give faint yellow crystals, m.p. 235°. It was soluble in $NaHCO_3$ solution and gave brown coloration with $FeCl_3$. *Anal.* Found: C, 66.76, 66.37; H, 5.44, 5.37.

Acetylation of (I)——A mixture of 10 g. of (I), 100 cc. of Ac_2O and 20 drops of conc. H_2SO_4 was warmed on a water bath for 3 hr. and after cooling, the mixture was poured into ice water. Brown precipitates that separated out were treated with MeOH and then recrystallized from a mixture of EtOH and benzene to yellow crystals, m.p. 172~173° (V). Yield, 4 g. It was optically inactive and gave deep-blue coloration with $FeCl_3$. This acetylation did not take place when warmed at 50~60°, as in the case of the acetylation of usnic acid. UV λ_{max} 212.5, 266, 318 and 390 mμ. Molecular weight, calcd. for $C_{21}H_{20}O_7$: 384. Found: 372.7 (Rast. Camphor). *Anal.* Calcd. C, 65.61; H, 5.24. Found: C, 65.76, 65.74, 65.70; H, 5.69, 5.35, 5.12.

Action of Conc. Sulfuric Acid on (V)——To a solution of 50 cc. of conc. H_2SO_4 10 g. of (V) was gradually added at 0~5° and the mixture was allowed to stand for 2 hr. at room temperature and then poured into ice water. Precipitates were recrystallized from benzene to give faint greenish yellow crystals (VI), m.p. 245~246°. Yield, 5.0 g. It was soluble in $NaHCO_3$ solution and gave blue-green coloration with $FeCl_3$ in EtOH solution. UV λ_{max} 212, 257, 271.5 and 377 mμ. *Anal.* Calcd. for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30. Found: C, 66.63, 66.67; H, 5.19, 5.33.

The authors express their gratitude to Dr. Y. Asahina, Prof. Emeritus, University of Tokyo, for his encouragement throughout this work, to Mr. Hiroshi Ogata, for supply of usnic acid and to Misses M. Hikita, A. Ogawa, and K. Kitade for co-operation. Thanks are also due to Mr. Yoshitaka Itaya, for elemental analyses.

Summary

Methyldihydrousnic acid was obtained by methylation of dihydrousnic acid and its constitution was elucidated as (I). The result that 3′-methyl-2′,6′-dihydroxyacetophenone was obtained from methyldihydrousnic acid indicates that the resorcinol type of compound is derived from B-ring of (I). This result also presents the experimental proof of formation of 3′-methyl-2′,6′-dihydroxyacetophenone, one of resorcinol type of compound, from B-ring of dihydrousnic acid.

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99. Kōtaro Takahashi, Akie Arai, Kazuko Ōshima, Yoshie Ueda, and Shūichi Miyashita: Usnic Acid. II*[1]. Methylusnic Acid.

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Robertson *et al.*[1] obtained methylated usnic acid $C_{19}H_{18}O_7$ (I), m.p. 136° and they assumed it to be an enol methyl ether compound of usnic acid. The facts, obtained during the course of the investigation of the constitution and proterties of methyldihydrousnic acid, indicate that the constitution of Robertson's substance can be formulated as (I). So it seemed to be necessary for us to reexamine the constitution and decomposition reactions of Robertson's compound.

On methylation with dimethyl sulfate and sodium hydroxide, *d*-usnic acid afforded a compound (I), m.p. 136°, yellow crystal which was assumed to be identical with the Robertson's compound. (I) gave red brown coloration with ferric chloride and 0.6 mole

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[*1] Part I: This Bulletin, **10**, 603 (1962.

[*2] Tsutitoribanaga-machi, Kanazawa, Ishikawa-ken (高橋幸太郎, 新井あき江, 大島和子, 上田芳枝, 宮下修一).

1) F. M. Dean, P. Halewood, S. Mongkolsuk, A. Robertson, W. B. Whalley: J. Chem. Soc·, **1953**, 1250.

of O-CH_3 group by the Zeisel method and 4 moles of C-CH_3 groups by the Kuhn-Roth method like usnic acid and was soluble in sodium bicarbonate solution.

