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Usnic Acid. XV.¹⁾ Alkaline Degradation of Usnic Acid

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The alkaline degradation product of usnic acid was identified as 4,6-dihydroxy-3,5-dimethylcoumaran-2-one on the basis of spectral and chemical evidence. The reaction mechanism is discussed.

Keywords—usnic acid; alkaline degradation; 4,6-dihydroxy-3,5-dimethylcoumaran-2-one; ¹³C-NMR; ¹H-NMR; reaction mechanism

Some reports have appeared on the alkaline degradation products of usnic acid in a hydrogen stream, indicating them to be benzofuran-type compounds, such as usnetic and decarbousnic acids.³⁾ This paper deals with a new alkaline degradation product of usnic acid in an oxygen stream. Usnic acid was hydrolyzed with 50% (w/v) sodium hydroxide solution in an oxygen stream and the hydrolysate was treated as mentioned in "Experimental" to afford colorless needles, C₁₀H₁₀O₄ (I), of mp 162°. Compound I shows ultraviolet (UV) absorption maxima at 210 nm (log ε 4.10, an end absorption), 278 nm (log ε 3.33) and 283 nm (log ε 3.33) and infrared (IR) absorption bands (cm⁻¹) at 3400 (OH), 1765 (β,γ-unsaturated γ-lactone), 1640 and 1530 (benzene ring), but it does not show IR bands at 1690 (α,β,γ,δ-unsaturated C=O) or 1540 (broad, characteristic of a triketone),⁴⁾ which are observed in the IR spectrum of usnic acid, suggesting that ring B of usnic acid was decomposed. Compound I was positive to the Gibbs test. On methylation with diazomethane, I afforded colorless needles of dimethyl ether, C₁₂H₁₄O₄ (II), of mp 122°, which showed IR bands at 1790 (β,γ-unsaturated γ-lactone), 1620, 1510 (benzene ring) and showed no OH band. Compound II gave proton magnetic resonance (¹H-NMR) signals (δ-value, ppm in CDCl₃) at 1.54 (d, 3H, J=7.5 Hz), 3.71 (q, 1H, J=7.5 Hz), assignable to a CH₃-CH< group, at 2.08 (s, 3H, an aromatic-CH₃ group), at 3.85 (s, 6H, two O-methyl groups) and at 6.20 (s, 1H, an aromatic proton). Compound I was proved to be identical with the compound obtained by hydrolysis of the ozonolysis product (III)³⁾ of diacetylusnic acid under the conditions described above, by mixed fusion and IR spectroscopy. This hydrolysate was identified as the desacetyl derivative of 7-acetyl-4,6-dihydroxy-3,5-dimethylcoumaran-2-one³⁾ on the basis of the spectral and chemical properties. These findings indicate that compound I is 4,6-dihydroxy-3,5-dimethylcoumaran-2-one (Chart 1). The ¹³C-NMR spectrum of II could be interpreted as shown in Table I.

Compound I was also obtained from usnic acid by hydrolysis in a nitrogen stream, but was not obtained from usnetic acid by hydrolysis in an oxygen stream.

The mechanism of the formation of I from usnic acid by hydrolysis in an oxygen stream or in a nitrogen stream was tentatively considered to be as shown in chart 1. Usnic acid, when attacked by OH⁻ at the C_{4a} carbon (the Michael reaction), might be converted to an intermediate (A⇌A'), which might be further converted to intermediate B by retro-Aldol

