[Chem. Pharm. Bull. 30(3) 903—908 (1982)]

Usnic Acid. XVII.[1] Alkaline Degradation of Tetrahydrodesoxyusnic Acid

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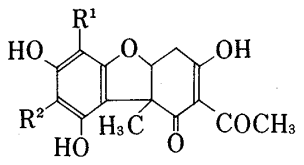
(Received August 13, 1981)

The structures of three new alkaline degradation products of tetrahydrodesoxyusnic acid (isotype) (Ib) were established to be IIb, III and IV, by chemical and spectral studies. The mechanisms of formations of IIb, III and IV from Ib are discussed.

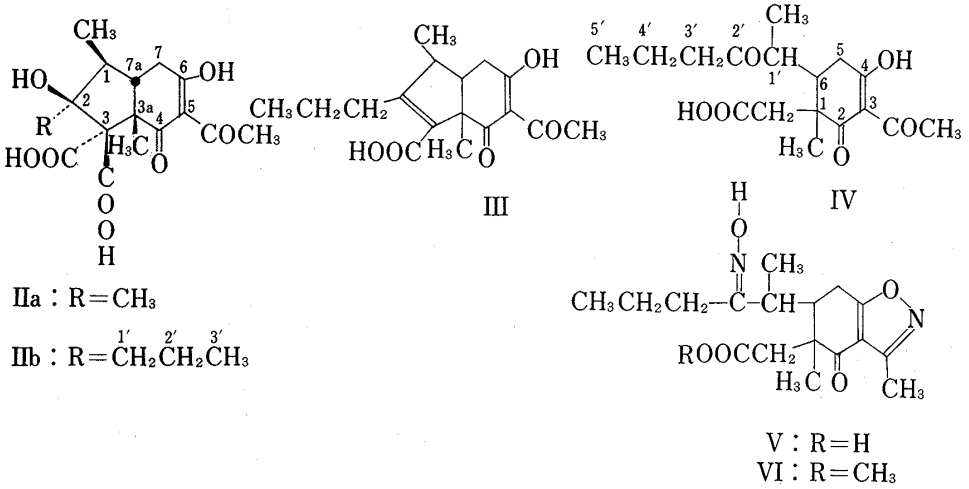
Keywords——tetrahydrodesoxyusnic acid (isotype); alkaline degradation; *rel*-(1*S*,2*S*,3a*S*,7a*S*)-5-acetyl-1,2,3,3a,7,7a-hexahydro-2,6-dihydroxy-1,3a-dimethyl-4-oxo-2-(1-propyl)-4*H*-indene-3,3-dicarboxylic acid; 3-acetyl-4-hydroxy-1-methyl-6-1′-methyl-2′-oxo-pentyl-2-oxo-3-cyclohexene-1-acetic acid; ^{1}H NMR; ^{13}C NMR; MS

In previous papers of this series, the authors reported the structural elucidation of the alkaline degradation products of dihydrousnic acid[1] and usnic acid[3] and proposed degradation mechanisms, indicating that dihydrousnic acid (Ia) is hydrolyzed through decomposition at ring A and usnic acid through decomposition at ring B. Dihydrousnic acid (Ia) afforded, on alkaline degradation, *rel*-(1*S*, 2*S*, 3a*S*, 7a*S*)-5-acetyl-1,2,3,3a,7,7a-hexahydro-2,6-dihydroxy-1,2,3a-trimethyl-4-oxo-4*H*-indene-3,3-dicarboxylic acid (IIa).[1] The proposed degradation mechanism of Ia was confirmed by elucidating the structures of the alkaline degradation products of tetrahydrodesoxyusnic acid (isotype)(Ib).[4] This paper deals with the structural elucidation of alkaline degradation products of tetrahydrodesoxyusnic acid (isotype)(Ib) and with the reaction mechanism.

