[Chem. Pharm. Bull. 33(3)1083—1087(1985)]

Structure Elucidation of Pantherine, a Flycidal Alkaloid from *Amanita pantherina* (DC.) FR.

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(Received July 16, 1984)

Pantherine is identified as 5-aminomethyl-3-hydroxyisoxazole by means of spectroscopic experiments and chemical correlation with synthetic compounds.

Keywords——isoxazole; 3-isoxazolone; 2-pyrrolidone; ^{1}H-NMR; ^{13}C-NMR

Pantherine (PA) is a flycidal alkaloid isolated from *Amanita pantherina* (DC.) FR. by Onda *et al.*[1] and characterized only by the melting point and the infrared (IR) spectrum. Later, Bowden *et al.*[2] isolated agarin (**1a** or **1b**) from *Amanita muscaria*. Takemoto *et al.*[3] and Eugster *et al.*[4] prepared the isoxazole **1a** from ibotenic acid, and they considered that PA and agarin are the same as **1a** on the basis of the similarity of the melting points and the IR spectra. Since identification has not been achieved by direct comparison of these compounds, their conclusion cannot be considered as definitive.

We recently had an opportunity to reinvestigate PA, and we now independently report the structure of PA.

PA is an amphoteric substance, and the molecular formula $C_4H_6N_2O_2$ was obtained by mass (MS) spectrometry and elemental analysis. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum (CF_3COOH) showed a broad three-proton singlet (δ_H 7.82), a one-proton singlet (δ_H 6.47) and a two-proton quartet (δ_H 4.59, J_{HH} 4 Hz). On addition of deuterium oxide, the signal at δ_H 7.82 disappeared, and that at δ_H 4.59 changed to a singlet. In addition, a coupling (4 Hz) was observed between the two signals by means of spin decoupling experiments. The ^{1}H-NMR spectrum (CF_3COOD) revealed a one-proton singlet (δ_H 6.47) and a two-proton singlet (δ_H 4.59), and a small long-range interaction was observed between these protons. These observations suggest the existence of an allylamine function in the molecule and lead to several possible compounds **1a**—**1f** having isoxazole, 5-isoxazolone (NH form) and 2-oxazolone (NH form) structures[5] for PA. However, among them, only **1a** is supported by the chemical shift (δ_C 102.0) of an olefinic carbon bearing one proton (δ_H 6.47) observed in the carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectrum (CF_3COOD) as well as by the IR spectrum showing no carbonyl band. The data obtained by gated decoupling and selective proton decoupling experiments were in accord with **1a** (Table I). The IR spectrum (KBr) showed that PA adopts the zwitterionic form in the solid state (see Experimental).

Acetylation of PA with acetic anhydride/pyridine gave a mixture of the diacetates **2** and **3**, which was converted into the monoacetate **4** during preparative thin-layer chromatography (prep. TLC) using silica gel or on treatment with hydrochloric acid in methanol. These changes were deduced by comparison of the chemical shifts of the acetyl methyl protons observed in the ^{1}H-NMR spectra: **2**,[6] δ_H 2.56 and 2.03 ($CDCl_3$); **3**,[6] δ_H 2.31 and 2.02 ($CDCl_3$); **4**, δ_H 1.96 [$(CD_3)_2CO$]. The formations of **2** and **3** imply that PA is essentially an

TABLE I. ^{13}C-NMR Data for PA (CF_3COOD)

C	$\delta^{a)}$ (ppm)	$^1J_{CH}$ (Hz)	$^{>1}J_{CH}$ (Hz)	Irradiated H	Resulting splitting
3	172.3 Sd		4	4-H	s
4	102.0 Ddd	190	6, 4	6-H_2	s
5	166.3 Sdt		7, 3	4-H	t (3 Hz)
				6-H_2	d (7 Hz)
6	38.1 Td	150	3	4-H	s

a) Capital and small letters refer to the splittings observed in the off-resonance and gated decoupled spectra, respectively.