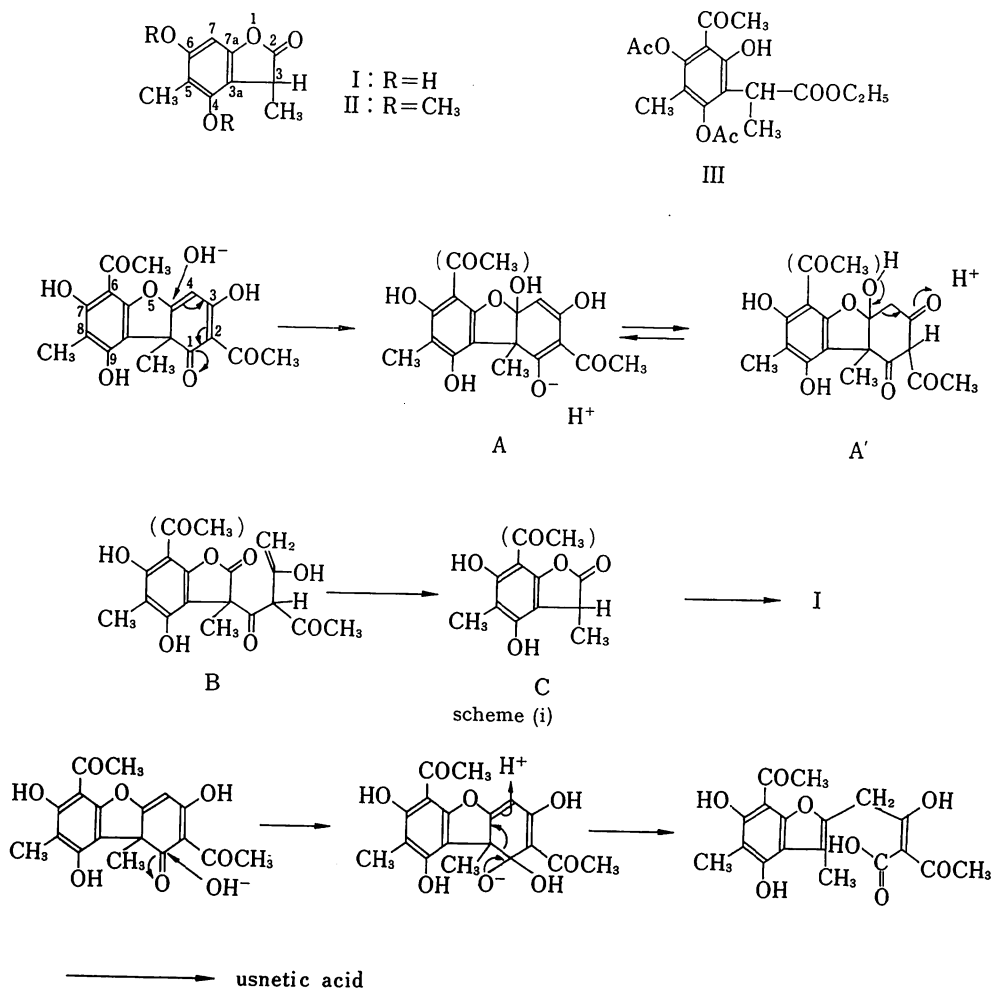
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2) Location: 13-1 Takaramachi, Kanazawa, 920, Japan.

3) Y. Asahina and S. Shibata: "Chemistry of Lichen Substances," 1954, p. 171. Japan Society for the Promotion of Science.

4) S. Shibata and J. Shoji: *Kagaku no Ryoiki*, **15**, 805 (1961).

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scheme (i)

scheme (ii)

Chart 1

TABLE I. NMR Data for II (δ -Values in CDCl_3 , 25.15 MHz, J in Hz)

	Chemical Shift ^{a)}	Multiplicity	$J^b)$
$\text{C}_5\text{-CH}_3$	8.1	q	$J_{\text{C-H}} = 128$
$\text{C}_3\text{-CH}_3$	15.3	q, d	$J_{\text{C-H}} = 131$, $J_{\text{CH}_3\text{-C}_1\text{H}} = 6$
C_3	37.9	d, q	$J_{\text{C}_1\text{-H}} = 135$, $J_{\text{C}_1\text{-C}_3\text{CH}_3} = 5$
C_7	90.7	d	$J_{\text{C}_7\text{-H}} = 156$
C_5	102.7	q, d	$J_{\text{C}_1\text{-C}_5\text{CH}_3} = 6$, $J_{\text{C}_1\text{-C}_5\text{H}} = 6$
C_{3a}	107.3	d, d	$J_{\text{C}_1\text{-C}_3\text{H}} = 5$, $J_{\text{C}_1\text{-C}_3\text{CH}_3} = 9$
C_4	152.9	q, d	$J_{\text{C}_1\text{-C}_4\text{CH}_3} = 4$, $J_{\text{C}_1\text{-C}_4\text{H}} = 4$
C_{7a}	154.3	broad	
C_6	159.1	q	$J_{\text{C}_1\text{-C}_6\text{CH}_3} = 4$
C_2	178.7	d, q	$J_{\text{C}_1\text{-C}_2\text{H}} = 5$, $J_{\text{C}_1\text{-C}_2\text{CH}_3} = 6$
OCH_3	55.5	q	$J_{\text{C-H}} = 144$
	55.9	q	$J_{\text{C-H}} = 144$

^{a)} ppm relative to TMS, measured with complete decoupling.

