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Reactions of Some Tocopherols with the Methyl Radical[1)]

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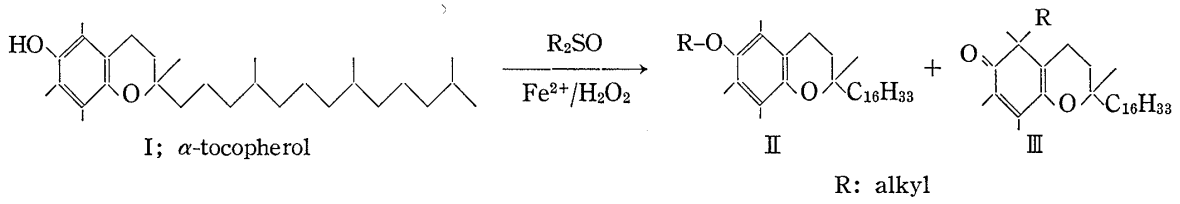
The reactivity of some tocopherols (vitamin E) with the methyl radical was examined. When the methyl radical was generated from dimethyl sulfoxide by the action of hydrogen peroxide in the presence of ferrous sulfate, either β-tocopherol or γ-tocopherol reacted with it to give the corresponding methyl ether and 2,5,5,7,8-pentamethyl-2-(4,8,12-trimethyltridecyl)chroman-6(5H)-one in low yields. Tocol afforded only a small amount of its methyl ether. On the other hand, 5,7-dimethyltocol was converted to its methyl ether and 2,5,5,7-tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6(5H)-one in 9 and 38% yields, respectively. Taken with the previous data on α-tocopherol, these results indicate that the radical scavenging abilities of tocopherols against the methyl radical are in the following order: α-tocopherol≧5,7-dimethyltocol>β-tocopherol=γ-tocopherol≧tocol.

Keywords——α-tocopherol; β-tocopherol; γ-tocopherol; tocol; 5,7-dimethyltocol; methyl radical; radical scavenging reaction; ^{13}C-NMR

Our previous studies on the radical scavenging reactions of α-tocopherol (I) with some alkyl radicals revealed that I is reactive with alkyl radicals and affords two types of compounds, α-tocopherol alkyl ethers (II) and 5-alkyl-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6(5H)-ones (III) (Fig. 1), and that the reactivity of I decreases with increase of the carbon numbers of alkyl radicals.[2,3)] We also unambiguously elucidated the structures of these products by ^{13}C nuclear magnetic resonance spectroscopy.[4,5)] We report here the results of studies on the radical scavenging reactions of other tocopherols with the methyl radical.



I; α-tocopherol II III

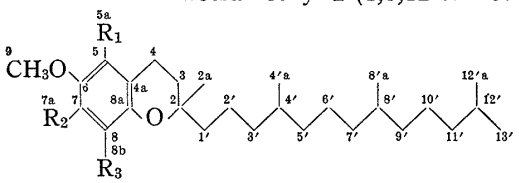
R: alkyl

Fig. 1

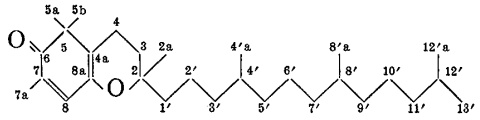
For comparative purposes, we investigated the reactions of four kinds of tocopherols, β-tocopherol (IV), γ-tocopherol (V), 5,7-dimethyltocol (VI) and tocol (VII), with the methyl radical, which was generated by the addition of hydrogen peroxide to a ferrous sulfate solution in dimethyl sulfoxide and allowed to react *in situ* with each tocopherol under conditions similar to those used for the reaction of I.[2)] Products were isolated from the reaction mixtures by silica gel column chromatography. Their structures were determined on the basis of the spectral data in Tables I and II and the reported data for the reaction products from I.[2,4,5)]

It was found that all the tocopherols employed here could react with the methyl radical (Fig. 2). However, the yields of the reaction products varied widely according to the number and position of methyl groups in the aromatic ring of each tocopherol. For example, VI was converted to its methyl ether (X) and 2,5,5,7-tetramethyl-2-(4,8,12-trimethyltridecyl)-chroman-6(5H)-one (XIII) in 9 and 38% yields, respectively, being completely consumed during the reaction. This is quite similar to the reaction of I: I gives rise to its methyl ether

TABLE I. ^{13}C Chemical Shifts of Some Tocopherol Methyl Ethers and 2,5,5,7-Tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6(5H)-one[a]



