Studies on Kojic Acid Derivatives : The Acylation of Kojic Acid

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Kojic acid, 5-hydroxy-2-(hydroxymethyl)-γ-pyrone, is a crystalline substance which can be produced in good yield by the action of a variety of microorganisms in a wide range of carbohydrate or other carbon sources. The acid was isolated in 1907 by Saito[1] from steamed rice on which Aspergillus oryzae had grown, and the structure was defined in 1924[2] by Yabuta, as shown in Fig. 1.

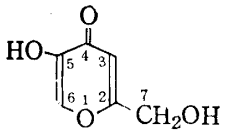


Fig. 1. Structure of Kojic acid

In our laboratory, studies on the metabolism of kojic acid by microorganisms have been made[3,4,5,6]. In connection with these studies our attention was turned to the research of derivatives of kojic acid and other γ-pyrone compounds.

Furthermore, kojic acid may serve as the starting material for the synthesis of many substances which have been known of their biological importance. Also the studies on the biological activity of the derivatives may have a stimulated interest.

Practically all the known derivatives of kojic acid were formed by reactions involving the two hydroxyl groups, by nuclear substitutions at position 6, or by the replacement of the ring oxygen atom with the nitrogen of ammonia or amines to give γ-pyridones.

Recently, Kotani[7] and Thomas[8] found that kojic acid reacts with hydrazinehydrate to pyrazol and pyridazine derivatives.

In the present paper authors describe the experimental results of the acylation of kojic acid with several saturated fatty acids, i.e. acetic, propionic, butyric, caproic, caprylic and capric acid, and discuss the chemical structures of the products.

Results and Discussion

The previously reported acylation of kojic acid are presented in Fig. 2, the acetyl and benzoyl derivatives were obtained by Yabuta[2,9], Wood[10,11,12], Brown[13], Hurd and Sims[14] and Beélik[15].

* This paper was already read at the meeting of Agricultural Chemical Society of Japan, Kansai branch in Osaka, December 16th, in 1961.

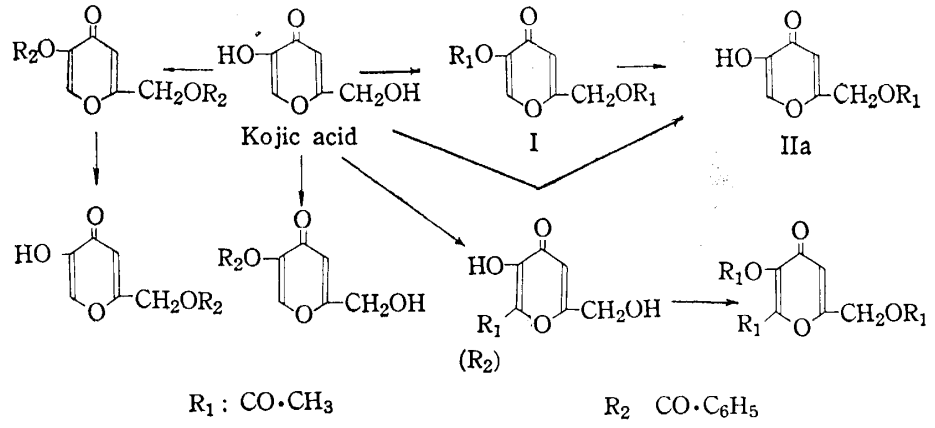


Fig. 2. Acylation of Kojic acid

In this experiment, syntheses of fatty acid esters of kojic acid were attempted by modifying the previous methods shown in Fig. 2.

Monoacyl esters (IIa, IIb, IIc, IId, IIe, IIf) were obtained in good yield, when kojic acid and fatty acid were heated with zinc chloride at 130–140°C. (see Fig. 3)

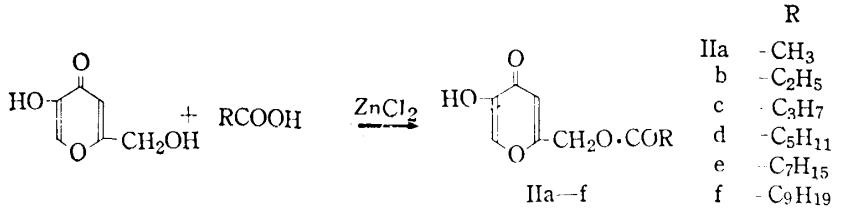


Fig. 3. Acylation with fatty acid

All the products obtained were colorless crystalline, which were positive for the ferric chloride test. Their U. V. absorption spectra are similar to each other whose λ_{max} are at 217 and 270 $m\mu$, respectively, as shown in Fig. 4. Also I.R. spectra are

