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Usnic Acid. XVI.¹⁾ Alkaline Degradation of Dihydrousnic Acid

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The structure of a new alkaline degradation product of 1-dihydrousnic acid was elucidated as 5-acetyl-1,2,3,3a,7,7a-hexahydro-2,6-dihydroxy-1,2,3a-trimethyl-4-oxo-4H-inden-3,3-dicarboxylic acid (I) by chemical and spectral studies, together with X-ray analysis. The mechanism of formation of I from 1-dihydrousnic acid is discussed.

Keywords—dihydrousnic acid; alkaline degradation; 5-acetyl-1,2,3,3a,7,7a-hexahydro-2,6-dihydroxy-1,2,3a-trimethyl-4-oxo-4H-inden-3,3-dicarboxylic acid; PMR; CMR; MS; X-ray analysis

In a previous paper of this series,¹⁾ it was reported that usnic acid afforded, on alkaline degradation, 4,6-dihydroxy-3,5-dimethylcoumaran-2-one, in addition to usnetic and pyrousnic acids. This finding prompted us to investigate the alkaline degradation of dihydrousnic acid, since its degradation reactions are remarkably different from those of usnic acid.³⁾ This paper deals with the structure elucidation of a new alkaline degradation product of dihydrousnic acid, and with the mechanism of its formation. 1-Dihydrousnic acid, $[\alpha]_D^{20} -97^\circ$ ($c=1.01$, dioxane), was hydrolyzed with 50% (w/v) sodium hydroxide solution in an oxygen or a nitrogen stream to afford $C_{16}H_{20}O_8$ (I), colorless plates of mp 145° (dec.), $[\alpha]_D^{20} +75.7^\circ$ ($c=1.03$, dioxane). Compound I shows infrared (IR) absorption bands (cm^{-1}) at 3520 (OH), 1720 (COOH), 1680 (α,β -unsaturated C=O), 1600 (C=O chelated with enol OH) and 1550 (broad, characteristic of a triketone¹⁾) and mass (MS) fragment ions at m/e 296 (M^+-CO_2) and m/e 252 ($M^+-2 \times CO_2$). Compound I was methylated with diazomethane to afford a dimethylate, $C_{18}H_{24}O_8$ (II), colorless triangular crystals of mp $76-78^\circ$, and a monomethylate, $C_{17}H_{22}O_8$ (III), colorless needles of mp 154° . Compound III showed an MS fragment ion at m/e 310 (M^+-CO_2) and 1H nuclear magnetic resonance (PMR) signals (δ -value, ppm) at 2.51 (s, 3H), 18.14 (s, 1H), 1.62 (s, 3H), 2.89 (d, 2H), and 2.12 (d, t, 1H), which could be assigned to a chelated $COCH_3$, a chelated enol OH, an angular CH_3 , and methylene and methine protons in a $-CH_2-\dot{C}H-$ group, respectively, as shown in Table I.

Compound I was pyrolyzed at $130-135^\circ$ *in vacuo* (3 mmHg) to afford $C_{15}H_{18}O_5$ (IV), colorless needles of mp $128-129^\circ$, by decarboxylation and dehydration, and on oximation with hydroxylamine hydrochloride and pyridine, I afforded $C_{15}H_{17}NO_4$ (V), colorless plates of mp 187° and $C_{15}H_{18}N_2O_4$ (VI), colorless plates of mp $228-230^\circ$; the former was proved to be identical with a mono-oxime monoanhydride of IV and the latter with a bisoxime monoanhydride of IV. Compound V afforded, on methylation with diazomethane, a monomethylate $C_{16}H_{19}NO_4$ (VII), colorless plates of mp $148-149^\circ$, which showed IR bands at 1710 ($COOCH_3$) and 1675 (α,β -unsaturated C=O). These chemical and spectral findings suggest that ring B of dihydrousnic acid (Chart 2) remains unchanged in the molecule of compound I. Compound III showed PMR signals at 1.09 (d, $J=6$ Hz, 3H), 1.87 (d, q, $J=9$ and 6 Hz, 1H), 2.12 (d, t,

1) Part XV: K. Takahashi and M. Takani, *Chem. Pharm. Bull.*, **28**, 177 (1980).

