R^1 = R^2 = CH_3$, (25 g.) was prepared from isobutyraldehyde (19 g.) and ethanol (15 cc.) according to Schmitt and Boord.[16c] It was not distilled, but was subjected directly to the action of bromine (28.7 g.) and converted into ethyl α,β-dibromo-*i*-butyl ether (40.2 g., 97%) XIV, $R^1 = R^2 = CH_3$.

A Grignard reagent was prepared as above from 0.86 g. of the chloride (VII). The mixture was cooled and filtered to remove excess magnesium and the insoluble coupling product, and to the filtrate was added 0.67 g. (65% of the theoretical amount) of the above dibromide. The mixture was refluxed for four hours and then allowed to stand at room temperature for two days, during which time a gummy solid separated. The mixture was decomposed with cold, dilute hydrochloric acid. The ether layer was removed and the aqueous layer was extracted once with ether. The combined ether solutions were washed with water, dried (sodium sulfate) and concentrated. The only product was a small amount of red oil which could not be crystallized. This oil was steam distilled and a small amount of dimethoxydurene was isolated from the distillate. Nothing crystalline could be obtained from the non-volatile residue.

Summary

1. A new general synthesis for 2,2-dialkyl-6-hydroxychromans has been described.

2. Four simple 2-alkyl-2,5,7,8-tetramethyl-6-hydroxychromans have been prepared by means of the new synthesis: those in which the 2-alkyl group is, respectively, methyl, ethyl, *n*-propyl and isobutyl. The last three of these are new.

3. α-Tocopherol prepared by the new synthesis has been shown to be identical with synthetic tocopherol prepared from phytol. Six tests for identity were used, including a biological assay for vitamin E activity.

4. Since the method leads unambiguously to a chroman structure, the preparation of α-tocopherol by these reactions affords a proof, by synthesis, that the hetero ring in α-tocopherol is a chroman.

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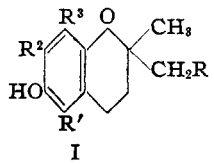
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Chemistry of Vitamin E. XXXIV. The Three Dimethylethyltocols[1]

BY LEE IRVIN SMITH AND W. B. RENFROW, JR.[2]

Although many *p*-hydroxychromans and *p*-hydroxycoumarans, as well as many other types of phenolic molecules, show slight vitamin E activity in the rat test,[3] it is not possible to modify the structure of 5,7,8-trimethyltocol (α-tocopherol) I, (R^1, R^2 and R^3 are CH_3, R is $C_{15}H_{31}$) very much and retain a high vitamin E activity.



I

Thus Karrer and his collaborators[4] have varied the nature of R (R^1, R^2 and R^3 = CH_3) in α-tocopherol (three "isoprene units") by addition or subtraction of "isoprene units," and they have found the biological activity to be affected adversely by a factor of ten to forty by these changes. John and Günther[5] have prepared an "isotocopherol" in which R is the straight chained C_{15} alkyl group, but they have not yet reported upon the biological activity of the substance.

Variations in the nature of R^1, R^2 and R^3 (R is $C_{15}H_{31}$, three "isoprene units") have also been made. These include, for the most part, variations in the number and position of hydrogen atoms and methyl groups, although Karrer and Hoffmann[6] have prepared 5,7-dimethyl-8-ethyltocol (I, $R^1 = C_2H_5$; $R^2 = R^3 = CH_3$), as well as a methyldiethyltocol (I, R^1 or R^2 = CH_3, the other two = C_2H_5)[7] and Karrer and Schläpfer have prepared a diethyltocol (I, $R^1 = R^2 = C_2H_5$; R^3 = H).[8] These substances all show a lower vitamin E activity than α-tocopherol, by factors of from 2 to about 5. These changes in activity are not due wholly to the weights of the alkyl groups introduced, for the evidence indicates that

(1) Paper XXXIII, THIS JOURNAL, **64**, 440 (1942).

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(3) Evans, Emerson, Smith and others, *J. Org. Chem.*, **4**, 376 (1939).

(4) See Karrer and Yap, *Helv. chim. acta*, **24**, 640 (1941), for a summary.

(5) John and Günther, *Ber.*, **74**, 879 (1941).

(6) Karrer and Hoffmann, *Helv. chim. acta*, **22**, 654 (1939).

(7) Karrer and Hoffmann, *ibid.*, **23**, 1126 (1940).

(8) Karrer and Schläpfer, *ibid.*, **24**, 298 (1941).