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.

MINNEAPOLIS, MINNESOTA RECEIVED NOVEMBER 21, 1941

[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

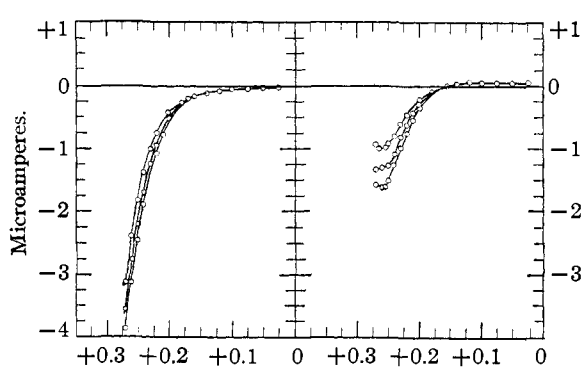
In a previous study[2] the polarographic behavior of 6-hydroxychromans and 5-hydroxycoumarans has been reported. These substances are closely related to the tocopherols. In the present study the anodic waves, at the dropping mercury electrode, have been determined under various conditions for different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

havior of α-tocopherol in an unbuffered solution of 0.1 *M* lithium nitrate in 75% ethanol was also investigated. Although mercury does not dissolve in this medium until a potential of +0.4 v. (*vs.* S. C. E.) is reached, it was not possible to obtain c. v. curves for α-tocopherol which showed a diffusion current. Pronounced maxima occurred which were not eliminated by gelatin, methyl red, tropaeolin OO or phenol red.

Better results were obtained in the aniline–anilinium perchlorate buffers given in Table I. The *p*H of the solutions was measured with the glass electrode, since the quinhydrone electrode did not give good results in the presence of aniline. However, it was found that the *p*H of 0.05 *M* perchloric acid in 75% ethanol (buffer VII, Table I), measured with the quinhydrone electrode, checked that measured with the glass electrode.

TABLE I

ANILINE–ANILINIUM PERCHLORATE BUFFERS IN 75% ETHANOL (VOL.)

Buffer	Concn. of aniline, molar	Concn. of perchloric acid, molar	*p*H
I	0.2	0.1	4.02
II	.150	.075	(4.02)[a]
III	.126	.063	(4.02)[a]
IV	.062	.031	(4.02)[a]
V	.3	.1	..
VI	.15	.1	3.77
VII	..	.05	1.66
VIII	..	.025	1.97

[a] The *p*H was not measured but the ratio of aniline to anilinium perchlorate was the same as in buffer I.

The values of half-wave potentials were corrected for the *iR* drop. The resistance was determined by the classical Wheatstone bridge method, the measurement being made when *R* had a minimum value (just before the drop fell), and the average resistance was calculated as $^1/_3$ *R* min.[4] Corrections for the *iR* drop were applied in the analyses of the waves.

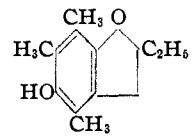
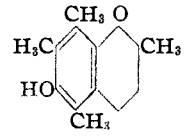
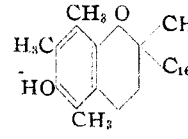
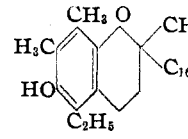
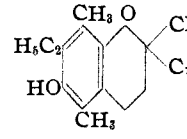
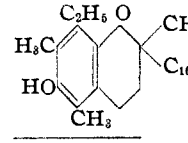
α-, β- and γ-tocopherols were synthesized by condensation of phytol and the appropriate hydroquinone.[5,6] 2-Ethyl-5-hydroxycoumaran and 2,5,7,8-tetramethyl-6-hydroxychroman were prepared by Wawzonek[2] and were recrystallized immediately before they were used. Specimens of dimethylethyl tocols were those prepared by Renfrow.[7]

Experimental Results and Discussion

The residual current measured in buffer I is shown in Fig. 2B. The values of i_d listed in Tables II and III have been corrected for the residual current. This correction was of great importance in work with tocols and related compounds, for if it was not applied, no indication of