2) Location: a) 13-1 Takaramachi, Kanazawa, 920, Japan; b) 17-85 Jusohonmachi, Yodogawa-ku, Osaka, 532, Japan.

3) Y. Asahina and S. Shibata, "The Chemistry of Lichen Substances," Japan Society for the Promotion of Science, Tokyo, Japan, 1954, p. 190.

TABLE I. PMR Data (δ -Value in CDCl_3 , 100 MHz, J in Hz)

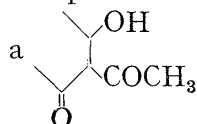
	$\text{C}_1\text{-CH}_3$	$\text{C}_{3a}\text{-CH}_3$	$\text{C}_2\text{-CH}_3$	X^b $\text{C}_5\text{-}\overset{\parallel}{\text{C}}\text{-CH}_3$	$\text{C}_1\text{-H}$	$\text{C}_{7a}\text{-H}$	$\text{C}_7\text{-H}_2$	OH	OMe
I ^{a)}	1.09 d, 3H $J=6$	1.61 s, 3H	1.42 s, 3H	2.51 s, 3H	1.98 d,q, 1H $J=8.6$	2.10 d,t, 1H $J=8.8$	2.88 d, 2H $J=8$		
III	1.09 d, 3H $J=6$	1.62 s, 3H	1.32 s, 3H	2.51 s, 3H	1.87 d,q, 1H $J=9, 6$	2.12 d,t, 1H $J=9, 9$	2.89 d, 2H $J=9$	4.36 br, 1H 13.38 br, 1H 18.14 s, 1H	3.75 s, 1H
IV	1.13 d, 3H $J=7$	1.51 s, 3H	1.98 d, 3H $J=1.5$	2.62 s, 3H	2.46 d,q, 1H $J=11, 7$	1.91 d,d,d, 1H $J=11, 6, 2$	3.01 d,d, 1H $J=19, 6$	12.96 br, 1H 18.63 s, 1H	
V	1.16 d, 3H $J=6$	1.53 s, 3H	1.95 d, 3H $J=1$	2.49 s, 3H	2.42 d,q, 1H $J=11, 6$	2.24 d,t, 1H $J=11, 3$	3.20 d, 2H $J=3$	12.60 br, 1H	
VI	1.11 d, 3H $J=6$	1.52 s, 3H	1.94 d, 3H $J=1$	2.57 s, 3H	2.31 d,q, 1H $J=11, 6$	2.09 d,t, 1H $J=11, 4$	3.04 d, 2H $J=4$		
VII	1.12 d, 3H $J=6$	1.58 s, 3H	1.96 d, 3H $J=1$	2.44 s, 3H	2.0–2.4 m, 2H		3.09 s-like 1H 3.13 d, 1H $J=3$		3.84 s, 3H
Dihydro- usinc acid		1.68 s, 3H $\text{C}_{9b}\text{-CH}_3$	1.98 s, 3H $\text{C}_8\text{-CH}_3$	2.56 s, 3H 2.63 s, 3H $2 \times \text{COCH}_3$		4.89 t, 1H $J=5$ $\text{C}_{4a}\text{-H}$	3.13 d, 2H $J=5$ $\text{C}_4\text{-H}_2$	9.53 s, 1H 13.37 s, 1H 18.28 s, 1H $3 \times \text{OH}$	

a) Some CD_3OD was added to dissolve the compound.

b) $\text{X}=\text{O}$ for I, III, IV and $\text{X}=\text{N}-\text{O}-$ for V, VI, VII.

Abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

$J=9$ and 9 Hz, 1H) and 2.89 (d, $J=9$ Hz, 2H), suggesting the presence of a $\text{CH}_3\text{-}\dot{\text{C}}\text{H-}\dot{\text{C}}\text{H-CH}_2\text{-}$ system in the molecule, and also gave PMR signals at 1.32 (s, 3H), and 4.36 (broad, s, 1H), which suggest the presence of a $-\dot{\text{C}}(\text{OH})\text{-CH}_3$ system, taking into consideration the observation that compound IV (decarboxy-dehydro derivative of I) shows a PMR signal at 1.98 (d, $J=1.5$ Hz, 3H), which is assignable to methyl protons of a $=\dot{\text{C}}\text{-CH}_3$ system, as shown in Table I. Compound III showed ^{13}C NMR (CMR) signals (δ -value, ppm) assignable to carbons of



system, three methyl, one methylene and two methine groups, a COOH , a COOCH_3 and three quaternary carbons, but III showed no signals assignable to aromatic carbons, as shown in Table II.

Based on the evidence described above, some structural features of the degradation product could be assumed, and X-ray analysis (Table III, Fig. 1 and Fig. 2) finally elucidated the structure of the degradation product as 5-acetyl-1,2,3,3a,7,7a-hexahydro-2,6-dihydroxy-1,2,3a-trimethyl-4-oxo-4*H*-inden-3,3-dicarboxylic acid (I) (final R-factor=4.6%) as shown in Chart

1. However, the absolute configuration still remains to be determined. Thus, compounds III, IV, V, VI, and VII could be formulated as shown in Chart 1, and their PMR and CMR spectra could be interpreted as shown in Table I and Table II, respectively.

The formation of I from dihydrousnic acid can be explained by the reaction mechanism postulated in Chart 2. In this mechanism, intermediate 1 derived from *l*-dihydrousnic acid

TABLE II. CMR Data (δ Value in CDCl_3 , 25.15 MHz, J in Hz)

Carbon	Shielding ^{a)}				
	I (X=O) ^{k)}	III (X=O)	IV (X=O)	V (X=N-O-)	Dihydrousnic acid
C ₁ -CH ₃	11.4 (q), [s] ^{b)}	11.4 (q, d) $J=127, 3$	15.6 (q, t), [s] ^{e)} $J=126, 4$	15.6 (q, t) $J=127, 4$	7.2 (q), [s] ⁱ⁾ C ₈ -CH ₃
C _{3a} -CH ₃	30.5 (q), [s] ^{c)}	30.5 (q, d) $J=131, 8$	22.1 (q, d), [s] ^{f)} $J=129, 4$	21.8 (q, q) $J=129, 4$	23.3 (q), [s] ^{j)} C _{9b} -CH ₃
X C ₅ -C-CH ₃	27.4 (q)	27.4 (q, d) $J=130, 3$	29.7 (q), [s] ^{g)} $J=130$	10.9 (q) $J=131$	31.2 (q) } 28.0 (q) } 2 × COCH ₃
C ₂ -CH ₃	23.5 (q), [s] ^{d)}	23.5 (q) $J=127$	14.1 (q), [s] ^{h)} $J=128$	14.4 (q) $J=129$	35.5 (t) C ₄
C _{3a}	57.0 (s)	57.1 (q) $J=4$	56.0 (s)	57.2 (q) $J=4$	54.4 (s) C _{9b}
C ₇	37.2 (t)	37.2 (t, t) $J=123, 3$	30.9 (t, t) $J=129, 3$	21.3 (t) $J=132$	85.8 (d) C _{4a}
C ₁	46.4 (d)	46.1 (d, q) $J=132, 5$	45.9 (d, m) $J=128, 3$	45.5 (d, q) $J=132, 4$	101.8 (s) C ₆
C _{7a}	49.8 (d)	49.7 (d) $J=131$	48.9 (d, q) $J=134, 4$	53.3 (d, m) $J=133, 4$	105.3 (s) C _{9a}
C ₃	75.4 (s)	75.1 (s)	132.9 (q) $J=5$	131.9 (d) $J=4$	106.6 (s) C ₃
C ₂	83.1 (s)	83.2 (q) $J=3$	157.7 (m) $J=4$	158.1 (s)	111.6 (s) C ₂
C ₅	111.3 (s)	111.0 (d) $J=6$	112.3 (s)	114.1 (q) $J=3$	158.6 (s) C _{5a}
C ₄	198.6 (s)	198.6 (m) $J=4$	198.5 (s)	180.8 (t) $J=9$	159.3 (s) C ₉
C ₆	201.3 (s)	201.4 (m) $J=3$	201.6 (q) $J=4$	200.0 (q) $J=4$	163.5 (s) C ₇
X C ₅ -C-CH ₃	205.9 (s)	205.7 (q) $J=3$	204.5 (q) $J=6$	156.8 (q) $J=4$	195.5 (s) } 197.4 (s) } C ₁ and C ₃
COOH and COOCH ₃	171.5 (s)	170.3 (s)	166.4 (s)	166.2 (s)	201.4 (s) } 202.8 (s) } 2 × COCH ₃
COOCH ₃	172.4(s)	171.7(s) $J=4$ 53.2 (q) $J=149$			

