Oxidation of Chromanols Related to Tocopherols*

Influence of Remote Alkyl Groups and of the Mills-Nixon Effect on Oxidative Coupling

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The oxidation of 5,8-dimethyl-6-chromanol and of 7,8-dimethyl-6-chromanol with alkaline ferricyanide has been studied. The former compound yields a trimer *8* as the main product while the latter is converted to the biphenylether type dimer *10*.

Formation of the trimer is due to a strong directing effect to the 5-position of the aromatic ring exerted by the annulated heterocyclic ring. Since a similar effect is not observed in analogous phenols with fused carbocyclic non-aromatic rings, an oxygen-heterocyclic ring must have a stronger directing effect (Mills-Nixon effect) on the oxidative coupling reaction than the corresponding alicyclic ring.

The naturally occurring tocopherols *1a — 4a* can be considered as two pairs of compounds, one pair where the substances carry a 5-methyl group as in α- and β-tocopherol (*1a* and *2a*) and one pair where the compounds are unsubstituted at the 5-position (γ- and δ-tocopherol; *3a* and *4a*). During our work on tocopherol oxidation, which has recently been reviewed,[1] we found that, upon treatment with alkaline ferricyanide, α- and β-tocopherol gave spiro dimers of type *7* through coupling *via* the methyl group in position 5 while γ- and δ-tocopherol gave spiroketal trimers of type *9* by coupling at the unsubstituted 5-position. This was elucidated using mainly the model compounds *1b — 4b*. We thus could show a strong preference for coupling at the 5-position of the molecule, an effect which was attributed to the directing influence of the heterocyclic ring.

Our work has now been extended to the oxidation of two new 6-chromanols, *5* and *6*, which have no alkyl substituents in position 2. Compound *5* corresponds to the β-tocopherol *2a* and compound *6* corresponds to the γ-tocopherol *3a*, the substituents in the heterocyclic ring being absent in both compounds.
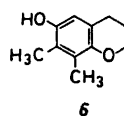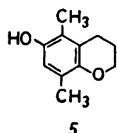
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It has previously been established that the natural tocopherols and their corresponding model compounds behave similarly on oxidation.[2] However, both these types of compounds have alkyl substituents in the 2-position and the behaviour of the chromanol moiety with no substituents in the 2-position has not been studied. To ascertain that the directing effect observed was due to the heterocyclic annulated ring, we studied the oxidation of the chromanols 5 and 6.
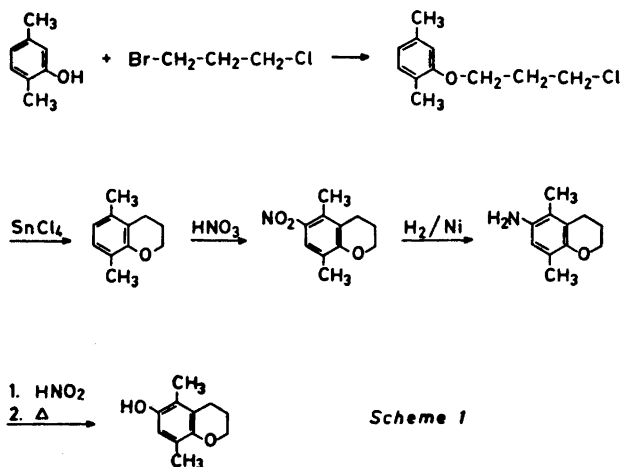
	R_1	R_2	
1.	CH_3	CH_3	α-tocopherol
2.	H	CH_3	β-tocopherol
3.	CH_3	H	γ-tocopherol
4.	H	H	δ-tocopherol
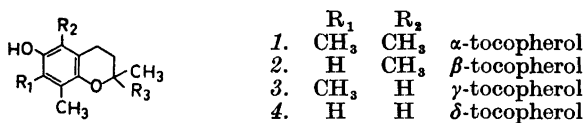
a	$R_3 = C_{16}H_{33}$	natural tocopherol
b	$R_3 = CH_3$	tocopherol model compound

5   6

SYNTHETIC PROCEDURES

The chromanols 5 and 6 were prepared by a five step synthesis from the corresponding dimethyl phenol as illustrated in Scheme 1 for 5,8-dimethyl-6-chromanol (5).

