6-ACETYL-8-HYDROXY-2,2-DIMETHYLCHROMENE, AN ANTIOXIDANT IN SUNFLOWER SEEDS; ITS ISOLATION AND SYNTHESIS AND ANTIOXIDANT ACTIVITY OF ITS DERIVATIVES[1]

Hideyuki Tsuda, Youichi Ishitani, Yoshiyuki Takemura, Yoshiaki Suzuki, and Tadahiro Kato*

Department of Chemistry, Faculty of Science, Science University of Tokyo,
Kagurazaka, Tokyo 162, Japan

Abstract-By the guide of assay toward inhibition of photooxidation of β-carotene, 6-acetyl-8-hydroxy-2,2-dimethylchromene (**1**) was isolated from sunflower seeds. In addition to **1**, the analogous compounds possessing the chromene (chromane) skeleton were synthesized and their antioxidant activities were examined.

As a part of exploitation of antioxidants from natural sources, we have explored antioxidants in sunflower seeds and their husks.[2] Here, we report the structure elucidation and synthesis of 6-acetyl-8-hydroxy-2,2-dimethylchromene (**1**), isolated by the guide of inhibition assay toward photooxidation of β-carotene.

The chromene compound (**1**) was isolated as an amorphous powder, which gave a HReims molecular ion at m/z 218.0940, indicating a molecular formula of $C_{13}H_{14}O_3$. ^1H Nmr spectrum (Table 1) contained three singlet methyls, a pair of cis olefinic protons, and a meta-coupled pair of two aromatic protons, respectively. The ir spectrum suggested the presence of hydroxyl (3300 cm^{-1}) and conjugated carbonyl (1668 cm^{-1}) groups in addition to benzene ring (1596 and 1486 cm^{-1}). The detailed phase sensitive NOESY experiment (Figure 1)[3] allowed the antioxidant to have 6-acetyl-8-hydroxy-2,2-dimethylchromene structure (**1**). Although the structure is simple and isolation of **1** from several natural sources has been precedented,[4] its antioxidant activity has remained unknown.

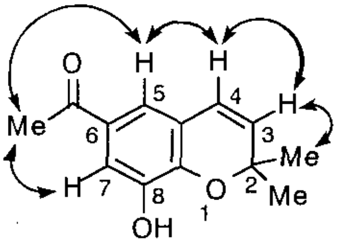
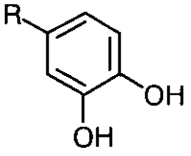


Figure 1 Structure of **1** and positive NOE between protons

Table 1. ^1H Nmr (500 MHz, $CDCl_3$) for **1**

protons	^1H δ, J in Hz
2-Me x 2	1.50 (s)
3-H	5.69 (d), J = 10.0
4-H	6.38 (d), J = 10.0
5-H	7.26 (d), J = 3.0
6-COMe	2.53 (s)
7-H	7.43 (d), J = 3.0
8-OH	5.46 (s)

Due to the limitted amounts of natural product (**1**), the synthesis of **1** was attempted starting from 4-acetylcatechol (**2**, R = COMe).[5] Our first protocol of the synthesis is an application of bromonium ion induced etherification[6] of dimethylallylcatechol (**4**, R = COMe). The most attractive and simple way of introduction of 3,3-dimethylallyl moiety to the 6-position of **2** may be the well precedented rearrangement of dimethylallyl ether (**3**) mediated by montmorillonite KSF.[7] Although catechol monoether (**3**, R = H) afforded the rearranged product (**4**, R = H) in moderate yield by the action of the clay, 4-acetyl derivative (**3**, R = COMe)[8] resulted in the formation of complex mixture, from which the objective (**4**, R = COMe) was isolated in less than 10% yield. All the trials to improve the yield were unsuccessful by protecting the carbonyl as well as hydroxyl groups. The literature procedures including rearrangement/cyclization of propargyl ether[9] or Friedel Craft type acylation or allylation at the requisite position of **2** were all unsuccessful.