From racemi usnic acid, optically inactive compound, m.p. 134°, was obtained.

That *o*-phenylenediamine reaction was negative suggests the absence of 1,3-diketone system of decarbousnic acid type in its molecule. The remarkable differences in ultraviolet and infrared absorption spectra were observed between (I) and usnic acid. (I) has maxima at 258, 305, and 358 mμ in ultraviolet and at 1690, 1650, and 1603 cm^{-1} in infrared spectra. When treated with concentrated sulfuric acid, (I) was recovered unchanged. By the action of 80% acetic acid, (I) yielded a compound $C_{18}H_{20}O_6$ (II), m.p. 86°, which had not a O-CH_3 group and gave violet coloration with ferric chloride and was positive to iodofrom reaction. The analytical figure showed it to correspond with methylated decarbousnic acid. As (II) reacts with *o*-phenylenediamine in acetic acid, giving red coloration, the 1,3-diketone system of decarbousnic acid type is assumed to be present in (II). The ultraviolet absorption maxima of (II) are present at 215, 274, 329, and 385 (shoulder) mμ, 30 mμ longer than that of decarbousnic acid (244, 294, and 353 mμ).

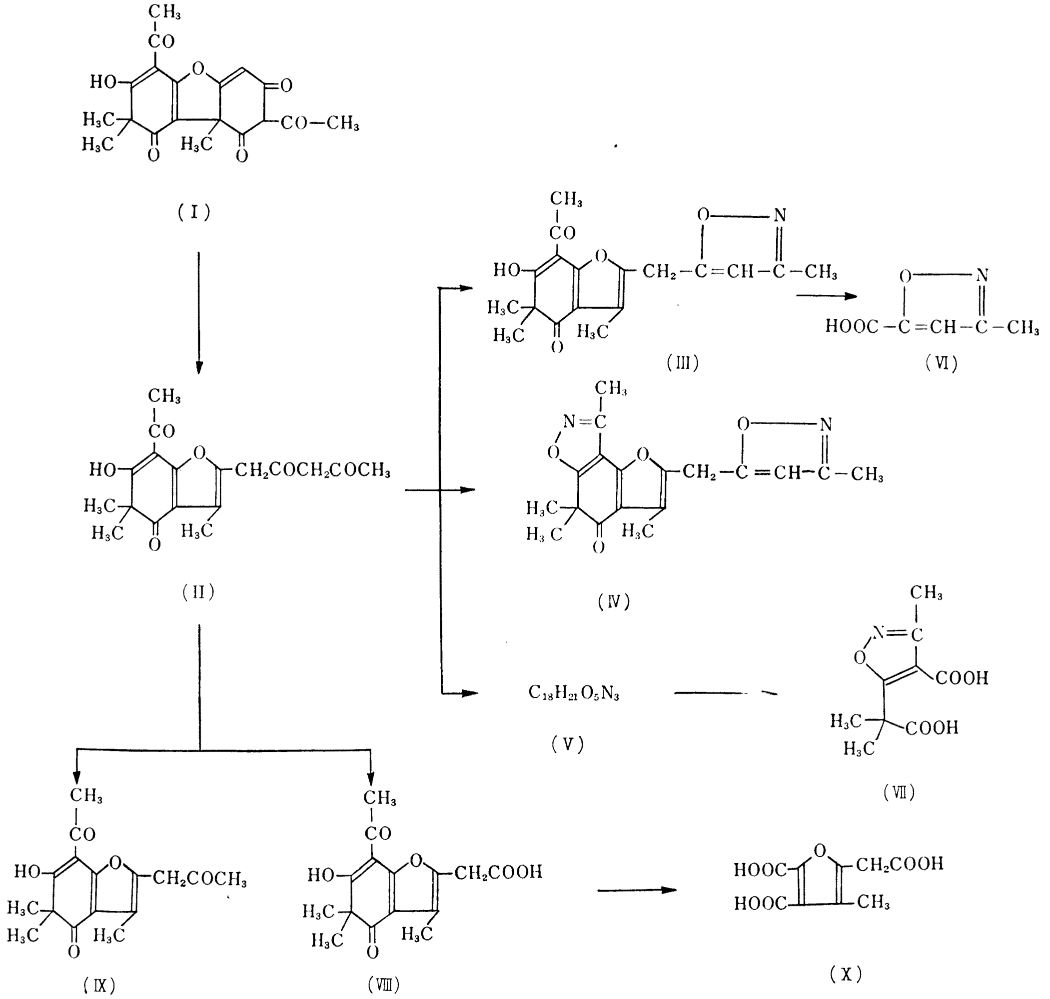

Chart 1.

