Hindawi Publishing Corporation
Research Letters in Organic Chemistry
Volume 2008, Article ID 742590, 4 pages
doi:10.1155/2008/742590

Research Letter

A Novel Dimer of α-Tocopherol

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Received 26 June 2008; Accepted 2 August 2008

Recommended by Kazuaki Ishihara

Decomposition of the complex **4**, formed between the α-tocopherol *ortho*-quinone methide (**2**) and NMMO, by fast heating from -78°C to 70°C in inert solvents produces a novel α-tocopherol dimer with 6*H*,12*H*-dibenzo[b,f][1,5]dioxocine structure (**5**) which—in contrast to the well-known spiro-dimer of α-tocopherol (**3**)—is symmetrical. This is the first example of a direct reaction of the highly transient zwitterionic, aromatic precursor **2a** in the formation of the *ortho*-quinone methide **2**.

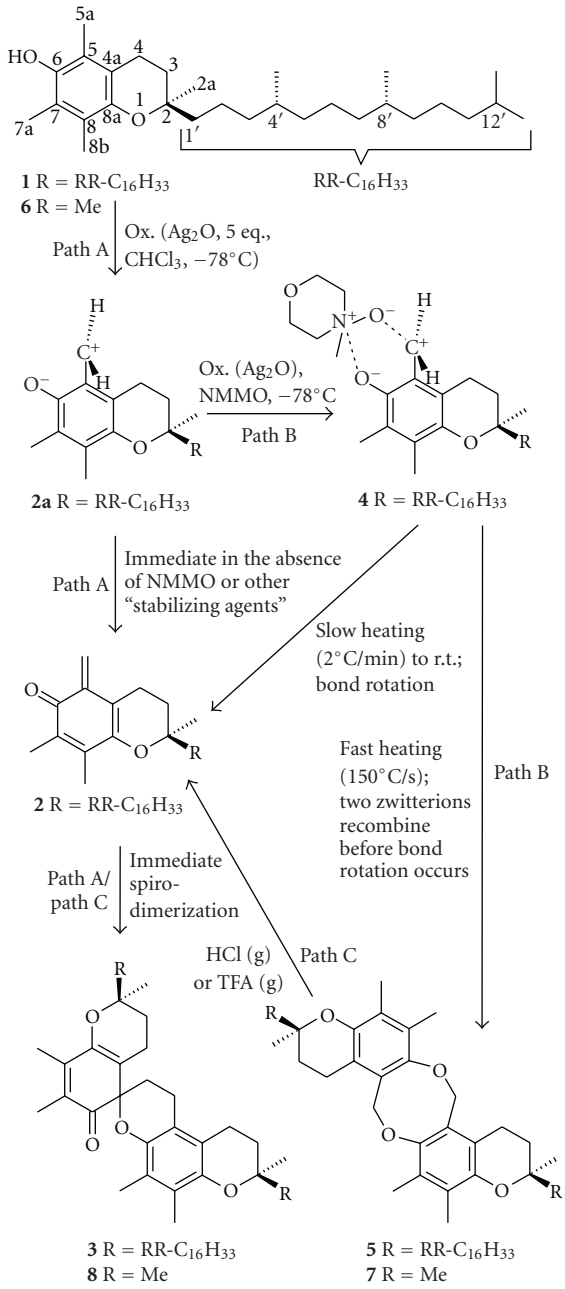
1. Introduction

Oxidation of α-tocopherol (**1**) [1, 2] in aprotic media affords an *ortho*-quinone methide (oQM, **2**) which is formed quite selectively at position C-5a [3]. If no coreactants or trapping agents, such as electron-rich dienophiles, are present, the oQM undergoes dimerization to the so-called spiro-dimer of α-tocopherol (**3**) [4, 5] (see Scheme 1, path A), one of the major tocopherol oxidation products both in vitro and in vivo. It was shown that a zwitterionic, aromatic species (**2a**)—carrying a perpendicular benzyl cation and a phenolate group—was an intermediate on the way from the phenol to the *ortho*-quinone methide. In-plane rotation of the exocyclic methylene group then enables the system to assume the energetically more favorable quinoid form (**2**) [3]. Recently, a method was found to stabilize the zwitterionic intermediate at low temperature with amine *N*-oxides [6] which also carry a zwitterionic moiety (see Scheme 1, path B). Recently, the structure of such complexes between zwitterionic oQM precursor **2a** and stabilizing zwitterionic species—in this case sulfonium ylide species derived from 2,5-dihydroxy-[1, 2, 6] benzoquinone—was proven by X-ray and NMR data [7].

2. Results and Discussion