Tetrahydrodesoxysnic acid (isotype)(Ib) was hydrolyzed in 50% (w/v) sodium hydroxide solution to afford $C_{18}H_{24}O_8$ (IIb), colorless needles of mp 138°C, $[\alpha]_D^{21°}$ +86° (c=1.00, dioxane), $C_{17}H_{22}O_5$ (III), colorless needles of mp 114°C, $[\alpha]_D^{24°}$ +210° (c=1.10, dioxane) and a pale yellow oil $C_{17}H_{24}O_6$ (IV), (M^+=m/e 324.155); the latter afforded a bisoxime monoanhydride $C_{17}H_{24}N_2O_5$ (V), colorless plates of mp 158°C, and a bisoxime monoanhydride methylate $C_{18}H_{26}N_2O_5$ (VI), colorless plates of mp 67—68°C. The ultraviolet spectrum (UV) of IIb, with maxima (nm, log ε) at 242 (3.99) and 272 (4.07), is nearly superimposable on that of IIa, with maxima at 242 (3.86) and 274 (3.95), indicating that IIa and IIb are structurally similar. Compound IIb, like IIa, shows infrared absorption (IR) bands (cm^{-1}) at 3550, 3200 (OH), 1735, 1725 (COOH), 1685 (α,β-unsaturated CO) and 1560 (broad, characteristic of the triketone of ring B of Ib). The mass spectra (MS) (relative intensity, formula) of IIa and IIb show similar fragmentation patterns. Compound IIb exhibits MS fragment ions at m/e 324.156 (8, $C_{17}H_{24}O_6$) ($M^+ - CO_2$), m/e 306.146 (54, $C_{17}H_{22}O_5$) ($M^+ - CO_2 - H_2O$), m/e 126.031 (22, $C_6H_6O_3$) [which is also observed in the MS of IIa], and m/e 180.114 (86, $C_{11}H_{16}O_2$) [which is 28 mass units (C_2H_4) larger than the fragment ion of IIa (m/e 152)]. The latter two of these fragment ions could be produced from the fragment ion of m/e 306.146 by retro Diels-Alder fragmentation. An additional fragment ion at m/e 281.103 (10, $C_{14}H_{17}O_6$) ($M^+ - CO_2 - C_3H_7$) is observed for compound IIb. The proton nuclear magnetic resonance (^{1}H NMR) spectrum (δ value, ppm) of IIb shows proton signals assignable to a >C(OH)n-C_3H_7 group, but no methyl signal assignable to a >C(OH)CH_3 group such as is observed for IIa. Except for the proton signals of these groups, IIb and IIa have nearly similar ^{1}H NMR signals, as shown in Table I. While the ^{13}C nuclear magnetic resonance (^{13}C NMR) spectrum (δ value, ppm) of IIa shows carbon signals of >C(OH)CH_3 at 83.1 and 23.5, compound IIb shows carbon signals at 85.0, 40.5, 17.5 and 14.9 which are assigned to >C(OH)$CH_2CH_2CH_3$. Table II shows that the other carbon signals



Ia : $R^1=COCH_3$, $R^2=CH_3$
Ib : $R^1=CH_3$, $R^2=C_2H_5$



IIa : $R=CH_3$
IIb : $R=CH_2CH_2CH_3$

III

IV

V : R=H
VI : $R=CH_3$

Chart 1

of IIa and IIb coincide with each other satisfactorily. The spectral evidence indicates that compound IIb differs from IIa by an alkyl group at the C_2-carbon and so compound IIb is concluded to be *rel*-(1*S*, 2*S*, 3a*S*, 7a*S*)-5-acetyl-1,2,3,3a,7,7a-hexahydro-2,6-dihydroxy-1,3a-dimethyl-2-(1-propyl)-4-oxo-4*H*-indene-3,3-dicarboxylic acid (Chart 1). Compounds IIb and IIa are assumed to have the same configuration, but their absolute configurations still remain to be determined.

Compound III, whose IR spectrum has bands at 1725 (COOH), 1685 (α,β-unsaturated CO) and 1560 (broad, characteristic of the triketone), was also obtained from IIb by decarboxylation and dehydration upon pyrolysis, so it may have the structure shown in Chart 1. The ^1H NMR and ^{13}C NMR spectra of III could be interpreted as shown in Tables I and II, respectively. The MS fragment ions of III observed at *m/e* 180.116 (95, $C_{11}H_{16}O_2$) and *m/e* 126.031 (8, $C_6H_6O_3$) are assumed to be produced by retro Diels–Alder fragmentation of ring B.

