The Stereochemistry of Fukiic Acid and Its Correlation with Piscidic Acid

Teruhiko YOSHIHARA, Akitami ICHIHARA, Hanako NUIBE, Sadao SAKAMURA,
Mieko SUGITA,* Shoji IMAMOTO* and Siro SENOH**

Department of Agricultural Chemistry, Faculty of Agriculture,
Hokkaido University, Sapporo

*The Institute of Food Chemistry, Osaka

**Central Research Institute, Suntory Ltd., Osaka

Received August 3, 1973

The stereochemistry of fukiic acid (I) was elucidated. The relative configuration was determined to be *erythro* by IR spectrum and the evidence of acetone formation. The absolute configuration of fukiic acid was assigned as *S*-configuration at C-2 and *R*-configuration at C-3, by Horeau's method and the identification of ozonolysis product to be hibiscus acid (10 a).

In previous papers,^{1,2)} we have reported the isolation and structural determination of fukiic acid (1) which was obtained from *Petasites japonicus*. In preliminary communication³⁾ we have demonstrated that fukiic acid has the same stereochemical relationship with that of piscidic acid⁴⁾ (3) from *Piscidia erythrina*. *Erythro* configuration for fukiic acid (1) was further confirmed by the synthesis of a fukiic acid derivative.⁵⁾ We describe in this report the details of the stereochemical studies of fukiic acid (1).

Since fukiic acid (1) contains two asymmetric centers in its molecule, four stereoisomers consisting of two *threo* and *erythro* compounds are possible. In order to decide the relative configuration at C₂ and C₃ in fukiic acid, it is necessary to convert fukiic acid to cyclic lactone in which the C₂-C₃ bond is rigidly fixed from free rotation. Therefore O,O'-dimethylfukiic acid dimethyl ester (2) was treated with sodium borohydride to yield a lactone. Since the lactone showed a peak at 1782 cm⁻¹ in the IR spectrum and signals at δ 4.00~4.32 due to -O-CH₂- and -CH- as

multiplets in the PMR spectrum, clearly lactone 6a or 6b was produced. For deciding correct structure the product was acetylated

with acetic anhydride in pyridine to yield a diacetate C₁₇H₂₀O₈, mp 112~113°C. Since in the PMR spectrum the diacetate exhibited

a signal at δ 5.48 assignable to the -CH which constituted X part of ABX system in PMR spectrum, the lactone should have the structure

FIG. 1.

FIG. 2.

FIG. 3.

FIG. 4.

depicted as 7. The infrared spectrum of the lactone (6a) in dilute carbon tetrachloride (3.1×10^{-4} mole) showed an intramolecular hydrogen bonded absorption band at 3575 cm^{-1} which afforded the evidence for hydrogen bonded structure 8a or 8b. If the lactone has a structure 8c or 8d, and absorption band due to a free hydroxyl group in higher frequency will be appeared. The result means that the lactone has a *cis* diol system. Further evidence for *cis* configuration was obtained by the formation of its acetonide. Thus the lactone was treated with acetone in the presence of *p*-toluenesulfonic acid to give an acetonide whose spectroscopic data and elemental analysis are precisely compatible with the structure 9.

FIG. 6.

FIG. 5.

The absolute configuration at C-2 in fukiic acid was established by the method developed by Horeau^{6,7)} for determining the configuration of asymmetric center containing a secondary hydroxyl group. Thus excess racemic α -phenylbutyric anhydride (3.47×10^{-4} mole) was treated with the lactone (6a, 1.87×10^{-4} mole) in pyridine. After hydrolysis, resultant product which exhibits corresponding signals to α -phenyl butyrate of the lactone in the PMR spectrum was obtained from neutral fraction. On the other hand, from acidic fraction, an acid which was identical with authentic α -phenyl butyric acid in the IR spectrum was obtained, and exhibited dextrorotatory, (+), then the absolute configuration at C-2 of the lactone is represented by formula A in which L refers to the sterically

large $\text{C}-\overset{\text{O}}{\underset{\text{C}}{\text{C}}}-$ group at C-3 and M to the sterically small $-\text{CH}_3-$ group at C-1. Based on the Horeau's procedure, C-2 asymmetric center of fukiic acid (1) must have the absolute configuration S. When acyclic compound (2) was used for Horeau's method, recovered α -phenylbutyric acid exhibited slight levorotatory, -1.1° . This result indicates that the configuration at C_2 is represented by formula B assuming the order of substituent group in

bulkiness as $-\text{COOCH}_3 > -\overset{\text{COOCH}_3}{\underset{\text{C}}{\text{C}}}-\text{OH}$ which

