To confirm the structure and determine the stereochemistry, an X-ray analysis was conducted for dioxime (**2**), which was prepared by a standard method. Crystallization of **2** from benzene gave pale yellow prisms, which contained one molar equivalent benzene as a solvent of crystallization, $C_{34}H_{46}N_2O_5$, mp 137.5—138.5°. The crystal system was orthorhombic, $a=16.165$ (5) Å, $b=18.453$ (4) Å, $c=10.990$ (1) Å, space group $P2_12_12_1$, and $z=4$. Independent reflections, 3265, were collected using Mo-$K\alpha$ radiation. The structure was solved by the direct method using MULTAN[5] and refined by the block-diagonal least-squares method. All the atoms including hydrogens of **2** were determined properly. The final R value was 0.058. Thus, the structure of the dioxime (**2**) was established except for its absolute configuration.

To our knowledge euglobal-III (**1**) is the first acetogenin-mevalonate metabolite which has potent granulation inhibiting activity from *Eucalyptus* species. It is also noteworthy that the euglobal-III (**1**) has a bicyclogermacrene structure, which is the biogenetically common precursor of aromadendrane-derivatives isolated from *Eucalyptus globulus*, such as gurjunene, aromadendrene and globulol. Further studies on the other active principles are in progress.

Acknowledgement We are most grateful to Dr. E. Ohmura, the director of the Central Research Division, Takeda Chemical Industries, Ltd., for his interest and encouragement throughout this work. We also wish to thank Dr. M. Nishikawa and the staff of the Chemical Research Laboratories, Takeda Chemical Industries, Ltd., for their helpful discussion and collaboration during various stages of this work.

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5) G. Germain, P. Main, and M.M. Woolfson, *Acta Crystallogr., Sect.* **A**, **27**, 368 (1971).

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Kuwanon G, a New Flavone Derivative from the Root Barks of the Cultivated Mulberry Tree (*Morus alba* L.)[1]

A new flavone derivative, containing condensed dihydrochalcone partial structure named kuwanon G, was isolated from the root barks of the cultivated mulberry tree (a variety of *Morus alba* L.). The structure was shown to be **1** on the basis of chemical and spectral data. The compound (**1**) to rabbit (1 mg/kg, *i.v.*) produced a significant hypotension.

Keywords——kuwanon G; flavone; mulberry tree; *Morus alba* L.; hypotensive action; C-13 NMR; 2′-hydroxy-2,4,4′-trimethoxychalcone

1) A part of this work was presented at the 100 th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April, 1980.

Some structures were reported in a series of prenylflavonoids isolated from the root barks of *Morus alba* L., a plant of Moraceae family.[2-4] In this paper, we report the isolation and structure determination of a new flavone derivative, kuwanon G (**1**), isolated from the ethyl acetate extract, and clarified as having hypotensive action in rabbit.[5]

The dried root barks of the cultivated mulberry tree were extracted successively with *n*-hexane, benzene, and ethyl acetate. The ethyl acetate extract was fractionated sequentially by the polyamide and silica-gel column chromatography, and then by the preparative thin layer chromatography over silica gel, resulting in the isolation of a new prenylated flavone derivative, kuwanon G (**1**) in 0.2% yield. The compound **1** to rabbit (1 mg/kg, *i.v.*) showed a marked hypotensive effect.[5]

