Oxidation of Tocopherols and Related Chromanols with Alkaline Ferricyanide*

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Oxidation of model compounds of α-, β-, γ-, and δ-tocopherol and of some other tocopherol analogs with alkaline ferricyanide produces two different types of products (Scheme 1). When the 6-chromanol has an unsubstituted 5-position, the coupling reaction gives rise to a spiroketal trimer (e.g. 13a) thus following the general reaction pattern of alkyl substituted p-alkoxyphenols oxidized with alkaline ferricyanide. However, when the 5-position carries a methyl group, as in the naturally occurring α- and β-tocopherol, spiro dimers are formed by reactions involving both carbon-oxygen and benzylic coupling (9).

The importance of the tocopherols as biological antioxidants has stimulated the interest in the course of their oxidation. A variety of reagents have been used and a diversity of products have been identified.1 Oxidation of α-tocopherol2,3 (1) or of its model compounds, 6-hydroxy-2,2,5,7,8-pentamethylchroman,4-6 with potassium ferricyanide in alkaline solution has been studied by a number of workers. This reagent is of particular interest since the initial oxidation step involving formation of a mesomeric aryloxy radical9a is apparently the same as in the enzymatic oxidation of phenols,9b hence potassium ferricyanide oxidation can be expected to imitate enzymatic oxidative coupling. The reaction is usually carried out in a two phase system consisting of an aqueous alkaline layer and an organic layer, and the main product, a yellow spiro dimer 9a is formed in high yield.4 In addition to the spiro dimer, small amounts of a trimer 10a have been isolated and characterized.8 The same two compounds have been isolated from rat liver and proposed as metabolites of α-tocopherol.3,10,11 Oxidation of other naturally occurring tocopherols (2–4) or tocol derivatives of synthetic origin (5–8) have


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OXIDATION OF TOCOPHEROLS

\[ R_\alpha \text{= C}_{10}H_{22} \text{ or CH}_3 \text{ (model compound)} \]

\[
\begin{array}{cccccc}
R_1 & R_2 & R_3 & R_4 & R_1 & R_2 & R_3 \\
1 & CH_3 & CH_3 & CH_3 & \alpha\text{-tocopherol} & 5 & H & CH_3 & CH_3 & 5,7\text{-dimethyltocol} \\
2 & CH_3 & H & CH_3 & \beta\text{-tocopherol} & 6 & H & CH_3 & H & 7\text{-methyltocol} \\
3 & CH_3 & CH_3 & H & \gamma\text{-tocopherol} & 7 & H & H & CH_3 & 5\text{-methyltocol} \\
4 & CH_3 & H & H & \delta\text{-tocopherol} & 8 & H & H & H & \text{tocol} \\
\end{array}
\]

attracted much less interest\textsuperscript{1} and their oxidation with alkaline ferricyanide has not been previously reported.

In an extensive study of the oxidation of 2- and 3-alkyl-4-methoxyphenols with alkaline ferricyanide, Hewgill \textit{et al.}\textsuperscript{12} have been able to establish that the formation of spiroketal trimers of type \textit{II} is a very general reaction pattern of these phenols. Similar oxidation of fully substituted compounds like 4-methoxy-2,3,5,6-tetramethylphenol\textsuperscript{12} gives a dimer \textit{II} formed by carbon-oxygen coupling. \textit{\alpha}-Tocopherol (\textit{I}), which has no unsubstituted positions in the aromatic ring and thus would be comparable to 4-methoxy-2,3,5,6-tetramethylphenol, does not give a dimer of type \textit{II}. Instead a spiro dimer \textit{IIa} is the main oxidation product, formation of which involves both carbon-oxygen and benzylic coupling. This exception of \textit{\alpha}\text{-tocopherol from the general oxidation pattern of alkyl substituted p-alkoxyphenols suggested the present investigation.

