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.

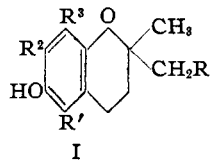
MINNEAPOLIS, MINNESOTA RECEIVED NOVEMBER 28, 1941

[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).

(2) Present address: Department of Chemistry, Occidental College, Los Angeles.

(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).

TABLE I

MEASUREMENTS ON THREE DIMETHYLETHYLTOCOLS

Tocol	Gold chloride titration,[a] % tocopherol	Emmerie and Engel[a,d]		Polarograph[e] $\pi^1/_2$ cor.	$\frac{i_d}{c}$	Antioxidant power[a,f]	U. v. spectrum[a,g] λ max., Å.	E.	Biological activity[h] % at 5 mg.	% at 10 mg.
5-Ethyl-7,8-dimethyl	93.2[b]	16.1	15.7	0.287	2.10	13.7	2930	3.05±0.1	50	100
7-Ethyl-5,8-dimethyl	92.5[c]	22.55	23.0	.292	2.00	13.7	2930	3.05±0.1	25	25[i]
8-Ethyl-5,7-dimethyl	98.2[c]	27.5	27.4	.291	2.10	13.7	2930	3.05±0.1	50	100

[a] The authors wish to thank Dr. T. J. Webb of Merck & Co., Inc., for carrying out these determinations. [b] Two identical results. [c] Three identical results. [d] Millimolecular extinction coefficients at 5250 Å. α-Tocopherol = 23.5; β-tocopherol = 19.2. [e] The authors wish to thank Mr. L. J. Spillane for carrying out these determinations: buffer, 0.1 *N* aniline–0.1 *N* anilinium perchlorate in 75% ethanol by volume, *p*H 4.02. The values given above for i_d/c are corrected to 100% purity, using the values obtained by gold chloride titration. α-Tocopherol, $\pi^1/_2 = 0.284$; $i_d/c = 2.20$. [f] Induction period in hours at 100°, one atmosphere of oxygen, 0.05 weight per cent. of the tocopherol as inhibitor, substrate freshly prepared ethyl oleate, actual up-take of oxygen followed. Induction period for α-tocopherol, 13.7 hours; for hydroquinone 0.012 weight per cent., 18 hours; blank, 1 hour. [g] E is millimolecular extinction coefficient. [h] The authors wish to thank Dr. H. M. Evans, of the Institute of Experimental Biology, University of California, for the bioassays. [i] A duplicate assay at the 10-mg. level failed to show any biological activity for this tocol.

the diethyltocol and the methyldiethyltocol have about the same activity and that they are both appreciably more active than 5,7-dimethyl-8-ethyltocol.[4,6,7,8]

In order to explore somewhat further the effects of the positions taken by the alkyl groups, we have synthesized the three dimethylethyltocols, and have made a comparative study of them with regard to the gold chloride titration, the Emmerie and Engel assay, polarographic analysis, antioxidant power, ultraviolet absorption spectra and biological assay. The results are shown in Table I. These results show that while the three tocols show almost identical properties in some respects (antioxidant power, ultraviolet spectra), there are minor differences in the values they give on polarographic analysis and wide differences in their behavior in the Emmerie and Engel determination and in their biological activity. There is no regularity in those differences; it is the 5-ethyl compound which shows the anomalous behavior in the Emmerie and Engel determination, and the 7-ethyl compound which shows the exceptional biological activity. One can only conclude, therefore, that the properties of tocols depend not only upon the groups present in the benzene ring but also upon the way these groups are distributed among the 5-, 7- and 8-positions.

Experimental[9]

The tocopherols were prepared by condensation of phytol with the appropriate dimethylethylhydroquinone[10] by a modification of the procedure previously described.[11] The dimethylethylhydroquinone (5.5 g.) was added to a hot (100°) solution of zinc chloride (2.5 g., freshly fused) in acetic acid (20 cc.). The solution was stirred and heated to 125–130° while phytol (10 g.) was added slowly (1–2 drops per second). After heating to 125–130° for two hours, the cooled reaction mixture was poured over ice (150 g.) containing sodium hydrosulfite (1 g.). The mixture was extracted with petroleum ether (50 cc., b. p. 60–68°). The organic layer was washed successively once with water, twice with aqueous alcoholic potassium hydroxide (50 cc. first time, 25 cc. second time, of 5% alkali in 50% aqueous ethanol) and once with aqueous ethanol (50%, containing a little sodium hydrosulfite). Each of the aqueous extracts was extracted with petroleum ether (20 cc.) and all the petroleum ether solutions were combined and dried (Drierite). Removal of the solvent left a dark red, viscous oil (14–15 g.) which was refluxed for one and one-half hours with methanol (50 cc.) containing potassium hydroxide (1.5 g.). The alkaline solution was poured over ice (100 g.) containing sodium hydrosulfite (1 g.). The mixture was extracted three times with petroleum ether, centrifuging to break up the stubborn emulsions. Removal of the solvent left 14 g. of dark oil, which was again refluxed with methanolic alkali and processed as above. After washing the combined extracts with aqueous ethanol, the solution was dried (Drierite), the solvent was removed under reduced pressure and the residual oil was distilled from a "pot still" under 10^{-5} mm. With a bath temperature of 185–190°, the material distilled smoothly. The light yellow distillate was collected in two parts: the first third (2.5–3.0 cc.) and the main portion (7.5–8.5

(9) Microanalyses by E. E. Renfrew and C. H. Stratton.