TABLE II

ANODIC WAVES OF COMPOUNDS STUDIED IN BUFFER I[8] (*p*H 4.02) AT 25°

Formula	Concn., *M* × 10³	i_d × 10⁶, microamp.	(i_d/c) × 10³	$\pi^1/_2$ (*vs.* S. C. E.)
	1.047	3.22	3.08	+0.267
	0.935	2.52	2.70	+ .280
	1.150	3.18	2.76	+ .277
	0.700	1.55	2.21	+ .281
	1.40	3.10	2.21	+ .281
	1.00	2.21	2.21	+ .286
	1.128	2.46	2.18	+ .285
	0.987	2.17	2.20	+ .284
	1.088	2.50	2.29	+ .286
	0.949[9]	2.03	2.14	+ .285
	1.035[10]	1.20	1.16	+ .286
	1.01[11]	2.29	2.27	+ .284
	0.755	1.48	1.96	+ .288
	0.950	1.88	1.98	+ .284
	1.51	2.92	1.93	+ .288
	0.745	1.40	1.88	+ .291
	1.02	1.88	1.84	+ .292
	1.49	2.74	1.84	+ .292
	0.739	1.55	2.10	+ .290
	1.01	2.05	2.03	+ .293
	1.477	3.00	2.03	+ .290
	0.954	1.99	2.09	+ .290

(4) Ilkovic, *Coll. Czech. Chem. Comm.*, **4**, 481 (1932); Brdicka, *ibid.*, **8**, 419 (1936).

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

(6) The authors are grateful to Dr. R. T. Major and Merck and Company, Inc., Rahway, N. J., for a gift of the synthetic α-, β-, and γ-tocopherols used in these experiments.

(7) Smith and Renfrow, THIS JOURNAL, **64**, 445 (1942).

(8) The anodic waves of β- and γ-tocopherols did not yield diffusion currents because the oxidation occurred at potentials too positive.

(9) A specimen of purified α-tocopherol prepared without using phytol; Smith and Miller, THIS JOURNAL, **64**, 440 (1942).

(10) Impure α-tocopherol prepared without using phytol; H. C. Miller, Ph.D. thesis, University of Minnesota, 1941, Part 3, p. 35.

(11) A mixture which was 1.01 × 10^{-3} *M* in α-tocopherol and 0.986 × 10^{-3} *M* in β-tocopherol. The value for i_d shown is corrected for the slight current due to β-tocopherol.

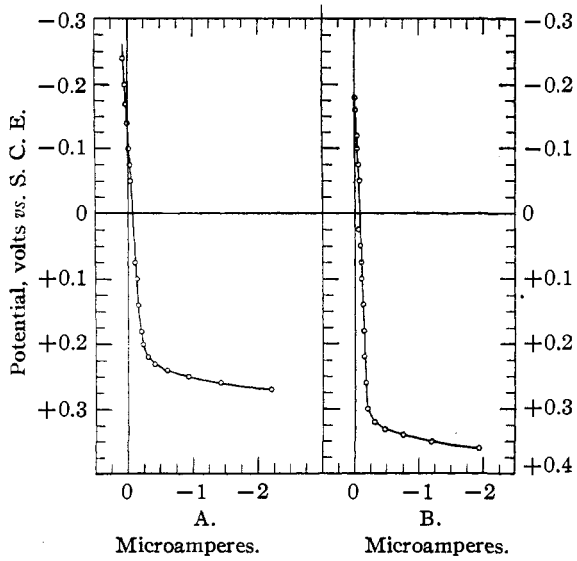


Fig. 2.—Residual currents: A, in 0.05 *M* sodium acetate–0.05 *M* acetic acid in 75% ethanol; B, in buffer I.

a diffusion current was obtained in many cases. This is shown, for example, in Fig. 3 in which the c. v. curves obtained for α-tocopherol in buffer I are given without correction (Fig. 3A), and with correction (Fig. 3B), for i_r. Table II summarizes the measurements, in buffer I, of the diffusion currents and half-wave potentials (against S. C. E.) of all compounds studied.