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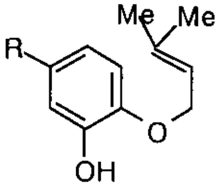

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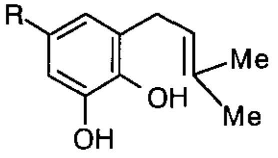

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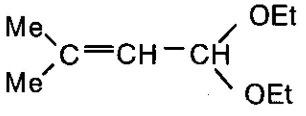
Finally, the construction of the chromene skeleton was achieved as follows. When catechol (**2**, R = H) was treated with 1,1-diethoxy-3-methyl-2-butene (**5**) in pyridine solution at 110℃ for 20 h,[10] chromene derivative (**6**, R = H) was isolated in moderate yield. Application of the same conditions to 4-acetylcatechol (**2**, R = COMe) provided a mixture of **6** (R = COMe) and **7**[11] in 40 and 15% yields, respectively. When 4-acetylcatechol (**2**, R = COMe) was treated with diethyl acetal (**5**) and pyridine (2 equiv) in refluxing xylene for 20 h, the objective (**6**, R = COMe) was furnished in 78% yield. The physical data of the synthetic chromene (**6**, R = COMe) were completely identical with those of natural product.


$\mathrm{Me_2C{=}CH{-}CH(OEt)_2}$

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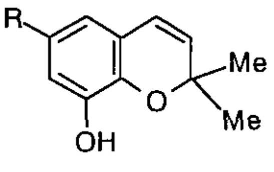

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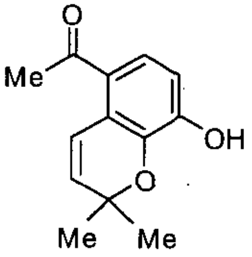

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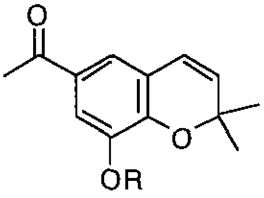
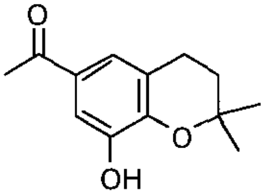
In order to examine the structure-activity relationship toward inhibition of photooxidation of β-carotene, methoxymethyl ether (**8**) and dihydro derivative (**9**)[12] of natural chromene (**1**), and some catechol derivatives (**10-13**) lacking the chromene ring[13] were prepared and their antiphotooxidation activities were measured (Table 2).[14] As compared with the original compound (**1**), the activity of chromane derivative (**9**) is almost same while the MOM-ether (**8**) is less active. The activity of methyl ethers (**11-13**) lacking the chromene ring is inferior to the original compound (**1**). These evidences suggest the importance of hydroxyl and the chromene ring for the manifestation of the antioxidant activity.

It was soon found that **14** and deacetyl derivatives (**15**-**16**)[15]show the superior antioxidant activity to the original natural product (**1**). The activities are almost same as those of typical antioxidants, BHA and vitamin E, the results being summarized in Table 3. These facts indicate that 8-hydroxychromene (chromane) derivatives may be the promising antioxidant for the practical purposes.



1 R=H
8 R=MOM



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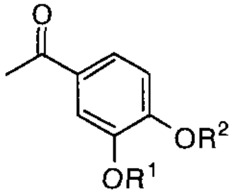
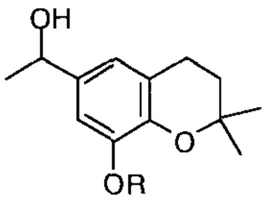


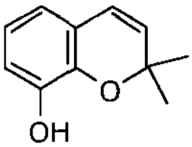
10 $R^1=R^2=H$
11 $R^1=R^2=Me$
12 $R^1=H$, $R^2=Me$
13 $R^1=Me$, $R^2=H$

Table 2. Antioxidant Activities at 20 ppm toward Photooxidation of β-Carotene

compounds	1	8	10	11	12	13	control
remaining β-carotene(%)	84.	75	85	65	67	56	48



14 (R = H)



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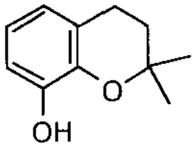

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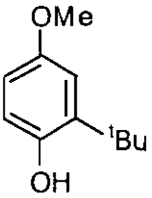

BHA

Table 3. Antioxidant Activities at 10 ppm toward Photooxidation of β-Carotene

compounds	1	14	15	16	BHA	vitamin E	control
remaining β-carotene(%)	80	92	97	95	93	95	59

REFERENCES AND NOTES

1. Dedicated to Professor Shigeru Oae for the celebration of his 77th Birthday.
2. In addition to the chromene (**1**), new antioxidants having arylindane skeleton were elucidated. The results will be reported elsewhere.
3. The arrows show the positive NOE between protons indicated.

