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PRENYLFLAVONOIDS FROM THE ROOT BARK OF THE CULTIVATED MULBERRY TREE[+]

Taro Nomura* and Toshio Fukai

Faculty of Pharmaceutical Sciences, Toho University,
2-2-1, Miyama, Funabashi-shi, Chiba 274, Japan

Our present knowledge is reviewed of the chemistry of prenylflavonoid derivatives isolated from the root bark of the Japanese cultivated mulberry tree by our group. The oxidative cyclization is also discussed on the flavone derivatives having a free hydroxyl group at C-2$'$ position and γ,γ-dimethylallyl group at C-3 position.

Contents

A. Introduction

Mulberry leaves have been widely cultivated in China and Japan as indispensable food of silkworms. On the other hand, the root bark of the mulberry tree (Morus alba L. and other plants of the genus Morus) has been used as an antiphlogistic, diuretic, expectolant, and laxative in the Chinese herb medicine. The constituents of this root bark have been studied by many investigators, and some phenolic compounds, triterpenoids, and a glyceride have been isolated.[1] In the pharmacological field, a few papers concerning hypotensive effects of mulberry root bark have been reported.[2] Katayanagi et al. reported that ether extract of the root bark to rabbit (6mg/Kg, i.v.) showed a marked hypotensive effect, and suggested that the hypotensive constituents seem to be phenolic compounds.[3] Considering the results reported by Katayanagi et al. our group studied the phenolic constituents of cultivated mulberry tree. This paper deals with the chemistry of the prenylflavonoids obtained from the root bark by our group.

B. Survey of prenylflavonoids

The initial work on the prenylflavones of the Morus alba root bark, reported by Deshpande *et al*. led to the structure postulated I-IV for mulberrin, mulberrochromene, cyclomulberrin, and cyclomulberrochromene, respectively. In each of these, the position of C-alkylation at C-6 of the flavone moiety was deduced by chemical correlation with artocarpin (V)^4(Chart 1).

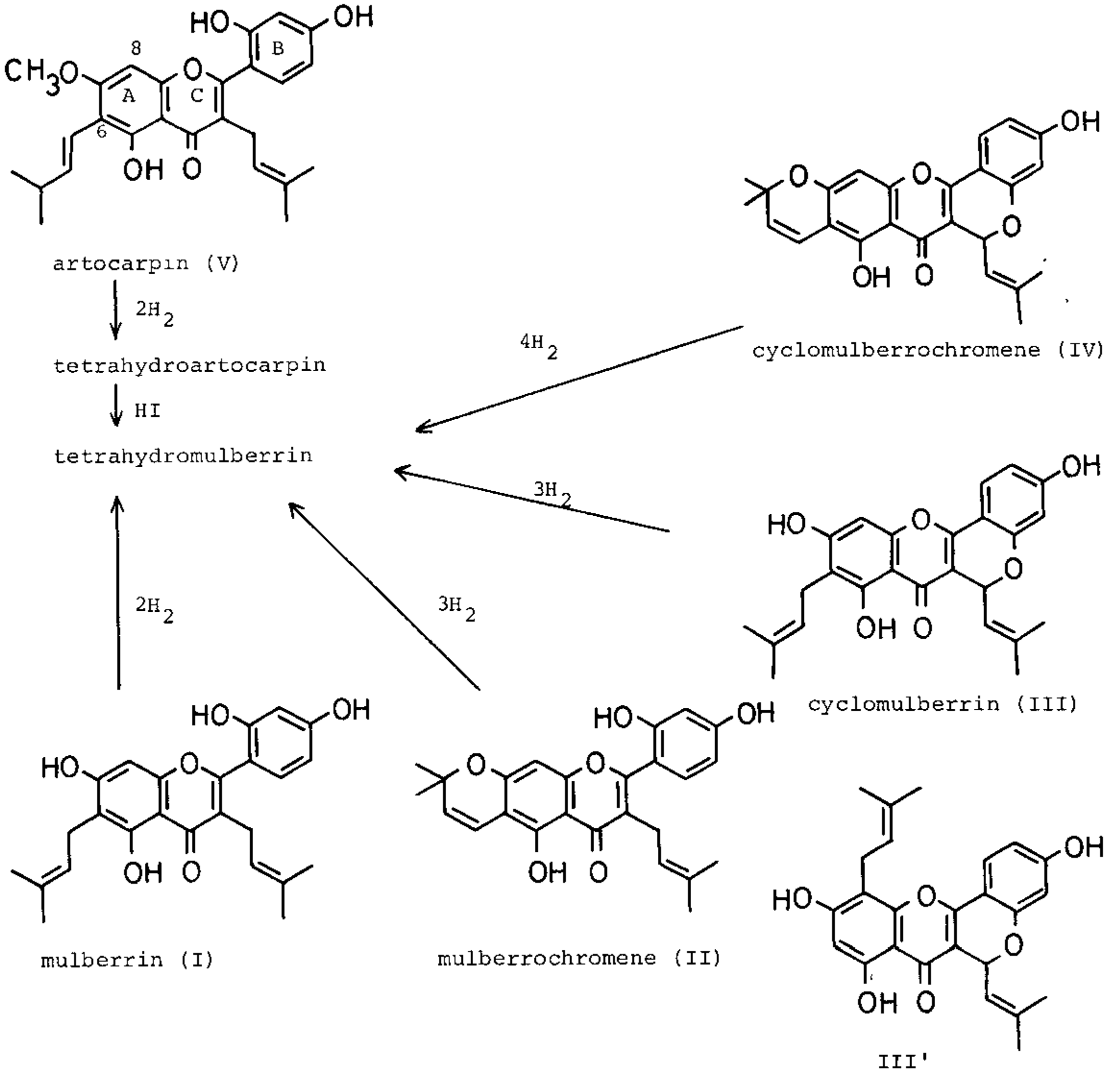


Chart 1

1. Isolation of prenylflavonoids

Ten new prenylflavonoids were obtained from the benzene extract of the root bark, as shown in Chart 2[5]. Morusin (VI) was obtained in 0.04% yield whereas the others as minor components.

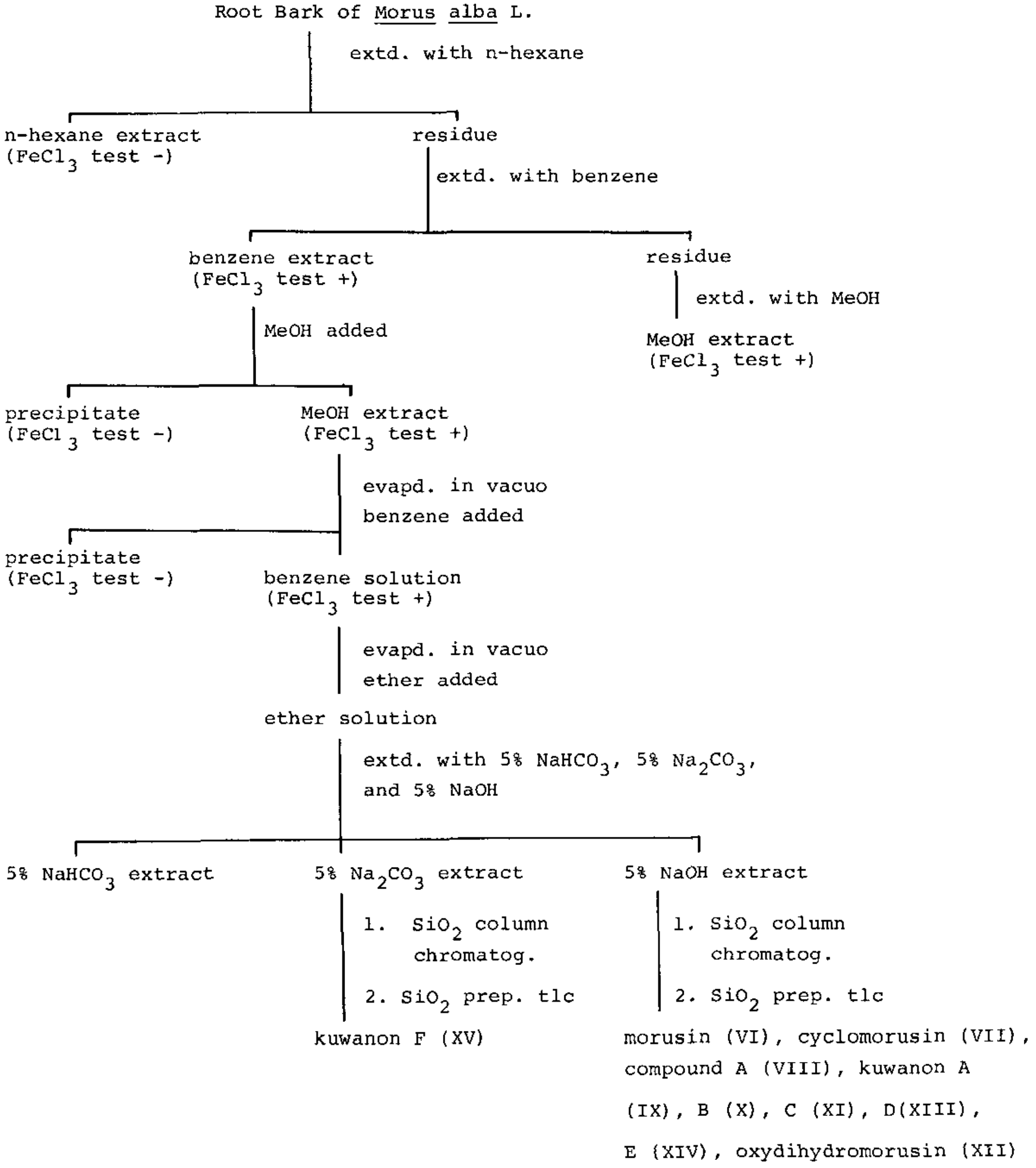


Chart 2

2. Structures of prenylflavonoids

(1) Morusin (VI)[5]

Morusin (VI), $C_{25}H_{24}O_6$, was obtained as two kinds of crystaline forms, one of them was pale yellow prisms, mp 214-216°, and the other was pale yellow needles, mp 140-146°, these crystals were polymorphic forms. Compound (VI) gave an intense green color with methanolic ferric chloride and was positive to the characteristic color reactions for flavones. The compound (VI) forms a dimethyl ether (VIa) with ethereal diazomethane and a trimethyl ether (VIb) with dimethyl sulfate. Treatment with acetic anhydride in pyridine yielded a diacetate (VIc) and a triacetate (VId). The former showed a green color with methanolic ferric chloride and was negative to the Gibbs test. A dihydro derivative (VIe) and a tetrahydro derivative (VIf) were obtained by hydrogenation. The UV spectrum of VI resembled those of prenylflavone derivatives which have a γ,γ-dimethylallyl group attached to the C-3 position of the pyrone ring.[4] The pmr spectrum of VI showed the characteristic chemical shift value of the C-6'-H of the C-3-prenylated flavones.[4,6] The mass spectrum of VI showed the following fragment ions: m/e 405 ($M^+ - CH_3$, XVI), 203(XVII, formed from the ion at 405 by a reverse Diels-Alder reaction).[7] From the above results and the analysis of pmr spectrum of VI (Table 3), the structure of VI seemed to be represented by the formula VI or II. The angular structure VI for morusin is supported by the changes in the chemical shift of chromene olefinic protons in its diacetate (VIc) as compared with that in the triacetate (VId)(Table 1). These changes are of the same sign and the same order of magnitude as those observed by many investigators for similar compounds.[7a,8] From these results, morusin is represented by the formula VI.

Table 1. Chemical Shift (ppm) for C-14-H and C-15-H in VIc and VId[a)]

compound	C-14-H	C-15-H
VIc	6.52	5.49
VId	6.60	5.59
Δ	- 0.08	- 0.10

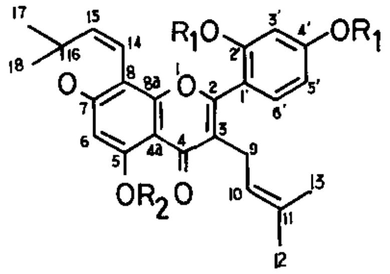
a) measured in $CDCl_3$.

(2) Cyclomorusin (VII)[5]

Cyclomorusin (VII), $C_{25}H_{22}O_6$, mp 246-248°, $[\alpha]^{20}_{589}$ +20° (from ORD measurement). The spectral data (pmr, UV, ir) suggest that the structure of cyclomorusin closely resembles that of cyclomulberrochromene (IV) rather than that of mulberrochromene (II).[4a,c] The structure (VII) for cyclomorusin is supported by its mass spectral fragment ion at m/e 363 (XVIII)[7b] and negative Gibbs test. Further evidence supporting the structure of VII was substantiated by the identity of the ir and the pmr spectrum with those of the compound obtained by the action of manganese dioxide on VI in nitrogen atmosphere.