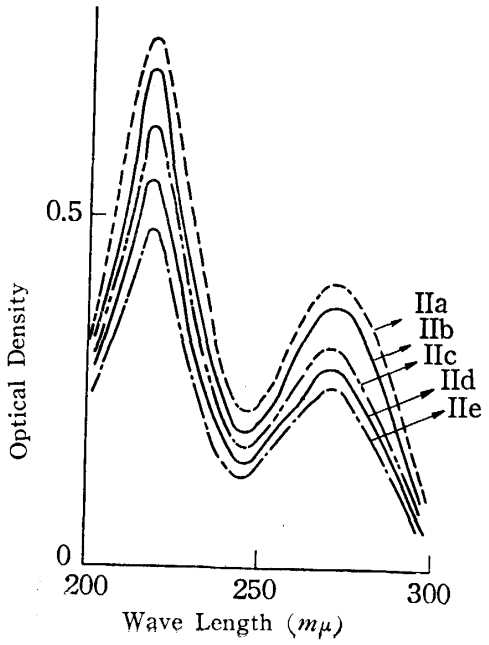
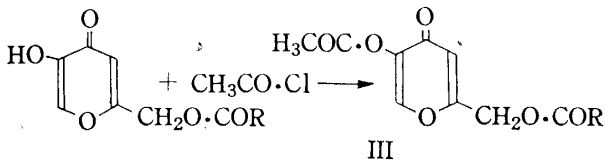


Fig. 4. U. V. Spectra of Monoacyl esters (IIa–e).



