Oxygenations of Vitamin E (α-Tocopherol) and Its Model Compound, 2,2,5,7,8-Pentamethylchroman-6-ol, in the Presence of Potassium Superoxide Suspended in Tetrahydrofuran and Unusual Acyloin Rearrangements[1]

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Received November 26, 1985

In the presence of potassium superoxide (KO_2) suspended in tetrahydrofuran under an oxygen atmosphere, α-tocopherol (vitamin E) (**1**) was converted to 6-hydroxy-2,6,7,8-tetramethyl-2-(4′,8′,12′-trimethyltridecyl)-chroman-5(6*H*)-one (**2**) and 5-hydroxy-2,5,7,8-tetramethyl-2-(4′,8′,12′-trimethyltridecyl)chroman-6(5*H*)-one (**3**), and a vitamin E model compound, 2,2,5,7,8-pentamethylchroman-6-ol (**4**), to 6-hydroxy-2,2,6,7,8-pentamethylchroman-5(6*H*)-one (**5**) and 5-hydroxy-2,2,5,7,8-pentamethylchroman-6(5*H*)-one (**6**). By the use of oxygen-18, molecular oxygen was found to be incorporated into a ketonic group in **5** and a hydroxy group in **6**. Since [6a-CD_3]**5** was derived from [5a-CD_3]**4** and since **3** and **6** were converted to **2** and **5**, respectively, in the presence of KO_2 quantitatively, an acyloin rearrangement is shown to occur in the formation of the end products, **2** and **5**. On treatment of potassium hydroxide suspended in tetrahydrofuran, **4** gave **5** though its yield was low. Thus, the intermediates, **3** and **6**, are considered to result from the base-catalyzed oxygenations of **1** and **4**, respectively. The striking characteristic of the KO_2-catalyzed reactions is that the products are obtained in high yield and, in particular, **5** and **6** in quantitative yield. A possible mechanistic scheme for the KO_2-catalyzed oxygenation of vitamin E is proposed. Due to the basicity of KO_2, **1** gives rise to α-tocopherolate. The reaction of the α-tocopherolate with molecular oxygen leads to its derivative bearing a hydroperoxy group at C_5. The O–O bond cleavage of the hydroperoxide, followed by hydrogen abstraction, affords **3**, which undergoes acyloin rearrangement to yield **2**.

The superoxide radical (O_2^-) is presumed to be a harmful agent in organisms[2] and to be formed in a large number of reactions of biological importance in enzymatic and non-enzymatic processes. The reaction of an organic substrate with O_2^- is a current interest in connection with the functional significance of the radical in vivo.

Vitamin E, which is represented by naturally occurring *RRR*-α-tocopherol (*RRR*-**1**) (Figure 1), is thought to be an efficient radical scavenger.[3] It is worthwhile seeing how vitamin E reacts with O_2^-. Previously, we found that an α-tocopherol model compound, 2,2,5,7,8-pentamethylchroman-6-ol, reacted with O_2^{-1}. Nishikimi and Machlin described that a water-soluble α-tocopherol model compound, 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, was oxidized in an O_2^--generating system (xanthine–xanthine oxidase) to give 2-hydroxy-2-methyl-4-(3,5,6-trimethylbenzoquinon-2-yl)butanoic acid.[4] Yagi and his associates reported that α-tocopherol gave rise to an unknown product in a mixture of *n*-hexane and ethanol (3:1 v/v) upon addition of KO_2 solubilized with dicyclohexano-18-crown-6[5] and to 8a-hydroxy-α-tocopherone [8a-hydroxy-2,5,7,8-tetramethyl-2-(4′,8′,12′-trimethyltridecyl)chroman-6(8a*H*)-one] in an aqueous emulsion with deoxycholate upon addition of the O_2^--generating system.[6] Sawyer and his associates claimed that O_2^- acted as a base in dimethylformamide and changed α-tocopherol into the α-tocopherolate anion, which reacted with molecular oxygen to give the α-tocopheroxyl radical.[7]

These results are somewhat inconsistent. Further, since no products were isolated and characterized in the studies by Yagi's and Sawyer's groups, the reactions remain to be established. The reactions of α-tocopherol with O_2^- in aprotic solvents appear to be different from those in protic solvents.

In order to elucidate the reaction of α-tocopherol in an aprotic solvent containing O_2^-, we examined extensively the oxygenations of α-tocopherol and its model compound in the presence of KO_2 suspended in tetrahydrofuran.

Results

Oxygenation of a Vitamin E Model Compound, 2,2,5,7,8-Pentamethylchroman-6-ol, in the Presence of Potassium Superoxide. The vitamin E model compound (**4**) (Figure 1) was treated with a triple molar amount of KO_2 suspended in tetrahydrofuran under an oxygen atmosphere to give **5** quantitatively (Table I, run 1). When nitrogen was bubbled through the mixture during the reaction, most of the starting material was recovered (Table I, run 2). The structure of **5** was deduced from its spectral data and elemental analysis data and finally determined by X-ray crystallographic analysis. As has been reported preliminarily,[1] **5** is 6-hydroxy-2,2,6,7,8-pentamethylchroman-5(6*H*)-one (Figure 1).

By means of mass spectrometry and elemental analysis, the molecular formula of **5** was proved to be $C_{14}H_{20}O_3$ which corresponded to that of **4** with an additional oxygen atom. The spectral data of **5** are presented in Table II and the Experimental Section. Figure 2 shows the X-ray crystal structure of **5**. The deviations of atoms from a least-squares plane are given in Table III. The bond lengths, bond angles, atomic coordinates, and thermal parameters are shown in the supplementary material. In

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Table I. Oxygenations of α-Tocopherol and Its Model Compound with Potassium Superoxide Suspended in Tetrahydrofuran

run	compd	KO_2 1 or 4	gas phase	reaction time, h	yield, % 5	6	4[a]	2a	2b	3a	3b	7
1	4	3	O_2	3	~100							
2	4	3	N_2	3			~95					
3	4	1	O_2	1	15	15	50					
4	1	3	O_2	3				16	20	6	6	nd[b]

[a] The starting material recovered. [b] Undetermined.

