ACTA CHEMICA SCANDINAVICA 22 (1968) 3160–3170

# Synthesis of Methyl Substituted 6-Hydroxychromans, Model Compounds of Tocopherols*

J. LARS G. NILSSON, HANS SIEVERTSSON and HANS SELANDER

*Department of Organic Chemistry, Kungl. Farmaceutiska Institutet, Box 6804, S-113 86 Stockholm, Sweden*

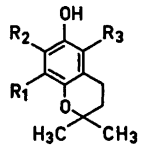
Synthetic models of α-, β-, γ-, and δ-tocopherol and of 5,7-dimethyltocol, 5-methyltocol, 7-methyltocol, and tocol, where the isoprenoid side-chain is replaced by a methyl group, have been synthesised by new improved methods. The compounds were prepared either by condensation of 1,1-dimethylallyl alcohol to the appropriate hydroquinone or by other methods that allowed unequivocal formation of the desired isomer. When 1,1-dimethylallyl alcohol was condensed with toluhydroquinone, all the three possible tocol models were formed, the 5-, 7-, and 8-methyltocol model being found in the ratio of 1:2.6:1.5.

During chromatographic fractionation of polar constitutents of corn oil [1] four dimers of tocopherols were isolated and their structures elucidated.[2] These dimers were also synthesized during a study of the oxidative dimerization of α-, β-, γ-, and δ-tocopherol in the presence of benzoquinone.[3] The investigation included naturally occurring tocopherols as well as model compounds, where the isoprenoid side chain had been replaced by a methyl group. In the reactions studied, the model compounds behaved analogously to the natural compounds and thus gave us the advantage of working with crystalline products of lower molecular weights. In an extension of the previous study,[3] model compounds of the naturally occurring tocopherols and of 5,7-dimethyltocol, 5-methyltocol, 7-methyltocol, and tocol have now been synthesized by new improved routes for the further study of oxidation and substitution reactions.

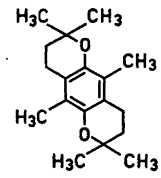
6-Hydroxy-2,2,5,7,8-pentamethylchroman (*1*), the model compound of α-tocopherol, was first synthesized by Smith and coworkers [4] by condensation of trimethylhydroquinone with isoprene in acetic acid using zinc chloride as catalyst. The usefulness of the compound in the study of tocopherol chemistry was soon realized and a number of workers [5–12] have used it, mainly in the

* Tocopherols V. Paper IV in this series: *Acta Pharm. Suecica* 5 (1968) 215.

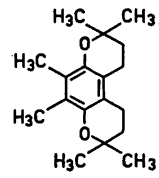
study of tocopherol oxidation. 6-Hydroxy-2,2,5,8-tetramethylchroman[13] (*2*) and 6-hydroxy-2,2,7,8-tetramethylchroman[13,14] (*3*), model compounds of $\beta$- and $\gamma$-tocopherol, respectively, and 6-hydroxy-2,2,5,7-tetramethylchroman[13] (*4*), a compound with no known naturally occurring tocopherol equivalent,



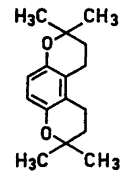
| | $R_1$ | $R_2$ | $R_3$ | |
|---|---|---|---|---|
| *1* | $CH_3$ | $CH_3$ | $CH_3$ | 5,7,8-Trimethyltocol model, $\alpha$-model |
| *2* | $CH_3$ | H | $CH_3$ | 5,8-Dimethyltocol model, $\beta$-model |
| *3* | $CH_3$ | $CH_3$ | H | 7,8-Dimethyltocol model, $\gamma$-model |
| *4* | H | $CH_3$ | $CH_3$ | 5,7-Dimethyltocol model, |
| *5* | $CH_3$ | H | H | 8-Methyltocol model, $\delta$-model |
| *6* | H | $CH_3$ | H | 7-Methyltocol model |
| *7* | H | H | $CH_3$ | 5-Methyltocol model |
| *8* | H | H | H | Tocol model |



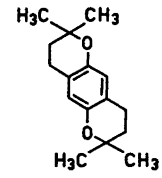
*9*



*10*



*11*



*12*

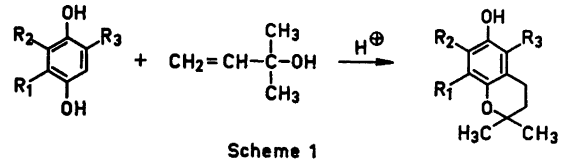
have also been prepared by condensation of isoprene with the appropriate hydroquinones. The yields in these syntheses were low, double chromans (*9* and *10*) being formed as one of the by-products. The chromanol with no aromatic methyl groups, 6-hydroxy-2,2-dimethylchroman (*8*) (tocol model), has been prepared by condensation of isoprene with *p*-methoxyphenol followed by demethylation of the 6-methoxychroman[15] formed, and by condensation of 3,3-dimethylallyldiphenylphosphate with hydroquinone[16]. The preparation of 6-hydroxy-2,2,8-trimethylchroman (*5*), the model compound of $\delta$-tocopherol, and of the isomeric 6-hydroxy-2,2,7-trimethylchroman (*6*) and 6-hydroxy-2,2,5-trimethylchroman (*7*) have not been previously reported.

The method of preparation of the $\alpha$-model compound (*1*) described by Smith *et al.*[4] is quite satisfactory even for large quantities of the compound. When the same method is applied to the synthesis of the dimethyltocol models (*2*—*4*) the yields are low and the reaction products can be purified only after extensive chromatography. In the case of the monomethyl tocol models (*5*—*7*), condensation of any five carbon unit with toluhydroquinone results in the formation of all the three possible monomethyl isomers in a mixture that is inseparable by ordinary chromatographic techniques on a preparative scale. Thus these compounds had to be synthesized by other routes.