Composition of complex **4**, formed from the zwitterionic intermediate **2a** and *N*-methylmorpholine-*N*-oxide (NMMO), by fast heating from -78°C to temperatures of 70°C produced a single minor product in reproducible yields of 3.5% besides spiro-dimer **3** (see Scheme 1, path B). Analytics of this compound were somewhat surprising as microanalysis and the molpeak in mass spectrometry were clearly indicative of spiro-dimer **3**, but the chromatographic behavior evidently proved the substance to be a different compound. The mass-spectrometric fragmentation pattern indicated a highly symmetric compound, and NMR finally proved the compound to be benzyl ether **5**, a "dioxocine dimer" of α-tocopherol. In the next step, the α-tocopherol model compound 2,2,5,7,8-pentamethylchroman-6-ol (PMC, **6**) was used for complex formation and subsequent thermal degradation of the complex. Unfortunately, all attempts to obtain crystals of the corresponding dioxocine dimer (**7**) in qualities sufficient for X-ray analysis failed; the substance precipitated in an amorphous form throughout.

Strictly speaking, dibenzodioxocine dimer **5** is not a reaction product of *ortho*-quinone methide **2**, but of its



Scheme 1: Oxidation of α-tocopherol (**1**) conventionally leads to its spiro-dimer (**3**) via *ortho*-quinone methide **2** (path A). The zwitterionic oQM precursor **2a** is stabilized by NMMO in complex **4**, which upon rapid heating produces small amounts of the new dioxocine dimer **5** (path B). Acid treatment of **5** causes quantitative conversion into spiro-dimer **3**, via oQM **2** (path C).

more transient precursor **2a** (see Scheme 1). As soon as the out-of-plane methylene group in **2a** rotates into the ring plane, the oQM **2** is formed, no reverse rotation is possible, and the spiro-dimer **3** results inevitably (see Scheme 1, path A). The formation of the dibenzodioxocine dimer **5** from complex **4** (see Scheme 1, path B), which consists actually of two simultaneous etherifications driven by charge recombination, is thus competing with this bond rotation and must be the faster of the two processes for the dioxocine dimer to form, thus rendering the yield of **5** naturally limited, according to the rate constants of the two processes. (Bond rotations have kinetic rate constants k_{rot} of $10^{-12}\,s^{-1}$ to $10^{-14}\,s^{-1}$, the recombination rate of the two zwitterions ions in solution k_{rec} cannot be faster than diffusion-controlled and is limited to about $10^{-7}\,l\,mol^{-1}\,s^{-1}$ to $10^{-9}\,l\,mol^{-1}\,s^{-1}$.)