Kuwanon G (**1**), amorphous powder, mp 213—219° (dec.), $[\alpha]_D^{22} = -534°$ ($c=0.232$ in methanol), had a molecular formula of $C_{40}H_{36}O_{11}$,[6] and the following color reactions: Mg–HCl test (red); Zn–HCl test (orange); $FeCl_3$ test (dark green→dark purple), IR ν_{max}^{Nujol} cm^{-1}: 3300, 1665 (sh), 1655, 1625; UV λ_{max}^{MeOH} nm (log ε): 212 (4.64), 265 (4.41), 280 (sh 4.22), 315 (4.13); $\lambda_{max}^{MeOH+AlCl_3}$ nm (log ε): 213 (4.68), 273.5 (4.46), 307 (4.22), 360 (3.89); $\lambda_{max}^{MeOH+NaOMe}$ nm (log ε): 275 (4.45), 336 (4.39). The ultraviolet (UV) spectra were similar to those of kuwanon C (**3**)[3b] suggesting that **1** possesses a kuwanon C partial structure. The treatment of **1** with dimethyl sulfate in acetone gave the following methyl ethers as amorphous powder: hexamethyl ether (**1a**), $C_{46}H_{48}O_{11}$ (M^+ 776), $FeCl_3$ test (green), proton magnetic resonance (PMR), δ (ppm) in acetone-d_6 13.18 and 13.26 (each 1H, s, 2×OH), Gibbs test[7] (positive); heptamethyl ether (**1b**), $C_{47}H_{50}O_{11}$ (M^+ 790), $FeCl_3$ test (green), PMR, δ in $CDCl_3$, 13.23 (1H, s, OH), Gibbs test (negative); heptamethyl ether (**1c**), $C_{47}H_{50}O_{11}$ (M^+ 790), $FeCl_3$ test (red), PMR, δ in $CDCl_3$, 12.82 (1H, s, OH), Gibbs test (positive); octamethyl ether (**1d**), $C_{48}H_{52}O_{11}$ (M^+ 804), $FeCl_3$ test (negative). These findings indicate that **1** has eight hydroxyl groups and two of them are hydrogen bonded. The mass spectrum (MS) of **1** showed the fragments[8] at *m/e* 692 (M^+, $C_{40}H_{36}O_{11}$), 582 ($C_{34}H_{30}O_9$), 555 ($C_{33}H_{31}O_8$, **4**), 420 ($C_{25}H_{24}O_6$, **5**), 377 ($C_{22}H_{17}O_6$), 354 ($C_{20}H_{18}O_6$), 147 ($C_9H_7O_2$, **6**), 137 ($C_7H_5O_3$, **7**), 110 ($C_6H_6O_2$, base peak). The xylene solution of **1a** (450 mg) was pyrolysed at 450° in a sealed tube. From the reaction product, 2′-hydroxy-2,4,4′-trimethoxychalcone (**8**, 36 mg) was obtained which was identified with authentic sample obtained from 2′-hydroxy-4′-methoxyacetophenone and 2,4-dimethoxybenzaldehyde. These findings indicate that **1** has a kuwanon C and dihydrochalcone partial structure.

The PMR spectrum of **1** was analysed as follows: δ in acetone-d_6, 1.48 (3H, s, 11-CH_3), 1.52 (3H, br s, 16-CH_3), 1.62 (3H, s, 11-CH_3), 1.80—2.20 (2H, m, 18-H×2), 3.17 (2H, br d, $J=7$ Hz, 9-H), 3.30—3.90 (1H, m, 19-H), 4.30—4.70 (2H, m, 14- and 20-H), 4.95—5.40 (2H, m, 10- and 15-H), 5.93, 6.08 (each 1H, dd, $J=2$ and 8, 26- or 32-H), 5.98 (1H, s, 6-H), 6.03, 6.21 (each 1H, d, $J=2$, 24- or 30-H), 6.55 (1H, dd, $J=2$ and 8,5′-H), 6.67 (1H, d, $J=2$,3′-H), 6.78 (1H, d, $J=8$, 33-H), 7.29, 7.41 (each 1H, d, $J=8$, 6′-or 27-H), 7.60—9.63 (6H, br, OH), 13.13, 13.23 (each 1H, s, 5- or 23-OH). The presence of a 3-methyl-2-biutenyl (prenyl) group was supported by the results described below. On the treatment of methanolic hydrochloric

2) V.H. Deshpande, P.C. Parthasarathy, and K. Venkataraman, *Tetrahedron Lett.*, **1968**, 1715.

3) *a*) T. Nomura, T. Fukai, S. Yamada, and M. Katayanagi, *Chem. Pharm. Bull.*, **26**, 1394 (1978); *b*) T. Nomura, T. Fukai, and M. Katayanagi, *ibid.*, **26**, 1453 (1978); *c*) *Idem*, *Heterocycles*, **9**, 745 (1978); *d*) T. Nomura and T. Fukai, *ibid.*, **9**, 1295 (1978); *e*) T. Nomura, Y. Sawaura, T. Fukai, S. Yamada, and S. Tamura, *ibid.*, **9**, 1355 (1978); *f*) T. Nomura and T. Fukai, *ibid.*, **12**, 943 (1979); *g*) *Idem*, *ibid.*, **12**, 1289 (1979).