III

IIIa : R CH_3

IIIb : R CH_2CH_3

Fig. 5. Acetylation of Monoacyl esters

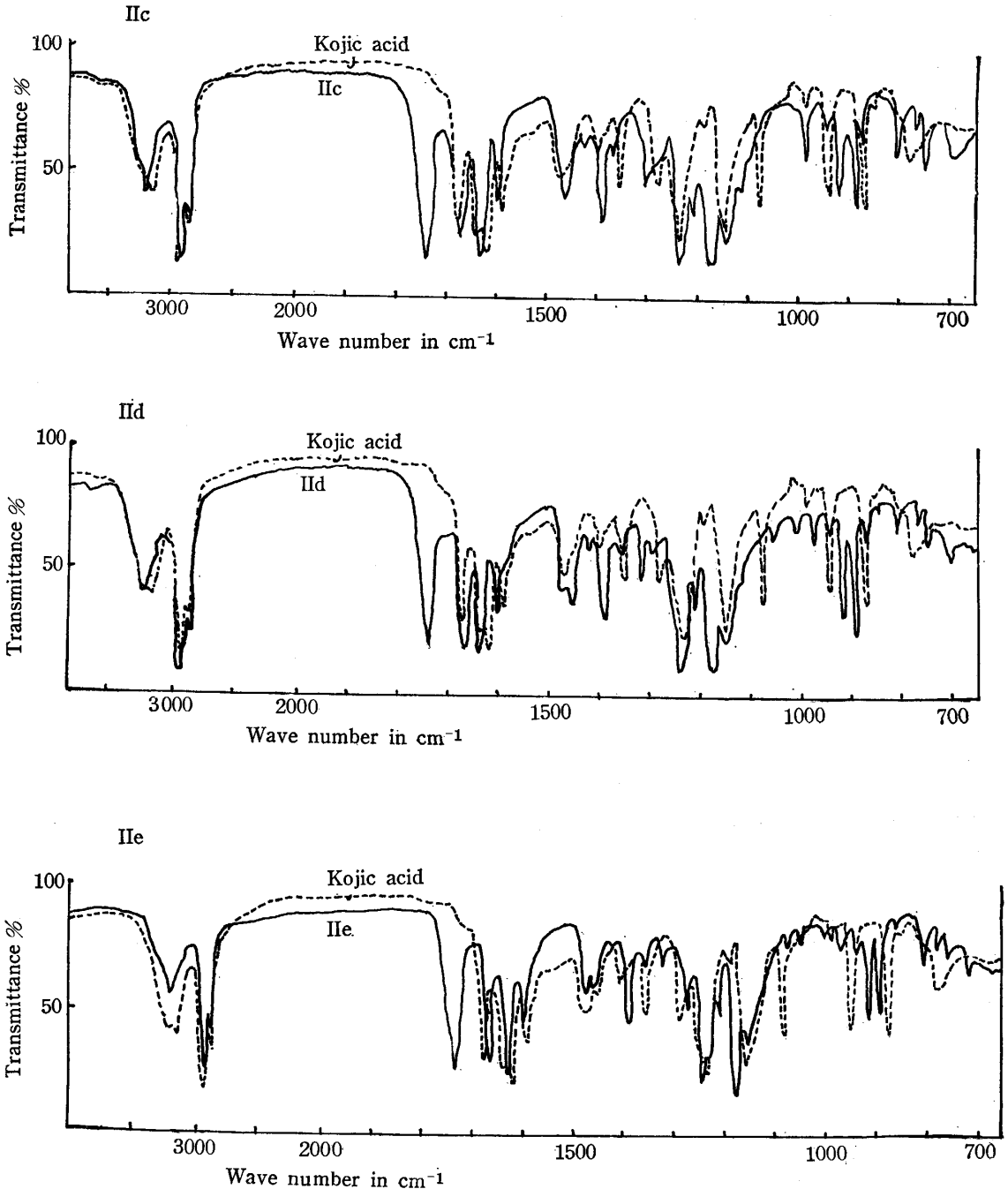


Fig. 6. Infrared spectra of IIc, IId, IIe,

shown in Fig. 6. The strong absorption bands which correspond to the primary alcohol group in kojic acid (at 1075, 1350 cm^{-1}) were not seen of these products. Whereas new intensive absorption bands of fatty acid esters were observed at 1175, 1735 cm^{-1}, respectively. Physical properties and analytical data for these compounds are given in Table 1. The analytical data agreed with Calcd. values.

Table 1. Acyl derivatives of Kojic acid.

	Acyl group	M.P. °C	Formula	Analyses %	
				Calcd.	Found
(IIa)	Acetyl	135 -135.5	$C_8H_8O_5$	C 52.23	C 51.99
				H 4.38	C 4.48
(IIb)	Propionyl	83 - 84	$C_9H_{10}O_5$	C 54.54	C 54.90
				H 5.09	H 5.12
(IIc)	Butyryl	63 - 64	$C_{10}H_{12}O_5$	C 56.60	C 56.92
				H 5.70	H 5.78
(IId)	Hexanoyl	66.5- 67	$C_{12}H_{16}O_5$	C 60.00	C 60.23
				H 6.71	H 6.80
(IIe)	Octanoyl	74.5- 75	$C_{14}H_{20}O_5$	C 62.67	C 62.85
				H 7.51	H 7.51
(IIf)	Decanoyl	83.5- 84.5	$C_{16}H_{24}O_5$	C 64.84	C 64.86
				H 8.16	H 8.16

Therefore, it was assumed that fatty acids reacted with hydroxymethyl group of kojic acid.

In order to determine whether Fries rearrangement occured, further acetylation of the compounds (IIa, IIb) were carried out with acetyl chloride. (see Fig. 5)

The acetylated products (IIIa, IIIb) were negative for the ferric chloride test. Compound (IIIa) was found to be identical with diacetyl kojic acid (I) by measuring melting point of the mixture and comparing I.R. spectra and analytical data. (see Table 2, Fig. 7)

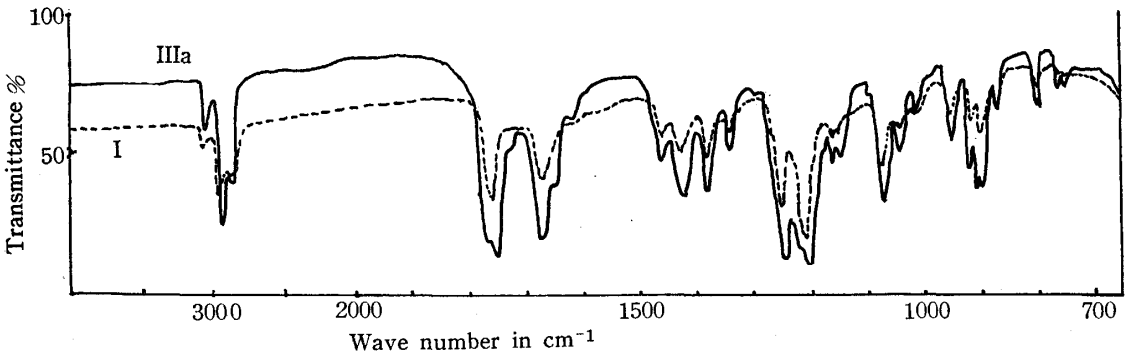


Fig. 7. Infrared spectra of (I and IIIa)

Table 2. Acetyl derivatives of Compounds (IIa, IIb).

