UDC 547.97 : 582.29

98. **Kōtaro Takahashi and Shūichi Miyashita** : Usnic Acid. I. Methyldihydrousnic Acid.

(*Pharmaceutical Faculty, University of Kanazawa*[*1])

The structural formula of usnic acid[1] which was previously advanced by Robertson, Schoepf and Asahina has been established by Barton and his co-workers[2] by their synthesis of racemi usnic acid which was accomplished by the oxidative condensation of methylphloroacetophenone. However, a remarkable difference of the behaviors in the degradation reactions observed between usnic acid and dihydrousnic acid still leaves some room for criticism. Recently, on methylation of usnic acid with dimethyl sulfate and sodium hydroxide, Robertson[3] obtained a compound $C_{19}H_{18}O_7$, m.p. 136°. They assumed it to be an enol methyl ether of usnic acid. In this paper, we report on a new product, methylation product of dihydrousnic acid, named methyldihydrousnic acid, and its decomposition reactions. On methylation with dimethyl sulfate and sodium hydroxide, *l*-dihydrousnic acid yielded *d*-methyldihydrousnic acid, $C_{19}H_{20}O_7$ (I), white crystals, m.p. 165~166°, $[\alpha]_D$ +218.1°, which had not a methoxy group by the Zeisel method. This compound was also obtained by catalytic hydrogenation of Robertson's methylation product of usnic acid which had about 0.6 mole of methoxy group by the Zeisel method. During these reactions, the inversion of optical rotation was observed. *d*-Usnic acid ($[\alpha]_D$ +493.7°) was methylated to *d*-Robertson's compound ($[\alpha]_D$ +364°) which was hydrogenated to *d*-methyldihydrousnic acid ($[\alpha]_D$ +215.0), but *d*-usnic acid was hydrogenated to *l*-dihydrousnic acid ($[\alpha]_D$ −81.4°) which was methylated to *d*-methyldihydrousnic acid ($[\alpha]_D$ +218.1°). From *dl*-dihydrousnic acid, by this methylation, *dl*-methyldihydrousnic acid, m.p. 140~141°, was obtained.

Methyldihydrousnic acid is soluble in sodium hydrogen carbonate solution and gives red brown coloration with ferric chloride but does not give the coloration with *p*-dimethylaminobenzaldehyde (Ehrlich reaction). By C-methyl determination (Kuhn-Roth), 4 moles of acetic acid were obtained, alike dihydrousnic acid.

The ultraviolet and infrared spectra are shown in Fig. 1 and Fig. 2 with those of

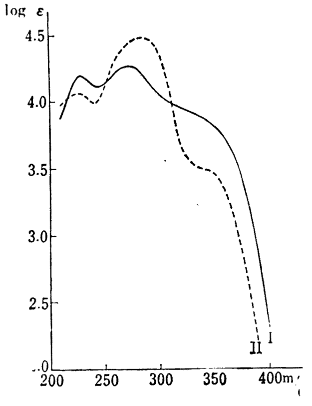

Fig. 1.

I : Methyldihydrousnic acid
(1.89 mg. in 200 cc. EtOH)
II : Dihydrousnic acid
(3.87 mg. in 520 cc. EtOH)

[*1] Tsutitoribanaga-machi, Kanazawa, Ishikawa-ken (高橋幸太郎, 宮下修一).

[1] Y. Asahina, S. Shibata : "The Chemistry of Lichen Substances," Japan Society for the Promotion of Science, Tokyo, Japan, **1954**.

[2] D.H.R. Barton, A.M. Delforin, O.E. Edwards : J. Chem. Soc., **1956**, 530.

[3] F.M. Dean, P. Halewood, S. Mongkolsuk, A. Robertson, W.B. Whalley : *Ibid.*, **1953**, 1250.