Table I. ^1H NMR Data (δ-Value in $CDCl_3$, 100 MHz, J in Hz)

	C_1–CH_3	C_{3a}–CH_3	$COCH_3$	C_1–H	C_{7a}–H	C_7–H_2	C_3'–H_3	C_2'–H_2	C_1'–H_2	C_2–CH_3
IIb[a)]	1.12 d, 3H $J=6$	1.60 s, 3H	2.50 s, 3H	2.10 m, 1H	2.19 m, 1H	2.89 m, 2H	0.88 t, 3H $J=7$	1.53—1.81 m, 4H		
IIa[a)]	1.09 d, 3H $J=6$	1.61 s, 3H	2.51 s, 3H	1.98 dq, 1H $J=8, 6$	2.10 dt, 1H $J=8, 8$	2.88 d, 2H $J=8$				1.42 s, 3H
III	1.14 d, 3H $J=7$	1.50 s, 3H	2.61 s, 3H	2.53 dq, 1H $J=11, 7$	1.93 ddd, 1H $J=11, 6, 3$	2.98 dd, 1H $J=18, 6$ 2.79 dd, 1H $J=18, 3$	0.80 t, 3H $J=7$	1.42 m, 2H	2.17 m, 1H 2.78 m, 1H	

	C_1'-CH_3	C_1-CH_3	X ‖ C-CH_3	C_5'-H_3	C_4'-H_2	C_6-H	C_5-H_2	C_1'-H	C_3'-H_2	C_1-CH_2	OH (OMe)
IV (X=O)	0.90 d, 3H J=7	1.43 s, 3H	2.56 s, 3H	0.90 t, 3H J=7	1.63 m, 2H		2.38—2.90 m, 8H				8.93 br, 1H 18.02, 18.34 1H
V (X=N-)	0.68 d, 3H J=7	1.50 s, 3H	2.43 s, 3H	0.94 t, 3H J=7	1.57 m, 2H	2.10 m, 1H	2.50—3.06 m, 7H				Unconfirmed
VI (X=N-)	0.68 d, 3H J=7	1.46 s, 3H	2.46 s, 3H	0.96 t, 3H J=7	1.57 m, 2H	2.10 m, 1H	2.40—3.14 m, 7H				(3.72 s, 3H)

a) Some CD_3OD was added to dissolve the compound.
Abbreviations: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad.

TABLE II. ^{13}C NMR Data (δ-Value in $CDCl_3$, 25.15 MHz)

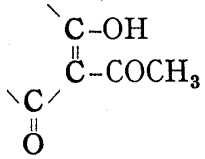
Carbon	Shielding[a] IIb	IIa
C_1-$\underline{C}H_3$	12.8(q)[b]	11.4(q)
C_{3a}-$\underline{C}H_3$	30.7(b)[b]	30.5(q)
$CO\underline{C}H_3$	27.4(q)	27.4(q)
C_2-$\underline{C}H_3$		23.5(q)
C_3'	14.9(q)[b]	
C_2'	17.5(t)	
C_1'	40.5(t)	
C_{3a}	57.1(s)	57.0(s)
C_7	37.1(t)	37.2(t)
C_1	46.9(d)	46.4(d)
C_{7a}	49.4(d)	49.8(d)
C_3	75.4(s)	75.4(s)
C_2	85.0(s)	83.1(s)
C_5	111.3(s)	111.3(s)
C_4	198.0(s)	198.6(s)
C_6	201.1(s)	201.3(s)
$\underline{C}OCH_3$	205.9(s)	205.9(s)
COOH	171.9(s)	171.5(s)
	172.5(s)	172.4(s)

