Yellow Reaction Products from Tocopherols and Trimethylamine Oxide

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Characteristic yellow substances obtained when tocopherols were treated with trimethylamine oxide under a nitrogen stream at 180°C were purified by means of silicagel column chromatography and preparative TLC. Their structures were determined by spectroscopic studies.

Treatment of α -tocopherol with trimethylamine oxide gave 7-formyl- β -tocopherol, 5-formyl- γ -tocopherol-3-en and 5-formyl- γ -tocopherol. Yellow reaction products from γ - and δ -tocopherols with trimethylamine oxide were 5-formyl- γ -tocopherol and 5-formyl- δ -tocopherol, respectively.

Many studies have been done on the oxidation products obtained from reactions between tocopherols (Toc) and various oxidizing agents^{1~9)} including oxygen.¹⁰⁾ However, the reaction products between Toc and materials having synergistic effects on Toc have never been investigated from the viewpoint of synergism.

During the investigations on the reactions between α -, γ -, and δ -Toc and trimethylamine oxide (TMAO), one of synergists for Toc, characteristic yellow spots were observed on thin-layer chromatograms and their structures were determined.

A mixture of α -Toc and TMAO in liquid paraffin was treated under a nitrogen stream at 180°C for 2 hr and a yellow substance was obtained by means of silicagel column chromatography and preparative TLC (benzene). On TLC with a solvent system, *n*-hexane-ether (9:1), this substance separated into the three yellow spots, *R_f* values of which were 0.74, 0.66 and 0.59 for products A, B and C, respectively.

In the IR spectra of these products no absorption band near 3600 cm⁻¹ due to an OH group was observed, whereas in the NMR spectra a peak due to an OH group was present near 12 ppm as shown in Fig. 1. The IR spectra exhibited a strong absorption band near

FIG. 1. NMR Spectrum of Product C (CCl₄, 60 MHz).

1630 cm⁻¹. These facts indicate that the OH group is tightly bonded with an ortho functional group, that is with a CHO group at the 5- or 7-position in a chroman ring. As for aromatic methyl protons, product A has two signals at 2.17 and 2.42 ppm, but products B and C have singlet signals at 2.22 and 2.17 ppm, respectively. Therefore, the CHO group in the chroman ring was found to exist at the 7-position for product A and at the 5-position for products B and C. In the NMR data of product B the appearance of signals of CH protons at 6.95 and 5.84 ppm and their observed coupling constants (10.0 Hz) indicate the presence of a double bond between the 3- and

FIG. 2. Structure of Products A~E.

4-positions in the chroman ring.

From the results obtained above, the structures of products A, B and C derived from α -Toc with TMAO were determined to be 7-formyl- β -Toc, 5-formyl- γ -Toc-3-en and 5-formyl- γ -Toc, respectively, as shown in Fig. 2.

Kohl *et al.*¹¹⁾ reported on plastochromenol-8 (solanochromene) as a substance having a double bond between the 3- and 4-positions, but such a substance has never been obtained in the case of Toc.

On the reaction of γ - and δ -Toc with TMAO, yellow substances, product D from γ -Toc and product E from δ -Toc, were obtained. Product D was found to be identical with product C when their spectral and chromatographic data were compared.

Product E has two possible structures, that is 5- or 7-formyl- δ -Toc. In the NMR spectrum the appearance of two protons triplet, assigned to the 4-position CH₂ protons, at lower field (3.02 ppm) is thought to be due to the effect of a CHO group at the 5-position in comparison with the data of product A and C.

Nilsson *et al.*¹²⁾ reported that a very strong preference existed for reaction at the 5-position versus the 7-position of Toc as a result of the directing effect of the heterocyclic ring.

The structure of product E from δ -Toc with TMAO, therefore, was determined to be 5-formyl- δ -Toc as seen in Fig. 2.

It is of interest for us that the treatment of

each Toc with TMAO gives 5-formyl derivatives regardless of whether the substituent in the 5-position is hydrogen or methyl. Skinner and Parkhurst,⁴⁾ and Fujimaki *et al.*¹⁰⁾ reported on a 5-formyl derivative of α -Toc model compound (a phytol group at the 2-position in a chroman ring is replaced with a methyl group), but the formyl derivatives of various Toc themselves have never been obtained.

EXPERIMENTAL

NMR spectra were recorded in deuteriochloroform and carbon tetrachloride on JEOL JNM-PS-100 (100 MHz) and Hitachi R-24 (60 MHz) NMR spectrometers, respectively. Mass spectrometry was carried out on JEOL JMS-01-SG and Hitachi RMU-6L mass spectrometers by a direct sample introducing method. Gas chromatographic analyses were carried out with a Shimadzu GC-5A gas chromatograph under the following conditions; Column: glass column (0.3×200 cm) packed with silicon GE-SE 30 (1.5%) on Chromosorb W, Detector: HFID, Column temperature: 235°C. Thin-layer plates (thickness, 0.5 mm) were prepared with Kieselgel G and HF₂₅₄ (Merck), and the chromatograms were detected with ultraviolet light and the Emmerie-Engel reagent.

dl- α -(100%), *d*- γ -(77%), and *d*- δ -Toc (98%) were kindly presented by Eisai Co.