(3) Compound A (VIII)[5]

Compound A (VIII), $C_{25}H_{24}O_7$, mp 258-260°, negative to the Gibbs test. Treatment of VIII with acetic anhydride in pyridine at room temperature yielded a diacetate (VIIIa), ir ν_{max}^{Nujol} 3510 cm^{-1}: negative to ferric chloride test. When treated with the same reagent on a water bath for 20 hr, VIII gave a triacetate (VIIIb). Compound (VIII) forms a monomethyl ether (VIIIc) which showed a green color with ferric chloride test. These results suggest the presence of two phenolic hydroxyls and a tertiary alcoholic hydroxyl group. Treatment of VIII with thionylchloride in pyridine gave a dehydrated product (XIX), $C_{25}H_{22}O_6$, pmr, δ in $CDCl_3$, 1.88($3H$,s,C-11-CH_3), 2.88-3.15(2H,m,C-9-Hx2), 4.83(1H,m,C-10-H), 4.93, 5.06(each 1H,s,C-11=CH_2). Compound (XIX) afforded a monoacetate (XIXa) and a diacetate (XIXb) which showed no ir absorption in the hydroxyl region. Further evidence supporting the structure of XIX was confirmed by comparing the spectral data, and mixed melting point with those of compound XIX obtained by the action of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) on VI. In the light of the DDQ reactions reported in the ealiar papers by Venkataraman et al.[4c,9] it is most likely that the action of DDQ on VI leads to XIX. From these considerations, compound A is represented by the formula VIII.



VI : $R_1=R_2=H$

VIa: $R_1=CH_3$, $R_2=H$

VIb: $R_1=R_2=CH_3$

VIc: $R_1=Ac$, $R_2=H$

VId: $R_1=R_2=Ac$

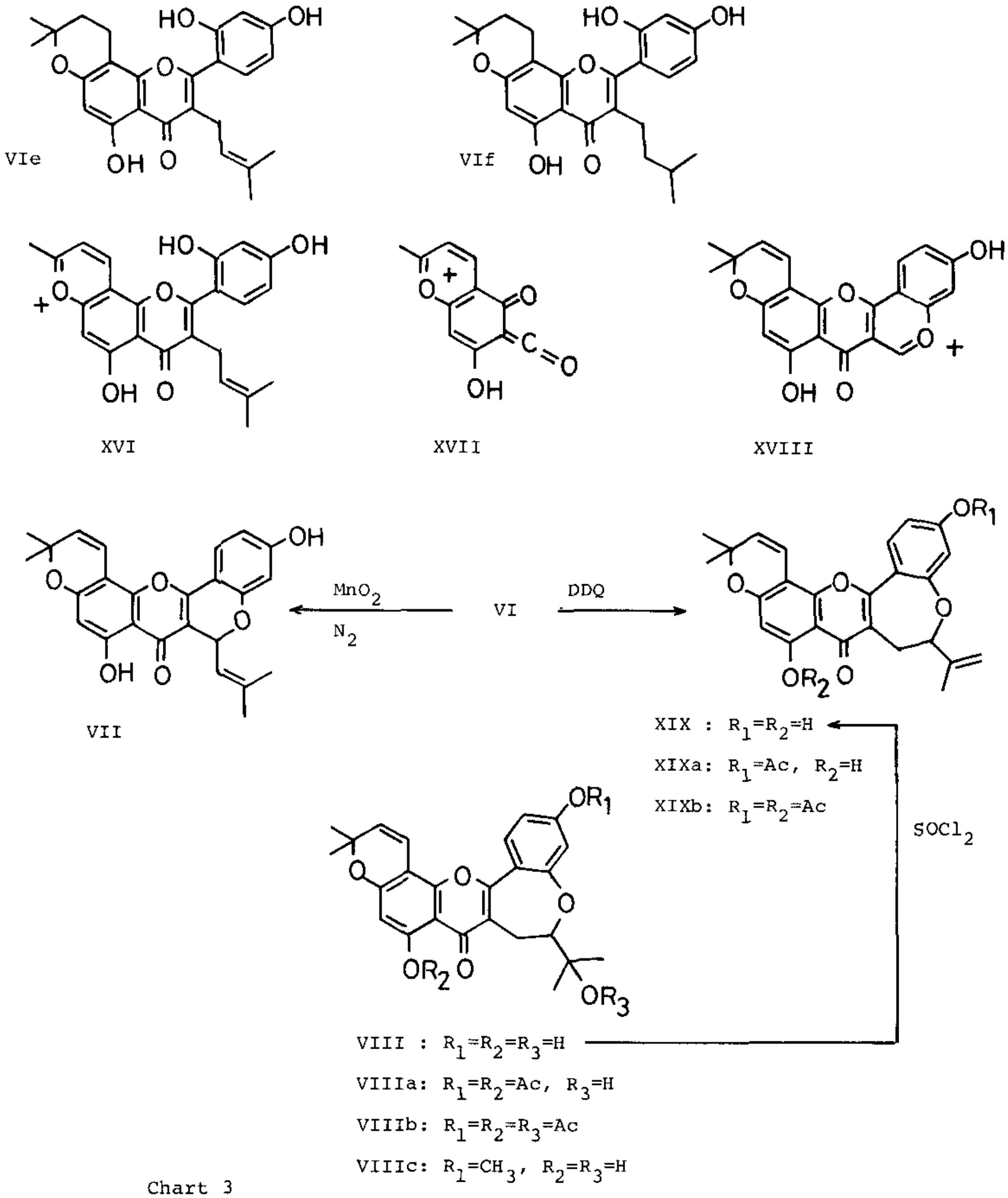


Chart 3

(4) Kuwanon A (IX) and kuwanon B (X)[10]

Kuwanon A (IX), $C_{25}H_{24}O_6$, amorphous powder, forms a dimethyl ether (IXa), mp 147°, and a diacetate (IXb), mp 167-169°, which showed a violet color with ferric chloride test and showed characteristic color reactions for flavone derivatives. Kuwanon B (X), $C_{25}H_{24}O_6$, mp 250-254°, forms a dimethyl ether (Xa) and a diacetate (Xb) which showed a similar color reaction with IX. The mass spectra of both IX and X gave the fragment ion at m/e 153 (XX). From the spectral data (UV, pmr, ms), both kuwanon A (IX) and B (X) can be regarded as flavone derivatives having the 2,2-dimethylchromene ring in the B ring and γ,γ-dimethyallyl group attached to the 3-position of chromone ring. The relation of C-14-H in chromene ring to the hydroxyl group in ring B is proposed to be peri both in IX and X on the basis of the changes in chemical shift for C-14- and C-15-H when IX and X are acethylated (Table 2). The changes for IX and X are of the same sign and of the same order of magnitude as those observed by many investigators for a number of similar compound, in which the hydroxyl group is peri to C-14-H.[7a,8] These results indicate that both kuwanon A and B are represented as formula IX or X. Final proof for the structures of kuwanon A and B was obtained by the photooxidation.[11] When a solution of X in chloroform was irradiated with a high-pressure merculy lamp, kuwanon B hydroperoxide (Xc) was obtained. On the other hand, this photooxidation did not occur in kuwanon A (IX). In the light of the result of photooxidation of morusin (VI),[11] it is concluded that kuwanon B (X) has the hydroxyl group at C-2' and the isolated double bond in γ,γ-dimethylallyl group attached to the 3-position of the chromone ring. From these consideration, the formula IX for kuwanon A and the formula X for kuwanon B are proposed.

Table 2. Chemical Shift (ppm) for C-14-H and C-15-H in IX, IXb, X, and Xb[a)]

compound	C-14-H	C-15-H
IX	6.75	5.69
IXb	6.53	5.88
Δ	+ 0.22	- 0.19
X	6.77	5.72
Xb	6.46	5.90
Δ	+ 0.31	- 0.18

a) measured in $(CD_3)_2CO$

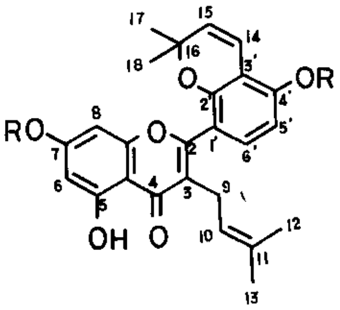
(5) Kuwanon C (XI)[10]

Kuwanon C (XI), $C_{25}H_{26}O_6$, mp 148-150°, the spectral data (UV, pmr, ms) suggest that the structure of kuwanon C closely resembles that of mulberrin (I).[4a,c]

Unequivocal evidences for the structure of kuwanon C (XI) were obtained as follows. When a solution of XI in chloroform was irradiated with high-pressure mercury lamp, kuwanon C hydroperoxide (XIa) was obtained in analogy with morusin (VI) and kuwanon B (X).[11] Treatment of XI with DDQ yielded morusin (VI) and compound (XIX). From the above results, the formura XI was proposed for kuwanon C.

(6) Oxydihydromorusin (Morusinol, XII)[10,12]

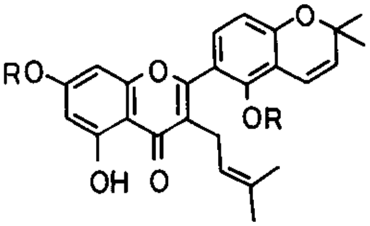
Oxydihydromorusin (morusinol, XII), $C_{25}H_{26}O_7$, mp 215-216°. From the spectral data, the structure of oxydihydromorusin was deduced as formula XII. Final proof for the structure XII assigned to oxydihydromorusin was obtained by comparing with the compound (XII) obtained by the action of 4% methanolic hydrogen chloride on morusin (VI).



IX : R=H

IXa: R=CH_3

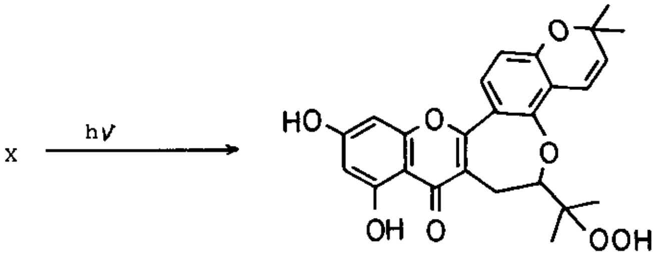
IXb: R=Ac



X : R=H

Xa: R=CH_3

Xb: R=Ac



Xc

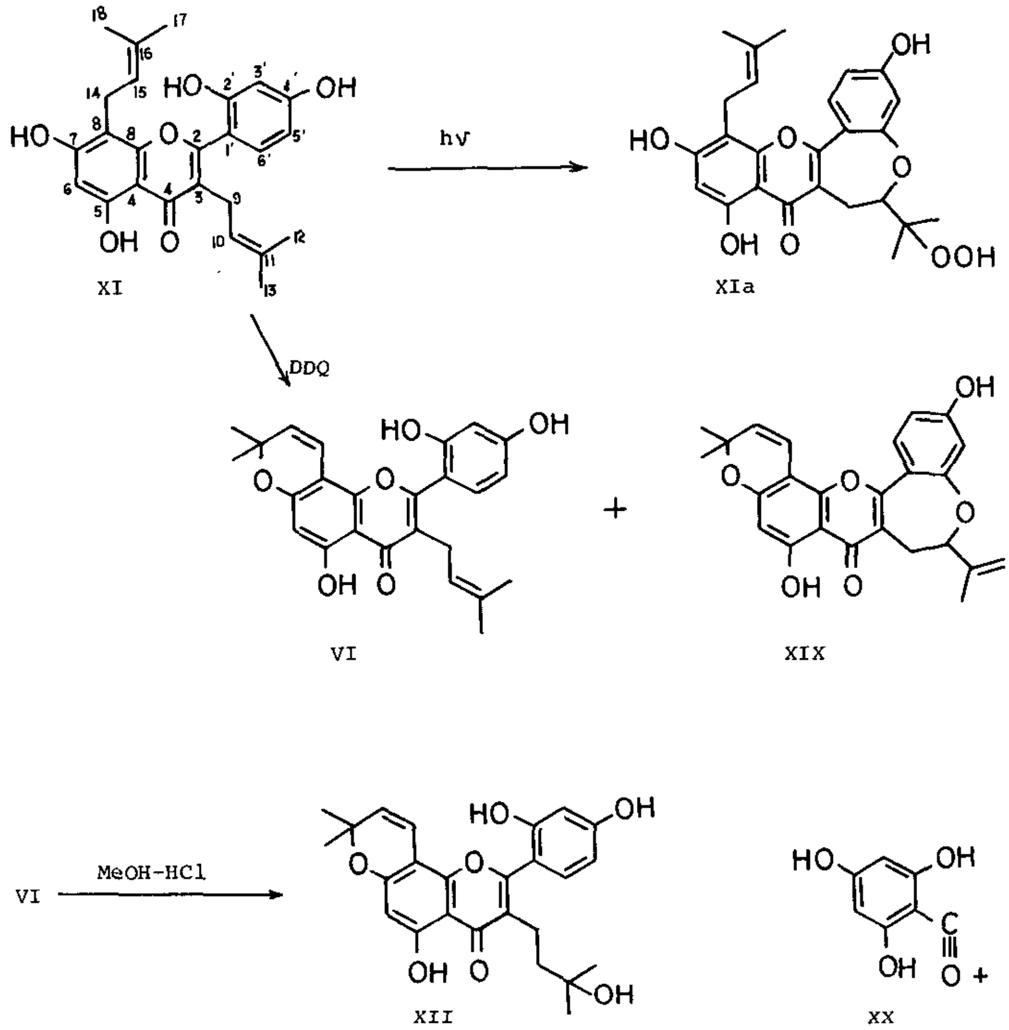


Chart 4

(7) Kuwanon D (XIII)[13]

Kuwanon D (XIII), $C_{25}H_{26}O_6$, mp 230-232°, was positive to magnesium-hydrochloric acid test and to sodium borohydride test,[14] but negative to zinc-hydrochloric acid test. The spectral data suggested that XIII has the 5,7,2',4'-tetraoxygenated flavanone structure. The mass spectrum of XIII gave the fragment at m/e 339 ($C_{19}H_{15}O_6$, base peak) corresponding to the oxonium-ions (XXI) which is expected for flavanon derivatives containing a pyran ring fused to the aromatic nucleus.[15] Thus the combined evidence pointed to the partial structure (XXII) plus a C_5 unit. The pmr spectrum of XIII showed the absence of signals for any olefinic protons, and XIII was recovered unchanged on the catalytic hydrogenation procedure using Adams catalyst. As there was no other double bond in the molecule, it was apparent that XIII has a hexacyclic structure, and the formula XIII was suggested for kuwanon D.