*Model compounds of trimethyltocol, dimethyltocols and tocol.* Isler *et al.*[17] have reported on the convenient use of isophytol in the preparation of dimethyltocols. Recently, Rüegg *et al.*[18] used the compound in the preparation of tocopheramines. Using the same idea, we employed an analogous reagent, 1,1-dimethylallyl alcohol * for the formation of the pyrane ring in the model compounds. Dimethylallyl alcohol, which is equivalent to the first isoprene unit of isophytol, has apparently not been used before in the preparation of hydroxychromans. Using this alcohol the yields of the tocopherol models were increased considerably and the reaction products could be purified in a simple chromatographic step.

Dimethylallyl alcohol condensed with trimethylhydroquinone in refluxing formic acid afforded the α-model compound in 82 % yield (Scheme 1). In this case, the method is no improvement over the synthesis *via* isoprene, which gives similar yields and a very pure product.

The model compounds of the dimethyltocols (Scheme 1) were prepared by the slow addition of one equivalent of dimethylallyl alcohol to two equivalents of dimethylhydroquinone in refluxing formic acid. Slow addition gave a better yield compared to when the alcohol was added all at once, probably because of decreased formation of double chromans (*9* and *10*). A hydrolysis step in the purification procedure eliminated what appeared to be formate esters in the primary reaction product and increased the yield. The melting point for the β-model (*2*) is 86—87.5° and for the γ-model (*3*) 75.5—76.5°. Curiously enough these melting points are almost the reverse of those previously reported for the same compounds prepared *via* the isoprene condensation[13] (β-model: 77—78°; γ-model 84.5—85.5°). The synthesis according to Frampton *et al.*[13] was therefore repeated but we found that the model compounds obtained in this way had the same melting points as those prepared using dimethylallyl alcohol.




Scheme 1

Synthesis of the tocol model (*8*) could also be achieved by this procedure (Scheme 1). An excess of five equivalents of hydroquinone was used and this made it possible to restrain the formation of the double chromans (*11* and *12*).

*Model compounds of monomethyltocols.* When toluhydroquinone and phytol are condensed in formic acid [19,20] a mixture of the three possible monomethyltocols is formed. This was later re-examined by Marcinkiewicz *et al.*[21] Using a paper chromatographic technique they were able to separate the compounds and determine that the condensation leads to a 1:2:1 mixture of 5-, 7-, and 8-methyltocol. Because of the difficulty in separating mixtures of monomethyltocols, condensation of dimethylallyl alcohol with toluhydroquinone

* 1,1-Dimethylallyl alcohol will in the following be referred to as dimethylallyl alcohol.

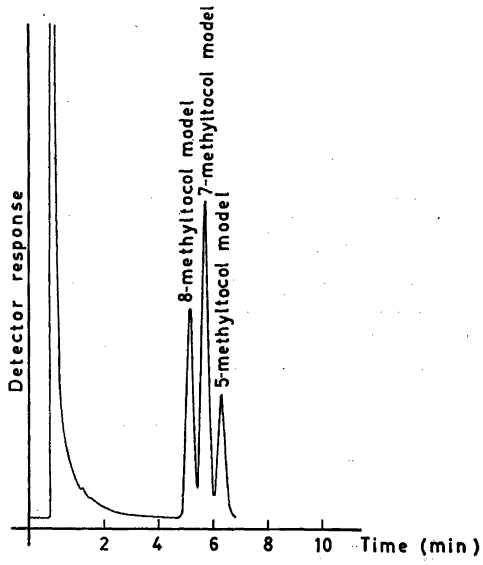
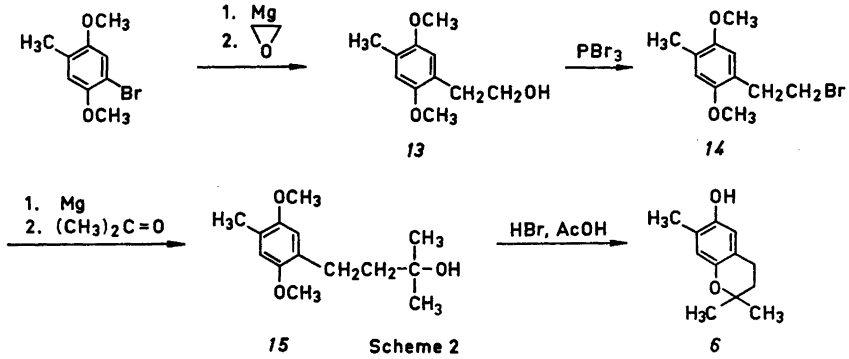



*Fig. 1.* Gas chromatogram of the reaction products formed when 1,1-dimethylallyl alcohol was condensed with toluhydroquinone in refluxing formic acid. Ratio 5-methyltocol:7-methyltocol:8-methyltocol = = 1:2.6:1.5.

was not considered to be a suitable route for the preparation of the pure model compounds of 8-, 7-, and 5-methyltocol (*5*—*7*), particularly since there is no reason for assuming that a greatly different ratio of products would be obtained when toluhydroquinone is condensed with dimethylallyl alcohol or with phytol. However, since we had the authentic monomethyltocol models (*5*—*7*) available as reference compounds we decided to perform the condensation and analyse the reaction mixture by gas-liquid chromatography. After purification of the products by column chromatography on silica gel, which did not separate the chromanols, the gas chromatogram showed, by comparisons of the peak areas, that the model compounds of 5-, 7-, and 8-methyltocol were formed in the ratio of 1:2.6:1.5 (Fig. 1).