Scheme 1

Mononitration of the dimethylchroman was accomplished in 60 % HNO_3 and the crystalline nitro chroman was catalytically hydrogenated to the corresponding amine. This was converted to the phenol by diazotization in dilute phosphoric acid and subsequent heating for a short period. We found that these mild conditions gave a much better yield of the chromanol than when the conversion was carried out in a stronger acid.

OXIDATION REACTIONS AND RESULTS

The oxidation of the chromanols was carried out in a two-phase systems as previously described [3,4] using an aqueous alkaline solution of potassium ferricyanide, which was rapidly stirred with a solution of the phenol in light petroleum. After the appropriate reaction times, the products were isolated by preparative TLC.

Oxidation of the chromanol 5 (related to β-tocopherol (2a)) gave as the main product (32 % yield) a colourless semi-solid substance different in type from the yellow spiro dimer 7 obtained upon similar oxidation [3] of the β-model compound 2b. The compound gave a weak brownish colour on TLC (silica gel G) when sprayed with Gibbs' reagent [5] at approximately the same R_F-value as the chromanol 5, but GLC, IR- and NMR-spectra revealed that the product was free from starting material.

The IR- and UV-spectra are very similar to those of a β-tocopherol trimer of type 8 previously described.[2] The trimeric structure was independently confirmed by molecular weight determination and mass spectrum. The latter shows a molecular ion of m/e 530 (10 %; $3 \times$ monomer $- 4$H). A trimer with the molecular weight 530 would have either a hydroxyl group or be a peroxide. The first alternative is ruled out by the IR-spectrum which shows no OH-absorption and a peroxide is unlikely since such compounds are not known to be formed in phenolic oxidations.[6] Previous studies of the mass spectra of tocopherol spiro dimers of type 7 revealed that these spectra exhibit the molecular ion at a value higher by two mass units than what would be expected from the structures of the compounds.[7,8] In analogy with this it is conceivable that also a molecule of type 8 would show this anomaly and that the molecular weight of the isolated trimer is 528 ($3 \times$ monomer $- 6$H).

The mass spectrum of the trimer shows the base peak at m/e 178 (chromanol monomer) and the fragmentation pattern is then similar to that of chromanols related to tocopherols.[9] The mechanism of formation of the peak due to the monomer in this apparently chromatographically pure sample is not understood, but similar fragmentation has previously been observed in the mass spectra of tocopherol dimers.[10]

Further evidence for the trimeric structure 8 was obtained from the NMR-spectrum. This shows two singlets at $\delta = 6.66$ and 6.61 ppm (together 2H) corresponding to two aromatic protons. A vinylic proton appears as a multiplet at 4.56 ppm and another multiplet at 4.30 − 3.90 ppm (6H) is due to heterocyclic ring protons ($-CH_2-O-Ar$). A large multiplet at $\delta = 2.90 - 1.70$ ppm ($\sim$23H) represents heterocyclic ring protons and ring methyl groups (2.14 and 1.80 ppm). A multiplet at 1.26 ppm (4H) represents heterocyclic ring protons probably from the central chroman unit of structure 8. These data are all consistent with the trimeric structure 8, a compound similar to that obtained by benzoquinone oxidation of the β-tocopherol model compound.[2]

Several other oxidation products were detected chromatographically in the oxidation mixture of 5. These were mostly dark coloured polar compounds that did not move in the chromatogram and were not further investigated.