Correctness of the structure of **5** was finally proven by using a mixture of 5a-trideuterated α-tocopherol (5-trideuteromethyl-γ-tocopherol, **9**) and β-tocopherol model compound (**10**) in the process of oxidation and NMMO-complexation. As expected, the respective spiro-dimers were obtained as the major products. (Three spiro-dimers were obtained, the spiro-dimer of **9**, the spiro-dimer of **10**, and the mixed spiro-dimer. Structures and analytical data will be reported elsewhere in due course.) Besides those spiro-dimers, also the dioxocine-dimers **11**, **12** formed from the deuterated α-tocopherol (**9**) and from β-tocopherol model (**10**), respectively, were found. (The choice of the starting materials with regard to the presence of side chains was performed in view of the chromatographic separability of the dioxocine products. With both of them having one (none) side chain, all dioxocine dimers would have two (none) side chains, and would be inseparable due to their nearly identical structure. Using **9** and **10** as the starting materials, one dimer has two side $C_{16}H_{33}$ side chains (**11**), one has none (**12**), and one has one (**13**), which renders the products sufficiently different to be chromatographically separated.) These two dimers **11** and **12** were symmetrical, similar to **5**, and the two "halves" of the molecules cannot be distinguished by NMR. However, also dioxocine dimer **13**—containing an α- and a β-tocopherol "half"—was found, which was crucial for definite structure confirmation of the dioxocine dimers. Through the different substitution pattern at the aromatic rings—β-tocopherol lacks the 7a-methyl group in comparison to α-tocopherol—the corresponding carbons in these moieties were rendered magnetically inequivalent (albeit only slightly by less than 1 ppm in the ^{13}C domain.). The two aromatic systems in **13** thus became distinguishable in contrast to the symmetric dimer **5**. Furthermore, the resonances of the two benzyl ether carbons became inequivalent due to deuteration in the α-part. This way, direct HMBC connectivities as indicated in Scheme 2 became observable, and the general dioxocine structure was thus considered as confirmed. (The ^5J long range coupling can only be observed due to the presence of the eightmembered ring system making two "coupling paths" along the ring system available, which add to each other.)

Treatment of **5** with acid at 50°C causes its decomposition and clean formation of spiro-dimer **3** (see Scheme 1, path C). Evidently, the two benzyl ether functions are cleaved, the resulting methylene groups immediately rotate into the plane forming oQM **2**, and this intermediate dimerizes according to the "conventional" pathway into **3**.

The value of the preparation of **5** lies in its contribution to general vitamin E chemistry and in affording further experimental proof of the occurrence of zwitterionic

intermediates in the formation of oQMs from the parent *ortho*-methylphenols and the first reaction of such an intermediate in vitamin E chemistry.

3. Experimental

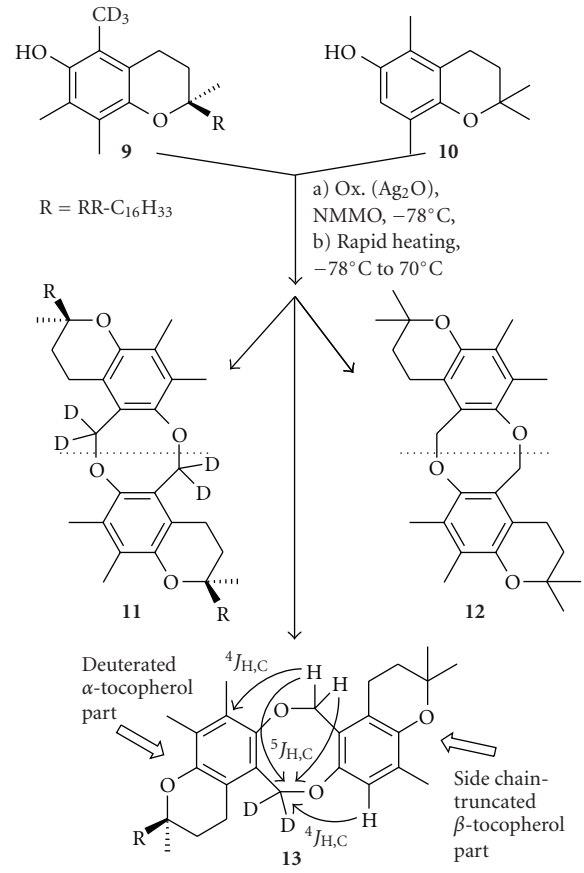
(*All-R*)-tocopherols (**1**, **10**) were used as the starting materials. The deuterated α-tocopherol (**9**) was available from previous work [8, 9], as was β-tocopherol model **10** [10]. ^{1}H NMR spectra were recorded at 400.13 MHz for ^{1}H and at 100 MHz for ^{13}C NMR in $CDCl_3$ if not otherwise stated. Chemical shifts, relative to TMS as internal standard, are given in δ values, coupling constants in Hz. ^{13}C peaks were assigned by means of APT, HMQC, and HMBC spectra. Resonances of the isoprenoid side chain are not listed as they are only negligibly affected (<0.1 ppm for ^{13}C) by modifications of the chroman skeleton [14].