On treatment with hydroxylamine hydrochloride and anhyd. sodium acetate in ethanol solution, (II) gave monoxime monoanhydride $C_{18}H_{19}O_5N$ (III), m.p. 89°, and bisoxime bisanhydride $C_{18}H_{18}O_4N_2$ (IV), m.p. 149°. The former gave blue coloration with ferric chloride and the latter gave no coloration with ferric chloride and both were negative to *o*-phenylenediamine reaction. In methanolic solution, (II) also gave monoxime $C_{18}H_{21}O_6N$, m.p. 174~175°, faint greenish white needles which gave blue coloration with ferric chloride. The monoxime derivative was converted by further treatment with hydroxylamine into $C_{18}H_{21}O_5N_3$ (V), m.p. 166°, white crystals which gave no coloration with ferric chloride and did not give *o*-phenylenediamine and Legal reactions. The analytical data showed it to correspond with trioxime monoanhydride of (II). They are all correspond to hydroxylamine derivative of methylated decarbousnic acid.

By hydrogen peroxide oxidation in alkaline solution, (III) gave a compound $C_5H_5O_3N$ (VI), m.p. 208°, which was identical with 3-methyl-5-isoxazolecarboxylic acid[2] by mixed melting point determination, infrared and ultraviolet spectra. This result indicates that the newly introduced methyl group is not situated at 1,3-diketone system in the molecule of (II). The trioxime monoanhydride derivative (V) gave, by hydrogen peroxide oxidation, white crystals $C_9H_{11}O_5N$, m.p. 216~217°, which were identical with α,α,3-trimethyl-4-carboxy-5-isoxazole acetic acid (VII)[*1] obtained by hydrogen peroxide oxidation of bisoxime bisanhydride of methyldihydrousnic acid, by mixed melting point determination and infrared spectra. This result indicates that a *gem*-dimethyl group is present in the molecule of (II).

By 20% alkaline decomposition in hydrogen stream, (II) gave faint green crystals, $C_{15}H_{16}O_6$ (VIII), m.p. 158°, and white crystals $C_{16}H_{18}O_5$ (IX), m.p. 87~88°. The former gave blue black coloration with ferric chloride and was titrated as dibasic acid and gave 3 mole of C-CH_3 groups as usnetic acid. The latter gave red orange coloration with ferric chloride and did not bubble in sodium bicarbonate solution. They correspond to methylated usnetic acid and methylated acetousnetol, respectively. The differences of the infrared absorption maxima between (VIII) (1700, 1663, 1603 cm^{-1} (br.)) and usnetic acid (1700, 1620 cm^{-1}) suggest that (VIII) has one more carbonyl group than usnetic acid and a *gem*-dimethyl group in its molecule as compared with usnetic acid. The infrared absorption maxima at 1600, 1480 and 1260 cm^{-1} indicate the presence of furan ring in both (VIII) and usnetic acid.

By oxidation with hydrogen peroxide in alkaline solution, (VIII) gave white crystals $C_9H_8O_7$, m.p. 250° (decomp.), and $C_{12}H_{14}O_6$, m.p. 158°. The former was identical with

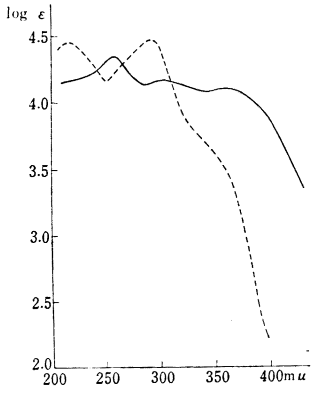

Fig. 1.

—— Methylusnic acid
(2.590 mg. in 300 cc. EtOH)
······ Usnic acid
(2.776 mg. in 330 cc. EtOH)

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2) L. Claisen : Ber., 42, 60 (1909).
3) Previous paper.