Carbon	Shielding[a] IV (X=O)	V (X=N-)	VI (X=N-)
C_1'-$\underline{C}H_3$	13.7(q)[b]	13.0(q)[b]	13.2(q)
C_1-$\underline{C}H_3$	24.1(q)[b]	24.7(q)[b]	24.5(q)
X ‖ C-$\underline{C}H_3$	28.7(q)[b]	10.7(q)[b]	10.7(q)
C_5'	12.1(q)[b]	14.3(q)[b]	14.3(q)
C_4'	17.3(t)	19.4(t)	19.4(t)
C_3'	42.8(t)	36.9(t)	36.6(t)
C_1	46.9(s)	48.1(s)	48.1(s)
C_5	39.0(t)	20.5(t)	20.4(t)
C_1'	45.8(d)	42.2(d)	42.1(d)
C_6	38.3(d)	39.3(d)	39.0(d)
C_1-$\underline{C}H_2$	30.9(t)	30.2(t)	29.5(t)
C_3	111.8(s)	113.1(s)	113.0(s)
C_2	198.7(s)	178.4(s)	178.7(s)
C_4	195.9(s)	195.7(s)	195.7(s)
X ‖ $\underline{C}$-CH_3	203.0(s)	157.8(s)	157.7(s)
C_2'	212.3(s)	163.7(s)	162.9(s)
COOH or $\underline{C}OOCH_3$	176.2(s)	176.9(s)	172.0(s)
$COO\underline{C}H_3$			51.6(q)

a) ppm relative to TMS measured with complete decoupling. The letters in parentheses designate the multiplicity of the carbon signal with off-resonance decoupling.
b) The multiplicity (q) of each methyl carbon became singlet with off-resonance decoupling by means of the proton selective decoupling technique (ref. Table I).
Some CD_3OD was added to dissolve the compounds (IIb and IIa).

Compound IV shows IR bands at 1730 (COOH), 1710 (CO), 1660 (α,β-unsaturated CO), 1550 (broad, characteristic of the triketone). Since IV gave bisoxime monoanhydride type compounds (V and VI), ring B of Ib probably remains unchanged in the molecule of IV. This is also supported by the presence of the MS fragment ion at m/e 126.031 (52, $C_6H_6O_3$) due to retro Diels–Alder fragmentation. This compound also shows MS fragment ions at m/e 265.145 (50, $C_{15}H_{21}O_4$), m/e 253.106 (5, $C_{13}H_{17}O_5$) ($M^+ - C_3H_7CO$), m/e 225.076 (100, $C_{11}H_{13}$-

O_5) ($M^+ - C_3H_7COCHCH_3$), *m/e* 99.083 (2, $C_3H_7COCHCH_3$), and *m/e* 71.050 (72, $C_3H_7C{\equiv}O$). Analysis of the ^1H NMR and ^{13}C NMR spectra of IV (Tables I and II) reveals the presence of four methyl groups ($-CH_2CH_3$, $>CHCH_3$, $COCH_3$ and $>C-CH_3$), four methylene groups, two methine groups, a quaternary carbon, a COOH group, a CO group and a



system in the molecule. On the basis of the evidence described above, IV is elucidated to be 3-acetyl-4-hydroxy-1-methyl-6-1′-methyl-2′-oxo-pentyl-2-oxo-3-cyclohexene-1-acetic acid (Chart 1), although its stereochemistry remains to be determined.

