UDC 547.97:582.29

84. Kōtarō Takahashi, Shūichi Miyashita, and Yoshie Ueda : Usnic Acid. IV*[1]. Isoanhydromethyldihydrousnic Acid.

(*Faculty of Pharmacy, Universiy of Kanazawa**[2])

It was reported in the preceding paper*[1] that the constitution of anhydromethyldihydrousnic acid (Ib) monoacetate, one of the acetylation products of methyldihydrousnic acid,[1] is formulated as Ia and that the reaction mechanism involves the Dienone-Phenol type rearrangement. The present communication deals with the constitution of another acetylation product of methyldihydrousnic acid, named isoanhydromethyldihydrousnic acid.

As reported previously,*[1] the crude acetylation product of methyldihydrousnic acid was treated with ethanol to give Ia as a solid. The ethanolic mother liquor of Ia on treatment with conc. sulfuric acid or 5% sodium hydroxide, gave pale yellow crystalline isoanhydromethyldihydrousnic acid, $C_{19}H_{18}O_6$ (IIa), m.p. 196°. IIa was acetylated to a monoacetate, $C_{21}H_{20}O_7$ (IIb), m.p. 142~143°, which was deacetylated to IIa, indicating that the acetylation of IIa to IIb was not accompanied by any rearrangement. The infrared spectrum of IIa shows bands at 1650 ($\alpha\beta$-$\alpha'\beta'$ unsatd. C=O), 1635 (chelated C=O), 1610, 1575, and 1500 (phenyl and furan), 1530~1550 (broad, triketone[2] in A ring) (cm^{-1}). (Fig. 1). The infrared spectrum of IIb shows bands at 1760 (phenolic acetate), 1680 ($Ar-COCH_3$), 1650 ($\alpha\beta$-$\alpha'\beta'$ unsatd. C=O), 1610 (chelated C=O), 1520~1550 (broad, triketone) (cm^{-1}).

Ozonolysis of IIb followed by treatment with ethanol, gave two solids, $C_{10}H_{10}O_5$ (III), m.p. 180° (decomp.) and $C_{14}H_{16}O_6$ (IV), m.p. 115~116°. III was proved to be identical with 3-acetyl-6-methyl 2,4-dihydroxybenzoic acid*[1] and gave γ-orcacetophenone (V) by vacuum distillation. IV was deacetylated to ethyl 3-acetyl-6-methyl-2,4-dihydroxybenzoate (VI), which was proved to be identical with the authentic sample, obtained by ethylation of 3-acetyl-6-methyl-2,4-dihydroxybenzoic acid. These facts indicate that a γ-orcacetophenone ring is present in both structures of I and II.

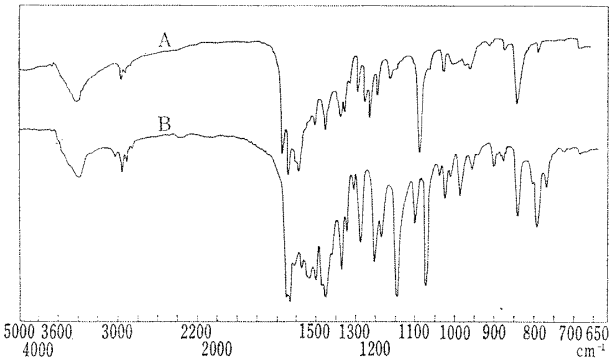

Fig. 1. IR spectra

A : Anhydromethyldihydrousnic acid (in KBr)
B : Isoanhydromethyldihydrousnic acid (in KBr)

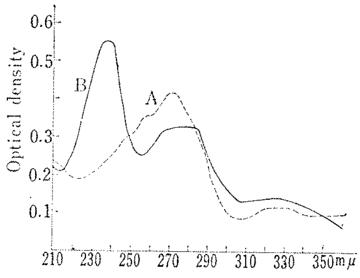

Fig. 2. UV spectra

A : Anhydromethyldihydrousnic acid 1.280 mg. in 210 cc. EtOH
B : Isoanhydromethyldihydrousnic acid 1.275 mg. in 210 cc. EtOH

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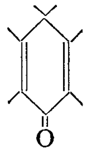
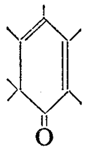
*[1] Part III : K. Takahashi, S. Miyashita : This Bulletin, **11**, 209 (1963).

*[2] Tsuchitoribanaga-machi, Kanazawa-shi, Ishikawaken (高橋幸太郎, 宮下修一, 上田芳枝).