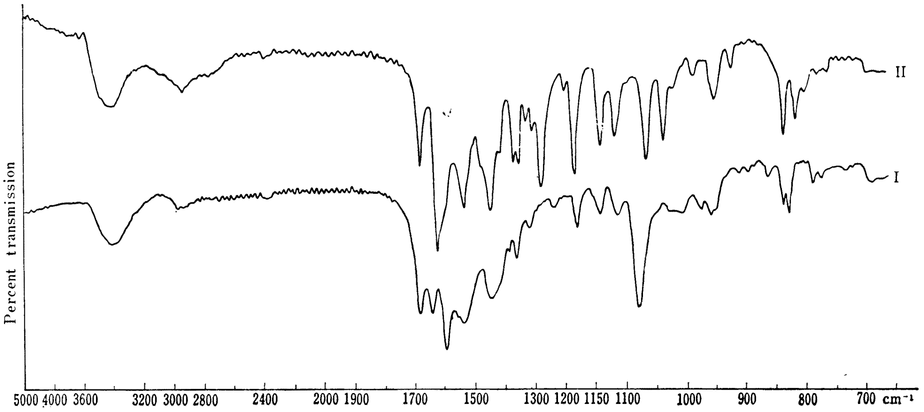

Fig. 2.

I : Methylusnic acid (KBr Pellet) II : Usnic acid (KBr Pellet)

3-methyl-4,5-dicarboxy-2-furanacetic acid[4] (X). The latter was titrated as dibasic acid. From above-mentioned results, it is elucidated that the newly introduced methyl group is situated at A-ring of usnic acid as C-CH_3, resulting in a *gem*-dimethyl radical. The determination of O-CH_3 of (I) is abnormal case of the Zeisel method. Consequently, the constitution of (I), (II), (III), (IV), (VI), (VII), (VIII), (IX) and (X) are elucidated as presented in Chart 1.

Experimental[*2]

Methylation of Usnic Acid——To a solution of 10 g. of *d*-usnic acid in NaOH solution (32 g. NaOH in 340 cc. water), 60 cc. of dimethylsulfate was dropped for 1 hr. under vigorous stirring at 10°. After another 1 hr's. stirring, the solution was acidified with 10% HCl and precipitate was filtered and boiled with 80% MeOH for 5 min. on a water bath. The MeOH-insoluble yellow substance was recrystallized from Me_2CO, giving yellow crystals, m.p. 136° (I). Yield, 4.5 g. It was soluble in $NaHCO_3$ solution and gave red brown coloration with $FeCl_3$. UV λ_{max} mμ (ε) : 258 (22,000), 305 (14,500), 358 (12,400). $[\alpha]_D$ +364° (c=0.43, $CHCl_3$). *Anal.* Calcd. for $C_{19}H_{18}O_7$: C, 63.68; H, 5.06. Found : C, 63.73; H, 4.94. O-CH_3 : Calcd. 8.66%. Found : 5.33%. *dl*-Methylusnic acid, m.p. 134°. *Anal.* Found : C, 63.53; H, 5.52.

C-CH_3 Estimation of (I)——With 22 cc. of CrO_3-H_3PO_4 solution 27.7 mg. of (I) was decomposed for 30 hr. and 2.90 cc. of 0.1*N* KOH was needed to neutralize the distilled AcOH. C-CH_3 : Found. 3.78. C-CH_3 estimation of usnic acid. Found : 3.58. With 2 cc. of conc. H_2SO_4, 0.5 g. of (I) was treated at room temp. for 3 hr. and poured into ice water to give (I).

Action of Acetic Acid on (I)——A solution of 5 g. of (I) in AcOH (50 cc. of glac. AcOH and 15 cc. of water) was boiled for 2 hr. and AcOH was distilled off *in vacuo* and resulting resinous material was crystallized from 50% MeOH to give yellow crystats (II), m.p. 85~86°. Yield, 3.4 g. It gave a dark violet coloration with $FeCl_3$ and was positive to *o*-phenylenediamine and CHI_3 reactions. Optically inactive. O-CH_3 : negative. UV λ_{max} mμ (ε) : 215 (17,700), 274 (14,600), 329 (11,900), 385 (6,600, shoulder). *Anal.* Calcd. for $C_{18}H_{20}O_6$: C, 65.05; H, 6.07. Found : C, 65.36; H, 6.06.