In the synthesis of the three monomethyltocol models (*5*—*7*) we used methods based on those employed by McHale *et al.*[22,23] in their synthesis



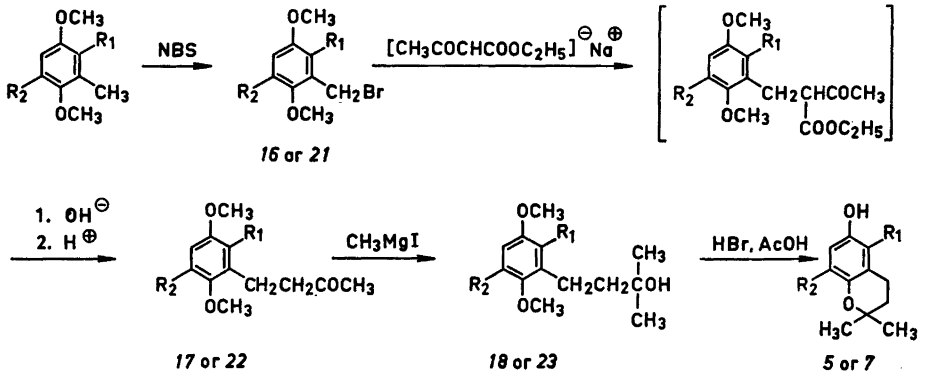

Scheme 2

of 5- and 7-methyltocol, but other methods were also tried, but were found to be less satisfactory.

*7-Methyltocol model* (6) (Scheme 2). The method described by McHale *et al.*[23] for the syntheis of 7-methyltocol was slightly modified. The advantage of this method over other routes to 7-methyltocol is the ready availability of the starting material 5-bromotoluhydroquinone, which allows the unequivocal introduction of the desired side chain at the right position of the aromatic ring. After methylation of the phenolic groups of the hydroquinone, the bromoether was converted into the Grignard reagent. When THF was used as solvent, the Grignard reagent was easily formed and the entrainment technique described by McHale *et al.*[23] could be dispensed with. The Grignard derivative was reacted with ethylene oxide and treatment of the formed primary alcohol *13* with phosphorus tribromide yielded the bromo compound *14*. This was converted into the Grignard derivative in THF, again without using the entrainment technique, affording 2-(2,5-dimethoxy-4-methylbenzyl)-1,1-dimethylethanol (*15*) upon reaction with acetone. A compound in which the elements of water apparently had been eliminated from the side chain was also formed. Since both compounds could be converted to the chromanol *6*, demethylation and cyclization was carried out on the mixture and the product was purified by column chromatography on silica gel.

Attempts were also made to introduce the side chain directly *via* the Grignard derivative of 5-bromotoluhydroquinone dimethyl ether by coupling with 3,3-dimethylallylbromide [24] in THF, but the reaction did not give any identifiable product.

*Models of 5- and 8-methyltocol* (*7 and* 5). These two compounds were prepared analogously to the synthesis of 5-methyltocol by McHale *et al.*[22] In the preparation of the *5-methyltocol model* (*7*) (Scheme 3) 2,3-dimethylhydroquinone dimethylether [22] was side chain brominated with *N*-bromosuccinimide. The resulting benzyl bromide *16* was reacted with ethyl acetoacetate in benzene yielding 3,6-dimethoxy-2-methylbenzylacetone (*17*). Conversion of this ketone




Scheme 3

to the tertiary alcohol *18* using methylmagnesium iodide followed by demethylation and cyclization with HBr in acetic acid gave the 5-methyltocol model. A similar route was used for the synthesis of the *8-methyltocol model* (*5*) ($\delta$-model) (*Scheme 3*) where 2,6-dimethylhydroquinone dimethylether was the starting material. 8-Methyltocol model (*5*) was also prepared by a method similar to the synthesis of 6-hydroxy-2,2-dimethylchroman [15] (tocol model)( *8*). 4-Methoxy-2-methylphenol [26] was condensed with excess of isoprene in acetic acid using zinc chloride as catalyst. The 6-methoxy-2,2,8-trimethylchroman formed, which was difficult to purify by column chromatography, was demethylated with HBr in acetic acid affording the 8-methyltocol model (*5*) in 1.6 % yield. Since several products of similar polarity was formed in this preparation, considerable difficulties arose in the purification procedure, and the method was considered unsuitable for preparative purposes.

The identity of the prepared chromanols were established by elementary analysis and by IR-, UV-, and NMR-spectroscopy. (See the experimental part for details). Particularly useful are the NMR-spectra in establishing the chroman structure. In the 2,2-dimethyl compounds studied, there are two pairs of methylene protons in positions 3 and 4. These protons appear in the spectrum as two well resolved triplets at approximately 1.7 ppm and 2.5 ppm, respectively, with a coupling constant of 6—7 cps. In the spectra of the non-cyclized analogs (*e.g. 18* or *23*) the side chain methylene protons show AA'XX'-patterns centered at about 2.1 ppm. The IR-spectra all exhibit a strong OH-stretching band at 3300—3500 $cm^{-1}$ and the UV-spectra have absorption bands in the region of 290—300 m$\mu$, which is in accord with the UV-absorption of tocopherols.