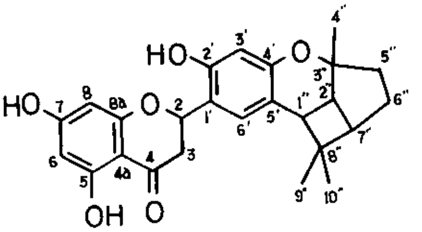
The "cyclol unit (XXIII)"[16] in the formula XIII was supported by the pmr spectrum of XIII (Table 4). The chemical shifts and the splitting patterns of the proton signals of the "cyclol unit" are similar to those of the corresponding protons of the compounds such as cannabicyclol (XXIV)[15b,c,16,17] and hydroxyeriobrucinol (XXV),[15e] which have the "cyclol unit" in the structure. In order to corroborate the structure of XIII, the cmr spectrum was analysed (Table 6). We tentatively proposed formula XIII for a structure of kuwanon D.

(8) Kuwanon E (XIV)[18]

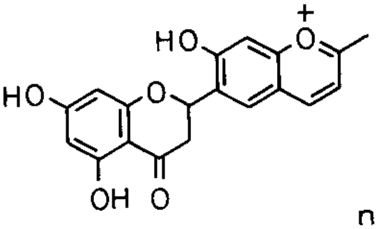
Kuwanon E (XIV), $C_{25}H_{28}O_7$, mp 132-136°, was positive both magnesium-hydrochloric acid test and sodium borohydride test. From the spectral data, XIV is suggested to have a 5,7,2',4'-tetraoxygenated flavanone structure. The mass spectrum of XIV showed the characteristic peak at m/e 301 (XXVI)[19] and 149 (XXVII)[19,20] which suggested the presence of a geranyl (or neryl) group on the B ring. The posibility of a geranyl group was supported by the NOE in the pmr spectrum of XIV. In order to corroborate the structure, the cmr spectrum was analysed (Table 6).

(9) Kuwanon F (XV)[21]

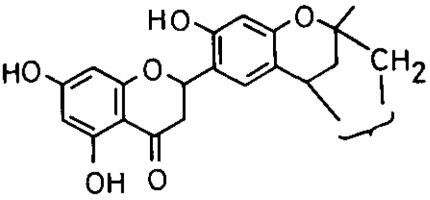
Kuwanon F (XV), $C_{25}H_{26}O_6$, amorphous powder, from the color reactions and the spectral data, XV is suggested to have a 5,7,2',4'-tetraoxygenated flavanone structure. The mass spectrum of XV showed the characteristic peak at m/e 187 (XXVIII) suggesting the presence of one hydroxyl group and 2-methyl-2-(4-methylpent-3-enyl)chromene ring in the ring B of the flavanone nucleus.[15a,19a] In order to corroborate the structure of XV, XV was derived from kuwanon E (XIV) by oxidation with DDQ.[19a,22]



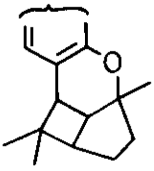
XIII



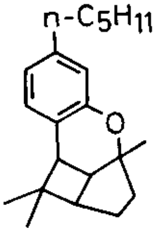
XXI



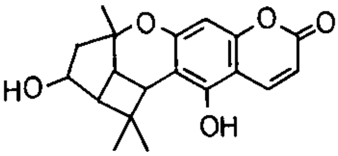
XXII



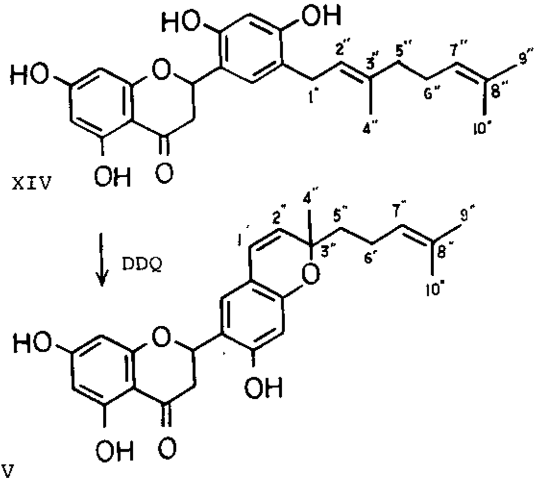
XXIII



XXIV

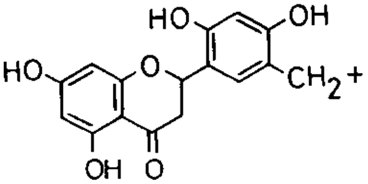


XXV

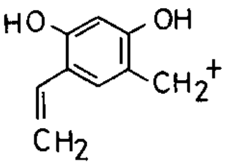


XIV

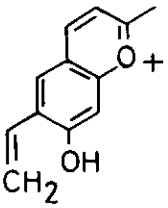
XV



XXVI



XXVII



XXVIII

Chart 5

(10) The synthesis of tetrahydrokuwanon C tetramethyl ether[23]

As mentioned above, morusin (VI), cyclomorusin (VII), compound A (VIII), oxydihydromorusin (XII), and kuwanon C (XI) were correlated to each other as shown in Chart 6. These structures were confirmed by synthesizing tetrahydrokuwanon C tetramethyl ether (XIb) from phloroglucinol *via* the route shown in Chart 7. Condensation of XXIX[24] with 5-methylhexanolic acid in the presence of boron trifluoride-etherate gave 2-hydroxy-3-isopenteyl-4,6-dimethoxy-isoheptophenone (XXX) in about 65% yield. The structure of XXX was accomplished on the basis of spectral data and color reactions. The compound (XXX) was positive to Gibbs test and the ir spectrum showed the absorption for a conjugated carbonyl group at 1630 cm^{-1}. In the low-field region of the pmr spectrum of XXX, a sharp singlet signal was observed at δ 13.97. The pmr spectral also indicated the presence of an isopentyl and a 5-methylhexanoyl group. From these results, the possibility of the formula, 2,6-dimethoxy-3-isopentyl-4-hydroxyisoheptophenone, for this condensation product was completely excluded. The flavone derivative (XIb) was obtained from the compound (XXX) and 2,4-dimethoxybenzoyl chloride by Baker-Venkataraman method,[25] and was identical with tetrahydrokuwanon C tetramethyl ether derived from kuwanon C (XI). From these results, the structure of morusin, cyclomorusin, compound A, kuwanon C, and oxydihydromorusin (morusinol), were determined as the formulae VI, VII, VIII, XI, and XII, respectively.

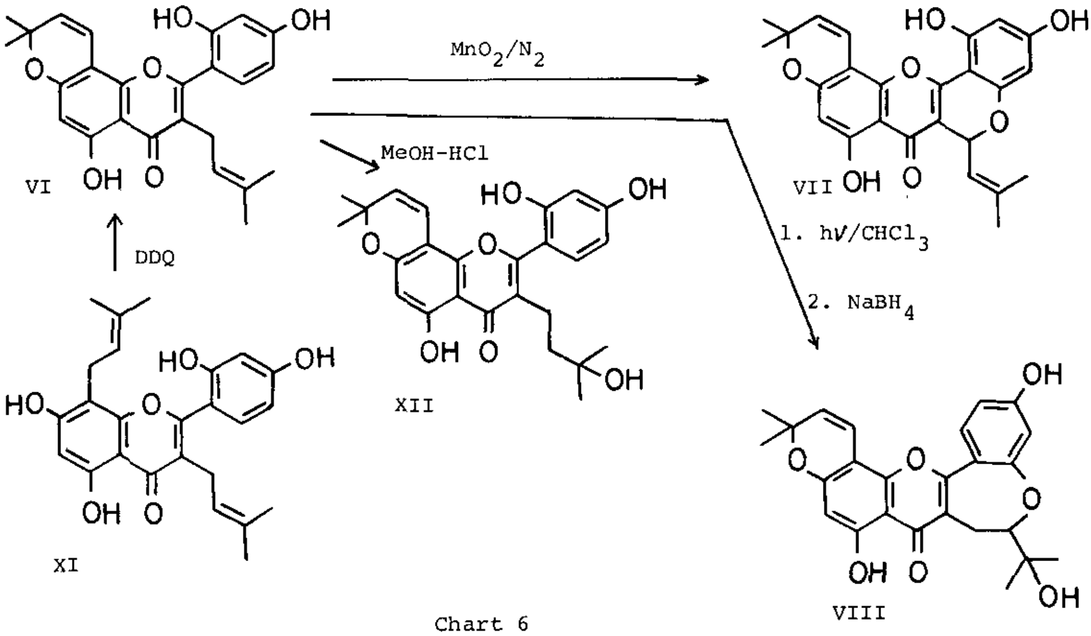


Chart 6

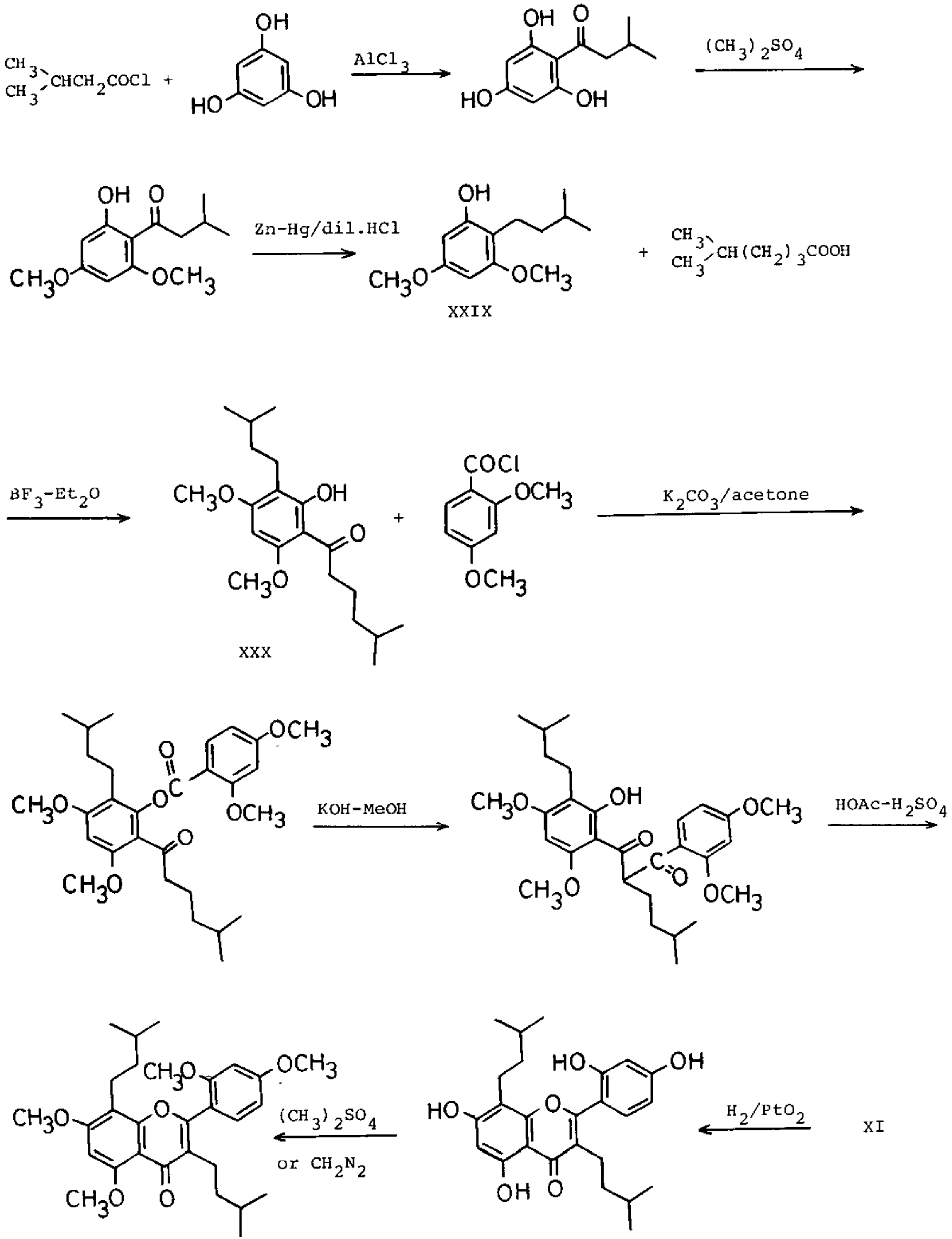

CH3 CH3 CHCH2COCl +
OH
HO
OH
AlCl3
(CH3)2SO4
OCH3
CH3O
Zn-Hg/dil.HCl
XXIX
CH3 CH3 CH(CH2)3COOH
BF3-Et2O
XXX
COCl
K2CO3/acetone
KOH-MeOH
HOAc-H2SO4
(CH3)2SO4
or CH2N2
H2/PtO2
XI
XIb
XIc

Chart 7

(11) On the structures of mulberrin, mulberrochromene, cyclomulberrin, and cyclomulberrochromene[26]

As mentioned above, Deshpande et al. reported the isolation and structure determination of the four prenylflavones, mulberrin (I), mulberrochromene (II), cyclomulberrin (III), and cyclomulberrochromene (IV), from Morus alba root bark.[4] On the other hand, our group reported a series of prenylflavonoids. The difference between the prenylflavones isolated by Deshpande et al. and those by our group is the position of the C_5 unit in ring A.