(10) Smith and Opie, *J. Org. Chem.*, **6**, 427 (1941).

(11) Smith, Ungnade, Stevens and Christman, THIS JOURNAL, **61**, 2615 (1939).

cc.). There was practically no fore-run, and only a small amount of black tarry residue was left in the still. The yield of tocol was 60–75%.

Anal. Calcd. for dimethylethyltocol, $C_{30}H_{52}O_2$: C, 81.02; H, 11.78. Found: 5-ethyl-7,8-dimethyltocol (A): C, 81.23; H, 12.08. 7-ethyl-5,8-dimethyltocol (B): C, 81.86; H, 11.77, 8-ethyl-5,7-dimethyltocol (C): C, 81.08; H, 11.65.

The 3-5-dinitrophenylurethans were prepared. These derivatives of A, B, and C melted at 46–48°, 67–69°, and 58–60°, respectively.[12]

(12) Smith and Sprung, THIS JOURNAL, **64**, 433 (1942).

Summary

1. The three dimethylethyltocols—two of them new tocopherols—have been prepared and studied. While the three isomeric substances show almost identical properties in some respects, there are important differences in other respects.

2. Two of the tocols show good vitamin E activities, but the third, 7-ethyl-5,8-dimethyltocol, has a very low activity.

3. The properties of the tocols depend not only upon the groups present in the benzene ring but also upon the way these groups are distributed among the three available positions.

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

The Chemistry of Vitamin E. XXXV. The Behavior of Tocopherols at the Dropping Mercury Electrode[1]

BY LEE IRVIN SMITH, LEO J. SPILLANE AND I. M. KOLTHOFF

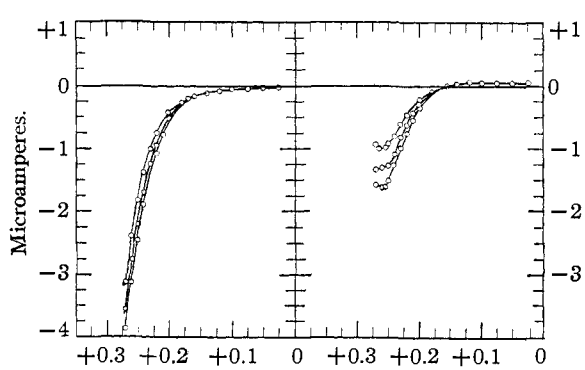
In a previous study[2] the polarographic behavior of 6-hydroxychromans and 5-hydroxycoumarans has been reported. These substances are closely related to the tocopherols. In the present study the anodic waves, at the dropping mercury electrode, have been determined under various conditions for different tocols.

Experimental

The manual apparatus was used as described in the previous study.[2] The experiments were performed under nitrogen which had been purified by the method of Fieser,[3] and which, before it entered the cell, was passed through two wash-bottles containing the solvent used in the experiment.

The capillary had the following characteristics. At a pressure of 62.7 cm. of mercury, the drop time in 0.1 *M* potassium nitrate, containing 0.001 *M* nitric acid, was 3.72 sec. (open circuit), m = 1.52 mg. sec.$^{-1}$ and $m^{2/3}t^{1/6}$ = 1.646. The diffusion current of 0.540 × 10^{-3} *M* lead nitrate in this solution was 3.43 microamperes (calcd., 3.37).

The current–voltage (c. v.) curves were determined at 25 ± 0.01° in acetic acid–sodium acetate buffers, and in aniline–anilinium perchlorate buffers, in a medium of 75% ethanol. The buffer solutions in 50% methanol, described in the previous paper,[2] could not be used because of the slight solubility of α-tocopherol in this medium. The acetate buffers had a *p*H of 6.2–6.6. After correction for the residual current (Fig. 2A), α-tocopherol gave an apparent diffusion current which was proportional to the concentration (Fig. 1), but the diffusion currents were abnormally small. No apparent i_d was found in the acetate buffers when the values were not corrected for i_r (Fig. 1A). This effect was not investigated further; possibly the acetate in 75% ethanol exerted a depolarizing effect by the formation of sparingly soluble mercurous acetate. The be-



(A) Curves uncorrected for i_r. (B) Corrected for i_r. Potential in volts *vs.* S. C. E.

Fig. 1.—α-Tocopherol in 0.05 *M* sodium acetate–0.05 *M* acetic acid in 75% ethanol (by volume).

(1) Paper XXXIV, THIS JOURNAL, **64**, 445 (1942).
(2) Smith, Kolthoff, Wawzonek and Ruoff, *ibid.*, **63**, 1018 (1941).
(3) Fieser, *ibid.*, **46**, 2639 (1924).