TABLE I. PMR, ORD AND CD DATA OF THE OZONOLYSIS PRODUCTS⁸⁾

	Solvent	C α		PMR		C β		C γ		ORD $\lambda_{\text{MeOH}} [\phi]$	CD $\lambda_{\text{MeOH}} [\theta]$
		H _A	H _B	H _B	OH	COOCH ₃	H	COOCH ₃			
Hibiscus acid dimethyl ester (10a)	d ₆ -DMSO	2.67 (d) $J=17.5$	3.27 (d)	7.83 (s) sharp	3.82 (s)	5.40 (s)	3.72 (s)	230 nm +10,887	214 nm +14,525		
Ozonolysis	from O,O'-dimethylfukiic acid dimethyl ester (2)	2.70 (d) $J=17$	3.23 (d)	5.54 (s) sharp	3.83 (s)	5.32 (s)	3.73 (s)	232 nm +11,100	215 nm +13,900		
	Product	2.70 (d) $J=17$	3.23 (d)	5.54 (s) sharp	3.83 (s)	5.32 (s)	3.73 (s)	232 nm +10,800	215 nm +12,500		
Garcinia acid dimethyl ester (10c)	d ₆ -DMSO	2.67 (d) $J=17.5$	3.16 (d)	7.0 (s) broad	3.76 (s)	5.03 (s)	3.70 (s)	228 nm + 4885	214 nm + 9504		

might be resulted from solvation of methyl ester group. This provides the same results as that of the cyclic compound 6a described above.

Further support for the absolute configuration was obtained by ozonolysis⁸⁾ of O,O'-dimethylfukiic acid dimethyl ester (2) to one of the known compounds, hibiscus acid dimethyl ester (10a), its enantiomer (10b), garcinia acid dimethyl ester (10c) and its enantiomer (10a) whose stereochemistries had been unequivocally established.⁹⁾ Thus ozonolysis of the ester (2) afforded a syrup whose PMR, ORD and CD data are quite compatible with those of hibiscus acid dimethyl ester (10a) (Table I). Since absolute configuration of C_β and C_γ in hibiscus acid are known as R and S respectively, it is concluded that fukiic acid has S-configuration at C-2 and R-configuration at C-3. This is the same result with that of Horeau's procedure. Based on all the evidences presented above, we propose stereostructure I for fukiic acid. And as hibiscus acid dimethyl ester (10a) was obtained from O-methylpiscidic acid dimethyl ester (5) in a similar manner, the stereochemistry for piscidic acid should be depicted as 3.

Finally, in order to confirm the identity of the stereochemistry of fukiic acid and that of piscidic acid, piscidic acid dimethyl ester (4) was *ortho*-hydroxylated through photo-oxygenation¹⁰⁾ and methylated. The resultant product was entirely identical with O,O'-dimethylfukiic acid dimethyl ester (2) in PMR, IR, mass spectrum, TLC and optical rotation. Therefore, according to the previous result, it is concluded that both compounds have the same absolute configuration.

EXPERIMENTAL

The mp were determined on a Yanaco digital micromelting point apparatus model MP-3D. PMR spectra were taken with a Hitachi H-60 (60 MHz) and Japan Electron Optics, JNM PS-100 (100 MHz) instruments using TMS as internal reference. The mass spectra were recorded on Hitachi RMS-4 mass spectrometer and the IR spectra on a Hitachi EPI-S2 infrared spectrometer. CD and ORD were measured

with JASCO ORD-UV-5. Optical rotations were determined with Hitachi POB polarimeter. *ortho*-Hydroxylation was carried out with Ushio ULI-5BQ.

