THE SYNTHESIS OF TETRAHYDROKUWANON C TETRAMETHYL ETHER+

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The synthesis of tetrahydrokuwanon C tetramethyl ether (XIV) was achieved by Baker-Venkataraman method from 2-hydroxy-3-isopentyl-4,6-dimethoxyisoheptophenone (X) derived from phloroglucinol. From this result, the structures of morusin, cyclomorusin, compound A, oxydihydromorusin (morusinol), and kuwanon C were confirmed as I, II, III, IV, and V, respectively.

In the previous papers[1,2] the authors have reported the structure determination of a series of prenylflavones such as morusin (I), cyclomorusin (II), compound A (III), oxydihydromorusin (morusinol[3], IV), and kuwanon C (V) obtained from the root bark of Morus alba L. These five flavones were correlated to each other as shown in Chart 1. These structures were confirmed in this work by synthesizing tetrahydrokuwanon C tetramethyl ether (XIV) from phloroglucinol via the route as shown in Chart 2. The Friedel-Crafts reaction of phloroglucinol and isovaleryl chloride gave phloroisovalerophenone[4] (VI),

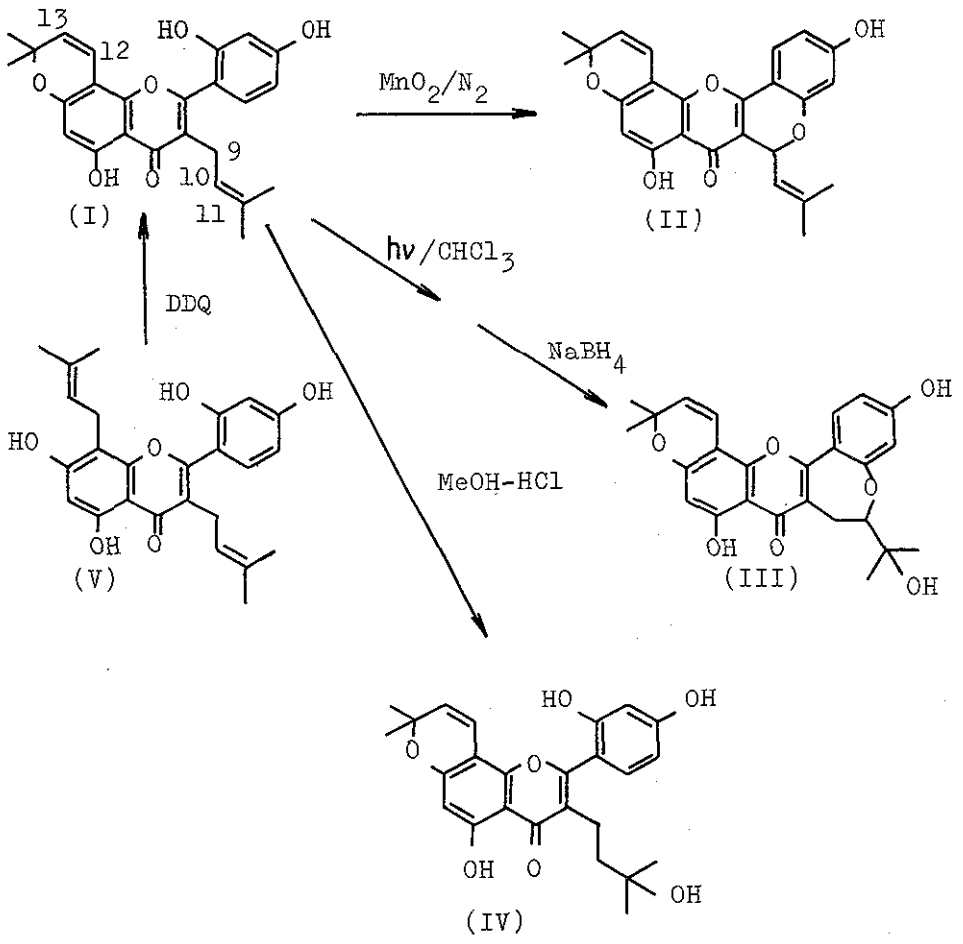

Chart 1

mp 146°, M^+ 210, and it formed a dimethyl ether[5] (VII), mp 51°, M^+ 238, $C_{13}H_{18}O_4$, on treatment with dimethyl sulfate and potassium carbonate in boiling acetone. The dimethyl ether (VII) was positive to the Gibbs test and showed the characteristic signal of hydrogen bonded hydroxyl group in its nmr spectrum at δ 14.10. The dimethyl ether (VII) was reduced with zinc amalgam and hydrochloric acid to give 2-isopentyl-3,5-dimethoxyphenol[5] (VIII), mp 55°, M^+ 224, $C_{13}H_{20}O_3$, which showed the signals of the benzylic protons at δ 2.55(2H, t,