1) Part I : K. Takahashi, *et al.* : *Ibid.*, **10**, 603 (1962).

2) S. Shibata, J. Shoji : Kagaku no Ryōiki, **15**, 805 (1961).

Oximation of IIa gave a dioxime monoanhydride, $C_{19}H_{18}O_5N_2$ (VII), m.p. 280° (decomp.), which then was oxidized by hydrogen peroxide to 4-carboxy-*α,α*, 3-trimethyl-5-isoxazoleacetic acid, $C_9H_{11}O_5N$ (VIII),¹⁾ m.p. 217°. This fact indicates that Ib and IIa possess the same locations of -$COCH_3$, enolic-OH and gem-dimethyl groups in the A ring.

As shown in Fig. 2,[*3] while anhydromethyldihydrousnic acid (Ib) has the ultraviolet absorption maxima at 257 mμ, 272 mμ, and 328 mμ, isoanhydromethyldihydrousnic acid (IIa) has the ultraviolet absorption maxima at 237 mμ, 277 mμ, and 328 mμ. As both Ib and IIa have the same *γ*-orcacetophenone ring in their structures, the difference of the ultraviolet absorption indexes between Ib and IIa mentioned above would be due to a difference of the conjugated system of A ring. The absorption maximum at 237 mμ of IIa could then be assigned to  chromophor and the absorption maximum at 272 mμ of Ib could be assigned to  chromophor. The bathochromic shift by 35 mμ in Ib is explained by the Woodward's rule.

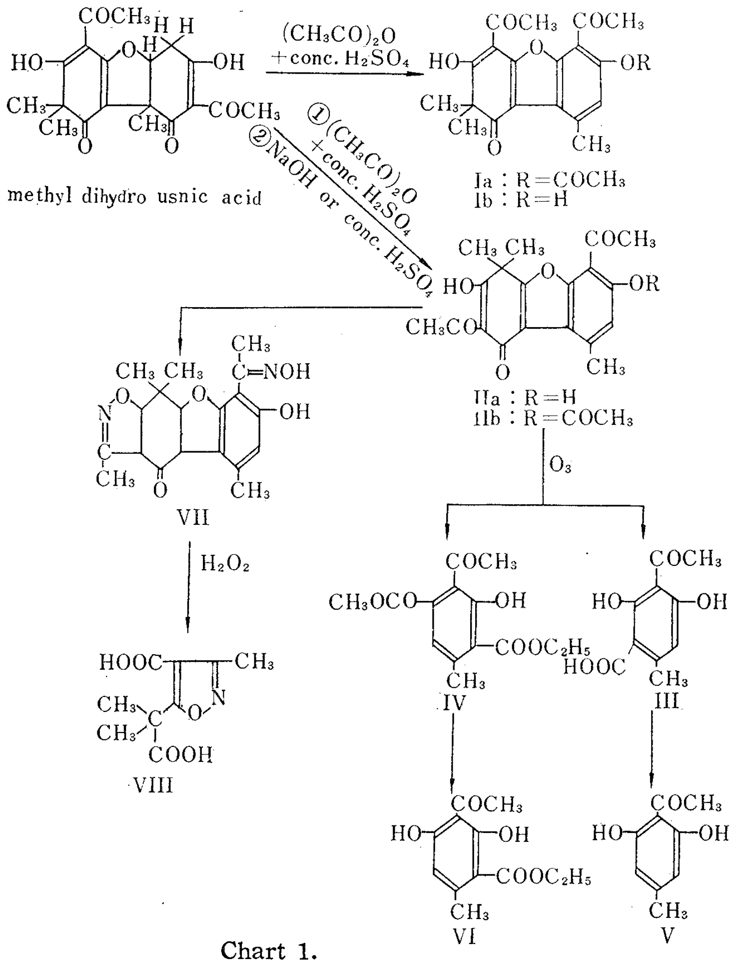


Chart 1.

[*3] The ultraviolet curve of Ib was slightly affected by the concentration used for measurement.

