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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; ^{13}C-NMR; ^{1}H-NMR; reaction mechanism

Some reports have appeared on the alkaline degradation products of usinc 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, $C_{10}H_{10}O_4$ (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 (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 ($\alpha,\beta,\gamma,\delta$-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, $C_{12}H_{14}O_4$ (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 (^{1}H–NMR) signals (δ-value, ppm in $CDCl_3$) at 1.54 (d, 3H, J=7.5 Hz), 3.71 (q, 1H, J=7.5 Hz), assignable to a CH_3– CH< group, at 2.08 (s, 3H, an aromatic-CH_3 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-one[3] 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 ^{13}C–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$\rightleftarrows$A′), which might be further converted to intermediate B by retro-Aldol

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2) Location: *13-1 Takaramachi, Kanazawa, 920, Japan.*
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4) S. Shibata and J. Shoji: *Kagaku no Ryoiki*, **15**, 805 (1961).
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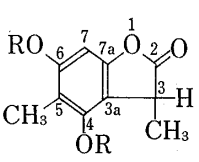
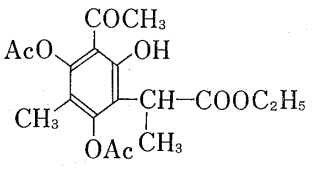
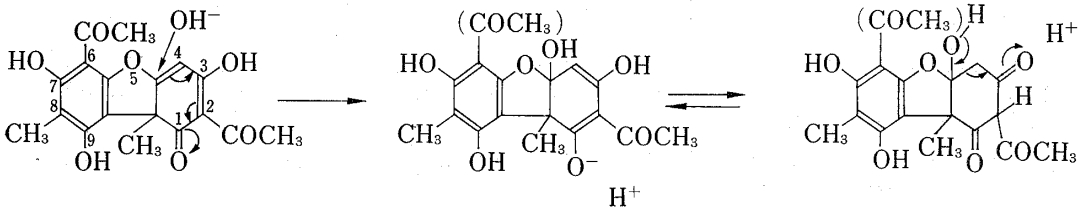


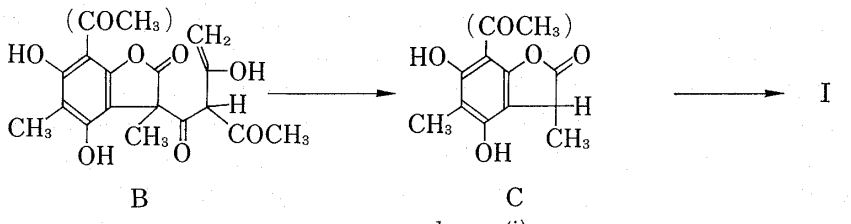
I : R=H
II : R=CH_3



III

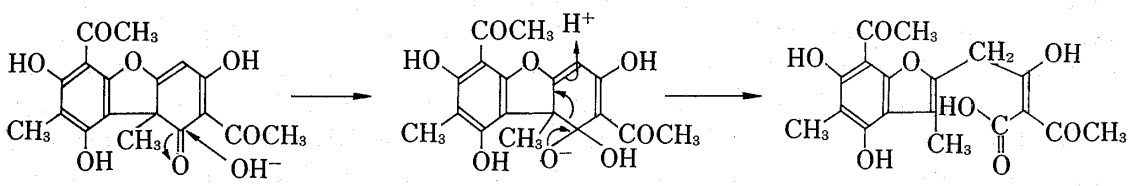


A A′



B C

scheme (i)



usnetic acid

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]
C_5-$\underline{C}H_3$	8.1	q	$J_{C-H}=128$
C_3-$\underline{C}H_3$	15.3	q, d	$J_{C-H}=131$, $J_{CH_3-C_3H}=6$
C_3	37.9	d, q	$J_{C_3-H}=135$, $J_{C_3-C_3CH_3}=5$
C_7	90.7	d	$J_{C_7-H}=156$
C_5	102.7	q, d	$J_{C_5-C_5CH_3}=6$, $J_{C_5-C_7H}=6$
C_{3a}	107.3	d, d	$J_{C_{3a}-C_7H}=5$, $J_{C_{3a}-C_3H}=9$
C_4	152.9	q, d	$J_{C_4-C_5CH_3}=4$, $J_{C_4-C_3H}=4$
C_{7a}	154.3	broad	
C_6	159.1	q	$J_{C_6-C_5CH_3}=4$
C_2	178.7	d, q	$J_{C_2-C_3H}=5$, $J_{C_2-C_3CH_3}=6$
OCH_3	55.5	q	$J_{C-H}=144$
	55.9	q	$J_{C-H}=144$

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 diacetylusnic acid by ozonolysis[3] and also from diacetyldihydrousnic acid[5] and diacetyltetrahydrodesoxyusnic acid[6] by pyrolysis in the absence of calcium chloride, and coumaran-2-one compounds of the resorcinol type have been obtained from dihydrousnic acid and tetrahydrodesoxyusnic 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 tetrahydrodesoxyusnic 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}H-NMR: JNM-FX-100S instrument at 100 MHz (^{13}C-NMR at 25.15 MHz), with $(CH_3)_4Si$ as an internal standard; mass spectra (MS): JMS-0ISG 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 (Rf=0.33, TLC, silica gel, impregnated with 0.1 N $(COOH)_2$, $CHCl_3$–acetone=10: 1) and pyrousnic acid (Rf=0.05, TLC, silica gel impregnated with 0.1 N $(COOH)_2$, $CHCl_3$–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 Rf 0.62 (TLC, ethyl acetate–$CHCl_3$=1: 1) (oil 0.85 g) was chromatographed on silica gel (100 g) with acetone–$CHCl_3$ (1: 5). The fraction of Rf 0.32 (TLC, silica gel acetone–$CHCl_3$=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). $[\alpha]_D^{32°}=0°$ (c=1.00, MeOH). The Rf values of I and the powder were the same. *Anal.* Calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found: C, 61.66; H, 5.09. ^{1}H-NMR (δ-value in C_5D_5N, 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 Rf 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 $C_{12}H_{14}O_4$: 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 Rf 0.32 (TLC, acetone–$CHCl_3$=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 $C_{10}H_{10}O_4$: 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 *Rf* 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 *Rf* 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 *Rf* 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 *Rf* 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 (*Rf* 0.33, TLC, silica gel impregnated with 0.1 N $(COOH)_2$, acetone–$CHCl_3$=1 : 10). The filtrate was extracted with ethyl acetate and the ethyl acetate layer showed spots at *Rf* 0.33 and *Rf* 0.05 on TLC, which could be assigned to usnetic acid and pyrousnic acid, respectively; no spot assignable to I (*Rf* 0.26, TLC, silica gel impregnated with 0.1 N $(COOH)_2$, acetone–$CHCl_3$=1 : 10) was detected.

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