Preparation of 2,3,4-trihydroxy-2-(3',4'-dimethoxybenzyl)-butyric acid γ -lactone (6a)

To a solution of 480 mg (1.46 mm) of the dimethyl ester (2) in 25 ml of ethanol, 83 mg (2.19 mm) of sodium borohydride was added and stirred for 2 hr at room temperature. After acidification with 1N-hydrochloric acid, the reaction mixture was concentrated *in vacuo* and the residue was extracted several times with chloroform. The combined extracts were concentrated and the concentrate was fractionated on a silica gel column (5 g) using chloroform as solvent. Each fraction was monitored by UV spectrum and fractions having absorption at 280 nm were collected and evaporated *in vacuo* to give 110 mg of the lactone (6a) in 28.2% yield. IR $\nu_{\text{max}}^{\text{CDCl}_3}$ cm⁻¹: 1782. PMR $\delta_{\text{TMS}}^{\text{dg-acetone}}$ (60 MHz): 2.95 (2H, s, ϕ -CH₂-), 3.76 (6H, s, 2CH₃O-), 4.0~4.32 (3H, m, $-\dot{\text{C}}\text{H}$ and $-\text{O}-\text{CH}_2-$), 6.82 (2H, s, ArH), 6.92 (1H, s, ArH). The IR spectrum of the lactone under high dilute solution (3.1×10^{-4} mole) in dried carbon tetrachloride using 50 mm quartz cell showed single peak at 3575 cm⁻¹ corresponding to intramolecular hydrogen bonded hydroxyl group.

Acetylation of the lactone (6a)

A mixture of 67 mg of the lactone (6a) in 1 ml of acetic anhydride and 1 ml of pyridine was allowed to stand for 3 days. The reaction mixture was concentrated *in vacuo* to give a residue which was recrystallized from chloroform-cyclohexane to yield 34.1 mg of a crystalline diacetate (7), mp 112~113°C. Anal. Found: C, 57.76; H, 5.60. Calcd. for C₁₇H₂₀O₈: C, 57.95; H, 5.68%. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 1785, 1755, 1240. PMR $\delta_{\text{TMS}}^{\text{CDCl}_3}$ (60 MHz): 2.06 (3H, s, CH₃CO-), 2.15 (3H, s, CH₃CO-), 3.28 (2H, s, Ar-CH₂-), 3.86 (6H, s, 2CH₃O-), 3.70~4.25 (2H, m, O-CH₂-), 5.48 (1H, dd, $-\dot{\text{C}}\text{H}$, J_{AX}=4.8, J_{BX}=7.8 Hz), 6.82 (3H, s, ArH).

The acetone (9) of the lactone (6a)

A solution of 42.7 mg of the lactone (6a) and 128 mg of *p*-toluenesulfonic acid in 1 ml of dry acetone was allowed to stand for 60 hr at room temperature. To the reaction mixture 25 ml of chloroform and 25 ml of 1% sodium bicarbonate solution was added. Organic layer was washed three times with water and dried over anhydrous sodium sulfate. The solution was evaporated *in vacuo* to yield a residue which was recrystallized from ethanol-petroleum ether to give 30.0 mg of the acetone (9), mp 135~136°C. Anal. Found: C, 62.38; H, 6.46. Calcd. for C₁₆H₂₀O₈: C, 62.34, H, 6.49%. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹ 1776, 1380.

PMR $\delta_{\text{TMS}}^{\text{CDCl}_3}$ (100 MHz): 1.27 (3H, s, $\text{CH}_3\text{-C}$), 1.44 (3H, s, $\text{CH}_3\text{-C}$), 3.05 and 3.25 (2H, ABq, $J=14$ Hz, $\text{Ar-CH}_2\text{-}$), 3.54 (1H, dd, A part of ABX, $J_{\text{AB}}=12$ and $J_{\text{AX}}=4$ Hz, $-\text{O-CH}_2\text{-}$), 3.87 (6H, s, $2\text{CH}_3\text{O-}$), 4.20 (1H, d, B part of ABX, $J_{\text{AB}}=12$ Hz, $-\text{O-CH}_2\text{-}$), 4.55