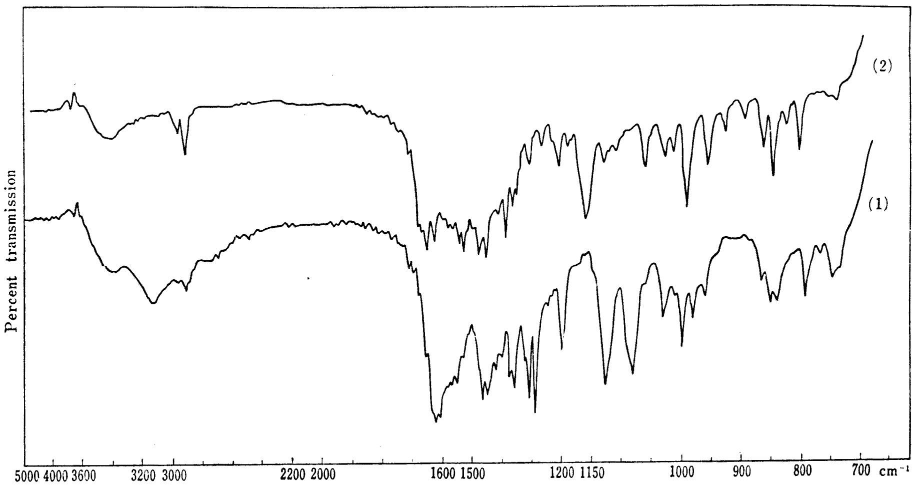

Fig. 2.

(1) Dihydrousnic acid (KBr Pellet) (2) Methyldihydrousnic acid (KBr Pellet)

dihydrousnic acid. The remarkable differences between infrared absorption curves of (I) and that of dihydrousnic acid, especially in the region of 1600~1700 cm^{-1} indicate the difference of carbonyl system in these two substances.

(I) yielded bisphenylhydrazone bisanhydride which appeared in two crystal forms, $C_{31}H_{28}O_3N_4 \cdot 2C_6H_6$, m.p. 136° and $C_{31}H_{28}O_3N_4 \cdot 2C_7H_8$, m.p. 114~116°, depending on the solvent used for crystallization. The ultraviolet curves of two forms in alcoholic solution were identical.

On treatment with hydroxylamine hydrochloride and sodium acetate in alcoholic solution, (I) gave bisoxime bisanhydride $C_{19}H_{18}O_5N_2$ (II), m.p. 197~198°. By oxidation of (II) with hydrogen peroxide, a product $C_9H_{11}O_5N$ (III), m.p. 216°, was obtained. By the molecular weight determination by the Rast method and acidimetry, (III) was a dicarboxylic acid and gave dimethyl ester by diazomethane, $C_{11}H_{15}O_5N$, b.p_{16} 150~160° (bath temp.). By decarboxylation at 220~230° and subsequent distillation at 16~17 mm Hg., (III) was converted to a monocarboxylic acid $C_8H_{11}O_3N$ (IV), m.p. 151~152°, which was proved to be identical with 3-methyl-5-isopropyl-4-isoxazolecarboxylic acid, synthesized by hydrolysis of oximated ethyl 2-isobutyrylacetoacetate, by the mixed melting point determination, infrared and ultraviolet spectra. Two constitutions are possible to this isoxazole monocarboxylic acid, one of which is 3-methyl-5-isopropyl-4-isoxazolecarboxylic acid (IV) and the other is 3-isopropyl-5-methyl-4-isoxazolecarboxylic acid, but the former is more likely from the view-point of the steric hindrance in the course of the synthesis and (III) has another carboxylic acid at the side-chain of (IV) and may be formulated as (III).

From the fact that methyl groups and acetyl groups in dihydrousnic acid molecule are situated at meta position and a *gem*-dimethyl group is not present, it is reasonable to assume that the methylation of dihydrousnic acid occured at C-methyl position, resulting in a *gem*-dimethyl group in A-ring of dihydrousnic acid molecule.*2 From these results and analytical point of view, the methyldihydrousnic acid can be formulated as (I).

On oxidation with potassium permanganate in 10% potassium hydroxide solution,

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*2 part II : This Bulletin, **10**, (1962).