Oximation of (II)——(A) Monoxime monoanhydride of (II). To a solution of 0.5 g. of hydroxylamine hydrochloride and 0.5 g. of anhyd. AcONa in 10 cc. of EtOH, 1 g. of (II) was added and warmed on a water bath for 2 hr. Yellow crystals (III), m.p. 89°(from 50% EtOH). It gives blue coloration with $FeCl_3$. UV λ_{max} mμ (ε) : 215 (20,900), 260 (7,600), 329 (10,200), 376 (7,900). *Anal.* Calcd. for $C_{18}H_{19}O_5N$: C, 65.64; H, 5.82; N, 4.25. Found : C, 65.49; H, 5.90; N, 4.53.

(B) Bisoxime bisanhydride of (II). Monoxime monoanhydride of (II) was oximated as above, white crystals, (IV), m.p. 149°(from dil. EtOH). The $FeCl_3$ reaction was negative. *Anal.* Calcd. for $C_{18}H_{18}O_4N_2$: C, 66.24; H, 5.56; N, 8.58. Found : C, 66.29; H, 5.63; N, 8.59.

[*3] Ultraviolet absorption spectra were taken in ethanol solution using Hitachi EPU-2A spectrophotometer. Infra-red absorption spectra were taken using Nippon Bunko Model IRS Infra code.

4) Y. Asahina, M. Yanagita : Yakugaku Zasshi, 57, 280 (1937).

(C) Monoxime of (II). To a solution of 0.8 g. of hydroxylamine hydrochloride and 0.8 g. of anhyd. AcONa, MeOH solution of 1.5 g. of (II) was added and warmed on a water bath at 60~70° for 20 min. After cooling, precipitated crystals were recrystallized from MeOH, green crystals, m.p. 175°. $FeCl_3$ reaction; blue, *o*-phenylenediamine reaction; negative. *Anal.* Calcd. for $C_{18}H_{21}O_6N$: C, 62.24; H, 6.10; N, 4.03. Found : C, 62.27; H, 6.14; N, 4.21.

(D) Oximation of monoxime of (II). To a solution of 1.5 g. of hydroxylamine hydrochloride and 1.5 g. of anhyd. AcONa, MeOH solution of 1.5 g. of monoxime of (II) was added and warmed at 80° for 1.5 hr. White crystals (V), m.p. 166° (from 50% MeOH). $FeCl_3$ and *o*-phenylenediamine and Legal reactions; negative. UV λ_{max} 219 mμ (ε 16,900). *Anal.* Calcd. for $C_{18}H_{21}O_5N_3$: C, 60.16; H, 5.89; N, 11.69. Found : C, 59.82; H, 6.04; N, 11.94.

Hydrogen Peroxide Oxidation of (III). Formation of 3-Methyl-5-isoxazolecarboxylic Acid (VI)——To a solution of 1 g. of (III) in 30 cc. of 3% KOH, 20 cc. of 3% H_2O_2 was added gradually. Then the solution was warmed at 70° on a water bath. Total 45 cc. of H_2O_2 was added during 7 hr. The mixture was acidified with dil. HCl, and extracted with Et_2O. The Et_2O was distilled off and the residue was crystallized from dil. EtOH to give white crystals, $C_5H_5O_3N$ (VI), m.p. 208°. It showed no m.p. depression with authentic sample of 3-methyl-5-isoxazolecarboxylic acid. *Anal.* Calcd. for $C_5H_5O_3N$: C, 47.25; H, 3.97; N, 11.02. Found : C, 47.19; H, 4.26; N, 10.60.