Chari et al.[27] reported that reappraisal of the cmr data on mulberrin (I) and mulberrochromene (II) which had been presented by Wenkert and Gottlieb,[28] indicated the revised structures for these two compounds as well as for cyclomulberrin (III) and cyclomulberrochromene (IV). The signals at 98.0 ppm and 98.9 ppm in the respective cmr spectra have been assigned to C-8 of mulberrin (I) and mulberrochromene (II) by Wenkert and Gottlieb.[28] But Chari et al. insisted[27] that these chemical shift values are ca. 4.0 ppm down field of the C-8 signal in 5,7-dihydroxyflavones, and that they are in the reasonable range expected for the corresponding unsubstituted C-6 by comparing with the C-8 signal of the cmr spectra of the linear chromeno-flavone and the C-4 signal of the chromeno-xanthone derivatives. From these results, Chari et al. reported[27] that the four mutually interrelated prenylated Morus flavones isolated by Deshpande et al. have the C-8 rather than the C-6-substitution as initially proposed. They described[27] that mulberrin (I) is identical with kuwanon C (XI), mulberrochromene (II) with morusin (VI), and cyclomulberrochromene (IV) with cyclomorusin (VII). In order to clear these point, we studied the cmr spectra of morusin and related prenylflavonoids (Table 6).[26] In the spectra of the these flavonoids, the C-6 signal appeared in the range of 97.9-100.2 ppm. These results are in good agreement with the literature.[27,29] Direct comparisons of mulberrin (I) with kuwanon C (XI), and mulberrochromene (II) with morusin (VI) were carried out. Mulberrin and mulberrochromene were proved to be identical with kuwanon C and morusin, respectively. These results indicate that the linear structures of the four prenylated Morus flavones, mulberrin (I), mulberrochromene (II), cyclomulberrin (III), and cyclomulberrochromene (IV) were reversed to the angular structures, XI, VI, III', and VII, respectively. Chari et al. insisted[27] that in the conversion of artocarpin (V) to tetrahydromulberrin (Chart 1), an isomerization must have taken place, and the only conceivable change is a Wessely-Moser rearrangement in the demethylation. In order to examine the possibility of the isomerization, the demethylation was carried out in tetrahydrokuwanon C tetramethyl ether (XIb) by hydroiodic acid. Tetrahydrokuwanon C (XIc) was obtained from the reaction products, but 3,6-diisopentyl-5,7,2',4'-tetrahydroxyflavone could not be obtained. On the ring isomeric change of 2'-hydroxyflavone derivatives, it was reported[30] that there was no isomeric change under ordinary conditions of demethylation with hydroiodic acid. If the Wesser-Moser rearrangement occured in the demethylation of tetrahydroartocarpin, as Chari et al. insisted on,[27] it seems to be interesting example so that we are now in progress to elucidate the possibility of isomerization of the prenylflavones obtained from the Morus root bark.

C. Photoreaction of morusin

(1) Photoreaction of morusin[11,31]

In the course of our studies on the constituents of the Morus root bark, the formation of morusin hydroperoxide (XXXI) was found in photoreaction of morusin (VI). When a solution of VI in chloroform was irradiated with a high-pressure mercury lamp or with a tungsten lamp, morusin hydroperoxide (XXXI), mp 204-206°, $C_{25}H_{24}O_8$, was obtained in ca. 80% yield. The reaction did not occur in the dark, and was dependent on the solvent. It proceeded in chloroform or benzene solution whereas did not in methanol, ethanol or tert-butylalcohol solution. When a solution of morusin dimethyl ether (VIa), or morusin diacetate (VIc) as well as tetrahydromorusin (VIf), was irradiated in chloroform, photoreaction did not occur, and starting material was recovered unchanged. However, 14,15-dihydromorusin hydroperoxide (XXXII) was obtained when a solution of 14,15-dihydromorusin (VIe) was irradiated. These findings indicate that this photooxidation requires the presence of the isolated double bond in the side chain attached to the 3-position and of the hydroxyl group in B ring. From the following experimental results, it was confirmed that the free hydroxyl group at C-2' is required for this photooxidation. Two isomers of morusin monomethyl ether, 2'-O-methyl morusin (VIg) and 4'-O-methyl morusin (VIh) were obtained by methylation of VI with ethereal diazomethane in isopropanol. When a solution of VIg was irradiated, the starting material was recovered unchanged. An irradiation of VIh, however, gave morusin hydroperoxide monomethyl ether (XXXIII). The structure of XXXI was confirmed by the following results.

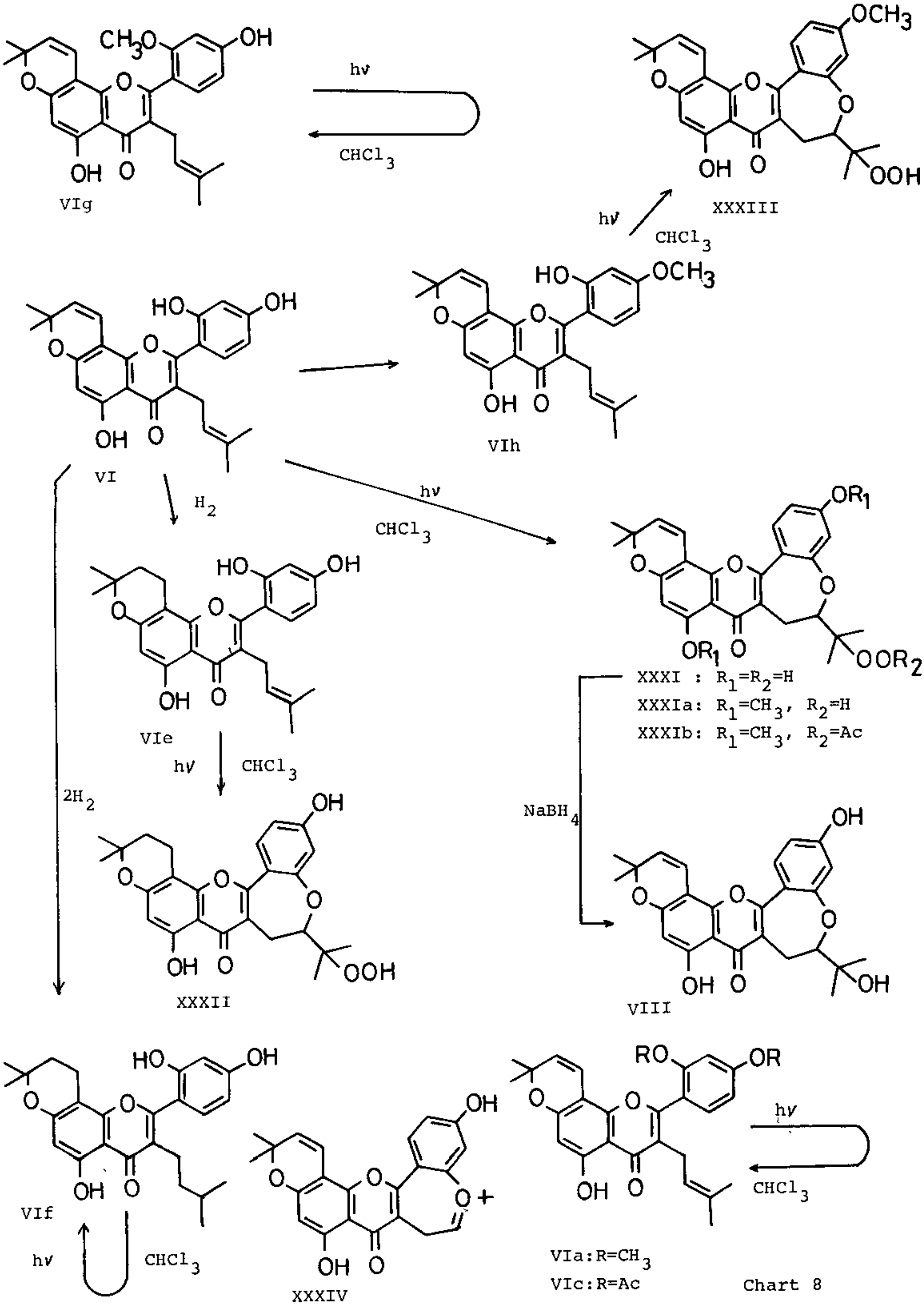

VIg
hν
CHCl$_3$
XXXIII
hν
CHCl$_3$
VIh
VI
H$_2$
hν
CHCl$_3$
XXXI : R$_1$=R$_2$=H
XXXIa: R$_1$=CH$_3$, R$_2$=H
XXXIb: R$_1$=CH$_3$, R$_2$=Ac
VIe
hν
CHCl$_3$
2H$_2$
NaBH$_4$
XXXII
VIII
VIf
hν
CHCl$_3$
XXXIV
hν
CHCl$_3$
VIa:R=CH$_3$
VIc:R=Ac

Chart 8

The UV spectrum (λ_{max}^{EtOH} 280 and 335 nm) resembled that of compound A (VIII) rather than VI or VII. When treated in methanol with diazomethane, XXXI gave the dimethyl ether (XXXIa) which was negative to ferric chloride test and showed the absorption for a hydroxyl group at 3300 cm^{-1}. Acetylation *of XXXIa gave the* dimethyl ether monoacetate (XXXIb) which showed absorption for a acetylperoxyl group at 1780 cm^{-1}.[32] The pmr spectrum of XXXI showed the signals of the characteristic AMX pattern such as δ 2.59 (1H,dd,J=10 and 18 Hz,C-9-H), δ 3.46 (1H,dd,J=2 and 18 Hz,C-9-H), and δ 4.38(1H,dd,J=2 and 10 Hz,C-10-H). The mass spectrum of XXXI gave fragments at m/e 436(M$^+$ - O),[33] 421(M$^+$ - O - CH$_3$), 377(M$^+$ - $C_3H_7O_2$, XXXIV). When XXXI was heated in dimethyl sulfoxide, compound A (VIII) was obtained as well as when treated with sodium borohydride, diphenylsulfide, triphenylphosphine, or trimethylamine in methanol. From these results, the structure of morusin hydroperoxide is deduced to be XXXI. The similar photooxidative cyclization occured in the cases of kuwanon B (X)[10] and kuwanon C (XI).[10]

(2) The reaction mechanism of photo-oxidative cyclization of morusin[34]

As reported by Matuura and his co-workers,[35] 5-hydroxy-flavone derivatives resist photoreaction. They described that the stability to photoreaction is due to hydrogen bonding of the 5-hydroxyl to the 4-carbonyl group, and that such an interaction causes an intramolecular hydrogen abstraction in the ecited state to yield a tautomer. Our group obtained the experimental results[36] which support the Matsuura's theory in the case of the photoreaction of morusin trimethyl ether (VIb). Although morusin (VI) is a flavone derivative which also has the intramolecular hydrogen bonding between the 5-hydroxyl and the 4-carbonyl group,[5] the photoreaction occured in chloroform or benzene solution.[31] In this respect, the photo-oxidative cyclization of VI is a novel reaction in the photochemistry of flavonoids, and the reaction mechanism was investigated by our group.

The following three possible mechanisms[37] can be proposed for the primary step of the photo-oxidative cyclization of VI : 1) a reaction mechanism involving "singlet oxygen", 2) a reaction *via* a phenoxy radical, 3) a reaction *via* a contact charge transfer complex. Above three possible mechanisms were examined on the basis of experimental results.