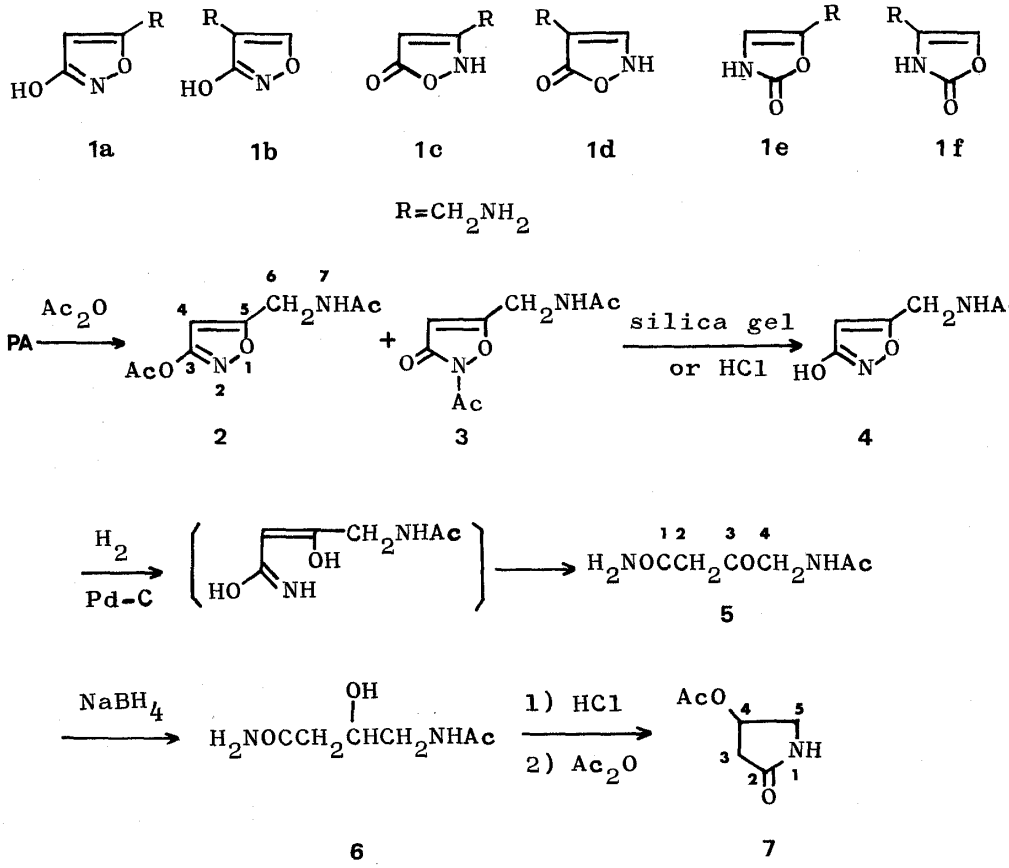

Chart 1

ambident nucleophile or exists in an equilibrium between the OH and NH forms in solution. The formation ratio of **2**/**3** was estimated to be 2/1 by comparison of the signal intensities of the corresponding protons observed in the ^{1}H-NMR spectrum of the mixture. The ^{1}H-NMR spectrum of **4** showed a doublet (6 Hz) for 6-H_2 coupled to 7-H exchangeable with deuterium oxide, supporting the presence of an acetamidomethyl group.

Hydrogenation of **4** over a palladium catalyst in ethanol afforded the keto diamide **5** *via* an N–O bond cleavage and two isomerizations. Its ^{1}H- and ^{13}C-NMR spectra (CD_3OD) showed no signals for 2-H_2 and C-2 because of exchange of 2-H_2 with deuterium.

Reduction of **5** with sodium borohydride in ethanol gave the *sec*-alcohol **6**, which was converted into the pyrrolidone **7** on acidic hydrolysis and acetylation with acetic anhydride/pyridine. The observed IR and NMR (^{1}H- and ^{13}C-) spectral data were in accord with **7** (see Experimental). The pyrrolidone **7** was identical with the compound which was prepared from

ethyl γ-chloroacetoacetate (**8**) as follows: (1) reduction of **8** with sodium borohydride in methanol gave the *sec*-alcohol **9** (60%), (2) amination of **9** with ammonia in methanol afforded the pyrrolidone **10** (66%) and (3) acetylation of **10** with acetic anhydride/pyridine provided **7** (75%).

The formation of **7** from PA through the reactions mentioned above can be reasonably explained on the basis of **1a** deduced for PA.

Finally, **1a** was synthesized from **8**.[7] Ketalization of **8** with ethyl orthoformate/hydrogen chloride/molecular sieve in ethanol gave the ketal **11** (68%), which was converted into the hydroxamic acid **12** (94%) on treatment with hydroxylamine in dioxane under nitrogen. Cyclization of **12** under acidic conditions to the isoxazole **13** (24%), followed by amination of **13** with concentrated aqueous ammonia, afforded **1a** (34%), which was shown to be identical with naturally occurring PA by direct comparison.