Hydrogen Peroxide Oxidation of (V)——To a solution of 0.5 g. of (V) in 30 cc. of 5% KOH was added 20 cc. of 3% H_2O_2 and warmed at 70~80°. Then 4 cc. of 3% H_2O_2 was added six times at an interval of 1 hr. and 1 cc. of 30% H_2O_2 eight times at an interval of 1 hr., that is, 24 cc. of 3% H_2O_2 and 8 cc. of 30% H_2O_2 were added in 14 hr. The solution was acidified with dil. HCl and extracted with Et_2O. After evaporation of Et_2O, white crystals were obtained, m.p. 216~217°. This showed no m.p. depression with 5-isoxazole acetic acid (VII)[3] and was identical in infrared absorption spectra. *Anal.* Calcd. for $C_9H_{11}O_5N$: C, 50.70; H, 5.20. Found : C, 50.39; H, 5.37.

Alkaline Decomposition of (II)——A solution of 3.5 g. of (II) in 37 cc. of 20% KOH was heated at 70° on a water bath for 1 hr. in H_2 stream and the solution was acidified with dil. HCl in ice to give resinous material, which was dried in a desicater and powdered and divided into benzene-soluble and benzene-insoluble fractions. The benzene-insoluble fraction was crystallized from dil. EtOH to give faint green white needles, $C_{15}H_{16}O_6$ (VIII), m.p. 158°. Yield, 1.3 g. It was soluble in $NaHCO_3$ solution and gave blue violet coloration with $FeCl_3$. It was positive to CHI_3 reaction but negative to *o*-phenylenediamine reaction. It gave 2.6 moles of $C-CH_3$ by the Kuhn-Roth method and had no methoxy group by the Zeisel method. UV λ_{max} mμ (ε) : 226 (17,100), 335 (10,100). *Anal.* Calcd. for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52. Found : C, 61.62; H, 5.64. Molecular weight; Found : 281 (Rast, Camphor), 308 (acidimetry as dibasic acid).

The benzene-soluble fraction gave red resinous substance after evaporation of benzene, which was treated with 50% EtOH. The 50% EtOH-soluble portion forms white needles by crystallization from dil. EtOH. $C_{16}H_{18}O_5$ (IX), m.p. 87~88°. Yield, 0.4 g. It was not soluble in $NaHCO_3$ solution in the cold and gave red orange coloration with $FeCl_3$ but no coloration with *o*-phenylenediamine. Molecular weight; 295 (Rast, Camphor). UV λ_{max} mμ (ε) : 217 (19,400), 271 (10,700). *Anal.* Calcd. for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found : C, 66.52; H, 6.43.

Hydrogen Peroxide Oxidation of (VIII)——To a solution of 0.5 g. of (VIII) in 5% KOH, 10 cc. of H_2O_2 was added and warmed on a water bath at 80°. The color of the solution turned from red orange to yellow, then 10 cc. of 3% H_2O_2 was added two times at an interval of 30 min. and 1 cc. of 30% H_2O_2 was added four times at an interval of 1 hr. Total 30 cc. of 3% H_2O_2 and 4 cc. of 35% H_2O_2 was added during 5.5 hr. The solution was acidified with dil. HCl and salted out with NaCl and extracted with AcOEt. After evaporation of solvent, white crystals remained in resinous substance. The crystals were recrystallized from a mixture of AcOEt and petr. ether to give white crystals, m.p. 250°(decomp.). It was identical with (X) by mixed melting point determination and IR and UV spectra. UV λ_{max} 283 mμ. *Anal.* Calcd. for $C_9H_8O_7$: C, 47.38; H, 3.53. Found : C, 47.20; H, 3.53.

From AcOEt more soluble fraction, white crystal was obtained, m.p. 158°. UV μ_{max} 221 and 277 mμ. Molecular weight; 280 (Rast, Camphor), 274 (acidimetry as dibasic acid). *Anal.* Found : C, 57.15, 57.35; H, 5.51, 5.66.

The authors express their gratitude to Dr. Y. Asahina, Prof. Emeritus, University of Tokyo, for his kind encouragement throughout this work, and Mr. Hiroshi Ogata, for supply of usnic acid. They are indebted to Mr. Yoshitaka Itatani of this faculty, for elemental analyses.

Summary

The constitution of methylusnic acid, the methylation product of usnic acid with dimethyl sulfate and sodium hydroxide, first reported by A. Robertson *et al.* was reinvestigated and elucidated as (I).

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