4) C. Konno, Y. Oshima, and H. Hikino, *Planta medica*, **32**, 118 (1977).

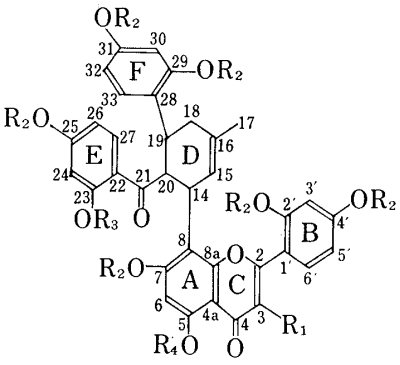
5) The detail will be reported on the hypotensive action of the compound in the next paper.

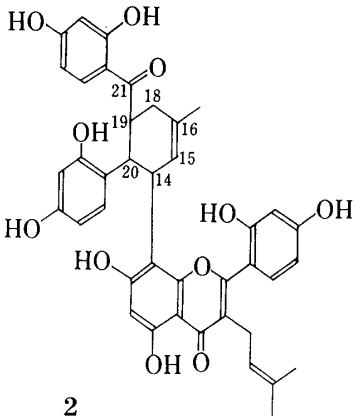
6) Elemental analysis gave a consistent result. High-resolution MS: Calcd for $C_{40}H_{36}O_{11}$ (M^+, *m/e*): 692.2255. Found: 692.2300.

7) H.D. Gibbs, *J. Biol. Chem.*, **72**, 649 (1927).

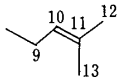
8) The formulae of the fragment ions were supported by the high-resolution mass spectrometry.

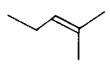
acid, **1a** gave compound **1e**, mp 145—148°, $C_{47}H_{52}O_{12}$,[9] by adding methanol.[10] And **1e** showed the following spectra: PMR, δ in acetone-d_6, 1.05 (6H, s, 11-CH_3), 1.52 (3H, br s, 16-CH_3), 1.54—1.80 (2H, m, 10-H×2), 2.25—2.55 (2H, m, 9-H×2), 3.01 (3H, s, 11-OCH_3), 5.22 (1H, br s, 15-H); MS *m/e*[8]: 494 ($C_{29}H_{34}O_7$, **5e**), 314 ($C_{18}H_{18}O_5$). The location of prenyl group was supported by photooxidative cyclization of **1** as described below. When a solution of **1** in chloroform was irradiated with a high pressure mercury lamp (100 W) for 72 hr, kuwanon G hydroperoxide (**1f**) was obtained. The compound **1f** showed the following data: FD-MS *m/e* 747 (M^+ +Na), 731 (747-O); PMR (δ in acetone-d_6) showing the AMX pattern of dihydro-