Oxidation of the chromanol 6 (related to γ-tocopherol) yielded a red coloured solid material from which three products were isolated by TLC, one of which

was the starting material (13 % recovered). A major oxidation product was
a very unstable yellow material that decomposed on the chromatogram to
green and red coloured substances. Attempts to use other purification tech-
niques including the chromatographic system employed in the purification
of the spiroketal trimers of tocopherol model compounds [3] failed. It is conceiv-
able that this unstable material is a spiroketal trimer of type *9* similar to that
formed from the γ-tocopherol model compound,[3] since a very similar colour
change was observed when this trimer decomposed. Two other products, of
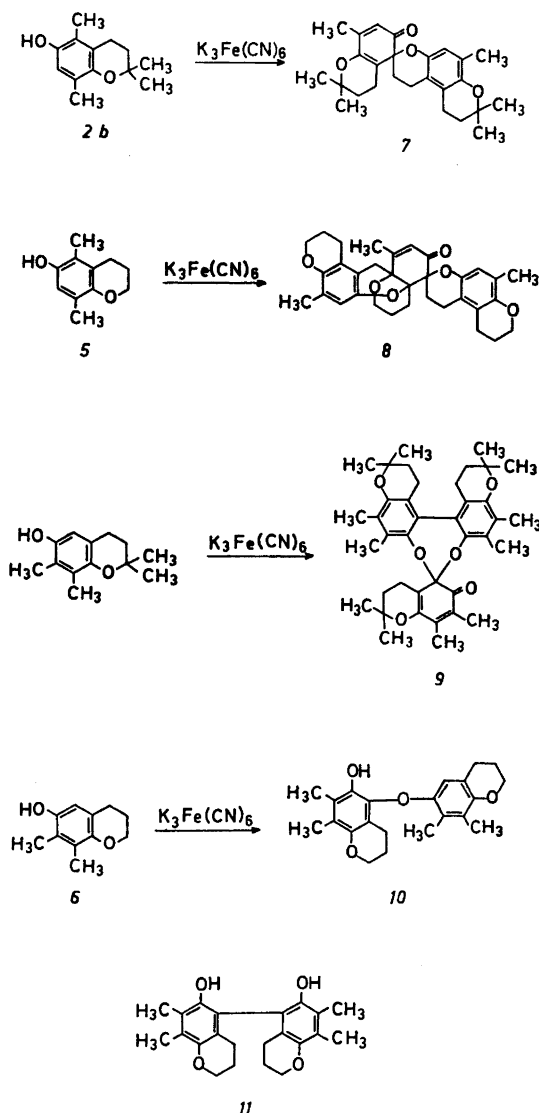
a type not detected in the oxidation of the γ-model compound *3b* were isolated from this oxidation of the chromanol *6*. The products were phenols (Gibbs' reagent [5]) obtained in 32 % and 1 % yield. Mass spectra of the compounds show that both are dimers of the chromanol *6* (molecular ion at m/e *354*) and the IR-spectra show OH-stretching bands at 3500 cm^{-1}. The NMR-spectrum of the major, less polar product shows a singlet at $\delta = 6.10$ ppm representing one aromatic proton. An OH-group gives rise to a broad signal at 5.10 ppm, and a multiplet at $4.25 - 3.95$ ppm (4H) is due to heterocyclic ring protons $(-CH_2-O-Ar)$. A large multiplet (20H) at $2.80 - 1.60$ ppm represents benzylic and aliphatic heterocyclic ring protons and aromatic methyl groups. The latter stand out from the multiplet as singlets at 2.30 ppm (1 CH_3), 2.20 ppm (1 CH_3), and 2.15 ppm (2 CH_3). These data are consistent with the formulation of the compound as the diphenylether dimer *10*, a compound analogous to the dimers formed from γ-tocopherol on oxidation with benzoquinone.[11] The more polar of the two isolated dimers (1 % yield) is formulated as the biphenyl dimer *11*, a structure consistent with the IR- and mass-spectra (m/e 354, M^+; ν_{max} (KBr) 3500 cm^{-1}).

DISCUSSION OF THE RESULTS

Oxidation of the model compounds of β- and γ-tocopherol (*2b* and *3b*) with alkaline ferricyanide gives as the main products the spiro dimer *7* and the spiroketal trimer *9*, respectively. Similar oxidation of the chromanols *5* and *6*, homologs of *2b* and *3b*, respectively, proceeded by a similar course, but also new types of products were formed.