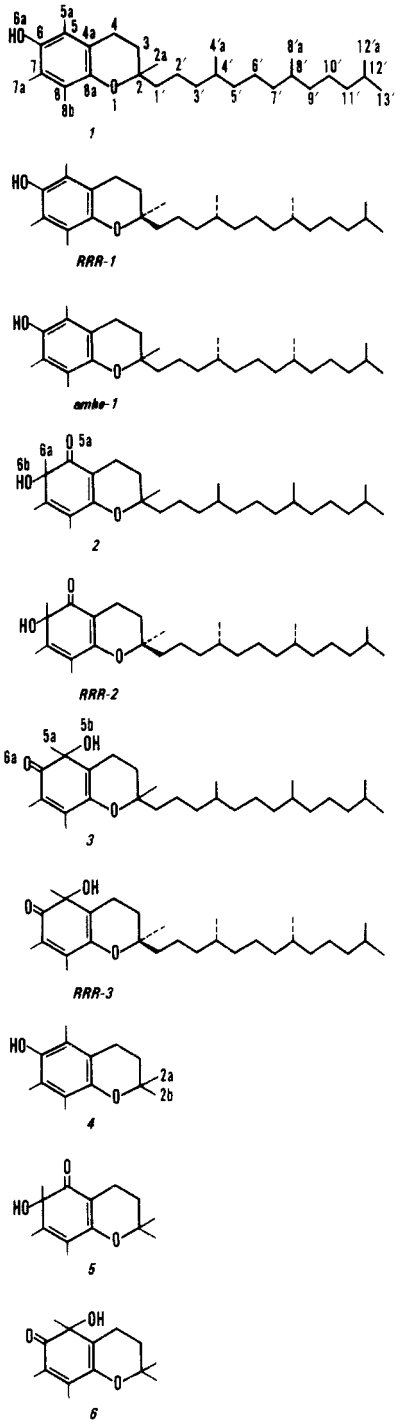

Figure 1. Molecular structures of 1, 2, 3, 4, 5, and 6.

Table II. ^{13}C NMR Chemical Shifts of the Reaction Products

carbon no.	5	2a	2b	6	3a	3b
2	75.8	75.8	75.7	73.8	76.0	76.1[a]
2a	26.0	23.3	24.4	26.4	23.4	23.4
2b	27.4			26.4		
3	31.7	29.9	30.1	32.2	30.7	30.9
4	15.5	15.1	15.3	17.5	17.2	17.3
4a	103.1	103.2	103.4	116.6	116.9	116.7
5	202.9	202.9	202.9	76.0	76.0	76.0[a]
5a				29.2	29.2	29.2
6	77.7	80.0	80.0	205.8	205.8	205.9
6a	30.1	30.2	30.1			
7	147.2	147.1	147.1	126.2	126.2	126.2
7a	13.7	13.7	13.7	11.1	11.1	11.1
8	122.2	122.3	122.3	148.8	149.0	148.8
8a	165.4	165.4	165.4	141.8	141.7	141.7
8b	11.4	11.5	11.5	14.2	14.2	14.1
1′		40.7	39.4		39.4	39.7
2′		20.9	20.9		20.9	20.9
3′,5′,7′,9′		37.4 (×4)	37.4 (×4)		37.4 (×4)	37.4 (×4)
4′		32.7[a]	32.6[a]		32.7[a]	32.6[a]
4′a,8′a		19.7 (×2)	19.7 (×2)		19.7 (×2)	19.7 (×2)
6′		24.5	24.4		24.5	24.5
8′		32.8[a]	32.8[a]		32.8[a]	32.8[a]
10′		24.8	24.8		24.8	24.8
11′		39.4	39.4		39.4	39.4
12′		28.0	28.0		28.0	28.0
12′a		22.6[a]	22.6[a]		22.6[a]	22.6[a]
13′		22.7[a]	22.7[a]		22.7[a]	22.7[a]

[a] Assigned tentatively.

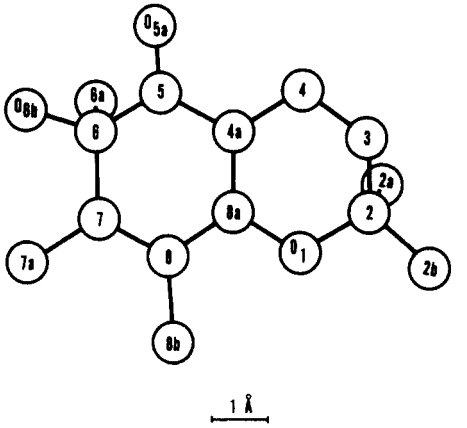

Figure 2. X-ray crystal structure of 5.

5, a ketonic group is at C_5 and hydroxy and methyl groups at C_6. The partial structure results from the migration of a methyl group at C_5 in the substrate as will be discussed later. The conjugation of double bonds in 5 extends along the bonds O_{5a}–C_5–C_{4a}–C_{8a}–C_8–C_7. From a molecular plane containing the conjugated double bonds, C_2 and C_3, as well as C_5 and C_6, are deviated in opposite directions to each other (Table III).

