CHEMISTRY LETTERS, pp.1-4, 1972. Published by the Chemical Society of Japan

THE SYNTHESIS AND CONFIGURATION OF FUKIIC ACID DERIVATIVES

Takashi MATSUMOTO, Kazuo HIDAKA, Teruko NAKAYAMA, and Kenji FUKUI
Department of Chemistry, Faculty of Science, Hiroshima University
Higashi-sendamachi, Hiroshima

Fukiic acid derivatives have been synthesized from 3,4-dimethoxyphenylpyruvic acid by a stereospecific method. The synthetic methyl (+)-erythro-2,3-dihydroxy-4-(3,4-dimethoxyphenyl)-3-methoxycarbonylbutyrate was shown to be identical with natural O,O′-dimethylfukiic acid dimethyl ester by a direct comparison.

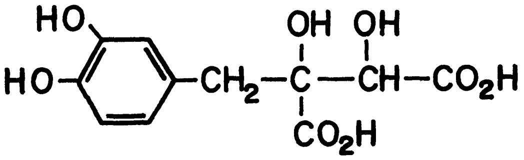
Recently a new polyphenol, fukinolic acid, was isolated from *Petasites japonicus* by Sakamura et al.[1] They also have reported that the alkaline hydrolysis of fukinolic acid gave caffeic acid and a new acid, named fukiic acid, in a molar ratio 1:1. On the basis of analytical and spectroscopic studies of its derivatives the structure of fukiic acid was proposed to be 2,3-dihydroxy-4-(3,4-dihydroxyphenyl)-3-carboxybutyric acid (I). Two racemic modifications (threo and erythro) are possible for I. However, since the stereochemistry of fukiic acid has not been reported, the present authors attempted a total synthesis of fukiic acid derivatives to confirm the proposed structure and to elucidate the stereochemistry of fukiic acid.

In this communication we wish to report on a stereospecific synthesis of fukiic acid derivatives and on their stereochemistry. 3,4-Dimethoxyphenylpyruvic acid (II) was methylated with diazomethane to the corresponding methyl ester (III), mp 99-102°C.[2] The Wittig reaction[3] with carbomethoxymethylenetriphenylphosphorane afforded a 96% yield of a mixture of geometric isomers, which were then successfully separated by means of column chromatography on silica gel into two crystalline esters in a 1:3 ratio. Since the chemical shifts of the olefinic protons in the above minor (mp 49-50°C) and major (mp 56.5-57°C) esters were observed respectively at δ ca. 6.8 ppm and at δ 5.67 ppm, the structures of the minor and major esters were assigned to be 1-(3,4-dimethoxybenzyl)fumaric acid dimethyl ester (IVa) and

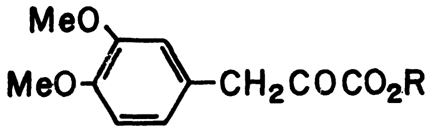
1-(3,4-dimethoxybenzyl)maleic acid dimethyl ester (IVb) respectively. These assignments were further supported by the chemical shifts of the methylene protons in IVa and IVb. That is, IVa showed the signal of the methylene protons at δ 4.12 ppm which suggests the presence of a cis methoxycarbonyl group relative to the methylene protons, because IVb showed the corresponding signal at δ 3.61 ppm. The cis-hydroxylation of IVa and IVb in methanol with an aqueous solution of potassium permanganate and magnesium sulfate at - 20°C gave methyl (±)-threo-2,3-dihydroxy-4-(3,4-dimethoxyphenyl)-3-methoxycarbonylbutyrate (Va), mp 93-94°C, and its (±)-erythro-isomer (Vb), mp 142°C, respectively. The dimethyl esters, (±)-Va and (±)-Vb, were then hydrolyzed with aqueous potassium hydroxide to the corresponding dicarboxylic acid derivatives, (±)-VIa, mp 188-190°C, and (±)-VIb, mp 179-180.5°C, which were methylated back into (±)-Va and (±)-Vb with diazomethane. This proved that there was no configurational change during the hydrolyses of (±)-Va and (±)-Vb. The NMR spectra of (±)-Vb in $CDCl_3$ and (±)-VIb in $(CD_3)_2CO$ showed signals due to the methylene protons at δ 3.05 and 3.27 ppm, and at δ 3.06 and 3.26 ppm respectively as well-defined AB-type quartets; while those of (±)-Va in $CDCl_3$ and (±)-VIa in $(CD_3)_2CO$ showed the corresponding signals at δ 3.07 ppm as a singlet and at δ 3.16 ppm as a slightly separated doublet respectively. In the NMR spectrum of natural fukiic acid monomethyl ester in $(CD_3)_2CO$ Sakamura et al.[1] had reported that the signal of the methylene protons was observed at δ 2.94 and 3.14 ppm as a AB-type quartet. From the similarity of these NMR spectra in the synthetic and natural compounds, it seemed that fukiic acid has an erythro configuration. To obtain further confirmation by a direct comparison of the optically-active synthetic compound with the corresponding natural sample, the resolution of the synthetic racemate was carried out as follows. Since an attempt on the resolution of (±)-VIb was not encouraging, it was converted to the corresponding monomethyl ester, (±)-VIIb (mp 185-186°C), by the treatment with methanol containing a small amount of concentrated hydrochloric acid. The (±)-VIIb acid in methanol was successfully resolved by means of brucine and one of the diastereomeric salt (mp 185-186°C dec.) was decomposed with dilute hydrochloric acid to give (+)-VIIb, mp 138-139°C, $[\alpha]_D$ + 40.8° (methanol). The mother liquor, after the separation of the above brucine salt, was also treated with dilute hydrochloric acid to give (-)-VIIb, mp 138-139°C, $[\alpha]_D$ - 38.0° (methanol). The alkaline hydrolyses of (+)-VIIb and (-)-VIIb gave (+)-VIb, mp 104-106°C, $[\alpha]_D$ + 40.3° (methanol) and (-)-VIb, mp 104-106°C, $[\alpha]_D$

