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TOCOPHEROLS VIII.[x] NEW DIMERS AND SPIROKETAL TRIMERS AS OXIDATION PRODUCTS OF TOCOL DERIVATIVES

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In this paper we demonstrate that the main oxidation products from methyl substituted 6-chromanols are dimers and spiroketal trimers. The type of products formed depends on the oxidising agent, as illustrated in the scheme below. The oxidative coupling takes place preferentially at the 5-position, and this is the sole site of reaction when the 5-position is unsubstituted.

The importance of tocopherols as biological antioxidants has stimulated the interest in their oxidation. α-Tocopherol (I) or its model compound 2,2,5,7,8-pentamethyl-6-chromanol has been extensively studied (1) but the oxidation of other naturally occurring tocopherols (II-IV) has attracted much less interest (1). Our previous work on this problem (1) suggested the present investigation.

Oxidation with alkaline ferricyanide. The reaction was carried out in a two-phase system where the tocol derivative (2), dissolved in light petroleum, was rapidly stirred with a solution of 3 equiv. of $K_3Fe(CN)_6$ in 0.2 N aqueous NaOH for 30 min. The products were isolated by preparative TLC.

The product from the α-tocopherol model (I) has been previously reported (3) as the spiro dimer VIa. The β-tocopherol model (II) also gave a dimer, the IR-, UV- and NMR-spectra of which (Table 1) are consistent with the β-spiro dimer VIb. The γ-tocopherol model (III) formed an unstable yellow product which was crystallized from ether at -20°. IR- and UV-spectra indicated an unsaturated ketone. The NMR-spectrum shows no signals due to aromatic protons. A singlet at δ=2.10 ppm (12H) represents four aromatic methyl groups, and two other methyl groups appear as singlets at δ=1.82 and 1.95 ppm. These data, which show that the compound is a trimer, are consistent with the

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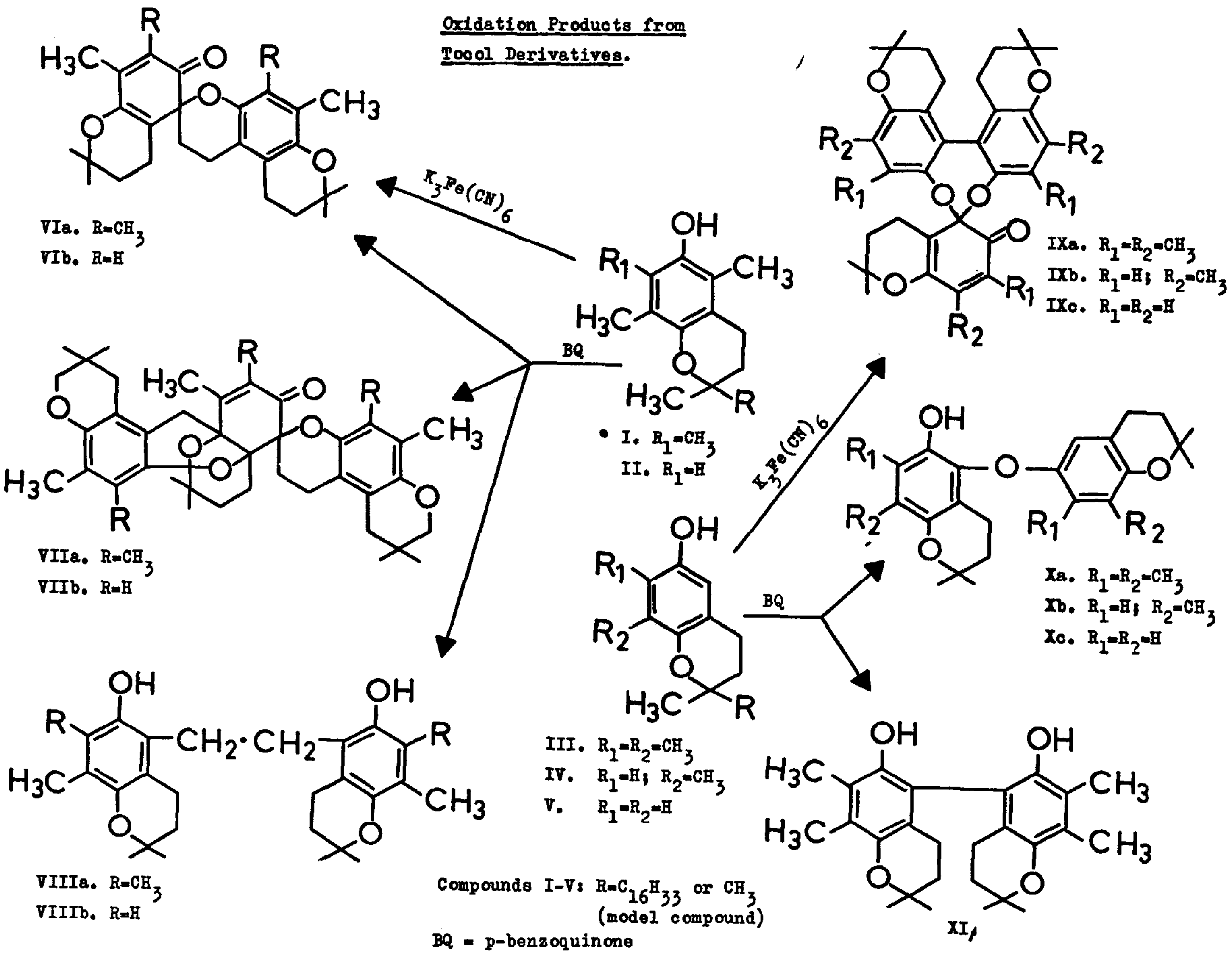
structure IXa, a spiroketal trimer similar to the compounds obtained by Hewgill (4) in the oxidation of 3-alkyl-4-methoxyphenols. The δ-tocopherol model (IV) and the tocol model (V) afforded similar spiroketal trimers IXb and IXc, respectively. The structures are assigned on the basis of their spectral properties (Table 1).