The results in our previous study\textsuperscript{1} imply that spiro dimers of type \textit{II} might not be formed from all the tocopherols (\textit{I}–\textit{IV}). The aim of this investigation was therefore to determine what oxidation products are formed from the different tocopherols upon treatment with alkaline ferricyanide. We also wanted to establish the structural requirements of the chromanol necessary for the formation of spirodimers of type \textit{II}. This knowledge may be of importance to the understanding of the biological function of the tocopherols. The mechanism suggested by Hewgill and Hewitt\textsuperscript{13} for the formation of spiroketals can very well be applied to the formation of similar ketals from \beta-, \gamma-, and \delta-tocopherol. Tocopherol dimers analogous to the proposed intermediates in this mechanism have been previously described.\textsuperscript{1}

OXIDATION REACTIONS AND RESULTS

Model compounds\textsuperscript{14} of the tocol derivatives where the isoprenoid side chain has been replaced by a methyl group, were used throughout. This gave us the advantage of working with crystalline compounds of lower molecular weight than the natural products.

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\( \beta \)-Tocopherol (2). Treatment of a solution of the \( \beta \)-model compound (2) in light petroleum with an alkaline solution of potassium ferricyanide at room temperature afforded as the main product (31%) a yellow crystalline compound melting at 151–154°. The molecular weight was determined to 415, indicating that the substance is a dimer of the \( \beta \)-model. The IR-spectrum, which is very similar to that of the \( \alpha \)-spiro dimer \(^1\) \( 9a \), exhibits two bands at 1650 and 1670 cm\(^{-1}\) indicating a conjugated unsaturated ketone.\(^{16}\) The UV-spectrum shows \( \lambda_{\text{max}} \) (hexane) 331 and 298 m\(\mu\), which is also in accord with the UV-absorption of \( 9a \), the compound is therefore assigned structure \( 9b \). The NMR-spectrum is consistent with this structure and exhibits two one-proton singlets at ppm 6.39 and 5.62 representing one aromatic and one vinylic proton, respectively, and singlets at ppm 2.05 and 1.98 (3H each) representing.
methyl groups assigned to the aromatic and the cyclohexadienone ring, respectively. This assignment is based on comparison with the spectrum of the \( \beta \)-model trimer \(^1\) (10b).

Further evidence for the structure 9b was obtained by treating the yellow compound with ascorbic acid in ethanol solution. This produced a white compound, m.p. 183—185\(^\circ\), which is more polar than the \( \beta \)-model (2) \((R_f=0.30\) and 0.36, respectively, in ether-light petroleum 3:10). The UV-spectrum exhibits \( \lambda_{\text{max}} \) (hexane) 298 m\( \mu \) and the IR-spectrum shows a broad OH-stretching band at 3400 cm\(^{-1}\). These data indicate that the compound is \( \beta \)-tocopherylthene (14b). In the NMR-spectrum, which is consistent with this structure, aromatic protons appear as a singlet (2H) at ppm 6.50; a triplet centered at 2.69 (8H) represents benzylic protons in two chroman moieties together with four protons from the interconnecting ethylene chain. These

\[
\begin{array}{cccc}
13a & R_1 & CH_3 & R_2 & CH_3 \\
13b & CH_3 & R_1 & CH_3 & H \\
13c & H & R_2 & CH_3 & H \\
13d & H & H & CH_3 & H \\
14a & CH_3 & R_1 & CH_3 & H \\
14b & CH_3 & R_2 & H & CH_3 \\
14c & H & H & H & CH_3 \\
\end{array}
\]

four protons appear as a singlet overlapping with the centre peak of the triplet.

Formation of \( \alpha \)-tocopherylthene (14a) by treatment of the \( \alpha \)-spiro dimer 9a with ascorbic acid has been reported by Nelan and Robeson.\(^4\) The \( \beta \)-tocopherylthene (14b) could also be reoxidized to the spiro dimer 9b using alkaline ferricyanide as described. These cumulative data form conclusive evidence that the main product formed in this oxidation of the \( \beta \)-model compound is the spiro dimer 9b.

TLC of the original crude oxidation mixture revealed several minor reaction products, most of them of polar nature. One of the products was further investigated and found to be identical with the previously described \(^1\) \( \beta \)-model trimer 10b, identified by co-chromatography and spectral comparisons.