## EXPERIMENTAL

*General comments.* Melting points were determined with calibrated Anschütz thermometers in an electrically heated metal block. Infrared absorption spectra were measured on a Perkin-Elmer 237 spectrophotometer and ultraviolet absorption spectra were measured with a Beckman DK-2 spectrophotometer with scale expansion 5 m$\mu$/cm. Nuclear magnetic resonance spectra were measured using $CCl_4$-solutions with a Varian Associates A 60 spectrometer. Chemical shifts are expressed in ppm relative to tetramethylsilane.* Deuterium exchange experiments to establish the identity of the OH-signals were carried out by shaking a $CCl_4$ solution of the compound with $D_2O$ and recording a new spectrum using the organic phase after separation of the layers. Thin layer chromatography was performed using silica gel G plates of 0.3 mm (analytical) and 1 mm (preparative) thickness. The plates were activated by heating at 130° for 1.5 h and were stored in a dry cabinet until used. Gas-liquid chromatography was performed using an Aerograph 204 gas chromatograph with a 6 ft. × 1/8 inch internal diameter glass column filled with 5 % SE-30 on GasChrom-P 100—200 mesh. Flow rate was 25 ml $N_2$/min, temp. 150°C.

Redistilled light petroleum, b.p. 40—60°, was used throughout.

The dimethylhydroquinones used as starting materials were prepared as described.[25]

*6-Hydroxy-2,2,7,8-tetramethylchroman (γ-model)* (3). 2,3-Dimethylhydroquinone [25] (8.0 g, 58 mmole) was dissolved in 75 ml of formic acid (98—100 %) and 20 ml of THF. The solution was heated to reflux and dimethylallyl alcohol (2.5 g, 29 mmole) in 10 ml of THF was added very slowly during 1 h. The solution was refluxed for another 3 h and then poured onto 100 g of crushed ice. Water (400 ml) was added and the mixture extracted with 5 × 50 ml of ether. Light petroleum (50 ml) was then added to the combined

* ($\delta_{TMS}$ = 0.00 ppm).

ether extracts and the mixture washed with 5 × 50 ml of water. In this way, most of the formic acid dissolved in the ether could be removed. The solvent was evaporated, the residue was dissolved in 75 ml of methanol, 1 ml of concentrated HCl was added and the solution refluxed for 20 min to hydrolyze any formate ester that might have been formed in the reaction. The methanol was then evaporated and the residue was dissolved in 150 ml of ether. After washing with water, with saturated $NaHCO_3$-solution and again with water, the solution was dried ($Na_2SO_4$) and evaporated *in vacuo*. The residue, which solidified, was extracted by stirring in 100 ml of refluxing light petroleum for 15 min. After cooling to room temperature, the unreacted 2,3-dimethylhydroquinone was filtered off and the filtrate evaporated. The residual oil was dissolved in a small portion of light petroleum and placed on a column of 100 g of silica gel (3 cm diameter). The column was eluted with 500 ml of ether-light petroleum (1:20) and the solvents evaporated, giving 1.1 g of a crystalline solid that was identified as the double chroman *10*, m.p. 101–102° (from light petroleum), lit.[13] 101–102°. The column was then eluted with 1000 ml of ether-light petroleum (1:5) affording 6-hydroxy-2,2,7,8-tetramethylchroman (*3*) (3.0 g, 47 % yield), m.p. 75.5–76.5° (from light petroleum). A sample prepared according to Frampton *et al.*[13] melted at 75–76°. Reported [13,14] 84.5–85.5°. (Found: C 75.5; H 8.52. Calc. for $C_{13}H_{18}O_2$: C 75.7; H 8.80). $\nu_{max}$(KBr) 3430 $cm^{-1}$ (OH); 1615 $cm^{-1}$ (aryl). NMR: Singlet at ppm 6.10 (1H, Ar*H*), broad singlet at 4.90 (1H, O*H*), triplet at 2.57 (2H, Ar–C*H*$_2$–, $J$=7.5 cps), singlet at 2.04 (6H, Ar–C*H*$_3$), triplet at 1.67 (2H, protons at position 3, $J$=7.5 cps) and singlet at 1.26 (6H, gem.-C*H*$_3$). $\lambda_{max}$(hexane) 294 (log $\varepsilon$=3.69) and 300 (log $\varepsilon$=3.68) m$\mu$.

*6-Hydroxy-2,2,5,8-tetramethylchroman (β-model)* (2) was prepared by the same procedure in 30 % yield; m.p. 86–87.5° (from light petroleum). A sample prepared according to Frampton *et al.* melted 86–87.5°. Reported [13] 77–78°. (Found C 75.8; H 9.05. Calc. for $C_{13}H_{18}O_2$: C 75.7; H 8.80). $\nu_{max}$(KBr) 3300 $cm^{-1}$ (OH), 1590 $cm^{-1}$ (aryl). NMR: Singlet at ppm 6.25 (1H, Ar*H*), singlet at 4.20 (1H, O*H*), triplet at 2.58 (2H, Ar–C*H*$_2$–, $J$=6.5 cps), singlet at 2.01 (6H, ArC*H*$_3$), triplet at 1.74 (2H, protons at position 3, $J$=6.5 cps) and singlet at 1.26 (6H, gem.–C*H*$_3$). $\lambda_{max}$(hexane) 293 (log $\varepsilon$=3.59) and 297 (log $\varepsilon$=3.59) m$\mu$.