Oxidation of *5* (with a 5-methyl group) gave the trimer *8*. This is probably formed *via* a quinone methide, a compound that has been detected as an intermediate in the oxidation of α-tocopherol.[4] However, whereas the oxidative coupling of α-tocopherol stopped at the dimer stage, the trimer is the main product when no alkyl groups occur in position 2 (as in *5*). A possible explanation for this has previously been discussed.[4]

It is evident that the strong preference for reaction at the 5-position can be observed also in 6-chromanols unsubstituted at position 2, since the trimer *8* is formed by benzylic type coupling *via* the 5-methyl groups and the unsubstituted 7-position of the molecule is not involved in the reaction. This also confirms our previous assumption [1,11] that the strong directing effect to position 5 in 6-chromanols is due to the heterocyclic ring and that this heterocyclic ring has a stronger influence on the aromatic ring than the corresponding carboxyclic ring, which does not show the same directive effect in oxidative coupling.[12]

Oxidation of the γ-tocopherol model compound *3b* with alkaline ferricyanide gives the spiroketal trimer *9* in high yield. It is likely that a similar spiroketal trimer is formed also in the oxidation of *6* but this trimer is apparently too unstable to be isolated. Instead, the dimeric ether *10* is the main product, formed together with small ammounts of the biphenyl dimer *11*. These types of dimers were formed on benzoquinone oxidation [11] of the tocopherols unsubstituted at position 5, but were not detected when alkaline ferricyanide was the oxidizing agent.[3]

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 with a Bausch & Lomb Spectronic 505 spectrophotometer. Nuclear magnetic resonance spectra were measured in $CDCl_3$-solutions with a Varian Associates A 60 instrument. Chemical shifts are expressed in ppm relative to tetramethylsilane ($\delta_{TMS} = 0.00$ ppm). Mass spectra were obtained using an LKB 9000 instrument at 70 eV. Molecular weight determinations were performed using a Hitachi Perkin-Elmer Model 115 Molecular Weight Apparatus with benzene as solvent. Thin layer chromatography was performed using silica gel G plates of 0.3 mm (analytical) and 1 mm (preparative) thickness, prepared and stored as previously described.[3] Redistilled light petroleum, b.p. 40—60°, was used throughout.

1-Chloro-3-(2,5-dimethylphenoxy)-propane. 2,5-Dimethylphenol (50 g, 0.41 mole) and 1-bromo-3-chloropropane (129 g, 0.82 mole) were added to a solution of sodium (9.4 g, 0.41 mole) in absolute ethanol (200 ml). The stirred mixture was refluxed overnight, cooled, the precipitated salts were filtered off and the solvent evaporated *in vacuo.* The residue was dissolved in ether, unreacted phenol was extracted with 50 ml portions of 5 N aqueous NaOH, the solution was washed with water, dried (Na_2SO_4) and evaporated *in vacuo.* The residue was distilled affording 61.4 g (76 %) of the phenyl ether, b.p. 145—148°/10 mm. (Found: C 66.9; H 7.97. Calc. for $C_{11}H_{15}ClO$: C 66.5; H 7.61).

1-Chloro-3-(2,3-dimethylphenoxy)-propane was similarly prepared in 50 % yield, b.p. 160°/22 mm. (Found: C 66.2; H 7.63. Calc. for $C_{11}H_{15}ClO$: C 66.5; H 7.61).

5,8-Dimethylchroman. A mixture of 1-chloro-3-(2,5-dimethylphenoxy)-propane (60 g) and anhydrous stannic chloride (6 g) was heated at 200° for 4 h. It was then poured into ice-water and extracted with ether. The ether extract was washed with saturated $NaHCO_3$-solution and with water, dried (Na_2SO_4), evaporated and the residue distilled, yielding 23 g (50 %) of an oil, b.p. 130—135°/22 mm. This compound has previously been prepared by Borowitz *et al.*[13] by another route, reported b.p. 114—116°/10 mm.