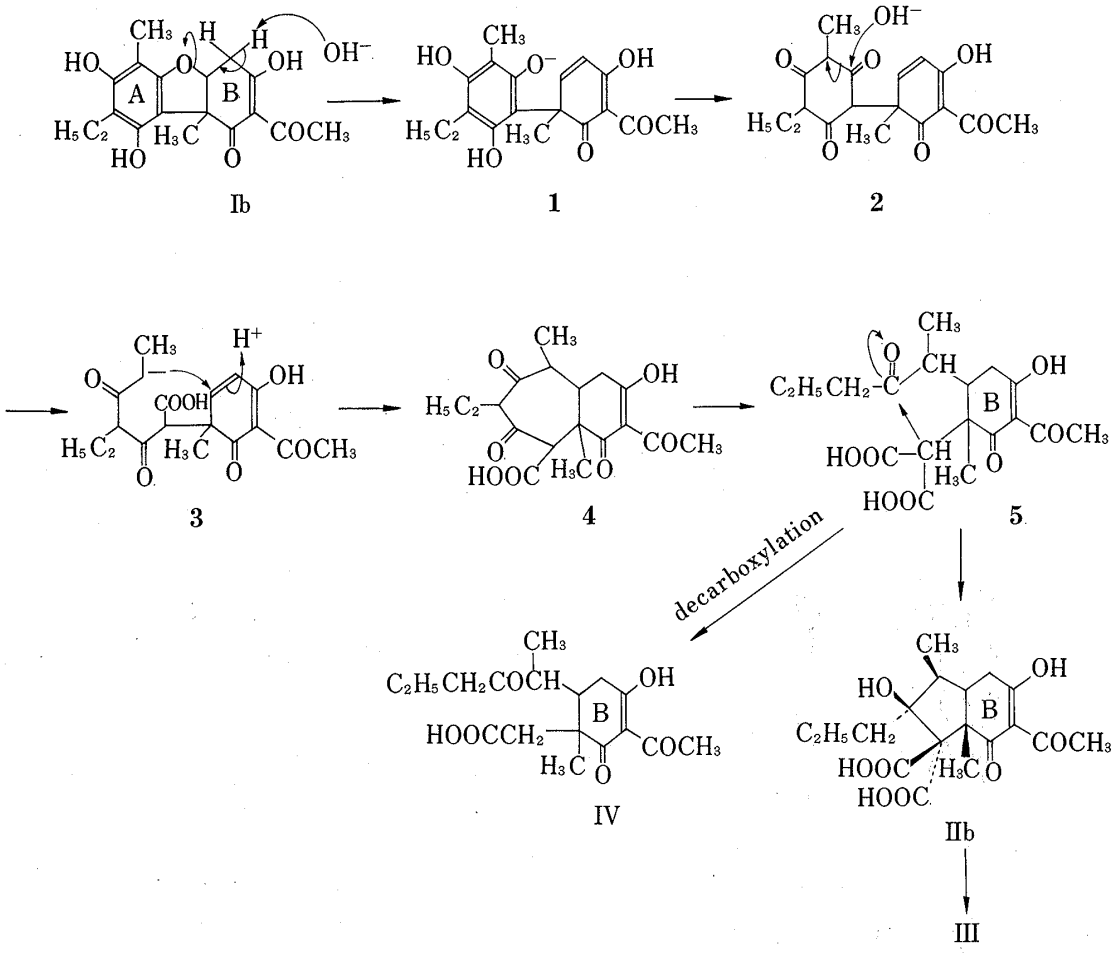


Chart 2

The formation of IIb, III and IV from tetrahydrodesoxyusnic acid (isotype) can be explained as in the case of dihydrousnic acid by the reaction mechanism shown in Chart 2. In this mechanism, intermediate 1 derived from Ib by retro Michael reaction affords intermediate 3 through intermediate 2 by basic cleavage of the 1,3-dicarbonyl system. The anion 3 thus formed then undergoes Michael reaction to give intermediate 4, which is converted to compound IIb through intermediate 5 by basic cleavage of the 1,3-dicarbonyl system, followed by Knoevenagel reaction. The intermediate 5 also affords IV by decarboxylation. By decarboxylation and dehydration, IIb affords III.

Compounds Ia and Ib are thus similarly hydrolyzed, because Ia was hydrolyzed to afford IIa and Ib was also hydrolyzed to afford IIb, III and IV. There is a remarkable difference between the chemical properties of usnic acid and tetrahydrodesoxyusnic acid in alkaline degradation.

Experimental

The following instruments were used for the measurements of physical data. Melting point, Yanagimoto micro-melting point apparatus (a hot plate type); UV (in EtOH), Hitachi 323 recording spectrometer; IR spectra (in KBr pellet), 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 reference; MS, Hitachi M-80 double focusing spectrometer [direct inlet: ionizing energy, 70 eV; source temperature, 120°C (IIb), 100°C (III, IV, VI)]; optical rotation at 589 nm, Nippon Bunko DIP-SL automatic polarimeter. Thin-layer chromatography (TLC) was carried out on glass plates coated with silica gel G (Merck) and column chromatography with silica gel (Merck) and silicic acid (Mallinckrodt), unless otherwise stated.