a) ppm relative to TMS measured with complete decoupling. The letters in parentheses, in the cases of I and dihydrousnic acid, designate the multiplicity of the carbon signal with off-resonance decoupling and in the cases of III, IV, and V, the multiplicity without decoupling, unless otherwise indicated. Multiplicity with off-resonance decoupling was determined on irradiation at b) 1.09, c) 1.61, d) 1.42, e) 1.13, f) 1.51, g) 2.62, h) 1.98, i) 1.98, j) 1.68 by means of the proton selective decoupling technique (see Table I).

k) Some CD₃OD was added to dissolve the compound.
Abbreviations: s, s-like; d, d-like; t, t-like; q, q-like (others, see Table I).

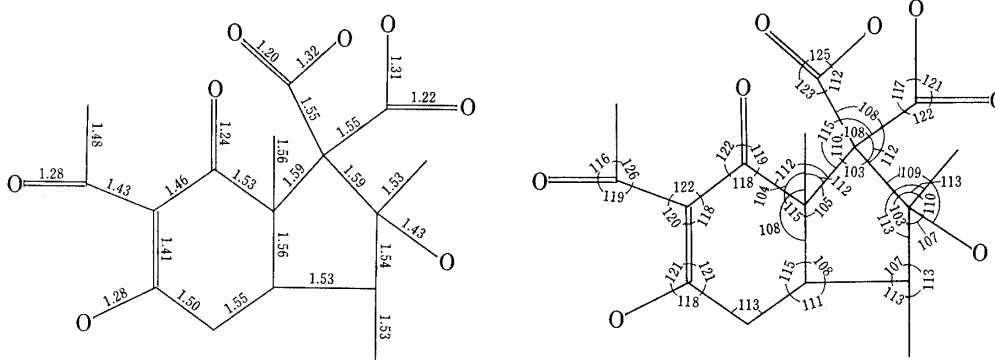


Fig. 1

TABLE III. Crystal Data for Compound I

Molecular formula	$C_{16}H_{20}O_8$
Molecular weight	340.34
Appearance of crystals	Colorless plate
Space group	$P 2_1 2_1 2_1$
Cell dimensions	$a = 10.32 \text{ \AA}$ $b = 15.16 \text{ \AA}$ $c = 10.30 \text{ \AA}$
Number of molecules in an asymmetric unit	1
Calculated density	1.402

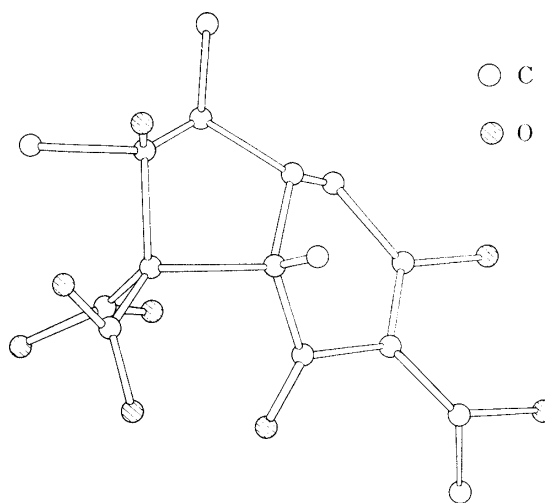
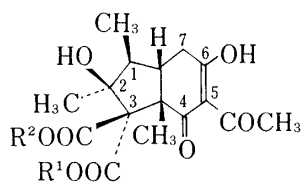
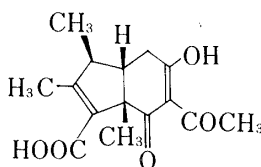


Fig. 2.