*6-Hydroxy-2,2,5,7-tetramethylchroman* (4) was prepared in 40 % yield by the same method. This compound was eluted from the silica gel column with ether-light petroleum (1:10). M.p. 91–92° (from light petroleum), lit.[13] 92.5–93.5°. (Found: C 75.4; H 8.51. Calc. for $C_{13}H_{18}O_2$: C 75.7; H 8.80). $\nu_{max}$(KBr) 3320 $cm^{-1}$ (OH), 1590 $cm^{-1}$ (aryl). NMR: Singlet at ppm 6.29 (1H, Ar*H*), singlet at 3.92 (1H, O*H*), triplet at 2.54 (2H, Ar–C*H*$_2$–, $J$=6 cps), two singlets at 2.10 and 2.05 (together 6H, ArC*H*$_3$), triplet at 1.73 (2H, protons at position 3, $J$=6 cps) and singlet at 1.23 (6H, gem.-C*H*$_3$). $\lambda_{max}$(hexane) 288 (log $\varepsilon$=3.57) and 294 (log $\varepsilon$=3.56) m$\mu$.

*6-Hydroxy-2,2,5,7,8-pentamethylchroman (α-model)* (1) was prepared from trimethylhydroquinone (5.0 g, 33 mmole) and dimethylallyl alcohol (3.4 g, 40 mmole) in 100 ml of formic acid (98–100 %). The product was extracted and the formate esters were hydrolyzed as before, giving 7.0 g of a brown crystalline product without chromatographic purification. After recrystallization from ethanol-water 5.9 g (82 %) of pure product was obtained, m.p. 93–94°, lit.[4] 94–95.5°. Mixed m.p. with material prepared according to Smith *et al.*[4] was undepressed. $\lambda_{max}$(hexane) 291 (log $\varepsilon$=3.56) and 297 (log $\varepsilon$=3.58) m$\mu$.

*6-Hydroxy-2,2-dimethylchroman* (8) *(tocol model)* was prepared from hydroquinone (66 g, 0.6 mole) and dimethylallyl alcohol (8.6 g, 0.1 mole) in 500 ml of formic acid (98–100 %) and the extraction of the product from the reaction mixture was performed as before. After hydrolysis of the formate esters and ether extraction, most of the ether was evaporated and 300 ml of light petroleum was added, which precipitated 45 g of unreacted hydroquinone. After evaporation of the filtrate, the residue was dissolved in 100 ml of ether-light petroleum (1:20) and placed on a column of 200 g of silica gel. Elution with 500 ml of ether-light petroleum (1:20) gave 2 g of a colourless oil that did not crystallize. The IR-spectrum of the oil showed no OH-stretching band but several absorption bands between 1170 and 1270 $cm^{-1}$ indicating a chroman structure.[13] This observation together with a remarkably low polarity ($R_F$ 0.85 compared to 0.60 for 6-hydroxy-2,2-dimethylchroman on silica gel G developed in ether-light petroleum 2:3) makes it likely that the oil is a mixture of the two double chromans *11* and *12* that can be formed in this reaction. The next fraction was eluted from the column with 1500 ml of ether-light

petroleum (1:5) which, after evaporation, gave 8.9 g of an oil. TLC indicated that it was the desired chromanol *8* contaminated with some hydroquinone. The oil crystallized upon standing and it was purified by crystallization from light petroleum-benzene yielding 5.4 g (30 %) of the white compound (*8*), m.p. 75–76°, lit.[15] 73–74°. (Found: C 73.7; H 7.63. Calc. for $C_{11}H_{14}O_2$: C 74.1; H 7.91). $\nu_{max}$(KBr) 3420 $cm^{-1}$ (OH). NMR: Multiplet at ppm 6.50–6.30 (3H, Ar*H*), singlet at 5.62 (1H, O*H*), triplet at 2.62 (2H, Ar–C*H*$_2$–, $J$=6.5 cps), triplet at 1.71 (2H, protons at position 3, $J$=6.5 cps), and singlet at 1.26 (6H, gem.–C*H*$_3$). $\lambda_{max}$(hexane) 295 (log $\varepsilon$=3.31) and 306.5 (log $\varepsilon$=3.18) m$\mu$.

*5-(2-Hydroxyethyl)-toluhydroquinone dimethyl ether* (13). A Grignard reagent was prepared from 4-bromo-2,5-dimethoxytoluene[23] (62 g, 0.305 mole) and magnesium (9.7 g, 0.397 mole) in 200 ml of dry THF. Ethylene oxide (44 g, 1 mole) in 100 ml of dry THF was added during 15 min at 0° and the mixture was then refluxed for 1.5 h with continuous stirring. During this time a thick jelly was formed that finally stopped the stirrer. 100 ml of $H_2SO_4$ (25 %) was then slowly added with external cooling and the mixture was extracted with ether. The extract was washed with water, with saturated $NaHCO_3$-solution, and again with water, dried ($Na_2SO_4$) and the ether was evaporated. The residue was distilled, affording 38 g (64 %) of *13*, b.p. 123–125°/0.6 mm; m.p. 56.5–57.5°; lit.[23] b.p. 123–124°/0.3 mm; m.p. 58–59°. $\nu_{max}$(KBr) 3300 $cm^{-1}$ (OH); 2840 $cm^{-1}$ (–$OCH_3$).