J = 7 Hz) and of the proton of the hydroxyl group at δ 4.88. Condensation of VIII with 5-methylhexanoic acid (IX) in presence of boron trifluoride-etherate gave 2-hydroxy-3-isopentyl-4,6-dimethoxyisoheptophenone (X), mp 95°, M^+ 336, $C_{20}H_{32}O_4$, in about 65 % yield. The structural elucidation of X was accomplished on the basis of the spectral data and color reaction as follows : The compound (X) 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 nmr spectrum of X, a sharp singlet signal was observed at δ 13.97, which disappeared on addition of D_2O indicating the presence of a chelated hydroxyl group. The nmr spectrum also indicated the presence of a isopentyl and a 5-methylhexanoyl group. [δ 0.85, 0.89 (each 6H, d, J = 7 Hz, C_{11} - CH_3 × 2 and C_{14} - CH_3 × 2), δ 1.10-1.85 (8H, m, C_9 - H × 2, C_{10} - H × 2, C_{11} - H, C_{13} - H × 2, and C_{14} - H), δ 2.53(2H, t, J = 7.5 Hz, C_{12} - H × 2), δ 2.93(2H, t, J = 7.5 Hz, C_8 - H × 2)]. From these results, the possibility of the formula, 2,6-dimethoxy-3-isopentyl-4-hydroxyisoheptophenone, for this condensation product was completely excluded.

Treatment of X with 2,4-dimethoxybenzoyl chloride (XI) and potassium carbonate in boiling acetone gave the ester (XII). Without purification of XII, the reaction products were hydrolyzed with 20 % methanolic potassium hydroxide, and then were treated with the mixture of acetic acid and sulfuric acid.[6] After purification of the reaction products by preparative TLC and vacuum distillation, 3,8-diisopentyl-5,7,2',4'-tetramethoxyflavone (XIV) was obtained in 42 % yield from X. The structure of this flavone (XIV) was supported by the following data. The compound (XIV) was obtained as colorless needles, mp 110°,