3.1. α-Tocopherol Dioxocine Dimer (5)

Freshly prepared silver oxide (25 mmol, 5.8 g) was suspended in chloroform (10 mL) at −78°C (acetone/dry ice colling), maintaining this temperature throughout. A r.t. solution of *N*-methylmorpholine-*N*-oxide (5.5 mmol, 0.64 g) in chloroform (5 mL) was added at once. The slurry was stirred vigorously and a solution of α-tocopherol (5 mmol, 2.15 g) in chloroform (3 ml) was added dropwise over about 3 minutes. After 1 minute (not longer as the formed complex **4** tends to decompose!), the slurry was quickly vacuum-filtered into a cooled vessel (−78°C). The solution was added dropwise into toluene (10 mL) heated to 70°C. Care must be taken that the temperature of the added solution is as close to −78°C as possible, and the heating (oil bath) must be sufficiently effective to guarantee maintenance of the temperature (70°C) also during addition of the cooled solution. After completion of the addition, the mixture was stirred for another 10 minutes, cooled to r.t., and concentrated to a volume of about 2 mL. The remainder was purified by column chromatography on silica gel (TEA/EtOAc/*n*-hexane, v/v/v = 0.01:1:20) to give spiro-dimer **3** (92.4%) and dibenzodioxocine dimer **5** as ivory wax (6.2%, 133 mg), mp: 25–28°C, TLC: R_f = 0.84 (*n*-hexane/diethyl ether, v/v = 9:1). ^{1}H NMR: δ 1.83 (m, 4H, 2×3-CH_2), 2.09 (s, 6H, 2×8b-CH_3); 2.13 (s, 6H, 2×7a-CH_3), 2.66 (t, 4H, ^3J = 7.0 Hz, 2 × 4-CH_2), 5.10 (s, 4H, 5a-CH_2). ^{13}C NMR: δ 11.6 (7a-CH_3), 13.0 (8b-CH_3), 21.0 (4-CH_2), 23.8 (2a-CH_3), 31.4 (3-CH_2), 71.6 (5a-CH_2), 74.7 (2-C), 115.9 (5-C), 117.8 (4a-C), 121.3 (7-C), 123.2 (8-C), 142.0 (6-C), 147.9 (8a-C). Anal. calcd for $C_{58}H_{96}O_4$ (857.41 g mol^{-1}): C 81.25, H 11.29; found: C 81.15, H 11.41.

3.2. PMC Dioxocine Dimer (7)

The compound was prepared according to the above procedure employing PMC (**6**, 5 mmol, 1.10 g). Chromatographic purification was performed on silica gel (TEA/EtOAc/*n*-hexane, v/v/v = 0.01:1:10) to give spiro-dimer **8** (88.4%) and dibenzodioxocine dimer **7** as white powder (8.1%, 89 mg), mp: 74–78°C, TLC: R_f = 0.44 (*n*-hexane/diethyl ether, v/v = 9:1). ^{1}H NMR: δ 1.28 (s, 12H, 4 × 2a-CH_3), 1.78 (t, 4H, ^3J = 7.1 Hz, 2 × 3-CH_2), 2.11 (s, 6H, 2 × 8b-CH_3); 2.15 (s, 6H, 2 × 7a-CH_3), 2.64 (t, 4H, ^3J = 7.1 Hz, 2 × 4-CH_2), 5.04 (s, 4H, 5a-CH_2). ^{13}C NMR: δ 11.7; 11.9 (7a-CH_3; 8b-CH_3), 20.4 (4-CH_2), 26.6 (2a-CH_3), 32.8 (3-CH_2), 71.8 (5a-CH_2), 72.5 (2-C), 115.5 (5-C), 117.9 (4a-C), 121.3 (7-C), 123.5 (8-C), 142.3 (6-C), 148.0 (8a-C). Anal. calcd for $C_{28}H_{36}O_4$ (436.60 g mol^{-1}): C 77.03, H 8.31; found: C 76.91, H 8.37.