5,7-Dimethyltocool model (5). When this compound was oxidized with alkaline ferricyanide as described for the \( \beta \)-model (2) a bright yellow crystalline compound was obtained in 38 \% yield. The molecular weight was determined to 410 indicating that the compound is a dimer of the tocol derivative 5. IR- and UV-spectra are very similar to those of the \( \beta \)-spiro dimer and are recorded in Table 1. The NMR-spectrum (CCl\(_4\)) exhibits a broad singlet at
ppm 6.36 (2H) which is split into two one-proton singlets at 6.52 and 6.65 when the spectrum is recorded using deuteropyridine as solvent, thus indicating the presence of one aromatic proton and one vinylic proton at the \( \beta \)-position to a carbonyl group. In the spectrum of the \( \beta \)-model spiro dimer 9b the vinylic proton, which in this case is in the \( x \)-position to the carbonyl group, appears as a singlet at ppm 5.62. The difference in chemical shift for vinylic protons at the \( x \)- and \( \beta \)-positions to the carbonyl group is apparently due to shielding alternatively deshielding of the protons by the keto group. A similar observation is also made in the spectrum of the spiroketal trimer of 3-t-butyl-4-methoxyphenol \(^{16} \) (11, \( R\!=\!(CH_3)_3C\text{--} \)) where one singlet, apparently representing the \( x \)-proton, appears at ppm 5.23 while the signal due to the \( \beta \)-proton falls at 5.83.

The spectrum in the CCl\(_4\)-solution also shows two signals at ppm 2.08 (s) and 1.82 (d) (3H each) representing methyl groups on aromatic and cyclohexadienone rings, respectively. These data are consistent with the structure 9c, a spiro dimer of the 5,7-dimethyltococ model (5). The structure was further established by ring opening with ascorbic acid as described for the \( \beta \)-spiro dimer which afforded a dihydroxy-dimer 14c analogous to the compounds formed from the \( x \)- and \( \beta \)-spiro dimers upon similar treatment (14a and 14b). Chromatographic and spectral data (Table 1) are consistent with this structural assignment. The dihydroxy dimer 14c was also re-oxidized to compound 9c using alkaline ferricyanide as described for \( \beta \)-tocopherylethane (14b).

The structure of the compound 9c as a spirodimer of the 5,7-dimethyltococ model compound formed by benzylic coupling involving the 5-methyl groups and not the alternative 7-methyl groups to give the structure 15 was determined by the NMR-spectroscopy. This showed a small splitting (\( J\sim 1 \text{cps} \)) in the peak representing the methyl group in the cyclohexadienone ring (ppm 1.82) which is apparently caused by coupling to the vinyl proton. This proton must thus be adjacent to the methyl group as in 9c and not as in structure 15.

![Diagram of compound 15](image.png)

Since the spiro dimer has a sharp melting point and is chromatographically pure, the third possible structure which could be formed by benzylic coupling between a 5-methyl group in one molecule and a 7-methyl in another, is highly unlikely. If such a coupling had occurred, a mixture of all the three structures would probably have been the result of the oxidation.

5-Methyltococ model (8). Oxidation of this compound was very similar to the oxidation of the \( \beta \)-model. By preparative TLC, two products were obtained with \( R_F \) 0.45 (yellow) and 0.52 (colourless) in ether-light petroleum 2:3. The IR-spectra of the two products revealed the presence of both carbonyl and hydroxyl groups, the latter confirmed by the NMR-spectra, which were complex and not well resolved. On the basis of the apparent chromatographic

purity of the products, they are considered to be adducts of more than three chromanol molecules. Their structures were not further investigated.