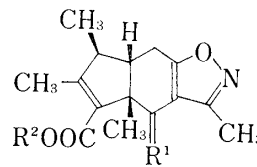
This model shows only the relative configuration of each substituent. It does not represent the absolute configuration.



- I: $R^1 = R^2 = H$
 III: $R^1 = CH_3, R^2 = H$ or
 $R^1 = H, R^2 = CH_3$



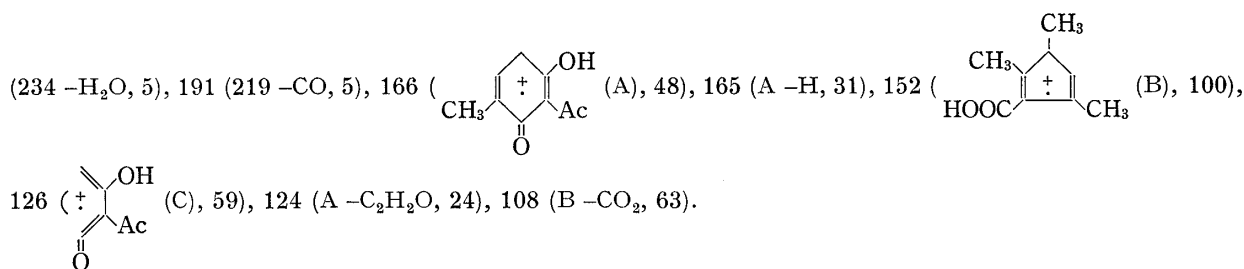
IV



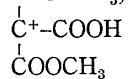
- V: $R^1 = O, R^2 = H$
 VI: $R^1 = NOH, R^2 = H$
 VII: $R^1 = O, R^2 = CH_3$

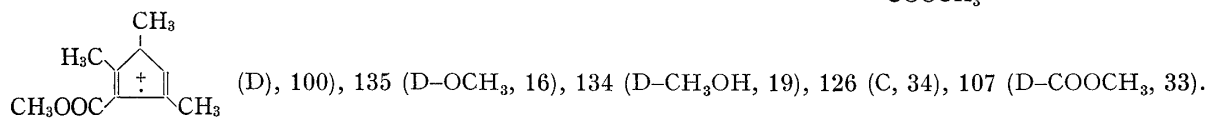
Chart 1

by retro Michael reaction affords the intermediate 4 through intermediates 2 and 3 by successive basic cleavages of the 1,3-dicarbonyl systems. The anion 4 thus formed then undergoes Michael reaction to afford the intermediate 5, which affords compound I through intermediate 6 by basic cleavage of the 1,3-dicarbonyl system, followed by Knoevenagel reaction (scheme 1). However, route 3'-7-5-6-I might not be excluded (scheme 2). It is interesting that the alkaline degradation of dihydrousnic acid preferentially destroys ring A, while the alkaline degradation of usnic acid destroys ring B.³⁾



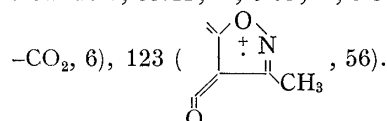
The fraction of *Rf* 0.04 (TLC, silica gel impregnated with 0.1 N $(COOH)_2$, *n*-hexane-acetone=5:1) was chromatographed on silica gel with $CHCl_3$ -acetone (5:1) and the resulting fraction of *Rf* 0.29 (TLC, $CHCl_3$ -acetone=5:1) (20 mg) was sublimed *in vacuo* at 70° to afford colorless needles (15 mg) of mp 106°; this material was identical with 4-methylresorcinol, obtained from 2,6-dihydroxy-3-methyl-acetophenone by hydrolysis with 50% NaOH (IR and mixed fusion). *Anal.* Calcd for $C_7H_8O_3$: C, 67.73; H, 6.50. Found: C, 67.27; H, 6.40. Compound I was also obtained from 1-dihydrousnic acid by hydrolysis in a nitrogen stream.