1) A reaction mechanism involving "singlet oxygen"

Considering the ultraviolet and visible absorption spectrum of VI,[5] it is probable that VI acts as a triplet sensitizer and produces singlet oxygen (Chart 9).

$$M \xrightarrow{h\nu} {}^{1}M^{*} \longrightarrow {}^{3}M^{*} + {}^{3}O_2 \longrightarrow M + {}^{1}O_2$$

Chart 9

When singlet oxygen is produced, two cases are possible : a) singlet oxygen reacts with the molecules of VI which produced singlet oxygen, and the reaction takes place intramolecularly, and b) singlet oxygen reacts intermolecularly with the molecules other than its donor molecules. In the former case, singlet oxygen is generated apparently in such a manner that its free circulation in solution is not permitted. Furthermore, the generation of singlet oxygen presumably occurs in the immediate vicinity of the flavone ring.[38]

To examine the latter mechanism, photosensitized oxidation of VI with hematoporphyrin was investigated.[34,40] The photosensitized oxidation afforded XXXV and XXXVI when a solution of VI in chloroform was irradiated in the presence of hematoporphyrin with a high-pressure mercury lamp throuh filter solution[39] to cut the radiation shorter than 500 nm under bubbling oxygen. Blank runs without any dye gave no reaction. These findings suggest that the products formed only <u>via</u> "ene" reaction must be detected if singlet oxygen reacts intermolecularly with the molecules of VI other than the donor molecules of oxygen.

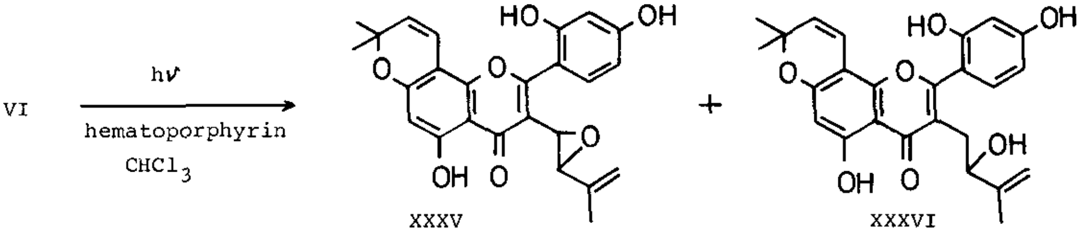


Chart 10

Moreover, following experiments suggest that VI can not generate singlet oxygen is also excluded. The visible and ultraviolet spectrum of morusin diacetate (VIc) was similar to that of VI. If VI can generate singlet oxygen, it can be expected that as well as VIc can generate singlet oxygen. If VIc generate singlet oxygen, it is probable that the oxygenated products are formed only via "ene" reaction,[34] and the oxidative-cyclization can not occur because of acetylated 2'-hydroxyl group.[31] When the chloroform solution of VIc was irradiated with a tungsten lamp, the starting material was recovered quantitatively. On the other hand, a solution of VIc and ergosterol in chloroform was irradiated, VIc and ergosterol were recovered in 80% yield, and ergosterol peroxide was not obtained. If VIc could have generated singlet oxygen, ergosterol peroxide[41] would have been formed (Chart 11).

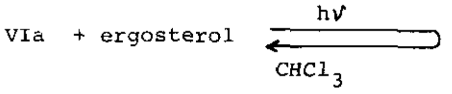


Chart 11

These data indicate that VIc does not generate singlet oxygen. Considering the similarity of the visible and ultraviolet spectrum of VI and VIc, it is probable that VI does not generate singlet oxygen as well as VIc does not. Thus, the reaction mechanism involving singlet oxygen can be excluded.

2) A reaction via a phenoxy radical

It has been described that a large number of natural products may be formed by the oxidative coupling of their phenol precursors.[42] In the case of photo-oxidative cyclization of VI, a reaction mechanism via phenoxy radical is supposed to be probable. So we attempted the oxidative cyclization of VI using one electron transfer oxidizing agents (manganes dioxide, silver oxide) in the dark.[40b,43] The reaction afforded morusin hydroperoxide (XXXI) and compound A (VIII). A similar reaction was carried out in the presence of 2,4,6 -tri-t-butylphenol, a radical quencher, to give compounds XXXVII, XXXVIII, IXL, and XL.[40b,43] On the basis of these results, the possible mechanism of this oxidative cyclization was postulated as in Chart 12. The similar mechanism via phenoxy radical (XLI) can be assumed in the case of photo-oxidative cyclization of VI. To investigate this assumption, the following experiments were carried out. A solution of VI and 2,4,6 -tri-t-butylphenol in benzene was irradiated with a high-pressure mercury lamp. From the reaction products, only the starting materials were obtained.[34] If the photo-oxidative cyclization proceeded via a phenoxy radical (XLI), the reaction could be blocked by addition of 2,4,6-tri-

t-butylphenol,[44] and the compounds coupled with 2,4,6-tri-*t*-butylphenoxy radicals, such as XXXVII, XXXVIII, IXL, XL, and the dimer (XLII)[45] would be formed.[44] In the case of photo-oxidative cyclization of VI, the reaction was completely blocked by the addition of 2,4,6-tri-*t*-butylphenol, and any other expected reaction products were not obtained. These findings allow a speculation that 2,4,6-tri-*t*-butylphenol does not act as a radical quencher although it blocks the photo-oxidative cyclization. The blocking mechanism of this phenomenon has not been clear. Considering above results, the reaction mechanism *via* a phenoxy radical is unlikely to operate.

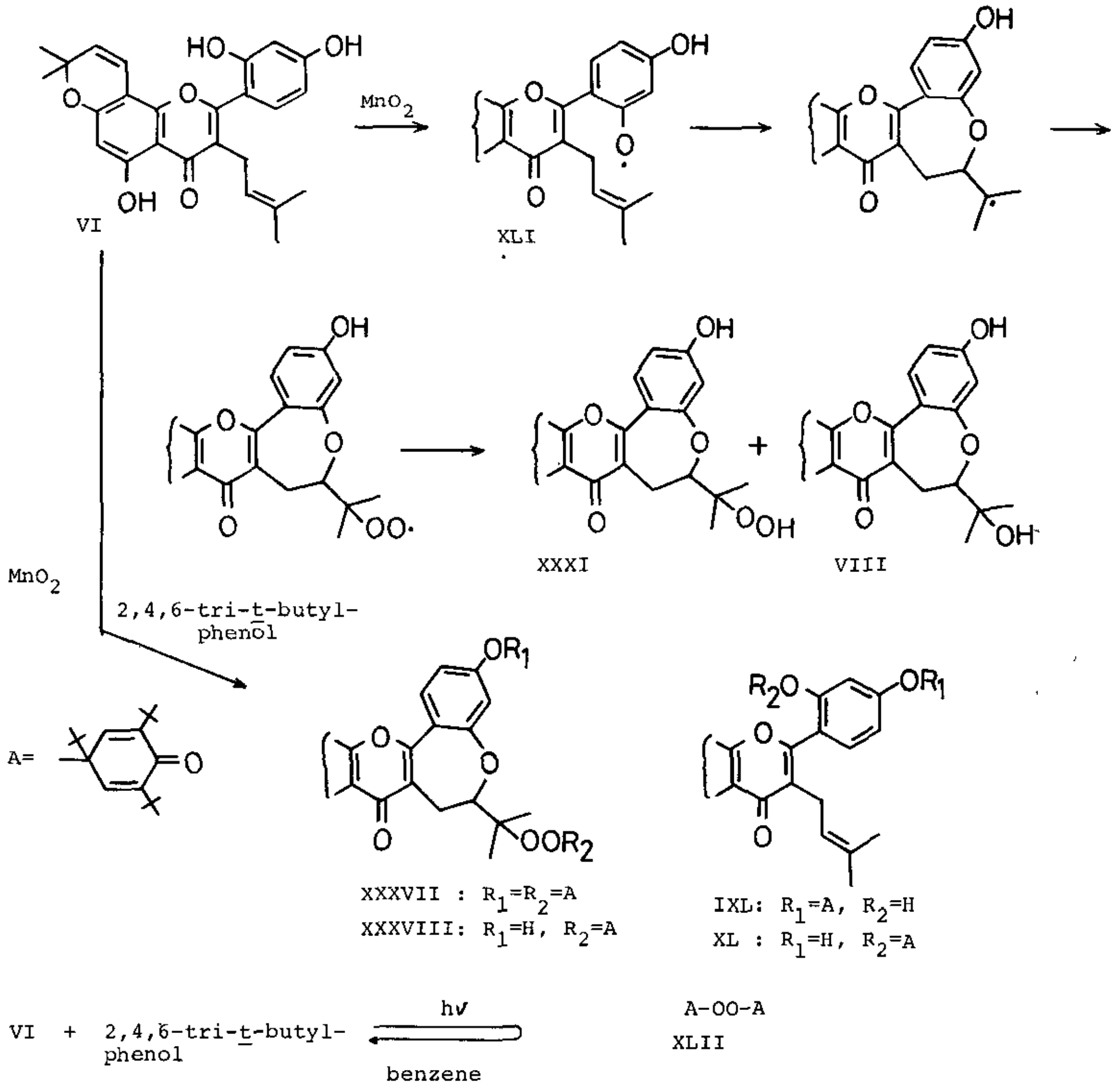


Chart 12

3) A reaction via a contact charge transfer complex

The third mechanism is depicted as follows. Morusin (VI) in the ground state interacts with an oxygen molecule to form a contact charge transfer complex (XLIII).[46] On irradiation, the complex (XLIII) give an excited charge transfer state that presumably leads to reaction species such as drown in Chart 13.

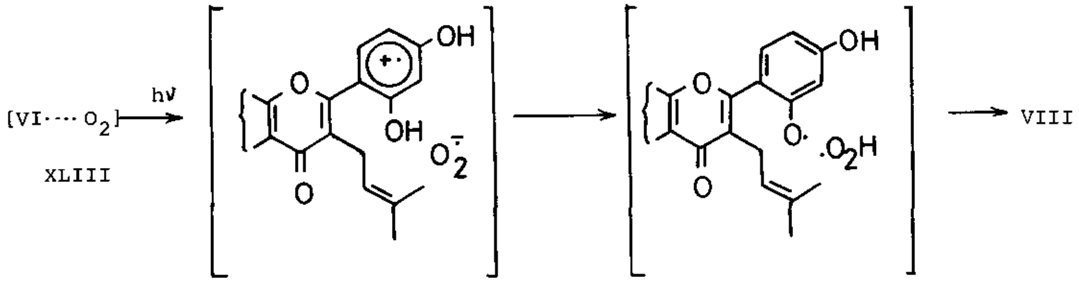


Chart 13

As mentioned above, a reaction mechanism involving singlet oxygen and a *mechanism via a phenoxy radical* could not explain the photo-oxidative cyclization of VI. The third mechanism is, therefore, more reasonable. Although the possible proof supporting this mechanism has not been obtained, the following experimental results will be explained by this hypothesis. The photo-oxidative cyclization of VI is dependent on the solvent and proceeds in chloroform, dichloromethane or benzene solution whereas the starting material is recovered unchanged in methanol, ethanol, or tert-buthylalcohol solution.[31] It is tempting to speculate that the contact charge transfer complex (XLIII) can not be formed in the solvent in which the photoreaction does not occur. On considering the present findings, the third mechanism mentioned above is suggested to be the most possible one which proceeds via a chrge transfer complex.

D. Hypotensive constituents of mulberry root bark[47-51,53]

The methanol extract (Chart 2) to rabbit (3 mg/Kg, i.v.) produced a significant hypotension.[50] The extract was fractionated as shown in Chart 14, and kuwanon G (XLIV) and kuwanon H (XLV) were isolated in 0.2 and 0.13% yield, respectively.[51] Intravenous injection of both compounds (0.1-3.0 mg/Kg) showed in almost equal manner a transient dose-dependent decrease in arterial blood pressure in anesthetized rabbit.[50]

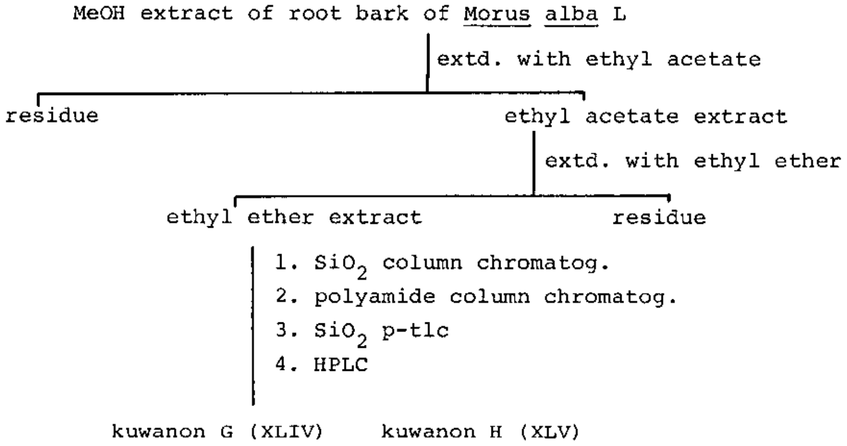
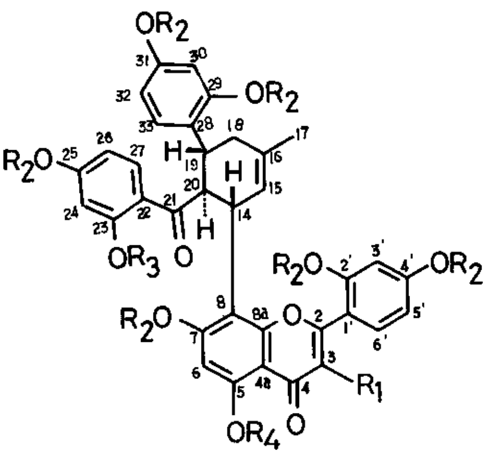