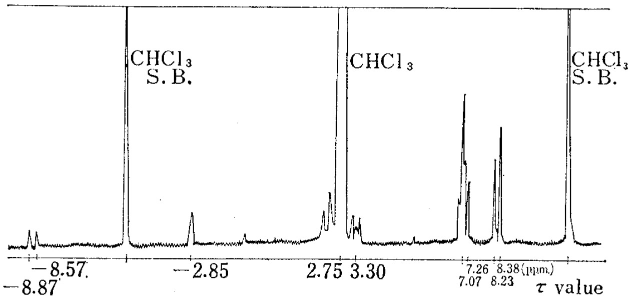
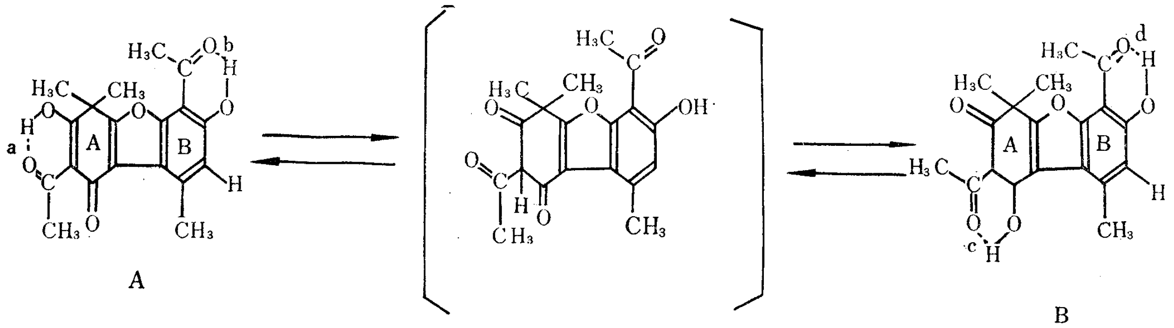


Fig. 3.
NMR Spectrum*[4] of
Isoanhydromethyldihydrousnic Acid

Therefore, isoanhydromethyldihydrousnic acid is concluded to be represented by IIa (Chart 1). The proposed structure (IIa) of isoanhydromethyldihydrousnic acid was also supported by the nuclear magnetic resonance analysis*[4] (Fig. 3) which was rationally explained as follows. Here it might be mentioned that isoanhydromethyldihydrousnic acid would be present in the tautomery forms,[3] (A) and (B), in respect to the location of hydrogen bonds.



The singlet at −2.85 should be assigned to the *b*(OH) in (A) and *d*(OH) in (B) which would be equivalent, while the chemical shift appeared in the doublet at −8.57 and −8.87 is reasonablly assigned to the unequivalent *a*(OH) in (A) and *c*(OH) in (B).

Considering the ratio of intensity of those signals and taking an assumption that *a*(OH) group is more strongly hydrogen bonded by a sterric effect of the neighbouring gem-dimethyl group than *c*(OH), the signals at −8.87 p.p.m. and −8.57 p.p.m. are assigned to *a* and *c*(OH) groups, respectively. The signals at 8.38 p.p.m. and 8.23 p.p.m. are assigned to the gem-dimethyl group and the shift of 0.15 p.p.m. (6 c.p.s. at 40 Mc.) may be due to the presence and contribution of those tautomers (A) and (B). The signal at 7.26 p.p.m. is assigned to the aromatic methyl group on B ring, because the signal appears in too low field for angular methyl group.

The triplet centered on 7.07 p.p.m. which is assigned to $COCH_3$ resulted by the presence of equivalent hydrogen bondings at *b* in (A) and *d* in (B), and unequivalent hydrogen bondings at *a* in (A) and *c* in (B) giving a recognizable chemical shift. The quartet centered on 3.30 p.p.m. is assigned to CH of $\underset{H_3C}{\rangle C}=\underset{H}{C\langle}$ grouping.

It might be added that these nuclear magnetic resonance data and the chemical evidences previously mentioned excluded the alternative constitutions (C) and (D) for isoanhydromethyldihydrousnic acid.

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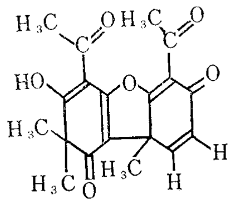
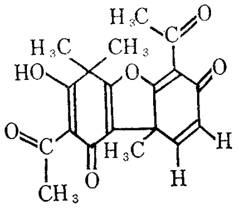
*[4] The nuclear magnetic resonace spectra were mearured using JNM-III spectrometer, Japan Optics Laboratory Co., Ltd. operating at 40 Mc. The position of resonances are measured by the side band technique and given as values of τ-values which are obtained in chloroform as an internal reference. The τ-value of chloroform was assumed to be 2.75 p.p.m.

3) S. Forsen, M. Nilsson: Acta. Chem. Scand., **13**, 1383 (1959).



C



D

The formation of isoanhydromethyldihydrousnic acid (IIa) from methyldihydrousnic acid would be explained by following reaction mechanism (Chart 2).