Compound *13* was then converted into *5-(2-bromoethyl)-toluhydroquinone dimethyl ether* (*14*) as described.[23]

*6-Hydroxy-2,2,7-trimethylchroman* (6). A Grignard reagent was prepared from 5-(2-bromoethyl)-toluhydroquinone dimethyl ether (*14*) (18.7 g, 72 mmole) and magnesium (2.3 g, 94 mmole) in 150 ml of dry THF. Acetone (8.4 g, 144 mmole) in 50 ml of dry THF was added to the stirred mixture during 15 min. After refluxing for 2 h, 2 N HCl (50 ml) was added and the stirring was continued for 20 min. The layers were separated and the water phase was extracted with ether. The combined organic extracts were washed with water, dried ($Na_2SO_4$) and evaporated. TLC (ether-light petroleum 1:4) showed that the residue (16 g oil) consisted of three components, one of which ($R_F$=0.76) was shown to be unreacted *14* by co-chromatography with authentic material. Of the other two components, the more polar one ($R_F$=0.1) is probably 2-(2,5-dimethoxy-4-methylbenzyl)-1,1-dimethylethanol (*15*) and the remaining compound ($R_F$=0.57) is probably 5-(3,3-dimethylallyl)toluhydroquinone dimethyl ether, formed by water elimination from *15*. Small amounts of these compounds were purified by preparative TLC, and the IR-spectra recorded are consistent with these structural assignments. Since both compounds can be converted to the desired chromanol (*6*) the oily mixture was used in the next step without further purification.

The oil was dissolved in 150 ml of glacial acetic acid, dry hydrogen bromide (15 g) was added and the solution refluxed for 12 h. Water (200 ml) was then added and the mixture extracted with 3×150 ml of ether. Light petroleum (50 ml) was added to the ether, and the mixture washed several times with water. The solvents were evaporated, the residue was dissolved in 150 ml of methanol, concentrated HCl (2 ml) was added and the solution was refluxed for 20 min. The solvent was evaporated, the residual oil was dissolved in ether and washed with water, with saturated $NaHCO_3$-solution and again with water and dried ($Na_2SO_4$). TLC (ether-light petroleum 2:3) showed that the ether solution contained two phenolic products, $R_F$ 0.48 and 0.35, both giving positive Emmerie-Engel reaction.[27] It was found that the more polar of the compounds ($R_F$=0.35) easily could be extracted into 0.5 N NaOH while the other remained in the ether layer. The alkali soluble substance is therefore probably a demethylation product derived from the small amounts of *14* that remained after the Grignard reaction. After the alkali extraction, the ether was dried ($Na_2SO_4$) and evaporated and the residue dissolved in light petroleum and was placed on a column (5 cm diameter) of 200 g silica gel. Small amounts of impurities were eluted with ether-light petroleum (1:20) and the 7-methyltocol model (*6*) was eluted with ether-light petroleum (1:5), affording 5.2 g of white crystals, m.p. 87–88° (from hexane). (Found: C 75.1; H 8.34. Calc. for $C_{12}H_{16}O_2$: C 75.0; H 8.39). $\nu_{max}$(KBr) 3370 $cm^{-1}$ (OH); 1620 $cm^{-1}$ (aryl). NMR: Singlets at ppm 6.43 and 6.26 (1H each, Ar*H*), singlet at 5.09 (1H, O*H*), triplet at 2.57 (2H, ArC*H*$_2$–, $J$=7 cps), singlet at 2.10 (3H, ArC*H*$_3$), triplet at 1.66 (2H, protons at position 3, $J$=7 cps) and singlet at 1.25 (6H, gem.-C*H*$_3$) $\lambda_{max}$(hexane) 294 (log $\varepsilon$=3.62) and 300 (log $\varepsilon$=3.61) m$\mu$.

*3,6-Dimethoxy-2-methylbenzylacetone* (17). To a stirred solution of ethyl acetoacetate (5.4 g, 41 mmole) in 50 ml of dry benzene was slowly added granulated sodium (0.94 g, 41 mmole). After all the sodium had reacted, a solution of 3-bromomethyltoluhydroquinone dimethyl ether [22] (*16*) (10 g, 41 mmole) in 10 ml of dry benzene was added to the suspension which was then stirred and refluxed overnight. After cooling, 75 ml of water was added, the benzene layer was separated and the water phase was extracted with ether. After evaporation of the combined organic extracts, the remaining oil (9.4 g) was rapidly stirred with 40 ml of 1 N NaOH for 5 h. Undissolved material was then separated, and the water layer acidified with $H_2SO_4$ (3 g) and stirred at room temperature overnight. The precipitate formed was extracted into ether which was dried ($Na_2SO_4$) and evaporated, yielding 3.5 g (38 %) of *17*, m.p. 70—71.5° (from light petroleum). (Found: C 70.5; H 8.33. Calc. for $C_{13}H_{18}O_3$: C 70.2; H 8.16). $\nu_{max}$(KBr) 2835 $cm^{-1}$ (—$OCH_3$), 1710 $cm^{-1}$ (C=O). NMR: Singlet at ppm 6.65 (2H, Ar*H*), singlet at 3.75 (6H, —OC*H*$_3$), multiplet at 3,.18—2.15 (4H, $A_2B_2$-pattern centered at 2.75, side chain —C*H*$_2$—), two singlets at 2.20 and 2.18 (3H each, ArC*H*$_3$ and —CO—C*H*$_3$ resp.). The singlet at 2.20 ppm is assigned to the aromatic methyl group since the same peak is present in the spectrum of 2-(3,6-dimethoxy-2-methylbenzyl)-1,1-dimethylethanol (*18*).