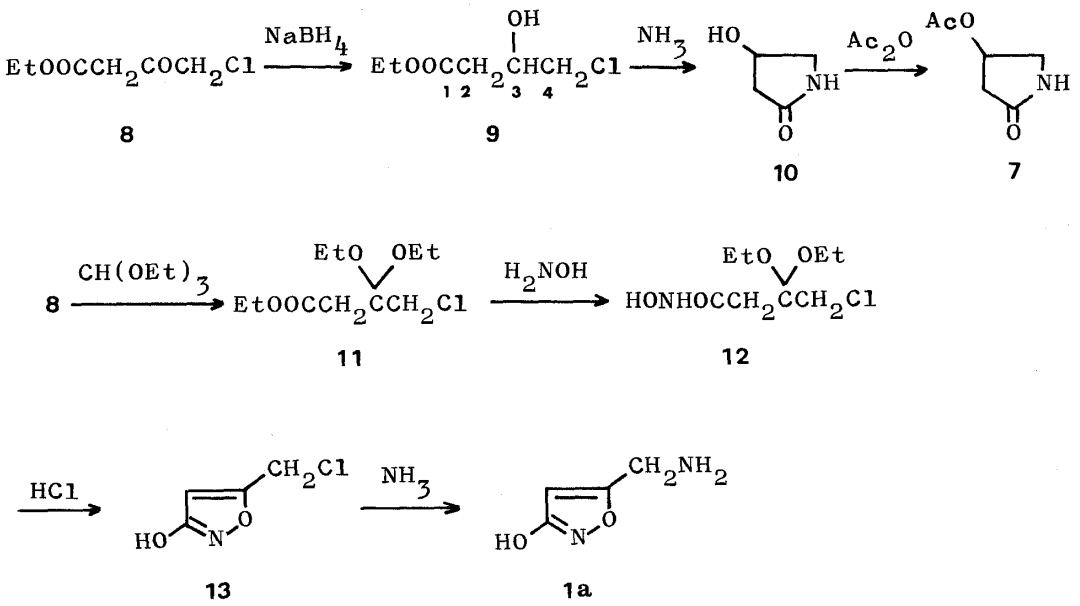

Chart 2

Experimental

Melting points were determined on a micro hot-stage apparatus and are uncorrected. Spectra were recorded on the following spectrometers: IR, Hitachi 260-30; ^{1}H-NMR, Varian EM-390 (90 MHz) (reference, Me_4Si); ^{13}C-NMR, JEOL JNM PFT-100 (25.2 MHz) (reference, Me_4Si); MS, JEOL JMS DX-300.

Pantherine——Colorless prisms of mp 174—176 °C (dec.) (from EtOH). IR (KBr): 3116—2940 ($\overset{+}{N}H_3$), 1632 cm^{-1} (C=C, C=N). ^{1}H-NMR (CF_3COOH) δ_H: 7.82 (3H, br s, 7-H_3),[8] 6.47 (1H, s, 4-H), 4.59 (2H, q, J_{HH} 4 Hz, 6-H_2);[9] ^{1}H-NMR (CF_3COOD) δ_H: 6.48 (1H, s, W_H 2.5 Hz, 4-H), 4.58 (2H, s, W_H 4.2 Hz, 6-H_2). Decoupling (CF_3COOD): δ_H 6.48 (4-H)→δ_H 4.58 (W_H 4.2 Hz→3.0 Hz, 6-H_2); δ_H 4.58 (6-H_2)→δ_H 6.48 (W_H 2.5 Hz→1.5 Hz, 4-H). ^{13}C-NMR: Table I. MS Calcd for $C_4H_6N_2O_2$: M, 114.043. Found *m/z*: M^+, 114.042. *Anal.* Calcd for $C_4H_6N_2O_2$: C, 42.10; H, 5.30; N, 24.55. Found: C, 42.12; H, 5.30; N, 24.56.