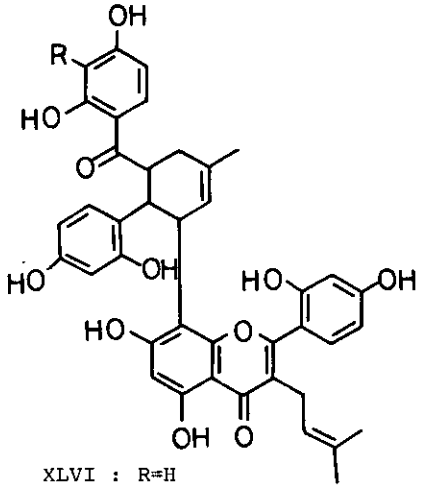
Chart 14

(1) kuwanon G (XLIV)[47,51]

Kuwanon G (XLIV), amoruphous powder, mp 213-219°(decomp.), $[\alpha]_D^{22}$-534°, has a molecular formula of $C_{40}H_{36}O_{11}$. The UV spectra were similar to those of kuwanon C (XI) suggesting that XLIV possesses a kuwanon C partial structure. The treatment with dimethyl sulfate gave the four kinds of methyl ethers such as hexamethyl ether (XLIVa), heptamethyl ether (XLIVb) which was negative to Gibbs test, heptamethyl ether (XLIVc) which was positive to Gibbs test, and octamethyl ether (XLIVd). The mass spectrum of XLIV showed the fragment at m/e 420($C_{25}H_{24}O_6$, L). The xylene solution of XLIVa was pyrolysed at 450°. From the reaction products, 2'-hydroxy-2,4,4'-trimethoxychalcone (LI) was obtained which was identified with authentic sample obtained from 2'-hydroxy-4'-methoxyacetophenone and 2,4-dimethoxybenzaldehyde. The presence of a γ,γ-dimethylallyl group was supported by the pmr spectra and the formation of compound XLIVe.[52] The location of γ,γ-dimethylallyl group was supported by the formation of kuwanon G hydroperoxide (LII) obtained by photo-oxidative cyclization.[31] In the light of the results of photo-oxidative cyclization of VI and other prenylflavones,[10,31] it is supported that XLIV has a γ,γ-dimethylallyl group at the 3-position. By comparing the cmr spectra of XLIV and XI (Table 6), the chemical shift values of C-3 and C-9 of XLIV were in good agreement with those of C-3 and C-9 of XI, whereas those of C-8 and C-14 were shifted to a lower applied magnetic field.

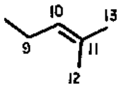
This result supported the presence of γ,γ-dimethylallyl group at C-3 position. The C-6 substituted prenylflavone structure for XLIV was excluded from the results of the Gibbs test of the heptamethyl ethers (XLIVb and XLIVc) and from the following cmr data: the chemical shift values of the C-6 and C-8 signals of XLIV were in good agreement with those of the C-8 substituted prenylflavones.[26,27] From these data, it is possible that the structure of kuwanon G is represented as XLIV or XLVI. The arrangement of substituents in the D ring was assumed by the pmr data of kuwanon G octadeuteromethyl ether (XLIVf) [δ in $CDCl_3$, 1.80-2.00 (2H,m,C-18-Hx2), 3.33-4.06(1H,m,$J_{19,20}$=10Hz,C-19-H), 4.35(1H,br d,$J_{14,20}$=10Hz, C-14-H), 4.85(1H,t,$J_{19,20}$=$J_{14,20}$=10Hz,C-20-H), 5.18(2H,m,C-10- and 15-H)]. The assignment of the signals at 19- and 20-H were further confirmed by the comparison with the pmr spectrum of alcohol (XLIVg) obtained by sodium borohydride reduction of XLIVf. The compound (XLIVg) showed the following pmr data : δ in $CDCl_3$, 1.33-2.08(11H,CH_3x3 and C-18-Hx2), 2.80-3.67(5H, C-9-Hx2, C-19-H,C-20-H, and C-21-OH), 4.00-4.70(2H,C-14-H and C-21-H), 5.00-5.20(2H, C-10-H and C-15-H). The signal of 20-H of XLIVg was shifted about 1.5 ppm to a higher applied magnetic field than that of XLIVf. If the structure of kuwanon G could be represented as XLVI, three proton signals (C-14-H, C-20-H, and C-21-H) would appear at 4.0-5.0 ppm. From above results the structure XLIV is considered to be more favorable than the structure XLVI (without stereochemistry). Considering the coupling constants ($J_{14,20}$=$J_{19,20}$=10 Hz) of the pmr spectrum of XLIVg, the three hydrogen (C-14-,C-19-, and C-20-H) are quassiaxially situated and are located in trans orientation to each other.[48c,49b]





XLVI : R=H

XLVII: R= γ,γ-dimethylallyl

XLIV : R$_1$=  , R$_2$=R$_3$=R$_4$=H

XLIVa: R$_1$=γ,γ-dimethylallyl, R$_2$=CH$_3$, R$_3$=R$_4$=H

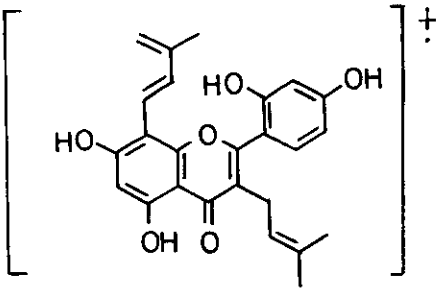
XLIVb: R$_1$=γ,γ-dimethylallyl, R$_2$=R$_3$=CH$_3$, R$_4$=H

XLIVc: R$_1$=γ,γ-dimethylallyl, R$_2$=R$_4$=CH$_3$, R$_3$=H

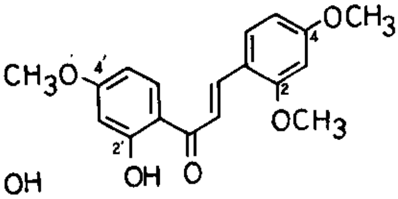
XLIVd: R$_1$=γ,γ-dimethylallyl, R$_2$=R$_3$=R$_4$=CH$_3$

XLIVe: R$_1$=  , R$_2$=CH$_3$, R$_3$=R$_4$=H

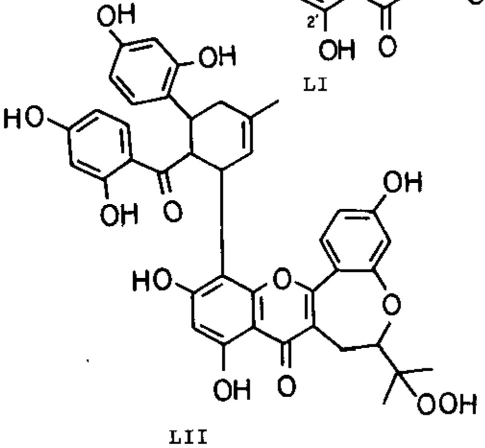
XLIVf: R$_1$=γ,γ-dimethylallyl, R$_2$=R$_3$=R$_4$=CD$_3$



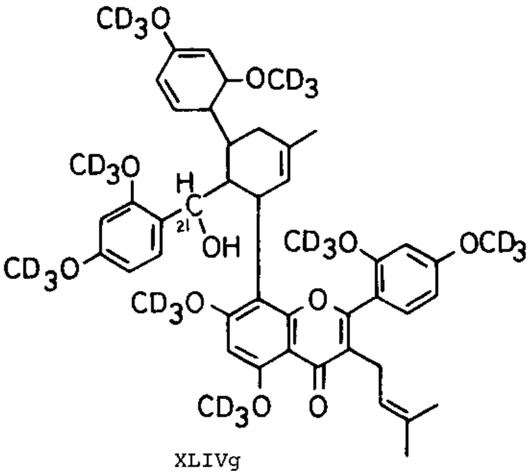
L



LI



LII



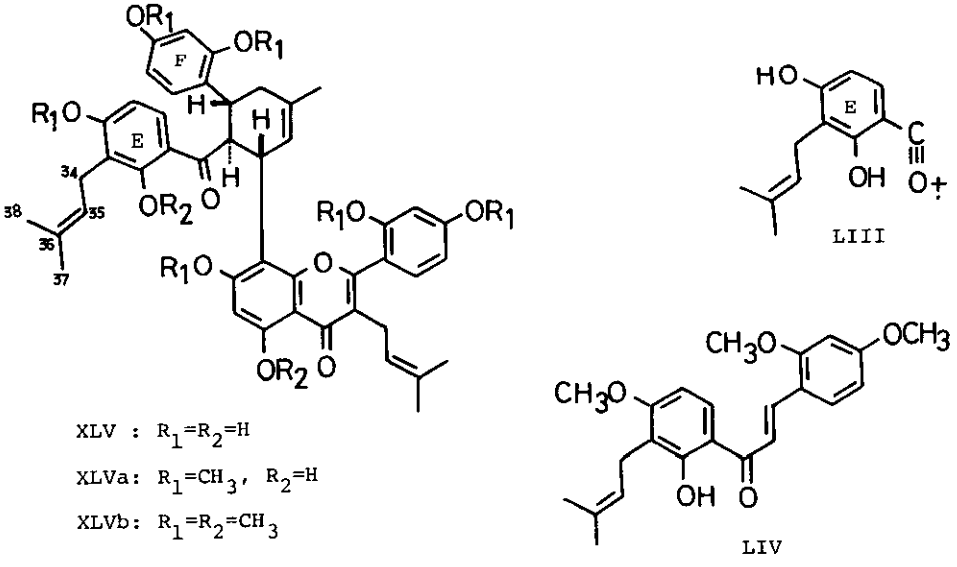
XLIVg

Chart 15

(2) Kuwanon H (XLV)[47,53]

Kuwanon H (XLV), amorphous powder, mp 186-190°(decomp.), $[\alpha]_D^{22}$ -536°, had a molecular formula of $C_{45}H_{44}O_{11}$. The UV spectra were similar to those of kuwanon C (XI) suggesting that XLV possesses a kuwanon C partial structure. The treatment of XLV with dimethyl sulfate gave a hexamethyl ether (XLVa) and a octamethyl ether (XLVb). The mass spectrum of XLV showed the fragments at m/e 420(L) and 205 (LIII). On the other hand, the mass spectrum of kuwanon G (XLIV) did not show the fragment at m/e 205. The hexamethyl ether (XLVa) was pyrolysed, and 2'-hydroxy-3'-γ,γ-dimethylallyl-2,4,4'-trimethoxychalcone (LIV)[54] was obtained from the reaction products. By comparing with the cmr and pmr spectra of XLIV and XLV (Table 5,6), these two compounds seemed to be probably the same skeletal structure. The only diference between the two compounds is the presence of γ,γ-dimethylallyl group at the C-24 of kuwanon H. From these results, the structure of kuwanon H is represented as structure XLV.

It should be noted that these two hypotensive components, kuwanon G (XLIV) and H (XLV), have a uniqe carbon skeleton regerded biogenetically as Diels-Alder adducts of two "natural" components.



LIII

LIV

XLV : $R_1=R_2=H$

XLVa: $R_1=CH_3$, $R_2=H$

XLVb: $R_1=R_2=CH_3$

Chart 16

Table 3. Pmr Spectra of Prenylflavones

	morusin (IV)	cyclomorusin (VII)
6-H	6.21(1H,s)	6.19(1H,s)
3'-H	6.45(1H,d,J=2.5)	6.46(1H,d,J=2)
5'-H	6.37(1H,dd,J=2.5, 7.5)	6.67(1H,dd,J=2, 9)
6'-H	7.14(1H,d,J=7.5)	7.82(1H,d,J=9)
9-H	3.02(2H,br d,J=8)	6.24(1H,br d,J=10)
10-H	5.03(1H,br t,J=8)	5.49(1H,br d,J=10)
11-CH_3	1.42, 1.57(each 3H,br s)	1.72, 1.98(each 3H,br s)
14-H	6.53(1H,d,J=10)	6.95(1H,d,J=10)
15-H	5.67(1H,d,J=10)	5.79(1H,d,J=10)
16-CH_3	1.42(6H,s)	1.46(6H,s)
5-OH	13.17(1H,s)	12.73(1H,s)
solvent	dmso-d_6	$(CD_3)_2CO$

	compound A (VIII)	kuwanon A (IX)
6-H	6.51(1H,s)	6.26(1H,d,J=2)
8-H		6.32(1H,d,J=2)
3'-H	7.05(1H,d,J=2)	
5'-H	7.02(1H,dd,J=2, 10)	6.68(1H,d,J=9)
6'-H	8.13(1H,d,J=10)	7.08(1H,d,J=9)
9-H	2.96(1H,dd,J=10, 16)	3.11(2H,br d,J=8)
	3.93(1H,dd,J=2, 16)	
10-H	4.28(1H,dd,J=2, 10)	5.13(1H,m)
11-CH_3	1.55, 1.58(each 3H,s)	1.45, 1.58(each 3H,s)
14-H	6.95(1H,d,J=11)	6.75(1H,d,J=10)
15-H	5.76(1H,d,J=11)	5.69(1H,d,J=10)
16-CH_3	1.48(6H,s)	1.40(6H,s)
5-OH	12.70(1H,s)	13.13(1H,s)
solvent	pyridine-d_5	$(CD_3)_2CO$

	kuwanon B (X)	kuwanon C (XI)
6-H	6.26(1H,d,J=2)	6.31(1H,s)
8-H	6.31(1H,d,J=2)	
3'-H		6.52(1H,d,J=2)
5'-H	6.46(1H,d,J=9)	6.43(1H,dd,J=2,8)
6'-H	7.08(1H,d,J=9)	7.20(1H,d,J=8)
9-H	3.12(2H,br d,J=6)	3.12(2H,br d,J=8)
10-H	5.11(1H,br t.J=6)	5.20(1H,m)
11-CH_3	1.42, 1.58(each 3H,s)	1.43, 1.57(each 3H,br s)
14-H	6.77(1H,d,J=10)	3.35(2H,br d,J=8)
15-H	5.72(1H,d,J=10)	5.20(1H,m)
16-CH_3	1.47(6H,s)	1.57(6H,br s)
5-OH	13.07(1H,s)	13.05(1H,s)
solvent	$(CD_3)_2CO$	$(CD_3)_2CO$

	oxydihydromorusin (XII)
6-H	6.46(1H,s)
3'-H	7.10(1H,d,J=2)
5'-H	6.87(1H,dd,J=2,7.5)
6'-H	7.54(1H,d,J=7.5)
9-H	2.98-3.28(2H,m)
10-H	2.00-2.30(2H,m)
11-CH_3	1.39(6H,s)
14-H	6.70(1H,d,J=10)
15-H	5.47(1H,d,J=10)
16-CH_3	1.39(6H,s)
solvent	pyridine-d_5