\( \gamma \)-Tocopherol (3). Treatment of the \( \gamma \)-model compound (3) as described for the \( \beta \)-model produced a reaction mixture that could not be separated by preparative TLC because of extensive decomposition of the originally yellow reaction product to green and red coloured materials on the silica gel plate. However, when the crude reaction mixture was dissolved in ether and stored at \(-20^\circ\), yellow crystals deposited (40\% yield). The UV-spectrum of the yellow compound shows \( \lambda_{\text{max}} \) (hexane) 345 and 301 \( \mu \) and the IR-spectrum, which has no OH-absorption band, exhibits two bands at 1650 and 1685 cm\(^{-1}\) indicating a conjugated unsaturated ketone.\(^{16}\) Conclusive structural evidence was obtained from the NMR-spectrum. This does not show any signals due to aromatic or vinylic protons, indicating that the structure is not a spirodimer similar to the main products from the oxidation of \( \alpha \)- and \( \beta \)-tocopherol (9a and 9b, respectively). A singlet at ppm 2.10 (12H) represents four aromatic methyl groups. Two other methyl groups appear as singlets at 1.82 and 1.95 and are assigned to a cyclohexadienone ring. These data, which show that the compound is a trimer, are consistent with the spiroketal structure 13a, similar to the compounds obtained by Hewgill et al.\(^{12}\) in the oxidation of 3-alkyl-4-methoxyphenols (11). The spiroketal trimer 13a has three pairs of geminal methyl groups at position 2 of the chroman moiety. These methyl groups appear as a twelve-proton singlet at ppm 1.32 together with two three-proton singlets at 1.24 and 1.18. This may indicate that two geminal methyl groups are shielded by one of the aromatic nuclei. We found that this trimer decomposed very easily; even moderate heating (<100\(^{\circ}\)) converted it to a red-coloured product. For that reason we were not able to recrystallize the compound nor could we get a sharp melting point.

\( \delta \)-Tocopherol (4). When the model compound of \( \delta \)-tocopherol (4) was oxidized with alkaline ferricyanide, a yellow product was formed which behaved very similarly to the trimer 13a obtained from the \( \gamma \)-model. This product could not be crystallized in the same way as 13a and it decomposed rapidly to green and red coloured substances when purification by preparative TLC was attempted on silica gel or aluminium oxide. However, by column chromatography on silica gel that had been washed with concentrated ammonia and activated at 130\(^{\circ}\), we were able to obtain a reasonably pure crystalline material. The UV-spectrum of the compound exhibits \( \lambda_{\text{max}} \) (hexane) 348 and 296 \( \mu \) and the IR-spectrum shows two bands at 1655 and 1700 cm\(^{-1}\) indicating a conjugated unsaturated ketone.\(^{16}\) The NMR-spectrum exhibits one-proton signals at ppm 6.89 (s), 6.74 (s), and 5.70 (s, broad) representing two aromatic and one vinylic proton, and three-proton signals at ppm 2.22 (s), 2.15 (s), and 2.00 (d) representing three methyl groups, the first two of which are assigned to aromatic rings and the remaining one to a cyclohexadienone ring. These data are consistent with the formulation of the oxidation product as the spiroketal structure 13b. The small coupling between the vinylic proton and the vinylic methyl group reveals that the trimer is formed by coupling reactions involving the 5-position of the chromanol.

Similarly, \( \gamma \)-methyltocol (6) and tocol (8) model compounds were oxidized with alkaline ferricyanide to unstable yellow products with similar chemical
properties as the γ-spiroketal trimer 13a (red decomposition products when chromatographed or heated). The compounds were purified as described for the δ-spiroketal 13b. The UV-, IR-, and NMR-spectra, recorded in Table 1, are consistent with the formulation of these compounds as the spiroketal trimers 13c and 13d, respectively. The structure of the spiroketal trimer 13d as a product formed by coupling at the 5-position is assigned by reason of the reaction specificities observed in the other chromanols.