Scheme 2: Oxidation of a mixture of deuterated α-tocopherol (**9**) and β-tocopherol (**10**). The corresponding NMMO-complexes produce the symmetric dioxocine dimers **11** and **12** (symmetry indicated by the dashed lines) and the "mixed" dimer **13** in which the two parts can be distinguished by NMR spectroscopy. The bent arrows indicate the long range HMBC connectivities that prove the presence of the dibenzodioxocine structure.

3.3. Mixed Dioxocine Dimer (13)

The compound was prepared according to the above procedure employing 5,5,5-trideutero-α-tocopherol (**9**, 2.5 mmol, 1.10 g) and β-tocopherol model **10** (2.5 mmol, 0.52 g) simultaneously. Chromatographic purification was performed on gel (TEA/EtOAc/*n*-hexane, v/v/v = 0.01:1:20) to give the spiro-dimer of **9**, dioxocine **11**, the mixed spiro-dimer of **9** and **10**, dioxocine **13**, spiro-dimer of **10**, and dioxocine **12**, in the order of elution. The fraction rich in dioxocine **13** was rechromatographed under similar conditions to provide neat

13 as a yellow wax (1.6% rel. to **9**, 17 mg), mp: 32-33°C, TLC: R_f = 0.64 (*n*-hexane/diethyl ether, v/v = 9:1). ^{1}H NMR: δ^1H NMR: δ 1.28 (s, 6H, 2a-CH_3, β, superimposed by resonances of the isoprenoid side chain of α), 1.79 (t, 2H, ^3J = 6.8 Hz, 2-CH_2, β), 1.81 (m, 2H, 3-CH_2, α), 2.08; 2.09; 2.11; 2.14 (4 × s, 4 × 3H, 8b-CH_3 and 7a-CH_3, each α and β), 2.61 (t, 2H, ^3J = 6.8 Hz, 4-CH_2, β), 2.64 (t, 2H, ^3J = 7.0 Hz, 4-CH_2, α), 5.06 (s, 2H, 5a-CH_2, β). 6.47 (s, 1H, H-7). ^{13}C NMR: δ 11.8 (7a-CH_3, α), 13.0 (8b-CH_3, α), 16.0 (8b-CH_3, β), 21.0 (4-CH_2, α), 21.5 (4-CH_2, β), 23.8 (2a-CH_3, α), 27.1 (2a-CH_3, ß), 31.2 (3-CH_2, α), 33.0 (3-CH_2, ß), 70.8 (pent, 5a-CD2, $J_{C\text{-}D}$ = 21 Hz, *a*), 71.6 (5a-CH_2, ß), 72.3 (2-C, ß), 74.6 (2-C, α), 115.20 (7-CH, ß), 115.9 (5-C, α), 117.8 (4a-C, α), 119.57 (5-C, ß), 120.52 (4a-C, ß), 121.3 (7-C, α), 123.2 (8-C, α), 124.45 (8-C, ß), 142.0 (6-C, α), 146.2 (6-C, ß), 146.8 (8a-C, ß), 147.5 (8a-C, α). Anal. calcd for $C_{42}H_{64}O_4$ (632.98 g mol^{-1}): C 79.70, H 10.19; found: C 79.74, H 10.08.

Acknowledgment

The financial support by the Austrian Fonds zur Förderung der wissenschaftlichen Forschung, Projects P-17428 and P-19081, is gratefully acknowledged.

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