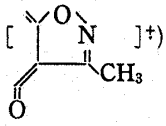
Hydrolysis of Tetrahydrodesoxyusnic Acid——Tetrahydrodesoxyusnic acid (isotype) (10 g) in 50% (w/v) sodium hydroxide solution (60 ml) was hydrolyzed in an oxygen stream on a boiling water bath for 1 h, and then the reaction mixture was poured into ice-water, acidified with conc. HCl and extracted with ethyl acetate. The ethyl acetate layer was washed with water, dried over sodium sulfate and concentrated *in vacuo* to afford an oily substance (10 g), which was column chromatographed on silicic acid (200 g) with benzene–acetone (20: 1). The fraction of *Rf* 0.40 (TLC, silica gel impregnated 0.1 N $(COOH)_2$, benzene–acetone= 20: 1) was crystallized from petr.ether–ether to afford colorless needles (III) of mp 114°C. Yield: 100 mg. *Anal.* Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.41; H, 7.16. $FeCl_3$ reaction: orange. IR ν_{max} cm^{-1}: 1725, 1685, 1615, 1600, 1560. UV λ_{max} nm (log ε): 232.0 (4.17), 273.5 (4.13). MS *m/e* (relative intensity, formula): 306.147 (64, $C_{17}H_{22}O_5$) (M^+), 288.136 (38, $C_{17}H_{20}O_4$) (M^+-H_2O), 180.116 (95, $C_{11}H_{16}O_2$), 178.104 (8, $C_{11}H_{14}O_2$), 151.076 (100, $C_9H_{11}O_2$) (180.116$-C_2H_5$), 138.070 (36, $C_8H_{10}O_2$), 136.122 (7, $C_{10}H_{16}$) (180.116$-CO_2$), 135.119 (24, $C_{10}H_{15}$), 126.031 (8, $C_6H_6O_3$), 107.086 (39, C_8H_{11}), 105.071 (18, C_8H_9), 98.037 (8, $C_5H_6O_2$) (126.031$-$CO).

The fraction of *Rf* 0.28 (TLC, silica gel impregnated with 0.1 N $(COOH)_2$, benzene–acetone=20: 1) was crystallized from acetone–*n*-hexane to afford colorless needles (IIb) of mp 138°C. Yield: 1.5 g. *Anal.* Calcd for $C_{18}H_{24}O_8$: C, 58.69; H, 6.57. Found: C, 58.35; H, 6.72. $FeCl_3$ reaction: red orange. MS *m/e* (relative intensity, formula): 368 (0.1) (M^+), 324.156 (8, $C_{17}H_{24}O_6$), 306.146 (54, $C_{17}H_{22}O_5$), 288.137 (32, $C_{17}H_{20}O_4$), 281.103 (10, $C_{14}H_{17}O_6$), 263.095 (16, $C_{14}H_{15}O_5$), 260.143 (7, $C_{16}H_{20}O_3$), 225.076 (10, $C_{11}H_{13}O_5$), 207.066 (7, $C_{11}H_{11}O_4$), 180.114 (86, $C_{11}H_{16}O_2$), 178.100 (5, $C_{11}H_{14}O_2$), 176.118 (15, $C_{12}H_{16}O$), 162.103 (9, $C_{11}H_{14}O$), 151.075 (100, $C_9H_{11}O_2$), 138.067 (35, $C_8H_{10}O_2$), 135.118 (20, $C_{10}H_{15}$), 126.031 (22, $C_6H_6O_3$), 107.086 (43, C_8H_{11}), 105.071 (19, C_8H_9), 98.036 (20, $C_5H_6O_2$).

The fraction of *Rf* 0.15 (TLC, silica gel impregnated with 0.1 N $(COOH)_2$, benzene–acetone=20: 1) afforded a liquid (IV). Yield: 1.73 g. *Anal.* Calcd for $C_{17}H_{24}O_6$: C, 62.95; H, 7.46. Found: C, 62.65; H, 7.62. MW Found: 324.155 ($C_{17}H_{24}O_6$). UV λ_{max} nm (log ε): 234.0 (4.01), 276.0 (4.05). MS *m/e* (relative intensity, formula): 324.155 (4, $C_{17}H_{24}O_6$) (M^+), 307.155 (5, $C_{17}H_{23}O_5$) (M^+-OH), 265.145 (50, $C_{15}H_{21}O_4$), (M^+-CH_2COOH), 264.135 (22, $C_{15}H_{20}O_4$) ($M^+-CH_2=C(OH)_2$), 253.106 (5, $C_{13}H_{17}O_5$), 236.107 (7, $C_{13}H_{16}O_4$) (264.135$-C_2H_4$), 225.076 (100, $C_{11}H_{13}O_5$), 221.084 (7, $C_{12}H_{13}O_4$) (264.135$-C_3H_7$), 207.070 (78, $C_{11}H_{11}O_4$) (225.076$-H_2O$), 126.031 (52, $C_6H_6O_3$), 100.088 (14, $[C_3H_7(HO)C=CHCH_3].^+$), 99.083 (2, $C_6H_{11}O$), 98.038 (38, $C_5H_6O_2$), 71.050 (72, C_4H_7O).