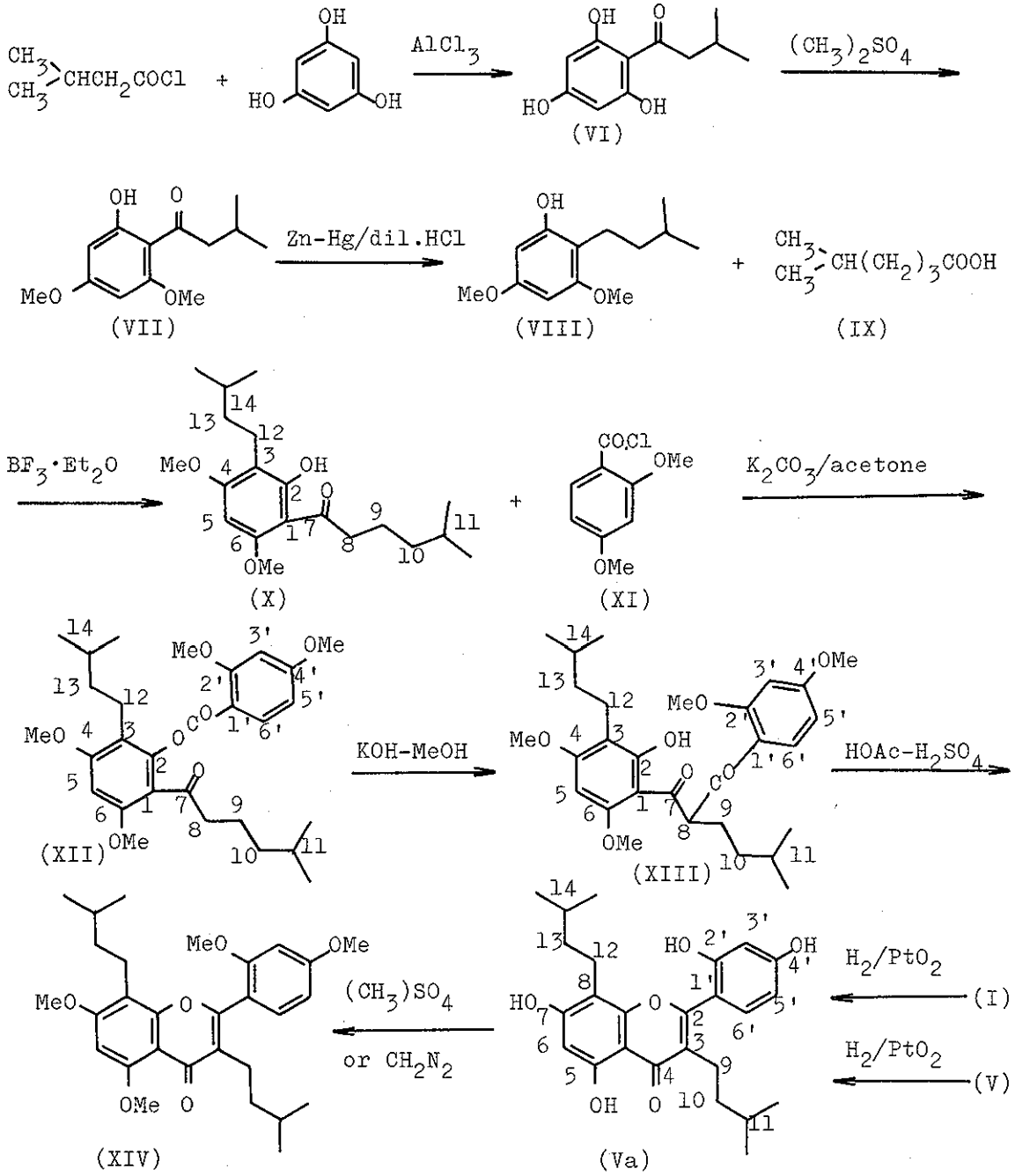
AlCl3
(CH3)2SO4
(VI)
Zn-Hg/dil.HCl
(VII)
(VIII)
(IX)
BF3·Et2O
(X)
(XI)
K2CO3/acetone
KOH-MeOH
(XII)
(XIII)
HOAc-H2SO4
(CH3)SO4
or CH2N2
(XIV)
(Va)
H2/PtO2
(I)
H2/PtO2
(V)

Chart 2

M^+ 482, $C_{29}H_{38}O_6$, which was positive to the color reaction test characteristic of flavone derivative. The nmr spectrum of XIV indicated the presence of two isopentyl group [δ 0.75, 0.81(each 6H, d, J = 7 Hz, C_{11} - CH_3 × 2 and C_{14} - CH_3 × 2), δ 1.10-1.60(6H, m, C_{10} - H × 2, C_{11} - H, C_{13} - H × 2, C_{14} - H), 2.20(2H, t, J = 7.5 Hz, C_9 - H × 2), 2.55(2H, t, J = 7.5 Hz, C_{12} - H × 2)]. From the following results, it is supported that the reaction from X to XIV proceeds through the intermediate formation of a diketone (XIII) : The reaction products of X and XI were purified by preparative TLC to give the ester (XII). Although XII was not obtained as crystal, it showed only one spot on TLC and the mass spectrum showed the molecular ion peak at m/e 500. The ester (XII) revealed the absorption band for ester carbonyl in the ir spectrum at 1745 cm^{-1}. The ester (XII) was treated with 10 % methanolic potassium hydroxide, and the reaction products were purified by preparative TLC to give the diketone (XIII) which showed only one spot on TLC. The diketone (XIII) was obtained as paste, M^+ 500, which gave an violet color with methanolic ferric chloride and was positive to the Gibbs test. The ir spectrum of XIII showed the absorption for a carbonyl group at 1670 cm^{-1}, and the nmr spectrum showed the characteristic methine proton signal at δ 5.07(1H, t, J = 6 Hz, C_8 - H) and the proton signal of hydrogen bonded hydroxyl group at δ 13.80(1H, s, C_2 - OH). The mass spectrum of XIII showed the fragment ion at m/e 251(M^+ - $C_{15}H_{21}O_3$)[7]. From these results, the diketone is represented by the formula XIII. The diketone (XIII) was cyclized to the flavone (XIV) with acetic acid and sulfuric acid.