The nature of the green and red materials produced from the spiroketalts on storage, on thin layer chromatography, and in the presence of acid was not further investigated. However, it is noteworthy that Hewgill\(^{16}\) reports similar reactions for the spiroketal trimer of 3-t-butyl-4-methoxyphenol (II, \(R=(\text{CH}_3)_3\text{C}⁻\)). When this trimer was treated with acetic acid, the colour of the solution passed through deep green to red. The red material, which appears to be the main product, was assumed to be polyphenolic, although it was not closely studied. Hewgill\(^{15}\) also reports as a characteristic observation that during the oxidation of the phenols with alkaline ferricyanide the organic layer assumed a transitory deep blue colour. We also observed this in the oxidation of the tocol derivatives 3, 4, 6, and 8, although the colour was not strongly blue but rather a fast fading green tone. However, in the oxidation of the 7-methylationtocol model (6) the organic layer stayed blue for several minutes.

The molecular weights of the spiroketal trimers could not be determined since they decomposed rapidly at elevated temperatures, particularly as solutions.

*Scheme* 1. Oxidation of methyl substituted 6-hydroxychromans with alkaline ferricyanide. \(R_1\) and \(R_2=\text{H}\) or \(\text{CH}_3\).

DISCUSSION OF THE RESULTS

Two different types of oxidation products are formed from tocot derivatives treated with alkaline ferricyanide, the type actually obtained depending apparently on the aromatic substitution pattern in the tocot (Scheme 1). The underlying reason for the difference seems to be the previously described strong preference for reaction at the 5-position versus the 7-position of the 6-chromanols. When the compounds have a hydrogen at position 5 (3, 4, 6, 8), they form spiroketal trimers (13a—d), thus following the general reaction pattern described by Hewgill et al. for oxidation of alkyl-substituted methoxyphenols. The spiroketal trimers of these chromanols are formed regardless of whether the substituent at the 7-position is a methyl group or a hydrogen.

α-Tocopherol (I), which has a fully substituted aromatic ring, forms a spiro dimer 9a after benzylic coupling involving the methyl group at the 5-position. 5,7-Dimethyltocot (5), which like α-tocopherol has both ortho positions of the hydroxyl group substituted with methyl groups, also forms a spiro dimer 9c by coupling involving only the 5-methyl groups. β-Tocopherol (2), which has a 5-methyl group and also an unsubstituted position ortho to the hydroxyl group, still reacts only via the 5-methyl group to give a spiro dimer 9b analogous to those obtained from α-tocopherol and from the 5,7-dimethyltocot model. No reaction products formed by coupling at the 7-position were observed. The 5-methyltocot model (7) gives polymeric material, probably formed by coupling at both the 5- and 7-positions.

The experimental results can be summarized as follows:

1) Oxidation of 6-chromanols with alkaline ferricyanide yields spiroketal trimers (13) if the chromanol has a hydrogen in the 5-position (3, 4, 6, 8) while chromanols with a methyl group in the 5-position (1, 2, 5) form spirodienone ether dimers (9) under the same conditions. The spiroketal trimers are formed via both carbon-carbon and carbon-oxygen coupling and the spirodienone ethers are formed by reactions involving carbon-oxygen and benzylic coupling (Scheme 1).

2) Benzylic coupling occurs easily with methyl groups at the 5-position regardless of whether the 7-position is substituted or not.

3) Benzylic coupling with methyl groups at the 7-position has not been observed.

4) A methyl group at the 8-position seems to facilitate the coupling at the 5-methyl group and suppress polymer formation (cf. 5-methyltocot (7)).

EXPERIMENTAL

General comments. Melting points were determined with calibrated Anschütz thermometers in an electrically heated metal block. Infrared absorption spectra were measured with a Perkin-Elmer 237 spectrophotometer and ultraviolet absorption spectra were measured with a Bauch & Lomb Spectronic 505 spectrophotometer. Nuclear magnetic resonance spectra were measured in CCl₄ solutions if not otherwise stated with a Varian Associates A 60 instrument. Chemical shifts are expressed in ppm relative to tetramethylsilane (δ₄−₅₆ = 0.00 ppm). Thin layer chromatography was performed using silica gel G plates of 0.3 mm (analytical) and 1 mm (preparative) thickness. The plates were heated at 130° for 1.5 h and were stored in a dry cabinet until used. Molecular weight determinations were performed using a Hitachi Perkin-Elmer Model 115 Molecular

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Table 1. Physical data for oxidation products of methyl-substituted 6-hydroxychromans.