5-Acetamidomethyl-3-acetoxyisoxazole (2) and 5-Acetamidomethyl-2-acetyl-3-isoxazolone (3)——A mixture of PA (10.0 mg), acetic anhydride (0.2 ml) and anhydrous pyridine (0.1 ml) was stirred at room temperature overnight. After addition of EtOH (2 ml), the reaction mixture was concentrated *in vacuo*, and the residue was dissolved in benzene. Removal of the solvent *in vacuo*, followed by prep. TLC (silica gel treated with HBO_3; C_6H_6 : Me_2CO = 1 : 1, v/v) of the residue, gave **2** (5.0 mg, 29%), *Rf* 0.31, and **3** (3.0 mg, 17%), *Rf* 0.53.

The Diacetate **2**: A colorless oil. IR ($CHCl_3$): 3452 (NH), 1726 (OC=O), 1680 (NC=O), 1634 cm^{-1} (C=C, C=N). ^{1}H-NMR ($CDCl_3$) δ_H: 6.07 (1H, br s, 7-H),[8] 5.70 (1H, t, J_{HH} 0.8 Hz, 4-H), 4.37 (2H, dd, J_{HH} 6, 0.8 Hz, 6-H_2),[9] 2.56 (3H, s, 3-$OCOCH_3$), 2.03 (3H, s, 7-$COCH_3$). Decoupling: δ_H 6.07 (7-H)$\xrightarrow{6\text{ Hz}}$$\delta_H$ 4.37 (6-H_2)$\xleftrightarrow{0.8\text{ Hz}}$$\delta_H$ 5.70 (4-H). NOE:[10] δ_H 5.70 (4-H)$\xleftarrow{8.0\%}$$\delta_H$ 6.07 (7-H)$\xrightarrow{4.0\%}$$\delta_H$ 2.03 (7-$COCH_3$). MS Calcd for $C_8H_{10}N_2O_4$: M, 198.064. Found *m/z*: M^+, 198.062.

The Diacetate **3**: A colorless oil. IR ($CHCl_3$): 3460 (NH), 1730 [NC(3)=O], 1682 [N(7)C=O], 1638 cm^{-1} (C=C). ^{1}H-NMR ($CDCl_3$) δ_H: 6.31 (1H, t, J_{HH} 0.8 Hz, 4-H), 5.97 (1H, br s, 7-H),[8] 4.51 (2H, dd, J_{HH} 6, 0.8 Hz, 6-H_2),[9] 2.31 (3H, s, 2-$COCH_3$), 2.02 (3H, s, 7-$COCH_3$). Decoupling: δ_H 6.31 (4-H)$\overset{0.8\,Hz}{\longleftrightarrow}\delta_H$ 4.51 (6-H_2)$\overset{6\,Hz}{\longleftrightarrow}\delta_H$ 5.97 (7-H). NOE: δ_H 6.31 (4-H)$\overset{3.0\%}{\longleftrightarrow}\delta_H$ 4.51 (6-H_2)$\overset{3.0\%}{\longrightarrow}\delta_H$ 2.02 (7-$COCH_3$). MS Calcd for $C_8H_{10}N_2O_4$: M, 198.064. Found *m/z*: M^+, 198.062.

5-Acetamidomethyl-3-hydroxyisoxazole (4)——a) A mixture of PA (5.0 mg), acetic anhydride (0.2 ml) and anhydrous pyridine (0.1 ml) was stirred at room temperature overnight. Work-up of the reaction mixture gave a mixture of **2** and **3**, which was purified by prep.TLC (silica gel; $CHCl_3$: MeOH = 10 : 1, v/v) to yield **4** (5.0 mg, 74%), *Rf* 0.08, as colorless needles of mp 143—145 °C (from C_6H_{14}–Me_2CO). IR (KBr): 3308 (NH, OH), 1654 (NC=O), 1630 cm^{-1} (C=C, C=N). ^{1}H-NMR [$(CD_3)_2CO$] δ_H: 7.78 (1H, br s, 7-H),[8] 5.92 (1H, t, J_{HH} 0.8 Hz, 4-H), 4.40 (2H, dd, J_{HH} 6, 0.8 Hz, 6-H_2),[9] 1.96 (3H, s, 7-$COCH_3$). Decoupling: δ_H 7.78 (7-H)$\overset{6\,Hz}{\longrightarrow}\delta_H$ 4.40 (6-H_2)$\overset{0.8\,Hz}{\longleftrightarrow}\delta_H$ 5.92 (4-H). ^{13}C-NMR (CD_3OD) δ_C: 174.1, 173.1, 172.5 (s each, C-3, -5, 7-$\underline{C}OCH_3$), 95.3 (d, C-4), 37.3 (t, C-6). MS Calcd for $C_6H_8N_2O_3$: M, 156.053. Found *m/z*: M^+, 156.054.

b) A solution of a mixture (16.0 mg) of **2** and **3** in 5% HCl–MeOH (1 ml) was stirred at room temperature for 1 h. Work-up of the reaction mixture gave **4** (12.0 mg, 95%) as colorless needles of mp 143—145 °C (from C_6H_{14}–Me_2CO).