Oxidation with benzoquinone. The reaction was carried out by dissolving the chromanol and one equivalent of benzoquinone in benzene. The solution was then kept at room temperature over night. The α-tocopherol model (I) yielded the spiro dimer VIa, the trimer VIIa and the tocopherylethane VIIIa. Similarly, the β-tocopherol model (II) afforded VIb, VIIb and VIIIb. The compounds were identified by chromatographical and spectral comparison with authentic materials (1). The γ-tocopherol model (III) afforded two dimers Xa and XI, analogous to the dimers obtained from natural γ-tocopherol (1). Similarly, the δ-tocopherol model formed a dimer Xb as the main product. By a deuterium labelling technique (5) and NMR-spectroscopy it could be demonstrated that the coupling had occurred exclusively at the 5-position. Oxidation of the tocol model (V) produced the dimer Xc. The NMR-signals due to the aromatic protons formed a multiplet and an AB-pattern (J=9 cps) consistent with the proposed structure. (Table 1).

Discussion of the results. Oxidation of the 6-chromanols studied here produces two different types of products depending on the substitution pattern of the chromanol. When alkaline ferricyanide is the oxidizing agent, the chromanols with an unsubstituted 5-position form spiroketal trimers (IXa-IXc) by carbon-carbon and carbon-oxygen coupling thus following the general reaction pattern of 3-alkyl-4-methoxyphenols (4). When the 5-position carries a methyl group, the spiro dimers VIa and VIb are formed by reactions involving both carbon-oxygen and benzylic coupling. Benzoquinone oxidation of 6-chromanols with an unsubstituted 5-position gives dimers (X and XI) by coupling exclusively at the 5-position. When the chromanol has a 5-methyl group benzylic coupling occurs via this methyl group yielding two dimers and a trimer (VI-VIII). In the oxidation of the β-tocopherol model (II), benzylic coupling occurs although there is an unsubstituted ortho position in the molecule. This appears to be the first reported example of a phenol with a free ortho position forming oxidation products via benzylic coupling. The observation that coupling occurs preferentially at the 5-position in the tocol series is interpreted as a result of the directing effect of the heterocyclic ring.

Full details on this work will be published in subsequent papers (5).

Oxidation Products from Tocol Derivatives.



VIa. R=CH_3
VIb. R=H

VIIa. R=CH_3
VIIb. R=H

VIIIa. R=CH_3
VIIIb. R=H

• I. R_1=CH_3
II. R_1=H

III. R_1=R_2=CH_3
IV. R_1=H; R_2=CH_3
V. R_1=R_2=H

IXa. R_1=R_2=CH_3
IXb. R_1=H; R_2=CH_3
IXc. R_1=R_2=H

Xa. R_1=R_2=CH_3
Xb. R_1=H; R_2=CH_3
Xc. R_1=R_2=H

XI,

Compounds I-V: R=$C_{16}H_{33}$ or CH_3
(model compound)

BQ = p-benzoquinone

Table 1. Physical Data for Oxidation Products of Tocol Derivatives.

Compound	Mol.wt.[a]	UV λ_{max}^{hexane} (mμ)	IR KBr-disc (cm^{-1})	NMR δ ppm[b,c]			
				Aromatic	Vinylic	Methyl groups	
						Aromatic	Vinylic
VIb	415	331 298	1650 1670	6.31 (s,1)	5.62 (s,1)	2.05 (s,3)	1.98 (s,3)
IXa	d	345 301	1650 1685	-	-	2.10 (s,12)	1.95 (s,3) 1.82 (s,3)
IXb	d	348 296	1655 1700	6.89 (s,1) 6.72 (s,1)	5.70 (m,1)[e]	2.22 (s,3) 2.15 (s,3)	2.00 (d,3)[e]
IXc	d	355 (sh) 295	1640 1680	6.55 (m)[f]	6.85 (s)[f]	-	-
Xa	398	297	3400	5.90 (s,1)	-	2.25 (s,3) 2.13 (s,3) 2.05 (s,3) 2.00 (s,3)	-
Xb	397	293 297	3400	6.59 (s,1) 6.43 (d,1) 6.26 (d,1)	-	2.10 (s,3) 2.06 (s,3)	-
Xc	348	294	3400	6.45 (m,3) 6.55 (q,2)	-	-	-
XI	395	300	3400	-	-	2.13 (s,6) 2.05 (s,6)	-

a. Molecular weights were determined using a Hitachi Perkin-Elmer 115 Molecular Weight Apparatus.

b. Sample in CCl_4-solution with TMS as an internal reference.

c. Aliphatic protons at δ = 1.35-1.10 and 1.70 ppm.

d. Decomposed during the determination.

e. Small coupling between vinylic proton and vinylic methyl group (J∼1 cps).

f. A pure sample could not be obtained, which makes the integration uncertain.

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