On the other hand, the hydrogenation of morusin (I) or kuwanon C (V) with Adams catalyst yielded tetrahydrokuwanon C (Va), followed by

methylation with dimethyl sulfate and potassium carbonate in boiling acetone or with ethereal diazomethane to give tetrahydrokuwanon C tetramethyl ether (XIV), mp 110°, which proved to be identical with the flavone, which had been derived from phloroglucinol, by mixed melting point and comparison of ir spectrum. From these results, the structures of morusin, cyclomorusin, compound A, oxydihydromorusin (morusinol), and kuwanon C were determined as the formulae I, II, III, IV, and V, respectively.

EXPERIMENTAL

All melting points were uncorrected. The nmr spectra were measured with tetramethylsilane as the internal reference. Abbreviations : s=singlet, d=doublet, t=triplet, m=multiplet, dd=double doublet, br= broad. The following instruments were used for measurements of the physical data : melting point; Mitamura Micromelting Point Apparatus (a hot-stage type). uv spectra; Hitachi 340 Recording Spectrophotometer. ir spectra; Hitachi 295 Infrared Spectrophotometer and Hitachi IR Spectrophotometer EPI-G3. nmr spectra; JEAL JNM-4H-100 NMR Spectrometer. ms; JEAL JMS ISG 2 Mass Spectrometer. For thin-layer chromatography (TLC) and preparative TLC, Wakogel B5-FM was used, and for column chromatography, Wakogel C-200.

Phloroisovalerophenone (VI)[4] —— A mixture of anhydrous phloroglucinol (10 g) and powdered aluminum chloride (20 g) was dissolved in nitrobenzene (150 ml), and isovaleryl chloride (7.9 g, synthesized from isovaleric acid) was then added to the solution at 0°. Five days later the reaction mixture was poured into an ice water, and extracted with ether. The extracts were treated as usual. The solvent was evaporated and nitrobenzene was removed by the steam distillation. On cooling, the aqueous solution deposited the ketone (VI). On repeated recrystallization from water, this compound (VI) formed the pale yellow prisms (7.0 g), mp 146°, ir [ν_{max}^{KBr}: 3300, 2950,

1650, 1605 cm^{-1}]. uv [λ_{max}^{EtOH} nm(log ε): 286(4.24)]. ms m/e; 210(M^+), 195, 153, 126. nmr (δ in CD_3OD)[0.94(6H, d, J=6.5Hz), 2.22(1H, m), 2.91(2H, d, J=7Hz), 5.80(2H, s)].

2-Hydroxy-4,6-dimethoxyisovalerophenone (VII)[5] ——— To a solution of VI (2.1 g) in dry acetone (25 ml) was added 2.0 ml of dimethyl sulfate and 3.0 g of anhydrous potassium carbonate. The mixture was heated under reflux for 8 hr, then filtered, and the solvent was evaporated. The resulting oil was chromatographed on silica gel (50 g), and the elution with benzene gave the crystalline solid. Recrystallization from ethanol-H_2O gave 2.0 g of the colorless needles (VII), mp 51°, blue-violet color with Gibbs test. Anal. Calcd. for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61. Found: C, 65.29; H, 7.70. ir [ν_{max}^{KBr}: 3100, 2950, 1630, 1590 cm^{-1}]. uv[λ_{max}^{EtOH} nm(log ε): 284(4.16)]. ms m/e: 238(M^+), 181, 154. nmr(δ in $CDCl_3$)[0.95(6H, d, J=7Hz), 2.21 (1H, m), 2.86(2H, d, J=6.5Hz), 3.82(3H, s), 3.87(3H,s), 5.91(1H, d, J=2Hz), 6.07(1H, d, J=2Hz), 14.10(1H,s)].