Methylation of I—Compound I (0.5 g) in MeOH (30 ml) was methylated with diazomethane and the product was column-chromatographed on silicic acid (100 g) with benzene-acetone (30:1) to afford fractions of *Rf* 0.18 and 0.33 (TLC, silica gel impregnated with 0.1 N $(COOH)_2$, benzene-acetone=50:1). The fraction of *Rf* 0.18 was chromatographed on silica gel (80 g) with *n*-hexane-acetone (5:1) and the resulting fraction of *Rf* 0.84 (TLC, *n*-hexane-acetone=5:1) was crystallized from petr-ether-ether to afford the dimethylate (II), colorless triangular crystals of mp 76—78°. *Anal.* Calcd for $C_{18}H_{24}O_8$: C, 58.69; H, 6.57. Found: C, 58.37; H, 6.60. The fraction of *Rf* 0.33, one of the two fractions mentioned above, was further chromatographed on silicic acid (50 g) with benzene-AcOEt (50:1) and the resulting fraction of *Rf* 0.41 (TLC, silica gel impregnated with 0.1 N $(COOH)_2$, benzene-AcOEt=50:1) was crystallized from petr-ether-ether to afford the monomethylate (III), colorless needles of mp 154°. Yield: 130 mg. *Anal.* Calcd for $C_{17}H_{22}O_8$: C, 57.62; H, 6.55. Found: C, 57.73; H, 6.46. IR (cm^{-1}): 3500 (OH), 1750 ($COOCH_3$), 1715 (C=O), 1610 (C=O chelated with enol OH), 1540 (broad, triketone). UV λ_{max} (nm, log ϵ): 274 (4.25). MS *m/e* (rel. intensity %): 354 (M^+ , 47), 336 ($M^+ - H_2O$, 5), 310 ($M^+ - CO_2$, 13), 292 (310 $-H_2O$, 53), 260 (292 $-CH_3OH$, 27), 232 (260 $-CO$, 12), 218 (260 $-C_2H_2O$, 16), 217 (260 $-CH_3CO$, 13), 180 ($CH_3-C=\overset{+}{C}-CH_3$, 43), 166 (A and/or 

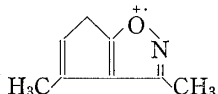


Pyrolysis of I—Compound I (0.5 g) was heated at 130—135° *in vacuo* (3 mmHg) for 40 min and when bubbling ceased, the resinous product (0.4 g) was chromatographed on silicic acid (200 g) with *n*-hexane-acetone (10:1). The fraction of *Rf* 0.2 (TLC, silica gel impregnated with 0.1 N $(COOH)_2$, *n*-hexane-acetone=10:1) was crystallized from petr-ether-ether to afford IV, colorless needles of mp 128—129°. Yield: 110 mg. *Anal.* Calcd for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.50; H, 6.43. IR (cm^{-1}): 1700 (COOH), 1665 (α,β -unsaturated C=O), 1590 (C=O chelated with enol OH), 1545 (broad, triketone). UV λ_{max} (nm, log ϵ): 225 (shoulder, 3.99), 272.5 (4.26). MS *m/e* (rel. intensity %): 278 (M^+ , 51), 260 ($M^+ - H_2O$, 11), 245 (260 $-CH_3$, 3), 234 ($M^+ - CO_2$, 3), 218 (260 $-C_2H_2O$, 4), 166 (A, 25), 152 (B, 100), 148 (A $-H_2O$, 12), 126 (C, 8), 124 (A $-C_2H_2O$, 9), 108 (B $-CO_2$, 22), 107 (B $-COOH$, 26), 98 (C $-CO$, 9), 93 (108 $-CH_3$, 28), 84 (C $-C_2H_2O$, 4).