When 4 was treated with an equimolar amount of KO_2, 5 and 6 each were isolated in 15% yield after silica gel separation (Table I, run 3). Both their molecular weights and molecular formulas are identical, and their spectral data are similar. The spectral data of 6 are presented in Table II and the Experimental Section. On the basis of the spectral and X-ray crystallographic data, 6 was identified as 5-hydroxy-2,2,5,7,8-pentamethylchroman-6-

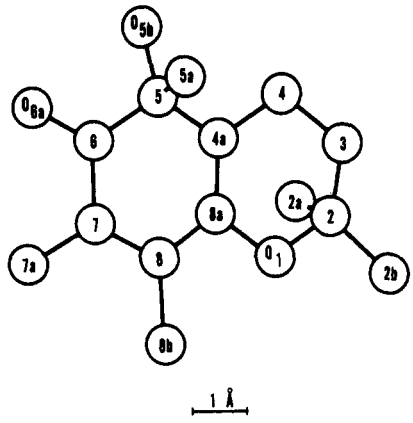

Figure 3. X-ray crystal structure of **6**.

Table III. Deviations of Atoms (Å) from Least-Squares Planes

atoms forming least-squares planes	5	6
C(4)	−0.024 (2)	0.006 (7)
C(4a)	0.033 (2)	−0.038 (7)
C(5)	−0.020 (2)	
C(6)		0.028 (7)
C(7)	0.038 (2)	−0.028 (7)
C(7a)	−0.006 (2)	0.007 (7)
C(8)	−0.063 (2)	−0.025 (7)
C(8a)	0.042 (2)	0.043 (7)
C(8b)		0.007 (7)
other atoms	**5**	**6**
O(1)	0.122 (2)	0.175 (6)
C(2)	0.471 (2)	0.523 (7)
C(2a)	1.971 (2)	2.036 (8)
C(2b)	0.050 (2)	0.088 (8)
C(3)	−0.318 (2)	−0.286 (7)
C(5)		−0.281 (7)
C(5a)	−0.237 (2)	−1.757 (8)
O(5b)		0.565 (6)
C(6)	0.328 (2)	
C(6a)	1.830 (2)	0.234 (6)
O(6b)	−0.406 (2)	
C(8b)	−0.290 (2)	

(5*H*)-one (Figure 1), which has been reported preliminarily;[8] it having hydroxy and methyl groups at C_5 and a ketonic group at C_6 is a positional isomer of **5**, and the conjugation of its double bonds extends along O_{6a}–C_6–C_7–C_8–C_{8a}–C_{4a}. Figure 3 shows the X-ray crystal structure of **6**. The deviations of atoms from a least-squares plane are presented in Table III. The bond lengths, bond angles, atomic coordinates, and thermal parameters are shown in the supplementary material.

Oxygenation of α-Tocopherol in the Presence of Potassium Superoxide. The reaction of 2-*ambo*-α-tocopherol (*ambo*-**1**) (Figure 1) in the presence of a triple molar amount of KO_2 suspended in tetrahydrofuran under an oxygen atmosphere gave five oxidation products, **2a**, **2b**, **3a**, **3b**, and **7** (Table I, run 4). The structures of **2a**, **2b**, **3a**, and **3b** were determined as described below, but the structure of **7** remains unclarified.

Their ultraviolet (UV), infrared (IR), and nuclear magnetic resonance (NMR) spectra (Experimental Section and Table II) show that **2a** and **2b**, as well as **3a** and **3b**, are quite similar. The ^{13}C-chemical shifts of **2a** are identical with those of **2b** with the exception of the chemical shifts of $C_{1'}$ (differential 1.3 ppm) and C_{2a} (1.1 ppm). The ^{13}C-chemical shifts of the corresponding carbon atoms in

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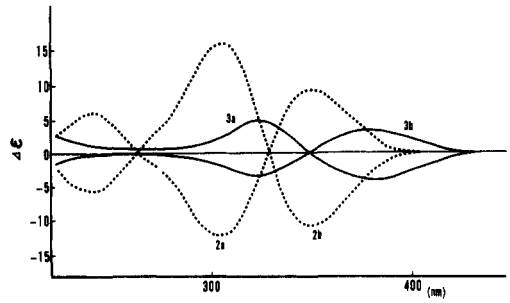


Figure 4. Circular dichroism spectra of **2a**, **2b**, **3a**, and **3b** in *n*-hexane.

3a and **3b** are coincident with no or small differences within 0.3 ppm. In addition, in the circular dichroism (CD) spectra of the oxygenation products obtained from optically active *RRR*-**1**, *RRR*-**2a**, **-2b**, **-3a**, and **-3b** all exhibit Cotton effects. As shown in Figure 4, the CD curves of *RRR*-**2a** and **-3a** are antipodal to those of *RRR*-**2b** and **-3b**, respectively. Therefore, **2a** is an epimer of **2b**, and **3a** of **3b**.

In regard to the UV and IR spectra, **2a** and **2b** are similar to **5**, and **3a** and **3b** to **6**. In addition, there is no difference between the chemical shifts of hydrogen and carbon atoms in *RRR*-**2a** and **-2b** and of the corresponding atoms in **5**, and between the chemical shifts of the atoms in *RRR*-**3a** and **-3b** and of the corresponding atoms in **6**. Thus, the structures of *RRR*-**2a** and **-2b** without an isoprenoid side chain are equivalent to that of **5** without a methyl group at C_2, and the structures of *RRR*-**3a** and **-3b** without an isoprenoid side chain to that of **6** without a methyl group at C_2: i.e., *RRR*-**2a** and **-2b** are the C_6-epimers of (2*R*,4′*R*,8′*R*)-6-hydroxy-2,6,7,8-tetramethyl-2-(4′,8′,12′-trimethyltridecyl)chroman-5(6*H*)-one, and *RRR*-**3a** and **-3b** are the C_5-epimers of (2*R*,4′*R*,8′*R*)-5-hydroxy-2,5,7,8-tetramethyl-2-(4′,8′,12′-trimethyltridecyl)chroman-6(5*H*)-one (Figure 1). These structures are supported by the elemental analysis data.