*2-(3,6-Dimethoxy-2-methylbenzyl)-1,1-dimethylethanol* (18). Methyl magnesium iodide was prepared from methyl iodide (9.6 g, 67.5 mmole) and magnesium (1.64 g, 67.5 mmole) in 100 ml dry ether. A solution of 3,6-dimethoxy-2-methylbenzylaceton (*17*) (10 g, 40 mmole) in 200 ml of dry ether was slowly added and the solution was left overnight. Water (15 ml) was then added, the ether layer was separated, dried ($Na_2SO_4$) and evaporated affording 9.9 g (92.5 %) of the tertiary alcohol *18*, m.p. 65—67° (from light petroleum). (Found: C 70.5; H 9.38. Calc. for $C_{14}H_{22}O_3$: C 70.6; H 9.31). $\nu_{max}$(KBr) 3400 $cm^{-1}$ (OH), 2835 $cm^{-1}$ (—$OCH_3$), no carbonyl absorption. NMR: Singlet at ppm 6.64 (2H, Ar*H*), singlet at 3.75 (6H, —OC*H*$_3$), multiplets at 2.92—2.55 and 1.80—1.43 (2H each, AA'XX' pattern centered at 2.16, side chain —C*H*$_2$—), singlet at 2.20 (3H, ArC*H*$_3$) and singlet at 1.28 (6H, gem.—$CH_3$).

*6-Hydroxy-2,2,5-trimethylchroman (5-methyltocol model)* (7). The tertiary alcohol *18* (9 g, 37.8 mmole) was added to 100 ml of a 10 % solution of HBr in glacial acetic acid and the mixture was refluxed overnight. Water (300 ml) was added and the reaction product was purified as described for the 7-methyltocol model (*6*) yielding 4 g (55 %) of *7* as a white crystalline material, m.p. 72—73° (from light petroleum). (Found: C 74.9; H 7.96. Calc. for $C_{12}H_{16}O_2$: C 75.0; H 8.39). $\nu_{max}$(KBr) 3415 $cm^{-1}$ (OH). NMR: Singlet at ppm 6.40 (2H, Ar*H*), singlet at 4.50 (1H, O*H*), triplet at 2.57. (2H, ArC*H*$_2$—, $J$=6.5 cps), singlet at 2.07 (3H, ArC*H*$_3$), triplet at 1.72 (2H, protons at position 3, $J$=6.5 cps) and singlet at 1.25 (6H, gem.—C*H*$_3$). $\lambda_{max}$(hexane) 291 (log $\varepsilon$=3.58) and 297.5 (log $\varepsilon$=3.57) m$\mu$.

*2,6-Dimethylhydroquinone dimethyl ether* (20). 2,6-Dimethylhydroquinone (100 g, 0.722 mole) in ethanol (500 ml) was heated to reflux. The heating was discontinued and to the stirred solution was added simultaneously dimethylsulphate (299 g, 1.81 mole) and 50 % NaOH (150 g, 1.88 mole) from two dropping funnels during 2 h. When the addition was complete, the stirred mixture was refluxed for 3 h then steam distilled. After 6 l of distillate had been collected, it was extracted with ether, dried ($Na_2SO_4$) and fractionated affording 70 g (59 %) of a clear oil. b.p. 80—82°/2 mm. $n_D^{20}$ 1.5134. (Found: C 72.2; H 8.29. Calc. for $C_{10}H_{14}O_2$: C 72.3; H 8.49). $\nu_{max}$(film) 2840 $cm^{-1}$ (—$OCH_3$), no OH-absorption.

*2-Bromomethyl-6-methylhydroquinone dimethyl ether* (21) was prepared from 2,6-dimethylhydroquinone dimethyl ether (*20*) (60 g, 0.36 mole) using *N*-bromosuccinimide according to McHale *et al.*,[22] affording 57.1 g (65 %) of *21*, b.p. 110—115°/1 mm, m.p. 48—50° (from light petroleum). (Found: C 48.9; H 5.11. Calc. for $C_{10}H_{13}BrO_2$: C 49.0; H 5.34). $\nu_{max}$(KBr) 2840 $cm^{-1}$ ($OCH_3$), 595 $cm^{-1}$ (C—Br). NMR: Two unresolved doublets at ppm 6.65—6.47 (2H, Ar*H*, $J \simeq 3$ cps), singlet at 4.42 (2H, ArC*H*$_2$Br), two singlets at 3.74 and 3.66 (3H each, —OC*H*$_3$), singlet at 2.18 (3H, ArC*H*$_3$).

*2,5-Dimethoxy-3-methylbenzylacetone* (22) was prepared as described for 3,6-dimethoxy-2-methylbenzylacetone (*17*). The product was obtained as an uncrystallizable oil in 41 % yield, b.p. 142—143°/1.5 mm, $n_D^{25}$=1.5175. (Found: C 70.1; H 7.95. Calc. for $C_{13}H_{18}O_3$: C 70.2; H 8.16). $\nu_{max}$(KBr) 2840 $cm^{-1}$ ($OCH_3$), 1710 $cm^{-1}$ (C=O). NMR: Singlet at ppm 6.43 (2H, Ar*H*), singlets at 3.68 and 3.64 (3H each, OC*H*$_3$), unresolved multiplet centered at 2.70 (4H, side chain —C*H*$_2$—), singlet at 2.23 (3H, ArC*H*$_3$), singlet at 2.05 (3H,

$-CO-CH_3$). The singlet at 2.23 is assigned to the aromatic methyl group since the same peak is present in 2-(2,5-dimethoxy-3-methylbenzyl)-1,1-dimethylethanol (*23*).

*2-(2,5-Dimethoxy-3-methylbenzyl)-1,1-dimethylethanol* (23) was prepared by adding the benzylacetone *22* to methyl magnesium iodide as described for *18* yielding *23* quantitatively as an oil that did not crystallize; b.p. 146–150°/2 mm, $n_D^{24}=1.5154$. (Found: C 70.4; H 8.98. Calc. for $C_{14}H_{22}O_3$: C 70.6; H 9.31). $\nu_{max}$(KBr) 3420 $cm^{-1}$ (OH), 2840 $cm^{-1}$ ($OCH_3$). NMR: Singlet at ppm 6.63 (2H, Ar*H*), singlets at 3.68 and 3.64 (3H each, $OCH_3$), multiplets at 2.80–2.46 and 1.84–1.50 (2H each, AA'XX' pattern centered at 2.15, side chain $-CH_2-$), singlet at 2.23 (3H, $ArCH_3$), singlet at 1.23 (6H, gem.-$CH_3$).