Table 4. Pmr Spectra of Prenylflavanones

	kuwanon D (XIII)	kuwanon E (XIV)
2-H	6.23(1H,dd,J=3, 13)	5.72(1H,dd,J=3, 13)
3-H	3.08(1H,dd,J=3, 17)	2.68(1H,dd,J=3, 18)
	3.47(1H,dd,J=13, 17)	3.16(1H,dd,J=13,18)
6-H	6.41(1H,d,J=2)	6.38* (1H,d,J=2)
8-H	6.49(1H,d,J=2)	6.47* (1H,d,J=2)
3'-H	6.87(1H,s)	6.52(1H,s)
6'-H	7.39(1H,s)	7.23(1H,s)
1"-H	3.02(1H,d,J=9.6)	3.23(2H,br d,J=8)
2"-H	2.52(1H,dd,J=7.5, 9.6)	5.37(1H,br t,J=8)
3"-CH_3	1.27(3H,s) or 1.33(3H,s)	1.72(3H,s)
5"-H	1.40-2.10(4H,m)	2.05(4H,br s)
6"-H		
7"-H	2.28(1H,m)	5.13(1H,br t,J=8)
8"-CH_3	0.78(3H,s)	1.58(3H,s)
	1.27(3H,s) or 1.33(3H,s)	1.63(3H,s)
5-OH	12.99(1H,s)	12.83(1H,s)
solvent	pyridine-d_5	$(CD_3)_2CO$ * pyridine-d_5

	kuwanon F (XV)
2-H	6.17(1H,dd,J=3, 13)
3-H	3.08(1H,dd,J=3, 18)
	3.42(1H,dd,J=13, 18)
6-H	6.46(1H,d,J=1.5)
8-H	6.53(1H,d,J=1.5)
3'-H	6.81(1H,s)
6'-H	7.50(1H,s)
1"-H	6.56(1H,d,J=10)
2"-H	5.53(1H,d,J=10)
3"-CH_3	1.44(3H,s)
5"-H	1.75-2.42(4H,m)
6"-H	
7"-H	5.17(1H,br t,J=7)
8"-CH_3	1.54, 1.65(each 3H,s)
5-OH	12.80(1H,s)
solvent	pyridine-d_5

Tablr 5. Pmn spectra of kuwanon G (XLIV) and H (XLV)

	kuwanon G (XLIV)	kuwanon H (XLV)
6-H	5.98(s)	5.99(s)
3'-H	6.67(d,J=2)	6.66(d,J=2)
5'-H	6.55(dd,J=2, 8)	6.58(dd,J=2, 8)
6'-H	7.29 or 7.41(d,J=8)	7.29(d,J=8)
9-Hx2	3.17(br d,J=7)	3.14(br d,J=7)
10-H	4.95-5.40(m)	4.90-5.50(m)
11-CH_3	1.48(s) 1.62(s)	1.48(s) 1.62(s)
14-H	4.30-4.70(m)	4.30-4.85(m)
15-H	4.95-5.40(m)	4.90-5.50(m)
16-CH_3	1.52(br s)	1.57(br s)
18-Hx2	1.80-2.20(m)	1.80-2.20(m)
19-H	3.30-3.90(m)	3.50-3.90(m)
20-H	4.30-4.70(m)	4.30-4.85(m)
24-H	6.03(d,J=2)	
26-H	5.93(dd,J=2, 8)	6.07(d,J=8)
27-H	7.29 or 7.41(d,J=8)	7.29(d,J=8)
30-H	6.21(d,J=2)	6.22(d,J=2)
32-H	6.08(dd,J=2, 8)	6.00(dd,J=2, 8)
33-H	6.78(d,J=8)	6.82(d,J=8)
34-Hx2		3.14(br d,J=7)
35-H		4.90-5.50(m)
36-CH_3		1.57(br s) 1.67(s)
OH	7.60-9.63(6H0	7.88(2H) 8.70-9.70(4H)
5-OH	13.19 or 13.23	13.16 or 13.58
23-OH	13.19 or 13.23	13.16 or 13.58
solvent	$(CD_3)_2CO$	$(CD_3)_2CO$

Table 6. Cmr spectra of Prenylflavonoids

carbon	morusin (VI)	compound A (VIII)	morusin hydroperoxide(XXXI)	kuwanon C (XI)	tetrahydro-kuwanon C (XIc)
2	158.6	159.7	159.8	158.9	158.2
3	120.2	117.2	117.1	119.4	121.8
4	181.8	181.7	181.7	181.8	183.6
4a	100.5	101.4	101.3	103.4	104.1
5	151.9	152.2	152.1	155.0	156.8
6	98.9	99.9	99.9	97.9	98.5
7	162.0	163.6	163.6	161.7	162.6[*1]
8	104.4	104.5	104.4	105.5	107.9[*2]
8a	160.7	161.4	161.6	160.3	162.0[*1]
9	23.7	25.5	22.7	23.5	23.6
10	121.6	90.9	86.0	121.7	38.1[*4]
11	131.3	71.9	82.9	131.2	28.3
12	25.4	25.2	25.9	25.4	22.6[*3]
13	17.3	27.6	20.3	17.3	22.6[*3]
14	114.3	115.4	115.4	21.1	20.8
15	127.6	127.6	127.6	122.1	38.9[*4]
16	78.0	78.3	78.3	130.7	28.3
17	27.7	28.1	28.1	25.4	22.8[*3]
18	27.7	28.1	28.1	17.3	22.8[*3]
1'	110.9	114.2	114.0	111.3	113.1
2'	156.7	151.1	158.2	156.5	153.9
3'	103.0	112.3	112.4	102.7	104.1
4'	161.1	162.4	162.4	161.2	160.3[*1]
5'	107.0	109.0	108.8	106.7	108.1[*2]
6'	131.3	130.7	130.8	131.2	132.1
solvent	dmso-d_6	pyridine-d_5	pyridine-d_5	dmso-d_6	pyridine-d_5

* Assignments may be reversed.

carbon		kuwanon D$^{1)}$ (XIII)	kuwanon E$^{1)}$ (XIV)
2		75.3	76.0
3		42.9	42.6
4		197.3	198.5
4a		103.1	103.3^{*1}
5		165.4	167.6
6		97.2	97.0
7		168.6	167.8
8		96.2	96.4
8a		164.8	165.0
1"		46.8	25.8
2"	3"	84.1	123.9
3"	2"	34.6	136.8
4"	5"	38.5	16.2
5"	6"	38.9	40.5
6"	7"	39.4	28.3
7"	8"	39.8	125.3
8"	4"	19.4	132.1
9"	9"	25.7	27.5
10"	10"	27.2	17.8
1'		119.4	120.8^{*2}
2'		155.2	154.1
3'		105.5	103.7^{*1}
4'		155.4	156.6
5'		115.7	117.3^{*2}
6'		128.9	128.8

1) measured in pyridine-d_5

2) measured in dmso-d_6

carbon	kuwanon G$^{2)}$ (XLIV)	kuwanon H$^{2)}$ (XLV)		
2	159.18	159.33		
3	119.69	119.80		
4	181.72	181.83		
4a	103.74	103.93		
5	155.21	155.29		
6	97.46	97.73		
7	161.34	161.61		
8	106.75	106.86		
8a	160.26	160.34		
1'	111.37	111.56		
2'	156.33	156.44		
3'	102.58	102.70		
4'	160.83	160.87		
5'	106.75	106.86		
6'	131.17	129.51		
9	23.53	23.76		
10	121.81	121.93		
11	131.17	131.25		
12	25.42	25.46		
13	17.33	17.49		
14	38.28**	39.77***		
15	123.23	123.43		
16	132.83	132.91		
17	22.45	22.57		
18	38.28**	39.20***		
19	38.28**	39.77***		
20	45.84	45.72		
21	208.11	208.41		
22	114.03	113.99		
23	164.22	162.07		
24	102.58	113.68		
25	164.22	161.61		
26	107.21	106.86		
27	130.83	131.25		
28	120.73	121.08		
29	155.79	155.90	34	21.37
30	101.97	102.70	35	122.39
31	155.79	155.90	36	130.52
32	106.75	106.86	37	25.46
33	132.36	131.25	38	17.49

* Assignments may be reversed

** measured in pyridine-d_5

*** measured in CD_3OD

Table 7. Ultraviolet Spectral Data

compound [solvent]	max Nm (log ε)	max (+ $AlCl_3$)
morusin (VI) [EtOH]	206(4.49), 220(sh 4.43), 270(4.60) 300(sh 4.00), 320(sh 3.90), 350(3.81)	279(4.63), 338(3.89), 415(3.79)
cyclomorusin (VII) [MeOH]	223(4.45), 255(4.38), 283(4.43), 383(4.19)	229(4.51), 265(4.35), 285(4.41), 379(4.24), 429(3.84)
compound A (VIII) [MeOH]	218(4.49), 234(4.49), 278(4.51), 334(4.24)	224(4.53), 260.5(4.41), 284(4.54), 360(4.33), 417(4.02)
kuwanon A (IX) [EtOH]	208(4.49), 260.5(4.26), 283(sh 4.11), 325(sh 3.93)	208(4.54), 269(4.33), 373(3.81)
kuwanon B (X) [MeOH]	234(4.49), 260(4.38), 280(sh 4.10), 330(sh 4.00)	214(4.52), 269(4.44), 376(3.94)
kuwanon C (XI) [EtOH]	210(4.63), 264.5(4.49), 315(4.06)	274.5(4.55), 335(4.02), 387(3.93)
oxydihydromorusin (XII) [MeOH]	206(4.38), 225(4.26), 242(4.26), 269.5(4.44), 300(sh 3.82), 350(sh 3.64)	206(4.42), 227(4.34), 278.5(4.47), 336(3.76), 409(3.61)
kuwanon D (XIII) [EtOH]	213(4.59), 227(sh 4.07), 290(4.30), 320(sh 3.86)	213(4.58), 220(sh 4.53), 308(4.39), 373(3.67)
kuwanon E (XIV) [EtOH]	212(4.56), 289(4.26), 320(sh 3.73)	211.5(4.55), 220(sh 4.19), 308(4.33), 374(3.57)
kuwanon F (XV) [MeOH]	225(4.49), 287.5(4.19), 325(sh 3.39)	222.5(4.56), 310(4.33), 375(3.54)
kuwanon G (XLIV) [MeOH]	212(4.64), 265(4.41), 280(sh 4.22), 315(4.13)	213(4.68), 273.5(4.46), 307(4.22), 360(3.89)
kuwanon H (XLV) [MeOH]	224(4.57), 263(4.45), 285(4.27), 325(sh 4.12)	224(4.59), 273.5(4.54), 325(4.08), 385(3.85)

REFERENCES AND FOOTNOTES

+ Dedicated to Professor Tetsuji Kametani on the retirement from the Chair of Organic Chemistry at the Pharmaceutical Institute of Tohoku University.

1a T. Tsukamoto and T. Ohtaki, Yakugaku Zasshi, 1948, 68, 287; b T. Uno, Sanshi Shikenjo Hokoku(Tokyo), 1970, 24, 437; c Y. Kondo and T. Takemoto, Chem. Pharm. Bull., 1973, 21, 2265; d H. Shibata, I. Mikoshiba, and S. Shimizu, Agr. Biol. Chem.(Tokyo), 1974, 38, 1745.

2a K. Fukutome, J. Phisiol. Soc. Japan, 1938, 3, 172; b H. Ohishi, Sanshi Shikenjo Ruiho, 1941, 59,1; c F. Suzuki and T. Sakuma, ibid., 1941, 59,9; d I. Tanemura, Folia Pharmacol. Japan, 1960, 56, 704; e Y. Yamatake , M. Shibata, and M. Nagai, Japan J. Pharmacol., 1976, 26, 461.