The absolute configurations at C_6 of *RRR*-**2a** and **-2b**, and at C_5 of RRR-**3a** and **-3b** were assigned on the basis of their lanthanide-induced shifts in ^1H NMR. The trends in the quantitatively Eu(fod)$_3$-induced shifts of three methyl groups at each of C_6, C_7, and C_8 in *RRR*-**2a**, *RRR*-**2b**, and **5** are consistent, and the trends in the Eu(fod)$_3$-induced shifts of three methyl groups at each of C_5, C_7, and C_8 in *RRR*-**3a**, *RRR*-**3b**, and **6** are consistent also. The profiles of their Eu(fod)$_3$-induced shifts are shown in supplementary material. When a certain amount of Eu(fod)$_3$ was added to 47 μmol of each compound, the Eu(fod)$_3$-induced shift of a methyl group at C_2 in *RRR*-**2a**, corresponding to that of one of two methyl groups at C_2 in **5**, is larger than the shift in *RRR*-**2b**, corresponding to that of the other methyl group at C_2 in **5**. Further, the Eu(fod)$_3$-induced shift of a methyl group at C_2 in *RRR*-**3a**, corresponding to that of one of two methyl groups at C_2 in **6**, is larger than the shift in *RRR*-**3b**, corresponding to that of the other methyl group at C_2 in **6**. The methyl groups at C_2 in *RRR*-**2a** and **-3a** are presumed to be closer to a hydroxy group spatially than the methyl groups at C_2 in *RRR*-**2b** and **-3b**, respectively. It is concluded from comparison between their molecular models that *RRR*-**2a**, **-2b**, **-3a**, and **-3b** are (2*R*,6*S*,4′*R*,8′*R*)-**2**, (2*R*,6*R*,4′*R*,8′*R*)-**2**, (2*R*,5*R*,4′*R*,8′*R*)-**3**, and (2*R*,5*S*,4′*R*,8′*R*)-**3**, respectively.

Oxygenation of the Vitamin E Model Compound in the Presence of Potassium Hydroxide. The vitamin E model compound, **4**, was treated with a triple molar amount of potassium hydroxide suspended in tetrahydrofuran under an oxygen atmosphere. A reaction

product, **5**, was obtained in 16% yield and no other reaction products could be isolated.

Acyloin Rearrangement. When 1 mmol of **6** was added to 1 mmol of KO_2 suspended in tetrahydrofuran, **5** was obtained quantitatively. Similarly, **3a** was converted to **2a**, and **3b** to **2b**. These results reveal that **6**, **3a**, and **3b** are the intermediates of **5**, **2a**, and **2b**, respectively. Acyloin rearrangement is assumed to lead the intermediates to the end products. Since the products, **3** and **6**, are stable under silica gel treatment, it is clear that the rearrangements were not catalyzed by silica gel.

Labeling Experiments for the Elucidation of the Reaction Mechanism. In the presence of an equimolar amount of KO_2, [5a-, 7a-, or 8b-CD_3]**4** gave labeled **5** and labeled **6**. In the ^1H NMR and ^{13}C NMR spectra of labeled **5** derived from [5a-CD_3]**4**, the intensity of a ^1H signal at 1.34 ppm due to three methyl groups at C_2 and C_6 is two thirds of that of **5**, a ^{13}C signal at 30.1 ppm due to a methyl group at C_6 in **5** disappears, and two ^1H signals at 1.99 and 1.82 ppm and two ^{13}C signals at 13.7 and 11.4 ppm due to two methyl groups attached to sp^2 carbon atoms (C_7 and C_8) in **5** remain unchanged. Thus, [5a-CD_3]**4** is proved to be converted into [6a-CD_3]**5**. On the basis of comparison between the ^1H NMR spectra of labeled **5** and **5** and between the ^1H NMR spectra of labeled **6** and **6**, [7a-CD_3]**5** is found to be formed from [7a-CD_3]**4**, [8b-CD_3]**5** from [8b-CD_3]**4**, [5a-CD_3]**6** from [5a-CD_3]**4**, [7a-CD_3]**6** from [7a-CD_3]**4**, and [8b-CD_3]**6** from [8b-CD_3]**4**. These findings are in accord with the fact that a methyl group at C_5 in **4** migrates to C_6 on the pathway from **4** to **5**.

Further, **4** reacted with an equimolar amount of KO_2 under an $^{18}O_2$ (90 atm %) atmosphere to yield [^{18}O]**5** and [^{18}O]**6**: the m/e's of molecular ions (M^+) are 236 for **5** and **6** and 238 for [^{18}O]**5** and [^{18}O]**6**.

By comparison of the IR spectra of **5** and of [^{18}O]**5**, the C=O stretching absorption band of [^{18}O]**5** (1613 cm^{-1}) is found to appear 26 cm^{-1} lower than the corresponding band of **5** (1639 cm^{-1}). On the other hand, the IR spectra of **6** and [^{18}O]**6** show the same C=O absorption band at 1641 cm^{-1}, but the respective OH absorption bands at 3470 and 3450 cm^{-1}.