2-Isoamyl-3,5-dimethoxyphenol (VIII)[5] ——— The compound (VII) (2.0 g) in 20 ml of methanol was added to amalgamated zinc (prepared by shaking for 30 min 50 g of powdered zinc with a solution containing of 40 ml of water, 15 ml of concd. hydrochloric acid, and 4.0 g of mercuric chloride, followed by decantation and washing). 6N-Hydrochloric acid (40 ml) was added and the mixture was heated at 80° for 7 hr (at 5 hr additional 10 ml of 6N-hydrochloric acid was added). The reaction mixture was extracted with ether and the extracts were subjected to the usual work-up and evaporated. The resulting oil was chromatographed on silica gel (60 g) and eluted with benzene. Recrystallization from n-hexane afforded 1.4 g of colorless needles (VIII), mp 55°. Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.58; H, 9.03. ir[ν_{max}^{KBr}: 3370, 2980, 1640, 1615 cm^{-1}]. ms m/e: 224(M^+), 168, 167, 154, 137, 109. nmr(δ in $CDCl_3$)[0.95(6H, d, J=6.5Hz), 1.20-1.60(3H, m), 2.55(2H, t, J=7Hz), 3.78(3H, s), 3.80 (3H, s), 4.88(1H, s), 6.02(1H, d, J=2Hz), 6.08(1H, d, J=2Hz)].

2-Hydroxy-3-isopentyl-4,6-dimethoxyisoheptophenone (X) ———

A mixture of VIII (3.0 g), 5-methylhexanoic acid (IX, 2.3 ml) and boron trifluoride-etherate (19 ml) was kept at room temperature for 24 hr, and then at 100° for 3 hr. The reaction mixture was poured into an ice water, and extracted with ether. The extracts were subjected to the usual work-up and evaporated. The resulting oil was chromatographed on silica gel (60 g) and eluted with benzene. Recrystallization from n-hexane afforded 3.0 g of pale yellow needles (X), mp 95°, blue-violet color with Gibbs test. Anal. Calcd. for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.59; H, 9.44. ir[ν_{max}^{KBr}: 2950, 1630, 1595 cm^{-1}]. uv[λ_{max}^{EtOH} nm(log ε): 288(4.10)]. ms m/e: 336(M^+), 318, 279, 261, 251. nmr(δ in $CDCl_3$)[0.85, 0.89(each 6H, d, J=7Hz, C_{11}-CH_3×2 and C_{14}-CH_3×2), 1.10-1.85(8H, m, C_9-H×2, C_{10}-H×2, C_{11}-H, C_{13}-H×2, and C_{14}-H), 2.53(2H, t, J=7.5Hz, C_{12}-H×2), 2.93(2H, t, J=7.5Hz, C_8-H×2), 3.86, 3.88(each 3H, s, OCH_3), 5.92(1H, s, C_5-H), 13.97(1H, s, C_2-OH, disappeared on addition of D_2O)].

3,8-Diisopentyl-5,7,2',4'-tetramethoxyflavone (XIV) ——— A mixture of X (500 mg), 2,4-dimethoxybenzoyl chloride (XI, 2.2 g), anhydrous potassium carbonate (20 g), and dry acetone (80 ml) was refluxed for 20 hr. After filtration acetone was removed under reduced pressure, and the residue was dissolved in 50 ml of 20 % methanolic potassium hydroxide. This mixture was heated for 30 min under reflux. After methanol was evaporated under reduced pressure, the residue was extracted with ether. The extracts were subjected to the usual work-up and evaporated. The residue was dissolved in acetic acid (8 ml) and sulfuric acid (0.8 ml), and 30 min after the solution was poured into excess of water under cooling. The solution was made alkaline with 5 % potassium hydroxide, and extracted with ether. The extracts were treated as usual and evaporated. The reaction products were purified by preparative TLC (chloroform) to give amorphous powder (XIV), which was distilled under reduced pressure (bp 230-240°, 0.03 mm Hg). Crystallization of the distillate from ether-n-hexane afforded 300 mg of colorless needles (XIV), mp 110°, wine color with Mg-HCl test, and reddish brown color with Zn-HCl test. Anal. Calcd. for $C_{29}H_{38}O_6$: C, 72.17; H, 7.94. Found: C, 71.85; H, 8.00. ir [ν_{max}^{KBr}: 2950, 1650,