Pyrolysis of IIb——IIb (250 mg) was heated at 125—130°C *in vacuo* (3 mmHg) for 20 min, and when bubbling ceased, the resinous product (210 mg) was chromatographed on silicic acid (60 g) with *n*-hexane–acetone (10: 1). The fraction of *Rf* 0.51 (TLC, silica gel impregnated with 0.1 N $(COOH)_2$, benzene–acetone= 10: 1) afforded colorless needles (III) of mp 114°C (mixed fusion and IR, ^{1}H NMR). *Anal.* Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.57; H, 7.48.

Oximation of IV——A mixture of IV (630 mg), $NH_2OH\cdot HCl$ (400 mg) in pyridine (0.5 ml) and EtOH (1 ml) was refluxed on a water bath for 3 h and the reaction mixture, after removal of the solvent by evaporation, was acidified with dil.HCl and extracted with chloroform. The chloroform fraction afforded an oil (0.6 g), which was chromatographed on silicic acid (100 g) with *n*-hexane–ether (1: 1). The fraction of *Rf* 0.34 (TLC, silica gel impregnated with 0.1 N $(COOH)_2$, *n*-hexane–ether=1: 1) (190 mg) was crystallized from *n*-hexane–ether to afford V, colorless plates of mp 157—158°C. Yield: 114 mg. *Anal.* Calcd for $C_{17}H_{24}N_2O_5$: C, 60.70; H, 7.19; N, 8.33. Found: C, 60.27; H, 7.38; N, 8.06. IR ν_{max} cm^{-1}: 3400 (OH), 1730 (COOH), 1680 (α,β-unsaturated CO). UV λ_{max} nm (log ε): 225.0 (3.83), 235.0 (shoulder 3.81).

Methylation of V——V (200 mg) in ether (20 ml) was methylated with diazomethane and the product was chromatographed on silica gel (60 g) with benzene–acetone (20: 1). The fraction of *Rf* 0.34 (TLC, benzene–acetone=20: 1) was crystallized from *n*-hexane–ether to afford VI, colorless plates of mp 67—68°C. Yield: 45 mg. *Anal.* Calcd for $C_{18}H_{26}N_2O_5$: C, 61.70; H, 7.48; N, 8.00. Found: C, 61.74; H, 7.52; N, 8.03. IR ν_{max} cm^{-1}: 3350 (OH), 1725 (COOMe), 1685 (α,β-unsaturated CO), 1610. UV λ_{max} nm (log ε): 225.5 (3.81), 235.0 (3.80). MS *m/e* (relative intensity, formula): 350.183 (1, $C_{18}H_{26}N_2O_5$) (M^+), 333.179 (3, $C_{18}H_{25}N_2O_4$) (M^+-OH), 319.163 (1, $C_{17}H_{23}N_2O_4$) (M^+-OMe), 277.151 (3, $C_{15}H_{21}N_2O_3$) (M^+-CH_2COOMe), 236.090 (14, $C_{12}H_{14}NO_4$) ($M^+-C_3H_7(CH_3CH)C=NOH$), 204.071 (7, $C_{11}H_{10}NO_3$) (236.090$-$MeOH), 123.031 (7, []$^+$),

115.100 (30, $[CH_3CH=(C_3H_7)NHOH].^+$), 114.091 (1, $C_3H_7(CH_3\overset{+}{C}H)C=NOH$), 100.077 (2, $C_5H_{10}NO$) (115.100−CH_3), 87.069 (31, $[CH_2=C(Et)NHOH]^+$).

Acknowledgement The authors are grateful to Prof. O. Yamauchi for his encouragement. Thanks are due to Mr. Y. Itatani for measuring NMR, to Miss Y. Arano for elemental analyses, to Miss T. Ueda for MS measurement and Mr. H. Ogata of Wako Junyaku Co. Ltd. for providing usnic acid.

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