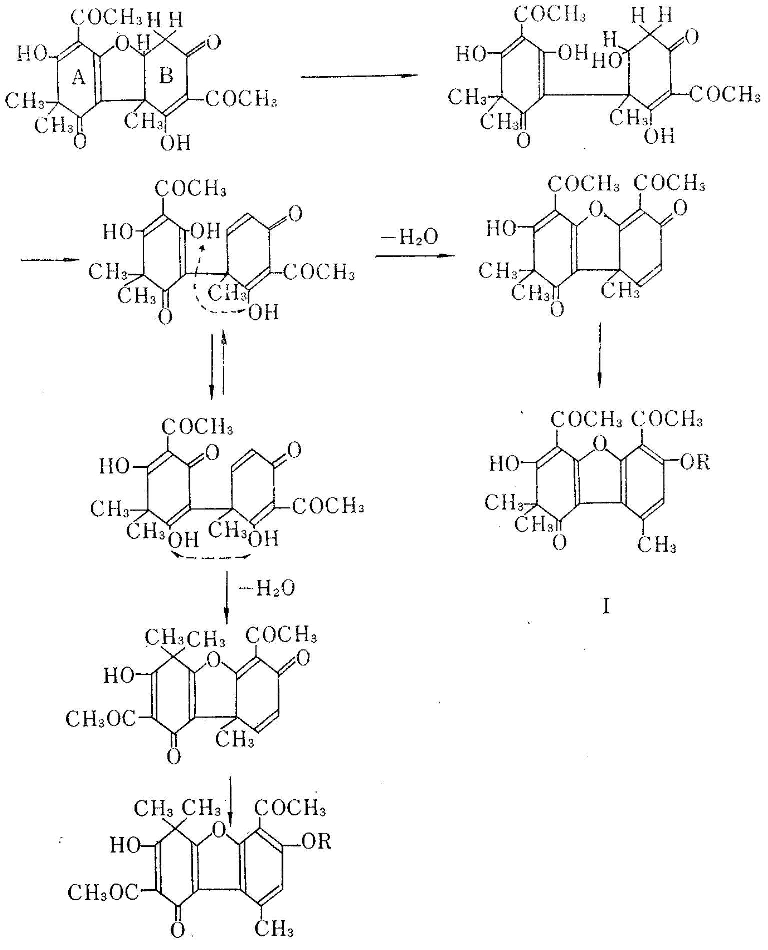


Chart 2.

At the first stage, the hydrolytic fission of -C-O-C- bond in furan ring takes place, and then the newly formed hydroxyl in B ring is removed by dehydration. The dehydration between the newly formed -OH in A ring and the enolic -OH originally present in B ring regenerate an ether bond, and finally the dienone ring undergoes the Dienone-Phenol type rearrangement, followed by deacetylation to give isoanhydromethyldihydrousnic acid (IIa).

The formation of anhydromethyldihydrousnic acid (Ib) and the iso-compound (IIa) would be resulted by the different mode of reaction at the second stage of dehydration.

The compound (IIb) has not been obtained directly from the reaction mixture of acetylation of methyldihydrousnic acid due to the experimental difficulties of separation.

Experimental[*5]

Acetylation of Methyldihydrousnic Acid : The Formation of Ia and IIa——Methyldihydrousnic acid (30 g.) was acetylated according to the procedure reported previously[2)] and anhydromethyldihydrousnic acid monoacetate (Ia), m.p. 172∼173° (12 g.) was obtained as an EtOH-insoluble solid. The ethanolic mother liquor was concentrated to give a resinous substance, which was hydrolyzed with 5% NaOH or conc. H_2SO_4. The resulting brown powder was recrystallized from benzene to give pale yellow crystals, $C_{19}H_{18}O_6$ (IIa), m.p. 196°. Yield 1 g. $FeCl_3$ reaction; violet-brown. UV λ_{max} mμ (log ε) : 237 (4.49), 277 (4.27), 328 (3.90). IR ν_{max} cm^{-1} : 1650 (s), 1635 (s), 1610 (w), 1575 (m), 1550∼1530 (broad, m), 1500 (m), 1470 (m), 1450 (s), 1420 (w), 1365 (m), 1340 (m), 1270 (m), 1200 (m), 1185 (m), 1145 (s), 1100 (m), 1070 (s), 1020 (m), 980 (m), 840 (m) and 795 (m). *Anal.* Calcd. for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30. Found : C, 66.74; H, 5.24. mol. wt. Found : 322 (camphor).