In the ^{13}C NMR spectrum of a 1:1 mixture of **5** and [^{18}O]**5**, the ^{13}C NMR resonances of the ketonic carbon atoms are split into two peaks with a space of 0.038 ppm. This shows that the signal of the ketonic carbon atom in [^{18}O]**5** (202.925 ppm) is shifted upfield 0.038 ppm by an ^{18}O-isotope effect relative to that in **5** (202.963 ppm). In the ^{13}C NMR spectrum of a 1:1 mixture of **6** and [^{18}O]**6**, a split peak appears at about 76.0 ppm (75.979 ppm for C_5 in **6** and 75.955 ppm for C_5 in [^{18}O]**6**; the ^{18}O-isotope effect 0.024 ppm). The magnitude of the ^{18}O-induced upfield shifts is reasonable when compared with the reported values of [^{18}O]ketones (acetone 0.050 ppm, benzophenone 0.045 ppm) and [^{18}O]alcohols (benzyl alcohol 0.023 ppm, isopropyl alcohol 0.023 ppm).[9] These findings show that the incorporation of molecular oxygen into an intermediate is necessary for the formation of **5** and then the migration of a methyl group from C_5 to C_6 in **5**, accompanying the interchange of hydroxy and ketonic groups at these carbon atoms, leads to **6**; the last step turns out to be acyloin rearrangement.

Discussion

The experimental data so far obtained indicate that O_2^- acts as a base, nucleophile, radical, or electron transfer reagent.[10] Here, it is noted that O_2^- is an effective Brønsted base in aprotic solvents. Sawyer and his associates examined the reaction of α-tocopherol with O_2^- in dimethylformamide by cyclic voltammetry and UV–visible absorption spectroscopy.[7] They proposed the following mechanism for the reaction on the basis of the basic character of O_2^-, where TOH = α-tocopherol, TO^- = α-tocopherolate, and TO· = the α-tocopheroxyl radical:

$$TOH + O_2^- \rightarrow TO^- + HO_2\cdot$$

$$HO_2\cdot + O_2^- \rightarrow HO_2^- + O_2$$

$$O_2 + TO^- \rightleftharpoons O_2^- + TO\cdot$$

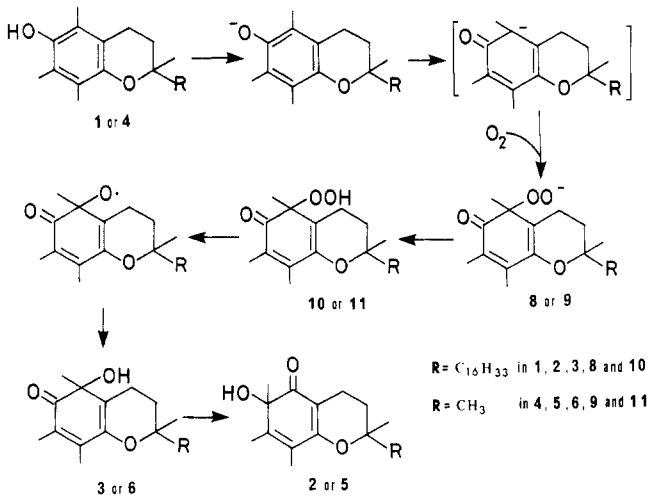
$$2TO\cdot \rightarrow \text{dimeric and dismutation products}$$

We observed, however, that when α-tocopherol reacted with KO_2 in tetrahydrofuran in the absence of water, molecular oxygen was incorporated into the substrate, and that no products from radical–radical coupling were obtained. These observations are incompatible with the above mechanism.

According to the common mechanistic explanation of base-catalyzed oxygenation,[11] the phenolate anion, which is derived from phenol in basic solvents, reacts with molecular oxygen to give the phenoxyl radical, and the phenoxyl radical either traps molecular oxygen or dimerizes. Our observations cannot be explained by this mechanism because the α-tocopheroxyl radical does not trap molecular oxygen[12] and because no dimerized products are produced under the reaction conditions used.

Recently, the phenolate anion has been suggested to react with molecular oxygen.[13] However, the spin-forbidden rule implies that the phenolate anion can hardly bond to molecular oxygen. Probably, the phenolate anion interacts on a π orbital of molecular oxygen to afford a triplet charge transfer complex, and then the complex undergoes intersystem crossing: i.e., one of the two unpaired electrons undergoes spin inversion, giving a singlet complex which is converted into a reaction product. The mechanism may account for the reactions of α-tocopherol

Scheme I



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and its model compound in the presence of KO_2 in tetrahydrofuran under an oxygen atmosphere; presumably the key steps are interactions between the α-tocopherolate anion and molecular oxygen and between the 2,2,5,7,8-pentamethylchroman-6-olate anion and molecular oxygen, through which peroxy anions, **8** and **9**, are given (Scheme I).

By proton transfer, **8** and **9** turn into hydroperoxides, **10** and **11**, respectively. The O–O bond cleavage of the hydroperoxides, followed by hydrogen abstraction, yields **3a**, **3b**, and **6**, which are converted to **2a**, **2b**, and **5**, respectively, in the presence of KO_2. The conversions of **3a**, **3b**, and **6** into the corresponding end products are considered to be acyloin rearrangements.

The acyloin rearrangement consists of the conversion of a hydroxycarbonyl compound, usually catalyzed by acid or base, into an isomeric hydroxycarbonyl compound with the interchange of the oxygen-containing groups and migration of an alkyl group to the adjacent carbon atom.[14] Hitherto, only a few examples of acyloin rearrangements in cyclic compounds have been found; 4-substituted-*p*-quinols undergo acyloin rearrangements under a base catalyst to give the corresponding 3-substituted hydroquinones and quinones.[15]

Possible pathways for the KO_2-catalyzed oxygenations of α-tocopherol and of its model compound are shown in Scheme I. The pathways are supported by the fact that **5** resulted from the KOH-catalyzed oxygenation of **4** though its yield was low. The striking characteristic of the KO_2-catalyzed oxygenations is that the products are obtained in high yield and, in particular, **5** and **6** in quantitative yield.