1640, 1600 cm^{-1}]. uv[λ_{max}^{EtOH} nm(log ε): 229(4.68), 257(4.65), 291(4.24), 318(4.38)]. ms m/e: 482(M^+), 467, 451, 439, 426, 425, 395. nmr(δ in CCl_4)[0.75, 0.81(each 6H, d, J=7Hz, C_{11}-CH_3×2 and C_{14}-CH_3×2), 1.10-1.60(6H, m, C_{10}-H×2, C_{11}-H, C_{13}-H×2, and C_{14}-H), 2.20(2H, t, J=7.5Hz, C_9-H×2), 2.55(2H, t, J=7.5Hz, C_{12}-H×2), 3.78, 3.83(each 3H, s, OCH_3), 3.88(6H, s, OCH_3×2), 6.27(1H, s, C_6-H), 6.45(2H, m, C_3, and $C_{5'}$-H), 7.20(1H, d, J=9Hz, $C_{6'}$-H)].

To isolate the intermediates of these reactions, the following experiments were carried out.

The isolation of 2-(2',4'-dimethoxybenzoxy)-3-isopentyl-4,6-dimethoxyisoheptophenone (XII): The reaction mixture of X, XI, anhydrous potassium carbonate, and dry acetone was evaporated under reduced pressure, and the residue was extracted with ether. The extracts were treated as usual and evaporated. The residue was purified by preparative TLC (chloroform) to give XII which showed only one spot on TLC. ir[ν_{max}^{neat}: 2950, 1745, 1715, 1605 cm^{-1}]. ms m/e: 500(M^+), 335, 165. nmr(δ in CCl_4)[0.82(12H, d, J=6.5Hz, C_{11}-CH_3×2 and C_{14}-CH_3×2), 1.00-1.70(8H, m, C_9-H×2, C_{10}-H×2, C_{11}-H, C_{13}-H×2, and C_{14}-H), 2.40(2H, br t, J=7Hz, C_{12}-H×2), 2.65(2H, t, J=7Hz, C_8-H×2), 3.75(3H, s, OCH_3), 3.79(9H, s, OCH_3×3), 6.29(1H, s, C_5-H), 6.40-6.50 (2H, m, C_3, and $C_{5'}$-H), 7.88(1H, d, J=8Hz, $C_{6'}$-H)].

The isolation of 2-hydroxy-3-isopentyl-4,6-dimethoxy-α-(2',4'-dimethoxybenzoyl)isoheptophenone (XIII): Thirty mg of XII was dissolved in 10 % methanolic potassium hydroxide (50 ml), and the mixture was heated for 30 min under reflux. After methanol was evaporated under reduced pressure, the residue was extracted with ether, and the extracts were treated as usual and evaporated. The reaction products were purified by preparative TLC (chloroform) to give XIII which showed only one spot on TLC. The compound (XIII) was positive to Gibbs test. ir[ν_{max}^{neat}: 2960, 2870, 1670, 1600 cm^{-1}]. ms m/e: 500(M^+), 483, 469, 335, 227, 251, 224, 165. nmr(δ in CCl_4)[0.88, 0.90(each 6H, d, J=6Hz, C_{11}-CH_3×2 and C_{14}-CH_3×2), 1.05-1.95(8H, m, C_9-H×2, C_{10}-H×2, C_{11}-H, C_{13}-H×2, and C_{14}-H), 2.46(2H, t, J=7Hz, C_{12}-H×2), 3.58, 3.64, 3.80, 3.81(each 3H, s, OCH_3), 5.07(1H, t, J=6Hz, C_8-H), 5.79(1H, s, C_5-H), 6.31(1H, d, J=2Hz, $C_{3'}$-H), 6.45(1H, dd, J=2 and 9Hz, $C_{5'}$-H), 7.88(1H, d, J=9Hz, $C_{6'}$-H), 13.80(1H, s, C_2-OH)].

The cyclization of 2-hydroxy-3-isopentyl-4,6-dimethoxy-α-(2',4'-dimethoxybenzoyl)isoheptophenone (XIII) with acids : Forty mg of XIII was dissolved in acetic acid (6 ml) and sulfuric acid (0.7 ml), and 30 min after the solution was poured into excess of water. The solution was made alkaline with 5 % methanolic potassium hydroxide and extracted with ether. The extracts were treated as usual and evaporated. The reaction products were purified by preparative TLC (chloroform:ether=4:1) to give XIV (30 mg, mp 110°).