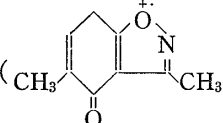
Oximation of I—A mixture of I (0.5 g), $NH_2OH \cdot HCl$ (0.5 g) in pyridine (0.5 ml) and EtOH (5 ml) was refluxed on a water bath for 5 hr and the reaction mixture, after removal of the solvent by evaporation, was acidified with dil. HCl and extracted with AcOEt. The ethyl acetate-soluble fraction afforded an oil (430 mg), which was chromatographed on silicic acid (100 g) with $CHCl_3$ -AcOEt (20:1). The fraction of *Rf* 0.53 (TLC, silica gel impregnated with 0.1 N $(COOH)_2$, $CHCl_3$ -AcOEt=20:1) (70 mg) was crystallized from petr-ether-ether to afford V, colorless plates of mp 187°. This oxime was identical with the mono-oxime monoanhydride of IV (mixed fusion and IR). *Anal.* Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.41; H, 6.05; N, 5.31. MS *m/e* (rel. intensity %): 275 (M^+ , 100), 257 ($M^+ - H_2O$, 20), 231 (M^+



The fraction of *Rf* 0.10 (TLC, silica gel impregnated with 0.1 N $(COOH)_2$, $CHCl_3$ -AcOEt=20:1) (60 mg) was further chromatographed on silica gel with $CHCl_3$ -EtOH (20:1) and the resulting fraction of *Rf* 0.36 (10 mg) (TLC, $CHCl_3$ -EtOH=20:1) afforded VI, colorless plates of mp 228—230°. *Anal.* Calcd for $C_{15}H_{18}N_2O_4$: C, 62.05; H, 6.25; N, 9.65. Found: C, 62.13; H, 6.33; N, 9.59. MS *m/e* (rel. intensity %): 290 (M^+ ,

89), 272 ($M^+ - H_2O$, 65), 255 (272 $-OH$, 100), 229 (255 $-C\equiv N$, 42), 152 (B, 11), 135 (, 18).

Methylation of V—Compound V (80 mg) in MeOH was methylated with diazomethane and the product was chromatographed on silica gel (80 g) with benzene–acetone (50:1). The fraction of R_f 0.27 (TLC, benzene–acetone=50:1) (50 mg) was crystallized from petr-ether–ether to afford VII, colorless plates of mp 148–149°. *Anal.* Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.36; H, 6.56; N, 5.12. IR (cm^{-1}): 1710 ($COOCH_3$), 1675 (α,β -unsaturated $C=O$). MS *m/e* (rel. intensity %): 289 (M^+ , 100), 258 ($M^+ - OCH_3$, 44), 257 ($M^+ - CH_3OH$, 57), 230 ($M^+ - COOCH_3$, 28), 166 (D, 40), 165 (D $-H$, 75), 163

(, 4), 134 (D- CH_3OH , 16), 133 (48), 126 (8), 125 (79), 107 (D- $COOCH_3$, 25).

Oximation of IV—Compound IV (80 mg) in EtOH (2 ml) was oximated with $NH_2OH \cdot HCl$ (50 mg) and pyridine (0.5 ml) and the product was chromatographed on silicic acid (35 g). The resulting fraction of R_f 0.53 (TLC, silica gel impregnated with 0.1 N $(COOH)_2$, $CHCl_3$ -AcOEt=20:1) (30 mg) was crystallized from petr-ether–ether to afford colorless needles of mp 187°; this material was identical with V (mixed fusion and IR). *Anal.* Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 65.12; H, 6.21; N, 5.27. The fraction of R_f 0.10 (TLC, silica gel impregnated with 0.1 N $(COOH)_2$, $CHCl_3$ -AcOEt=20:1) was further chromatographed on silica gel with $CHCl_3$ -EtOH (20:1) and the resulting fraction of R_f 0.36 (TLC, $CHCl_3$ -EtOH=20:1) afforded VI, mp 228–230° (mixed fusion and TLC).

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