^{b)} Measured without decoupling and assigned tentatively.

Digital resolution was 1.2 Hz.

transformation, and intermediate B might then be converted to compound I by ketonic fission. The reaction probably does not involve auto-oxidation. On the other hand, usnic acid, when attacked by OH^- at its C_1 carbon, might be converted to usnetic acid, as shown by scheme (ii) in Chart 1.

Coumaran-2-one compounds of the phloroglucinol type have been obtained from diacetyl-usnic acid by ozonolysis³⁾ and also from diacetyldihydrousnic acid⁵⁾ and diacetyltetrahydro-desoxyusnic acid⁶⁾ by pyrolysis in the absence of calcium chloride, and coumaran-2-one compounds of the resorcinol type have been obtained from dihydrousnic acid and tetrahydro-desoxyusnic acid by pyrolysis in the presence of calcium chloride.⁷⁾ The authors have already reported^{6,7)} on the mechanism of the pyrolysis of dihydrousnic acid and tetrahydrodesoxy-usnic acid. It is interesting that compound I, of coumaran-2-one type, is obtained from usnic acid by hydrolysis, in addition to usnetic acid and pyrousnic acid.

Experimental

The following instruments were used for determining physical data. Melting point: Yanagimoto micro-melting apparatus (a hot plate type); UV spectra (in EtOH): Hitachi 323 recording spectrometer; IR spectra (in KBr, cm^{-1}): Nippon Bunko IR-G spectrometer; $^1\text{H-NMR}$: JNM-FX-100S instrument at 100 MHz ($^{13}\text{C-NMR}$ at 25.15 MHz), with $(\text{CH}_3)_4\text{Si}$ as an internal standard; mass spectra (MS): JMS-01SG spectrometer (direct inlet, with an ionizing current of 200 μA , ionizing energy of 75 eV and source temperature of 95°); thin-layer chromatography (TLC) was carried out on glass plates coated with silica gel G (Merck) and column chromatography with silica gel (Merck), unless otherwise stated. Abbreviations: s: singlet, d: doublet, t: triplet, q: quartet m: multiplet.

Hydrolysis of Usnic Acid in an Oxygen Stream—Usnic acid (7.2 g) in 50% (w/v) sodium hydroxide solution (45 ml) was hydrolyzed in an oxygen stream on a boiling water bath for 1 hr, then the reaction mixture was poured into ice-water and acidified with conc. HCl to afford a precipitate, which contained usnetic acid ($R_f=0.33$, TLC, silica gel, impregnated with 0.1 N $(\text{COOH})_2$, CHCl_3 -acetone=10:1) and pyrousnic acid ($R_f=0.05$, TLC, silica gel impregnated with 0.1 N $(\text{COOH})_2$, CHCl_3 -acetone=10:1) were detected. The acidic aqueous layer was extracted thoroughly with ethyl acetate and the ethyl acetate layer was concentrated *in vacuo*, after washing with water then drying with sodium sulfate, to afford an oily substance. This was column chromatographed twice on silica gel with ethyl acetate- CHCl_3 (1:1) and the fraction of R_f 0.62 (TLC, ethyl acetate- $\text{CHCl}_3=1:1$) (oil 0.85 g) was chromatographed on silica gel (100 g) with acetone- CHCl_3 (1:5). The fraction of R_f 0.32 (TLC, silica gel acetone- $\text{CHCl}_3=1:5$) afforded a powder, which was purified by sublimation *in vacuo* at 130° to afford colorless needles (I) of mp 162°. (Yield: 0.36 g). $[\alpha]_{\text{D}}^{25}=0^\circ$ ($c=1.00$, MeOH). The R_f values of I and the powder were the same. Anal. Calcd for $\text{C}_{10}\text{H}_{10}\text{O}_4$: C, 61.85; H, 5.19. Found: C, 61.66; H, 5.09. $^1\text{H-NMR}$ (δ -value in $\text{C}_6\text{D}_6\text{N}$, 60 MHz): 1.67 (d, 3H, $J=7.3$ Hz, C_3 - CH_3), 2.35 (s, 3H, C_5 - CH_3), 3.98 (q, 1H, $J=7.3$ Hz, C_3 -H), 6.35 (s, 1H, C_7 -H), 11.33 (s, 2H, C_4 -OH and C_6 -OH). MS (m/e , relative intensity): 194 (M^+ , 64.5), 179 (M^+-CH_3 , 6.3), 166 (M^+-CO , 100), 165 (m/e 166-H, 17), 151 (m/e 166- CH_3 , 25), 138 (m/e 166-CO, 8), 123 (m/e 138- CH_3 , 15). IR (cm^{-1}): 3400, 1765, 1640, 1530, 1470, 1430, 1370, 1240, 1220, 1165, 1080, 1060, 1020, 825. Gibbs test: red-violet in the Clark and Lubs buffer solution (boric acid-KCl-NaOH, pH=9.4).

