84. Kōtarō Takahashi, Shūichi Miyashita, and Yoshi Ueda: 
Usnic Acid. IV*1. Isoanhydromethylidihydrosunic Acid.

(Faculty of Pharmacy, University of Kanazawa*)

It was reported in the preceding paper*1 that the constitution of anhydromethyl-
dihydrosunic acid (Ib) monoacetate, one of the acetylation products of methylidihydros-
uscnic 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 methylidihydrosunic acid, named isoanhydromethylidihydros-
uscnic acid.

As reported previously,*1 the crude acetylation product of methylidihydrosunic 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
isoanhydromethylidihydrosunic acid, C_{19}H_{18}O_{6} (IIa), m.p. 196°. IIa was acetylated to a
monoacetate, C_{21}H_{22}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 (αβ~α′β′ unsatd. C=O), 1635 (chelated C=O),
1610, 1575, and 1500 (phenyl and furan), 1530~1550 (broad, triketone*3) in A ring (cm^{-1})
(Fig. 1). The infrared spectrum of IIb shows bands at 1760 (phenolic acetate), 1680 (Ar-
COCH_{3}), 1650 (αβ~α′β′ 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_{19}H_{18}O_{5} (III),
m.p. 180° (decomp.) and C_{19}H_{18}O_{4} (IV), m.p. 115~116°. III was proved to be identical with
3-acetyl-6-methyl 2,4-dihydroxybenzoic acid*4 and gave γ-orocetophenone (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 ethylolation of
3-acetyl-6-methyl-2,4-dihydroxybenzoic acid. These facts indicate that a γ-oracetophenone ring is present in both structures of I and II.

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*2 Tsuchitoriibana-machi, Kanazawa-shi, Ishikawaken (高橋幸太郎, 宮下修一, 上田芳枝).
Oximation of IIa gave a dioxime monoanhydride, C₁₀H₉O₂N₄(II), m.p. 280° (decomp.), which then was oxidized by hydrogen peroxide to 4-carboxy-α,α, 3-trimethyl-5-isoxazoleacetic acid, C₃H₁₁O₂N(III), m.p. 217°. This fact indicates that Ib and IIa possess the same locations of −COCH₃, enolic-ÖH and gem-dimethyl groups in the A ring.

As shown in Fig. 2, while anhydromethyldihydrous acid (Ib) has the ultraviolet absorption maxima at 257 mμ, 272 mμ, and 328 mμ, isoanhydromethyldihydrous acid (IIa) has the ultraviolet absorption maxima at 237 mμ, 277 mμ, and 328 mμ. As both Ib and IIa have the same γ-orcectophenone 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.

*3 The ultraviolet curve of Ib was slightly affected by the concentration used for measurement.
Therefore, isoanhydromethylidihyrousnic acid is concluded to be represented by IIa (Chart 1). The proposed structure (IIa) of isoanhydromethylidihyrousnic acid was also supported by the nuclear magnetic resonance analysis (Fig. 3) which was rationally explained as follows. Here it might be mentioned that isoanhydromethylidihyrousnic acid would be present in the tautomery forms, (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 reasonably assigned to the unequivocal 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 steric 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 COCH₃ resulted by the presence of equivalent hydrogen bondings at b in (A) and d in (B), and unequivocal 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 \( \text{H}_3C\text{C}-\text{C}\) 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 isoanhydromethylidihyrousnic acid.

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\*4 The nuclear magnetic resonance spectra were measured 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 \( \tau \)-values which are obtained in chloroform as an internal reference. The \( \tau \)-value of chloroform was assumed to be 2.75 p.p.m.

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

At the first stage, the hydrolytic fission of \(-\text{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 \(-\text{OH}\) in A ring and the enolic \(-\text{OH}\) 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 isoanhydromethylidihydroursinic acid (IIa).

The formation of anhydromethylidihydroursinic 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 methylidihydroursinic acid due to the experimental difficulties of separation.
Experimental

Acetylation of Methylidihydronic Acid: The Formation of Ia and IIa—Methylidihydronic acid (30 g.) was acetylated according to the procedure reported previously and anhydromethylidihydronic acid monoacetate (Ia), m.p. 172–173° (12 g.) was obtained as an EtOH-insoluble solid. The ethanolic mother liquor was concentrated to give aresinous substance, which was hydrolyzed with 5% NaOH or conc. H2SO4. The resulting brown powder was recrystallized from benzene to give pale yellow crystals, C8H8O4 (Ia), m.p. 196°. Yield 1 g. FeCl3 reaction; violet-brown. UV λmax μm (log ε): 237 (4.49), 277 (4.27), 328 (3.90). IR νmax 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), 960 (m), 840 (m) and 795 (m). Anal. Calcd. for C13H18O5: C, 66.66; H, 5.30. Found: C, 65.74; H, 5.24. mol. wt. Found: 322 (camphor).