Isolation of products A, B and C

A mixture of α -Toc (1 g) and TMAO (500 mg) in liquid paraffin (8 ml) was treated under a nitrogen stream at 180°C for 2 hr, dissolved in *n*-hexane and then applied on a column of silicagel (Kanto Chemical Co.) equilibrated with *n*-hexane. After the liquid paraffin was washed away with *n*-hexane, eluent with an increasing ratio of benzene to *n*-hexane gave a yellow spot (*R*_f 0.75) on TLC by using benzene as a solvent. Fractions containing this material were combined and then applied to the thin-layer plates for purification. The development was carried out with a solvent system: *n*-hexane-ether (9:1). The three yellow bands, *R*_f values of which were 0.74, 0.66 and 0.59 for products A, B and C, respectively, were removed from the plates.

The properties of each product are as follows: Product A, MS *m/e*: 444(M⁺), 219, 217, 179. IR $\nu_{\text{max}}^{\text{CCl}_4}$ cm⁻¹: 1635 (C=O). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 241, 283 (10670) 395 (2870). NMR (CDCl₃) δ : 11.90 (1H, OH), 10.40 (1H, CHO), 2.70 (2H, 4-CH₂), 2.42 (3H, CH₃), 2.17 (3H, CH₃), 1.84 (2H, 3-CH₂). GLC (*t*_R): 45.1 min (α -Toc, 31.5 min). TLC (*R*_f): 0.19 (*n*-hexane-chloroform=2:1). Yield: 17 mg. Product B, MS *m/e*: 442 (M⁺), 427, 217, 189, 159. IR $\nu_{\text{max}}^{\text{CCl}_4}$ cm⁻¹: 1638 (C=O). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 243, 249, 289~296 (broad,

11560), 412 (3720). NMR (CDCl_3) δ : 12.07 (1H, OH), 10.40 (1H, CHO), 6.95 (1H, d, 4-CH, $J=10.0$ Hz), 5.84 (1H, d, 3-CH, $J=10.0$ Hz), 2.22 (6H, 2CH_3). GLC (t_R): 34.8 min. TLC (R_f): 0.23. Yield: 16 mg. Product C, MS m/e : 444 (M^+), 220, 217, 179. IR $\nu_{\text{max}}^{\text{CCl}_4}$ cm^{-1} : 1630 (C=O). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 239, 287 (13610), 391 (4200). NMR (CDCl_3) δ : 12.20 (1H, OH), 10.32 (1H, CHO), 3.04 (2H, 4- CH_2), 2.17 (6H, 2CH_3), 1.84 (2H, 3- CH_2). GLC (t_R): 44.0 min. TLC (R_f): 0.25. Yield: 120 mg.

Isolation of product D

γ -Toc (ca. 77% in purity) was purified by repeating preparative TLC. A mixture of γ -Toc (800 mg) and TMAO (400 mg) in liquid paraffin (6 ml) was treated under a nitrogen stream at 180°C for 1 hr. On TLC (benzene) a yellow substance (R_f 0.75) was obtained and this gave a single spot (R_f 0.59) when TLC was carried out with a n -hexane-ether (9: 1) solvent system.

The properties of product D are the same as those of product C. Yield: 60 mg.

Isolation of product E

δ -Toc (710 mg) was treated with TMAO (355 mg) under the same conditions as in product D. A yellow spot (R_f 0.68) on TLC (benzene) was collected.

The analytical data of product E are as follows: MS m/e : 430 (M^+), 412, 264, 219, 205, 149. IR $\nu_{\text{max}}^{\text{CCl}_4}$ cm^{-1} : 1640 (C=O). UV $\lambda_{\text{max}}^{\text{EtOH}}$ nm (ϵ): 241, 279 (10290), 382 (3570). NMR (CCl_4) δ : 10.48 (1H, OH), 10.13 (1H, CHO), 6.55 (1H, Ar-H), 3.02 (2H, 4- CH_2), 2.16 (3H, CH_3), 1.80 (2H, 3- CH_2). GLC (t_R): 38.5 min (δ -Toc, 21.5 min). TLC (R_f): 0.85 (chloroform). Yield: 28 mg.

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REFERENCES

- 1) D. R. Nelan and C. D. Robeson, *J. Am. Chem. Soc.*, **84**, 2963 (1962).
- 2) D. McHale and J. Green, *Chem. Ind.*, **1963**, 982; *idem, ibid.*, **1964**, 366.
- 3) W. A. Skinner and R. M. Parkhurst, *J. Org. Chem.*, **29**, 3601 (1964).
- 4) W. A. Skinner and R. M. Parkhurst, *ibid.*, **31**, 1248 (1966).
- 5) W. A. Skinner and P. Alaupovic, *ibid.*, **28**, 2854 (1963).
- 6) M. Komoda, N. Onuki and I. Harada, *Agr. Biol. Chem.*, **31**, 461 (1967).
- 7) M. Komoda and I. Harada, *J. Am. Oil Chem. Soc.*, **46**, 18 (1969).
- 8) J. L. G. Nilsson, *Acta Pharm. Suecica*, **6**, 1 (1969).
- 9) L. Telegdy-Kovats and E. Berndorfer-Kraszner, *Period. Polytech. Chem. Eng.*, **15**, 23 (1971).
- 10) M. Fujimaki, K. Kanamaru, T. Kurata and O. Igarashi, *Agr. Biol. Chem.*, **34**, 1781 (1970).
- 11) D. H. Kohl, P. M. Wood, M. Weissman and J. R. Wright, *Magn. Resonances Biol. Res.*, Rep. Int. Conf., ed. by Franconi, Cafiero; Gordon and Breach, New York, 1969, p. 189.
- 12) J. L. G. Nilsson, G. D. Daves, Jr. and K. Folkers, *Acta Chem. Scand.*, **22**, 207 (1968); J. L. G. Nilsson, H. Sievertsson and H. Selander, *ibid.*, **23**, 859 (1969).