<table>
<thead>
<tr>
<th>Compound</th>
<th>M.p.  °C</th>
<th>Chromatography ((R_f)^a)</th>
<th>UV Hexane (\lambda_{max}) (m(\mu))</th>
<th>IR KBr-disc ((cm^{-1}))</th>
<th>NMR (\delta)-values(^{b,c})</th>
<th>Methyl groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Aromatic</td>
<td>Vinylec</td>
</tr>
<tr>
<td>(\beta)-Spirodimer (9b)</td>
<td>161—164</td>
<td>0.79</td>
<td>331, 298</td>
<td>1650, 1670</td>
<td>6.39 (s, 1)</td>
<td>5.62 (s, 1)</td>
</tr>
<tr>
<td>(\beta)-Tocopheryl-ethane (14b)</td>
<td>183—185</td>
<td>0.55</td>
<td>298</td>
<td>3400</td>
<td>6.50 (s, 2)</td>
<td>—</td>
</tr>
<tr>
<td>5,7-Dimethyltocol spirodimer (9c)</td>
<td>132—135</td>
<td>0.92</td>
<td>341, 300</td>
<td>1650, 1670</td>
<td>6.36 (e)</td>
<td>6.36 (e)</td>
</tr>
<tr>
<td>5,7-Dimethyltocol dihydroxydimer (14c)</td>
<td>178—180</td>
<td>0.65</td>
<td>294</td>
<td>3400</td>
<td>6.52 (s, 2)</td>
<td>—</td>
</tr>
<tr>
<td>(\gamma)-Spiroketal trimer (13a)</td>
<td>d</td>
<td>e</td>
<td>345, 301</td>
<td>1650, 1685</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>(\delta)-Spiroketal trimer (13b)</td>
<td>d</td>
<td>e</td>
<td>348, 296</td>
<td>1655, 1700</td>
<td>6.89 (s, 1)</td>
<td>6.74 (s, 1)</td>
</tr>
<tr>
<td>7-Methyltocol spiroketal trimer (13c)</td>
<td>d</td>
<td>e</td>
<td>345 (sh) 292</td>
<td>1640, 1690</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Tocol spiroketal trimer (13d)</td>
<td>d</td>
<td>e</td>
<td>355 (sh) 295</td>
<td>1640, 1680</td>
<td>6.55 (m)(^k)</td>
<td>6.85 (s)(^k)</td>
</tr>
</tbody>
</table>

\(^a\) On silica gel G developed in ether-light petroleum (2:3).
\(^b\) Sample in CCl\(_4\)-solution.
\(^c\) Aliphatic protons at ppm 1.35—1.10 and 1.70, benzyllic protons usually not well resolved.
\(^d\) No sharp melting point obtained.
\(^e\) Decomposed on the silica gel plate.
\(^f\) Benzyllic protons at 2.69 (t, 8H).
\(^g\) Aromatic and vinylc protons of this compound have the same shift in CCl\(_4\)-solution. When the spectrum was recorded using a pyridine-\(d_5\)-solution the peak was split into two singlets at ppm 6.52 and 6.65.
\(^h\) Benzyllic protons at 2.75 (t, 8H).
\(^i\) A small coupling between vinylc proton and vinylc methyl group \((J<1 \text{ cps})\).
\(^j\) Broad unresolved peak at 6.45 (aromatic and vinylc protons, 3H).
\(^k\) A pure sample could not be obtained, which makes the integration uncertain.
weight apparatus allowing an accuracy of ±2 % in the determinations. Redistilled light petroleum, b.p. 40—60°, was used throughout. The structure of each compound described is assigned on the basis of its characteristic spectral properties (Table 1).