Acetylation of Ia: The Formation of IIB—Ia (4 g.) was dissolved in a mixture of anhyd. AcOH (40 cc.) and conc. H2SO4 (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 C12H18O4 (IIB), m.p. 142–143° were obtained. FeCl3 reaction: Red-orange. Anal. Calcd. for C12H18O4: C, 65.61; H, 5.24. Found: C, 65.32; H, 5.20.

Decacylation of IIB to IIa with conc. Sulfuric Acid—IIB (0.3 g.) was dissolved in ice cold conc. H2SO4 (2 cc.) and after 5 min., the mixture was poured into ice water to give IIa, m.p. 194–195°. Anal. Found: C, 65.71, H, 5.30. The decacylation also took place by hydrolysis with 5% NaOH solution at room temperature.

Ozonolysis of IIB—IIB (1.5 g.) was dissolved in CHCl3 (20 cc.) and ozonized O3 was passed through for 1.5 hr. under cooling. Then EtOH (19 cc.) and H2O (1 cc.) were added to the CHCl3 solution and the mixture was warmed on a steam bath for 30 min., and then the solvent was distilled off to give aresinous substance, which was dissolved in EtO and treated with 5% aqueous NaHCO3 solution. The aqueous layer was acidified with dil. HCl, extracted with Et2O and the ethereal solution was evaporated to give a crystalline substance, which was distilled from acetonitrile, C10H16O3 (III), m.p. 180° (decomp.). FeCl3 reaction: Red-violet. It was proved to be identical with 3-acetyl-6-methyl-2,4-dihydroxybenzoic acid (α-or-acetophenone carboxylic acid) by comparison of both IR and UV spectra and mixed melting point determination. Anal. Calcd. for C10H16O3: 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 C10H16O3 (IV), m.p. 115–116° were obtained. FeCl3 reaction: Red-violet. Analytical data corresponded to ethyl 2-hydroxy-3-acetyl-4-acetoxy-6-methylbenzoate. IR νmax cm⁻¹: 1770 (acetate), 1695 (ester C=O), 1640 (chelated C=O). Anal. Calcd. for C14H18O6: 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, C12H18O3 (V), m.p. 146° (from dil. EtOH). It was proved to be identical with an authentic sample of 4′-methyl-2′,5′-dihydroxyacetophenone by mixed fusion and by comparison of IR and UV spectra. Anal. Calcd. for C12H16O3: C, 65.05, H, 6.07. Found: C, 65.24; H, 6.06.

Decacylation 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 C10H16O2 (VI), m.p. 89–90° were obtained. FeCl3 reaction: Red-violet. IR νmax cm⁻¹: 1640 (chelated ester), 1620 (chelated COCH3). Anal. Calcd. for C10H16O2: C, 60.50, H, 5.92. Found: C, 60.62; 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-dihydroxybenzoic acid with diazomethane in Et2O, m.p. 89–90°. Anal. Calcd. for C10H16O2: C, 69.50; H, 5.52. Found: C, 69.03; H, 5.01.

Dioxime Mononhydroxide of IIa—A mixture of II (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 C10H16O2Na (VII), m.p. 280° (decomp.). FeCl3 reaction: Dark green. Yield 1 g. UV λmax μm (log ε): 236, 284 (shoulder), 320. Anal. Calcd. for C10H16O2Na: 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% H2O2 (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 not provided in the description.
becam brown. 3% H₂O₂ (10 cc.) was successively added three times and 30% H₂O₂ (2 cc.) ten times at the interval of 30 min. and then 30% H₂O₂ (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 Et₂O. After drying with anhyd. Na₂SO₄, the ethereal solution was distilled off to give colorless crystals, which were recrystallized from water to m.p. 217°, C₃H₇O₂N (III). 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. Caled. for C₃H₇O₂N: C, 50.70, H, 5.20. Found: C, 50.52, H, 5.18.

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Summary

The structure of isoanhydromethylidihydrosnic acid, one of the products by the acetylation of methylidihydrosnic acid has been shown as being (IIa). The reaction mechanism of the dehydration reaction has been discussed to show that it involves 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 anhydromethylidihydrosnic acid (Ia) or iso-anhydromethylidihydrosnic acid (IIa).

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(Research Laboratory, Asahi Denka Kogyo Co., Ltd.)

Since Osipow, et al., 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 K₂CO₃, 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.

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*1 Ogu-machi, 9-2850, Arakawa-ku, Tokyo (功刀一張).