VIII: $R_1=R_3=CH_3$, $R_2=H$
IX: $R_1=H$, $R_2=R_3=CH_3$
X: $R_1=R_2=CH_3$, $R_3=H$
XI: $R_1=R_2=R_3=H$



XIII

Carbon No.[b]	VIII	IX	X	XI	XIII
2	74.5	75.3	74.9	75.6	75.2
2 a	23.9	24.1	23.9	24.1	23.4
3	31.5	31.5	31.0	31.0	31.0
4	20.8	22.7	20.5	22.6	18.5
4 a	120.4	117.2	118.0	121.5	138.3
5	122.0[c]	108.4	128.8	113.3[c]	47.5
5 a	10.9	—	11.8	—	25.5 25.1
5 b	—	—	—	—	
6	150.0	150.5	149.7	152.2	191.1
7	112.0	124.1	129.2	113.8[c]	119.1
7 a	—	11.8	16.0	—	15.2
8	123.2[c]	125.7	116.5	117.6	131.2
8 a	145.9	145.7	149.6	147.9	140.5
8 b	16.2	11.8	—	—	—
1′	39.9	40.2	40.0	39.9	39.7
9	56.3	56.0	60.0	55.6	—

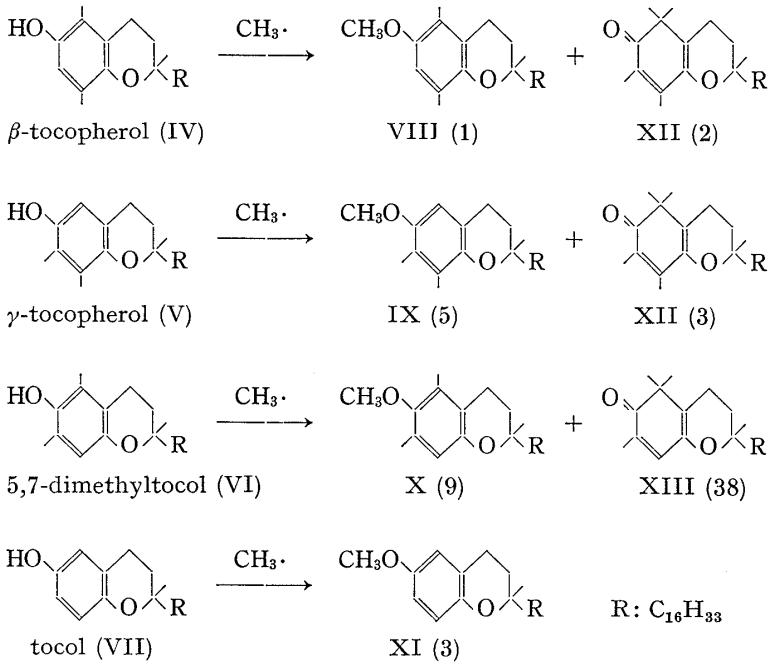
a) In ppm relative TMS.
b) The chemical shifts of C-2′ to C-13′ are not listed because they are similar to the corresponding shifts of the isoprenyl chain in α-tocopherol.[4]
c) Tentative assignment.

TABLE II. Spectral Data for Some Tocopherol Methyl Ethers and 2,5,5,7-Tetramethyl-2-(4,8,12-trimethyltridecyl)chroman-6(5H)-one

		VIII[a]	IX[a]	X[a]	XI[a]	XIII[a]
Mass	(M^+)	430	430	430	402	430
UV	λ_{max}^{hexane} nm (ε)	290 (3900)	291 (2200)	281 (1900)	284 (3000)	258 s (14700) 340 (3000)
IR	ν_{max}^{neat} cm^{-1}	1094	1090	1080	1090	1645 1606
^1H-NMR	$\delta_{TMS}^{CDCl_3}$	0.87 (d, 12H, J=6.0 Hz) 1.00—1.63 (m, 24H) 1.77 (t, 2H, J=6.5 Hz) 2.06 (s, 3H) 2.15 (s, 3H) 2.59 (t, 2H, J=6.5 Hz) 3.73 (s, 3H) 6.56 (s, 1H)	0.88 (d, 12H, J=6.0 Hz) 1.00—1.65 (m, 24H) 1.74 (t, 2H, J=6.5 Hz) 2.11 (s, 6H) 2.70 (t, 2H, J=6.5 Hz) 3.72 (s, 3H) 6.40 (s, 1H)	0.87 (d, 12H, J=6.0 Hz) 1.00—1.65 (m, 24H) 1.78 (t, 2H, J=6.5Hz) 2.14 (s, 3H) 2.21 (s, 3H) 2.56 (t, 2H, J=6.5 Hz) 3.64 (s, 3H) 6.48 (s, 1H)	0.86 (d, 12H, J=6.0 Hz) 1.00—1.65 (m, 24H) 1.78 (t, 2H, J=6.5 Hz) 2.72 (t, 2H, J=6.5 Hz) 3.73 (s, 3H) 6.60(bd.s,2H) 6.69(bd.s,1H)	0.88 (d, 12H, J=6.0 Hz) 1.00—1.57 (m, 30H) 1.67 (t, 2H, J=6.5 Hz) 1.87 (s, 3H) 2.14 (t, 2H, J=6.5 Hz) 6.61 (s, 1H)

a) See Table I.