4) A. Spassow : Ber., **70**, 2381 (1937).

followed by distillation, as in the case of dihydrousnic acid,[5] (I) yielded 3-methyl-2, 6-dihydroxy-acetophenone and a compound, m.p. 235°, faint yellow crystals.

Although some arguments have been presented for the mechanism of the formation of resorcinol type of compounds on Robertson's formula of dihydrousnic acid, an unequivocal experimental proof has not been obtained as yet. But the result that one of resorcinol type of compounds is obtained from methyldihydrousnic acid indicates that 3-methyl-2,6-dihydroxyacetophenone is derived from one of nucleus of dihydrousnic acid which is not methylated by this method, namely from the B-ring of dihydrousnic acid. (I) did not give the coumaranone derivative[6] which was obtained from dihydrousnic acid, by the vacuum distillation with calcium chloride or without it.

On acetylation, (I) was converted to a compound (V), $C_{21}H_{20}O_7$, m.p. 172~173°, by obtaining one acetyl group and liberating one mole of water. When treated with concentrated sulfuric acid in the cold or 10% sodium hydroxide on a water bath, liberating one mole of acetyl group, (V) yielded a compound $C_{19}H_{18}O_6$(VI), m.p. 245~246°, which corresponds to anhydromethyldihydrousnic acid which was reacetylated to (V).

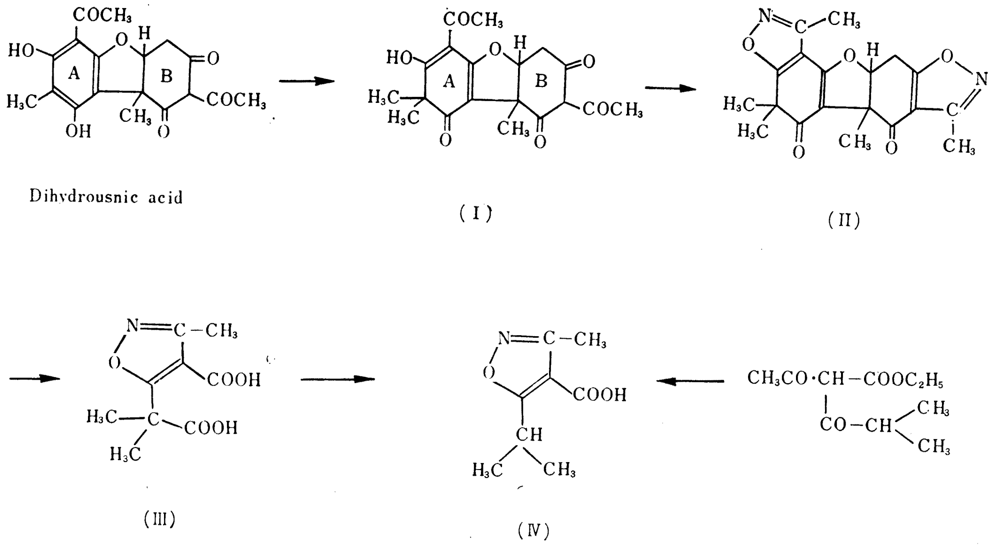

Chart 1.

The authors are now studying on this anhydromethyldihydrousnic acid and will report shortly on its constitution and decomposition reactions.

Experimental*3

Methylation of Dihydrousnic Acid——To a solution of 15 g. of *l*-dihydrousnic acid in 600 cc. of 2*N* NaOH, 45 cc. of dimethyl sulfate was dropped for 30~40 min. under vigorous stirring at 15~20°. After 1 hr stirring, the solution was neutralized with 10% HCl. The precipitate was filtered off and recrystallized from EtOH giving white crystals, *d*-methyldihydrousnic acid (I), m.p. 165~166°. Yield, 11 g. It was soluble in $NaHCO_3$ solution and gave red brown coloration with $FeCl_3$ in EtOH solution. It had no methoxy group and gave no melting point depression on admixture with hydrogenated product of Robertson's methylation product of usnic acid, and both had the same IR absorption

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

5) Y. Asahina, M. Yanagita : Yakugaku Zasshi, **59**, 699(1939).