Derivatives	M. P. °C	Formula	Analyses %	
			Calcd.	Found
IIIa	102	$C_{10}H_{10}O_6$	C 53.10 H 4.46	C 52.78 H 4.37
IIIb	57 - 58	$C_{11}H_{12}O_6$	C 55.00 H 5.04	C 55.24 H 5.23

Furthermore, compound (IIa) was brominated by Yabuta's method[16]. The product (IV) (m.p. 128°C) gave a positive ferric chloride test. It may be presumed that the hydrogen atom at 6 position in pyrone ring was substituted with bromine.

Typical U. V. spectra of kojic acid, its acyl and other derivatives are shown in Fig. 8. The differences among these absorption spectra may be attributed to the posi-

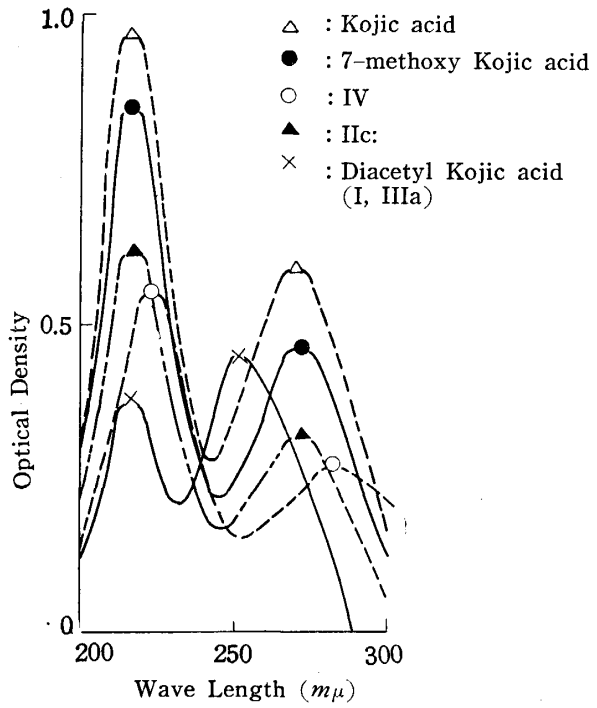


Fig. 8. U. V. spectra of Kojic acid, its acyl and other derivatives.

tion of the substituted groups in pyrone ring.

As a result of the above experiments, the compounds (IIa-f) may be concluded to be 7-acyl kojic acids. Also, it may be expected that the diacyl derivative is produced from the reaction of these compounds with fatty acid chloride.

Experimental

Acylation of kojic acid with saturated fatty acid.

A mixture of 0.1 mole of pure fatty acid and 0.03 mole of fused zinc chloride was heated to 130-140°C on an oil bath. To it 0.03 mole of kojic acid was added portionwise with stirring during thirty minutes, further heating and stirring were continued for additional two and half hours. At the end of the reaction period, the resulting mixture was stood for over night and then was separated from excess zinc chloride

by washing with water. The residue was twice extracted by 150 ml of ethyl ether. The ether extract was neutralized with sodium bicarbonate solution to remove free fatty acid. After evaporating ether under reduced pressure, crude crystalline product could be obtained. The crude crystalline products were twice recrystallized from ether or ethyl acetate. The recrystallized products were colorless, whose yields were between 35 and 41% except for compound (IIa), for which, the yield was more than 55%.

Acetylation of Compounds (IIa or IIb).

A mixture of 0.01 mole of the compound (IIa or IIb) and 0.02 mole of acetyl chloride was heated for 30 minutes on a water bath under reflux. The reaction mixture was evaporated under reduced pressure, to removed an excess of hydrogen chloride and acetyl chloride. The residue was disolved into ethanol and the product was obtained by recrystallizing three times from ethanol.

Bromination of compound (IIa).

A solution of 1.85 g of compound (IIa) in 200 ml of water was well stirred in an ice bath. A solution of 1.6 g of bromine in 50 ml of water was then added into it in small portions. After the reaction was completed the mixture was evaporated to 100 ml under reduced pressure. The crude crystalline product obtained from the concentrated mixture was twice recrystallized from ethanol.

Summary

Mono acyl derivatives of kojic acid were prepared by using several fatty acids in the presence of zinc chloride. Acetyl, propionyl, butyryl, hexanoyl, octanoyl and decanoyl derivatives were obtained and their chemical structures were discussed.

Acknowledgment

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