Experimental Section

General. All melting points were determined with a Yanagimoto microapparatus and are uncorrected. Proton and carbon-13 nuclear magnetic resonance spectra were recorded on a Varian XL-200 spectrometer with $CDCl_3$ as the solvent and with tetramethylsilane as the internal standard. Mass spectra were obtained with a Shimazu 9000 gas chromatograph–mass spectrometer. Infrared spectra of samples in KBr tablets or liquid films were taken on a JASCO IR-2 spectrometer. Ultraviolet spectra were measured with a Cary 118C spectrometer. Circular dichroism spectra of samples in *n*-hexane were obtained using a JASCO J-500A spectrometer. α-Tocopherol was purified by high-performance liquid chromatography using a Waters PrepLC System 500A with a PrepPAK-500 silica column, followed by distillation at 220 °C under a reduced pressure of 0.05 torr. A vitamin E model compound, 2,2,5,7,8-pentamethylchroman-6-ol, was prepared by the method of Lar et al.[16] and obtained as colorless needles.

X-ray Crystallography. Intensities were measured on a Philips four-circle diffractometer using graphite-monochromated Cu K_α radiation. The structures were solved by the direct method and refined by the block-diagonal least-squares method.

The crystal data of **5** are as follows: monoclinic, space group $C2/c$, $Z = 8$, $D_{calc} = 1.192$ g/cm^3, $a = 18.869$ (9), $b = 8.377$ (5), $c = 16.731$ (8) Å, $\beta = 95.04$ (5)°, $V = 2634$ Å^3. A total of 2401 reflections was observed as above the $2\sigma(I)$ level out of 3100 within the 2θ range of 6° through 156°. The final R value was 0.064, when all hydrogen atoms were included except for one alcoholic hydrogen H(O_{6b}). The average standard deviations were estimated as $\alpha_{(C-C)} = 0.003$ Å, $\sigma_{(C-C-C)} = 0.2°$.

The crystal data of **6** are as follows: monoclinic, space group $P2_1/n$, $Z = 4$, $D_{calc} = 1.166$ g/cm^3, $a = 16.465$ (8), $b = 9.473$ (5), $c = 8.656$ (4) Å, $\beta = 94.04$ (6)°, $V = 1346$ Å^3. A total of 1641 reflections was measured as above the $2\sigma(I)$ level within the 2θ range of 6° through 120°. The final R value was 0.118. Further refinement was not attempted due to the rather poor quality of the intensity data which resulted from the twinning of the crystals. The average standard deviations were 0.011 Å and 0.7° (see a paragraph at the end of paper regarding supplementary material).

Oxygenation of 2,2,5,7,8-Pentamethylchroman-6-ol (4) in the Presence of KO_2. (A) With Three Equivalents of KO_2. A solution of **4** (220 mg, 1 mmol) in dry tetrahydrofuran (THF, 20 mL) was added to a stirred suspension of KO_2 (213 mg, 3 mmol) in dry THF (50 mL) at 0 °C under an oxygen atmosphere. The mixture was stirred at 0 °C for 3 h, and then excess KO_2 was decomposed by the addition of water (10 mL). The mixture was extracted with ethyl ether. The organic phase was washed with brine, dried over anhydrous sodium sulphate, and filtered. The solvent was removed under reduced pressure, and the resulting solid residue was purified by silica gel column chromatography using a mixture of *n*-hexane and ethyl ether (1:1) as eluent. Crude 6-hydroxy-2,2,6,7,8-pentamethylchroman-5(6*H*)-one (**5**) was obtained in quantitative yield as a slightly brown solid. Recrystallization from *n*-hexane gave a pure sample of **5**: colorless needles; mp 104–105 °C; MS, m/e 236 (M^+); UV (CH_3CN) λ 327 (ε 2800), 249 nm (5500); IR (KBr) ν 3420, 1655, 1639 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.50 (s, 1 H, OH), 2.60–2.20 (m, 2 H, 4-CH_2), 1.99 (s, 3 H, 7a-CH_3), 1.82 (s, 3 H, 8b-CH_3), 1.80–1.50 (m, 2 H, 3-CH_2), 1.34 ppm (s, 9 H, 2a- and 2b-CH_3 and 6a-CH_3); ^{13}C NMR in Table II. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.08; H, 8.54.

(B) With One Equivalent of KO_2. The oxygenation of **4** was carried out under the above conditions excepting that 70 mg, instead of 213 mg, of KO_2 was used, and the reaction mixture was stirred for 1 h. The reaction products were separated by silica gel column chromatography using a mixture of *n*-hexane and ethyl ether (3:1) as eluent. Half of the starting material was recovered in the first fraction. 5-Hydroxy-2,2,5,7,8-pentamethylchroman-6(5*H*)-one (**6**) (36 mg) was obtained in the second fraction in 15.2% yield: yellow prisms; mp 75–76 °C (from *n*-hexane); MS, m/e 236 (M^+); UV (CH_3CN) λ 376 (ε 1580), 340^s nm (1460); IR (KBr) ν 3470, 1641 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.35 (s, 1 H, OH), 2.53–2.10 (m, 2 H, 4-CH_2), 1.99 (s, 3 H, 8b-CH_3), 1.90 (s, 3 H, 7a-CH_3), 1.73–1.64 (m, 2 H, 3-CH_2), 1.33 (s, 3 H, 5a-CH_3) and 1.24 ppm (s, 6 H, 2a- and 2b-CH_3); ^{13}C NMR in Table II. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.09; H, 8.69. In the third fraction, **5** (36 mg) was obtained in 15.2% yield.