6) *Idem* : *Ibid.*, **59**, 702 (1939).

curves. UV λ_{max} mμ (ε) : 230 (16,000), 274 (18,700). $[\alpha]_D$: +218.1°(c=1.16, $CHCl_3$). *Anal.* Calcd. for $C_{19}H_{20}O_7$: C, 63.33; H, 5.59. Found : C, 63.32, 63.06; H, 5.42, 5.51.

***dl*-Methyldihydrousnic Acid**——m.p. 140~141°. This was obtained by the methylation of *dl*-dihydrousnic acid. *Anal.* Found : C, 63.28; H, 5.74.

Catalytic Hydrogenation of Robertson's Methylation Product of Usnic Acid——*d*-Rotatory substance (4 g.), dissolved in tetrahydrofuran (30 cc.), was hydrogenated with Pd-black. After half an hour's shaking, when 370 cc. (ca. 1.4 moles) of H_2 was absorbed, the solvent was removed *in vacuo* and the residue was recrystallized from MeOH to give white crystals, m.p. 166°. $[\alpha]_D$: +215.0°(c=1.275, $CHCl_3$). *Anal.* Calcd. for $C_{19}H_{20}O_7$: C, 63.33; H, 5.59. Found : C, 62.98; H, 5.52.

C-Methyl Determination of (I) and Dihydrousnic Acid by the Kuhn-Roth Method——To neutralize AcOH obtained from 0.0988 g. of (I), 9.587 cc. of 0.1*N* KOH was required. Found : C-CH_3, 3.88 mole. To neutralize AcOH obtained from 0.1013 g. of dihydrousnic acid, 10.30 cc. of 0.1*N* KOH was required. Found : C-CH_3, 3.52 moles.

Bisphenylhydrazone Bisanhydride of (I)——A mixture of 3 g. of (I), 3 g. of phenylhydrazine hydrochloride, 1.7 g. of anhyd. AcONa and 60 cc. of EtOH was boiled on a water bath for 3 hr. After evaporation of EtOH *in vacuo*, water was added and the precipitate was recrystallized. From benzene it forms white crystals, m.p. 135~136°(decomp.). *Anal.* Calcd. for $C_{31}H_{28}O_3N_4 \cdot 2C_6H_6$: C, 78.15; H, 6.10; N, 8.48. Found : C, 78.01; H, 6.18; N, 8.66 (dried on $CaCl_2$ at ordinary pressure). UV λ_{max} mμ (ε) : 209 (28,200), 251 (24,700). From toluene it forms white crystals, m.p. 114~116°(decomp.). UV λ_{max} mμ (ε) : 210 (35,200), 251 (32,800). *Anal.* Calcd. for $C_{31}H_{28}O_3N_4 \cdot 2C_7H_8$: C, 78.46; H, 6.44; N, 8.13. Found : C, 78.22; H, 6.44; N, 8.27. On heating with alcoholic HCl on water bath, both were recovered unchanged.

Bisoxime Bisanhydride of (I)——A mixture of 2 g. of (I), 1.0 g. of anhyd. AcONa and 0.9 g. of hydroxylamine hydrochloride in EtOH was refluxed for 4 hr. The solution was concentrated to one-half of its volume and was poured into water. When the precipitate separated out, which was chromatographed on alumina with benzene. The benzene solution was distilled to give crystals (Ⅱ), m.p. 197~198^c. Yield 0.9 g. UV λ_{max} mμ (ε) : 212 (21,800), 260 (4,900), 271 (7,100), 330 (5,000). *Anal.* Calcd. for $C_{19}H_{18}O_5N_2$: C, 64.40; H, 5.12; N, 7.91. Found : C, 64.36; H, 5.35; N, 8.29.