4-Acetamido-3-oxobutyramide (5)——A solution of **4** (10.0 mg) in EtOH (5 ml) was hydrogenated over 10% Pd–C (8 mg) at room temperature for 2 h. The reaction mixture was filtered and concentrated *in vacuo*. The residue was recrystallized from acetone to yield **5** (8.0 mg, 80%) as colorless needles of mp 153—154 °C. IR ($CHCl_3$): 3504, 3480, 3465 (NH_2, NH), 1680 cm^{-1} (C=O, NC=O). ^{1}H-NMR (CD_3OD) δ_H: 4.22 (2H, s, 4-H_2), 2.05 (3H, s, 4-NHCOC$\underline{H}_3$). ^{13}C-NMR (CD_3OD) δ_C: 202.3 (s, C-3), 174.2, 171.8 (s each, C-1, 4-NH$\underline{C}$OCH$_3$), 50.5 (t, C-4), 22.4 (q, 4-NHCO$\underline{C}$H$_3$). *Anal.* Calcd for $C_6H_{10}N_2O_3$: C, 45.56; H, 6.37; N, 17.71. Found: C, 45.26; H, 6.36; N, 17.61.

4-Acetamido-3-hydroxybutyramide (6)——$NaBH_4$ (5 mg) was added to a solution of **5** (8.0 mg) in EtOH (10 ml), and the mixture was stirred at room temperature for 30 min. After addition of acetic acid (0.1 ml), the reaction mixture was concentrated *in vacuo*, and the residue was extracted with chloroform. Removal of the solvent *in vacuo* gave an oil, which was purified by prep. TLC (Al_2O_3; $CHCl_3$: MeOH = 3 : 1, v/v) to yield **6** (6.0 mg, 75%), *Rf* 0.39, as a colorless oil. IR ($CHCl_3$): 3550, 3456, 3416, 3350 (OH, NH_2, NH), 1668 cm^{-1} (NC=O). ^{1}H-NMR [$(CD_3)_2CO$] δ_H: 7.24 (2H, br s, 1-NH_2),[8] 6.42 (1H, br s, 4-N$\underline{H}$COCH$_3$),[8] 4.76 (1H, br s, 3-OH),[8] 4.06 (1H, m, 3-H), 3.28 (2H, m, 4-H_2), 2.32 (2H, m, 2-H_2), 1.93 (3H, s, 4-NHCOC$\underline{H}_3$). MS Calcd for $C_6H_{12}N_2O_3$: M, 160.084. Found *m/z*: M^+, 160.085.

4-Acetoxy-2-pyrrolidone (7)——A solution of **6** (6.0 mg) in 10% HCl (5 ml) was heated at 80 °C overnight in a sealed tube. The reaction mixture was concentrated *in vacuo*, and the residue was stirred in a mixture of acetic anhydride (0.2 ml) and anhydrous pyridine (0.1 ml) at room temperature for 2 h. Work-up of the reaction mixture, followed by prep. TLC (Al_2O_3; $CHCl_3$: MeOH = 20 : 1, v/v) to yield **7** (4.0 mg, 87%), *Rf* 0.83, as colorless needles of mp 91—92 °C (from C_6H_6–C_6H_{14}). IR (KBr): 3224 (NH), 1740 (OC=O), 1698 cm^{-1} (NC=O). ^{1}H-NMR ($CDCl_3$) δ_H: 6.22 (1H, br s, 1-H),[8] 5.36 (1H, m, 4-H), 3.73 (1H, dd, J_{HH} 12, 6 Hz, 5-H), 3.38 (1H, ddd, J_{HH} 12, 3, 0.5 Hz, 5-H),[9] 2.67 (1H, dd, J_{HH} 18, 7 Hz, 3-H), 2.38 (1H, dd, J_{HH} 18, 3 Hz, 3-H), 2.06 (3H, s, 4-$OCOCH_3$). ^{13}C-NMR ($CDCl_3$) δ_C: 176.5 (s, C-1), 170.1 (s, 4-O$\underline{C}$OCH$_3$), 69.8 (d, C-4), 49.0 (t, C-5), 37.2 (t, C-3), 21.0 (q, 4-OCO$\underline{C}$H$_3$). *Anal.* Calcd for $C_6H_9NO_3$: C, 6.34; H, 50.34; N, 9.79. Found: C, 6.29; H, 50.42; N, 9.66.