Acetylation of IIa : The Formation of IIb——IIa (4 g.) was dissolved in a mixture of anhyd. AcOH (40 cc.) and conc. H_2SO_4 (4 drops) and the mixture was warmed on a steam bath for 3 hr. and worked up as usual. After recrystallization from EtOH, colorless needles $C_{21}H_{20}O_7$ (IIb), m.p. 142∼143° were obtained. $FeCl_3$ reaction : Red-orange. *Anal.* Calcd. for $C_{21}H_{20}O_7$: C, 65.61; H, 5.24. Found : C, 65.32; H, 5.20.

Deacetylation of IIb to IIa with conc. Sulfuric Acid——IIb (0.3 g.) was dissolved in ice cold conc. H_2SO_4 (2 cc.) and after 5 min., the mixture was poured into ice water to give IIa, m.p. 194∼195°. *Anal.* Found : C, 66.71, H, 5.30. The deacetylation also took place by hydrolysis with 5% NaOH solution at room temperature.

Ozonolysis of IIb——IIb (1.5 g.) was dissolved in $CHCl_3$ (20 cc.) and ozonized O_2 was passed through for 1.5 hr. under ice cooling. Then EtOH (19 cc.) and H_2O (1 cc.) were added to the $CHCl_3$ solution and the mixture was warmed on a steam bath for 30 min., and then the solvent was distilled off to give a resinous substance, which was dissolved in Et_2O and treated with 5% aq. $NaHCO_3$ solution. The aqueous layer was acidified with dil. HCl, extracted with Et_2O, and the ethereal solution was evaporated to give a crystalline substance, which was recrystallized from aq. MeOH to give a crystalline powder, $C_{10}H_{10}O_5$ (III), m.p. 180° (decomp.). $FeCl_3$ reaction : Red-violet. It was proved to be identical with 3-acetyl-6-methyl-2,4-dihydroxybenzoic acid (γ-orcacetophenone carboxylic acid) by comparison of both IR and UV spectra and mixed melting point determination. *Anal.* Calcd. for $C_{10}H_{10}O_5$: C, 57.14, H, 4.80. Found: C, 56.85; H, 4.96. From the ethereal layer, after evaporation and recrystallization from dil. EtOH, colorless crystals $C_{14}H_{16}O_6$ (IV), m.p. 115∼116° were obtained. $FeCl_3$ reaction : Red-violet. Analytical data corresponded to ethyl 2-hydroxy-3-acetyl-4-acetoxy-6-methylbenzoate. IR ν_{max}^{Nujol} cm^{-1} : 1770 (acetate), 1695 (ester C=O), 1640 (chelated C=O). *Anal.* Calcd. for $C_{14}H_{16}O_6$: C, 59.99; H, 5.75. Found: C, 59.46; H, 5.80.

Decarboxylation of III to V——III (0.1 g.) was heated at 180° and after end of bubbling, it was distilled at 180∼200° under 1 mm.Hg pressure to give crystals, $C_9H_{10}O_3$ (V), m.p. 146° (from dil. EtOH). It was proved to be identical with an authentic sample of 4′-methyl-2′,6′-dihydroxyacetophenone by mixed fusion and by comparison of IR and UV spectra. *Anal.* Calcd. for $C_9H_{10}O_3$: C, 65.05, H, 6.07. Found : C, 65.24; H, 6.06.

Deacetylation of IV to VI——On treatment of IV with 5% NaOH on a steam bath for 1 hr. and after acidification with dil. HCl, colourless crystals $C_{12}H_{14}O_5$ (VI), m.p. 89∼90° were obtained. $FeCl_3$ reaction : Red-violet. IR ν_{max} cm^{-1} : 1640 (chelated ester), 1620 (chelated -$COCH_3$). *Anal.* Calcd. for $C_{12}H_{14}O_5$: C, 60.50, H, 5.92. Found : C, 60.02; H, 5.88. It was proved to be identical with the authentic sample of ethyl 3-acetyl-6-methyl-2,4-dihydroxybenzoate by mixed melting point determination.

Ethyl 3-acetyl-6-methyl-2,4-dihydroxybenzoate was synthesized by ethylation of 3-acetyl-6-methyl-2,4-dihyroxybenzoic acid with diazoethane in Et_2O, m.p. 89∼90°. *Anal.* Calcd. for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found : C, 60.83; H, 6.01.