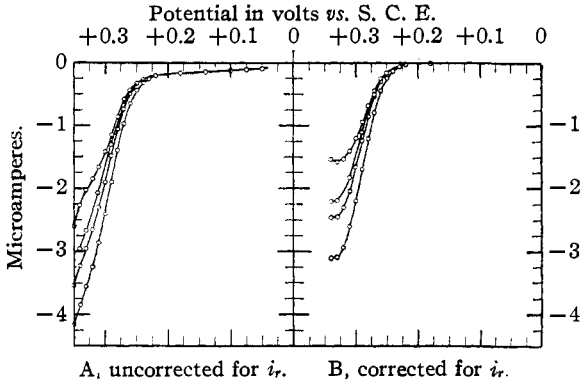
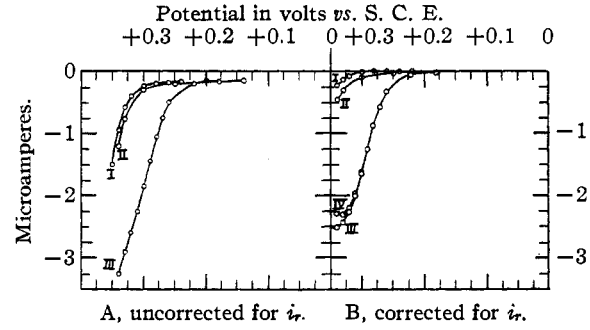


Fig. 3.—α-Tocopherol in buffer I.

From the data it follows that the half-wave potential of α-tocopherol agrees much more closely with that of the simple chroman than with that of the simple coumaran.[12] The differences in the half-wave potentials among α-tocopherol and the three dimethylethyltocols are too slight to be of practical importance. The fact that β- and γ-tocopherols require a more positive potential for oxidation than either α-tocopherol or the dimethylethyltocols, is in accord with the known effect of the number of alkyl groups on the oxidation potentials of quinones. Also in agreement with the known properties of quinone—hydroquinone systems, is the fact that an increase in the *size* of the alkyl group has little effect on the ease of oxidation.

The values of i_d/c, and also of the half-wave potentials, are constant within the concentration range investigated. Therefore, the compounds listed can be determined polarographically, and can be detected by their half-wave potentials. Moreover, α-tocopherol can be detected polarographically in the presence of β- and γ-tocopherols. Even if the diffusion current is not corrected for β-tocopherol, α-tocopherol can be determined with an accuracy of 10% or better, if the concentration of β-tocopherol does not exceed appreciably that of α-tocopherol. If the diffusion current is corrected for the β-tocopherol, a much greater accuracy can be obtained. An example of the current voltage curve of a mixture of α- and β-tocopherols is given in Figs. 4 A and B.



Curve	Compound	Concn. (molar × 10^3)
I	β-Tocopherol	1.00
II	γ-Tocopherol	1.01
III	Mixt. α-Tocopherol	1.01
	β-Tocopherol	0.986
IV	Curve III for α-tocopherol cor. for β-tocopherol	

Fig. 4.—α-, β- and γ-tocopherols in buffer I.

The large difference between the values of i_d/c for α-tocopherol (av. 2.20) and that of the dimethylethyltocols (av. for 5-ethyl, 1.96; 7-ethyl, 1.85; and 8-ethyl, 2.06) was at first glance very striking. However, gold chloride titration showed the dimethylethyltocols to be impure (5-ethyl, 93.2%; 7-ethyl, 92.5%; 8-ethyl, 98.2%). When these values of i_d/c are corrected to 100% purity, they show much better agreement among them-

(12) See ref. 2 for further comparisons between 6-hydroxychromans and 5-hydroxycoumarans in this respect.

selves (5-ethyl, 2.10; 7-ethyl, 2.00; 8-ethyl, 2.10), although they are still slightly lower than the value obtained for α-tocopherol. On the other hand, in view of the large i_r correction, the accuracy of the determination of i_d/c is probably not greater than 5%.

An interesting case in which the purification of a sample of crude α-tocopherol was followed polarographically is shown in Table II (the two samples of α-tocopherol were prepared by H. C. Miller by a method which did not involve the use of phytol). The first product, purified by distillation alone, gave a correct carbon and hydrogen analysis, but the value of i_d/c was only 1.16, indicating that the sample contained only about 53% of α-tocopherol. Moreover, the half wave potential (+0.286 v.) showed that the impurity was inert to the dropping mercury anode. When this tocopherol was purified by the method of Tishler and Wendler,[13] there resulted a product whose i_d/c was 2.14, only slightly below the values obtained for the other samples of synthetic α-tocopherol.