Synthesis of 4-Acetoxy-2-pyrrolidone (7)

Ethyl 4-Chloro-3-hydroxybutyrate (9)——$NaBH_4$ (50 mg) was added to a solution of **8** (330 mg) in EtOH (10 ml), and the mixture was stirred at 0 °C for 30 min. Work-up of the reaction mixture gave an oil, which was purified by prep. TLC (Al_2O_3; $CHCl_3$: MeOH = 10 : 1, v/v) to yield **9** (200 mg, 60%), *Rf* 0.90, as a colorless oil. IR (film): 3468 (OH), 1728 cm^{-1} (OC=O). ^{1}H-NMR ($CDCl_3$) δ_H: 4.17 (2H, q, J_{HH} 7 Hz, 1-OC$\underline{H}_2$CH$_3$), *ca.* 4.17 (1H, 3-H), 3.58 (2H, d, J_{HH} 6 Hz, 4-H_2), 3.18 (1H, d, J_{HH} 4 Hz, 3-OH),[8] 2.62 (2H, d, J_{HH} 6 Hz, 2-H_2), 1.28 (3H, t, J_{HH} 7 Hz, 1-OCH$_2$C$\underline{H}_3$). Decoupling: δ_H 4.17 (3-H)→δ_H 3.58 (4-H_2), 3.18 (3-OH), 2.62 (2-H_2) (d each→s each). MS Calcd for $C_6H_{11}ClO_3$: M, 168.037 and 166.040. Found *m/z*: $(M+H)^+$, 169.046 (169.045) and 167.051 (167.048).

4-Hydroxy-2-pyrrolidone (10)——A solution of **9** (150 mg) in MeOH (7 ml) saturated with NH_3 was heated at 70 °C overnight in a sealed tube. Concentration of the reaction mixture *in vacuo*, followed by prep. TLC (Al_2O_3; $CHCl_3$: MeOH = 3 : 1, v/v) of the residue, gave **10** (60 mg, 66%), *Rf* 0.59, as colorless plates of mp 123—125 °C (from Me_2CO). IR (KBr): 3248 (OH), 3148 (NH), 1670 cm^{-1} (NC=O). ^{1}H-NMR [$(CD_3)_2CO$] δ_H: 6.65 (1H, br s, 1-H),[8] 4.56 (1H, m, 4-H), 4.30 (1H, d, J_{HH} 4 Hz, 4-OH),[8] 3.61 (1H, dd, J_{HH} 10, 6 Hz, 5-H), 3.24 (1H, ddd, J_{HH} 10, 6, 0.5 Hz, 5-H),[9] 2.46 (1H, dd, J_{HH} 17, 6 Hz, 3-H), 2.07 (1H, dd, J_{HH} 17, 3 Hz, 3-H). Decoupling: δ_H 6.65 (1-H)→δ_H 3.24 (ddd, J_{HH} 10, 6, 0.5 Hz→dd, J_{HH} 10, 6 Hz, 5-H). MS Calcd for $C_4H_7NO_2$: M, 101.048. Found *m/z*: M^+, 101.048.

4-Acetoxy-2-pyrrolidone (7)——A mixture of **10** (30.0 mg), acetic anhydride (0.2 ml) and anhydrous pyridine (0.4 ml) was stirred at room temperature overnight. Work-up of the reaction mixture gave an oil, which was purified by prep. TLC (Al_2O_3; $CHCl_3$: MeOH = 20 : 1, v/v) to yield **7** (32.0 mg, 75%), *Rf* 0.83, as colorless needles of mp 91—92 °C (from C_6H_6–C_6H_{14}). This compound was shown to be identical with the pyrrolidone **7** derived from PA by direct comparison.