Methylation of I—Compound I (300 mg) in MeOH was methylated with excess diazomethane in ether for 3 days. The crude methylate was chromatographed on silica gel with CHCl_3 -benzene (1:1) and the fraction of R_f 0.67 (TLC, CHCl_3 -benzene=1:1) afforded a colorless substance, which was crystallized from ethanol to afford the methylate (II), as colorless needles of mp 122°. Anal. Calcd for $\text{C}_{12}\text{H}_{14}\text{O}_4$: C, 64.85; H, 6.35. Found: C, 64.83; H, 6.34.

Alkaline Degradation of III in an Oxygen Stream—Compound III (2 g) in 50% (w/v) NaOH solution (12 ml) was hydrolyzed in an oxygen stream on a boiling water bath for 1 hr. The reaction mixture was poured into ice-water, acidified with conc. HCl and extracted with ethyl acetate. The extract afforded an oily substance (0.3 g), which was chromatographed on silica gel (40 g) with acetone- CHCl_3 (1:5). The fraction of R_f 0.32 (TLC, acetone- $\text{CHCl}_3=1:5$) (powder, 235 mg) was purified by sublimation *in vacuo* at 130° to afford colorless needles of mp 162°, which were proved to be identical with compound I by mixed fusion and IR. Anal. Calcd for $\text{C}_{10}\text{H}_{10}\text{O}_4$: C, 61.85; H, 5.19. Found: C, 61.56; H, 5.05. IR: 3400, 1765, 1645, 1530, 1470, 1430, 1370, 1240, 1220, 1165, 1125, 1080, 1060, 1020, 825.

Alkaline Degradation of Usnic Acid in a Nitrogen Stream—Usnic acid (7.2 g) in 50% (w/v) NaOH solution (44 ml) was hydrolyzed in a nitrogen stream on a boiling water bath for 1 hr. The reaction mixture

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7) K. Takahashi and M. Takani, *Chem. Pharm. Bull.*, **19**, 2079 (1971).

was treated as described for the hydrolysis of usnic acid in an oxygen stream. The ethyl acetate-soluble fraction (3.27 g) was chromatographed on silica gel with ethyl acetate- CHCl_3 (1:1) and the fraction of R_f 0.62 (TLC, ethyl acetate- CHCl_3 =1:1) (0.94 g) was again chromatographed on silica gel with acetone-*n*-hexane (1:1). The fraction of R_f 0.64 (TLC, acetone-*n*-hexane=1:1) (0.63 g) was further chromatographed on silica gel with CHCl_3 -acetone (5:1) and the fraction of R_f 0.32 (TLC, CHCl_3 -acetone=5:1) (0.37 g) afforded colorless needles of mp 162° , after sublimation at 130° *in vacuo* (3 mmHg); these were identical with compound I (mixed fusion, IR, and R_f value).

Alkaline Degradation of Usnetic Acid in an Oxygen Stream—Usnetic acid (1.5 g) in 50% (w/v) NaOH solution was hydrolyzed on a boiling water bath for 1 hr. The reaction mixture was poured into ice-water and acidified to afford a precipitate (0.5 g), from which usnetic acid was recovered (R_f 0.33, TLC, silica gel impregnated with 0.1 N $(\text{COOH})_2$, acetone- CHCl_3 =1:10). The filtrate was extracted with ethyl acetate and the ethyl acetate layer showed spots at R_f 0.33 and R_f 0.05 on TLC, which could be assigned to usnetic acid and pyrousnic acid, respectively; no spot assignable to I (R_f 0.26, TLC, silica gel impregnated with 0.1 N $(\text{COOH})_2$, acetone- CHCl_3 =1:10) was detected.

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