- 40.5° (methanol), respectively. The methylation of (+)-VIb or (+)-VIIb with diazomethane gave (+)-Vb, mp 116-117°C, $[\alpha]_D$ + 40.5° (methanol), which was shown to be identical with natural O,O′-dimethylfukiic acid dimethyl ester by a mixed-melting-point determination and by comparisons of their IR and NMR spectra. The acids, (-)-VIb and (-)-VIIb, were also methylated to (-)-Vb, mp 116-117°C, $[\alpha]_D$ - 39.7° (methanol). (±)-VIa was also converted to the corresponding monomethyl ester, (±)-VIIa, mp 159-160°C.

From the present study it is evident that natural fukiic acid has an erythro configuration.[4)]

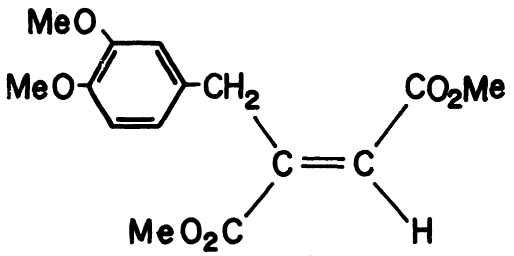


I

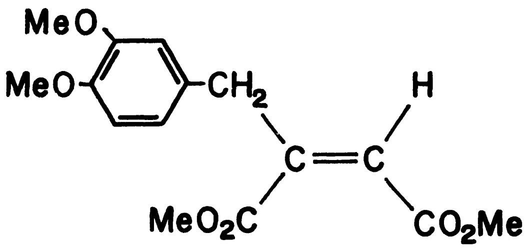


II R=H

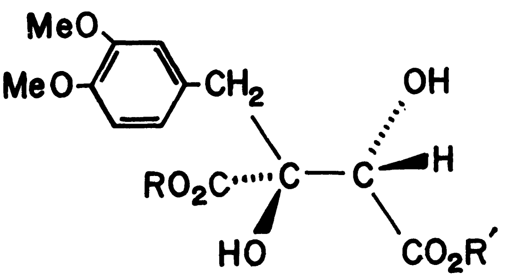
III R=Me

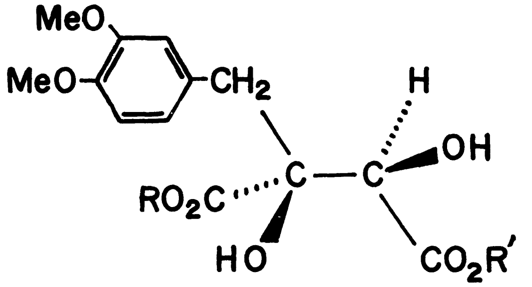


IVa



IVb





Va	R=R′=Me	Vb
VIa	R=R′=H	VIb
VIIa	R=H, R′=Me or R=Me, R′=H	VIIb

Acknowledgment. The authors are grateful to Professor S. Sakamura, Department of Agricultural Chemistry, Faculty of Agriculture, Hokkaido University, for his permission to publish this work and for the generous supply of a sample and copies of IR and NMR spectra of natural O,O′-dimethylfukiic acid dimethyl ester. Thanks are also due to Assistant Professor S. Yasuda, Department of Chemistry, Faculty of General Education of this University, for the measurements of the optical rotation.

REFERENCES

1 S. Sakamura, T. Yoshihara, and K. Toyoda, Agr. Biol. Chem. (Japan), 33, 1795 (1969).

2 Satisfactory elemental analyses and spectroscopic data were obtained for all new compounds for which m. p. data are reported.

3 A. Maercker, "Organic Reactions," Vol. 14, Wiley, New York (1965), p. 270.

4 In a recent private communication from Professor S. Sakamura, he states that he and his co-workers have also been reached to the same conclusion by a different synthesis of (±)-O,O′-dimethylfukiic acid dimethyl ester and they also have assigned absolute configuration of fukiic acid; the detail of their work was submitted to Tetrahedron Letters and Agr. Biol. Chem. (Japan).

(Received October 1, 1971)