7,8-Dimethylchroman was similarly prepared from 1-chloro-3-(2,3-dimethylphenoxy)-propane in 57 % yield, b.p. 82—84°/1 mm. (Found: C 81.0; H 8.68. Calc. for $C_{14}H_{14}O$: C 81.4; H 8.70).

2,5-Dimethyl-6-nitrochroman. 5,8-Dimethylchroman (18 g, 0.11 mole) was slowly added to 60 % nitric acid (100 ml) at 15—20° during 20 min. The green mixture was then kept at 20° for 10 min, poured into 500 ml of ice-water and the mixture extracted with ether. The extract was washed with water and saturated $NaHCO_3$-solution, dried (Na_2SO_4) and evaporated. The residue was distilled, affording 10 g (45 %) of the nitro chroman, b.p. 160—165°/2.5 mm; m.p. 72—74° (from ligroin). (Found: C 63.7; H 6.10; N 6.79. Calc. for $C_{11}H_{13}NO_3$: C 63.8; H 6.32; N 6.76).

7,8-Dimethyl-6-nitrochroman was similarly prepared from 7,8-dimethylchroman in 45 % yield, b.p. 157—158°/1.2 mm, m.p. 52—53° (from light petroleum). (Found: C 63.7; H 6.40; N 6.77. Calc. for $C_{11}H_{13}NO_3$: C 63.8; H 6.32; N 6.76).

6-Amino-5,8-dimethylchroman. An ethanolic solution of 5,8-dimethyl-6-nitrochroman was hydrogenated over Raney-Ni W-2 at room temperature in a Parr apparatus at an initial pressure of 3 kg/cm² until the theoretical amount of hydrogen had been consumed. After filtration through celite the solvent was evaporated, the residue dissolved in ether and HCl-gas introduced to precipitate the amine hydrochloride. This was crystallized from ethanol-ether to yield 5 g (54 %) of pure amine hydrochloride, m.p. 290° (decomp. sublimation). (Found: C 61.7; H 6.96; N 6.56. Calc. for $C_{11}H_{16}ClNO$: C 61.8; H 7.08; N 6.56).

6-Amino-7,8-dimethylchroman was prepared by the same procedure in 76 % yield, m.p. 300—301° (decomp. sublimation). (Found: C 61.7; H 7.58; N 6.59. Calc. for $C_{11}H_{16}ClNO$: C 61.8; H 7.08; N 6.56).

5,8-Dimethyl-6-chromanol (5). To a stirred solution of 6-amino-5,8-dimethylchroman hydrochloride (5 g; 0.0236 mole) in phosphoric acid (100 ml; 1.5 M) at 0° was added slowly a solution of sodium nitrite (3.7 g; 0.053 mole) in 25 ml of water. The solution was kept at 0° for 2 h whereupon 0.5 g of urea was added to destroy excess of nitrite. The stirred solution was then heated to 85° for 30 min, cooled and extracted with ether. The extract was washed with water, dried (Na_2SO_4) and evaporated to yield 4.5 g of a dark oil. This

was placed on a column of silica gel (100 g) which was successively eluted with ether-light petroleum mixtures of increasing polarity. The chromanol 5 was eluted in 500 ml of ether-light petroleum 1:4, which upon evaporation gave 2.5 g (60 % yield) of a pale yellow substance, m.p. 126−127° (from light petroleum). (Found: C 73.8; H 7.74. Calc. for $C_{11}H_{14}O_2$: C 74.1; H 7.92) ν_{max} (KBr) 3250 cm^{-1} (OH).

NMR: $\delta = 6.46$ ppm (s, 1H, ArH); 5.25 ppm (s, broad, 1H, OH); 4.30−3.90 ppm (m, 2H, −CH_2−O−Ar); 2.85−2.40 ppm (m, 2H,−CH_2Ar) and 2.30−1.70 (m; 8H, ArCH_3 and heterocyclic ring protons). The aromatic methyl groups gave a sharp signal at 2.10 ppm.