[II (R=Me)] and 2,5,5,7,8-pentamethyl-2-(4,8,12-trimethyltridecyl)chroman-6(5H)-one [III (R=Me)≡XII] in 8 and 42% yields, respectively.[2] In contrast, VII gave only a small amount of its methyl ether (XI) and more than 90% of VII used was recovered from the reaction mixture. Interestingly, a common product, XII, was obtained in the reactions of IV and V with the methyl radical, being accompanied by β-tocopherol methyl ether (VIII) or γ-tocopherol methyl ether (IX). Presumably, aromatic methylation at C-7 in IV and C-5 in V may take place to yield I prior to the formation of a *gem*-dimethylcyclohexadienone through methyl-radical attack on C-5. The radical scavenging efficiency of IV or V, however, seems to be rather low because about 50% of each of them remained unchanged when the reaction was stopped. These results suggest that the radical scavenging abilities of tocopherols against the methyl radical are in the following order: α-tocopherol (I)≥5,7-dimethyltocol (VI)>β-tocopherol (IV)=γ-tocopherol (V) ≥tocol (VII). It appears that the two methyl groups at C-5 and C-7 in tocopherols are very important for methyl-radical scavenging ability.



Figures in parentheses show the yields (%) of the compounds.

Fig. 2

Experimental

Materials——*dl*-β-Tocopherol, *dl*-γ-tocopherol, *dl*-5,7-dimethyltocol and *dl*-tocol were prepared in our laboratory according to the method of Nilsson *et al.*[6] Silica gel C-200 and dimethyl sulfoxide were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). All other chemicals were obtained from well-known suppliers.

Methods——^{1}H and ^{13}C Nuclear magnetic resonance spectra were recorded on a Varian XL-100-12 WG spectrometer equipped with a Varian 620/L computer and operating at 100 MHz (^{1}H) and 25.16 MHz (^{13}C) at about 30°. Samples were dissolved in $CDCl_3$ with tetramethylsilane as an internal standard. Mass, UV and IR spectra were taken as described previously.[2]

To a mixture of 2.4 mmol of a tocopherol and 0.5 mmol of ferrous sulfate heptahydrate in 5 ml of dimethyl sulfoxide (DMSO), 1 ml of 30% hydrogen peroxide in 1 ml of DMSO was added dropwise with stirring under a nitrogen atmosphere at 60° for 15 min. The reaction mixture was poured into ice water and extracted with chloroform. The chloroform layer was washed with water and dried over sodium sulfate. After filtration, the chloroform solution was concentrated *in vacuo* to afford a viscous oil. The yellowish residue was applied to a silica gel column and eluted with a mixture of *n*-hexane and benzene (5: 1 v/v). Each fraction collected was analyzed by gas–liquid and thin–layer chromatography.

References and Notes

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A Direct Reductive Deamination of Amidines with Sodium Borohydride. Formation of Deaminated Compounds and Secondary Amines

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The reaction of 3-substituted-4-amino-1*H*-1,5-benzodiazepines (**1a, b**) with sodium borohydride afforded deaminated compounds (**4a, b** and **6a, b**). On the other hand, acyclic amidines were converted by treatment with sodium borohydride to the corresponding secondary amines (**13**) under the same conditions.

Keywords——1,5-benzodiazepines; deamination; amidines; mass analysis; IR absorption of cyano group; H-NMR; ^{13}C-NMR

There is considerable interest in reductive deamination in connection with organic syntheses and biological reactions. The reaction involves net replacement of an amino group attached to carbon by hydrogen. Chemical procedures that accomplish this change for aromatic amines are well known[1,2] and in aliphatic series a direct method was reported by Nickon and coworkers.[3] Enzymatic and radiolytic deaminations have also been studied.[4,5]

In this report, we describe a simple direct method for reductive deamination of amidines using sodium borohydride. When sodium borohydride was added to an aqueous solution of 4-amino-1*H*-1,5-benzodiazepine-3-carbonitrile hydrochloride (**1a**),[6] the deamination occurred rapidly in good yield (see Chart 1). Thin layer chromatographic (TLC) analysis revealed that the product consisted of two components, 3-cyano-4,5-dihydro-1*H*-1,5-benzodiazepine (**4a**) and 3-cyano-2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine (**6a**). The later compound **6a** was isolated in 37% yield by means of column chromatography on aluminum oxide with cholroform as an eluant. However, **4a** was gradually decomposed during the column chromatography, and only a small amount of **4a** was isolated as needles. Similarly, the reaction of ethyl 4-amino-1*H*-1,5-benzodiazepine-3-carboxylate hydrochloride (**1b**)[6] with sodium borohydride was carried out. A deaminated compound, 3-ethoxycarbonyl-4,5-dihydro-1*H*-1,5-benzodiazepine (**4b**), was obtained, but the tetrahydro derivative (**6b**) could not be isolated. During purification by column chromatography on aluminum oxide with chloroform as an eluant, **4b** was also decomposed.

The structures of **6a**, **4b** and **4a** were determined on the basis of nuclear magnetic resonance (NMR), mass (MS) and infrared (IR) spectral data. The H–NMR spectrum of **6a** showed multiplet signals for four aromatic protons at 6.55—6.58 ppm, and multiplet signals for one methine and four methylene protons at 3.00—3.65 ppm where signals for two amino protons