Oxidation of (II) with Hydrogen Peroxide——To a solution of 3 g. of (Ⅱ) in 80 cc. of 3% KOH, 30 cc. of 3% H_2O_2 was added. On warming on a water bath at 70~80°, the solution became green after 10~15 min. Then 10 cc. of 3% H_2O_2 was added one time at interval of an hour. After 7 hr. the solution became faint brown. After acidification with dil. HCl and salting out with NaCl, it was extracted with Et_2O. After drying with anhyd. Na_2SO_4, Et_2O was distilled off to give white crystals (Ⅲ), m.p. 216°(from water). It was soluble in $NaHCO_3$ solution with bubbling. UV : λ_{max} 222 mμ (ε 5,800). *Anal.* Calcd. for $C_9H_{11}O_5N$: C, 50.70; H, 5.20; N, 6.57. Found : C, 50.33; H, 5.33; N, 6.56. Acidimetry. Calcd. as dicarboxylic acid, COOH %, 42.30%. Found : 42.80%.

Decarboxylation of (III)——On heating 2 g. of (Ⅲ) at 220~230°(bath temp.) for 10 min., it melted with vigorous evolution, and then was distilled *in vacuo* (bath temp. 160~190°, 16 mm. Hg.) giving oil which solidified in crystals. It was recrystallized from dil. EtOH to give white crystals (Ⅳ), m.p. 151~152°, which was soluble in $NaHCO_3$ solution with evolution. UV : λ_{max} 216 mμ (ε 7,200). *Anal.* Calcd. for $C_8H_{11}O_3N$: C, 56.79; H, 6.55; N, 8.28. Found : C, 57.15; H, 6.88; N, 8.53. Molecular weight. Calcd. 169. Found : 175 (Rast. Campfer). Acidimetry. Calcd. as monocarboxylic acid, COOH %, 26.62%. Found : 26.60%.

Synthesis of 3-Methyl-5-isopropyl-4-isoxazolecarboxylic Acid——A mixture of 0.4 g. of ethyl isobutyryl acetoacetate and 0.14 g. of hydroxylamine hydrochloride in 3 cc. of EtOH was kept at room temperature overnight. After evaporation of EtOH, a small volume of water was added to give oily substance which was extracted with Et_2O. The Et_2O solution was evaporated and water was added to it. After acidification with dil. HCl, white crystals separated out, which was recrystallized from dil. EtOH, m.p. 151°. It was proved to be identical with (Ⅳ) by mixed fusion, IR and UV spectra. UV λ_{max} 216 mμ (ε 6,900). *Anal.* Calcd. for $C_8H_{11}O_3N$: C, 56.79; H, 6.55; N, 8.28. Found : C, 56.92; H, 6.51; N, 8.01.

Oxidation of (I). Formation of 3′-methyl-2′,6′-dihydroxyacetophenone——A solution of 3.2 g. of (I) in 40 cc. of 10% KOH was diluted to 1 L. with water. To this solution, 100 cc. of 4% $KMnO_4$ was dropped during 3 hr. under vigorous stirring at room temperature. erature The filtered alkaline solution was acidified with dil. HCl and then extracted with $CHCl_3$. After evaporation of $CHCl_3$ *in vacuo*, the resulting oil was distilled at 1 mm. Hg. (bath temp. 150~250°). The distillate solidified partially after standing and then was seperated into Et_2O-soluble (A) and Et_2O-insoluble (B) fractions.

The Et_2O-soluble fraction (A) was recrystallized from benzene to give yellow needles, m.p. 136~137°, which was identical with 3′-methyl-2′,6′-dihydroxyacetophenone by mixed melting point determination, IR and UV spectra. UV λ_{max} mμ (ε) : 223 (12,800), 271 (13,900), 353 (3,800). *Anal.* Calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found : C, 65.06; H, 6.09.

The Et_2O-insoluble fraction (B) was recrystallized from a mixture of benzene and petr. ether to 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.

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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.

(*Pharmaceutical Faculty, University of Kanazawa*[*2])

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.