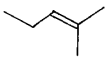


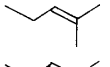


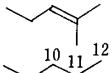
2

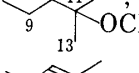
1 : R_1=  , $R_2=R_3=R_4=H$

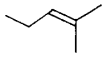
1a : R_1=  , $R_2=CH_3$, $R_3=R_4=H$

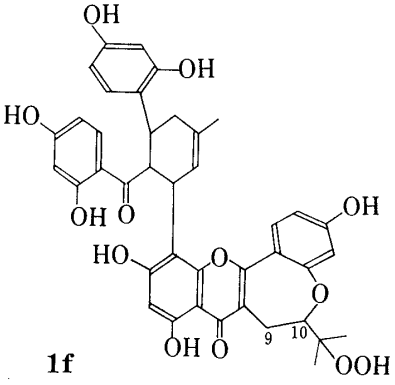
1b : R_1=  , $R_2=R_3=CH_3$, $R_4=H$

1c : R_1=  , $R_2=R_4=CH_3$, $R_3=H$

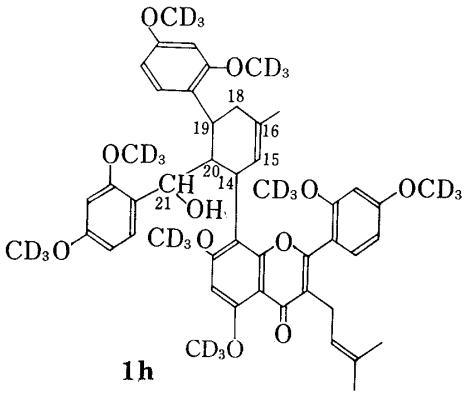
1d : R_1=  , $R_2=R_3=R_4=CH_3$

1e : R_1=  , $R_2=CH_3$, $R_3=R_4=H$

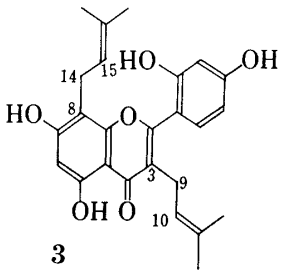
1g : R_1=  , $R_2=R_3=R_4=CD_3$



1f



1h



3

Chart 1

9) Elemental analysis gave a consistent result.
10) T. Saitoh and S. Shibata, *Chem. Pharm. Bull.*, **17**, 729 (1969).

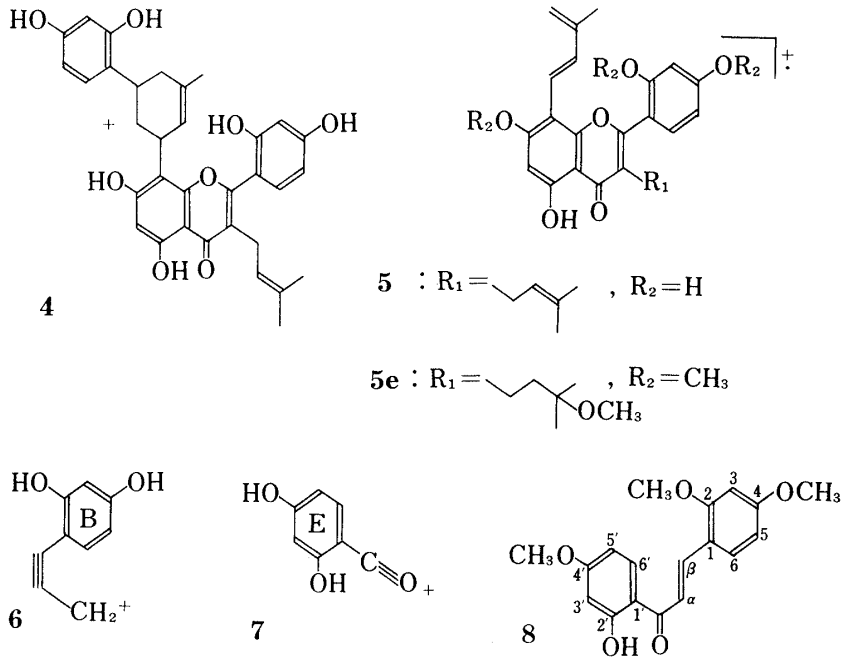


Chart 2

oxepin ring,[3b,11] such as 2.46 (1H, dd, J=10 and 18,9-H), 3.66 (1H, dd, J=2 and 18,9-H), 4.45 (1H, dd, J=2 and 10,10-H). In the light of the results of photooxidative cyclization of **3** and other prenylflavones,[3b,11] it is supported that **1** has a prenyl group at the 3-position.

The CMR spectrum was analysed as follows: δ in DMSO-d_6, 17.33 (q, C-13), 22.45 (q, C-17), 22.92 (d, C-14 or -19), 23.53 (t, C-9), 25.42 (q, C-12), 45.84 (d, C-20), 97.46 (d, C-6), 101.97 (d, C-30), 102.58 (d, C-24 and -3′), 103.74 (s, C-4a), 106.75 (s and d, C-8, -32, and -5′), 107.21 (d, C-26), 111.37 (s, C-1′), 114.03 (s, C-22), 119.69 (s, C-3), 120.73 (s, C-28), 121.81 (d, C-10), 123.23 (d, C-15), 130.83 (d, C-27), 131.17 (s and d, C-11 and -6′), 132.36 (d, C-33), 132.83 (s, C-16), 155.21 (s, C-5), 155.79 (s, C-29 and -31), 156.33 (s, C-2′), 159.18 (s, C-2), 160.26 (s, C-8a), 160.83 (s, C-4′), 161.34 (s, C-7), 164.22 (s, C-23 and -25), 181.72 (s, C-4), 208.11 (s, C-21); δ in pyridine-d_5, 38.28 (d, C-14 or -19), 38.28 (t, C-18). Assignments of the carbon atoms in **1** were performed by the off-resonance decoupling technique as well as by comparison of the CMR spectra of the model compounds, kuwanon C (**3**)[3g] and 2′,4′-dihydroxyacetophenone.[12] By comparing with the spectra of **1** and **3**, the chemical shift values of the C-3 and C-9 were in good agreement with those of the C-3 and C-9 of **3**, whereas those of the C-8 and C-14 were shifted to lower applied magnetic field. This result supported the presence of prenyl group at C-3 position. The C-6 substituted prenylflavone structure for **1** was excluded from the results of the Gibbs test of the heptamethyl ethers (**1b** and **1c**)[13] and from the following CMR data: the chemical shift values of the C-6 and C-8 signals of **1** were in good agreement with those of the C-8 substituted prenylflavones.[3g,14] From the above results, it is possible that the structure of kuwanon G is represented as **1** or 2.