7,8-Dimethyl-6-chromanol (6) was similarly prepared and purified. The pure compound was obtained in 48 % yield, m.p. 142−143° (from light petroleum). (Found: C 73.7; H 8.08, Calc. for $C_{11}H_{14}O_2$: C 74.1; H 7.92). ν_{max} (KBr) 3350 cm^{-1} (OH) NMR: δ 6.35 ppm (s, 1H, ArH), 4.50 ppm (s, broad, OH), 4.30−3.90 ppm (m, 2H, −CH_2−O−Ar); 2.90−2.50 ppm (m, 2H, −CH_2−Ar) and 2.20−1.70 ppm (m, 8H, ArCH_3 and heterocyclic ring protons). The aromatic methyl groups give a sharp signal at 2.10 ppm.

Oxidation reactions. A solution of 5,8-dimethyl-6-chromanol (5) (250 mg; 1.4 mmole) in light petroleum (60 ml) was stirred for 30 min with a solution of potassium ferricyanide (1.4 g; 4.2 mmole) in 0.2 N aqueous sodium hydroxide (50 ml). The organic layer was separated, washed with two 25 ml portions of water and dried (Na$_2$SO$_4$). Evaporation of the solvent gave a red oil that was subjected to preparative TLC in ether-light petroleum (3:10). One yellow band appeared on the plates and two other bands were detected when the edges of the plates were sprayed with Gibbs' reagent.[5] The area near the origin of the plate was dark coloured. The bands were removed separately from the plates, eluted with ether and the solvent was evaporated under a stream of nitrogen. The least polar compound (black with Gibbs' reagent, R_F 0.75) weighed about 1 mg and was not further investigated.

The main product appearing at R_F 0.45 (weak brown reaction with Gibbs' reagent [5]) weighed 79 mg. As described above, the product was identified as the trimer 8 by its spectral data and molecular weight which was determined to 519 by the apparatus described above. λ_{max} (hexane) 292 nm; ν_{max} (KBr): No OH-absorption. 1670 cm^{-1}; 1680 cm^{-1} (C=C and C=O). The spectrum also has strong absorption at 1475 cm^{-1}; 1230 cm^{-1}; 1195 cm^{-1}; 1080 cm^{-1} and 1010 cm^{-1}. The NMR-spectrum has been described above. The mass spectrum which also has been described above, shows prominant peaks at m/e 530 (10 % M$^+$), 354 (3.5 %), 179 (16 %) 178 (100 %), 177 (44 %), 163 (16 %), 162 (10 %), 150 (55 %), 149 (16 %), 122 (18 %), 121 (10 %), 107 (16 %), 91 (44 %), 77 (12 %), 41 (10 %), and 39 (10 %).

The third yellow band, (R_F 0.35, 5 mg) shows λ_{max} (hexane), 330 and 298 nm, similar to the absorptions of the β-spiro model dimer 7.[3] The compound was not further investigated.

Oxidation of 7,8-dimethyl-6-chromanol (6)(178 mg; 1 mmole) was carried out as described for 5. This yielded a yellow oil that was subjected to preparative TLC in ether-light petroleum 1:5. The main portion of this material turned green and then red on the plate and apparently decomposed to much more polar material, as discussed above. Two bands, however, giving a dark brown colour when sprayed with Gibbs' reagent [5] separated distinctly from the red decomposition products. The bands were removed from the plates and eluted with ether. The more polar material was identified as the starting material 6 (23 mg, 13 %). The less polar material was re-chromatographed on preparative TLC in ether-light petroleum 1:50. The plate was run three times in this solvent. When the edge of the plate was sprayed with Gibbs' reagent [5] two bands were detected which were eluted separately to yield 56 mg (32 %) and 2 mg (1 %) of material identified as the dimers (10) and (11), respectively, as described above.

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