Dioxime Monoanhydride of IIa——A mixture of IIa (1 g.), hydroxylamine hydrochloride (1 g.) and anhyd. AcONa (1 g.) in EtOH (10 cc.) was refluxed on a steam bath for 5 hr. At the end of the reaction, a white crystalline powder separated out. After cooling, the precipitate was filtered off and recrystallized from benzene-EtOH to give colorless crystals $C_{19}H_{18}O_5N_2$ (VII), m.p. 280° (decom.). $FeCl_3$ reaction : Darkgreen. Yield 1 g. UV λ_{max} mμ : 236, 284 (shoulder), 320. *Anal.* Calcd. for $C_{19}H_{18}O_5N_2$: C, 64.40; H, 5.12; N, 7.91. Found : C, 64.86; H, 5.14; N, 7.47.

Oxidation of VII with Hydrogen Peroxide : Formation of VIII——To a solution of VII (0.5 g.) in 10% KOH (20 cc.), 3% H_2O_2 (10 cc.) was added. On warming on a steam bath at 80∼90°, the solution

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[*5] The IR spectra were taken in KBr pellet, if not otherwise stated, by Nippon Bunko I. R. S. infracode, the UV spectra were measured in EtOH solution by Hitachi Recording Spectrophotometer Type 2U and the NMR spectrum was taken by a Japan Electron Optics Laboratory Co., Ltd. JNM-III operating at 40 Mc. Some of the weak bands of IR spectra were omitted in description.

becam brown. 3% H_2O_2 (10 cc.) was successively added three times and 30% H_2O_2 (2 cc.) ten times at the interval of 30 min. and then 30% H_2O_2 (6 cc.) two times at the interval of 1 hr. After acidification with dil. HCl and salting out with NaCl, the reaction mixture was extracted with Et_2O. After drying with anhyd. Na_2SO_4, the ethereal solution was distilled off to give colorless crystals, which were recrystallized from water to m.p. 217°, $C_9H_{11}O_5N$ (Ⅷ). Yield 50 mg. It was proved to be identical with 4-carboxy-α,α,3-trimethyl-5-isoxazoleacetic acid by mixed fusion and by comparison of IR spectra. *Anal.* Calcd. for $C_9H_{11}O_5N$: C, 50.70, H, 5.20. Found : C, 50.52, H, 5.18.

The authors wish to express their deep gratitude to Dr. Y. Asahina, Emeritus Professor of University of Tokyo, for his encouragement throughout the course of this study and Dr. S. Shibata, Professor of University of Tokyo, for the gift of usnic acid. The authors wish to thank Dr. M. Takeuchi and Japan Electron Optics Laboratory Co. Ltd. and Dr. S. Matsuoka of this University, for discussing and measurement of NMR spectra. Thanks are due to Mr. Y. Itatani, this Faculty, for elemental analysis.

Summary

The structure of isoanhydromethyldihydrousnic acid, one of the products by the acetylation of methyldihydrousnic acid has been shown as being (Ⅱa). The reaction mechanism of the dehydration reaction has been discussed to show that it involes the fission and reformation of -C-O-C- linkage in the furan nucleus and successive Dienone-Phenol rearrangement. The difference in the mode of reaction at the intermediate dehydration process would result anhydromethyldihydrousnic acid (Ia) or iso-anhydromethyldihydrousnic acid (Ⅱa).

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UDC 547.458.2'29

85. **Kazuya Kunugi** : Studies on the Syntheses of Sucrose Fatty Acid Esters. I. Contents of Ester Parts in the Products of Alcoholyses.

(*Research Laboratory, Asahi Denka Kogyo Co., Ltd.*[*1])

Since Osipow, *et al.*,[1] have developed the syntheses of sucrose fatty acid esters, interests about these compounds have increased in their application to food-additives and emulsifiers.

In order to synthesize the sucrose stearate, for example, Osipow, *et al.*, applied the alcoholysis reaction of methyl stearate by sucrose. These were reacted in the solvent of dimethyl formamide (DMF) with a catalyst K_2CO_3, the reaction mixture being boiled and the volatile methyl alcohol, which was produced during reaction, being stripped off through a fractionating column.

In the industrial manufacturing, the composition of the product of the alcoholysis under various conditions, especially under various molar ratios of sucrose/methyl stearate is an important problem. As for the composition of the product of the reaction, almost no report in the literature is available except the one mentioned above.

[*1] Ogu-machi, 9-2850, Arakawa-ku, Tokyo (功刀一彌).

[1] L. Osipow, *et al.* : Ind. Eng. Chem., 48, 1459 (1956); J. Am. Oil Chem. Soc., 34, 185 (1957).