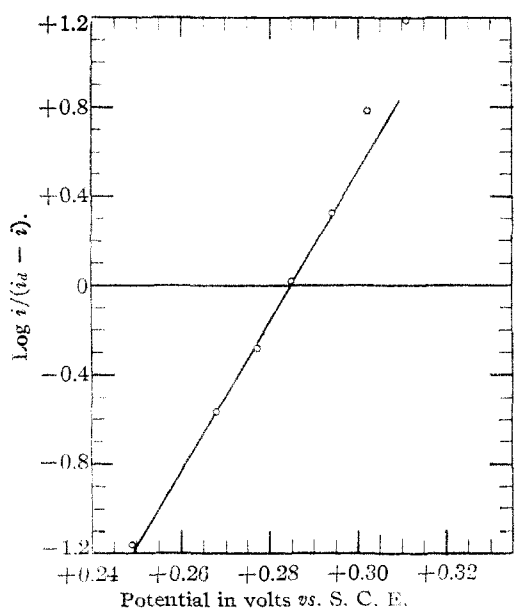


Fig. 5.—Analysis of current-voltage curve for 1.128×10^{-3} M α-tocopherol in buffer I.

An example of the analysis of the waves is given in Fig. 5. When the values of log $i/i_d - i$ (corrected for i_r) were plotted against the potential, there resulted a straight line with a slope of 0.0295, corresponding to a transfer of two electrons.

(13) Tishler and Wendler, THIS JOURNAL, **63**, 1532 (1941).

The data in Table III show the effects of a change in the concentration of aniline and perchloric acid in the buffers, and of a change in pH, upon the anodic waves of α-tocopherol and 5,7-dimethyl-8-ethyltocol.

TABLE III

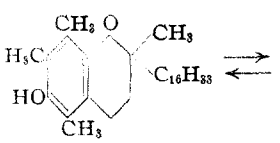
ANODIC WAVES OF α-TOCOPHEROL AND 5,7-DIMETHYL-8-ETHYLTOCOL IN ANILINE–PERCHLORIC ACID BUFFERS

Buffer	pH	Concn. $M \times 10^3$	i_d, microamp.	$i_d/c \times 10^3$	$\pi^1/_2$ (S. C. E.) (cor. for iR)
		α-Tocopherol			
V	..	1.63	3.56	2.18	+0.248
I	4.02	0.987	2.17	2.20	+ .284
II	(4.02)[a]	0.912	2.27	2.49	+ .288
VI	3.73	0.951	2.31	2.43	+ .299
VII	1.66	1.31	3.05	2.33	+ .407
		5,7-Dimethyl-8-ethyltocol			
I	4.02	0.739	1.55	2.10	+0.290
II	(4.02)[a]	1.07	2.45	2.29	+ .294
III	(4.02)[a]	0.976	2.29	2.35	+ .295
IV	(4.02)[a]	1.101	2.61	2.37	+ .297
VI	3.73	1.02	2.33	2.29	+ .304
VIII	1.97	0.978	2.02	2.07	+ .412
VII	1.66	0.987	2.15	2.18	+ .418

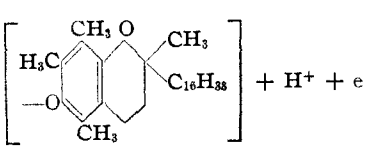
[a] The ratio of aniline to anilinium perchlorate was the same as that in buffer I, but the pH was not experimentally determined.

There is a slight, but definite, increase in the diffusion currents of α-tocopherol and of 5,7-dimethyl-8-ethyltocol as the concentration of aniline decreases in the buffer. The data in Table III, when used to calculate $\Delta\pi^1/_2/\Delta p$H for α-tocopherol, give a value of 0.052 volt in a pH range between 4.0 and 1.7, while the average value for 5,7-dimethyl-8-ethyltocol in the same pH range is 0.055.

From their measurements of the "apparent oxidation potential," Golumbic and Mattill[14] proposed the following reaction mechanism for the oxidation of α-tocopherol

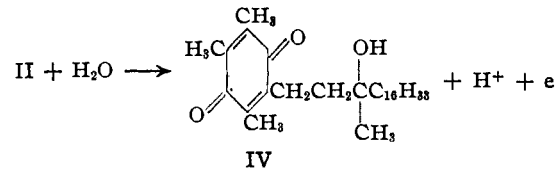


I



II

(14) Golumbic and Mattill, *J. Biol. Chem.*, **134**, 535 (1940).