*6-Hydroxy-2,2,8-trimethylchroman (8-methyltocol model, δ-model)* (5) A. Prepared as described for the 5-methyltocol model (*7*) from 15 g of *23* yielding 8 g (67 %) of the chromanol *5*, m.p. 83–84° (from light petroleum). (Found: C 74.9; H 8.49. Calc. for $C_{12}H_{16}O_3$: C 75.0; H 8.39). $\nu_{max}$(KBr) 3420 $cm^{-1}$ (OH). NMR: Two doublets centered at ppm 6.36 and 6.20 resp. (2H together, Ar*H*, $J=3$ cps) singlet at 5.68 (1H, O*H*), triplet at 2.59 (2H, $ArCH_2-$, $J=7$ cps), singlet at 2.03 (3H, $ArCH_3$), triplet at 1.68 (2H, protons at position 3, $J=7$ cps) and singlet at 1.26 (6H, gem.-$CH_3$). $\lambda_{max}$(hexane) 292 (log $\varepsilon=3.62$) and 298 (log $\varepsilon=3.60$) mμ.

B. 4-methoxy-2-methylphenol [25] (18.5 g, 134 mmole) was condensed with isoprene (20 g, 295 mmole) as described.[4] The oily reaction product, which was shown by TLC to contain several components of similar polarity, was treated with HBr in acetic acid.[15] After chromatographic purification as described for the γ-model (*3*) 44 mg (1.6 %) of the δ-model compound (*5*) was obtained, identified by co-chromatography and spectral comparison with material prepared by method A.

*Acknowledgement.* We wish to thank Professor Richard Dahlbom for his sincere interest in this work and for his many valuable suggestions.

## REFERENCES

1. Nilsson, J. L. G, Redalieu., E., Nilsson, I. M. and Folkers, K. *Acta Chem. Scand.* **22** (1968) 97.
2. Nilsson, J. L. G., Daves, Jr., G. D. and Folkers, K. *Acta Chem. Scand.* **22** (1968) 200.
3. Nilsson, J. L. G., Daves, Jr., G. D. and Folkers, K. *Acta Chem. Scand.* **22** (1968) 207.
4. Smith, L. I., Ungnade, H. E., Hoehn, H. H. and Wawzonek, S. *J. Org. Chem.* **4** (1939) 311.
5. John, W. and Emte, W. *Z. Physiol. Chem.* **268** (1941) 85.
6. Inglett, G. E. and Mattill, H. A. *J. Am. Chem. Soc.* **77** (1955) 6552.
7. Schudel, P., Mayer, H., Metzger, J., Rüegg, R. and Isler, O. *Helv. Chim. Acta* **46** (1963) 636.
8. Skinner, W. A. and Alaupovic, P. *Science* **140** (1963) 803.
9. Skinner, W. A. and Alaupovic, P. *J. Org. Chem.* **28** (1963) 2857.
10. Skinner, W. A. and Parkhurst, R. M. *J. Org. Chem.* **29** (1964) 3601.
11. Skinner, W. A. and Parkhurst, R. M. *J. Org. Chem.* **31** (1966) 1248.
12. Skinner, W. A., Parkhurst, R. M., Scholler, J., Alaupovic, P., Crider, Q. E. and Schwarz, K. *J. Med. Chem.* **10** (1967) 657.
13. Frampton, V. L., Skinner, W. A., Cambour, P. and Baily, P. S. *J. Am. Chem. Soc.* **82** (1960) 4632.
14. Smith, L. I. and Tess, R. W. H. *J. Am. Chem. Soc.* **66** (1944) 1523.
15. Marcinkiewicz, S., Green, J. and McHale, D. *J. Chromatog.* **10** (1963) 42.
16. Miller, J. A. and Wood, H. C. S. *Chem. Commun.* **1965** 39.
17. Isler, O., Schudel, P., Mayer, H., Würsch, J. and Rüegg, R. *Vitamins and Hormones* **20** (1962) 389.
18. Rüegg, R., Mayer, H., Schudel, P., Schwieter, U., Tamm, R. and Isler, O. In Lang, K. *Tocopherole*, Steinkopff Verlag, Darmstadt 1967, p. 14.
19. Karrer, P. and Fritzsche, H. *Helv. Chim. Acta* **22** (1939) 260.
20. Pendse, H. K. and Karrer, P. *Helv. Chim. Acta* **41** (1958) 396.
21. Marcinkiewicz, S., McHale, D., Mamalis, P. and Green, J. *J. Chem. Soc.* **1959** 3377.
22. McHale, D., Mamalis, P., Marcinkiewicz, S. and Green, J. *J. Chem. Soc.* **1959** 3358.

23. McHale, D., Mamalis, P., Green, J. and Marcinkiewicz, S. *J. Chem. Soc.* **1958** 1600.
24. Claisen, L. *J. prakt. Chem.* **105** (1922) 65.
25. Nilsson, J. L. G., Sievertsson, H. and Selander, H. *Acta Pharm. Suecica* **5** (1968) 215.
26. Acheson, R. M. *J. Chem. Soc.* **1956** 4232.
27. Baxter, J. G., Robeson, C. D., Taylor, J. D. and Lehman, R. W. *J. Am. Chem. Soc* **65** (1943) 918.

Received May 16, 1968.