(1H, d, X part of ABX, $J_{\text{AX}}=4$ Hz, $-\overset{\text{OH}}{\text{CH}}\text{-}$), 6.76 (3H, s, ArH). MS m/e : 308 (M^+), 293 ($\text{M}^+-\overset{\text{MeO}}{\text{C}_6\text{H}_4}\text{-CH}_2\text{-}$), 157 ($\text{M}^+-\text{CH}_2\text{Ar}$), 151 ($\text{MeO-}\overset{\text{MeO}}{\text{C}_6\text{H}_4}\text{-CH}_2\text{-}$, base peak), 59 ($\text{CH}_3\text{-C}\equiv\text{CH}$), 43 ($\text{CH}_3\text{-C}\equiv\text{O}$).

Determination of absolute configuration

a) By Horeau's method. A solution of 50.0 mg (0.187 mm) of the lactone (6a) and 115.8 mg (0.374 mm) of freshly prepared α -phenylbutyric anhydride in 4 ml of pyridine was allowed to stand for 24 hr at room temperature under dark. To the reaction mixture, 20 ml of water was added and stand for additional 2.5 hr. After addition of 100 ml of water the mixture was extracted three times with 25 ml of chloroform and the combined extracts were washed with 100 ml of water and three times with 50 ml of 5% sodium bicarbonate and finally with 75 ml of water. The extracts were dried over anhydrous sodium sulfate and evaporated *in vacuo* to give 64.0 mg of esterified compound as neutral fraction. PMR $\delta_{\text{TMS}}^{\text{d}_6\text{-acetone}}$ (60 MHz): signals due to lactone; 3.0 (2H, s, $\text{Ar-CH}_2\text{-}$), 3.76 (6H, s, $2\text{CH}_3\text{O-}$), 3.90~4.4 (2H, m, $\text{O-CH}_2\text{-}$), 5.1~5.4 (1H, m, $-\overset{\text{OH}}{\text{CH}}\text{-}$), 6.80 (2H, s, ArH), 6.87 (1H, s, ArH). Signals due to α -phenylbutyric acid; 0.84 (3H, t, $J=7.2$ Hz, $\text{CH}_3\text{-}$), 1.7~2.6 (overlapped with signals of acetone, $-\text{CH}_2\text{-}$), 3.60 (1H, t, $J=7.8$ Hz, $-\overset{\text{OH}}{\text{CH}}\text{-}$), 7.3 (5H, s, ArH). The alkaline layer was extracted with 150 ml of chloroform and acidified with 2 N-hydrochloric acid. The acidic solution was extracted three times with 200 ml of ether. The combined extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure to give 79.4 mg of optically active α -phenylbutyric acid. The IR and PMR spectra were identical with those of authentic sample. $[\alpha]_{\text{D}}^{18} +7.97^\circ$ ($c=3.97$, benzene) optical yield 25%.

b) By ozonolysis of the dimethyl ester (2) to hibiscus acid dimethyl ester (10a). To a solution of 22 mg of the ester (2) in 20 ml of distilled water, ozone was bubbled for 3 hr at 0°C . The reaction mixture was heated with 2 ml of 30% aqueous hydrogen peroxide solution on water bath for 30 min to decompose the ozonide. After concentration of the mixture under reduced pressure, 30 ml of methanol saturated with dry hydrogen chloride was added and the solution was refluxed gently for 3 hr. The reaction mixture was evaporated to dryness and the residue was separated

on a preparative TLC using silica gel. Ether extraction from the fraction at about R_f 0.4 on the TLC gave 3.1 mg of hibiscus acid dimethyl ester (10a). PMR, ORD and CD data of the ozonolysis product are summarized on Table I.