Tetrahydrokuwanon C (Va) ——— a) From morusin (I): Morusin (70 mg) in 2-ethoxyethanol (20 ml) was hydrogenated over PtO_2 (70 mg) as the catalyst, 7 hr after 70 mg of PtO_2 was added and the hydrogenation was continued for 10 hr. After removal of the catalyst, the solvent was evaporated under reduced pressure, and the residue was purified by preparative TLC (chloroform:ether=4:1) to give Va and 10, 11, 12, 13-tetrahydromorusin (XVI).[1,8] Crystallization from methanol-H_2O afforded yellow prisms, mp 234-235° (Va, 7.6 mg) and yellow prisms, mp 244-246°, (XVI, 27.4 mg). Va: Anal. Calcd. for $C_{25}H_{30}O_6 \cdot \frac{1}{2}H_2O$: C, 68.97; H, 7.13. Found: C, 68.79; H, 7.21. ir[ν_{max}^{KBr}: 3460, 3280, 2960, 2870, 1665, 1625 cm^{-1}]. ms m/e: 426(M^+), 409, 383, 369, 314, 165. uv[λ_{max}^{EtOH} nm (log ε): 261(4.43), 303(3.94), 332(3.90)]. nmr(δ in acetone-d_6)[0.76, 0.84(each 6H, d, J=7Hz, C_{11}-CH_3×2 and C_{14}-CH_3×2), 1.15-1.60(6H, m, C_{10}-H×2, C_{11}-H, C_{13}-H×2, and C_{14}-H), 2.40(2H, t, J=7.5Hz, C_9-H×2), 2.65(2H, t, J=7.5Hz, C_{12}-H×2), 6.26(1H, s, C_6-H), 6.50(2H, m, C_3, and C_5,-H), 7.22(1H, d, J=9Hz, C_6,-H), 13.04(1H, s, C_5-OH, disappeared on addition of D_2O)].[9] XVI: ms m/e: 424(M^+), 409, 407, 381, 368, 367, 353, 165.

b) From kuwanon C (V) : Kuwanon C (30 mg) in 2-ethoxyethanol (14 ml) was hydrogenated over PtO_2 (30 mg) as a catalyst, 8 hr after 30 mg of PtO_2 was added and the hydrogenation was continued for 8 hr. After removal of the catalyst, the solvent was evaporated under reduced pressure, and the residue was purified by preparative TLC (chloroform: ether=4:1) to give Va. Crystallization from methanol-H_2O afforded yellow prisms, mp 234-235° (Va, 7.6 mg). The compound (Va) obtained here was identified (mixed mp) with tetrahydrokuwanon C (Va) which was obtained from I.

Tetrahydrokuwanon C Tetramethyl Ether (XIV) ——— a) With dimethyl sulfate : A mixture of Va (12 mg), dimethyl sulfate (1 ml), anhydrous potassium hydroxide (2 g), and acetone (20 ml) was refluxed for 5 hr, and the reaction mixture was worked up as usual, and the products were purified by preparative TLC (chloroform) to give XIV. Crystallization from n-hexane-ether afforded colorless needles, mp 110° (XIV, 8 mg). This compound (XIV) obtained here was identified (ir spectrum and mixed mp) with XIV which was derived from phloroglucinol.
b) With ethereal diazomethane : To a solution of Va (20 mg) in methanol (5 ml) was added excess ethereal diazomethane, and the mixture was allowed to stand at 5° for 40 hr, and treated as usual. The products were then purified by preparative TLC, and crystallized from ether-n-hexane to give colorless needles, mp 110° (XIV, 6 mg).

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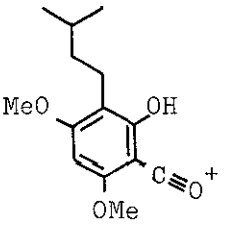
7 The fragment ion (m/e 251) is supposed to be the formula (XV).



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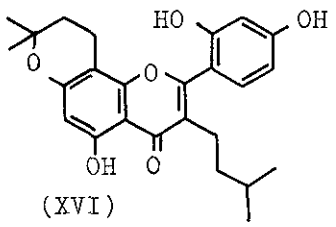

(XVI)

9 The nmr spectrum of Va was measured on Varian FT-80 NMR Spectrometer.

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