IV

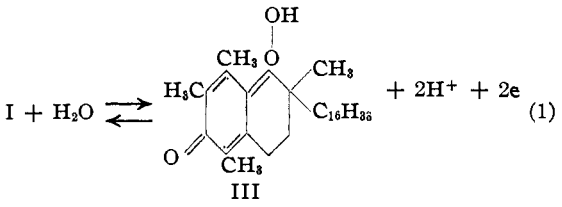
If the oxidation occurred in this manner at the dropping electrode, the equation of the wave would be given by

$$\pi = \pi_{1/2} - 0.0591 \log i/i_d - i$$

Actually the following relation was found to hold

$$\pi = \pi_{1/2} - \frac{0.0591}{2} \log i/i_d - i$$

The validity of this expression lends support to the mechanism proposed by Smith, Kolthoff, Wawzonek and Ruoff[2] for the oxidation of *p*-hydroxychromans at the dropping mercury electrode. Applied to α-tocopherol it is written as follows



III

III ⟶ IV (2)

The reversible reaction (1) involves a change in the half-wave potential of 0.0591 volt per unit change of *p*H. The experimentally determined value is in reasonable agreement with the calculated one. If the half-wave potential of α-tocopherol in buffer I is extrapolated to a *p*H of zero, a value of +0.77 volt is found (*vs.* normal hydrogen electrode). This is about 0.16 volt more positive than the "apparent oxidation potential" reported by Golumbic and Mattill. According to Adkins and Franklin[15] there is, in general, no relation between an "apparent oxidation potential" and the half-wave potential.

Summary

1. α-Tocopherol, and three isomeric dimethylethyltocols, are oxidized at the dropping mercury anode in 75% ethanol solutions containing aniline–anilinium perchlorate, or perchloric acid, as buffers and supporting electrolytes. In acetate buffers, however, the mercury is oxidized before a limiting current is reached.

2. β- and γ-tocopherols are oxidized at the dropping mercury electrode at more positive potentials than is α-tocopherol.

3. The equation of the waves for the oxidation of α-tocopherol and 5,7-dimethyl-8-ethyltocol supports the mechanism proposed by Smith, Kolthoff, Wawzonek and Ruoff for the oxidation of *p*-hydroxy-chromans and -coumarans.

4. α-Tocopherol and the three dimethylethyltocols can be determined polarographically. The accuracy is of the order of 5%. In an aniline–anilinium perchlorate buffer of given composition the diffusion current (corrected for i_r) is found to be proportional to the concentration. Within certain limits it is possible to determine polarographically α-tocopherol in the presence of β- and γ-tocopherols.

(15) Adkins and Franklin, THIS JOURNAL, **63**, 2381 (1941).

MINNEAPOLIS, MINN. RECEIVED DECEMBER 13, 1941

[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

The Preparation of β-Keto Amines by the Mannich Reaction

BY F. F. BLICKE AND J. H. BURCKHALTER[1,2]

Tertiary amines of the type $RCOCH_2CH_2NR'_2$ (R = aryl, R′ = alkyl) can be obtained readily by means of the Mannich reaction

$$RCOCH_3 + CH_2O + HNR'_2 \cdot HCl = RCOCH_2CH_2NR'_2 \cdot HCl + H_2O$$

The extent to which this reaction might be serviceable for the preparation of corresponding secondary amines, $RCOCH_2CH_2NHR'$, has hardly been investigated. It might be predicted, however, that its usefulness for this purpose would be a very limited one.

Mannich and Heilner[3] found that acetophenone, formaldehyde and methylamine hydrochloride react readily, when mixed in the proportions shown in equation A, to yield methyldi-(β-benzoylethyl)-amine hydrochloride (I), in 31% yield,

(1) This paper represents part of a dissertation to be submitted to the Horace H. Rackham School of Graduate Studies by J. H. Burckhalter in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

(2) Parke, Davis and Company Research Assistant, 1940.

(3) Mannich and Heilner, *Ber.*, **55**, 362 (1922).