Ozonolysis of *O*-methyl piscidic acid dimethyl ester (5)

To a solution of 92.9 mg of the ester (5) in 25 ml of distilled water, ozone was bubbled for 10 hr at 0°C . The reaction mixture was heated with 3 ml of 30% aqueous hydrogen peroxide solution for 30 min at 100°C . After concentration of the mixture, the same treatment described above gave 15 mg of oil whose PMR, ORD and CD data are summarized on Table I.

ortho-Hydroxylation of piscidic acid dimethyl ester (4)

After nitrogen was introduced for 30 min into the aqueous solution (17 ml) of piscidic acid dimethyl ester (4) (250 mg) obtained from *Narcissus poeticus*¹¹ and 30% aqueous hydrogen peroxide solution (2 ml), the mixture was irradiated with low-pressure mercury lamp (2537 Å) at room temperature for 2 hr. After concentrating to about 1 ml, the reaction mixture was separated by preparative paper chromatography using *n*-butanol-acetic acid-water (4:1:5, v/v). The main band (R_f value at about 0.8) which is colored with phenol reagent¹²) was scissored, extracted with water (300 ml) and the extracts were evaporated to dryness. A solution of the phenol compound in a small amount of acetone was treated three times with about 0.3 M diazomethane (20 ml). The methylated mixture was passed over a silica gel column (10 g) eluting with 70% chloroform in cyclohexane. Monitoring with UV spectrophotometer fractions which have absorption band at 280 nm, the major peak (175~250 ml) were collected and evaporated *in vacuo*. The residue was crystallized from chloroform-cyclohexane. Yield 21 mg, mp 116.0°C (lit.,²) $117\sim118^\circ\text{C}$). Anal. Calcd. for $\text{C}_{15}\text{H}_{20}\text{O}_8$: C, 54.87; H, 6.14. Found: C, 54.90; H, 6.13%. $[\alpha]_{\text{D}}^{24.5} +48.2$ ($c=0.975$, EtOH) (*O,O'*-dimethylfukiic acid dimethyl ester; $[\alpha]_{\text{D}}^{25} +50.2^\circ$ ($c=1$, EtOH)). MS m/e : 328 (M^+), 151 (base peak,

$\text{MeO-}\overset{\text{MeO}}{\text{C}_6\text{H}_4}\text{-CH}_2\text{-}$). PMR $\delta_{\text{max}}^{\text{CDCl}_3}$ (100 MHz): 3.04 and 3.32 (2H, ABq, $J=13$ Hz, $\text{Ar-CH}_2\text{-}$), 2.6~3.4 (2H, br, $-\text{OH}$), 3.76 (3H, s, $-\text{OCH}_3$), 3.86 (3H, s, $-\text{OCH}_3$), 4.55 (1H, s, $-\overset{\text{OH}}{\text{CH}}\text{-}$), 6.6~6.9 (3H, m, ArH). TLC: benzene-acetone (8:2, v/v), R_f 0.17; ethyl acetate-cyclohexane (1:1, v/v), R_f 0.15.

REFERENCES

- 1) S. Sakamura, T. Yoshihara and K. Toyoda, *Agr. Biol. Chem.*, **33**, 1795 (1969).
- 2) *Idem, ibid.*, **37**, 1915, (1973).

- 3) T. Yoshihara, A. Ichihara, S. Sakamura, M. Sugita, S. Imamoto and S. Senoh, *Tetrahedron Letters*, **1971**, 3809.
 - 4) W. Bridge, F. Coleman and A. Robertson, *J. Chem. Soc.*, **1948**, 257.
 - 5) T. Yoshihara, A. Ichihara and S. Sakamura, *Agr. Biol. Chem.*, **35**, 1822 (1971).
 - 6) A. Horeau, *Tetrahedron Letters*, **1961**, 506.
 - 7) *Idem, ibid.*, **1962**, 965.
 - 8) S. Senoh, Y. Maeno, S. Imamoto, A. Komamine, S. Hattori, K. Yamashita and M. Matsui, *Bull. Chem. Soc. Japan*, **40**, 379 (1967).
 - 9) P. M. Boll, E. Sørensen and E. Balieu, *Acta Chemica Scand.*, **23**, 286 (1969).
 - 10) K. Omura and T. Matsuura, *Tetrahedron*, **2**, 3475 (1968).
 - 11) R. R. Smeby, V. Zbinovsky, R. H. Burris and F. M. Strong, *J. Amer. Chem. Soc.*, **76**, 612 (1954).
 - 12) O. Folin and V. Ciocalteu, *J. Biol. Chem.*, **7**, 627 (1927).
-