Oxygenation of *RRR*-α-Tocopherol in the Presence of KO_2. A dry THF (20 mL) solution of *RRR*-α-tocopherol (*RRR*-**1**) (2.0 g, 4.65 mmol) was added to a suspension of KO_2 (1 g, 14.1 mmol) in THF (50 mL) at 0 °C under an oxygen atmosphere. Experimental procedures similar to those for the oxygenation of **4** were taken. Five products were isolated by silica gel column chromatography. The first elution with a mixture of *n*-hexane and ethyl ether (5:1) gave **7** (123 mg). The second elution with a mixture of *n*-hexane and ethyl ether (3:1) brought two yellow eluates, **3a** and **3b**. **3a** [(2*R*,5*R*,4′*R*,8′*R*)-5-hydroxy-2,5,7,8-tetramethyl-2-(4′,8′,12′-trimethyltridecyl)chroman-6(5*H*)-one]: yield 120 mg, 5.8%; yellow oil; UV (THF) λ 375 (ε 1230), 335 nm (1400); CD (*n*-hexane) λ 376 (Δε −3.9), 348 (0.0), 320 nm (+4.7); IR (neat) ν 3480, 1646 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.40 (s, 1 H, OH), 1.99 (s, 3 H, 8b-CH_3), 1.90 (s, 3 H, 7a-CH_3), 1.34 (s, 3 H, 5a-CH_3), 1.20 ppm (s, 3 H, 2a-CH_3); ^{13}C NMR in Table II. Anal. Calcd for $C_{29}H_{50}O_3$: C, 77.97; H, 11.28. Found: C, 78,11; H, 11.56. **3b** [(2*R*,5*S*,4′*R*,8′*R*)-5-hydroxy-2,5,7,8-tetramethyl-2-(4′,8′,12′-trimethyltridecyl)chroman-6(5*H*)-one]: yield 121 mg, 5.8%; yellow oil; UV (THF) λ 375 (ε 1230), 335 nm (1300); CD (*n*-hexane) λ 376 (Δε +3.3), 348 (0.0), 320 nm (−3.4); IR (neat) ν 3480, 1649 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.43 (s, 1 H, OH), 1.99 (s, 3 H, 8b-CH_3), 1.89 (s, 3 H, 7a-CH_3), 1.33 (s, 3 H, 5a-CH_3), 1.19 ppm (s, 3 H, 2a-CH_3); ^{13}C NMR in Table II. Anal. Calcd for $C_{29}H_{50}O_3$: C, 77.97; H, 11.28. Found: C, 77.24; H, 11.44. The third elution with a mixture of *n*-hexane and ethyl ether (1:1) gave two colorless elutes, **2a** and **2b**. **2a** [(2*R*,6*S*,4′*R*,8′*R*)-6-hydroxy-2,6,7,8-tetramethyl-2-(4′,8′,12′-trimethyltridecyl)chroman-5(6*H*)-one]: yield 321 mg, 15.5%; colorless oil; UV (THF) λ 318 (ε 3450), 242^s nm (3230); CD (*n*-hexane) λ 349 (Δε +9.1), 327 (0.0), 304 (−12.2), 262 (0.0), 240 nm (+5.4); IR (neat) ν 3420, 1638 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ

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3.54 (s, 1 H, OH), 2.00 (s, 3 H, 7a-CH_3), 1.83 (s, 3 H, 8b-CH_3), 1.34 (s, 3 H, 6a-CH_3), 1.27 ppm (s, 3 H, 2a-CH_3); ^{13}C NMR in Table II. Anal. Calcd for $C_{29}H_{50}O_3$, C, 77.97; H, 11.28. Found: C, 77.68; H, 11.50. **2b** [(2*R*,6*R*,4′*R*,8′*R*)-6-hydroxy-2,6,7,8-tetramethyl-2-(4′,8′,12′-trimethyltridecyl)chroman-5(6*H*)-one]: yield 410 mg, 19.8%; colorless oil; UV (THF) λ 318 (ε 2990), 245 nm (5030); CD (*n*-hexane) λ 349 (Δε −10.7), 327 (0.0), 304 (+15.6), 262 (0.0), 240 nm (−5.6); IR (neat) ν 3420, 1638 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.51 (s, 1 H, OH), 2.00 (s, 3 H, 7a-CH_3), 1.83 (s, 3 H, 8b-CH_3), 1.33 (s, 3 H, 6a-CH_3), 1.28 ppm (s, 3 H, 2a-CH_3); ^{13}C NMR in Table II. Anal. Calcd for $C_{29}H_{50}O_3$: C, 77.97; H, 11.28. Found: C, 77.68; H, 11.49.

Oxygenation of 2,2,5,7,8-Pentamethylchroman-6-ol (4) in the Presence of Potassium Hydroxide. A solution of **4** (220 mg, 1 mmol) in dry THF (20 mL) was added to a stirred suspension of KOH (179 mg, 3 mmol) in dry THF (50 mL) at 0 °C under an oxygen atmosphere. After being stirred for 3 h at 0 °C, the reaction mixture was treated as described above. In 16% yield, **5** (38 mg) was isolated.

Acyloin Rearrangement. A solution of **6** (236 mg, 1 mmol) in dry THF (20 mL) was added to a stirred suspension of KO_2 (70 mg, 1 mmol) in dry THF (50 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. On its thin-layer chromatogram [silica gel G-200/*n*-hexane–ethyl ether (1:1) v/v)] only **5** was found. In 95% yield, **5** (224 mg) was obtained.

With silica gel (1.5 g) suspended in a mixture of *n*-hexane and ethyl ether (1:1 v/v, 10 mL), **6** (15 mg) was stirred for 1.5 h at room temperature. The reaction mixture was filtered and concentrated under reduced pressure. The thin-layer chromatogram and ^1H NMR spectrum revealed that the residue was **6** without **5**. This indicates that silica gel does not act as a catalyst of the conversion from **6** to **5**.