3 M. Katayanagi, H. Wakana, and T. Kimura, Abstracts of Papers, "The 12th Annual Meeting of the Pharmaceutical Society of Japan", 1959, p. 289

4a V.H. Deshpande, P.C. Parthasarathy, and K. Venkataraman, Tetrahedron Letters, 1968, 1715; b V.H. Deshpande, P.V. Wakharkar, and A.V. Rama Rao, Indian J. Chem., 1976, 14B, 647; c K. Venkataraman, Phytochemistry, 1972, 11, 1571.

5 T. Nomura, T. Fukai, S. Yamada, and M. Katayanagi, Chem. Pharm. Bull., 1978, 26, 1394.

6 P.C. Parthasarathy, P.V. Radhakrishnan, S.S. Rathi, and K. Venkataraman, Indian J. Chem., 1969, 7, 101.

7a B. Jackson, P.J. Owen, and F. scheinmann, J. Chem. Soc. (c), 1971, 3389; b A.V. Rama Rao, S.S. Rathi, and K. Venkataraman, Indian J. Chem., 1972, 10, 989.

8a A. Arnone, G. Cardillo, L. Merlini, and R. Mondelli, Tetrahedron Letters, 1967, 4201; b M. Shabbir, A. Zaman, L. Crombie, B. Tuck, and D.A. Whiting, J. Chem. Soc. (c), 1968, 1899.

9a V.H. Deshpande, A.V. Rama Rao, R. Srinivasan, and K. Venkataraman, Indian J. Chem., 1972, 10, 681; b A.V. Rama Rao, S.S. Rathi, and K. Venkataraman, ibid., 1972, 10, 905.

10 T. Nomura, T. Fukai, and M. Katayanagi, Chem. Pharm. Bull., 1978, 26, 1453.

11 T. Nomura, T. Fukai, S. Yamada, and M. Katayanagi, Chem. Pharm. Bull., 1978, 26, 1431.

12 C. Konno, Y. Oshima, and H. Hikino, Planta medica, 1977, 32, 118.

13 T. Nomura, T. Fukai, and M. Katayanagi, Heterocycles, 1978, 9, 745.

14 R.M. Horowitz, J. Org. Chem., 1957, 22, 1733.

15a J.M. Rao, K. Subrahmanyam, and K.V.J. Rao, Indian J. Chem., 1974, 12, 762;

b U. Claussen, F. von Spulak, and F. Korte, *Tetrahedron*, 1968, **24**, 1021;

c L. Crombie and R. Ponsford, *J. Chem. Soc. (c)*, 1971, 796;

d S.P. Kureel, R.S. Kapil, and S.P. Popli, *Tetrahedron Letters*, 1969, 3857;

e P.R. Jefferies and G.K. Worth, *Tetrahedron*, 1973, **29**, 903.

16 M.J. Begley, L. Crombie, R.W. King, D.A. Slack, and D.A. Whiting, *J. Chem. Soc. Perkin I*, 1977, 2393.

17a R. Mechoulam and Y. Gaoni, *Fortschr. Chem. Org. Naturstoffe*, 1967, **25**, 175;
b L. Crombie and R. Ponsford, *Chem. Comm.*, 1968, 894; c L. Crombie, R. Ponsford, A. Shani, B. Yagnitinsky, and R. Mechoulam, *Tetrahedron Letters*, 1968, 5771; d V.V. Kane and R.K. Razdan, *J. Am. Chem. Soc.*, 1968, **90**, 6551; e M.J. Begley, D.G. Clarke, L. Crombie, and D.A. Whiting, *Chem. Comm.*, 1970, 1547; f Y. Gaoni and R. Mechoulam, *J. Am. Chem. Soc.*, 1971, **93**, 217.

18 T. Nomura and T. Fukai, *Heterocycles*, 1978, **9**, 1295.

19a A. Ueno, M. Ichikawa, T. Miyase, S. Fukushima, Y. Saiki, and K. Morinaga, *Chem. Pharm. Bull.*, 1973, **21**, 1734; b V.H. Deshpande, A.V. Rama Rao, K. Venkataraman, and P.V. Wakharkar, *Indian, J. Chem.*, 1974, **12**, 431.

20 H. Audier, *Bull. Soc. Chim. France*, 1966, 2892.

21 T. Nomura and T. Fukai, *Heterocycles*, 1979, **12**, 943.

22 G. Cardillo, R. Cricchio, and L. Merlini, *Tetrahedron*, 1968, **24**, 4825.

23 T. Nomura, Y. Sawaura, T. Fukai, S. Yamada, and S. Tamura, *Heterocycles*, 1978, **9**, 1355.

24 R.A Finnegan, B. Gilbert, E.J. Eisenbraun, and C. Djerassi, *J. Org. Chem.*, 1960, **25**, 2169.

25a H.S. Mahal and K. Venkataraman, *J. Chem. Soc.*, 1934, 1767; b J.E. Gowan and T.S. Wheeler, *J. Chem. Soc.*, 1950, 1925; c S. Matsuura, *Yakugaku Zasshi*, 1956, **77**, 328; d K.G. Dave, R. Mani, and K. Venkataraman, *J. Sci. Industr. Res.*, 1961, **20B**, 112; e K. Nakazawa and T. Miyata, "The Synthetic Method of Organic Compounds" ed. by the Society of Synthetic Organic Chemistry Japan, Giho-do, Tokyo, 1966, **13**, 111.

26 T. Nomura and T. Fukai, *Heterocycles*, 1979, **12**, 1289.

27 V.M. Chari, S. Ahmad, and B-G. Österdahl, *Z. Naturforsch*, 1978, **33b**, 1547.

28 E. Wenkert and H.E. Gottlieb, *Phytochemistry*, 1977, **16**, 1811.

29a H. Wagner, V.M. Chari, and J. Sonnenbichler, *Tetrahedron Letters*, 1976, 1799; b V.M. Chari, M. Ilyas, H. Wagner, A. Neszmélyi, F. Chen, L. Chen, Y. Lin, and Y. Lin, *Phytochemistry*, 1977, **16**, 1273.

30 T.R. Seshadri, "The Chemistry of Flavonoid Compounds", ed. by T.A. Geissman, Pergamon Press, Oxford, 1962, p. 188.

31 T. Nomura, T. Fukai, S. Yamada, and M. Katayanagi, *Chem. Pharm. Bull.*, 1977, **25**, 1155.

32 P.D. Bartlett and R.R. Hiatt, *J. Am. Chem. Soc.*, 1958, **80**, 1398.

33 L. Crombie, D.E. Games, N.J. Haskins, and G.F. Reed, *J. Chem. Soc. Perkin I,* 1972, 2241.

34 T. Nomura and T. Fukai, *Heterocycles*, 1978, **9**, 635.

35a T. Matsuura and H. Matsushima, *Tetrahedron*, 1968, **24**, 6615; b T. Matsuura, T. Takemoto, and R. Nakashima, *Tetrahedron*, 1973, **29**, 3337; c R. Nakashima, K. Okamoto, and T. Matsuura, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 3353.

36 T. Nomura, T. Fukai, and M. Amagai, *Heterocycles*, 1979, **12**, 1329.

37 T. Matsuura and I. Saito, "Photochemistry of Heterocyclic Compounds", ed. by O. Buchardt, John Wiley & Sons, New York, 1976, p. 436.

38 C.D. Snyder and H. Rapoport, *J. Am. Chem. Soc.*, 1969, **91**, 731.

39 J.G. Calvent and J.N. Pitts, Jr. "Photochemistry", John Wiley & Sons, New York, 1967, p. 740.

40a T. Nomura and T. Fukai, *Heterocycles*, 1977, **8**, 443; b T. Nomura, T. Fukai, and J. Matsumoto, *J. Heterocyclic Chem.*, 1980, **17**, 641.

41 L.F. Fieser and M. Fieser, "Steroids", Maruzen Asian ed., Reinhold Publishing Corporation, New York, 1959, p. 96.

42a T. Kametani and K. Fukumoto, "Phenol Oxidation", Gihodo, Tokyo, 1970; b T. Matsuura and A. Nishinaga, in "Chemistry of Free Radicals", H. Sakurai and T. Tokumaru, Eds., Nanko-do, Tokyo, 1967, p. 161.

43 T. Nomura, T. Fukai, and M. Katayanagi, *Heterocycles*, 1977, **6**, 1847.

44 K. Maruyama, "Free Radicals", Kagakudojin, Kyoto, 1972, p. 59.

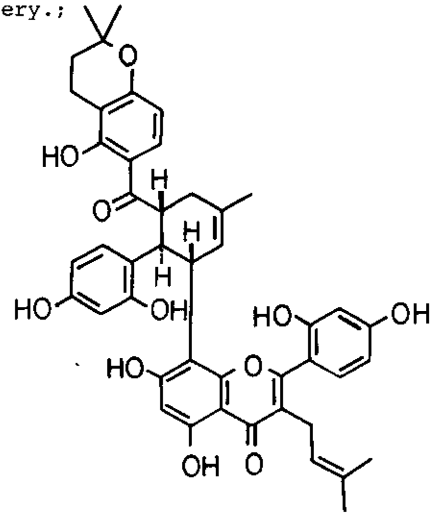
45a E. Müller and K. Ley, *Chem. Ber.*, 1954, **87**, 922; b T. Matsuura, K. Omura, and R. Nakashima, *Bull. Chem. Soc. Jpn.*, 1965, **38**, 1358.

46a V.I. Stenberg, R. D. Olson, C.T. Wang, and N. Kulevsky, *J. Org. Chem.*, 1967, **32**, 3227; b V.I. Stenberg, C.T. Wang, and N. Kulevsky, *J. Org. Chem.*, 1970, **35**, 1774; c H. Tsubomura, T. Yagishita, and H. Toi, *Bull. Chem. Soc. Jpn.*, 1973, **46**, 3051; d K. Maeda, A. Nakane, and H. Tsubomura, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 2448; e H. Tsubomura and H. Hori, *Yuki Gosei Kagaku Kyokai Shi*, 1968, **26**, 929; f K.S. Wei and A.H. Adelman, *Tetrahedron Letters*, 1969, 3297.

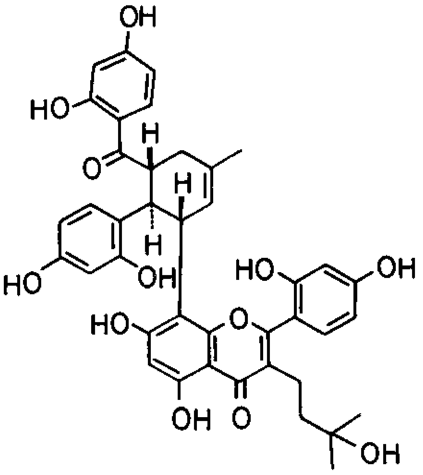
47 T. Nomura, T. Fukai, Y. Momose, and T. Narita, Abstracts of Papers, "23nd

Symposium the Chemistry of Natural Products", Nagoya, October 25, 1980, p. 552.

48a Proff. H. Hikino, Tohoku University, and his co-workers isolated the hypotensive compounds, moracenin A,B,C, and D, form the root bark of mulberry tree and determined the structures as structure XLVII,[48c] XLVI,[48b] XLVIII,[48d] and IL,[48e] respectivery.;



XLVI II



IL

b Y. Oshima, C. Konno, H. Hikino, and K. Matsushita, *Tetrahedron Letters*, 1980, 3381; c *idem*, *Heterocycles*, 1980, 14, 1287; d *idem*, *ibid.*, 1980, 14, 1461; e idem, Abstructs of Papers, "23nd Symposium the Chemistry of Natural Products", Nagoya, October 25, 1980, p. 544.

49a Dr. M. Takasugi, Hokkaido University, and his co-workers isolated two antifungal compounds, albanin F and G from mulberry. Albanin F identified with kuwanon G and albanin G is with kuwanon H by tlc and comparing with the pmr spectra (Dr. M. Takasugi, a private letter to T.N., June, 23, 1980). Hokkaido University group determined the structures of albanin F and albanin G as structure XLII[49b] and XLIII,[49b] respectively(Dr. M. Takasugi, a private letter to T.N., September, 3, 1980).; b M. Takasugi, S. Nagao, S. Ishikawa, T. Masamune, A. Shirata, and K. Takahashi, Abstracts of Papers, "23nd Symposium the Chemistry of Natural Products", Nagoya, October 25, 1980, p. 560.

50 T. Nomura, T. Fukai, Y. Momose, and R. Takeda, Abstracts of Papers, "Third Symposium on the Development and Application of Naturally Occuring Drug Materials", Tokyo, August 1, 1980, p. 13.

51 T. Nomura and T. Fukai, *Chem. Pharm. Bull.*, 1980, **28**, 2548.

52 T. Saitoh and S. Shibata, *Chem. Pharm. Bull.*, 1969, **17**, 729.

53 T. Nomura, T. Fukai, and T. Narita, Heterocycles, in press.

54 The compound (LIV) was identified with authentic sample obtained from 2'-hydroxy-3'-γ,γ-dimethylallyl-4'-methoxyacetophenone and 2,4-dimethoxybenzaldehyde.

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