Oxidation of β-tocopherol model compound (2). A solution of the β-model (0.3 g, 1.45 mmoles) in light petroleum (60 ml) was stirred for 30 min with a solution of potassium ferricyanide (1.43 g, 4.35 mmoles) in 0.2 N aqueous sodium hydroxide (20 ml). The organic layer was separated, washed twice with 25 ml of water and dried (Na₂SO₄). Evaporation of the solvent gave a thick oil that did not crystallize. When the oil was dissolved in a small amount of ether and stored at -20°, 96 mg (31 % yield) of a yellow crystalline compound, assigned structure 9b, precipitated. m.p. 151—154° (from ether).

From the filtrate was isolated 20 mg (7 %) of the β-model trimer 10b by preparative TLC, characterized by co-chromatography and spectral comparison with authentic material.

Reaction of the β-spiro dimer 9b with ascorbic acid. A solution of the β-spiro dimer (200 mg, 0.49 mmole) and ascorbic acid (1.3 g, 7.3 mmole) in ethanol (32 ml) and water (1 ml) was stirred for 15 h at room temperature, by when the yellow colour had disappeared. Water (100 ml) was added and the mixture extracted with light petroleum (3 × 50 ml) which after drying (Na₂SO₄) was evaporated in vacuo. This afforded 142 mg (72 %) of the β-tocopheryl methylene model (14b), m.p. 183—185°. A sample of this compound was oxidized with alkaline ferricyanide as described above, yielding the β-spiro dimer (9b) quantitatively.

Oxidation of the 5,7-dimethyltocanol model (5) was performed as described for the β-model. The product was purified by preparative TLC in ether-light petroleum (2:3) yielding 38 % of the spirol dimer 9c, m.p. 132—135° decomp. (from hexane). (Found: C 76.2; H 8.09; M.W. 410. Calc. for C₃₂H₄₄O₄: C 76.4; H 7.90; M.W. 408.5). When the spiro dimer was treated with ascorbic acid as described for the β-spiro dimer a dihydroxydimer 14c, analogous to β-tocopheryl methylene (14b), was formed, m.p. 178—180° (from ligroin-toluene). The dihydroxydimer 14c was re-oxidized with alkaline ferricyanide to the spiro dimer 9c as described above.

Oxidation of the 5-methyltocanol model (7) was performed as described for the β-model. Two products, isolated by preparative TLC with ether-light petroleum (2:3), were found to be adducts of more than three chromanol molecules as described above.

Oxidation of γ-tocopherol model compound (3). When the γ-tocopherol model compound (3) (0.3 g, 1.45 mmoles) was treated with potassium ferricyanide (1.43 g, 4.35 mmoles) as described for the β-model, a brownish yellow colour appeared in the organic layer. After separation and evaporation of the organic layer a dark yellow non-crystallizable oil was obtained. Attempts to chromatograph this oil on silica gel failed because the yellow reaction product decomposed to more polar green and red coloured materials. A similar colour change was obtained when the yellow oil was treated with acetic acid. When an ethereal solution of the oil was stored at -20° overnight, yellow crystals melting over a temperature ranging from 145 to 175° were obtained in 40 % yield. This m.p. interval was not changed by recrystallization from ether at -20°. (Found: C 76.3; H 7.97. Calc. for C₃₀H₄₀O₄: C 76.4; H 7.90). Elemental analysis and spectral data (Table 1) are consistent with the assignment of the compound as the spiroketal trimer 13a.

Oxidation of model compounds of δ-tocopherol (4), 7-methyltocanol (8) and tocot (8). Oxidation of these compounds was performed as described for the β-model. This produced dark yellow non-crystallizable unstable oils. The compounds were purified by column chromatography on silica gel that had been washed first with concentrated aqueous ammonia, then with water until the filtrate was neutral and finally dried at 130° for 24 h. A solution of the test compound in light petroleum was placed on the column which was then eluted with ether-light petroleum (1:1). This usually separated the yellow compound from the green and red coloured materials and the eluate containing the yellow band was collected as one fraction. Reasonably pure products could be obtained by this procedure although some decomposition to green and red materials also took place during this chromatography procedure. The structures of the oxidation products are as assigned as the spiroketal trimers (13b—d).

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