A solution of **3a** (40 mg, 0.09 mmol) in [D_8]THF (0.5 mL) was added to the suspension of KO_2 (40 mg, 0.56 mmol) in [D_8]THF (0.5 mL) at 0 °C. The reaction mixture was stirred for 5 min. In the ^1H NMR spectrum of its supernatant, all the signals due to **2a** and no signals due to **3a** were observed. On the thin-layer chromatogram [silica gel G-200/*n*-hexane–ethyl ether (1:1 v/v)], only **2a** was found. By silica gel column chromatography, **2a** (32 mg) was isolated in 80% yield.

Labeling Experiments. (A) Labeling of Methyl Groups in 5 and 6. [5a-CD_3, 7a-CD_3, or 8b-CD_3]**4** was synthesized from 2,2,7,8-, 2,2,5,8-, or 2,2,5,7-tetramethylchroman-6-ol, respectively, and [D_2]formaldehyde in the presence of [D]hydrochloric acid and $SnCl_2$ in isopropyl ether.[17] Using equimolar KO_2, [5a-CD_3, 7a-CD_3, or 8b-CD_3]**4** was oxygenated. Labeled **5** and **6** were obtained after the same work up as described above. [6a-CD_3]**5** from [5a-CD_3]**4**: MS, *m/e* 239 (M^+); ^1H NMR the intensity of a peak at 1.34 ppm is reduced from 9 H to 6 H; ^{13}C NMR no peak at 30.1 ppm. [7a-CD_3]**5** from [7a-CD_3]**4**: MS, *m/e* 239 (M^+); ^1H NMR no peak at 1.99 ppm. [8b-CD_3]**5** from [8b-CD_3]**4**: MS, *m/e* 239 (M^+); ^1H NMR no peak at 1.82 ppm. [5a-CD_3]**6** from [5a-CD_3]**4**: MS, *m/e* 239 (M^+); ^1H NMR no peak at 1.33 ppm. [7a-CD_3]**6** from [7a-CD_3]**4**: MS, *m/e* 239 (M^+); ^1H NMR no peak at 1.90 ppm. [8b-CD_3]**6** from [8b-CD_3]**4**: MS, *m/e* 239 (M^+); ^1H NMR no peak at 1.99 ppm.

(B) Labeling with $^{18}O_2$. For the oxygenation of **4**, a high-vacuum manifold equipped with a reaction flask, a mercury manometer, and an ampule containing $^{18}O_2$ (300 mL, ^{18}O 90 atom %, The British Oxygen Company Ltd., London, UK) was used. In the reaction flask, **4** (1.32 g, 6 mmol), KO_2 (430 mg, 6 mmol) and dry THF (50 mL) were placed. The mixture was frozen with liquid nitrogen. Dissolved air was removed by a freeze–thaw procedure, which was repeated five times in vacuo. A sealed end of the ampule in the degassed manifold was broken and $^{18}O_2$ was introduced into the flask. The reaction mixture was stirred for 1 h at 0 °C. After purification by silica gel column chromatography, [^{18}O]**5** (170 mg, 18.3 %) and [^{18}O]**6** (125 mg, 13.4 %) were obtained. [^{18}O]**5**: MS, *m/e* 238 (M^+), ^{18}O incorporation 85%; IR (KBr) ν 3420, 1655, 1613 cm^{-1}; ^{13}C NMR ($CDCl_3$, a 1:1 mixture of **5** and [^{18}O]**5**) δ 202.925 ([^{18}O]**5**, C=^{18}O), 202.963 ppm (**5**, C=^{16}O). [^{18}O]**6**: MS, *m/e* 238 (M^+), ^{18}O incorporation 85%; IR (KBr) ν 3450, 1641 cm^{-1}; ^{13}C NMR ($CDCl_3$, a 1:1 mixture of **6** and [^{18}O]**6**) δ 75.955 ([^{18}O]**6**, C–^{18}OH), 75.979 ppm (**6**, C–^{16}OH).

Registry No. *RRR*-**1**, 59-02-9; **2a**, 101226-09-9; **2b**, 101313-10-4; **3a**, 101226-08-8; **3b**, 101313-09-1; **4b**, 950-99-2; **5**, 80311-41-7; **6**, 65223-11-2.

Supplementary Material Available: A listing of bond lengths, bond angles, atomic coordinates, and thermal parameters and the profiles of Eu(fod)$_3$-induced shifts of **2a**, **2b**, **3a**, **3b**, **5** and **6** (7 pages). Ordering information is given on any current masthead page.

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Additions of Singlet Oxygen to Alkoxy-Substituted Butadienes. An Unexpectedly Large s-Cis/s-Trans Ratio in an (*E,Z*)-Diene or a Kinetic Anomeric Effect?

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Received October 22, 1985

A study of the rates of reaction of (*E,E*)-, (*E,Z*)-, and (*Z,Z*)-1,4-di-*tert*-butoxy-1,3-butadiene with singlet oxygen demonstrated that rapid physical quenching and/or dioxetane formation do not competitively inhibit endoperoxide formation in the (*E,E*)-diene. Instead we suggest that an abnormally large s-cis/s-trans equilibrium constant for the (*E,Z*)-diene is the reason for the larger observed rate constant ($k_{obsd} = K_{eq}k$) for endoperoxide formation in the (*E,Z*)-diene in comparison to its *E,E* isomer. The possibility that anomeric interactions in the transition state for the reaction of the (*E,Z*)-diene contribute to the large rate of endoperoxide formation cannot be unequivocally ruled out.

Fritzsche[1] described in 1867 the photooxidation of napthacene. Although unrecognized at the time it was one of the first reported 4 + 2 cycloadditions preceeding by more than 60 years the monumental report of Diels and Alder.[2] Ascaridole, the first structurally established transannular epidioxide, was not reported by Wallach until 1912.[3] Since these early reports the 4 + 2 cycloaddition

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