The arrangement of substituents in the D ring was assumed by the following PMR data. The PMR spectrum ($CDCl_3$) of kuwanon G octadeuteromethyl ether (**1g**) showed the signals at δ 1.80—2.00 (2H, m, 18-H×2), 3.33—4.06 (1H, m, 19-H), 4.35 (1H, br d, J=10, 14-H),

11) *a*) T. Nomura, T. Fukai, S. Yamada, and M. Katayanagi, *Chem. Pharm. Bull.*, **26**, 1431 (1978); *b*) T. Nomura and T. Fukai, *Heterocycles*, **9**, 635 (1978).
12) B. Ternal and K.R. Markham, *Tetrahedron*, **32**, 565 (1976).
13) If the structure of kuwanon G is represented as the C-6 substituted structure, both the heptamethyl ether (**1b** and **1c**) would give positive Gibbs reaction.
14) V.M. Chari, S. Ahmad, and B.-G. Österdahl, *Z. Naturforsh.*, **33b**, 1547 (1978).

4.85 (1H, t, J=10, 20-H),[15] 5.18 (2H, m, 10- and 15-H). The irradiation on the signals at δ 1.80—2.00 changed the multiplet at δ 3.33—4.06 to a broad doublet (J=10 Hz), while the triplet at δ 4.85 and the broad doublet at δ 4.35 remained unchanged. The irradiation on the signal at δ 3.33—4.06 changed the triplet at δ 4.85 to a broad doublet (J=10 Hz), and the multiplet at δ 1.80—2.00 to a broad singlet. The irradiation of the signals at δ 5.18 affected the broad doublet at δ 4.35. The assignments of the signals at 19- and 20-H were confirmed by the comparison with the PMR spectrum of alcohol (**1h**)[16] obtained by soldium borohydride reduction of **1g**. The compound **1h** showed the following data: amorphous powder; MS m/e 830 (M^+, $C_{48}H_{30}D_{24}O_{11}$); IR ν_{max}^{Nujol} cm^{-1}: 3520; PMR, δ in $CDCl_3$, 1.33—2.08 (11H, $CH_3\times3$ and 18-H$\times$2), 2.80—3.67 (5H, 9-H$\times$2, 19-H, 20-H, and 21-OH), 4.00—4.70 (2H, 14-H and 21-H), 5.00—5.20 (2H, 10-H and 15-H); CMR, δ in $CDCl_3$, 177.71 (C-4), 68.72 (C-21). The signal[17] of 20-H of **1h** was shifted about 1.5 ppm to a higher applied magnetic field than that of **1g**. If the structure of kuwanon G could be represented as **2**, three proton signals (14-, 20-, and 21-H) would appear at 4.0—5.0 ppm. From the above results, the structure **1** is considered to be more favorable than the structure **2**.[18,19]

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15) The signal appeared at lower aplied magnetic field. From the molecular model, the proton may be receiving a deshielding effect of aromatic anisotropy.
16) This compound may be a mixture of diastereoisomers.
17) The assignment of the signal was supported by double irradiation.
18) Prof. H. Hikino, Tohoku University, communicated to T.N. his results by letter (May 14, 1980). Tohoku University group determined the structure of hypotensive compound obtained from the root bark of mulberry tree as structure **2**.
19) At the 100 th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 2, 1980, our group proposed orally the formula **1** and **2** for a structure of kuwanon G and suggested that the structure **1** is more favorable than the structure **2**.