Synthesis of 5-Aminomethyl-3-hydroxyisoxazole (1a)

Ethyl 4-Chloro-3,3-diethoxybutyrate (11)——A mixture of **8** (1.0 g), ethyl orthoformate (1.8 g) and 4A molecular sieve 1/16-in. pellets (1.5 g) in EtOH (5 ml) saturated with dry HCl was heated at 70 °C for 10 h in a sealed tube. The reaction mixture was filtered and concentrated *in vacuo*, then extracted with ethyl acetate. Removal of the solvent *in vacuo* and chromatography of the residue over Al_2O_3 (45 g) using benzene as an eluent gave **12** (0.98 g, 68%) as a colorless oil. IR (film): 1730 cm^{-1} (OC=O). ^{1}H-NMR ($CDCl_3$) δ_H: 4.07, 3.46 [2H each, q, J_{HH} 7 Hz, 3-($OC\underline{H}_2CH_3$)$_2$], 3.66 (2H, s, 4-H_2), 2.73 (2H, s, 2-H_2), 1.25, 1.15 [3H each, t, J_{HH} 7 Hz, 3-($OCH_2C\underline{H}_3$)$_2$]. MS Calcd for $C_{10}H_{19}ClO_4$: M, 240.094 and 238.097. Found *m/z*: $(M-OC_2H_5)^+$, 195.061 (195.060) and 193.064 (193.063).

4-Chloro-3,3-diethoxybutyrohydroxamic Acid (12)——A solution of **11** (604 mg) in dioxane (5 ml) was added to a mixture of $NH_2OH\cdot HCl$ (263 mg) and NaOH (355 mg) in water (5 ml), and the whole was stirred at room temperature under N_2 for 25 h. The reaction mixture was concentrated *in vacuo* to one-third of its original volume and extracted with chloroform. The water phase was acidified with 10% HCl and extracted with ethyl acetate. Removal of the solvent *in vacuo* gave **12** (536 mg, 94%) as a colorless oil (a sole product). IR ($CHCl_3$): 3520, 3400, 3225, 3170 (OH, NH), 1705 cm^{-1} (NC=O). ^{1}H-NMR ($CDCl_3$) δ_H: 9.28 (2H, br s, 1-$N\underline{H}O\underline{H}$),[8] 3.72 (2H, s, 4-$H_2$), 3.60 [4H, q, J_{HH} 6.5 Hz, 3-($OC\underline{H}_2CH_3$)$_2$], 2.82 (2H, s, 2-H_2), 1.16 [6H, t, J_{HH} 6.5 Hz, 3-($OCH_2C\underline{H}_3$)$_2$]. MS Calcd for $C_8H_{16}ClNO_4$: M, 227.074 and 225.077. Found *m/z*: $(M+H)^+$, 228.080 (228.082) and 226.084 (226.085).

5-Chloromethyl-3-hydroxyisoxazole (13)——A solution of **12** (400 mg) in acetic acid (5 ml) saturated with dry HCl was heated at 60—80 °C for 30 h in a sealed tube. Concentration of the reaction mixture *in vacuo* and extraction of the residue with ether (10 ml), followed by extraction of the ether-soluble part with chloroform (5 ml), afforded an oil (121 mg). Prep. TLC (silica gel; C_6H_6 : Me_2CO = 5 : 1, v/v) gave **13** (57.0 mg, 24%), *Rf* 0.20, as colorless needles of mp 99—101.5 °C (lit.,[7] mp 97—101 °C) (from C_6H_{14}–CCl_4). IR ($CHCl_3$): 3000 (OH), 1620 cm^{-1} (C=C, C=N). ^{1}H-NMR ($CDCl_3$) δ_H: 7.53 (1H, br s, 3-OH),[8] 6.01 (1H, s, 4-H), 4.47 (2H, s, 5-H_2). MS Calcd for $C_4H_4ClNO_2$: M, 134.990 and 132.993. Found *m/z*: M^+, 134.991 and 132,995.

5-Aminomethyl-3-hydroxyisoxazole (1a)——A solution of **13** (84.0 mg) in concentrated aqueous ammonia (5 ml) was heated at 60—80 °C for 32 h in a sealed tube. The reaction mixture was concentrated *in vacuo*, and the residue was extracted with hot EtOH (10 ml). The EtOH-soluble part was recrystallized from 95% EtOH to yield **1a** (35.0 mg, 34%) as colorless prisms of mp 173—175 °C (dec.). This compound was shown to be identical with naturally occurring PA by direct comparison.

References and Notes

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8) On addition of deuterium oxide, these signals disappeared.
9) On addition of deuterium oxide, these splittings were simplified due to disappearance of the protons exchangeable with deuterium oxide.
10) Nuclear Overhauser effect.