4 a). M. I. Aguilar, G. Delgado, R. Bye, and E. Linares, *Phytochemistry*, 1993, **33**, 1161. The related references cited therein.

b). F. Bohlmann, P. K. Mahanta, A. A. Natu, R. M. King, and H. Robinson, *Phytochemistry*,1978, **17**, 471.

5. K. W. Rosenmund and H. Lohfert, *Ber.*, 1928, **61B**, 2601.
6. For an example, T. Kato, I. Ichinose, T. Hosogai, and Y. Kitahara, *Chem. Lett.*, 1976, 1187.
7. W. G. Dauben, J. M. Cogen, and V. Behar, *Tetrahedron Lett.*, 1990, **31**, 3241.
8. Prepared in 73% yield from **2** (R = COMe), 3,3-dimethylallyl chloride (2.5 equiv), and Na_2CO_3 (2.5 equiv) in the presence of catalytic amounts of TBAI in DMF at room temperature.
9. M. Harfenist and E. Thom, *J. Org. Chem.*, 1972, **37**, 841.
10. J. T. North, D. R. Kronenthal, A. J. Pullockaran, S. D. Real, and H. Y. Chen, *J. Org. Chem.*, 1995, **60**, 3397.
11. The yield is not optimized. Physical evidence of **7**. ^{1}H Nmr (270 MHz, $CDCl_3$) δ 7.35 (1H, d, 8.3 Hz), 7.28 (1H, d, 10.2 Hz), 6.82 (1H, d, 8.3 Hz), 6.05 (1H, br s), 5.76 (1H, d, 10.2 Hz), 2.55 (3H, s), and 1.46 (6H, s). ^{13}C Nmr (68 MHz, $CDCl_3$) δ 199.6 (s), 148.5 (s), 139.9 (s), 132.3 (d), 126.2 (s), 124.5 (d), 121.1 (s), 120.9 (d), 113.3 (d), 76.6 (s), 28.8 (q), and 27.6 (q) x 2.
12. Prepared from **8** by catalytic hydrogenation to give **14** (R = MOM) followed by oxidation with PCC and then deprotection of MOM group by HCl treatment.
13. Prepared from 4-acetyl catechol (**2**, R = $COCH_3$) by the action of K_2CO_3 (1.1 equiv) and MeI (1.0 equiv) in DMF to give **11** (14%) and **12** (69%). By treatment with MOMCl (2.1 equiv) and $^iPr_2NEt$ (2.5 equiv), para-hydroxyl group of **2** (R = $COCH_3$) was converted to MOM ether in 58% yield, which was successively treated with MeI (5.0 equiv) and K_2CO_3 (5.4 equiv) in DMF, and then with HCl-MeOH to give **13** in 70% yield.
14. The values (%) show the concentration ratio of β-carotene in solution before and after photooxidation. The concentrations were estimated by measurement of absorbance at 500 nm due to β-carotene. The photooxidation was carried out in the absence (control) or presence of the examined compounds at the described concentration.
15. 8-Hydroxychromene compounds are known as stabilizer of photographic silver halide materials.[16]

16 a). Japanese Patents (JP) 61-158331: 18, July,1986. H. Takagaki, M. Watanabe, S. nakanishi, K. Yamazaki, H. Ishihama, T. Ota, and K. Kawamura, *Chem. Abstr.,* 1987, **107**; 769.

b).Patent Cooperation Treaty (PCT). International Publication Number: WO 91-11749. 8, August 1991.

Received, 26th April, 1996